

***LETTER OF INTENT TO APPLY FOR<sup>1</sup>*****THE TERRY FOX NEW FRONTIERS PROGRAM PROJECT GRANT (PPG) (2018)*****Deadline: Tuesday August 8<sup>th</sup>, 2017 5:00 pm Pacific Daylight Time******Email to [ppg@tfri.ca](mailto:ppg@tfri.ca)*****Full Name of Project Leader:** MALKIN, David, Dr**Project Leader Mailing Address:** The Hospital for Sick Children, Division of Hematology/Oncology, 555 University Avenue, Toronto, Ontario. M5G 1X8**Project Leader Email:** [david.malkin@sickkids.ca](mailto:david.malkin@sickkids.ca)**Project Leader Telephone #:** 416-813-5348**Project Leader Laboratory Telephone #:** 416-813-6541

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**PROGRAM TITLE:** The Terry Fox New Frontiers Program Project Grant in the Early Detection and Prevention of Cancer in Li-Fraumeni Syndrome

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**PROPOSED START DATE:** July 1, 2018

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**RESEARCH INSTITUTES:** The Hospital for Sick Children, IWK Health Centre, Ontario Institute for Cancer Research, Princess Margaret Cancer Centre

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Names of the Institutes	Names of Project Investigators
The Hospital for Sick Children	David Malkin, Anna Goldenberg, Adam Shlien, Andrea Doria, Ran Kafri, Anita Villani
IWK Health Centre	Jason Berman
Princess Margaret Cancer Centre/UHN	Trevor Pugh, Gang Zheng

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<sup>1</sup> The Project Leader should refer to the 2018 PPG LOI Guide before completing this proposal form.

[Expand table as required]

#### **LIST OF PROJECTS & CORES INCLUDED IN THE PROGRAM PROJECT GRANT APPLICATION**

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#	Short Title of Project / Core	Principal Investigator
1	The clinical implications of intra-tumoural heterogeneity in LFS	Adam SHLIEN/Anita VILLANI
2	Predictive Modeling of Age of Onset and Tumor Type in LFS	Anna GOLDENBERG
3	Early Tumor Detection by Circulating Tumor DNA Biomarkers in LFS	David MALKIN/Trevor PUGH/Adam SHLIEN
4	Novel Approaches to Molecular / Tissue Imaging and Clinical Surveillance in LFS: Multicentric Validation Study	Andrea DORIA/Gang ZHENG/Anita VILLANI
5	Using the zebrafish as a model for chemoprevention for <i>TP53</i> mutation carriers	Jason BERMAN
6	Pharmacologic Prevention of Malignancy in LFS	David MALKIN/Ran KAFRI/Anita VILLANI/Jason BERMAN
7	LFS Sequencing and Data Repository	Anna GOLDENBERG/David MALKIN

[Expand table as required]

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**LIST OF INVESTIGATORS INCLUDED IN THE PROGRAM PROJECT GRANT APPLICATION**

#	<i>Full Name</i> <i>Role in Program Project Grant Application</i>	<i>Institutional Affiliation</i> <i>Signature</i>
1	David MALKIN Project Leader, Co-Principal Investigator Project #3, Co-investigator Project #6 and CORE	
2	Adam SHLIEN Principal Investigator of PROJECT #1, Co-Investigator Projects #2 and #3	
3	Anna GOLDENBERG Principal Investigator of PROJECT #2 and Principal Investigator of CORE	
4	Andrea DORIA Principal Investigator of PROJECT #4	
5	Jason BERMAN Principal Investigator of PROJECT #5, Co-Investigator Project #6	
6	Ran KAFRI Principal Investigator of PROJECT #6	
7	Gang ZHENG Co-Investigator of PROJECT #4	

8	Trevor PUGH	
	Co-Principal Investigator of PROJECT #3	
9	Anita VILLANI	
	Co-Investigator of PROJECTS #1, 4 and 6	

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**1. SCIENTIFIC ABSTRACT (*max 1 page*)**

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**Background:** Li-Fraumeni syndrome (LFS) is a highly penetrant autosomal dominantly inherited cancer predisposition disorder with a population frequency of ~1:5000. Germline *TP53* mutations cause >80% of LFS, and are linked to a wide spectrum of cancers including adrenocortical carcinoma, rhabdomyosarcoma, brain tumors, and early onset breast cancer even in the absence of a family cancer history. Understanding the genetic and phenotypic heterogeneity of LFS formed the basis of our initial TFRI PPG. In the first two years of this Program, we reported an association of differential global methylation with tumor phenotype in *TP53* mutation carriers, validated our novel surveillance protocol for early tumor detection, established F1 progeny of *tp53* (LFS) mutant zebrafish to utilize for chemical screens, created an algorithm that accurately predicts age-of-onset in *TP53* mutation carriers, and generated data suggesting a unique molecular architecture in LFS-derived tumors.

**Overall Goals:** We now build on this progress and introduce new investigators and collaborators who bring expertise in innovative imaging and ctDNA surveillance technologies, in addition to introduction of novel biologic agents that restore wtp53 function. This will lead us to resolve the two major challenges faced by LFS patients: 1) Improve sensitivity and specificity of early tumor detection leading to improved survival; and 2) Develop and implement rational chemoprevention strategies for *TP53* mutation carriers.

**Expected Outcomes:** NGS sequencing of tumors and germline samples (**Project 1**) will reveal a molecular LFS signature to be used as a specific, sensitive ctDNA biomarker in both our *Trp53* knock-in mouse and prospective human studies (**Project 3**). Introduction of porphyrin lipoprotein-mimicking (PLP) nanoparticles will enable enhanced imaging surveillance to complement our evolving MRI approaches (**Project 4**) and correlations with molecular biomarkers (**Project 3**). Multilevel analysis of sequencing, clinical and imaging data (amalgamated in the **Core**) will define algorithms for precise predictive measures of age-of-onset and tumor type in LFS (**Project 2**). Our *tp53* murine and zebrafish models will be used for both comprehensive surveillance (**Projects 3+4**) and chemical screens (**Project 5**), respectively, and as pre-clinical platforms, together with patient-derived cell lines exhibiting a spectrum of heterozygous *TP53* mutations to study the chemopreventive and therapeutic effects of promising new agents including p53 refolders (APR246), peptides (CAP50) and modulators of mutant p53 function (statins and mTOR inhibitors) (**Project 6**). Our findings will support development and implementation of the first prospective studies of molecular surveillance for early tumor detection in LFS and introduction of early phase clinical trials for prevention and treatment of cancer for this devastating disease.

**2. OVERALL DESCRIPTION OF APPLICATION (*max 5 pages*)**

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**BACKGROUND:** Individuals with Li-Fraumeni Syndrome (LFS) (OMIM#151623) account for 17% of all patients in cancer susceptibility syndromes. Germline *TP53* mutations are the causative event in 80% of all LFS patients (1). Since the initial discovery of the link between germline *TP53* mutations and LFS in 1990 (2), studies of this genetically and phenotypically heterogeneous disorder have led to better understanding of the mechanisms of cancer susceptibility and p53 function, role of genomic instability in cancer predisposition, and introduction of an internationally accepted approach to clinical surveillance for early tumor detection (3). The spectrum of malignancies in LFS is diverse, and age of onset is typically substantially younger than in their sporadic counterparts. Heterogeneity in tumor subtype and age of onset may result from coincident alterations of genes that modify the phenotypic effects of the underlying *TP53* mutation. Our group has been a long-standing leader in understanding the genetic/genomic basis of LFS, and in providing insight in the potential value this information has in refining cancer risk prediction in *TP53* mutation carriers. Prior work from our group demonstrated that polymorphisms in *TP53* and *MDM2*, an integral component of p53 function, influence age of cancer onset in LFS; that accelerated telomere attrition is associated with younger age at first cancer diagnosis in *TP53* mutation carriers (4); that DNA copy number variation (CNV) is higher in *TP53* mutation carriers (5); and that chromothripsis occurs in tumors of patients with germline *TP53* mutations (6). Work conducted in the course of the first two years of this TFRI PPG identified potential roles of two miRNAs, miR605 (7) and miR34A (8,9), in the phenotypic heterogeneity characteristic of LFS; differential methylation in *TP53* mutation carriers (Samuel 2016b) that appears associated with tumor phenotype; creation of a predictive algorithm of age of onset in *TP53* mutation carriers based on methylation profile (Brew 2017, in preparation); creation of a zebrafish model harboring LFS-associated heterozygous mutations (Prykhozhij 2017, in preparation); and an enhanced multi-modality clinical surveillance protocol for early tumor detection in LFS (Villani 2016). Observations from the latter study demonstrated that while 100% of tumors presenting clinically in patients who did not undergo surveillance were malignant, >60% of those detected by surveillance were pre-malignant and low-grade, suggesting that tumors may actually have a pre-malignant or dormant phase which could be exploited both in terms of more refined early detection techniques (such as use of circulating tumor DNA (ctDNA)), or molecularly targeted imaging modalities, as well as for development of preventive measures by agents that modify or abrogate mutant p53 function.

Notwithstanding the great progress that our integrated Program Team has made in understanding the role for inherited and acquired (epi)genetic events that modify the cancer phenotype in *TP53* mutation carriers, our tools to detect and predict tumor onset for a specific individual with LFS are still crude. Furthermore, it has only been recently that data has emerged demonstrating potential efficacy of p53 modifying drugs in pre-clinical models of somatic alterations in p53. We propose that the combined use of novel ‘molecular’ imaging and ctDNA surveillance will substantially improve the sensitivity and specificity of early tumor detection in *TP53* mutation carriers. We also propose that emerging agents designed to structurally modify mutant p53 and activate wild-type p53, some of which are already in clinical trials in the context of sporadic cancer, can be harnessed as chemopreventive agents in LFS. We have expanded our Program significantly to engage the remarkable expertise of world-leading Canadian scientists (**Pugh, Zheng, Kafri**) and clinical researchers (**Villani**) in the study and application of ctDNA (**Project 3**), porphyrin lipoprotein-mimicking (PLP) nanoparticles (**Projects 4 and 6**), live cell/single cell imaging and functional genomics (**Project 6**), and to complement the expertise of the investigators in our initial application (**Malkin, Shlien, Goldenberg, Doria, Berman**) to build on the productivity generated from our sequencing (**Project 1**), predictive modeling (**Project 2**), imaging surveillance (**Project 4**), and zebrafish (**Project 5**) work.

**OBJECTIVES:** The overarching objectives of this comprehensive multi-investigator Program is to use complex molecular and clinical determinants of LFS to resolve the two major challenges faced by LFS patients: 1) Improve sensitivity and specificity of early tumor detection leading to improved survival; and 2) Develop and implement rational chemoprevention strategies for *TP53* mutation carriers. These objectives will be met through the following specific aims encompassed by each of the six integrated projects and supported by a comprehensive sequencing and data/tissue repository Core.

**Aim 1:** Define the molecular heterogeneity of LFS tumors and utilize this information to create a molecular signature of LFS cancers to be used as a molecular biomarker of early detection (ctDNA);

**Aim 2:** Create a multi-level risk model to predict age of onset and tumor type in *TP53* mutation carriers;

**Aim 3:** Use a murine *Trp53* mutant model and prospective human studies to develop and validate a sensitive and specific ctDNA biomarker predictive of tumor onset in LFS;

**Aim 4:** Develop and validate novel imaging modalities utilizing novel MRI and PLP platforms to improve early tumor detection;

**Aim 5:** Utilize our mutant *tp53* zebrafish models to determine the contribution of secondary mutations to tumorigenesis and identify effective agents for tumor prevention through chemical screens and direct exposure to recently identified p53 modifying agents;

**Aim 6:** Create and utilize a novel LFS cancer cell observatory and *in vivo* models to evaluate the biologic effects of agents identified through the zebrafish chemical screen or modulators of mutant p53 function.

**IMPORTANCE AND NOVELTY:** *TP53* mutation carriers have a strikingly elevated lifetime cancer risk. Germline *TP53* mutations are the initiating event in a cascade of molecular and epigenetic alterations that ultimately lead to malignant transformation in selected target organs. While *TP53* mutation carrier rate in the general population is cited as ~1:5000, somatic *TP53* mutations in sporadic tumors remain the most frequently altered gene in human cancer. Murine mutant p53 knock-in or p53 deletion (p53 null) models, *in vitro* models to interrogate p53 function, and biochemical and biologic studies of the p53 regulatory pathway, provide major insights into human carcinogenesis. The study of LFS, and the more precise molecular profiling of *TP53* mutation carriers has led to improved survival through implementation of novel multi-modality clinical surveillance protocols (Villani 2016). Expansion of these surveillance studies through use of innovative techniques such as porphyrin lipoprotein-mimicking (PLP) nanoparticles and PET-MRI offer opportunities to improve both sensitivity and specificity of early tumor detection. Definition of LFS-specific molecular signatures, expanding from our current studies of genome and methylome to include miRNAs will provide a biomarker for detection by novel ctDNA techniques. Utilization of the *Trp53* mutant mouse (R270H) to study early tumor detection with both ctDNA and prospective imaging will complement the studies in our human LFS population. These mice, together with our novel zebrafish model, and the unique cancer observatory designed for live cell imaging and functional analysis, provide the ideal platforms to determine the biological effects of emerging promising agents that modify mutant p53 function (statins, mTOR inhibitors, peptides and p53 refolders) provided to us through our international collaborators. The combination and complementarity of expertise in whole genome, exome, methylome and miRNA sequencing, computer based modeling of multi-level genetic, biologic and clinicopathologic data, emerging powerful imaging techniques and model organism and cell system platforms, and the exciting introduction of viable drugs to modify mutant p53 function in both pre-clinical and clinical settings represent a unique ‘marriage’ of scientific disciplines that define what we believe to be a powerful and highly novel approach to define the true molecular basis of tumor formation in LFS and to alter the natural course of the disease.

**COLLABORATION AND SYNERGY:** The initial two years of this Program has seen a rapid, effective evolution of this creative team. PIs jointly oversee projects, with joint authorship for manuscripts and meeting presentations across all labs. At the time of this submission, four new manuscripts are in preparation: creation of the zebrafish models; sequencing of p53-wild-type LFS families to identify other causal genetic events; modeling of age-of-onset predictions utilizing the methylation data and retrospective evaluation of the MRI surveillance which has demonstrated dormancy of LFS tumors. The addition of new investigators to the Program derive from direct interactions with these individuals on related projects, and extension of their studies to the p53-LFS story. The direction of the Program continues to evolve with new coinvestigators and collaborators bringing opportunities in adapting new imaging (PLP)(Zheng), new ctDNA platforms (Pugh), cellular imaging and functional analysis techniques (Kafri) , and new drugs (collaborators Rotter, Prives, Del Sal, Wiman, Selimanova). We believe this expanded, yet focused team, represents the most comprehensive of its kind in the world.

**TRAINING AND MENTORSHIP:** Drs. Malkin, Berman, Doria and Zheng are well-established investigators with strong track records in training graduate students, post-doctoral research fellows and MD trainees. Drs. Goldenberg, Shlien, Kafri, Pugh and Villani are extraordinarily talented ‘young investigators’ who have already trained outstanding students. The integration of senior, mid-career and junior investigators in this Program Project lends itself especially well to mentorship among the investigators themselves. During the first 2 years of the Program, the team had monthly face-to-face meetings in the Research building at SickKids (skyping in Dr. Berman’s team from Halifax). Students would present their current work which allowed for dynamic interactive discussion. In addition, the Berman team came to Toronto for a face-to-face meeting (October 2016) and a second meeting is planned in November 2017. All students have had the opportunity to present their work in poster or platform format at no less than 30 individual meetings (national and international). These opportunities allow students to ‘test’ their ideas and results to a larger audience, and to meet many of the leaders in their respective fields. Importantly, students also have the opportunity to meet LFS families (either at the biennial LFS Symposia (next one to be hosted in Toronto April 2018) or through Dr. Malkin’s Cancer Genetics clinic. These training and mentorship activities will continue throughout the duration of this renewal grant.

**INSTITUTIONAL COMMITMENTS:** Each PI has committed lab space and significant infrastructure resources. Drs. Malkin, Shlien, Goldenberg, Kafri and Doria’s labs are in the Peter Gilgan Centre for Research and Learning (PGCRL) at SickKids. Drs. Zheng and Pugh’s labs are at the MaRS building (Ontario Institute for Cancer Research and Ontario Cancer Institute) - a 10 minute walk to SickKids. Dr. Berman’s

recently expanded laboratory is arguably the most state-of-the-art zebrafish facility in the country. The SickKids labs are in complementary research neighborhoods (Cancer and Stem Cell Biology (DM, RK), Genetics and Genome Biology (AS, AG) and Clinical Health and Evaluative Sciences (AD, AV)) which boast extraordinary core infrastructures to support the conduct of all the proposed studies. As Associate Director of the Molecular Diagnostics Laboratory and Director of the Translational Genomics Program, Dr. Shlien is particularly well-positioned to facilitate the Program's sequencing elements. The diagnostic imaging department has dedicated research MRI PET-MRI facilities, and the animal studies are already underway with housing and MRI/CT imaging facilities at the nearby Centre for Phenogenomics.

**ROLE OF PARTNERS:** Several key partners are engaged to facilitate this Program. Dr. Malkin is Chair of the International Li-Fraumeni Exploration (LiFE) Consortium which comprises over 25 major cancer centres worldwide, including in the US (Dana-Farber Cancer Institute, MD Anderson Cancer Center, City of Hope, Huntsmann Cancer Institute at University of Utah, the NIH, St. Jude Children's Research Hospital, Children's Hospital of Philadelphia, and others), Europe (University of Manchester, Great Ormond Street, London; the French Li-Fraumeni consortium (Lyons, Paris, Rouen); DFKZ, Heidelberg and Hannover), Brazil (AC Carmago Hospital, Sao Paolo; Cancer Genetics Center, Porto Allegre), and elsewhere. Samples from patients are readily available from all these centres and several collaborative projects have been completed over the last 20 years among these institutions and investigators affiliated with them. Several are identified collaborators on this renewal application. A centralized data registry has been established at City of Hope and each centre maintains its own institutional registry. Thus, the data and material available to the Program, particularly for validation studies, is extremely rich. In addition to this support, we have confirmed new collaborations with several scientists who have made major contributions in the development of emerging therapies including Prof. Varda Rotter (Weizmann Institute of Science, Israel) who has developed a series of peptides (CAPs) that refold mutant p53 to wild-type function; Prof. Galina Selimanova and Klas Wiman (Karolinska Institute, Sweden), lead scientists at APREA that developed the family of mutant p53 activators (APR246, etc) now in early clinical trials in ovarian cancer, melanoma and lymphoma; and Prof. Carol Prives (Columbia University, NY) and Giannani Del Sal (Cancer Research Institute, Trieste, Italy) who have extended the use of statins in pre-clinical applications to activate p53, and (Del Sal) who has identified a unique miRNA (miR30d) that is secreted exclusively by mutant p53 expressing cells. All are leaders in the study of p53 and have enthusiastically provided us the agents to work with. In addition, we maintain close collaborations with colleagues in our individual respective fields to enhance the intellectual capacity of the Program – and to generate discussion and input on novel approaches and techniques as required.

**PROGRESS REPORT (*max 3 pages*)**

Over the course of the first two years of our TFRI Frontiers Program, we have made great progress in all four initial interlinked projects and several manuscripts are currently in nearing completion. We have met our initial goals, anticipate completing most of our deliverables by the end of year 3, and are poised, with the addition of new co-investigators/ collaborators, to extend our scope.

**PROJECT 1: Molecular modifiers of in germline *TP53* mutation carriers (PI: Malkin)**

We performed genome-wide methylation analyses and targeted bisulfite sequencing of peripheral blood leukocyte DNA in germline *TP53* mutation carriers (n = 72) and individuals with wild type *TP53* with histologically comparable malignancies (n = 111). In 183 patients, distinct DNA methylation signatures were associated with deleterious *TP53* mutations. *TP53*-associated DNA methylation marks occurred in genomic regions harboring p53 binding sites and genes encoding p53 pathway proteins. Loss-of-function *TP53* mutations were significantly associated with differential methylation at the locus encoding miR-34A, a key component of the p53 regulatory network, and validated in an independent patient cohort (n = 76). These collective results provide a framework to understand the endogenous role of miR-34A signaling and identify novel transcripts and pathways regulated by the miR-34A-p53 tumor suppressor network (8,9). They also support the work in **Project 4 (new Project 5)** in modeling miR-34A in the *tp53* mutant zebrafish model as a modifier of cancer phenotype.

**PROJECT 2A: Li-Fraumeni Syndrome tumour evolution project update (PI: Shlien)**

To investigate the pattern of tumor evolution in LFS, we are performing WGS (30-40X depth) of multiple tumor regions and matched blood from *TP53* mutation carriers and age-matched wild-type controls with the same tumor type. We used our SickKids LFS patient database and accessed sequencing datasets from the Pediatric Cancer Genome Project (PCGP). Two germline *TP53* mutant tumors and one control tumor were analysed by multi-region sequencing (2-3 regions/tumor) with adjacent normal. We analysed these datasets and 8 tumor-normal adrenocortical carcinoma (ACC) whole genome datasets downloaded from PCGP with in-house alignment, variant calling and filtering pipelines. Our first ACC was from a patient with a germline *TP53* mutation (S240G) (pt 1). DNA extracted from 3 regions and one section of adjacent normal and matched blood were submitted for WGS. MuTect analysis called > 1000 SNVs for each region (including the adjacent normal) and few structural variants. Most variants were specific to individual tumour regions. Two additional ACCs were analysed from patients with a deletion of exons 10-11 (pt 2) and R158H mutation (pt 3), respectively. Tumor from pt 2 had a similar mutational profile to that of pt 1, with 1377 SNVs and 36 SVs. However, tumor from pt 3 had a substantially increased mutational load (4909

SNVs and 1851 SVs). Chromothriptic-like rearrangements were observed, particularly in chromosome 8. To date, we have identified intratumor heterogeneity in LFS tumors with many mutations being private to individual tumor regions; we identified chromothripsis in an LFS ACC, and expect this to be a frequent feature in LFS tumors; we identified mutational signature 3 in LFS tumor regions and not adjacent normal. Signature 3 has been associated with *BRCA1* and *BRCA2* mutations, and failure of double strand break repair by homologous recombination. Sequencing of a larger tumor set is underway, and this data will inform our ctDNA early detection work (**new Project 3**).

#### **PROJECT 2B: Predicting age of onset of cancer in children with LFS 2B (PI: Goldenberg)**

We initially focused on age of onset prediction by building a pipeline to combine clinical and methylation data (from our LFS bank samples) and testing various machine learning models. The strategy is two-fold: (1) predict age of onset as a continuous variable (regression), and (2) whether a child is likely to get cancer before age of 4 (classification). We built a pipeline of code to clean the clinical data, impute missing values on the methylation data, and allow our model flexibility in variable selection. In addition, we map the methylation probe sites to the nearest gene as well as keeping the original CpG locations. We then merge each of our methylation data sets with the clinical data and implement machine learning models. The features (variables) used in the models are selected using results from our bumphunter analysis as well as the full set of variables. We used our SickKids LFS cohort (277 *TP53* mutation carriers and 272 non-carrier family members) in our predictive model of age of onset. Of the 277 carriers, 91 currently have or have had cancer. For 81 of those patients, we 1) selected methylation probes that differentiated a cohort of LFS cancer patients from healthy controls; 2) identified regions that distinguished between *TP53* mutant patients that did not have cancer from *TP53* wt controls. Our machine learning model (Elastic Net) achieved 86% correlation between true and predicted values of the age of onset. Our classification model predicted whether an individual will be diagnosed before or after the age of 4 with 91% accuracy. Thus, we established that germline methylation profiles can aid in cancer surveillance in LFS and are potentially predictive of age of onset.

#### **PROJECT 3: Enhancing early tumor detection by surveillance in LFS (PI: DORIA; co-PI: Malkin)**

In 2016, we reported long-term followup of the first clinical surveillance protocol for early tumor detection in LFS and demonstrated it to be associated with decreased mortality and treatment-related morbidity (Villani et al 2011, 2016). Project 3 takes two complementary approaches to enhance both the sensitivity and specificity of tumor detection: 1) we hypothesized that <sup>18</sup>FDG-PET MRI would be more sensitive than whole body (WB)-diffusion weighted (DW) MRI and WB-short tau inversion recovery (STIR) MRI for

diagnosis of hypermetabolic tumors. However, if necrosis was present early in the tumor (highly aggressive tumors) DW-MRI would be more sensitive and the combination of WB-STIR and DW would be more diagnostic than <sup>18</sup>FDG-PET MRI; 2) we hypothesized that detection of circulating DNA (cfDNA) would accurately reflect very early tumor detection that predates both clinical and imaging surveillance. Extensive regulatory constraints delayed initiation of the imaging aspects of the study. Health Canada approval for use of <sup>18</sup>FDG-PET MRI in this study was obtained in April 2017, thus no patients have yet been recruited to this part of the study. Recruitment of patients for WB-STIR and DW MRI studies started in September 2016. To date, 12 patients underwent STIR and DW MR imaging. No areas of abnormal signal intensity were noted in any examinations. We tested feasibility and value of comparing cfDNA levels and imaging phenotypes in a small cohort of patients (**new Project 3**). We concurrently evaluated a prospectively followed cohort of LFS patients (N=43), identifying cases in which peak cfDNA levels corresponded to abnormal imaging features (phenotypic expression). WB MR imaging was crucial for diagnosis of tumors in two LFS patients since corresponding cfDNA levels did not show any peak at the time of diagnosis or only started to peak by the time the tumor was much larger in size.

#### **PROJECT 4: Harnessing a zebrafish model of LFS (PI: Berman)**

**Aim 1a: Generating zebrafish models of LFS using CRISPR/Cas9 technology.** We modeled the most frequent *TP53* mutations in human LFS patients (R175H and R248H), which correspond to R143H and R217H in the zebrafish *tp53* gene. We designed CRISPR/Cas9 targeting strategies based on the idea of identifying effective sgRNAs binding as close as possible to the codons to be mutated, using an efficient anti-sense asymmetric ssODNs of 126 nucleotides (consisting of 36 and 90-nt homology arms). Sequencing data revealed that 70-90 % of all *tp53* knock-in reads are fully correct. AS-PCR identified several R143H and R217H founders at the level of germline transmission. F1 embryos are being used for experiments genotyping and sequenced now for use in new Project 5/6. (14)

**Aim 1b: Developing and validating modifiers of the *TP53* genotype in the zebrafish.** To inactivate *miR34a* (**Project 1**), we chose a CRISPR/Cas9-based deletion strategy, with 3 sgRNA sites flanking the gene. Founders carrying *miR34a* deletions were identified and one was found to transmit the deletion to almost a half its progeny. Upon radiation exposure, all embryos in both wild-type and *miR34a* +/- in-cross clutches had a high level of apoptosis suggesting that *miR34a* loss did not significantly protect against irradiation. We also observed that p53 induction using the DNA-damaging agent, camptothecin, increased mir34a levels. These results provide tools for more advanced experiments on the mechanisms of miR-34a function and for investigating its contributions to tumorigenesis due to *TP53* mutations.

**4a. INDIVIDUAL PROJECTS – PROJECT #1: The clinical implications of intra-tumoural heterogeneity in LFS (PI: Adam SHLIEN; co-PI: Anita VILLANI)**

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**BACKGROUND:** LFS cancers arise early by molecular mechanisms that are not fully described. *TP53*, impacting nearly every cancer hallmark, is mutated from early in embryogenesis, thus ‘priming’ every cell. It is surprising that while the spectrum of cancers in LFS is wide, the vast majority are confined to a few cell types. We hypothesized that a detailed understanding of the somatic evolution of LFS tumors would help untangle this unanswered question. Based on compelling data from our initial submission, we will broaden our study of the timing and mutational signatures in LFS. Then, we will initiate a tumor sequencing program for LFS patients with active cancer, leveraging our existing precision medicine infrastructure. This program will recruit from centres in the international Li-Fraumeni Exploration (LiFE) Consortium (Chaired by Dr. Malkin), will be the first for tumor-prone families, will determine the association between intra-tumoral heterogeneity and survival, will pinpoint critical secondary mutations for every major LFS cancer, and will assemble the cohort for whom future clinical trials will be designed.

**PRELIMINARY DATA.** *Multi-site sequencing of LFS and matched sporadic cancers revealed staggering heterogeneity.* To determine the temporal order of somatic mutations in LFS cancers, we established a robust protocol for partitioning small tumor specimens into sections (3-8/tumor), after evaluation by an experienced pathologist, then extracting high quality DNA/RNA for deep sequencing. For every LFS tumor, we analyzed a matched sporadic tumor of the same histotype from a patient without germline *TP53*. In these data, we found a staggering amount of intra-tumoral heterogeneity in LFS. From tumor sections less than 1cm apart, we observed large differences in mutational burden and ~2,000 private substitutions, indicating early divergence. As expected, we observed sudden, coordinated rearrangements in LFS tumors (‘chromothripsis’). To our surprise, these **sudden rearrangement bursts were very common and appeared to be enriched at specific loci.** In one LFS adrenocortical carcinoma, we found increased mutational load (4909 SNVs), with an enrichment for inversions. Chromothriptic-like rearrangements were clustered in a few chromosomes, particularly chr8. We also saw signatures that pointed to defective homologous recombination (HR). Taken together, these unpublished data suggest a defined signature for LFS tumourigenesis.

**AIM 1: RECONSTRUCT THE EVOLUTIONARY HISTORY OF LFS CANCER.** Our unpublished data highlighted the association between germline *TP53* chromothripsis. Why these are less frequent when *TP53* is *somatically* mutated is unclear. In some cases, chromothripsis disrupted key oncogenes, including

negative regulators of *TP53* itself. In one rhabdomyosarcoma we saw hundreds of rearrangements near *MDM2*, which targets *TP53* for degradation. To answer these questions, and expand on these exciting findings, we have gathered 60 LFS tumors for multi-site whole genome sequencing. These are SickKids patients with full clinical information. To this, we will add 40 LFS tumors from our colleagues in the LiFE Consortium and individual institutions who refer patients to our program. The 100 tumors will be microdissected and multi-site sequenced (five sites/tumor). In this rich dataset - representing the largest collection of sequenced genomes from a hereditary cancer and the only to have been multi-site sequenced - **we will determine the landscape of chromothripsis in LFS, whether it is restricted to specific tumors, if it is always early and which genes it recurrently targets.** Our data supports the notion that LFS cancers acquire chromothripsis early, that this is shared by every cell in the tumor upon which clonal diversion occurs. In some cases, the late divergence involves many new rearrangements (e.g. fusion associated translocations), but not point mutations. Imagining this as an evolutionary tree, LFS cancers have a wide trunk containing more mutations than similar sporadic cancers. These data indicate that multiple branches emerge, with widespread intra-tumoral heterogeneity, but when they arise and whether they contain new drivers is unknown. **We will also analyse intra-tumoral heterogeneity, construct phylogenetic trees of LFS surrounding stromal cells and tumors from different organ systems.** We will follow this up with a novel single cell RNA-Seq experiment to determine whether somatic genetic diversity leads to transcriptional heterogeneity. The ‘signatures’ generated from these studies will inform the ctDNA biomarker work (**Project 3**), predictive algorithm studies (**Project 2**), and emerging therapeutics (**Project 6**).

**AIM 2: DEVELOP AN INTERNATIONAL TUMOR PROFILING PROGRAM FOR LFS.** We will initiate an LFS precision medicine program, making clinical-grade genomics available to every LFS patient with active cancer, no matter where they are from. Using a multi-site sequencing test, we will capture actionable mutations missed due to somatic heterogeneity, including mutations for which there are known therapies (e.g. activating fusions in kinases), detection of hypermutation (immune checkpoint inhibition) and mutational signatures (for HR deficient tumors that may respond to PARP inhibition). This program will leverage existing clinical infrastructure (co-I **Dr. Anita Villani**, co-lead of the SickKids Cancer Sequencing (KiCS) program), and will be the first to offer “universal coverage” for patients whose cancer risk is ~ 100%. The LFS Advocacy groups (LFS Association and Living LFS) have expressed enthusiasm in engaging families to enroll on these studies. We expect to be able offer testing to >500 patients per year. In this cohort, we will determine which secondary mutations are common in LFS, and whether intra-tumoural heterogeneity is associated with poor survival or the presence of advanced disease.

**4b. INDIVIDUAL PROJECTS – PROJECT #2: (*Predictive Modeling of Age of Onset and Tumor Type in LFS (PI: Anna GOLDENBERG)*)**

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**BACKGROUND:** LFS is characterized by great heterogeneity in tumor type and age of onset. This feature complicates strategies for early tumor detection. While our studies of ongoing surveillance of *TP53* mutation carriers have demonstrated reduced mortality, the complex imaging and biochemical blood test based protocol is particularly challenging to use in very young children, and detection specificity and sensitivity are still suboptimal for standard radiologic interpretation. A predictive model of age of onset could help indicate in what age window a patient is at risk to develop cancer and determine when a patient should be subjected to more invasive surveillance. This more precise approach will ultimately decrease the cost of surveillance while simultaneously lead to better health outcomes for LFS patients.

**PRELIMINARY DATA:** In the last two years, we used a cohort of LFS patients and their families (277 *TP53* mutation carriers and 272 non-carrier family members) collected at SickKids in our predictive model of age of onset. Of the 277 carriers, 91 currently have or have had cancer. From our published germline methylation data, (~450,000 probe sites), for 81 of those patients, we performed two types of analysis. First, we selected methylation probes that differentiated a cohort of LFS cancer patients from healthy controls. Second, we identified regions that distinguished between *TP53* mutant patients that did not have cancer from *TP53* wt controls. Our machine learning model (Elastic Net) achieved 86% correlation between true and predicted values of the age of onset. Additionally, we tested the ability of our models to predict whether an individual will be diagnosed before or after the age of 4. Our classification model on average achieved 91% accuracy. We verified that our model does not simply predict age of sample collection by using our cohort of LFS patients that do not have cancer yet (n = 40). In our preliminary results we have established that germline methylation profiles can aid in cancer surveillance of LFS patients and are potentially predictive of age of cancer onset. Based on our preliminary data we have multiple hypotheses and questions we would like to address as part of our prediction of predisposition and early detection of the time of onset and tissue type pipeline, as follows: 1) Methylation patterns may also be effective in predicting tissue type; 2) To understand the mechanism by which methylation affects age of onset, we need to combine it with other omics type data to characterize the state of the cell in more detail; 3) We can aid surveillance by integrating methylation and imaging data to detect which features give the earliest indications of the tumor onset.

**RESEARCH PLAN:**

**AIM 1. Identify methylation regions predictive of primary tumor type:** We will identify differentially methylated regions in the germline of patients with different cancer types and, using these regions, build a classifier to predict which patients are predisposed to which kinds of cancer. This analysis pipeline is very similar to what we have already done for detecting whether or not an LFS patient will get cancer before the age of 4 years. Our preliminary data indicates that the methylation signatures in a small number of patients exhibit different patterns between different types of cancer (Samuel 2016); thus, we are likely to identify regions predictive of the cancer type as well.

**AIM 2. Integrate mRNA, miRNA, DNA-sequencing data to understand mechanisms leading to early onset, prioritizing therapeutically targetable methylation regions:** We will harness the power of the newly collected data in this project to analyze the biological mechanism by which methylation or regulation in general might be affecting the age and type of cancer of each patient. For this purpose, once data is collected and processed in the **Data Core Facility**, we will utilize the novel regulatory annotation that the Goldenberg lab is building. Based on a per-gene *in silico* analysis of 25 cancer types, we have discovered that each gene may fall into a different type of regulation, which we termed ‘mode of regulation’. For example, methylation of the promoters explains much more variance of the gene expression of master regulators, than cytokines. Thus, we will collect miRNA and RNA-seq data to identify the cellular mechanisms by which genes implicated by our methylation profiles are regulated. We will then prioritize resulting mechanisms for potential therapeutic targets for **Projects 5 and 6**.

**AIM 3. Identify whether methylation can aid imaging in identifying earlier onset of cancer.** We will incorporate imaging data (**Project 4**) into the predictive pipeline. We will establish features that are considered clinically predictive. In addition, we will take whole images and use established deep learning classifiers to extract *in silico* features that are early detectors of the tumor. Finally, we will integrate features of the cellular mechanisms identified in **Aim 2** together with the imaging features to build the earliest possible detector of the tumor given the available data.

Ultimately, we aim to **produce several deployable predictive systems** that take methylation and other types of germline omics data and predict age of onset and tumor type. We will also produce a list of therapeutic targets that can be tested in **Projects 5 and 6**. Finally, we will help to identify *in silico* features of earlier detection in the imaging data (**Project 4**).

**4c. INDIVIDUAL PROJECTS – PROJECT #3: (Early tumor detection by circulating tumor DNA (ctDNA) in LFS) (co-PI: David MALKIN; co-PI: Trevor PUGH; co-PI: Adam SHLIEN)****BACKGROUND AND PRELIMINARY DATA: Mutation detection using ctDNA sequencing**

Imaging surveillance, while effective, is challenging in terms of patient compliance and sensitivity/specificity. We are exploring ctDNA biomarkers as an alternative or complementary approach to early tumor detection in LFS. To enable full-length sequence analysis of all exons in genes of interest or any other arbitrary genomic region, the Pugh Lab developed a ctDNA sequencing assay (*Liquid Biopsy Sequencing* (LB-Seq)) that combines a hybrid-capture method with a novel bioinformatics algorithm (10). We developed LB-Seq as part of MYELSTONE (“MYEloma STOp NEedle”), a study of patients with multiple myeloma to assess whether cfDNA sequencing was comparable to the clinical standard of analyzing cells from bone marrow (BM) aspirates. By sequencing all exons from 5 genes in 48 patients, we found 96% mutation concordance between ctDNA versus matched BM, and >98% specificity. We are translating this method into a 38-gene clinical test within the UHN CAP/CLIA-certified molecular diagnostics laboratory. This methodology is highly flexible; we currently maintain custom (16-300 kb) for ongoing studies of clonal monitoring and early detection of >10 different cancer types. In our cfDNA work over the last two years in LFS patients, we have used ddPCR as a platform to measure both volumetric changes in ctDNA volume – demonstrating it to rise in 5 patients with evidence of disease and are currently evaluating our methylation profile to determine ability to capture it as a ctDNA marker. The technology developed by the Pugh lab will be integral to enhanced ctDNA detection in LFS.

**RESEARCH PLAN:**

**AIM 1. Tailor a cell-free DNA sequencing assay to query blood samples for the presence of tumor-derived fragments harbouring somatic mutations and epigenetic marks.** To tailor such a panel for LFS, we will leverage WGS data and methylation profiles generated from **Project 1**. For the mutation detection portion of the assay, we will bait frequently mutated genes in LFS tumours (all exons of *TP53* being the most obvious) as well as sequence contexts that are more likely to be mutated in LFS tumours. For the epigenetic profiling arm of the test, we will leverage an antibody-based pull-down method to isolate methylcytosines followed by bioinformatics analysis of LFS-specific CpG islands.

**AIM 2: cfMeDIP-seq: Epigenetic analysis of circulating tumour DNA.** Recently, the De Carvalho lab developed methodology to detect circulating DNA containing epigenetic marks indicative of cancers arising from specific tissues using cfMeDIP-seq (cell-free Methylated DNA Immunoprecipitation and high-

throughput sequencing). By surveying 100,000's of differentially methylated regions simultaneously, this technique can differentiate tumors arising from multiple tissues as well as detect ctDNA in early-stage disease. This method will be used to find global DNA demethylation models that are suitable for monitoring LFS tumors. Distinguishing the site of origin would help guide further targeted organ-specific surveillance (**Projects 2 and 4**). Many LFS patients are at risk of tumors in multiple organs. Identifying the potential organ site of tumourigenesis would be a tremendous advance in the personalized surveillance of these patients.

**AIM 3. Molecular barcoding: Ultrasensitive detection of low frequency mutations in ctDNA.** To further improve the sensitivity of both mutational and epigenetic profiling methods, Drs. Pugh and De Carvalho are collaborating with Dr. Scott Bratman to adapt a Duplex Consensus Sequence molecular barcoding method for error suppression in ctDNA analysis (11) This enables correction for PCR bias and strand-specific errors arising from DNA damage introduced during extraction or library construction. We have demonstrated that this approach successfully suppresses background sequencer error, enabling mutation detection down at least 1:10<sup>4</sup> molecules. This approach is a significant advance for molecular profiling of patients with LFS, particularly for detection of low concentrations of ctDNA in early disease.

**AIM 4. Determine whether miR-30d is an effective biomarker for tumor detection in LFS.** Our collaborator, Giannini Del Sal (Triest, Italy) has recently demonstrated that miR-30d is a paracrine mediator of mutant p53, in that serum levels of miR-30d correlate with p53 mutational status in healthy wild-type mice and tumor-bearing p53R172 ki and p53ko mice, suggesting miR-30d could be a marker of mutant p53 expressing tumors. To determine if this effect is broadly evident in LFS patients with a spectrum of mutations, the assays noted in Aims 2 and 3 will be used to specifically detect miR-30d ctDNA and, determine if they correlate with tumor detection (**Project 4**). A similar approach will be used to determine whether detection of miR-30d precedes tumor development in the *Trp53 R270H* mice (**Aim 5**) and correlates with radiologic evidence of tumor development.

**AIM 5. Detection of ctDNA in a murine model of LFS.** We have generated a colony of mice (in collaboration with Dr. Gigi Lozano) that harbour a heterozygous germline R270H mutation (= R273H in humans). Blood is drawn q2 weeks and plasma extracted and stored for ctDNA analysis (as per Aims1-3). In addition, sequencing WB MRI (q 6weeks) will be performed to correlate ctDNA 'spikes' with radiologic or clinical evidence of tumor formation – we anticipate that the ctDNA will be a more sensitive marker of early detection and, based on work from Aim 3, may also be able to define the tumor site. This work will thus inform the technique as well in the human.

**4d. INDIVIDUAL PROJECTS – PROJECT #4: (Novel Approaches to Molecular / Tissue Imaging and Clinical Surveillance in LFS: Multicentre Validation Study) (PI: Andrea DORIA; co-PI: Gang ZHENG; co-PI: Anita VILLANI)**

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**BACKGROUND:** We recently reported the long-term outcomes of a clinical surveillance protocol for early tumor detection in *TP53* mutation carriers and demonstrated it to be associated with decreased mortality and treatment-related morbidity (3). In our initial submission, we took two complementary approaches to enhance both the sensitivity and specificity of tumor detection. First, we hypothesized that <sup>18</sup>FDG-positron emission tomography (PET) MRI would be more sensitive than whole body (WB)-diffusion weighted (DW) MRI and WB-short tau inversion recovery (STIR) MRI for diagnosis of hypermetabolic tumors. However, if necrosis was present early in the tumor (highly aggressive tumors) DW-MRI would be more sensitive and the combination of WB-STIR and DW would be more diagnostic (higher sensitivity and specificity) than <sup>18</sup>FDG-PET MRI. Second, we hypothesized that detection of circulating DNA (cfDNA) would accurately reflect very early tumor detection that predates both clinical and imaging surveillance. This ctDNA work is now encompassed in **Project 3**, and results will be correlated and linked to new imaging approaches proposed here.

**PRELIMINARY DATA:** Extensive regulatory constraints delayed initiation of the novel imaging aspects of the study. Health Canada approval for use of FDG PET-MRI in this study was obtained in April 2017. Recruitment of patients for WB-STIR and DW MRI studies started in September 2016. To date, 14 patients consented to participate in the study, and 12 underwent STIR and DW MR imaging studies. No areas of abnormal signal intensity were noted in any of the WB-STIR or DW MRI examinations. No recruited patients have as yet fulfilled the criteria for having a PET-MRI. However, we were able to test the feasibility and value of comparing cfDNA levels and imaging phenotypes in a small cohort of patients. We concurrently evaluated a prospectively followed cohort of LFS patients (N=43) and identified cases in which peak levels of cfDNA corresponded to abnormal WB-STIR imaging features (phenotypic expression). WB MR imaging was crucial for diagnosis of tumors in two LFS patients since corresponding cfDNA levels did not show any peak at the time of diagnosis or only started to peak by the time the tumor was much larger in size. These constitute examples of the important role of imaging in the surveillance of LFS patients and support the need for further investigation on optimized imaging methods for diagnosis of early tumors in this population. A larger number of subjects should be followed over time in order to allow for detection of the relatively small number of new tumors expected during the time period. We will address

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our primary hypotheses that these enhanced imaging approaches will increase sensitivity and specificity of imaging surveillance through the following specific Aims:

**AIM 1: Expand the initial pilot study into a multicentre North American study** to determine the sensitivity (false-negative rate) and specificity (false-positive rate) of WB-STIR MRI, WB-DW, and <sup>18</sup>F-FDG PET-MRI for detection of early tumor as compared with corresponding histology (reference standard) in order to establish an optimal imaging surveillance program for LFS individuals. To date, we have confirmed participation of the imaging centres at Children's Hospital of Philadelphia, Packard Children's Hospital at Stanford University, St. Jude Children's Research Hospital (Memphis) and Texas Children's Hospital. Approximately 100 patients would be anticipated to be accrued with this multicenter cohort.

**AIM 2: Improve detection of incipient tumors by non-invasive diagnostic methods in LFS individuals.** The use of noninvasive imaging for early diagnosis of tumor and gene expression profiling is a fast and reliable technique which has the potential to replace high-risk invasive biopsy procedures. Because of the widespread occurrence of *TP53* mutations in sporadic cancers, there is also potentially a general benefit in ultimately being able to "marry" functional and molecular imaging of this project to genomic platforms ("radiogenomic paradigm") (**Project 1**) to refine the signature of molecular modifiers. This strategy could provide targets which could ultimately generate radiogenomic tags for even more precise and sensitive imaging surveillance. We will create a descriptive algorithm for cases where one or more tumors are detected as a result of the surveillance program associating six proposed imaging traits (STIR signal heterogeneity, mass effect, neurovascular bundle involvement, necrosis, signal:necrosis ratio, mean <sup>18</sup>F-FDG uptake) with corresponding gene expression patterns generated from **Project 1**.

**AIM 3: Introduce porphysome nanotechnology to improve the imaging surveillance for early tumor detection** in LFS patients and to develop novel therapeutic strategies (**Project 6**) to ultimately improve cure rates. Porphysomes are 1<sup>st</sup>-in-class organic nanoparticles with intrinsic multifunctional imaging and therapeutic properties stemming from a single, nontoxic, porphyrin-lipid building block. These diverse properties include the ability to bind metals to enable MRI and PET imaging, transform locally delivered light energy into heat, sound waves, reactive oxygen species to kill cancer cells or fluorescence to illuminate them, and efficiently ferry toxic drugs into cancer cells. We will build upon porphysomes' inherent multifunctionality to develop a novel image-guided drug delivery strategy that will allow us to take advantage of progress made to date in our initial program by integrating biomarkers (identifying cancer signatures (**Project 1**) to direct porphysome targeting), drug screen (identifying drug candidates as porphysome payload (**Project 6**)), and surveillance (imaging methods that can be augmented by porphysomes as PET and/or MRI contrast agents (**Project 4**)).

**4d. INDIVIDUAL PROJECTS – PROJECT #5: (Using the zebrafish as a model for chemoprevention for TP53 mutation carriers) (PI: Jason BERMAN)**

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**BACKGROUND:** The zebrafish is a powerful *in vivo* system for modeling genetic diseases and cancer due to conserved genetics and imaging facility in transparent embryos (12). The advent of clustered regularly interspaced short palindromic repeats (CRISPR)-based genome editing strategies now enables gene insertions of precise point mutations, providing a robust tool for the study of cancer predisposition syndromes, like LFS. Using an innovative approach employing anti-sense asymmetric single-stranded oligodeoxynucleotides (ssODNs), we introduced R143H and R217H mutations in the zebrafish *tp53* gene corresponding to R175H and R248H, respectively, the most frequent *TP53* mutations in human LFS patients. We also employed a highly sensitive novel allele specific PCR (AS-PCR) strategy to identify R143H and R217H founder fish and their mutation-carrying F1 progeny. We validated the presence of these mutations in adult F1 zebrafish at both genomic and mRNA levels. F1 generation “LFS fish” are now poised to be phenotyped and used to identify genetic and chemical modifiers. An apoptosis phenotype (acridine orange, activated caspase 3 staining) will be evaluated in embryos at 30 hours post-fertilization (hpf) 6 hours after they are subjected to DNA damage treatment by 30 Gray of  $\gamma$ -irradiation with available *tp53* null TALEN mutants and wild type embryos serving as controls.

**AIM 1: Genetic modifiers of LFS.** We have generated a knockout zebrafish of the *miR34a* gene found to be epigenetically silenced in a subset of *TP53* tumors (Samuel 2016a,b). Using qRT-PCR, we observed that p53 induction by the DNA-damaging agent, camptothecin, increased levels of mir34a but not mir34b or mir34c in wild type zebrafish embryos. Double *tp53* R143H or R217H and *mir34a* mutants are now being generated. While these fish may be informative in elucidating the relative role of mir34a in tumorigenesis, secondary mutations are usually somatically acquired in a particular tissue. More recent advances in CRISPR-based technology in the zebrafish, such as the ability to drive Cas9 enzyme expression exclusively in specific cell populations now permits spatial control where given mutations are expressed. We will take advantage of this technology to functionally interrogate the series of LFS-tumor specific mutations and signatures generated from **Project 1** and our **Core** LFS germline sequencing data.

**Aim 2a: Chemical modifiers of LFS.** The facility with which zebrafish embryos can be subjected to high-throughput chemical screens provides an unprecedented opportunity to evaluate compounds that restore apoptosis *in vivo*, thereby representing potential therapeutic compounds. There has been dramatic progress in the development of small-molecule compounds capable of re-activating several missense

mutant *TP53* variants. These compounds are capable of restoring normal TP53 function of loss-of-function *TP53* mutants leading to induction of apoptosis and cell-cycle arrest after DNA damage. In addition, it is conceivable that other rescue mechanisms of apoptosis after DNA damage exist in *tp53* mutant cells. Another advantage of screening in zebrafish is compounds can undergo *in vivo* modifications and can be simultaneously assessed for effectiveness and toxicity in the whole animal context of zebrafish larvae. We will use zebrafish to identify compounds, which can rescue apoptosis in the LFS *tp53* mutant fish and serve as lead compounds for treatment of LFS and other p53-related cancers.

**Experimental Plan:** Using a unique small particle biosorter ideally suited to zebrafish embryos, we will employ known bioactive compounds from Sigma Lopac 1280 and Biomol ICCB (Enzo) libraries, which comprise a total of 1760 chemical agents and are readily available in the Berman laboratory. Many of these compounds represent previously approved Federal Drug Agency (FDA)/Health Canada drugs, which will enable the rapid translation of promising “hits” to Phase I clinical trials as a re-purposed therapy. In addition, we can obtain and employ the National Cancer Institute (NCI) Diversity library consisting of almost 2000 compounds. This library was used in several successful drug screens aimed at identifying p53-reactivating compounds (13). Thus, in employing these particular libraries, we have the opportunity to discover truly new prospective agents, as well as repurpose known medications. LFS *tp53* mutants, *tp53*-null and wild type embryos will be arrayed at 24 hpf, 3 embryos to a well in 96-well plates. Compounds will be transferred from library to embryo plates and irradiated embryos will be analyzed to identify compounds that restore cellular apoptosis and other measures of p53 reactivation in a p53-mutant background. Similarly, candidate drugs, namely TP53 targeting compounds (statins, APR246, CAP250 peptides and mTOR inhibitors) (**Project 6**) will also be tested in this system.

**AIM 2b: Toxicity screening of promising compounds.** Since detailed toxicity screening is not feasible in the context of a high-throughput chemical screen, we will perform in parallel toxicity and efficacy screening of hit compounds found in **Aim 2a** and TP53 candidate compounds (**Project 6**). The zebrafish provides a unique whole organism context with conserved organ systems and metabolism in which to effectively and efficiently conduct these studies. Such additional screening is important for establishing the lowest effective concentrations of compounds that do not cause significant toxicities that may prohibit their translation to individuals with LFS. We can examine overall morphological abnormalities, cardiac phenotypes (structural abnormalities, alterations in heart rate), glomerular filtration rate and lateral line neuromast phenotypes, the latter serving as a proxy for ototoxicity in humans.

**4d. INDIVIDUAL PROJECTS – PROJECT #6: (Pharmacologic prevention of Malignancy in LFS) (PI: Ran Kafri; co-PI: David Malkin)**

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**BACKGROUND:** Treatment of malignancies in LFS are particularly challenging in light of the wide spectrum of histologic types, lifelong risk of multiple cancers in an individual, and inherent concerns of toxicity and second malignancy risk due to inefficient repair in *TP53* mutation carriers, with the use of conventional DNA damaging agents. An attractive alternative is the pharmacological prevention of tumour onset. In recent years, exciting cumulative evidence points to several rational opportunities to explore chemoprevention strategies in LFS using *in vitro* and *in vivo* systems to ultimately inform clinical trial development: 1) We have previously shown that cell size and lifespan may be regulated by mTOR signaling activity. Surprisingly, mTOR inhibition (with Rapamycin) also causes lifespan extension and delayed tumor onset in mice with oncogenic mutations in *TP53* (15). Whether this chemopreventive effect is evident in the presence of constitutional wild-type p53 is not known; 2) the mevalonate pathway can be activated by a direct interaction of mutant p53 with SREBP, the master regulator of cholesterol biosynthesis. Recent observations by our collaborators (Del Sal and Prives) suggest that inhibition of the mevalonate pathway in cancer/untransformed cells restores the inherent instability and/or prevents stabilization of mutant p53 by functionally disrupting the molecular mechanism protecting mutant p53 from inhibition by MDM2. Statins (Cerivastatin) reduce mutant p53 levels across a spectrum of cancer cell lines harboring different mutations while wild-type p53 levels are unaffected. These findings pave the way to explore statins as chemopreventive agents in the context of germline mutant p53; 3) the mutant p53-targeting compound APR-246 (PRIMA-1Met) has been shown to reactivate mutant p53 to induce apoptosis, growth arrest and other cellular functions (13). It is currently in phase I trials in lymphoma and prostate cancer patients and in phase II study in high-grade serious ovarian cancer; 4) Several p53 conformation activating peptides (CAP) have been developed in the Rotter lab (17) and these peptides appear to shift the mutant conformation to wild-type through a refolding mechanism.

Cell transformation events are highly infrequent and, therefore, hard to study. To overcome this challenge, we will establish the cancer cell observatory in the context of LFS in which the ‘single rare’ event is the *TP53* mutation – an experimental system to continuously observe millions of single live cells over extended periods of time, seeking and investigating the rare events that are the seeds of cancer.

**Aim 1: Establish and apply a cancer cell observatory to determine effects of p53 modifying agents on cellular transformation.** The Kafri lab has created a unique technology - cancer cell observatory - an

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experimental system for high throughput monitoring of single cell dynamics over time using incubated-chamber time lapse microscopy. Software that is continuously being developed in the Kafri lab is used to track thousands of single live cells and quantify morphological properties and protein expression over real time (16). This ability to computationally monitor millions of patient derived fibroblasts over long periods of time will allow detection and characterization of the very rare events of malignant transformation, which are the seeds of tumor formation. Our software will automatically classify fibroblasts into distinct, computationally characterized morphologies. Morphological distinctions are known to represent distinctions in cell function. Our preliminary experiments demonstrated that transformation in LFS derived fibroblasts correlates with identifiable morphological changes that can be detected with our software. Using this technology, we will be able to molecularly and functionally characterize the effect of exposure to mTOR inhibition, statins, refolding peptides and APR246 in our bank of skin-derived fibroblasts exhibiting a wide spectrum (missense, frameshift, splice-site) *TP53* mutations. The cancer cell observatory will provide a first of a kind dataset – mapping morphological changes of single cells with molecular characterization, biochemical/biological readouts specific to the molecular pathway being targeted, and clinical phenotypes. Each specific cell line has been or is currently characterized for genome-wide methylation patterns, RNAseq and whole genome sequencing (**Project 1**).

**Aim 2: Determine the effects of p53 pathway reactivation in the context of heterozygous *TP53* mutations associated with LFS *in vivo*.** The data generated from Aims 1 and 2 will inform selection of agents to examine *in vivo* in the R270H mouse and the mutant *tp53* zebrafish. Rather than the biological endpoint that can be examined in the Cancer Observatory, the endpoints from Aim 3 will be: 1) measure of toxicity – which we anticipate to be different from early data in the *Trp53* mutant mouse models (our model retains the wild-type *TP53* allele); and 2) latency of tumor formation. This data will be of great value in determining how to utilize these agents in early clinical trial development as chemopreventive strategies and will complement the early tumor detection *in vivo* work outlined in **Project 3** in the murine LFS model.

#### 5a. INDIVIDUAL CORE TECHNOLOGY PLATFORM – CORE #1: (*max 2 pages*) (*optional*)

**Li-Fraumeni Syndrome Sequencing and Data Repository Core (PIs: Anna GOLDENBERG and David MALKIN)**

The goal of establishing a data core for our project is to provide a unified easily and efficiently accessible repository containing comprehensive phenotypic and omic characterization of LFS patients. The core will serve as the end point for the data collection projects, where all of the data will be quality controlled and stored and as the starting point for all the analyses and inference projects, where any subset of the data can be efficiently retrieved and analyzed. The core is thus characterized by the data that will be stored and the services that it will provide as described below.

**Data elements include:****CLINICAL DATA (PROJECT 1)**

*Demographic* (includes age, sex, ethnicity (where available))

*Germline TP53 Mutation Status* (as well as data extracted from the Clinical Cancer Genetics Program (CGP) Database which includes currently over 5000 samples (from ~3000 patients) including >350 with Li-Fraumeni syndrome

*Family history* (derived from Clinical CGP Database)

*Pathology of tumor* (Data Warehouse (Clinical Pathology database at SickKids and pathology reports of all samples received from other centres)

*Clinical status of patient* (Alive with Disease, Alive without disease, Dead of Disease)

**IMAGING DATA (PROJECT 2)**

MRI (STIR, DW), PET-MRI, Porphysome

**OMIC DATA (PROJECTS 1, 2, 3 and CORE Sequencing)**

## DNA sequencing

- Tumor
- Germline (blood)

## Methylation (850K Epic array)

- ctDNA
- Germline (blood)
- Tumor (?)

## mRNA-sequencing

- Germline (blood)
- ctDNA
- Tumor

## miRNA-sequencing

- Germline
- Tumor

**FUNCTIONAL DATA (PROJECTS 5, 6)**

Functional readouts of mutant *tp53* zebrafish model chemical screen, toxicity assays and response to mutant p53 targeted agents (Project 5)

Functional readouts and live cell imaging (Project 6) of LFS fibroblasts, and in *Trp53* mutant mouse of latent tumor formation and functional responses *in vitro*

The data will provide a resource project wide and potentially, upon completion, to the whole LFS community. To process and curate the data we will need the expertise of a

- Technician that can extract samples from patients
- Clinical data manager/coordinator - to ensure the completeness and provenance of all the clinical and sample data
- Bioinformatician to establish and perform QC on the sequencing and other types of omic datasets as they come off the biotechnological machines
- Database analyst to develop a specialized database that can store all of the diverse types of data that need to be collected and ensure efficient retrieval of the subsets necessary for various projects
- Biostatistician/data scientist to appropriately curate and QC data for the great variety of queries that will be asked of this data

This team will establish a resource unprecedented in the heterogeneity of the types of data that it stores, paving the way for many projects that aim to fully characterize patients and streamline storage and data retrieval for the integrative analyses.

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8. Samuel N, Wilson G, Lemire M, et al. Genome-wide DNA methylation analysis reveals epigenetic dysregulation of *microRNA-34A* in *TP53*-associated cancer susceptibility. *J Clinical Oncol* 34: 3697. 2016.
9. Samuel N, Wilson G, Id Said B, et al. Transcriptome-wide characterization of the endogenous miR-34A-p53 tumor suppressor network. *Oncotarget* 7(31): 49611, 2016.
10. Kis O, Kaedbey R, Chow S, et al. Circulating tumour DNA sequence analysis as an alternative to multiple myeloma bone marrow aspirates. *Nat Commun.* 8:15086, 2017.
11. Lovell JF, Jin C, Huynh E, et al. Porphysome nanovesicles generated by porphyrin bilayers for use as multimodal biophotonic contrast agents. *Nature Materials* 10:324, 2011.
12. Chakroaborty C, Hsu CH, Wen ZH, Lin CS, Agoramoothy G. Zebrafish: a complete animal model for in vivo drug discovery and development. *Curr Drug Metab* 10: 116, 2009.
13. Bykov VJ, Wiman KG. Mutant p53 reactivation by small molecules makes its way to the clinic. *FEBS Lett* 588 (16): 2622, 2014.
14. Prykhozhij SV, Steele SL, Razaghi B, Berman JN. A rapid, effective method for screening, sequencing and reporter verification of engineered frameshift mutations in zebrafish. *Dis Model Mechan* 10 (6): 811, 2017.
15. Komarova EA, et al. Rapamycin extends lifespan and delays tumorigenesis in heterozygous p53+/- mice. *Aging* 4: 709, 2012.
16. Kafri R, et al. Dynamics extracted from fixed cells reveal feedback linking cell growth to cell cycle. *Nature* 494: 480, 2013.
17. Tal P, Eisenberger S, Cohen E, et al Cancer therapeutic approach based on conformational stabilization of mutant p53 protein by small peptides. *Oncotarget* 7(11): 11817, 2016.

## 7. HIGH-LEVEL BUDGET REQUEST

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[Refer to 2018 PPG LOI Guide before completing this section.]

**(i) Request to Terry Fox Research Institute**

<i>PPG Component</i>	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
Program Overview (Program Coordinator, Travel)	\$110000	\$110000	\$110000	\$110000	\$110000	\$550000
Project 1: [Intra-tumoral heterogeneity in LFS] Operating	\$305000	\$305000	\$305000	\$305000	\$305000	\$1525000
Project 1: Equipment	\$100000					\$100000
Project 2: [Predictive Modeling in LFS] Operating	\$90000	\$90000	\$90000	\$90000	\$90000	\$450000
Project 2: Equipment	\$0					\$0
Project 3: [Early Tumor Detection in LFS] Operating	\$165000	\$165000	\$165000	\$165000	\$165000	\$825000
Project 3: Equipment	\$0					\$0
Project 4: [Imaging Surveillance in LFS] Operating	\$205000	\$205000	\$205000	\$205000	\$205000	\$1025000
Project 4: Equipment	\$0					\$0
Project 5: [Zebrafish Chemoprevention Model of LFS] Operating	\$190000	\$190000	\$190000	\$190000	\$190000	\$950000
Project 5: Equipment	\$0					\$0

Equipment						
Project 6: [Pharmacologic prevention of Cancer in LFS]	\$190000	\$190000	\$190000	\$190000	\$190000	\$950000
Operating						
Project 6: Equipment	\$0					\$0
Core 1: [LFS Sequencing/Data Bank]	\$180000	\$180000	\$180000	\$180000	\$180000	\$900000
Operating						
Core 1: Equipment	\$100000					\$100000
<i>Operating Total</i>	\$1435000	\$1435000	\$1435000	\$1435000	\$1435000	\$7175000
<i>Equipment Total</i>	\$200000					\$200000
<b>ANNUAL TOTAL</b>	<b>\$1635000</b>	<b>\$1435000</b>	<b>\$1435000</b>	<b>\$1435000</b>	<b>\$1435000</b>	<b>7375000</b>

[Expand table as required]

## (ii) Short Budget Justification

**Program Overview/Coordinator:** This is a critical element to our now significantly expanded program.

The Coordinator will manage the project from a budgetary, reporting, team meeting coordination perspective. Travel for the entire project team is included in this budget item.

**Project 1:** Funding will cover costs for bioinformatician, PDF, graduate student, and multi-region sequencing throughout the project duration. Omic data storage for the project (which will be directly linked to the Core data repository) is requested in Year 1 – to cover data for Project 1 throughout. Funds for Aim 2 sequencing (Panel, RNAseq of the international LFS tumor cohort) are not budgeted for in this application as they will be covered by budget in the Malkin Cancer Genetics Program budget at SickKids (~\$600K over 5 years (100 samples/year)).

**Project 2:** Funding will cover costs for 0.7 Bioinfomatician (who is currently working on this project from the initial application) and grad student/PDF (also working on the project). No storage costs requested as all data will be stored and accessed through the Core Facility. The remainder of the 0.3 Bioinformatician costs will be within the Core budget.

**Project 3:** Funding will cover ctDNA mutational profiling costs (\$1000/sample) in both the humans and the mouse model. Further costs attributed to mouse housing and veterinary care and two PhD students (both currently working on this project).

**Project 4:** Funding will primarily cover STIR and DW-MRI imaging costs as well as PET-MRI. A 0.3FTE Information coordinator will continue her role as currently defined in our project. Some funds are also set aside to reimburse patients for out-of-pocket expenses for their visits, and for the reagents related to the Protoporphyrin work in Aim 3.

**Project 5:** Funding will cover costs of maintaining zebrafish, reagents and supplies to generate mutants, as well as for the chemical screens. As well, salary for the Research Associate who has been leading this project will continue.

**Project 6:** Funds are requested to cover salaries for PDF and research technologist. In addition, reagent costs are required. The drugs/peptide/agents are being generously supplied by our collaborator. Some animal services costs will be covered in this project (shared with Project 3).

**Core:** Funding is requested to purchase data storage (which will be used for the duration of the grant). A Biostatistician, Technician, Data Base Manager and 0.3 Bioinformatician (shared with Project 1) will also be supported in the Core.

## 8. LIST OF SUGGESTED REVIEWERS

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Please suggest a minimum of three scientific peers who would be able to evaluate your whole program.  
 Please also suggest a minimum of two scientific peers per component (project/core) in the table below  
 to review your application.

Full Name	Email Address	Expertise Keywords
Affiliation	Telephone Number	Component of PPG to review
Sir David Lane	<a href="mailto:dplane@p53lab.a-star.edu.sg">dplane@p53lab.a-star.edu.sg</a>	P53, genome stability, functional biology, in vivo modeling
A*Star 8A Biomedical, Singapore		Projects 1,2,3,5,6
Arnold Levine	<a href="mailto:alevine@ias.edu">alevine@ias.edu</a>	P53, genome instability, DNA repair, functional biology, in vivo modeling
Institute of Advanced Studies, Princeton University		Projects 1,2,3,5,6
Gareth Bond	<a href="mailto:Gareth.bond@ndm.ox.ac.uk">Gareth.bond@ndm.ox.ac.uk</a>	P53, p53 modulators, SNPs, p53 sequencing, GWAS
Oxford University – Ludwig Institute		Projects 1,2
Heike Daldrup-Link	<a href="mailto:heiked@stanford.edu">heiked@stanford.edu</a>	MRI/PET imaging
Stanford University		Project 4
Paul Babyn	<a href="mailto:Paul.babyn@saskatoonhealthregion.ca">Paul.babyn@saskatoonhealthregion.ca</a>	MRI/PET imaging
University of Saskatchewan		Project 4
James Amatruda	<a href="mailto:James.amatruda@utsouthwestern.edu">James.amatruda@utsouthwestern.edu</a>	Zebrafish modeling; sarcomas

UT Southwestern		Project 5
Elizabeth Patton	<a href="mailto:e.patton@igmm.ed.ac.uk">e.patton@igmm.ed.ac.uk</a>	Zebrafish modeling;
University of Edinburgh		Project 5
Judy Garber	<a href="mailto:Judy_garber@dfci.harvard.edu">Judy_garber@dfci.harvard.edu</a>	P53, LFS
Dana-Farber Cancer Institute		Projects 1,3,4,6
Michael Resnick	<a href="mailto:resnick@niehs.nih.gov">resnick@niehs.nih.gov</a>	P53, therapeutic models
NIEHS, Bethesda		Projects 1,2,3,5,6
Joaquin Espinosa	<a href="mailto:joaquin.espinosa@UCDenver.edu">joaquin.espinosa@UCDenver.edu</a>	P53, functional genomics, p53 pharmacology
University of Colorado, Denver		Projects 1,2, 6

#### 9. LIST OF REVIEWERS TO EXCLUDE

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Please provide a list of reviewers who you feel would not provide an objective review of your application and a brief rationale for exclusion for each.

<i>Full Name</i>	<i>Affiliation</i>	<i>Rationale for Exclusion</i>

[Expand table as required]

**APPENDICES – CVs**

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[In the table below provide a list of all the brief CVs supplied with this Letter of Intent]

	<i>Curricula Vitae Provided</i>	<i>Role</i>
1	David Malkin	Project Leader
2	Adam Shlien	Principal Investigator
3	Anna Goldenberg	Principal Investigator
4	Andrea Doria	Principal Investigator
5	Jason Berman	Principal Investigator
6	Ran Kafri	Principal Investigator
7	Trevor Pugh	Principal Investigator
8	Gang Zheng	Principal Investigator
9	Anita Villani	Principal Investigator

[Expand table as required]

**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

<b>FULL NAME:</b> David Malkin	
<b>POSITION TITLE:</b> Professor of Pediatrics, University of Toronto / Staff Physician/Senior Scientist	
<b>INSTITUTION:</b> The Hospital for Sick Children	
<b>FULL ADDRESS:</b> 555 University Avenue, Toronto, Ontario M5G 1X8	
TELEPHONE: 416 813 5348 / 416 813 7753	EMAIL: david.malkin@sickkids.ca
WEB-ADDRESS:	

<b>ACADEMIC BACKGROUND</b>			
<i>Degree Type</i>	<i>MM/YY</i>	<i>Discipline/Field/Specialty</i>	<i>Institution &amp; Country</i>
Post-Doc	1989-1992	Molecular Genetics	Massachusetts General Hospital, Harvard University, Boston, USA
Fellowship	1987-1989	Ped Hematology/Oncology	The Hospital for Sick Children, University of Toronto, Toronto, Canada
FCRPC/FAAP	1984-1988	Pediatrics	The Hospital for Sick Children, Toronto, Canada
M.D.	1980-1984	Medicine	Faculty of Medicine, University of Toronto, The Hospital for Sick Children, Toronto, Canada
	1978-1980	Arts & Sciences	University of Toronto, Toronto, Canada

<b>WORK EXPERIENCE</b>				
<i>Position, Organization</i>	<i>Department/Division</i>	<i>Start Date</i>	<i>End Date</i>	
Active Staff	Division of Oncology, Department of Paediatrics The Hospital for Sick Children	1995	Present	
Senior Scientist	Genetics and Genome Biology Program, Research Institute The Hospital for Sick Children	2005	Present	
Co-Director	Cancer Genetics Program The Hospital for Sick Children	2000	Present	
Full Professor	Departments of Pediatrics and Medical Biophysics, University of Toronto	2003	Present	
Medical Director	Pediatric Oncology Group of Ontario (POGO)	2011	2016	
POGO Chair	Childhood Cancer Control, University of Toronto	2011	2016	
Associate Chief of Research (Clinical)	Research Institute The Hospital for Sick Children	2005	2011	
Chair	Scientific Review Board, Division of Haematology/Oncology The Hospital for Sick Children	2003	2006	
Senior Scientist	Cancer Research Program, Research Institute The Hospital for Sick Children	2003	2005	
Associate Professor	Department of Pediatrics and Medical Biophysics University of Toronto	1997	2003	
Scientist	Programs in Cancer & Blood Research and Genetics & Genome Biology Program, Research Institute The Hospital for Sick Children	1997	2003	
Member	Department of Medical Biophysics, School of Graduate Studies, University of Toronto	1996	1997	

Member	Institute of Medical Sciences, School of Graduate Studies University of Toronto	1994	Present
Associate Member	Institute of Medical Sciences, School of Graduate Studies University of Toronto	1993	1994
Project Director	Division of Immunology and Cancer Research, Research Institute, The Hospital for Sick Children	1992	1997
Associate Staff	Division of Haematology/Oncology, Department of Paediatrics, The Hospital for Sick Children	1992	1995

**A. Personal Statement (*max one page*)**

*Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.*

I have dedicated my research and clinical oncology career to the study of and care for children with cancer in the context of familial cancer syndromes. As a post-doc, I discovered that germline mutations of the *TP53* tumor suppressor gene cause >80% of LFS, and are linked to an increased risk of second tumors and early onset osteosarcoma, even in the absence of a family history of cancer. Since 1992, my research group has refined the molecular definitions of LFS, characterized genetic events that modify the phenotypic effects of an underlying germline *TP53* mutation, and elucidated a model of tumor initiation/progression in LFS (Shlien PNAS 2008) in which a constitutional (or possibly early somatic) *TP53* mutation favours the accumulation of epigenetic/genetic events (Samuel, JCO 2016; Samuel Oncotarget 2016), that facilitate accelerated telomere attrition, catastrophic/punctuated genomic events (eg. chromothripsis) (Rausch Cancer Cell 2012), and subsequent somatic cell transformation. Translating our work into direct clinical relevance, we developed a surveillance protocol, the so-called “Toronto Protocol” that takes advantage of innovative imaging techniques such as rapid whole-body MRI (Villani Lancet Oncology 2016). This protocol has been adopted worldwide, has been validated in several recent publications from other centres, has changed health policy particularly in the US where WBMRI is now generally covered by insurers, and demonstrates feasibility of early tumor detection with substantial survival benefit. As Director of the Cancer Genetics Program at SickKids, we have amassed over 5000 samples from children with a wide variety of cancer susceptibility disorders, sarcomas and other cancers. To complement the molecular work, I have established and published from rich collaborations exploring the ethical and psychosocial impact of cancer predisposition and genetic/genome research in pediatrics. I am Director of the SickKids Cancer Sequencing (KiCS) Program at SickKids – whose primary objective is to use NGS (whole genome and whole exome sequencing, RNAseq and a unique 800+ cancer gene panel) to identify potential actionable targets in children with metastatic, relapsed, refractory or otherwise difficult to treat cancers (total budget \$1.7M/3 years). Since the official launch of KiCS, we have sequenced 100 patient tumors completely and are partially though sequencing another 32 enrolled; of which almost 40% have been identified to have actionable targets. A smaller number (42) of patients have also been enrolled on a second arm to identify germline variants (using exome and panel followed by WGS if the other two platforms are non-informative). To date, ~10 informative variants have been identified and genetic counseling / surveillance has been instituted. In addition, I am Director of the national TFRI-catalysed PRrecision Oncology For Young PeopLE (PROFYLE) project (total budget \$25M/5 years). The overarching objective of PROFYLE is to perform NGS (WGS, RNAseq, WES, panel) on all patients (<29 years of age) in Canada. All 16 pediatric and 3 of the largest adult cancer centres are represented. In addition, several other nodes are included in this study, including proteomics, a centralized data and biorepository, biomarker node, modeling node for novel variants, a clinical trials node – that has developed mechanisms for basket and umbrella trials (with partnerships with industry, NCIC CTG and others, and an ethics node that has developed SOPs and standardized consents and return of results process for the entire country. All these efforts reflect my ability to lead major, multidisciplinary programs cutting across basic, clinical and translational sciences, and multiple national institutions with key international partnerships. Over the last 20 years, I have been active in the international p53 world, being on the scientific organizing committees for several of the international p53 workshops and mutant p53 workshops. I am Chair of the Li-Fraumeni Syndrome Exploration (LiFE) consortium and chaired two of the three LFS biennial meetings (hosting the next one in April 2018). During the last 5 years, I have published 84 peer-reviewed papers, given 109 invited lectures and 2 patent applications. During the same period, I have also supervised 4 research staff, 3 postdocs, 13 graduate students (8 PhD/5 MSc), thesis committee member for 13, and more than 30 summer students and clinical fellows. My extensive collaboration networks

and internationally recognized leadership in the fields of pediatric cancer genetics and clinical pediatric oncology have facilitated and enhanced the focus of my academic program: to develop a fundamental understanding of the molecular basis of Li-Fraumeni syndrome specifically and cancer predisposition in general, and apply this knowledge to transform the clinical management of children and families at genetic risk of cancer.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (*max four pages*)**

*In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).*

My most significant research during the last 5 years has been the development, implementation and reporting of our multi-modality surveillance protocol (Toronto protocol) for *TP53* mutation carriers (*Lancet Oncology* 2011, 2016). Patients who underwent surveillance have improved long-term outcomes compared to those who did not undergo surveillance. These observations demonstrate the feasibility of pre-symptomatic germline *TP53* mutation testing in children and suggest a beneficial impact of early tumor detection strategies on survival. This protocol is now used worldwide, is now recommended by the NCCN, and has been instrumental in advancing health policy in terms of funding by third-party payers. This was identified as one of the Top 10 Cancer Breakthroughs of 2011 and 2016 by the Canadian Cancer Society.

Beyond the surveillance and early detection work, our recent studies of genome-wide methylation in the germline of LFS patients has led to the first observation of differential methylation in the context of cancer susceptibility (*Samuel JCO* and *Oncotarget* 2016). This observations opens the door for the application of methylation marks as biomarkers of tumor formation in LFS, as well as of a molecular signature unique to LFS tumors. This study was the basis for the prestigious NextGen Star Award to the PhD student (Nardin Samuel) from the AACR – one of only 6 awards in 2017.

Expanding beyond the LFS studies, development and leadership of both the KiCS and PROFILE programs has led to the first national precision oncology program in Canada, as well as one of only two in the world in the context of pediatrics. The mechanisms of adapting unique clinical trial design to a small patient cohort, that are being developed for these two initiatives are directly adaptable to the development of rational clinical trial design for a chemoprevention or therapeutic study for LFS.

The work we have accomplished over the last 5 years in particular have been instrumental in international recognition of genetic susceptibility as a key element in the etiology of childhood cancer, development of recommendations for surveillance for over 50 childhood cancer tumors (published in a series in *Clinical Cancer Research*, 2017), and inclusion of this area of research in virtually all major scientific meetings in cancer research.

***Selected Service (Last 5 Year):***

co-Chair, Organizing Committee. 6<sup>th</sup> International Mutant p53 Workshop. June 15-18, 2013. Toronto, ON

Member, Scientific Organizing Committee; Canadian Cancer Research Alliance National Symposium. November 7-10, 2015. Montreal, PQ.

Chair, Organizing Committee. 4<sup>th</sup> International Li-Fraumeni Syndrome Conference. June 1-3, 2016, Columbus, OH.

Co-Chair, Organizing Committee. American Association for Cancer Research Childhood Cancer Predisposition Workshop. October 6-8, 2016. Boston, MA.

Member, Program Committee. 7<sup>th</sup> International Mutant p53 Workshop. October 26-28. Melbourne, Australia.

Member, International Organizing Committee. 17<sup>th</sup> International p53 Symposium. July 8-12, 2017. Singapore.

NIH Review: CEER (Centers in Excellence in Ethics Research], Member, 2012, 2015

NIH Review: Site Visit, Genetics Branch, Member, 2015

CIHR Review: Cancer Therapeutics and Progression (CT2) Panel, Chair, 2010-2015

AACR Annual Meeting Program Committee (2018), Member

**Notable trainee awards received during the last 5 years:**

Holmes PDF Award, National Science and Engineering Research Council (NSERC), 2011-2013 (Adam Shlien)  
Minority Scholar Award, American Association for Cancer Research, 2012 (Diana Merino)  
Vanier Graduate Scholarship, Canadian Institutes of Health Research (2012-2015) (Diana Merino)  
Scholar-in-Training Award, American Association for Cancer Research, 2013 (Nardin Samuel)  
Associate Member Council, American Association for Cancer Research (2013-2015)[elected] (elected Chair – 2015-2017) (Diana Merino)  
Vanier Graduate Scholarship, Canadian Institutes of Health Research (2014-2017) (Nardin Samuel)  
Associate Member Council, American Association for Cancer Research (2015-2018) [elected] (Nardin Samuel)  
James Lepock Memorial Award, Department of Medical Biophysics, University of Toronto, 2015 (Diana Merino)  
James Lepock Memorial Award, Department of Medical Biophysics, University of Toronto, 2015-2016 (James Tran)  
Marshall-Walker Award, Department of Medical Biophysics, University of Toronto, 2015 (Diana Merino)  
Dalton Whitebread Scholarship Fund, School of Graduate Studies, University of Toronto, 2016 (Anna Pan)  
AACR NextGen Star Award, Amerian Association for Cancer Research, to be presented at Annual Meeting, April 2017 (Nardin Samuel) [1 of only 6 awarded among > 10000 trainees registrants)

**C. Honours & Awards (selected)**

*List any honours and personal awards in chronological order.*

- 1992 Abbott Pharmaceuticals Young Investigator Award (1992-1994)
- 1992 Queen Elizabeth II Scientist Award, Medical Research Council of Canada (1992-1997) (declined)
- 1992 Scholarship, Medical Research Council of Canada, (1992-1997)
- 1997 Dr. Harold E. Johns Award, Outstanding Research Scientist. Canadian Cancer Society [salary award 1997-2003]
- 2006 Physician Researcher Award for Scientific Accomplishment, Department of Pediatrics, The Hospital for Sick Children, University of Toronto
- 2007 13<sup>th</sup> Annual Gold Lecturer, Academy of Medicine, Toronto
- 2008 Man of Distinction Award, Israel Cancer Research Fund
- 2011 Senior Fellow (Elected), Massey College, University of Toronto
- 2011 POGO Chair in Childhood Cancer Control, University of Toronto
- 2013 Transformational Leadership Award, Canadian Cancer Society
- 2015 Henry Friesen Award, Canadian Society for Clinical Research/Royal College of Physicians and Surgeons of Canada
- 2017 Denis Daneman Faculty Development Award, Department of Pediatrics, University of Toronto

**Overview & Details of Research Support (Past 5 Years)**

*Provide an overview of your current areas of research focus including supports of your research / laboratory (max one page). Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.*

**Funding Source & Program Name:** Canadian Institutes of Health Research (CIHR); Foundation Scheme

**Project Title:** Molecular Determinants of the Li-Fraumeni Syndrome

**Total Award:** \$3,444,000 Canadian

**Total Award to You:** \$3,444,000 (Canadian)

**Start Date:** September, 2015

**End Date:** September, 2022

**Main Objective:** The objective is to characterize the molecular basis of germline variants in LFS and to determine how these variants modify the phenotype in LFS families

**Outline of Methodology:** WGS is used to sequence trios of LFS families, as well as patients with LFS phenotype who do not harbor a TP53 mutation

**Budget Details:** Salaries: 1,500,000; Supplies and expenses: \$1,940,000

**Personnel Details:** Research Fellow, two Post-docs (clinical), research coordinator and Technician

**Relationship to 2017 PPG application:** Overlap with Project 1 sequencing (aim 2). No budget requested for Aim 2 as this will be funded through this CIHR grant – analysis will be done through TFRI New Frontiers grant

**Funding Source & Program Name:** Terry Fox Research Institute (TFRI)

**Project Title:** Precision Oncology for Young People (PROFYLE)

**Total Award:** \$25,000,000 (Canadian)

**Total Award to You:** \$25,000,000

**Start Date:** July, 2016

**End Date:** June, 2021

**Main Objective:** To develop and implement a precision medicine program for molecular target identification and enrollment on basket, umbrella, n-of-1 or other clinical trial for all young people with refractory, relapsed or metastatic cancer in Canada.

**Outline of Methodology:**

**Budget Details:** complex budget with distribution across 6 nodes, 16 centres for sequencing, bioinformatics, biorepository, regulatory/ethics SOP development, modeling, proteomics, clinical trials support. \$5,000,000 from TFRI and remainder from multiple partners

**Personnel Details:** multiple personnel (PDF, grad students, tech, support staff, admin support).

**Relationship to 2017 PPG application:** No overlap

**Funding Source & Program Name:** Garron Family Cancer Centre, KiCS Program

**Project Title:** SickKids Cancer Sequencing (KiCS) Program

**Total Award:** \$1,750,000 (Canadian)

**Total Award to You:** \$1,750,000

**Start Date:** September, 2015

**End Date:** September, 2018

**Main Objective:** To develop and implement a precision medicine program for molecular target identification and enrollment on basket, umbrella, n-of-1 or other clinical trial for all young people with refractory, relapsed or metastatic cancer at SickKids Hospital.

**Outline of Methodology:**

*Budget Details: ~\$1 milion for personnel, and \$750K for sequencing and informatics*

*Personnel Details: supports 1 bioinformatician, 0.5 genetic counselor, 1.0 information coordinator*

*Relationship to 2017 PPG application: No overlap*

**Funding Source & Program Name:** Canadian Institutes of Health Research (CIHR)

**Project Title:** DNA Copy Number Variation in Li-Fraumeni Syndrome

**Total Award:** \$1,084,000 (Canadian)

**Total Award to You:** \$1,084,000

**Start Date:** January, 2013

**End Date:** February, 2018

**Main Objective:** To characterize the role of DNA copy number variation in cancer susceptibility in LFS

**Outline of Methodology:** Microarray (and more recently WGS of LFS patients to identify extent of germline CNVs across generations in LFS families.

*Budget Details: 50% personnel; 50% reagents and supplies*

*Personnel Details: Technician (x 2), PDF and 2 graduate students*

*Relationship to 2017 PPG application: No overlap (this grant is complete and was rolled into the CIHR Foundation Grant)*

**Funding Source & Program Name:** Terry Fox Research Institute (TFRI)

**Project Title:** Application of Genetic Determinants of Li-Fraumeni Syndrome

**Total Award:** \$2,449,993 (US)

**Total Award to You:** \$2,449,993

**Start Date:** July, 2014

**End Date:** July, 2017

**Main Objective:** To apply molecular basis of LFS to enhance early detection of tumors in TP53 mutation carriers and explore chemoprevention models and application.

**Outline of Methodology:** Large scale sequencing of LFS tumors to identify molecular signatures for use as ctDNA marks, predictors of age of onset and tumor type, and modeling in zebrafish

*Budget Details: ~ 50% budget to supplies and reagents and 50% to personnel (students, techs, RAs)*

*Personnel Details:*

*Relationship to 2017 PPG application: No overlap (this is the application for which the current renewal is based)*

**Funding Source & Program Name:** Ewing Sarcoma Foundation Canada

**Project Title:** The transcriptional consequences of somatic mutations in Ewing sarcoma

**Total Award:** \$100,000 (Canadian)

**Total Award to You:** \$100,000

**Start Date:** September, 2014

**End Date:** September, 2016

**Main Objective:** To characterize the molecular signatures of Ewing sarcoma beyond the classical EWS-FLI fusion

**Outline of Methodology:** Deep sequencing of Ewing sarcomas and bioinformatic imputation to identify molecular signatures unique to this tumor type

*Budget Details: \$25K to student salary; \$75K to sequencing*

*Personnel Details:*

*Relationship to 2017 PPG application: No overlap*

*Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)*

*Project Title: Targeting the Integrin-Linked Kinase (ILK) Pathway in Rhabdomyosarcoma*

*Total Award: \$381,270 (Canadian)*

*Total Award to You: \$381,270 (Canadian)*

*Start Date: January, 2012*

*End Date: November, 2015*

*Main Objective: To decipher the role of ILK inhibition in impeding growth and tumorigenicity of RMS*

*Outline of Methodology: RMS xenografts used to study effect of QLT agents (ILK inhibition) in RMS*

*Budget Details: salary for 1 graduate student; mouse and other supplies and reagents*

*Personnel Details: 1 graduate (PhD) student*

*Relationship to 2017 PPG application: No overlap*

*Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)*

*Project Title: Molecular Determinants of Li-Fraumeni Syndrome Tumors*

*Total Award: \$750,150 (Canadian)*

*Total Award to You: \$750,150 (Canadian)*

*Start Date: July, 2010*

*End Date: July, 2015*

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to 2017 PPG application:*

*Funding Source & Program Name: Genome Canada*

*Project Title: Stratifying and Targeting Pediatric Medulloblastoma Through Genomics*

*Total Award: \$9,724,200 (Canadian)*

*Total Award to You: \$400,000 (Canadian)*

*Start Date: July, 2011*

*End Date: July, 2014*

*Main Objective: Molecular characterization of MBL subgroups. Our project was to explore molecular signatures of MBL risk (incorporated into collaboration with Dr. Stefan Pfister, Heidelberg)*

*Outline of Methodology: WGS of 120 MBL patient germlines*

*Budget Details: one PDF and remaining funds to sequencing/bioinformatics*

*Personnel Details:*

*Relationship to 2017 PPG application: No overlap*

**D. LIST OF PUBLICATIONS**

Provide a full list of all your scientific publications.

1. **Malkin D**, Balfour R, Bayliss CE: Validation studies of a new model of myocardial perfusability. *University of Toronto Journal* 1982; 14: pp 121-123. [R] PA
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**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

<b>FULL NAME:</b> Adam Shlien	
<b>POSITION TITLE:</b> Associate Director, Scientist	
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<b>ACADEMIC BACKGROUND</b>			
<i>Degree Type</i>	<i>MM/YY</i>	<i>Discipline/Field/Specialty</i>	<i>Institution &amp; Country</i>
postdoc	05/13	Cancer Genomics	Wellcome Trust Sanger Institute, UK
PhD	09/10	Medical Biophysics/Cellular and Molecular Biology	University of Toronto, Canada
BSc	05/01	Science/Biology and Computer Science	Concordia University, Montreal QC, Canada

<b>WORK EXPERIENCE</b>			
<i>Position, Organization</i>	<i>Department/Division</i>	<i>Start Date</i>	<i>End Date</i>
Scientist, The Hospital for Sick Children	Research Institute – Genetics and Genome Biology	06/13	Present
Associate Director, The Hospital for Sick Children	Dept. Pediatric Laboratory Medicine – Genome Diagnostics	06/13	present

[expand tables as required]

**A. Personal Statement (max one page)**

Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.

My lab works on translational childhood cancer genomics. We recently described a remarkable new mechanism of cancer initiation where massive numbers of point mutations are simultaneously acquired over a short time (Shlien A. *Nature Genetics*). This phenomenon leads to early onset tumors that are marked by distinctive genomes. These tumors are sparked by a single variant that results in the complete ablation of DNA replication repair, and a flood of subsequent mutations. Our findings highlight a unique and novel mechanism for cancer initiation that differs considerably from the existing paradigm. This was the first report of a somatic mutation required for cancer development in a homozygous cancer syndrome, and therefore offers hope for specific targeted therapies for individuals with this devastating syndrome. This work was accompanied by commentaries in *Nature Genetics*<sup>1</sup>, *Lancet Oncology*<sup>2</sup>, *Genome Medicine*<sup>3</sup>, *Cancer Discovery*<sup>4</sup>, *Nature Middle East* ([link](#)), and *Nature Asia* ([link](#)) and has been discussed in a number of review articles<sup>5-9</sup>. As a direct result of this discovery, we predicted that these cancers would express a great number of neoepitopes and that this could be exploited using immunotherapy. Two patients were enrolled on a clinical trial and both have sustained clinical response to otherwise fatal diseases (Bouffet E ... Shlien A and Tabori U, *J Clin Oncol*). Other patients on clinical trial at SickKids were enrolled on the basis of evidence from molecular tests I developed and validated (e.g. ALK and BRAF digital PCR). I established a translational research project, called KiCS, to study how to best use genome sequencing to manage hard-to-treat childhood cancers. I developed a proposal with 15 other clinical and research leaders at SickKids, obtained \$1.8 million in funding from the Cancer Centre after two rounds of peer review, and have enlisted >140 patients thus far. Also, I lead genomics for a \$25 million 5-year Pan Canadian Precision Medicine Program, PROFYLE, in which we are linking sequencing programs from Montreal, Vancouver and Toronto, with the goal of offering whole genome sequencing to every child and young adult in Canada with a hard-to-treat tumor.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (max four pages)**

In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).

**Novel mechanism of cancer initiation.** In my first publication as an independent investigator, in which I was co-corresponding and first author, we described a remarkable new mechanism of cancer initiation where massive numbers of point mutations are simultaneously acquired over a short time (**Shlien A. Nature Genetics**). This phenomenon leads to early onset tumors that are marked by distinctive genomes. These tumors are sparked by a single variant that results in the complete ablation of DNA replication repair, and a flood of subsequent mutations. Our findings highlight a mechanism that differs considerably from the existing paradigm. As a direct result of this, we predicted that these cancers would express a great number of neoepitopes and that this could be exploited using immunotherapy. Patients enrolled on a clinical trial have sustained clinical response to otherwise fatal diseases (**Bouffet E .... Shlien A, Tabori U, J Clin Oncol.**). We followed this up in a recent study in which we described the spectrum, timing and processes for hypermutation in ~100,000 sequenced tumors (**Campbell B ... Shlien A. Cell. 2<sup>nd</sup> Review**).

We reported the first observation of somatically-acquired processed pseudogenes in cancer (**Cooke SL, Shlien A ... Campbell PJ. Nature Communications**). 660 cancer samples were screened for evidence of somatically acquired pseudogenes. This represents a new class of mutation responsible for tumourigenesis.

**Transcriptional output of cancer (Shlien A ... Campbell PJ. Cell Reports).** This manuscript, in which I was co-corresponding and first author, provides the first comprehensive study of transcriptional consequences of mutation in cancer. A large number of breast cancer whole genomes and complete transcriptomes were sequenced. The data were integrated using a set of bespoke algorithms, primarily designed by me. We provide novel insights into the relationship between the genome and transcriptome and reveal the varied, complex, and surprising methods in which cancer cells interpret somatic mutations. We also provide the first example of transcriptional amplification in breast cancer.

**Translational genomics.** I designed and led the development of an automated system for running next generation sequencing experiments on a massive scale in our hospital. This system has been clinically validated, processed >3,000 samples, is used by Lab Directors, Coordinators and Genetic Counselors and has helped contribute to the repatriation of >\$4 million worth of genetic testing licenses. More recently, my group developed a targeted assay with >95% sensitivity for the detection of mutations in pediatric cancer that is now being used across Canada. Also, I lead genomics for a \$25 million 5-year Pan Canadian Precision Medicine Program, PROFYLE, in which we are linking sequencing programs from Montreal, Vancouver and Toronto, with the goal of offering whole genome sequencing to every child and young adult in Canada with a hard-to-treat tumor.

**Timing and mechanisms of early mutagenesis.** In 2008, we demonstrated that constitutional DNA copy number variation is excessive in *TP53* mutation carriers (**Shlien A, PNAS**). The study provides provocative data to suggest that cancer in fact finds its genetic roots in the germline of the host. In 2010, following a screen of over 4,000 patients, we identified 8 individuals harboring microdeletions encompassing the *TP53* locus. We defined a critical genomic region associated with developmental delay, which contains six underexpressed genes. We further demonstrated that genomic loss of a full copy of *TP53* does not cause cancer predisposition (**Shlien A, AJHG**). Recently, we uncovered a novel early process for generating canonical gene fusions, associated to DNA replication, used by many sarcoma types (**Anderson N ... Shlien A. Science. Under Review**).

**C. Honours & Awards**

List any honours and personal awards in chronological order.

2011/10 - 2013/5 H.L. Holmes Award - 200,000 (Canadian dollar) National Research Council Canada Prize / Award

2011/7 Long Term Fellowship, European Molecular Biology Organization - 86,000 (Canadian dollar)  
European Molecular Biology Laboratory Prize / Award

Early tumor detection and prevention in Li-Fraumeni Syndrome	Shlien, Adam
2011/2	Fellowship, Canadian Institutes of Health Research (2011-2013)- Declined - 80,000 (Canadian dollar) Canadian Institutes of Health Research Prize / Award
2010/9	Finalist for the Walker/Marshall Prize Department of Medical Biophysics, University of Toronto Distinction
2010/9	Shortlisted for a Newton International Fellowship British Academy and Royal Society Distinction
2009/5	Frederick Banting and Charles Best Canada Graduate Scholarship (CGS) Doctoral Award, (Canadian dollar) Canadian Institutes of Health Research Prize / Award
2009/2	From Gene Discovery to Cancer Screening - 900 (United States dollar) Pediatric Cancer Genetics Prize / Award
2009/1	Molecular Medicine Collaborative Training - 1,000 (Canadian dollar) Canadian Institutes of Health Research Prize / Award
2008/6	1st prize for senior Trainee - Basic Science The Hospital for Sick Children Department of Paediatrics Prize / Award

#### D. Overview & Details of Research Support

*Provide an overview of your current areas of research focus including supports of your research / laboratory. Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.*

##### **Current Research Support**

*Funding Source & Program Name:* Canadian Institute of Health Research

*Project Title:* Novel Implications of THOR hypermethylation in telomere maintenance and gliomagenesis.

*Your Role:* (PI, co-PI, collaborator etc) Co-applicant

*Total Award:* \$990,000 CAD

*Total Award to You:*

*Start Date:* 2014-03

*End Date:* 2019-03

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to and overlap with 2018 PPG application:*

##### **Current Research Support**

*Funding Source & Program Name:* The Terry Fox Frontiers Program Project Grant

*Project Title:* Understanding LFS through data integration: from zygote to tumor.

*Your Role:* (PI, co-PI, collaborator etc) Principal Investigator

*Total Award:* \$714,020

*Total Award to You:*

*Start Date:* 2015-06

*End Date:* 2018-06

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to and overlap with 2018 PPG application:*

##### **Current Research Support**

**Early tumor detection and prevention in Li-Fraumeni Syndrome**

Shlien, Adam

*Funding Source & Program Name:* The Hospital for Sick Children

*Project Title:* Startup Funds

*Your Role:* (PI, co-PI, collaborator etc) Principal Applicant

*Total Award:* \$720,000

*Total Award to You:*

*Start Date:* 2013-06

*End Date:* 2018-06

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to and overlap with 2018 PPG application:*

**Current Research Support**

*Funding Source & Program Name:* Genome Canada 2015 Bioinformatics and Computational Biology Competition

*Project Title:* SANGRE (systematic analysis of blood gene regulation by sequencing) – bringing RNA-seq to clinical diagnostics

*Your Role:* (PI, co-PI, collaborator etc) Principal Investigator

*Total Award:* \$250,000

*Total Award to You:*

*Start Date:* 2016-06

*End Date:* 2018-06

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to and overlap with 2018 PPG application:*

**Current Research Support**

*Funding Source & Program Name:* Canadian Cancer Society Research Institute (CCSRI)

*Project Title:* Targeting the telomere maintenance pathway for cancer diagnostics and therapeutics

*Your Role:* (PI, co-PI, collaborator etc) Co-applicant

*Total Award:* \$1,249,935

*Total Award to You:*

*Start Date:* 2015-02

*End Date:* 2018-02

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to and overlap with 2018 PPG application:*

**Current Research Support**

*Funding Source & Program Name:* The Hospital for Sick Children – The Garron Family Cancer Centre

*Project Title:* The implementation of next generation sequencing into routine clinical care at Sick Kids

*Your Role:* (PI, co-PI, collaborator etc) Principal Investigator

*Total Award:* \$1,723,375

*Total Award to You:*

*Start Date:* 2015-02

*End Date:* 2018-02

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to and overlap with 2018 PPG application:*

## E. List of Publications

Provide a full list of all your scientific publications.

1. Campbell BB\*, Light N\*, Fabrizio D, Zatzman M, de Borja R, Davidson S, Fuligni F, Edwards M, Elvin J, Hodel KP, Zahurancik WJ, Suo Z, Lipman T, Hussen K, Wimmer K, Kratz CP, Bowers DC, Laetsch TW, Dunn GP, Tanner J, Grimmer MR, Smirnov I, Larouche V, Samuel D, Bronsema A, Osborn M, Stearns D, Cole KA, Storm PB, Oren M, Opocher E, Mason G, Thomas GA, Sabel M, George B, Ziegler DS, Lindhorst S, Issai VM, Constantini S, Toledano H, Elhasid R, Farah R, Dvir R, Dirks P, Huang A, Galati M, Chung B, Ramaswamy V, Irwin MS, Aronson M, Durno C, Taylor MD, Rechavi G, Maris JM, Bouffet E, Hawkins C, Costello JF, Meyn MS, Pursell Z, Malkin D, Tabori U, Shlien A. The spectrum and timing of hypermutation reveals drivers of human cancer that can be traced to the germline. *Cell*. 2<sup>nd</sup> Review.
2. Anderson N, de Borja R, Young M, Rosic A, Roberts ND, Fuligni F, Hajjar S, Novokmet A, Kowalski PE, Anaka M, Davidson S, Zarrei M, Id-Said B, Schreiner LC, Marchand R, Sitter J, Gogkoz N, Brunga L, Graham GT, Fullam A, Pillay N, Toretsky JA, Yoshida A, Shibata T, Metzler M, Somers G, Scherer SW, Flanagan AM, Campbell PJ, Shago M, Wunder JS, Andrusiak I, Malkin D, Behjati S, Shlien A. Replication-associated rearrangement bursts generate canonical gene fusions in bone and soft tissue tumors. *Science*. 2017 Jun. Under Review.
3. Behjati S, Tarpey PS, Haase K, Ye H, Young MD, Alexandrov LB, Farndon SJ, Collard G, Wedge DC, Martincorena I, Cooke SL, Davies H, Mifsud W, Lidgren M, Martin S, Latimer C, Maddison M, Butler AP, Teague JW, Pillay N, Shlien A, McDermott U, Futreal PA, Baumhoer D, Zaikova O, Bjerkehagen B, Myklebost O, Amary MF, Tirabosco R, Van Loo P, Stratton MR, Flanagan AM, Campbell PJ. Recurrent mutation of IGF signalling genes and distinct patterns of genomic rearrangement in osteosarcoma. *Nat Commun*. 2017 Jun 23;8:15936.
4. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, Schrock A, Campbell B, Shlien A, Chmielecki J, Huang F, He Y, Sun J, Tabori U, Kennedy M, Lieber DS, Roels S, White J, Otto GA, Ross JS, Garraway L, Miller VA, Stephens PJ, Frampton GM. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017 Apr 19; 9(1):34.
5. Behjati S, Gundem G, Wedge DC, Roberts ND, Tarpey PS, Cooke SL, Van Loo P, Alexandrov LB, Ramakrishna M, Davies H, Nik-Zainal S, Hardy C, Latimer C, Raine KM, Stebbings L, Menzies A, Jones D, Shepherd R, Butler AP, Teague JW, Jorgensen M, Khatri B, Pillay N, Shlien A, Futreal PA, Badie C, ICGC Prostate Group, McDermott U, Bova GS, Richardson AL, Flanagan AM, Stratton MR, Campbell PJ. (2016). Mutational signatures of ionizing radiation in second malignancies. *Nat Commun*. 2016 Sep 12; 7:12605.
6. Shlien A, Malkin D, Tabori U. (2016). Translational Childhood Cancer Genomics: The Future Is Now. *JAMA Oncol*. 2016 Mar; 2(3):384-5.
7. Shlien A, Raine K, Fuligni F, Arnold R, Nik-Zainal S, Dronov S, Mamanova L, Rosic A, Ju YS, Cooke SL, Ramakrishna M, Papaemmanuil E, Davies HR, Tarpey PS, Van Loo P, Wedge DC, Jones DR, Martin S, Marshall J, Anderson E, Hardy C, ICGC Breast Cancer Working Group, Oslo Breast Cancer Research Consortium, Barbashina V, Aparicio SA, Sauer T, Garred Ø, Vincent-Salomon A, Mariani O, Boyault S, Fatima A, Langerød A, Borg Å, Thomas G, Richardson AL, Børresen-Dale AL, Polyak K, Stratton MR, Campbell PJ. (2016). Direct Transcriptional Consequences of Somatic Mutation in Breast Cancer. *Cell Rep*. 2016 Aug 16; 16(7):2032-46.
8. Bouffet E, Larouche V, Campbell BB, Merico D, de Borja R, Aronson M, Durno C, Krueger J, Cabric V, Ramaswamy V, Zhukova N, Mason G, Farah R, Samina Afzal S, Yalon M, Rechavi G, Magimairajan V, Walsh MF, Constantini S, Dvir R, Elhasid R, Reddy A, Osborn M, Sullivan M, Hansford J, Dodgshun A, Klauber-Demore N, Peterson L, Patel S, Lindhorst S, Atkinson J, Cohen Z, Laframboise R, Dirks P, Taylor M, Malkin D, Albrecht S, Dudley RWR, Jabado N, Hawkins CE, Shlien A and Tabori U. (2016). Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. *J Clin Oncol*. 2016 Jul 1;34(19):2206-11
9. Mistry M, Zhukova N, Merico D, Rakopoulos P, Krishnatry R, Shago M, Stavropoulos J, Alon N, Pole JD, Ray PN, Navickiene V, Mangerel J, Remke M, Buczkowicz P, Ramaswamy V, Guerreiro Stucklin A, Li M,

- Young EJ , Zhang C , Castelo-Branco P , Bakry D , Laughlin S , Shlien A , Chan J , Ligon KL , Rutka JT , Dirks PB , Taylor MD , Greenberg M , Malkin D , Huang A , Bouffet E , Hawkins CE , Tabori U. (2015). BRAF mutation and CDKN2A deletion define a clinically distinct subgroup of childhood secondary high-grade glioma. *J Clin Oncol.* 2015 Mar 20; 33(9):1015-22.,
10. Debora Fumagalli, David Gacquer, Françoise Rothé, Anne Lefort, Frederick Libert, David Brown, Naima Khedoumi, Adam Shlien, Tomasz Konopka, Roberto Salgado, Denis Larsimont, Kornelia Polyak, Karen Willard-Gallo, Christine Desmedt, Martine Piccart, Marc Abramowicz, Peter J Campbell, Christos Sotiriou, Vincent Detours,. (2015). Principles governing A-to-I RNA editing in the breast cancer transcriptome. *Science Translational Medicine.* 74: 840-851.
11. Ammar R, Paton TA, Torti D, Shlien A, Bader GD. (2015). Long read nanopore sequencing for detection of HLA and CYP2D6 variants and haplotypes. *F1000Res.* 2015 Jan 21; 4:17.
12. Fumagalli D , Gacquer D , Rothé F , Lefort A , Libert F , Brown D , Khedoumi N , Shlien A , Konopka T , Salgado R , Larsimont D , Polyak K , Willard-Gallo K , Desmedt C , Piccart M , Abramowicz M , Campbell PJ , Sotiriou C , Detours V. (2015). Principles Governing A-to-I RNA Editing in the Breast Cancer Transcriptome. *Cell reports.* 13(2): 277-89.
13. Shlien A , Campbell BB , de Borja R , Alexandrov LB , Merico D , Wedge D , Van Loo P , Tarpey PS , Coupland P , Behjati S , Pollett A , Lipman T , Heidari A , Deshmukh S , Avitzur N , Meier B , Gerstung M , Hong Y , Merino DM , Ramakrishna M , Remke M , Arnold R , Panigrahi GB , Thakkar NP , Hodel KP , Henninger EE , Göksenin AY , Bakry D , Charames GS , Druker H , Lerner-Ellis J , Mistry M , Dvir R , Grant R , Elhasid R , Farah R , Taylor GP , Nathan PC , Alexander S , Ben-Shachar S , Ling SC , Gallinger S , Constantini S , Dirks P , Huang A , Scherer SW , Grundy RG , Durno C , Aronson M , Gartner A , Meyn MS , Taylor MD , Pursell ZF , Pearson CE , Malkin D , Futreal PA , Stratton MR , Bouffet E , Hawkins C , Campbell PJ , Tabori U , for the Biallelic Mismatch Repair Deficiency Consortium. (2015). Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra- hypermutated cancers. *Nat Genet.* 2015 Mar; 47(3):257-62.,
14. Merino DM , Shlien A , Villani A , Pienkowska M , Mack S , Ramaswamy V , Shih D , Tatevossian R , Novokmet A , Choufani S , Dvir R , Ben-Arush M , Harris BT , Hwang EI , Lulla R , Pfister SM , Achatz MI , Jabado N , Finlay JL , Weksberg R , Bouffet E , Hawkins C , Taylor MD , Tabori U , Ellison DW , Gilbertson RJ , Malkin D. (2015). Molecular characterization of choroid plexus tumors reveals novel clinically relevant subgroups. *Clin Cancer Res.* 2015 Jan 1;21(1):184-92,
15. Tubio JM, Li Y, Ju YS, Martincorena I, Cooke SL, Tojo M, Gundem G, Pipinikas CP, Zamora J, Raine K, Menzies A, Roman-Garcia P, Fullam A, Gerstung M, Shlien A, Tarpey PS, Papaemmanuil E, Knapskog S, Van Loo P, Ramakrishna M, Davies HR, Marshall J, Wedge DC, Teague JW, Butler AP, Nik-Zainal S, Alexandrov L, Behjati S, Yates LR, Bolli N, Mudie L, Hardy C, Martin S, McLaren S, O'Meara S, Anderson E, Maddison M, Gamble S; ICGC Breast Cancer Group; ICGC Bone Cancer Group; ICGC Prostate Cancer Group, Foster C, Warren AY, Whitaker H, Brewer D, Eeles R, Cooper C, Neal D, Lynch AG, Visakorpi T, Isaacs WB, van't Veer L, Caldas C, Desmedt C, Sotiriou C, Aparicio S, Foekens JA, Eyfjörd JE, Lakhani SR, Thomas G, Myklebost O, Span PN, Børresen-Dale AL, Richardson AL, Van de Vijver M, Vincent-Salomon A, Van den Eynden GG, Flanagan AM, Futreal PA, Janes SM, Bova GS, Stratton MR, McDermott U, Campbell PJ.(2014). Mobile DNA in cancer. Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes. *Science.* 2014 Aug 1; 345(6196).
16. Ly T, Ahmad Y, Shlien A, Soroka D, Mills A, Emanuele MJ, Stratton MR, Lamond AI. (2014). A proteomic chronology of gene expression through the cell cycle in human myeloid leukemia cells. *Elife.* 2014 Jan 1;3:e01630
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18. Susanna L Cooke, Adam Shlien ... Peter J Campbell. (2014). Processed pseudogenes acquired somatically during cancer development. *Nat Commun.* 2014 Apr 9;5:3644
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- Cancer Group , ICGC Chronic Myeloid Disorders Group , ICGC Prostate Cancer Group , Foster CS , Warren AY , Whitaker HC , Brewer D , Eeles R , Cooper C , Neal D , Visakorpi T , Isaacs WB , Bova GS , Flanagan AM , Futreal PA , Lynch AG , Chinnery PF , McDermott U , Stratton MR , Campbell PJ. (2014). Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer. *Elife*. 2014 Oct 1; 3.
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32. Pasic I , Shlien A , Durbin AD , Stavropoulos DJ , Baskin B , Ray PN , Novokmet A , Malkin D. (2010). Recurrent focal copy-number changes and loss of heterozygosity implicate two noncoding RNAs and one tumor suppressor gene at chromosome 3q13.31 in osteosarcoma. *Cancer Res.* 2010 Jan 1; 70(1):160-71.
33. Shlien A , Baskin B , Achatz MI , Stavropoulos DJ , Nichols KE , Hudgins L , Morel CF , Adam MP , Zhukova N , Rotin L , Novokmet A , Druker H , Shago M , Ray PN , Hainaut P , Malkin D. (2010). A common molecular mechanism underlies two phenotypically distinct 17p13.1 microdeletion syndromes. *Am J Hum Genet.* 2010 Nov 12; 87(5):631-42.
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35. Tabori U , Shlien A , Baskin B , Levitt S , Ray P , Alon N , Hawkins C , Bouffet E , Pienkowska M , Lafay-Cousin L , Gozali A , Zhukova N , Shane L , Gonzalez I , Finlay J , Malkin D. (2010). TP53 alterations determine clinical subgroups and survival of patients with choroid plexus tumors. *J Clin Oncol.* 2010 Apr 20; 28(12):1995-2001.
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37. Shlien A , Malkin D. (2009). Copy number variations and cancer. *Genome Med.* 2009 Jun 16; 1(6):62.
38. Shlien A , Tabori U , Marshall CR , Pienkowska M , Feuk L , Novokmet A , Nanda S , Druker H , Scherer SW , Malkin D. (2008). Excessive genomic DNA copy number variation in the Li-Fraumeni cancer predisposition syndrome. *Proc Natl Acad Sci U S A.* 2008 Aug 12; 105(32):11264-9.,
39. Buteau J , Shlien A , Foisy S , Accili D. (2007). Metabolic diapause in pancreatic beta-cells expressing a gain-of-function mutant of the forkhead protein Foxo1. *J Biol Chem.* 2007 Jan 5; 282(1):287-93.
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**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

<b>FULL NAME:</b> Dr. Anna Goldenberg	
<b>POSITION TITLE:</b> Scientist, Assistant Professor	
<b>INSTITUTION:</b> The Hospital for Sick Children, The University of Toronto	
FULL ADDRESS: Peter Gilgan Centre for Research and Learning, 686 Bay Street Rm 12.9708, Toronto, ON, M5G 0A4	
TELEPHONE: 416-813-7654 X301564	EMAIL: Anna.Goldenberg@utoronto.ca
WEB-ADDRESS: <a href="http://goldenberglab.ca/">http://goldenberglab.ca/</a>	

<b>ACADEMIC BACKGROUND</b>			
<i>Degree Type</i>	<i>MM/YY</i>	<i>Discipline/Field/Specialty</i>	<i>Institution &amp; Country</i>
Doctorate	<b>06/07</b>	<b>Computational and Statistical Learning, Computer Science</b>	<b>Carnegie Mellon University</b>
Master's Thesis	<b>10/01</b>	<b>Knowledge Discovery &amp; Data Mining, Computer Science</b>	<b>Carnegie-Mellon University</b>
Bachelor's	<b>05/00</b>	<b>Engineering Mathematics and Computer Science, Computer Science</b>	<b>University of Louisville</b>

<b>WORK EXPERIENCE</b>				
<i>Position, Organization</i>	<i>Department/Division</i>	<i>Start Date</i>	<i>End Date</i>	
Assistant Professor	Computer Science, St. George Campus, University of Toronto	<b>2012-01</b>	-	
Scientist	Genetics & Genome Biology Program, The Hospital for Sick Children	<b>2011-09</b>	-	
Research Intern	Microsoft Research, Seattle, WA, USA	<b>02-2004</b>	<b>10-2004</b>	
Member of Technical Staff	Bell Labs, Lucent Technologies, Murray Hill, NJ, USA	<b>06-2001</b>	<b>05-2002</b>	

**A. Personal Statement (*max one page*)***Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.*

Dr Goldenberg is a Scientist in the Genetics & Genome Biology program at the Hospital for Sick Children (SickKids) Research Institute and an Assistant Professor in the Department of Computer Science at the University of Toronto (UofT). She is also a fellow of the Canadian Institute for Advanced Research (CIFAR) Child & Brain Development program. Dr Goldenberg trained in machine learning and statistics at Carnegie Mellon University (CMU), with a post-doctoral focus in computational biology. She is an expert in developing machine learning approaches for biological and medical data and of network methods for big data.

In the last five years, Dr Goldenberg has emerged as a leader in developing computational methods to integrate omic and medical data. Her work in statistical network analysis (300+ citations) is a cornerstone of network analysis courses and in symposiums at UofT, CMU, Berkeley and Harvard. In computational biology and medicine, her contributions range from methods that detect aberrant genes and miRNAs causing downstream transcriptional changes to models of disease heterogeneity that increase the power of associated variant detection. Dr Goldenberg's genome wide omic data integration method, called Similarity Network Fusion (SNF), significantly improved patient survival outcome predictions for seven cancers (five highlighted in her own work, medulloblastoma (Cancer Cell, 2017) and pancreatic

adenocarcinoma (*Cancer Cell*, 2017), a result that highlights the medical relevance of her computational work. Published in *Nature Methods*, SNF is the first method that can integrate genomic, clinical and imaging data and take advantage of common and complementary signals in the data. It was featured as one of the top network--based papers of 2014 at Intelligent Systems for Molecular Biology (ISMB), one of the largest conferences in the computational biology field. SNF is the foundation of Dr Goldenberg's work with Canadian and international collaborators, such as questionnaire and imaging data integration in neurodevelopmental disorders (Centre for Addiction and Mental Health, Toronto), and combining omic and clinical profiles of spondyloarthritis (SpA) patients (Canada Netherlands SpA Network). The utility of her SNF-based software package, SNFtool, is recognized by research groups around the world, with >10,000 downloads. Her work continues to be exemplary; examples include new papers in *PLOS Computational Biology*, *Cell Systems*, the computer science journal *IEEE Intelligent Systems*, and *Nature Communications*. The latter publication details Dr Goldenberg's successful solution to the issue of predicting treatment response in rheumatoid arthritis patients.

In transitioning from the field of machine learning to the field of computational biology 10 years ago, Dr Goldenberg set her goal: to improve the decisions made in the clinic, such as diagnosis, prognosis and treatment, by developing novel computational models, and thus lead the field of computational medicine. The cornerstone of her research lies in realization of substantial heterogeneity among patients with the same diagnosis: heterogeneity that is evident in both symptom presentation and the cellular and molecular profiles of each patient. Dr Goldenberg and her lab develop methods to combine these diverse types of information to refine patients' diagnoses, prognosis and predictions of response to treatment. The excellence of Dr Goldenberg's research in this area has attracted > \$1,659,179 CAD in competitive, peer--reviewed funding from the Canadian Cancer Society, Canadian Institutes for Health Research (CIHR), Natural Sciences and Engineering Research Council and Terry Fox Foundation. In March, 2016, the Government of Ontario recognized her emergence as a world-class researcher with an Early Researcher Award from the Ministry of Research, Innovation and Science. Just this past June, Dr Goldenberg became a CIFAR Fellow in Child & Brain Development, joining a global set of research programs that connect the world's best minds, across borders and between disciplines. She is poised to continue to emerge as a world leader in the computational medicine field.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (max four pages)**

*In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).*

1. Genome-wide data integration: As data collections grow in size and diversity, it is essential to devise more sophisticated methods to combine all these data to yield meaningful insights into the heterogeneity of diseases and modes of treatment. Dr Goldenberg invented a new method, called Similarity Network Fusion (SNF), for this type of data integration (Wang et al, 2014). Published in *Nature Methods*, SNF is the first method that integrates omic, imaging, and clinical data. It is applicable to small patient cohorts, scales to very large numbers of variables and is very fast. She also proposed a new method for predicting survival that accounts for patient similarities and dissimilarities, and showed that it improves survival outcome predictions in 5 different cancers. Dr Goldenberg's lab used SNF to solve problems of cancer drug similarity and to identify the genetic variants underlying juvenile idiopathic arthritis heterogeneity. Since its publication, SNF has been downloaded >7,000 times and was used by labs around the world to combine data in applications ranging from mapping a comprehensive brain atlas and assembling fungal gene networks.
2. Drug response prediction: Healthcare is moving towards precision medicine, where every patient will eventually be treated according to their own personal biological profile. To improve the power of drug response prediction for a given patient, Dr Goldenberg is establishing a computational protocol which accounts for patient, mouse and cell line data all in one model. Her group has shown that combining patient and model system data improves predictive power (Cheng et al, 2016). She has secured ~\$1M CAD in funding to implement this type of analysis for lung cancer patients, and to assist with in-hospital clinical decision making for patients with breast cancer.
3. Identifying influential genes and miRNAs in cancer: One of the major problems in detecting genes and miRNAs in lung and many other cancers is the relatively late diagnosis. While there may be a few genes of importance that trigger

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cancer initiation and growth, by the time of the diagnosis there are so many genome wide changes that it becomes very hard to identify the few important initiators. Identifying the genes and miRNAs most likely to give rise to the transcriptomic landscape upon tumor diagnosis leads to improved detection, characterization and understanding of cancer. Dr Goldenberg published several approaches to identify genes and miRNAs of influence in cancer (Goldenberg et al, 2012; Mezlini et al, 2013; Alshalalfa et al, 2012; Li et al, 2013; Mezlini et al, 2017; Wang et al, 2017). Genes explaining the genome wide change in transcriptomic landscape of lung cancer and miRNAs potentially of high significance in colorectal and glioblastoma cancers were found.

4. Modeling missing heritability: Currently, for most complex diseases, there is a great disconnect between the theoretical estimates of how heritable a complex disease is and the genetic studies that aim to identify the genetic component that would explain the estimated heritability. A major reason for the gap between theoretical estimates and empirical findings is patient heterogeneity. Many patients with the same diagnosis have substantial clinical and biological differences, implying that different parts of the same biological process may be driving the disease in these patients. Dr Goldenberg developed several statistical methods to address this issue. Her methods simultaneously divide patients into subtypes and identify the underlying genetic variants (Warde-Farley et al, 2012; Colak et al, 2015). These approaches were used to find novel variants associated with type 2 diabetes. These methods serve an important role in bringing more power to understand the genomic contribution to the risk of complex human diseases.
5. Crowdsourcing computational competitions: One of the main bottlenecks in proving the value of novel computational work in biology and medicine is access to large high quality datasets. Over the last 8 years DREAM Challenges have established themselves as a benchmark for computational model testing. DREAM Challenges offer access to unique, curated, very large genetic, genomic and clinical data that allow computational scientists to contribute their models and compete in a fairly evaluated setting. Dr Goldenberg contributed a winning model to the rheumatoid arthritis challenge, where the goal was to predict drug response to anti-TNF treatment in rheumatoid arthritis patients. Her results recently published in Nature Communications (2016) were surprising: the genetic signal available in the largest collected to date rheumatoid arthritis anti-TNF response dataset does NOT significantly improve response predictions based on the clinical data alone. This finding is important to the field of rheumatology, encouraging researchers to invest in collecting other types of biological data to improve their drug response prediction models.

## C. Honours & Awards

*List any honours and personal awards in chronological order.*

2017-2022	Tier 2 Canada Research Chair (\$500,000.00CAD)
2016-	CIFAR - Child and Brain Development Fellow Research Support (\$30,000.00)
2016-2019	Fellow of the Canadian Institute for Advanced Research (CIFAR) program in Child & Brain Development program
2016	Department of Computer Science Award for exceptional mentoring and outstanding commitment to graduate student recruitment, UofT
2016-2021	Early Researcher Award from the Ministry of Research and Innovation (\$140,000 CAD)
2013	Winner of the best poster presentation award at the Young Investigator Meeting, organized by the CIHR Institute of Cancer Research
2010	MITACS Award - for a workshop entitled Networks Across Disciplines: Theory and Applications Prize/Award - \$4,000 CAD
2006	Finalist of the Microsoft Research Fellowship competition
2005	Siebel Scholar Award, Siebel Foundation – for outstanding academic performance and qualities of leadership Prize/Award - \$5,000. USD
2002	Citation in Washington Post – Washington Post - Distinction

**D. Overview & Details of Research Support**

*Provide an overview of your current areas of research focus including supports of your research / laboratory. Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.*

**Current Research Support**

*Funding Source & Program Name: Genome Canada, Genomics Technology Platforms, Operations Support and Technology Development*

*Project Title: Canadian Centre for Computational Genomics (C3G)*

*Your Role: Co-applicant*

*Total Award: \$ 7,048,312.00 CAD*

*Total Award to You: \$309,000.00 CAD*

*Start Date: June 2017*

*End Date: May 2022*

*Main Objective: Implement and further develop machine learning and other data integration methods, including SNF, as a technology platform available to the whole hospital*

*Outline of Methodology: Implementation of Similarity Network Fusion and a new machine learning method for exome+transcriptome integration at a professional software level*

*Budget Details: Salary for post-doctoral research fellow for 5 years*

*Personnel Details: Post-doctoral fellow, 5 years.*

*Relationship to and overlap with 2018 PPG application: none*

*Funding Source & Program Name: Tel Aviv University and the University of Toronto Joint Research Projects in Big Data in Health and Biomedical Research*

*Project Title: A Network Propagation Approach to Drug Repurposing*

*Your Role: Co-applicant*

*Total Award: \$25,000.00 CAD*

*Total Award to You: \$12,500.00 CAD*

*Start Date: May 2017*

*End Date: April 2019*

*Main Objective: Establish a new collaboration between UofT and TAU*

*Outline of Methodology: Develop a novel method for drug target identification using networks. This would be based on Dr Roded Sharan's work and Dr Goldenberg's involvement in cell line/patient data integration effort*

*Budget Details: travel to Israel*

*Personnel Details: grad student travel*

*Relationship to and overlap with 2018 PPG application: none*

*Funding Source & Program Name: Canadian Institute for Advanced Research (CIFAR)*

*Project Title: The epigenetic growth chart of child development*

*Your Role: Co-Investigator*

*Total Award: \$87,000.00 CAD*

*Total Award to You: \$43,500.00 CAD*

*Start Date: November 2016*

*End Date: October 2019*

*Main Objective: The goal of this study is to study the epigenetic landscape over time as a function of the child's development, in order to understand normal epigenetic dynamics and use this understanding to identify deviations from these trajectories that lead to phenotypic outcomes such as psychiatric disorders.*

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*Outline of Methodology: Identify critical time periods of development; build epigenetic networks; identify subnetworks that are a) conserved over time; b) change over time in healthy population.*

*Budget Details: Salary for post-doctoral research fellow for 5 years*

*Personnel Details: 1 postdoctoral fellow*

*Relationship to and overlap with 2018 PPG application: none*

*Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)*

*Project Title: UCAN CAN-DU: Canada-Netherlands Personalized Medicine Network in Childhood Arthritis and Rheumatic Disease*

*Your Role: Co-applicant*

*Total Award: \$8,000,000.00 CAD*

*Total Award to You: \$250,000*

*Start Date: October 2016*

*End Date: September 2021*

*Main Objective: The goal of this project/network is to provide evidence-based tools for pharmacotherapy decision-making in childhood arthritis through innovative omics technologies, machine learning methods, economic modeling and electronic information technology.*

*Outline of Methodology: Build predictive model and biomarkers indicative of response to anti-TNF therapy in juvenile arthritis patients*

*Budget Details: Salary for post-doctoral research fellow for 5 years*

*Personnel Details: one postdoctoral fellow*

*Relationship to and overlap with 2018 PPG application: none*

*Funding Source & Program Name: CREF MbD Award*

*Project Title: Cells to Tissues in 4D: Understanding How Single Cell Behaviour Drives Tissue Generation, Degeneration and Regeneration*

*Your Role: Co Principal Investigator*

*Total Award: \$75,000.00 CAD*

*Total Award to You: \$25,000.00 CAD*

*Start Date: September 2016*

*End Date: August 2017*

*Main Objective: The goal of this study is to establish mathematical models that define how single cell behaviours drive regeneration and tissue morphogenesis.*

*Outline of Methodology: dynamic models that capture 3D morphogenesis of the cell*

*Budget Details: \$20,000.00 CAD for Salaries, 5,000.00 CAD for equipment*

*Personnel Details: 1/3 of a postdoctoral fellow*

*Relationship to and overlap with 2018 PPG application: none*

*Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)*

*Project Title: Identifying integrative biomarkers of risk and resilience in childhood psychopathology*

*Your Role: Principal Investigator*

*Total Award: \$588,665.00 CAD*

*Total Award to You: \$588,665.00 CAD*

*Start Date: July 2016*

*End Date: June 2020*

*Main Objective: The goal of this study is to identify robust and predictive biological and psychological measurements that help to predict which children are at risk of mental disorders and to form targeted and personalized interventions aimed at both reducing the severity of onset of mental disorders and negative outcomes that accompany them.*

*Outline of Methodology: develop methodology based on Gaussian processes that will take advantage of uniquely rich longitudinal epigenetic, environmental, and phenotypic data to identify integrative biomarkers that will improve on the*

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current state-of-the-art early detection of mental disorders. We will ascertain factors that differentiate those who do and do not succumb to childhood mental illness given the same set of known early life risk factors.

Budget Details: Salary of 1 postdoctoral fellow, 1 bioinformatician

Personnel Details: 1 postdoctoral fellow, 1 bioinformatician

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Ontario Ministry of Research and Innovations

Project Title: Integrating big data to improve precision medicine in cancer

Your Role: Principal Investigator

Total Award: \$150,000.00 CAD

Total Award to You: \$150,000.00 CAD

Start Date: March 2016

End Date: March 2021

Main Objective: Combine drug testing on model organisms and cell lines with patient data to improve prediction of patient drug response

Outline of Methodology: Develop deep learning methodology that performs domain adaptation when learning from PDX and cancer cell lines to predict patient response

Budget Details: Graduate student salary, \$150,000.00CAD/5 years

Personnel Details: 2 Graduate Students/5 years

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)

Project Title: Precision medicine in breast cancer: from the computer to the clinic

Your Role: Principal Investigator

Total Award: \$250,233.00 CAD

Total Award to You: \$150,000.00 CAD

Start Date: October 2015

End Date: September 2018

Main Objective: The goal of this study is to build a computational prediction system combining genomic and transcriptional profiles from thousands of well-characterized preclinical models and patient profiles with drug sensitivity data which will yield highly accurate personalized drug response predictions for breast cancer patients.

Outline of Methodology: build prediction models of drug response in breast cancer combining cell lines and clinical trials in breast cancer

Budget Details: 1 postdoctoral researcher at \$50,000 per year

Personnel Details: 1 postdoctoral researcher

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: The Terry Fox Foundation

Project Title: Li Fraumeni Syndrome: Applying Genetic Determinants of Cancer Risk to Cancer Surveillance and Prevention

Your Role: Principal Investigator

Total Award: \$2,248,993.00 CAD

Total Award to You: \$175,000

Start Date: May 2015

End Date: April 2018

Main Objective: The goal of this study is to utilize complex molecular and clinical determinants of LFS to define opportunities for chemoprevention and improved surveillance strategies for early tumor detection.

Outline of Methodology: Predict age of onset of LFS patients from germline probes whole genome epigenetic probes using machine learning approaches (including regularized regression)

Budget Details: bioinformatician at \$50,000+benefits per year

Personnel Details: 1 bioinformatician (Ben Brew)

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*Relationship to and overlap with 2018 PPG application: 50% overlap (this is the precursor to the current application)*

**Funding Source & Program Name:** Canadian Cancer Society Research Institute (CCSRI)

**Canadian Cancer Society Research Institute**

**Project Title:** Improving drug response prediction in non-small cell lung cancer.

**Your Role:** Principal Investigator

**Total Award:** \$199,815.00 CAD

**Total Award to You:** \$90,000.00 CAD

**Start Date:** February 2015

**End Date:** February 2018

**Main Objective:** The goal of this study is to build an integrative computational tool to predict personalized response to therapy in lung cancer patients.

**Outline of Methodology:** Use machine learning approaches (several) to build the best predictor of drug response in lung cancer, primarily from the gene expression PDX data

**Budget Details:** 1 graduate student at \$30,000/yr

**Personnel Details:** 1 graduate student

**Relationship to and overlap with 2018 PPG application:** none

**Funding Source & Program Name:** Natural Sciences and Engineering Research Council of Canada (NSERC)

**Project Title:** Network-based machine learning framework for data integration in medical applications

**Your Role:** Principal Investigator

**Total Award:** \$120,000.00

**Total Award to You:** \$120,000.00

**Start Date:** September 2014

**End Date:** September 2019

**Main Objective:** The goal of this study is to develop network-based machine learning methods that can integrate a wider variety of data types identifying an integrative set of features that can explain observed similarities and differences among subjects.

**Outline of Methodology:** comprehensive suite of machine learning methods that integrate different types of patient data, make accurate diagnostic and prognostic predictions and identify testable disease mechanisms for complex human diseases. Goldenberg Lab is working in close collaboration with clinicians at the Hospital for Sick Children and internationally and groups interested in visualization to make sure that the methods are applied to real data and can be used and evaluated by clinicians in the process of their development

**Budget Details:** 1 Master's student at \$25,000/year

**Personnel Details:** 1 Master's student

**Relationship to and overlap with 2018 PPG application:** none

**Funding Source & Program Name:** Canadian Institutes of Health Research (CIHR)

**Project Title:** The PREDICTS Platform - Precision Decisions In Childhood Arthritis And Uveitis Treatments

**Your Role:** Co-Investigator

**Total Award:** \$2,500,000.00 CAD

**Total Award to You:** \$100,000

**Start Date:** September 2014

**End Date:** September 2019

**Main Objective:** predict whether to stop giving the biologic-based treatment to the JIA patients at 6 months

**Outline of Methodology:** Use SNF to integrate omics data to predict treatment response

**Budget Details:** ½ of a postdoc at \$20,000

**Personnel Details:** ½ of a postdoc

**Relationship to and overlap with 2018 PPG application:** none

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Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)

Project Title: Male-Female Differences in Pubertal Timing: Use of Perturbations of the Lin28/let-7 Axis to Examine Mechanisms

Your Role: Co-applicant

Total Award: \$556,000.00 CAD

Total Award to You: \$100,000

Start Date: April 2014

End Date: April 2018

Main Objective: The goal of this study is to identify a regulatory network that will inform understanding of the basis of pubertal disorders, including precocious and delayed puberty, of links between pubertal onset and health outcomes, and of how diet affects puberty in males vs. females.

Outline of Methodology: Dynamic network based methods that capture gene expression across genes over time

Budget Details: 1 graduate student at \$25,000/yr

Personnel Details: 1 graduate student

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)

Project Title: Canadian Children Inflammatory Bowel Disease Network: A Joint Partnership of CIHR and the C.H.I.L.D. Foundation

Your Role: Co-Investigator

Total Award: \$5,000,000.00 CAD

Total Award to You: \$50,000

Start Date: April 2013

End Date: April 2018

Main Objective: Identify main differences between southeast Asian population and Caucasian population in IBD patients

Outline of Methodology: SNF based method to integrate omics data to identify the differences between south-east Asian population and Caucasian population

Budget Details: 1 graduate student for the last two years of the grant at \$25,000/year

Personnel Details: 1 graduate student

Relationship to and overlap with 2018 PPG application: none

#### **Pending Research Support**

N/A

**E. List of Publications**

*Provide a full list of all your scientific publications.*

Note: In computer science conference publications are valued as highly and reviewed as rigorously as journal publications in other fields.

1. Cavalli, F.M., Remke, M., Rampasek, L., Peacock, J., Shih, D.J., Luu, B., Garzia, L., Torchia, J., Nor, C., Morrissy, A.S. and Agnihotri, S. (2017). Intertumoral Heterogeneity within Medulloblastoma Subgroups. *Cancer Cell.* 31(6): 737-754.
2. Leung, M., Bassani, D.G., Racine-Poon, A., Goldenberg, A., Ali, S.A., Kang, G., Premkumar, P.S. and Roth, D.E. (2017). Conditional random slope: A new approach for estimating individual child growth velocity in epidemiological research. *American Journal of Human Biology.*
3. Rampasek, L., and Goldenberg, A. (2017). Dr. VAE: Drug Response Variational AutoencoderAPA. Preprint arXiv: 1706.08203.
4. H. Hou, L. Uuskula-Reimand, M. Makarem, S. Saleh, C. Corre, A. Metcalf, A. Goldenberg, M. Palmert, M. Wilson. (2017). Gene expression profiling of puberty-associated genes reveals abundant tissue and sex-specific changes across postnatal development. *American Journal of Human Genetics.*
5. C. Azencott, DREAM Idea Challenge Consortium, T. Norman, S. Friend, G. Stolovitzky, A. Goldenberg. (2017). From data-driven models back to model-driven data in the high throughput era. *Nature Methods.*
6. TCGA Consortium. (2017). Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. *Cancel Cell.*
7. Florence MG Cavalli, Marc Remke, Anna Goldenberg, Vijay Ramaswamy, Michael D Taylor. (2017). Intertumoral heterogeneity within medulloblastoma subgroups. *Cancel Cell.*
8. N. El-Hachem, D. Gendoo, L. Ghoraie, Z. Safikhani, P. Smirnov, C. Chung, K. Deng, A. Fang, E. Birkwood, C. Ho, R. Isserlin, G. Bader, A. Goldenberg, and B. Haibe-Kains. (2017). Integrative cancer pharmacogenomics to infer large-scale drug taxonomy. *Cancer Research.*
9. A. Mezlini, A. Goldenberg. (2017). Being Bayesian about Networks to Find Gene Drivers for Complex Human Diseases. *PloS Computational Biology.*
10. B. Wang, L. Huang, Y. Zhu, A. Kundaje, S. Batzoglou, A. Goldenberg. (2017). Vicus: Exploiting Local Structures to Improve Biological Network Analysis. *PloS Computational Biology.*
11. Safikhani, Z., El-Hachem, N., Smirnov, P., Freeman, M., Goldenberg, A., Birkbak, N.J., Beck, A.H., Aerts, H.J.W.L., Quackenbush, J., Haibe-Kains, B. (2016). Safikhani et al. reply. *Nature.* 540(7631): E2-E4.
12. Smirnov, P., Safikhani, Z., El-Hachem, N., Wang, D., She, A., Olsen, C., Freeman, Selby, H., Gendoo, D., Grossman, P., Beck, A., Aerts, H., Lupien, M., Goldenberg, A., Haibe-Kains, B.(2016). PharmacoGx: an R package for analysis of large pharmacogenomics datasets. *Bioinformatics.* 32(8): 1244-1246.
13. L Rampasek and A Goldenberg. (2016). TensorFlow: Biology's Gateway to Deep Learning? *Cell Systems.* 2: 12-14.

14. B Brew, D Hidru, A Goldenberg. (2016). A Protocol for Data Integration in the Presence of Incomplete Samples. *Nature Protocols.*
15. Erdman, L., Sharma, E., Unternahrer, E., Dass, S. H., O'Donnell, K., Mostafavi, S., ... & Goldenberg, A. (2016). Modeling trajectories of mental health: challenges and opportunities. Preprint arXiv:1612.01055.
16. Mezlini, A. M., Fuligni, F., Shlien, A., & Goldenberg, A.(2015). Combining exome and gene expression datasets in one graphical model of disease to empower the discovery of disease mechanisms. Preprint arXiv:1508.07527.
17. Safikhani, Z., Freeman, M., Smirnov, P., El-Hachem, N., She, A., Quevedo, R., Goldenberg, A., Birkbak, N.J., Shi, L., Beck, A.H., Aerts, HJWL., Quackenbush, J. & Haibe-Kains, B. (2015). Revisiting inconsistency in large pharmacogenomic studies. *bioRxiv.* 026153
18. Corre, C., Shinoda, G., Zhu, H., Cousminer, DL., Crossman, C., Bellissimo, C., Goldenberg, A., Daley, GQ., Palmart, MR.(2015). Sex specific regulation of weight and puberty by Lin28/let-7 axis. *Journal of Endocrinology.*
19. Cheng Zhao, Ying Li,Zahleh Safikhani, Benjamin Haibe-Kains, Anna Goldenberg. (2015). Integrating in vitro and ex vivo genomic data to improve drug response predictions in clinical trials. *Genome Medicine.*
20. Wang, B., Huang, L., Zhu, Y., Kundaje, A., Goldenberg, A. (2015). Vicus: Local spectrum for weighted Networks. *PNAS.*
21. R. Colak, T. Kim, H Kazan, Y Oh, M Cruz, A Valladares, J Peralta, J Escobedo, E Parra, P.M. Kim and A. Goldenberg. (2015). JBASE: Joint Bayesian Analysis of Sub-phenotypes and Epistasis. *Bioinformatics.* 32(2): 203-210.
22. Zhao, C., Li, Y., Safikhani, Z., Haibe-Kains, B., & Goldenberg, A. (2015). Using Cell line and Patient samples to improve Drug Response Prediction. Preprint *bioRxiv,* 026534.
23. Saria, S., Goldenberg, A. (2015). Subtyping: what it is and its role in precision medicine. *IEEE Intelligent Systems Magazine.* 30(4): 70-75.
24. Hidru, D., & Goldenberg, A. (2014). EquiNMF: graph regularized multiview nonnegative matrix factorization. Preprint arXiv: 1409.4018.
25. Wang, B., Goldenberg, A. (2014). Gradient-based Laplacian Feature Selection. Preprint arXiv 1404.2948.
26. B Wang, A Mezlini, F Demir, M Fiume, T Zu, M Brudno, B Haibe-Kains and A Goldenberg.(2014). Similarity network fusion for aggregating data types on a genomic scale. *Nature Methods.* 11(3): 337-347.
27. Mezlini AM, Wang B, Deshwar A, Morris Q, Goldenberg A. (2013). Identifying Cancer Specific Functionally Relevant miRNAs from Gene Expression and miRNA-to-Gene Networks Using Regularized Regression. *PloS one.* 8(10): E73168.
28. Mezlini AM, Smith EJ, Fiume M, Buske O, Savich GL, Shah S, Aparicio S, Chiang DY, Goldenberg A, Brudno M. (2013). iReckon: simultaneous isoform discovery and abundance estimation from RNA-seq data. *Genome research.* 23(3): 519-29.
29. Li Y, Goldenberg A, Wong KC, Zhang Z. (2013). A probabilistic approach to explore human miRNA targetome by integrating miRNA-overexpression data and sequence information. *Bioinformatics (Oxford, England).* 5: 621-8.

30. Sara Mostafavi, Anna Goldenberg, Quaid Morris. (2012). Labeling nodes using three degrees of propagation. *PLoS one*. 7(12): e51947.
31. Alshalalfa M, Bader G, Goldenberg A, Morris Q, Alhajj R. (2012). Detecting microRNAs of high influence on protein functional interaction networks: a prostate cancer case study. *BMC systems biology*. 6(112)
32. Warde-Farley D, Brudno M, Morris Q, Goldenberg A. (2012). Mixture model for sub-phenotyping in GWAS. *Pacific Symposium on Biocomputing*. 2012: 363-74.
33. Goldenberg A, Mostafavi S, Quon G, Boutros PC, Morris QD. (2011). Unsupervised detection of genes of influence in lung cancer using biological networks. *Bioinformatics (Oxford, England)*. 27(22): 3166-72.
34. Mostafavi S, Goldenberg A, Morris Q. (2011). Predicting node characteristics from molecular networks. *Methods in molecular biology (Clifton, N.J.)*. 781: 399-414.
35. A Goldenberg, A Zheng, S Fienberg and E Airoldi. (2009). A Survey of Statistical Network Models. *Foundations and Trends in Machine Learning*. 2((2)): 123-233.
36. A Goldenberg, A Zheng. (2006). Exploratory Study of a New Model for Evolving Networks. *Lecture Notes in Computer Science*. 4503: 75-89.
37. Goldenberg A, Shmueli G, Caruana RA, Fienberg SE. (2002). Early statistical detection of anthrax outbreaks by tracking over-the-counter medication sales. *Proceedings of the National Academy of Sciences*. 99(8): 5237–5240.
38. M Kantardzic, A Goldenberg, T Howe and P Fagey. (2001). Artificial Neural Network Approach to Data Analysis and Parameter Estimation in Experimental Spectroscopy. *Informatica*. 25(1): 19-26.

**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

<b>FULL NAME:</b> Andrea Schwarz Doria	
<b>POSITION TITLE:</b> Radiologist, Clinician-Scientist	
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<b>ACADEMIC BACKGROUND</b>			
<i>Degree Type</i>	<i>MM/YY</i>	<i>Discipline/Field/Specialty</i>	<i>Institution &amp; Country</i>
M.Sc.	01/2004	Clinical Epidemiology	University of Toronto, Canada
Ph.D.	07/2000	Medical Sciences	Universidade de Sao Paulo, Brazil
M.D.	01/1992	Medicine	Universidade Federal do Parana, Brazil

<b>WORK EXPERIENCE</b>			
<i>Position, Organization</i>	<i>Department/Division</i>	<i>Start Date</i>	<i>End Date</i>
Full Professor of Radiology	Faculty of Medicine, Faculty of Medicine	July 2016	On-going
Vice-Chair of Research, Injury Inflammation Degeneration	Department of Medical Imaging, University of Toronto, Toronto, Canada	April 2014	On-going
Chair of Clinical Investigator Program, Residency of Radiology	Department of Medical Imaging, University of Toronto, Toronto, Canada	December 2008	On-going
Research Director	Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada	June 2008	On-going
Associate Professor	Faculty of Medicine, University of Toronto, Toronto, Canada	April 2008	On-going
Scientist	Department of Physiology and Experimental Medicine, Research Institute, The Hospital for Sick Children, Toronto, Canada	July 2007	On-going
Staff Radiologist	Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada	February 2004	On-going
Clinical-Research Fellow	Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada	July 2000	June 2003
Chief Fellow	Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada	January 2002	December 2002

[expand tables as required]

**A. Personal Statement (*max one page*)**

*Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.*

In "italic underlined" one can find how my past experience and qualifications make me well-suited for my role in this application.

I have held **influential international roles** as Co-Chair of Imaging Working of International Prophylaxis Study Group (IPSG) (2007-2014, 8 members from Canada, U.S.A., Sweden, India) during which term (2007-2012) I have secured funding as PI of multiple research studies (\$1,043,235 since 2008; \$1,821,246 lifetime) and led the development and validation of the currently IPSG-endorsed MRI scoring system for assessment of joints in hemophilic arthritis through international collaborations (India, Brazil, China). I have also helped building a team of investigators for the development of a scientific collaborative network (as PI of a CIHR Dissemination Grant 2011-2012) for the validation of MRI scoring systems in juvenile idiopathic arthritis and has served as Co-Chair of a Special Interest Group in MRI in Juvenile Idiopathic Arthritis of Outcomes Measures in Rheumatic Diseases (OMERACT) since 2011 (36 members from Canada, U.S.A., Netherlands, Germany, Switzerland, Italy, Norway, Denmark, Spain, United Kingdom). Proof of international recognition for my work is the fact that I have been invited as Keynote speaker in 39 conferences in 13 countries (Canada, U.S.A., Turkey, Netherlands, China, Brazil, United Arab Emirates, Malaysia, United Kingdom, Austria, India, France, Australia) since 2008. In 2014 I have been nominated "Big Data" Leader of the Pediatric Imaging Research Committee of the American College of Radiology, member of the Pediatric Radiology Scientific Committee of the Radiological Society of North America, and Co-Chair of Musculoskeletal Outcomes Novonordisk Symposium, Toronto, including 40 participants from 8 countries (Canada, U.S.A., Netherlands, Italy, Spain, India, China, Brazil). This past leadership experience has provided me the tools that I will need to successfully lead the imaging group (2 collaborators for PET-MRI and one collaborator for whole body MRI) in this project.

My past research has made relevant contributions to:

(i) **Knowledge / Research Advancement:** Improved our understanding on the biologic rationale for hypoxia in inflamed joints (BOLD MRI) which was successfully translated from animals to humans; proved the feasibility of novel imaging techniques for assessment of arthritis in animal models (USPIO for assessment of intra-synovial macrophages' hemosiderin; T2 mapping of cartilage; dynamic MRI and contrast-enhancement ultrasound [US] and positron emission tomography (PET) for evaluation of synovitis) and humans (ultra-short TE for improved quantification of joint blood products; T2 mapping of cartilage; 3DUS and fusion US-MRI of joints' parts and whole body MRI for assessment of the entire body of arthritic patients). Concerning this project, my experience on whole body MRI and PET imaging for assessment of arthritis can be promptly translated into the required knowledge for the imaging surveillance proposed in this project.

(ii) **Health Care / Outcomes:** Determined the most appropriate approaches for US data acquisition in childhood arthritis (applicable to both juvenile idiopathic [JIA] and hemophilic arthritis), led the development of scales and atlases for US and MRI interpretation, and conducted (as PI) international retrospective research on the validation of these tools, thus starting the process on improvement of diagnosis and follow-up of children with arthritis;

(iii) **Health Systems and Knowledge Translation:** Led evidence-based knowledge syntheses on the diagnostic accuracy of US and MRI for assessment of JIA (peripheral and axial skeletons), hemophilia, osteoporosis, hip dysplasia and appendicitis, and participated in the development of evidence-informed policies/guidelines in the field, which should improve resource allocation on utilization of drugs for childhood disorders. This experience can be of tremendous value for the knowledge translation results of this project.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (max four pages)**

*In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).*

My research program resulted in several knowledge translation outputs: publications in high calibre radiology journals: 105 lifetime papers (up to 286 citations per paper; average of 88 citations per year; H-factor of 23, 30 as first author, 37 as senior author, 10 book chapters and 8 invited commentaries/editorials), in discussions of results with patients' families, members of committees she leads, media (2009 and 2014 research featured of the Radiology and American Roentgen Ray Society InPractice magazines, 2009 U.S.A. ReachMD podcast) and through workshops for health allied professionals. A paper on application of novel methodological research techniques in radiology (meta-analysis) was recommended by the website "Faculty of 1000 Medicine" as one of the 1000 best medical papers published in 2006. Lifetime I have presented 83 posters and 59 scientific papers.

Research outputs from international collaborations include videos on ultrasound (US) protocols for joint assessment translated into Chinese, Portuguese and Spanish; an atlas on x-rays, US and MRI of different stages of hemophilic arthropathy (to be used as a companion tool for developed imaging scales. I have served as an expert panel for the development of evidence-based reports (guidelines) of the U.S. Government Agency for Healthcare Research and Quality's and of the Society of Pediatric Radiology on clinical policies in the evaluation and management of childhood disorders. Concerning the current application the scientific papers / chapters / abstract below relate to the imaging techniques that will be used in this project.

My research program has also contributed to the advancement of education in research capacity both nationally and internationally. Lifetime my innovative academic-Industry training program attracted 20 undergraduate, 11 MD, 20 post-doc (from 10 countries) and 5 graduate (supervisor/co-supervisor) students, out of whom 10 undergraduate/MD, 2 post-doc and 2 graduate students received prestigious salary awards. Her training program increased from 5 to 12 students (240%) per year from 2008 to 2014. Except 2 all her past students remained in academia (96%), 4 of them currently hold leadership positions (Radiologist In-Chief, Research Director) in radiology nationally and internationally, and 5 (45%) prior MD students pursued residency in radiology. This experience will allow me to confidently supervise trainees during the conduct of the project who should benefit from the academic environment developed and nurtured in my program throughout the last decade.

**PEER REVIEWED PUBLICATIONS****Refereed Papers Published or Accepted for Publication (N=105, Lifetime)**

**Principal Author (PA): N=30**

**Co-Principal Author (CPA): N=15**

**Collaborator (C): N=23**

**Senior Responsible Investigator (SRI): N=37**

1. Tolend M, Twilt M, Cron RQ, Tzaribakev N, Guleria S, Koos B, von Kalle T, Miller E, Stimec J, Vaid Y, Larheim T, Herlin T, Spiegel L, Inarejos E, Moineddin R, van Rossum M, Saurenmann T, Doria A.S., Kellenberger C.J. (**Double Senior Authorship**). Towards Establishing a Standardized Magnetic Resonance Image Interpretation Protocol for Temporomandibular Joints in Juvenile Idiopathic Arthritis. *Arthritis Care & Research* 2017 In Press **SRI**
2. Chauvin N, Doria A.S. Ultrasound Imaging of Juvenile Idiopathic Arthritis. *Pediatric Radiology* 2017 In Press **SRI**
3. Ligocki C, Abadeh A, Wang K, Adams-Webber T, Blanchette V, Doria A.S. A Systematic Review of Ultrasound Imaging as a Tool for Evaluating Hemophilic Arthropathy in Children and Adults. *Haemophilia* 2017 In Press **SRI**
4. Soliman M, Daruge P, Dertkilil S, De Avila Fernandes E, Negrao J, de Aguiar Vilela Mitraud S, da Rocha ACF, Zhang N, Huo A, Li Y-J, Zhou F, Bordalo-Rodrigues M, Mohanta A, Blanchette V, Doria A. Imaging of Hemophilic Arthropathy in Growing Joints: Pitfalls in Ultrasound and MRI. *Haemophilia* 2017 In Press **SRI**

5. Larheim T.A., Parra D., Doria A.S. Juvenile idiopathic arthritis and temporomandibular joint involvement - an interdisciplinary approach. *Seminars in Orthodontics* 2015;21(2), s 102- 110 **SRI**
6. Keshava S., Gibikote S., Doria A.S. Imaging evaluation of haemophilia. *Musculoskeletal Approach. Sem Thromb Haemost* 2015; 41 (8): 880-893 **SRI**
7. Nasui C., Chan M W., Crawley A., Miller E., Belik J., Cheng H.L., Kassner A., Rayner T., Weiss R., Zhong A., Moineddin R., Jong R., Rogers M., Doria A.S. Physiologic Characterization of Inflammatory Arthritis in a Rabbit Model with BOLD and DCE MRI at 1.5 Tesla. *Eur Radiol* 2014; 24(11):2766-78 **SRI**
8. Doria A.S., Keshava S, Gibikote S. Hemosiderin Detection with Ultrasound: Reality or Myth? Reply to a Letter to the Editor. *Am J Roentgenol* 2016 Jan;206(1):W31-35
9. Fischer K, Poonnoose P, Dunn A, Babyn P, Manco-Johnson M, John J, van der Net J, Feldman B, Berger, K, Carcao M, de Kleijn P, Silva M, Hilliard P, Doria A.S., Srivastava A, Blanchette V. Choosing outcome assessment tools in haemophilia care and research: a multidisciplinary perspective. *Haemophilia* 2017 In Press **C**
10. Church PC, Greer MC, Cyttar-Kuint R, Doria AS, Griffiths AM, Turner D, Walters TD, Feldman BM. Magnetic resonance enterography has good inter-rater agreement and diagnostic accuracy for detecting inflammation in pediatric Crohn disease. *Pediatr Radiol* 2017 Mar 10 **C**
11. Berntorp E, Dargaud Y, Hart D, Lobet S, Mancuso ME, d'Orion R, Perry D, Pollard D, van den Berg M, Blatný J, Chambost H, Doria A.S., Holme PA, Kaczmarek R, Mantovani L, McLaughlin P, Nanayakkara L, Petrini P, Sannié T, Laane E, Maia R, Dettoraki A, Farrell A, Halimeh S, Raza S, Taylor S. The Second Team Haemophilia Education (THE) Meeting, 2016, Frankfurt, Germany. *Eur J Haematol* 2017; 98 Suppl 85:1-15 **C**
12. Hemke R, Nusman C.C., van Veenendaal M., VAN DER Berg M., van der Heijde D., Doria A.S., Maas M., Kuijpers T.W., van Rossum M.A.J. Frequency of joint involvement in Juvenile Idiopathic Arthritis; a 5-year follow-up overview. *Rheumatol Int* 2015; 35(2):351-7 **C**
13. Wang K.C., Amirabadi A., Uleryk E., Doria A.S. Evidence-Based Systematic Review on Diagnostic Accuracy of Quantitative Ultrasound for Assessment of Pediatric Osteoporosis. *Pediatric Radiology* 2014; 44(12):1573-87 **SRI**
14. Doria A.S., Keshava S. N., Mohanta A., Srivastava A., Blanchette V., Man C., Thilak M., Moineddin R., Kavitha ML, Poonnoose P., Hilliard H., Gibikote S. Diagnostic Accuracy of Ultrasound for Assessment of Hemophilic Arthropathy. MRI Correlation. *Am J Roentgenol* 2015 204(3):W336-47 **PA**
15. Shaikh F., Voicu L., Tole S., To T., Doria A.S., Sung L, Alexander S. The Risk of Traumatic Lumbar Punctures in Children with Acute Lymphoblastic Leukemia. *European J Cancer* 2014 50(8):1482-9 **C**
16. Doria A.S., Zhang N, Lundin B, Hilliard P, Man C, Weiss R, Detzler G, Blanchette V, Moineddin R, Eckstein F, Sussman M. Quantitative versus Semi-Quantitative MR Imaging of Cartilage in Blood-Induced Arthritic Ankles. *Pediatr Radiol* 2014; 44(5):576-586 **PA**
17. Chan MW, Nathanael G, Kiss A, Amirabadi A, Zhong A, Weiss R, Moineddin R, Crawley A, Doria A.S.. Systematic Protocol for Assessment of the Validity of BOLD MRI in a Rabbit Model of Inflammatory Arthritis at 1.5 Tesla. *Pediatr Radiol* 2014; 44(5):566-575 **SRI**
18. Hemke R, Doria A.S., Tzaribachev N, Maas M, Van der Heijde D, Van Rossum M. Selecting Magnetic Resonance Imaging (MRI) Outcome Measures for Juvenile Idiopathic Arthritis (JIA) Clinical Trials: First Report of the MRI in JIA Special Interest Group. *J Rheumatol*. 2014; 41(2):354-358 **CPA**
19. Munir S, Twilt M, Miller E, Spiegel L, Uleryk E, Doria A.S. Evidence-Based Outcomes of Studies Addressing Diagnostic Accuracy of MR Imaging of The Axial Skeleton in Juvenile Idiopathic Arthritis. *AJR* 2014; 202(1): 199-210 **SRI**
20. Chan M.W., Xavier F., Blanchette V., Doria A.S. MR Imaging as a Screening Tool for Early Detection of Arthropathy in Hemophilic Children. Systematic Review and Recommendations. *Haemophilia* 2013 19(6):e324-334 **SRI**
21. Doria AS. Abdominal pain duration impacts the accuracy of ultrasound for diagnosing paediatric appendicitis. *Evid Based Med.* 2013 Dec;18(6):224-5. **PA**
22. Doria A.S., Crawley A., Babyn P., Rayner T., Feldman B. BOLD MRI at 1.5 Tesla in Juvenile Idiopathic Arthritis: Preliminary Experience. *Clinics* 2013; 68(5): 721-724 **PA**
23. Kraft JK, Blanchette VS, Babyn PS, Cloutier S, Feldman BM, Israels SJ, Klaassen R, Pai MK, Poon MC, Price V, Rivard G, Wu J, Gomer S, McLimont M, Moineddin R, Doria AS. Magnetic Resonance Imaging and Joint

- Outcomes in Boys with Severe Hemophilia A Treated with Tailored Primary Prophylaxis in Canada. *J Thromb Haemost* 2012;10(12):2494-2502 **SRI**
24. Lundin B, Manco-Johnson ML, Ignas DM, Moineddin R, Blanchette VS, Dunn AL, Gibikote SV, Keshava SN, Ljung R, Manco-Johnson MJ, Miller SF, Rivard GE, Doria A.S.; The International Prophylaxis Study Group. An MRI scale for assessment of haemophilic arthropathy from the International Prophylaxis Study Group. *Haemophilia* 2012;18(6):962-970 **SRI** 2010 JCR Science Edition Impact Factor: 2.364
25. Nasui C, Nathanael G, Miller E, Belik J, Crawley A, Weiss R, Detzler G, Zhong A; Moineddin R, Doria AS. Responsiveness of BOLD MRI to Short-Term Temperature Changes in Rabbit Knees with Inflammatory Arthritis. *Rheumatology (Current Research)* 2012 ISSN: 2161-1149 (Suppl 2):1-9 **SRI**
26. Xavier F, Zhang N, Mohanta M, Hilliard P, Man C, Drossmann D, Stain AM, Blanchette V, Doria AS. Sonography for assessment of elbows in haemophilic children: a systematic protocol. *Rheumatology (Current Research)* 2012 ISSN: 2161-1149 (Suppl 2):1-9 **SRI**
27. Monahan PE, Doria A.S., Ljung R, Jimenez-Yuste V. Optimizing Joint Function: New Knowledge and Novel Tools and Treatments. *Haemophilia* 2012; 18 (Suppl 5):17-26 **CPA**
28. Miller E, Daneman A, Doria AS, Blaser S, Traubici J, Jarrin J, Moineddin R, Moore A, Shroff M. Color Doppler Ultrasound of Cerebral Venous Sinuses in Neonates: a Comparison with MR Venography. *Pediatr Radiol* 2012; 42(9):1070-1079 **C**
29. Pope E, Doria AS, Theriault M, Mohanta A, Laxer RM. Topical Imiquimod 5% Cream for Pediatric Plaque Morphea: A Prospective, Multiple-Baseline, Open-Label Pilot Study. *Dermatology* 2011; 223(4):363-369 **CPA**
30. Doria AS, Crawley A, Gahunia H, Moineddin R, Rayner T, Tassos V, Zhong A, Pritzker K, Mendes M, Jong R, Salter RB. Correlative BOLD MR imaging of stages of synovitis in a rabbit model of antigen-induced arthritis. *Pediatr Radiol* 2012; 42(1): 63-75 **PA**
31. Doria A.S., Wang Chenghua, Zhong A, Rayner T, Belik J, Moineddin R, Crawley A. Reliability and convergent validity of different BOLD MRI frameworks for data acquisition in experimental arthritis. *Acad Radiol* 2011; 18(5): 615-626 **PA**
32. Roposch A, Odeh O, Doria AS, Wedge JH. The presence of an ossific nucleus does not protect against osteonecrosis after treatment of developmental dysplasia of the hip. *Clin Orthop Relat Res*. 2011;469(10):2838-2845 **C**
33. Sulowski C, Doria A.S., Langer J., Stephens J.C., Schuh S. Clinical Outcomes in Obese Children with Suspected Appendicitis. *Acad Emerg Med* 2011; 18: 167-173 **CPA**
34. Schuh S, Man C, Cheng A, Murphy A, Mohanta A, Moineddin R, Tomlinson G, Langer J.C., Doria A.S.. Predictors of non-diagnostic ultrasound in children with suspected appendicitis. *J Pediatr* 2011; 158: 112-118 **SRI**
35. Doria A.S. State-of-the-art imaging techniques for evaluation of hemophilic arthropathy: present and future. *Haemophilia* 2010; Suppl 5: 107-114 **PA**
36. Li S, Liebling M.S., Ramji F, Opitz S, Mohanta A, Kornyat T, Zhang S, Dempsey-Robertson M, Hamer C, Edgerton S, Jarrin J, Malone M, Doria A.S. Sonographic evaluation of pediatric localized scleroderma: preliminary disease assessment measures. *Pediatr Rheumatol* 2010, 8:14 **SRI**
37. Silva CT, Doria A.S., Traubici J, Moineddin R, Davila J, Shroff M. Do additional views improve the diagnostic performance of cervical spine radiography in pediatric trauma? *AJR Am J Roentgenol*. 2010; 194 (2): 500-508 **CPA** \**Doria A.S.: Correspondent Author*.
38. Doria A.S., Chaudry GA, Nasui C, Rayner T, Wang C, Moineddin R, Babyn PS, White LM, Sussman MS. The use of parallel imaging for MRI assessment of knees in children and adolescents. *Pediatr Radiol* 2010; 40 (3): 284-293 **PA**.
39. Khan U, Bogue C, Ungar WJ, Hilliard P, Carcao M, Moineddin R, Doria A.S. Cost-effectiveness analysis of different imaging strategies for diagnosis of haemophilic arthropathy. *Haemophilia* 2009; 16 (2): 322-332 **SRI**.
40. Keshava, S., Gibikote, S., Mohanta A., Doria A.S. Refinement of a Sonographic Protocol for Assessment of Haemophilic Arthropathy. *Haemophilia* 2009; 15 (5): 1168-1171 **SRI**.
41. Junqueira B.L.P., Allen L.M., Spitzer R.F., Lucco K.L., Babyn P.S., Doria A.S. Müllerian duct anomalies and mimics in children and adolescents: correlative intraoperative assessment with clinical imaging. *Radiographics* 2009; 29: 1085-1103 **SRI**.

42. Miller E., Uleryk E., Doria A.S. Evidence-Based Outcomes of Studies Addressing Diagnostic Accuracy of MR Imaging of Juvenile Idiopathic Arthritis. Am J Roentgenol 2009; 192 (5): 1209-1218 **SRI**.
43. Miller E., Roposch A., Uleryk E., Doria A.S. Juvenile Idiopathic Arthritis: Quality of Reporting of Diagnostic Accuracy for MRI. Acad Radiol 2009; 16 (6): 739-757 **SRI**.
44. Ortiz-Neira C., Laffan E., Roposch A., Ohlsson A., Fong K., Babyn P., Doria A.S. Color Doppler Ultrasound Assessment of the Normal Neonatal Hip. Can Assoc Radiol J 2009; 60 (2): 79-87 **SRI**.
45. Doria A.S. Optimizing the role of imaging in appendicitis. Pediatr Radiol 2009; 39 (Suppl 2):S144-S148 **PA**.

### **INVITED COMMENTARIES / PUBLICATIONS**

1. Chauvin N, Doria A.S. Ultrasound Imaging of Juvenile Idiopathic Arthritis. Pediatric Radiology 2017 In Press
2. Doria A.S., Keshava S, Gibikote S. Hemosiderin Detection with Ultrasound: Reality or Myth? Reply to a Letter to the Editor. Am J Roentgenol 2016 Jan;206(1):W31-35
3. Larheim T.A., Parra D., Doria A.S. Juvenile idiopathic arthritis and temporomandibular joint involvement - an interdisciplinary approach. Seminars in Orthodontics In Press
4. Keshava S., Gibikote S., Doria A.S. Imaging evaluation of haemophilia. Musculoskeletal Approach. Sem Thromb Haemost In Press
5. Doria A.S. Evidence-Based Medicine 2013. Commentary on: Bachur RG, Dayan PS, Bajaj L, Macias CG, Mittal MK, Stevenson MD, Dudley NC, Sinclair K, Bennett J, Monuteaux MC, Kharbanda AB; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. The effect of abdominal pain duration on the accuracy of diagnostic imaging for pediatric appendicitis. Ann Emerg Med. 2012 Nov;60(5):582-590.
6. Monahan PE, Doria A.S., Ljung R, Jimenez-Yuste V. Optimizing Joint Function: New Knowledge and Novel Tools and Treatments. Haemophilia 2012; 18 (Suppl 5):17-26
7. Doria A.S. State-of-the-art imaging techniques for evaluation of hemophilic arthropathy: present and future. Haemophilia 2010; Suppl 5: 107-114
8. Doria A.S. Optimizing the role of imaging in appendicitis. Pediatr Radiol 2009; 39 (Suppl 2):S144-S148

### **BOOKS**

**Title:** Research Methodology in Radiology

Chief Editor: Doria A.S.

Co-Editors: Tomlinson G, Moineddin R

Publisher: Thieme

Expected release date: Spring 2017

**Title:** Pediatric Radiology: Practical Imaging Evaluation of Infants and Children

Chief Editor: Lee E.Y. (Thoracic / Cardiac imaging)

Associate Editors:

Doria A.S. (Musculoskeletal imaging); Chu W. (Neuroimaging); Dillman J. (Abdominal imaging); Restrepo R. (Image Editing). Publisher: Lippincott Williams & Wilkins. Expected release date: Spring 2017

### **BOOK CHAPTERS**

1. Ortiz-Neira CL, Stimec J, Torre Moreira M, Doria A.S. Chapter 22. Title: Musculoskeletal Infectious and Inflammatory Diseases Pediatric Radiology: Practical Imaging Evaluation of Infants and Children. Chief Editor: Lee EY. Springer-Verlag. To be released in Nov 2017
2. Restrepo R, Lee EY, Babyn P, Doria A.S. Chapter 25. Title: Endocrine / Metabolic / Arthropathies. Pediatric Radiology: Practical Imaging Evaluation of Infants and Children. Chief Editor: Lee EY. Springer-Verlag. To be released in Nov 2017
3. Roposch A, Doria A.S. Chapter 1. Overview of Research Designs Applied to Radiology. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017

4. Tomlinson G, Lebovic G, Marras C, Doria A.S. Chapter 3. Statistical Methods for Analysis of Diagnostic Tests. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017
5. Easson AM, Tomlinson G, Doria A.S. Chapter 4. Measurement: Validity, Reliability, and Responsiveness. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017
6. Doria A.S., Stinson J, Shah P. Chapter 7. Systematic Reviews, Evidence-based Imaging, and Knowledge Translation. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017
7. Doria A.S., Strouse P, Adams-Webber T. Chapter 10. Conducting and Publishing Research. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017
8. Meaney C, Shaikh M, Doria A.S., Moineddin R. Chapter 14. Linear and Logistic Regression. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017
9. Shaikh M, Beyene J, Doria A.S., Chapter 15. Sample Size Estimation. Editors: Doria A.S., Tomlinson G, Beyene J, Moineddin R. Thieme. To be released in Nov 2017
10. Doria A.S.; Babyn P. – Radiologic Investigation of Pediatric Rheumatic Diseases. 6<sup>th</sup> Edition of Textbook of Pediatric Rheumatology. Editors: Cassidy, Petty, Laxer, Lindsley. 2014.
11. Doria A.S.; Lundin B. - Imaging Modalities for Assessment of Hemophilic Arthropathy. Textbook of Hemophilia. Editor: Christine A Lee. 2014. Submitted in January 2013.
12. Doria A.S.; Babyn P.S. - 12<sup>th</sup> Edition of Caffey's Pediatric Diagnostic Imaging. Title: Arthritides and Other Inflammatory Disorders. 2013
13. Babyn P.; Doria A.S. – Radiologic Investigation of Pediatric Rheumatic Diseases. 6<sup>th</sup> Edition of Textbook of Pediatric Rheumatology. Editors: Cassidy, Petty, Laxer, Lindsley. 2011.
14. Doria A.S.; Lundin B. - Imaging Modalities for Assessment of Hemophilic Arthropathy. Textbook of Hemophilia. Editor: Christine A Lee. 2009.
15. Miller E., Doria A.S. - Juvenile Idiopathic Arthritis. Evidence-Based Imaging in Pediatrics. Optimizing Imaging in Pediatric Patient Care. Editors: Medina L.S., Craig Blackmore C., Applegate K.E. Springer-Verlag, 2009.
16. Doria A.S.; Babyn P.S. - Imaging Investigation of Arthritis in Children. Diagnostic Imaging of Rheumatologic Diseases. Editor: Weissman S. Elsevier, 2009

**INVITED LECTURES: N=84 (Lifetime); N=47 (Past 5 years)****Selected lectures:**

1. 2017 – Speaker – Musculoskeletal Ultrasound Symposium, Seattle, WA. State of Musculoskeletal Ultrasound (MSKUS) in Hemophilia: an International Exchange. September 29-30, 2017
2. 2017 – International Visiting Professor of the Radiological Society of North America, Colombo, Sri Lanka, August 22-September 3, 2017.
3. 2017 – Speaker – Novo Nordisk Hemophilia Meeting. Using Ultrasound as a Diagnostic Tool for Assessment of Hemophilic Arthropathy. Taipei, Taiwan, June 3, 2017.
4. 2017 – Speaker - Society of Pediatric Radiology Meeting, Vancouver, BC. Ultrasound protocol session. Ultrasound inRheumatology Protocols. May 20, 2017
5. 2017 – Speaker - Society of Pediatric Radiology Meeting, Vancouver, BC. Musculoskeletal Categorical Course. Imaging of Arthritis. May 19, 2017
6. 2017 – Speaker - American Society of Pediatric Hematology/Oncology Meeting, Montreal, QB. Advances in the Detection of Early Hemophilic Arthropathy: from Clinical Tools to Advanced Musculoskeletal Imaging. April, 2017
7. 2016 - Speaker – American Society of Hematology Meeting, San Diego, CA. Point-of-Care- Ultrasound in Hemophilic Arthropathy. December 5, 6, 2016.
8. 2016 – 102nd Scientific Assembly and Annual Meeting of the Radiological Society of North America – Chicago, IL, USA. Moderator: RC213 – Pediatric Series: Musculoskeletal. November 30, 2016.

9. 2016 - Speaker – American College of Rheumatology Meeting, Washington, DC. Imaging in Scleroderma. November 14, 15, 2016.
10. 2016 - Speaker – Novo Nordisk Hemophilia Meeting. Ultrasound. Improving Access to Joint Monitoring. Berlin, Germany, November 1-4, 2016.
11. 2016 – Speaker – Pediatric Body Imaging Update, Toronto, Ontario, Inflammatory vs. Infectious Arthropathies, October 1, 2016.
12. 2016 - Speaker – World Federation of Hemophilia World Congress, Orlando, FL. The Ankle. Radiographic Work Up and Evaluation. July 25, 2016
13. 2016 - Speaker – Team Hemophilia Education Meeting, Frankfurt, Germany. What Imaging at What Time? May 19, 20, 2016.
14. 2015 - Speaker – Comprehensive Hemophilia Joint Care National Advisory Board, Novo Nordisk, Toronto, ON. Radiological Changes in Hemophilia-Related Arthropathies. I Can See What You Can't See. November 21, 2015.
15. 2015 - Speaker – Visiting Professor - Department of Diagnostic Radiology, Dalhousie University, Halifax, NS. Molecular Imaging of Pediatric Musculoskeletal Disorders. Evidence-Based Imaging. May 14 and 15, 2015.
16. Critical Thinking Skills: Evidence-Based Imaging
17. Imaging of Pediatric Arthropathies. Today and Tomorrow
18. Acute Appendicitis in Children: Optimization of Imaging Techniques for Diagnosis
19. 2015 – Keynote Speaker – 14<sup>th</sup> International Musculoskeletal Congress, World Federation of Hemophilia, Belfast, Ireland. May 9 and 10, 2015.
20. Have We Made Any Progress in Radiographic Outcome Measures for Hemophilic Arthropathy
21. Joint Assessment of Hemophilic Joints Based on Imaging Studies
22. 2015 – Speaker – 4th Global Haemophilia Network Meeting, Rome, Novo Nordisk, Italy. Joint Imaging. Why and When? March 16, 17 2015.
23. 2015 - Speaker – Visiting Professor – Department of Radiology, Nanfang Hospital, Guangzhou, China. X-Ray, Ultrasound and MRI in Hemophilic Arthropathy: Scoring and Clinical Application. February 11, 2015.
24. 2014 – Co-Chair - Novonordisk Symposium – Toronto, ON. Assessment of Hemophilic Arthropathy : Current status and Future Directions. October 17-19, 2014.
25. 2013 – Speaker – Visiting Professor - Departments of Radiology and Hematology, Immunology and Infectious Diseases, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, Netherlands. Advanced Imaging of Arthritis. November 22, 2013.
26. 2013 – Speaker – Visiting Professor - Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, USA, November 14, 2013.
27. -Functional and Molecular Imaging of Pediatric Arthropathies
28. Acute Appendicitis in Children: Optimization of Imaging Techniques for Diagnosis
29. Common Pediatric Musculoskeletal Malignancies. Today and Tomorrow.
30. Critical Thinking Skills: Evidence-Based Imaging
31. 2013 - Speaker - 99th Scientific Assembly and Annual Meeting of the Radiological Society of North America – Chicago, IL, USA – Refresher Course – Pediatric Musculoskeletal Benign and Malignant Neoplasms. December, 2013. Keynote.
32. 2013 – Speaker – Global Research Forum – World Federation of Hemophilia, Montreal, QB. Imaging of joints – What is practical? April 16, 2013.
33. 2011 - Visiting Professor - Department of Radiology, Lucile Packard Children's Hospital, Stanford University, Palo Alto, CA, USA. Functional and Molecular Imaging of Pediatric Arthropathies. May 19, 2011.
34. 2011 – College of Radiology Annual Scientific Meeting. Radiology: Beyond Imaging Interpretation. Kuala Lumpur, Malaysia - April 8, 9 2011. Keynote Speaker.  
Acute Appendicitis in Children: Optimization of Imaging Techniques for Diagnosis. The Brain in Children: Is Contrast-Enhancement Really Needed After a Normal Unenhanced CT Result?  
Imaging of Early Changes in Hemophilic Arthropathy. Today and Tomorrow.  
Pediatric Bone Tumors.  
Functional and Molecular Imaging of Musculoskeletal Disorders. What Does This Add to Conventional Imaging?

**C. Honours & Awards**

List any honours and personal awards in chronological order.

1. 2016 – **Faculty Research Award:** Department of Medical Imaging, University of Toronto. On-line voting system by residents, fellows and staff of the Department of Medical Imaging, University of Toronto (The Hospital for Sick Children, Toronto General Hospital, Mount Sinai Hospital, St Michael's Hospital, Toronto Western Hospital and Sunnybrook Hospital) – 1 annual award offered by the Department of Medical Imaging, University of Toronto
2. 2016 - **Excellence in Teaching Award:** Department of Medical Imaging, University of Toronto. On-line voting system by residents and fellows of the Department of Medical Imaging, University of Toronto (The Hospital for Sick Children, Toronto General Hospital, Mount Sinai Hospital, St Michael's Hospital, Toronto Western Hospital and Sunnybrook Hospital)
3. 2014 - Research featured on the 2014 January magazine, ARRS InPractice, of the American Journal of Roentgenology: Munir S, Twilt M, Miller E, Spiegel L, Uleryk E, Doria A.S. Evidence-Based Outcomes of Studies Addressing Diagnostic Accuracy of MR Imaging of The Axial Skeleton in Juvenile Idiopathic Arthritis. AJR 2014; 202(1): 199-210.
4. 2013 Kenneth Fellows Memorial Lecture (November 14, 2013), The Children's Hospital of Philadelphia, University of Pennsylvania, PA.
5. 2011 – **Honorable Mention for Best Basic Science Paper.** Title: Assessment of Cortical Bone Loss with Quantitative Ultrasound, Peripheral CT and Micro-CT in Post Mortem Knee Specimens of a Rabbit Model of Inflammatory Arthritis. Date: May 27-31, 2011. Amirabadi A, Wang J, Gordon C, Tomlinson C, Grynpas M, Moineddin R, Doria A.S. Conjoint Meeting of The Society of Pediatric Radiology and European Society of Pediatric Radiology, London, England.
6. 2011 - XXII Congress of the International Society of Thrombosis and Haemostasis - Kyoto, Japan. Lundin B, Manco-Johnson ML, Ignas D, Doria A.S. An MRI scale for Assessment of Hemophilic Arthropathy. International Prophylaxis Study Group. The work has been presented as a poster at the International Society of Thrombosis and Haemostasis (ISTH) Conference in Kyoto, Japan, July 2011, and was assigned a ribbon reward for being among the top 15% abstracts.
7. 2010 – **Poster Award** (1 of 10 finalists in the General Clinical Specialties track for a poster award) at the 57<sup>th</sup> Annual Meeting of the Society of Nuclear Medicine. Title: Pilot study of FDG PET/CT for Hemophilic Arthropathy in a Rabbit Model. Date: June 8, 2010. Shammas A, Doria A.S., Charron M, Metser U. Salt Lake City – Utah – U.S.A.
8. 2009 - Research featured on the website of the February 2009, volume 250, issue 2 of Radiology: Wan M.J., Krahn M., Ungar W., Sung L., Doria A.S. Acute Appendicitis in Young Children: Cost-effectiveness of US versus CT in Diagnosis--A Markov Decision Analytic Model. Radiology 2008; 250 (2):378-386.
9. 2009 - Speaker at the U.S.A. ReachMD podcast in 2009 on “Cost and Risk Analysis for Imaging of Acute Appendicitis in Children” from the series on Advanced in Medical Imaging.
10. 2008 - **Excellence in Teaching Award:** Department of Medical Imaging, University of Toronto
11. 2003 – **John Kirkpatrick Young Investigator Award** (annual award offered by the Society for Pediatric Radiology for the best paper presented by a fellow). Number of papers: 24. Title: Which is the best imaging technique for diagnosis of appendicitis in children as compared with adults? A meta-analysis. Date: May 10, 2003. Doria A.S., Moineddin R, Kellenberger C, Epelman M., Babyn P.S., Dick P., et al. San Francisco - CA – U.S.A. The paper that resulted from this review was recommended by the website “Faculty of 1000 Medicine”

Early tumor detection and prevention in Li-Fraumeni Syndrome

Doria, Andrea

([www.f1000medicine.com/article/id/1047375/evaluation](http://www.f1000medicine.com/article/id/1047375/evaluation)), February 2<sup>nd</sup>, 2007) as one of the 1000 best medical papers published in 2006, being referred in renowned medical journals, such as JAMA.

12. 2002 – **John Caffey Award for Basic Science Research** (annual award offered by the Society for Pediatric Radiology for the best basic science paper). Number of papers: 98. Title: Understanding the Functional Angiogenic Process in an Antigen-Induced Arthritis Model: Correlative BOLD MR Imaging (fMRI) of the Stages of Synovitis along the Time Course of the Disease. Date: May 1, 2002 Doria A.S., Babyn P.S., Crawley A., Noseworthy M., Pritzker K., Salter R.B. Philadelphia – PA – U.S.A.

#### **D. Overview & Details of Research Support**

*Provide an overview of your current areas of research focus including supports of your research / laboratory (max one page). Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.*

##### **Current Research Support**

*Funding Source & Program Name:*

*Project Title:*

*Total Award:*

*Total Award to You:*

*Start Date:*

*End Date:*

*Main Objective:*

*Outline of Methodology:*

*Budget Details:*

*Personnel Details:*

*Relationship to 2015 PPG application:*

##### **Current Research Support – Active Grants**

Title	Funding Body	Total Amount	Principal Investigator	Date of Initiation (Duration Period)	Co-Investigators
<b>2017</b> Radiogenomics: Personalized Imaging of Arthropathy in Boys with Hemophilia in China	Baxalta Grants	\$1,107,678 (=US\$ 822,043)	Doria A.S. / Wu R.	2017-2020	Ningning Zhan Yun Peng Pamela Hilliard Victor Blanchette
<b>2016</b> Can Ultrasound “See” What Clinicians Cannot in Hemophilic Arthropathy? Point-of-Care Ultrasound and Physical	Access to Insight Clinical Research Grant (Novo Nordisk)	\$211,275	Doria A.S.	2016-2018	Victor Blanchette Pamela Hilliard Jennifer Stimec

Examination  
Perspectives

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**2016**

Gadolinium Enhancement in Paediatric Sacroiliac Joint Magnetic Resonance Imaging: Is It Really Necessary?	SPARCC Research Pilot Project Program	\$25,000	Rumsey D.	2016-2017	Andrea S. Doria, Jacob Jaremko J, Shirley Tse, Jennifer Stimec, Nina Stein
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**2015**

Development of a Joint Visualizer for Stages of Hemophilic Arthropathy in Ankles	Bayer HealthCare Pharmaceuticals (Canada)	\$22,902	Doria A.S.	2015-2016
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**2015**

A Systematic Review on Ultrasound Imaging as a Diagnostic Tool for Assessment of Hemophilic Arthropathy	Novo Nordisk	\$55,000	Doria A.S.	2015-2016	Victor Blanchette
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**2015**

MRI for Diagnosis of Equivocal Ultrasounds in Suspected Appendicitis: Ultrasound First, MRI Second Approach	Physician's Services Incorporated (PSI) Foundation	\$169,690 (\$134,500)	Doria A.S.	2015-2017	Suzanne Schuh Co-PI) Paul Wales George Tomlinson Wendy Ungar
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**2015**

Li Fraumeni Syndrome: Applying Genetic Determinants of Cancer Risk to Cancer	Terry Fox Foundation	\$2,249,993 Project 3 (Imaging): \$646,963	Malkin D. (Nominated PI) Doria A.S. (PI Project 3)	2015-2018	Anna Goldenberg Adam Shlien Jason Bernan
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Surveillance  
and Prevention**2015**

FAZA Molecular Imaging of Hypoxia in Childhood Sarcomas: Feasibility Steps Towards Personalized Medicine	Garron Family Cancer Centre	\$49,908	Doria A.S.	2015-2016	Amer Shammas Reza Vali Abha Gupta David Malkin Joseph Fisher Hai-Ling Cheng Gino Somers Rahim Moineddin
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**2014**

Functional MR Imaging of Hypoxia in Childhood Sarcomas: Feasibility Steps Towards Personalized Medicine	Society of Pediatric Radiology	\$63,051 (US \$49,595)	Doria A.S.	2015-2016	Amer Shammas Reza Vali Abha Gupta David Malkin Joseph Fisher Hai-Ling Cheng Gino Somers Rahim Moineddin
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**2013**

Simple Bone Cysts in Kids	Canadian Institutes of Health Research (CIHR)	\$968,080	Wright J.G.	July 1, 2013 – 2018	Andrea S. Doria, Hopyan Sevan
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**TOTAL (Active Grants)**

CAD\$  
**2,351,467**  
**(as PI)**  
+ CAD\$  
\$968,080 (as  
Co-  
Investigator)

Note: None of the aforementioned research projects have a direct relationship with the current application. Concerning the project entitled BOLD / Diffusion-Weighted MR Imaging of Hypoxia in Childhood Sarcomas its objective is to test the feasibility of using Blood Oxygen Level Dependent [BOLD] and Diffusion-Weighted [DW] MRI quantification of hypoxia measurements to determine “response to therapy” of pediatric STS in comparison with the conventional RECIST criteria which is considered a poor indicator of treatment response.

**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

<b>FULL NAME:</b> Jason Noah Berman	
POSITION TITLE: Professor, Departments of Pediatrics, Microbiology & Immunology, and Pathology	
Associate Chair Research, Department of Pediatrics	
INSTITUTION: IWK Health Center/ Dalhousie University	
FULL ADDRESS: 5850/5980 University Ave. P.O. 9700, Halifax, NS B3K 6R8	
TELEPHONE: 902-470-8048	EMAIL: jason.berman@iwk.nshealth.ca
WEB-ADDRESS:	

**ACADEMIC BACKGROUND**

Degree Type	MM/YY	Discipline/Field/Specialty	Institution & Country
Post-doc	2005	Molecular Oncology	Dana-Farber Cancer Institute/Harvard Medical School
Fellowship	2004	Pediatric Oncology	Boston Children's Hospital/Harvard Medical School
Residency	2000	Pediatrics	Hospital for Sick Children, Toronto, Ontario
M.D.	1997	Faculty of Medicine	University of Toronto, Toronto, Ontario
BSc.	1993	Biology	York University, Toronto, Ontario

**WORK EXPERIENCE**

Position, Organization	Department/Division	Start Date	End Date
Interim Vice President Research, IWK Health Centre		2017	Present
Associate Chair Research, Dalhousie University	Department of Pediatrics	2017	Present
Full Professor, Dalhousie University	Depts. of Pediatrics, Pathology and Microbiology & Immunology, Faculty of Medicine	2016	Present
Director, Clinician Scientist Graduate Program, Dalhousie University		2014	Present
Director, Clinician Investigator Program, Royal College of Physicians and Surgeons of Canada, Dalhousie University		2014	Present
Associate Professor, Dalhousie University	Depts. of Pediatrics, Pathology and Microbiology & Immunology, Faculty of Medicine	2011	2016
Assistant Professor, Dalhousie University	College of Pharmacy	2010	2011
Associate Professor, Dalhousie University	Depts. of Pediatrics and Microbiology & Immunology, Faculty of Medicine	2005	2011
Research Fellow, Harvard Medical School		2004	2005
Staff Scientist, Children's Hospital, Boston		2004	2005
Research Associate, DFCI	Department of Pediatric Oncology	2004	2005
Research Fellow, DFCI	Department of Pediatric Oncology	2002	2004
Clinical Fellow, DFCI, Boston Children's Hospital/Harvard Medical School	Department of Pediatric Hematology/Oncology	2001	2004
Associate Chief Resident, Hospital for Sick Children	Department of Pediatrics	2000	2001

**A. Personal Statement (max one page)**

*Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.*

My laboratory is expert in generating zebrafish models of childhood cancer using both transgenic and xenograft approaches. We have pioneered primary leukemia xenografts into zebrafish embryos and have optimized assays to evaluate proliferation and cell migration of both leukemia cells and solid tumors. We are also the first lab to identify zebrafish mast cells and demonstrate conserved development and function to their mammalian counterparts. I have clinical expertise in childhood myeloid disease and am co-chair of AAML1531, a Phase III Children's Oncology Group study of risk-stratified therapy for AML in Down syndrome. My goal is to translate findings from our zebrafish models to improve the outcome for childhood cancers, mast cell diseases and other rare genetic disorders.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (max four pages)**

*In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).*

1. My laboratory was the first to identify and characterize a mast cell lineage in the zebrafish, and demonstrate conserved function with its mammalian counterpart, thereby expanding the profile of identifiable immune cells in this organism and demonstrating that the opportunities afforded by the zebrafish system for interrogating other blood lineages can be applied to mast cell development. We provided new insights into mast cell fate determination by demonstrating that dependence on the Notch pathway for mast cell development in the zebrafish. We modeled the human disease, systemic mastocytosis, in the zebrafish using transgenic techniques, providing an *in vivo* model for drug screening.

  - a. Dobson JT, Seibert J, Teh EM, Da'as S, Fraser RB, Paw BH, Lin TJ and Berman JN. Carboxypeptidase A5 identifies a novel mast cell lineage in the zebrafish providing new insight into mast cell fate determination. *Blood*. 2008 Oct 1;112(7):2969-72. PMID: 18635811
  - b. Da'as SI, Teh EM, Dobson JT, Nasrallah GK, McBride ER, Wang H, Neuberg DS, Marshall JS, Lin TJ, and Berman JN. Zebrafish mast cells possess an Fc $\epsilon$ RI-like receptor and participate in innate and adaptive immune responses. *Dev Comp Immunol.*, 2011 Jan; 35(1):125-34. PMID: 20849876
  - c. Da'as SI, Coombs AJ, Balci TB, Grondin CA, Ferrando AA, and Berman JN. The zebrafish reveals dependence of the mast cell lineage on Notch signaling *in vivo*. *Blood*, 2012 Apr 12;119(15):3585-94. PMID: 22368273
  - d. Balci TB, Prykhozhij SV, Teh EM, Da'as SI, McBride E, Liwski R, Chute IC, Leger D, Lewis SM, and Berman JN. A transgenic zebrafish model expressing KIT-D816V recapitulates features of aggressive systemic mastocytosis. *Br J Haematol* 2014 Oct;167(1):48-61. PMID: 24989799
2. My laboratory has also pioneered the xenotransplantation of human breast cancer, leukemia and sarcomas into zebrafish embryos, developed quantitative *ex vivo* *in silico* cell proliferation and *in vivo* cell migration assays and demonstrated the ability to chemically target molecular abnormalities inherent in the human cancer cells by exposure of the embryo to the compound in question. We have used this approach to test novel compounds in acute myeloid leukemia and demonstrate drug response-tumour genotype correlations in primary patient derived T-cell acute lymphoblastic leukemia (T-ALL) samples. We also used T-ALL zebrafish xenografts to reveal that novel cardioprotectant drugs identified in a small molecule screen conducted by the Peterson laboratory (Mass Gen Hospital) in zebrafish embryos treated with doxorubicin did not compromise leukemic cytotoxicity while mitigating cardiotoxicity, demonstrating the ability of the zebrafish xenograft model to serve as a valuable *in vivo* platform for evaluating both drug efficacy and toxicity. We have also adapted this approach to examine cancer cell migration and metastasis and applied this to sarcomas, breast cancer, prostate cancer, and neuroblastoma. In collaboration with

the Sorensen laboratory at the University of British Columbia/BC Cancer Agency, we revealed that the Y-Box 1 transcription/translation factor is a critical player in sarcoma metastasis and directly regulated HIF1 $\alpha$  expression.

- a. Corkery D, Dellaire G, Berman JN. Leukemia xenotransplantation in zebrafish - chemotherapy response assay in vivo. *Br J Haematol.*, 2011 Jun;153(6):786-9. PMID: 21517816
  - b. Liu Y, Asnani A, Zou L, Bentley VL, Yu M, Wang Y, Dellaire G, Sarkar KS, Dai M, Chen HH, Sosnovik DE, Shin JT, Haber DA, Berman JN, Chao W, and Peterson RT. Visnagin protects against doxorubicin-induced cardiomyopathy through modulation of mitochondrial malate dehydrogenase. *Science Transl Med.* 2014; 6(266):266ra170 PMID: 25504881
  - c. Veinotte CJ, Dellaire G, and Berman JN. Hooking the Big One: The Potential of Zebrafish Xenotransplantation to Reform Cancer Drug Screening in the Genomic Era. *Dis Mod Mech* 2014 Jul;7(7):745-54. PMID: 24973744
  - d. Bentley VL, Veinotte CJ, Corkery D, Pinder J, Leblanc MA, Bedard K, Weng AP, Berman JN\*and Dellaire G.\* Focused chemical genomics using zebrafish xenotransplantation as a pre-clinical therapeutic platform for T-cell acute lymphoblastic leukemia. *Haematologica.* 2015 Jan;100(1):70-6 PMID 25281505 \*Co-corresponding authors
  - e. El-Naggar AM, Veinotte CJ, Tognon CE, Corkery DP, Cheng H, Tirode F, Grunewald TGP, Kyle AH, Baker JH, Mathers J, Somasekharan SP, LePard NE, McKinney S, Bennewith KL, Minchinton AI, Delattre O, Wang Y, Dellaire G, Berman JN, and Sorensen PH, Translational activation of HIF1 $\alpha$  by YB-1 promotes sarcoma metastasis. *Cancer Cell*, 2015 May 11;27(5):682-97. PMID: 25965573
3. Together with the Sorensen laboratory at the University of British Columbia/BC Cancer Agency, we demonstrated that loss of the HACE1 tumour suppressor protein results in elevated NADPH oxidase-mediated reactive oxygen species. We have recently determined that this conserved ubiquitin-dependent molecular mechanism that controls Rac1-dependent NOX complexes in cancer, also underlies the role of HACE1 in cardiac development, constituting the first known example of a tumor suppressor that directly regulates ROS in vertebrates.
- a. Daugaard M, Nitsch R, Razaghi B, McDonald L, Jarrar A, El-Naggar A, Rotblat B, Li L, Castillo-Lluva, Malliri A, Berman JN, Penninger JM, and Sorensen PHB. Hace1 controls ROS generation of vertebrate Rac1-dependent NADPH oxidase complexes. *Nat Commun.*, 2013;4:2180. PMID: 23864022
  - b. Razaghi B, Steele SL, Prykhozhij SV, Hill JA, Cooper MD, McDonald L, Lin W, Daugaard M, Chute I, Leger D, Lewis S, Scott IC, Sorensen PHB, and Berman JN. Hace1 influences zebrafish cardiac development via ROS-dependent mechanisms (under review)
4. Using transgenic approaches with generated a zebrafish model of high risk acute myeloid leukemia expressing the human *NUP98-HOXA9* fusion gene. We demonstrated that adult fish develop a myeloproliferative neoplasm in approximately 25% of cases and embryos have perturbed hematopoiesis with myeloid cell expansion at the expense of erythropoiesis. We subsequently used this model to evaluate downstream targets in this subtype of leukemia and found overexpression of DNA methyltransferase 1 (dnmt1) for the first time. We also found high DNMT1 levels associated with poor outcome in human AML. We determined that treatment with demethylating agents and other epigenetic regulators could restore normal blood cell development in our zebrafish model, identifying a new class of potential therapeutic agents in this disease.
- a. Forrester AM, Grabher C, McBride ER, Boyd ER, Vigerstad MH, Kai F-B, Da's SI, Edgar A, Payne E, Look AT, Berman JN. NUP98-HOXA9-transgenic zebrafish develop a myeloproliferative neoplasm and provide new insight into mechanisms of myeloid leukemogenesis. *Br J Haematol.* 2011 Oct;155(2):167-81. PMID: 21810091
  - b. Deveau AP, Forrester AM, Coombs AJ, Wagner GS, Grabher C, Chute I, Leger D, Mingay M, Alexe G, Rajan V, Liwski R, Hirst M, Stegmaier K, Lewis S, Look AT and Berman JN. Epigenetic therapy restores normal

- Early tumor detection and prevention in Li-Fraumeni Syndrome  
Berman, Jason  
hematopoiesis in a zebrafish model of NUP98-HOXA9-induced myeloid disease. *Leukemia*, Leukemia. 2015 Oct;29(10):2086-97. PMID: 26017032
- c. Deveau AP, Bentley VL, Berman JN. Using zebrafish models of leukemia to streamline drug screening and discovery *Exp Hematol* 2016 Oct 6. PMID: 27720937
5. We have been developing means to optimize the use of the CRISPR/Cas9 genome editing system in zebrafish and developed an in silico tool to facilitate the design of guide RNAs (<http://www.multicrispr.net>), particularly for targeting multiple paralogous genes simultaneously or identifying unique sites in the genome. We have developed unique tools to functionally validate CRISPR-induced frameshift mutations and have applied these to develop models of rare genetic disorders.
- Prykhozhij SV, Rajan V, Gaston D, and Berman JN, CRISPR MultiTargeter: a web tool to find common and unique CRISPR single guide RNA targets in a set of similar sequences. *PLoS One*. 2015 Mar 5;10 PMID: 25742428
  - Prykhozhij SV, Rajan V, Berman JN. A Guide to Computational Tools and Design Strategies for Genome Editing Experiments in Zebrafish Using CRISPR/Cas9. *Zebrafish*. 2016 Feb;13(1):70-3. PMID: 26683213
  - Cesar SA, Rajan V, Prykhozhij SV, Berman JN, Ignacimuthu S. Insert, remove or replace: A highly advanced genome editing system using CRISPR/Cas9. *Biochim Biophys Acta*. 2016 Sep;1863(9):2333-44. Epub 2016 Jun 24. PMID: 27350235
  - Prykhozhij SV, Steele SL, Razaghi B, Berman JN. A rapid and effective method for screening, sequencing and reporter verification of engineered frameshift mutations in zebrafish *Dis Mod Mech* 2017 Jun 1;10(6):811-822 (cover image).

#### C. Honours & Awards

List any honours and personal awards in chronological order.

- 1993 – 1995 **Walter F. Watkins Scholarship**, Faculty of Medicine, University of Toronto For high academic standing in the first and second medical years
- 1993 – 1997 **Honours Standing**, Years 1-4, Faculty of Medicine, University of Toronto
- 2001 **Pediatric Scientist Development Program**, Fellowship Award (commencing June 2003)
- 2002 **Abraham Fellowship** – Dana-Farber Cancer Institute, Boston, MA
- 2003 **Molecular Biology in Clinical Oncology Workshop Travel Award** – American Academy of Cancer Research
- 2005 **Terry Fox Foundation Post MD Research Fellowship** – National Cancer Institute of Canada (application ranked first in this category) - declined
- 2011 **Peggy Davison Clinician Scientist Award** – Cancer Care Nova Scotia
- 2012 **Excellence in Innovation Award** – Cancer Care Nova Scotia to the Berman Laboratory
- 2016 **Research Excellence Award (Senior Investigator)** – Department of Pediatrics, Dalhousie University

#### D. Overview & Details of Research Support

Provide an overview of your current areas of research focus including supports of your research / laboratory. Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.

##### **Current Research Support**

Funding Source & Program Name: Rare Disease Models and Mechanisms Network (CIHR) – renewal grant

Project Title: Profound eosinophilia and immune dysregulation caused by JAK1 A634D gain-of-function mutations- phenotype evaluation in the zebrafish model

Your Role: (PI, co-PI, collaborator etc) PI

Total Award: 25,000

Total Award to You: 25,000

Start Date: 08/2017

## Early tumor detection and prevention in Li-Fraumeni Syndrome

Berman, Jason

End Date: 07/2018

Main Objective: Develop a transgenic zebrafish model of the human JAK1A634D mutation to characterize the impact on hematopoiesis.

Outline of Methodology: Zebrafish transgenesis, whole mount *in situ* hybridization, RNASeq

Budget Details: 16,000 personnel; 9,000 reagents, fish care

Personnel Details: 0.4 post-doctoral fellow

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name:

Project Title: Preclinical therapeutic development of targeted cardioprotectants for use in cancer patients receiving anthracycline chemotherapy

Your Role: (PI, co-PI, collaborator etc) co-applicant

Total Award: 188,356

Total Award to You: 30,000

Start Date: 02/2017

End Date: 01/2019

Main Objective: Develop CRISPR induced zebrafish models of mutations found to impact cardiotoxicity from anthracycline chemotherapy and test prospective compounds in these models

Outline of Methodology: CRISPR based genome editing, zebrafish human cancer cell xenotransplantation, drug applications

Budget Details: \$15,000/yr for student salary support and reagents to conduct zebrafish studies

Personnel Details: 0.25 graduate student, undergraduate student

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Beatrice Hunter Cancer Research Institute Seed Grant

Project Title: An *in vivo* model to study gold-nanoparticle aided radiotherapy using a photon beam generated from a low Z target

Your Role: (PI, co-PI, collaborator etc) co-PI

Total Award: 10,000

Total Award to You: 10,000

Start Date: 01/2017

End Date: 12/2017

Main Objective: The goals of this project are to 1) develop a zebrafish xenograft model with which irradiation with clinical linacs can be used to study radiosensitivity in different types of tumours; 2) study the efficacy of GNP activation with low Z target-generated beams; 3) study the *in vivo* efficacy of GNP cancer treatment in the xenograft model.

Outline of Methodology: 1) Proliferation assay: Cells will be co-labelled *in vitro* with GNPs and a lipophilic fluorescent dye. Labelled cells will be injected into the yolk sac of dechorinated zebrafish embryos (Casper) which will subsequently be irradiated using the low-Z target beam or a conventional target beam at the Nova Scotia Cancer Centre. Tumor progression and other downstream effects of radiotherapy will be compared. (2) GNPs will be injected intravenously in (*Fli1a:EGFP*) fish which have fluorescent vasculature. They will subsequently be immobilized and irradiated using the low-Z target beam or a conventional target beam. Damage to the endothelium will be assessed via microscopy.

Budget Details: AuroVist 15 nm gold nanoparticles (Nanoprobes) \$270/40 mg vial, microCT facility \$150/hr, Core facility costs (FACS, confocal microscopy, IHC)

Personnel Details: radiation oncology resident (no salary support); Honours undergraduate student (no salary support); summer technician

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Rare Disease Catalyst Network (CIHR)

Project Title: ADAM10 and IQGAP1 as novel causes of FEVR (familial exudative vitreoretinopathy)

Your Role: (PI, co-PI, collaborator etc) PI

Total Award: 25,000

Total Award to You: 25,000

Start Date: 01/2017

End Date: 12/2017

Main Objective: Develop zebrafish models of two recently identified putative causes of FEVR

Outline of Methodology: Definitive knock-out will be accomplished using CRISPR/Cas9 genome editing. CRISPR/Cas9-based knock-out will be facilitated using CRISPR MultiTargeter software that we developed, which is specifically geared toward finding common sgRNA sites in paralogous or duplicated genes, thus enabling targeting two or more genes with the same sgRNA(s). After the initial injections, fish carrying single or double mutations can be identified and then bred to produce relevant mutants.

Budget Details: 0.33 research associate, CRISPR and *in situ* reagents, confocal microscope service fee

Personnel Details: 0.33 research associate

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Beatrice Hunter Cancer Research Institute Bridge Grant

Project Title: The microenvironment as a therapeutic target in high risk neuroblastoma

Your Role: (PI, co-PI, collaborator etc) PI

Total Award: 25,000

Total Award to You: 25,000

## Early tumor detection and prevention in Li-Fraumeni Syndrome

Berman, Jason

Start Date: 11/2016

End Date: 10/2017

Main Objective: Exploit cytokine expressing zebrafish developed in the lab to examine the impact of these factors on neuroblastoma cell metastasis.

Outline of Methodology: Xenotransplantation of neuroblastoma cell lines and primary samples into cytokine zebrafish, proliferation and migrations studies, CRISPR-based kinase screen

Budget Details: Salary budget includes 0.5 FTE of an experienced technician or research associate for xenotransplant studies, approx. annual salary of \$32,000/year + 21% benefits in accordance with institutional policy (PhD students Jaime Wertman and Vinothkumar Rajan are independently funded). Consumable supplies include zebrafish husbandry supplies, tissue culture supplies (ex. DMEM and FBS), AMD3100, Addgene pooled library, and lentiviral reagents. Professional services includes flow cytometry services and microscope maintenance contracts.

Personnel Details: 0.5 technician, 2 graduate students

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: ACOA, Atlantic Innovation Fund

Project Title: A Scientific and Clinical Hub for Orphan Drug Development

Your Role: (PI, co-PI, collaborator etc)

Total Award: 4.5M

Total Award to You: 773,106

Start Date: 09/2016

End Date: 08/2012

Main Objective: Develop zebrafish models of neuromuscular diseases and other rare genetic disorders

Outline of Methodology: CRISPR and transgenic based strategies

Budget Details: 75,000 salary support for research associates; 75,000 consumables and reagents

Personnel Details: 2x 0.5 research associates

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Ewing Cancer Foundation of Canada/C17 Canadian Childhood Cancer Network

Project Title: Stromal Antigen 2 (STAG2): A novel metastatic pathway in Ewing sarcoma

Your Role: (PI, co-PI, collaborator etc) PI

Total Award: 100,000

Total Award to You: 100,000

Start Date: 07/16

End Date: 06/18

Main Objective: Determine the role of loss of STAG2 on the metastatic potential of Ewing sarcoma in the zebrafish model

Outline of Methodology: xenotransplantation of STAG2 CRISPR KO cell lines into zebrafish embryos, evaluation of migration and proliferation

Budget Details: 30,000 per year towards grad student salary and technician support; 20,000 per year for consumables

Personnel Details: full time grad student, 0.33 technician

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Leukemia Lymphoma Society of Canada Operating Grant

Project Title: Elucidating pathogenesis and downstream targets in NUP98-NSD1 induced AML

Your Role: (PI, co-PI, collaborator etc)

Total Award: 160,000

Total Award to You: 160,000

Start Date: 07/16

End Date: 06/18

Main Objective: Characterize a transgenic zebrafish model of NUP98-NSD1 AML and identify downstream pathways and screen for compounds that restore normal hematopoiesis.

Outline of Methodology: Transgenic zebrafish generation, whole mount *in situ* hybridization on embryos, histology and immunohistochemistry on adult transgenic fish, RNASeq and ChIPSeq on embryos

Budget Details: 40,000 per year salary support 40,000 consumables including *in situ* reagents, animal costs, RNASeq and ChIPSeq

Personnel Details: full time graduate student and 0.5 research associate

Relationship to and overlap with 2018 PPG application: none

Funding Source & Program Name: Canadian Cancer Society Research Institute (CCSRI) Innovation Grant

Project Title: Contribution of the tumour microenvironment to the progression of the myeloid leukemia of Down syndrome: *In vivo* analysis using a zebrafish-based approach

Your Role: (PI, co-PI, collaborator etc) PI

Total Award: 200,000

Total Award to You: 200,000

Start Date: 02/16

End Date: 01/18

Main Objective: Aim 1: To determine the relative importance of GM-CSF/SCF, IGF2 and the SDF1 axis on DS TMD and AML cell behaviour.

## Early tumor detection and prevention in Li-Fraumeni Syndrome

Berman, Jason

*Aim 2: To identify the contribution of genes expressed on chromosome 21 to the tumour microenvironment.*

*Outline of Methodology: Xenografts of DS-AML cell lines and primary patient samples from COG clinical trials into cytokine expressing transgenic zebrafish; cell membrane proteomics screen in DS-AML cells for novel cell surface receptors.*

*Budget Details: 50,000 salary support; 50,000 reagents, fish care, proteomics service costs.*

*Personnel Details: full time graduate student and 0.5 technician*

*Relationship to and overlap with 2018 PPG application: none*

**Funding Source & Program Name:** Canadian Institutes of Health Research (CIHR) Operating Grant

**Project Title:** Mechanisms and Risk Stratification for Treatment of Acute Myeloid Leukemia in Children with Down syndrome

**Your Role:** (PI, co-PI, collaborator etc) co-applicant

**Total Award:** 773,060

**Total Award to You:** 0

**Start Date:** 09/2015

**End Date:** 08/2020

**Main Objective:** Determine if molecularly based minimal residual disease (MRD) testing in DS-AML is superior to flow cytometry based approaches and can allow for more refined therapeutic risk stratification. Identify secondary mutations following the pathognomonic GATA1 mutation and how these contribute

*Outline of Methodology: Error corrected sequencing with validation by digital droplet PCR; next generation sequencing*

*Budget Details: Reagent and personnel costs to the Hitzler and Druley labs*

*Personnel Details: 2 full time research technicians, 1 full time graduate student and 0.5 research associate*

*Relationship to and overlap with 2018 PPG application: none*

**Funding Source & Program Name:** Biomarker, Imaging and Quality of Life Funding Program (BIQSFP) Cancer Therapy Evaluation Program (CTEP), National Cancer Institute

**Project Title:** Risk-Stratified Therapy for Acute Myeloid Leukemia in Down Syndrome

**Your Role:** (PI, co-PI, collaborator etc) PI

**Total Award:** 371,094 (USD)

**Total Award to You:** 0

**Start Date:** 11/2015

**End Date:** 06/2020

**Main Objective:** Fund flow cytometry based minimal residual disease monitoring for patients with Down syndrome and myeloid leukemia on a clinical trial COG AAML1531

*Outline of Methodology: flow cytometry*

*Budget Details: costs of shipping, running samples and technician salaries at Hematologics (Seattle, WA)*

*Personnel Details: technician salaries at Hematologics*

*Relationship to and overlap with 2018 PPG application: none*

**Funding Source & Program Name:** The Terry Fox New Frontiers Program Project Grant - Terry Fox Research Institute -

**Project Title:** The Terry Fox New Frontiers Program Project Grant in Li-Fraumeni Syndrome: Applying Genetic Determinants of Cancer Risk to Cancer Surveillance

**Your Role:** (PI, co-PI, collaborator etc) co-applicant

**Total Award:** 2,249,993

**Total Award to You:** 524,595

**Start Date:** 07/2015

**End Date:** 06/2018

**Main Objective:** Project 4: Develop zebrafish models of Li-Fraumeni syndrome; introduce collaborating mutations; screen for drugs that promote apoptosis in zebrafish models.

*Outline of Methodology: CRISPR-induced genome editing; transgenesis; whole mount *in situ* hybridization; acridine orange; activated caspase 3 assays*

*Budget Details: 95,000 per year in salaries, 80,263 per year in consumables and services*

*Personnel Details: 0.5 post-doctoral fellow, full time research associate, 0.5 technician, 0.1 computational biologist*

*Relationship to and overlap with 2018 PPG application: original PPG application*

**Funding Source & Program Name:** Canada Foundation for Innovation (CFI)

**Project Title:** Research Program for Rare Pediatric Diseases (RaPiD)

**Your Role:** (PI, co-PI, collaborator etc) co-applicant

**Total Award:** 21,000,000

**Total Award to You:** 6.7M to Dalhousie

**Start Date:** 07/2015

**End Date:** 06/2018

**Main Objective:** Infrastructure support for studying rare genetic disorders

*Outline of Methodology: Zebrafish models, imaging, drug screening*

## Early tumor detection and prevention in Li-Fraumeni Syndrome

Berman, Jason

*Budget Details: purchase of an embryo biosorter, Lightsheet microscope, and other equipment*

*Personnel Details: IOF funds to support technical support for biosorter*

*Relationship to and overlap with 2018 PPG application: equipment to be used for PPG project, no scientific overlap*

*Funding Source & Program Name: Canadian Institutes of Health Research (CIHR) Operating Grant*

*Project Title: Inherited bone marrow failure syndromes: from gene discovery to pathobiology*

*Your Role: (PI, co-PI, collaborator etc) Co-applicant*

*Total Award: 760,000*

*Total Award to You: 110,000*

*Start Date: 03/13*

*End Date: 02/18*

*Main Objective: The first 2 specific aims of the study are part of a discovery phase:*

*Aim 1: Discovering novel IBMFS genes and defining novel syndromes*

*Aim 2: Determining whether the candidate novel IBMFS genes are critical for blood cell formation*

*The last 2 aims are a characterization phase using the PARN-associated IBMFS as an example:*

*Aim 3: Dissecting the downstream transcriptome effects of mutations in the novel IBMFS gene, PARN*

*Aim 4: Modeling of the novel PARN-associated IBMFS in zebrafish*

*Outline of Methodology: transgenesis and CRISPR induced genome editing in the zebrafish; fluorescent reporter lines; FACS; whole mount in situ hybridization; RNASeq*

*Budget Details: 0.5 salary support for research assistant and consumables*

*Personnel Details: 0.5 research associate*

*Relationship to and overlap with 2018 PPG application: none*

*Funding Source & Program Name: Canadian Institutes of Health Research (CIHR) Operating Grant*

*Project Title: New insights into mast cell development and contribution to malignant progression –further exploitation of the zebrafish model*

*Your Role: (PI, co-PI, collaborator etc) PI*

*Total Award: 565,415*

*Total Award to You: 565,415*

*Start Date: 03/13*

*End Date: 02/17- extension x 1 yr*

*Main Objective: 1. To identify novel genes involved in MC development using a forward genetic ENU mutagenesis screen.*

*2. To utilize a transgenic zebrafish model of KIT D816V-mediated SM to determine the contribution of molecular pathways, such as mTOR that can be targeted in this disease. 3. To generate a zebrafish MC-specific fluorescent reporter line and employ it in xenograft (XT) experiments to directly observe MC-tumour interactions.*

*Outline of Methodology: ENU mutagenesis; morpholinos; drug screens; whole mount in situ hybridization; transgenesis; xenotransplantation*

*Budget Details: approximately 90,000 in salary support per year; 50,000 in consumables, reagents per year*

*Personnel Details: full time post-doctoral fellow, research assistant, graduate student and technician*

*Relationship to and overlap with 2018 PPG application: none*

## E. List of Publications

*Provide a full list of all your scientific publications.*

### **PEER-REVIEWED PUBLICATIONS (supervised trainees are underlined):**

#### **Published or in progress:**

1. Cloney K, Steele SL, Stoyek M, Croll R, Smith F, Prykhozhij SV, Midgen C, Blake K, **Berman JN**. Intestinal innervation, motility, and morphology defects associated with chd7 loss of function in a zebrafish model of CHARGE syndrome (submitted)
2. Melong N, Steele SL, MacDonald M, Holly A, Collins C, Zoubedi A, **Berman JN\***, Dellaire G\*. Enzalutamide inhibits testosterone-induced growth of human prostate cancer xenografts in zebrafish and can induce bradycardia. *Sci Reports* (under review). \*co-corresponding authors
3. Corkey DP, Clarke L, Gebremeskel S, Salsman J, Pinder J, Le Page C, Xu Z, Mes-Masson A-M, **Berman JN**, Johnston B, Dellaire G. *Oncogene* (under review).

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4. Razaghi B, Steele SL, Prykhozhij SV, Hill JA, Cooper MD, McDonald L, Lin W, Daugaard M, Chute I, Leger D, Lewis S, Scott IC, Sorensen PHB, **Berman JN**. Hace1 influences zebrafish cardiac development via ROS-dependent mechanisms. *Dev Dyn* (under review).
5. Prykhozhij SV, Caceres L, **Berman JN**. New Developments in CRISPR/Cas-based Functional Genomics and their Implications for Research using Zebrafish. *Curr Gene Therapy* (under review).
6. Leung AWY, Veinotte CJ, Melong N, Oh MH, Chen K, Enfield KSS, Backstrom I, Warburton C, Yappa D, **Berman JN**, Bally MB, Lockwood WW. Vivo Validation of PAPSS1 (3'-phosphoadenosine 5'-phosphosulfate synthase 1) as a Cisplatin-Sensitizing Therapeutic Target. *Clin Cancer Res* (in press).
7. Taub JW, **Berman JN**, Hitzler JK, Sorrell AD, Lacayo NJ, Mast K, Head D, Raimondi S, Hirsch B, Ge Y, Gerbing RB, Wang Y, Alonzo T, Campana D, Coustan-Smith E, Mathew P, Gamis AS. Improvement in Outcomes of Patients with Myeloid Leukemia of Down Syndrome: Results of the AAML0431 Trial. A Report from the Children's Oncology Group. *Blood* 2017 Jun 22;129(25):3304-3313.
8. Prykhozhij SV, Steele SL, Razaghi B, **Berman JN**. A rapid and effective method for screening, sequencing and reporter verification of engineered frameshift mutations in zebrafish. *Dis Mod Mech*. 2017 Jun 1;10(6):811-822 (cover image).
9. Barrett R, Morash B, Roback D, Pambrun C, Marfleet L, Ketterling RP, Harrison K, **Berman JN**. A cryptic t(8;16) (p11.2;p13.3) identified by FISH in spontaneously remitting congenital AML: A case for changing current practice. *Ped Blood Cancer* (in press).
10. Couturier AM, Fleury H, Patenaude AM, Bentley VL, Rodrique A, Coulomb Y, Niraj J, Pauty J, **Berman JN**, Dellaire G, DiNoia J, Mes-Masson AM, Masson JY. Roles for APRIN (PDS5B) in homologous recombination and in ovarian cancer prediction. *Nuc Acids Res* 2016 Dec 15;44(22):10879-10897.
11. Deveau AP, Bentley VL, **Berman JN**. Using zebrafish models of leukemia to streamline drug screening and discovery *Exp Hematol*. 2017 Jan;45:1-9.
12. Moore JC, Mulligan TS, Torres Yordán N, Castranova D, Pham VN, Tang Q, Lobbardi R, Anselmo A, Liwski RS, **Berman JN**, Sadreyev RI, Weinstein BM, Langenau DM. T cell immune deficiency in zap70 mutant zebrafish. *Mol Cell Biol*. 2016 Sep [Epub ahead of print]
13. Rajan V, Dellaire G, **Berman JN**. Modeling Leukemogenesis in the Zebrafish Using Genetic and Xenograft Models. *Methods Mol Biol*. 2016;1451:171-89.
14. Ceasar SA, Rajan V, Prykhozhij SV, **Berman JN**, Ignacimuthu S. Insert, remove or replace: A highly advanced genome editing system using CRISPR/Cas9. *Biochim Biophys Acta*. 2016 Sep;1863(9):2333-44. Epub 2016 Jun 24.
15. Wertman J, Veinotte CJ, Dellaire G, **Berman JN**. The Zebrafish Xenograft Platform: Evolution of a Novel Cancer Model and Preclinical Screening Tool. *Adv Exp Med Biol*. 2016;916:289-314.
16. LeBlanc MA, Bettle A, **Berman JN**, Price VE, Pambrun C, Yu Z, Tiller M, McMaster CR, Fernandez CV. Study of Glycine and Folic Acid Supplementation to Ameliorate Transfusion Dependence in Congenital SLC25A38 Mutated Sideroblastic Anemia. *Pediatr Blood Cancer*. 2016 Jul;63(7):1307-9.
17. Sultana S, Truong NY, Vieira DB, Wigger JG, Forrester AM, Veinotte CJ, **Berman JN**, van der Spoel AC. Characterization of the Zebrafish Homolog of  $\beta$ -Glucosidase 2: A Target of the Drug Miglustat. *Zebrafish*. 2016 Jun;13(3):177-87.

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18. J Fernández-Murray JP, Prykhozhij SV, DufayN, Steele SL, Gaston D, Nasrallah GK, Coombs AJ, Fernandez CV, **Berman JN**, and McMaster CR. Glycine and Folate Ameliorate Models of Congenital Sideroblastic Anemia. *PLoS Genetics*. 2016 Jan 28;12(1).
19. Prykhozhij SV, Rajan V, **Berman JN**. A Guide to Computational Tools and Design Strategies for Genome Editing Experiments in Zebrafish Using CRISPR/Cas9. *TechnoFish Methods*. *Zebrafish* 2016 Feb;13(1):70-3.
20. Dhanraj S, Nissbeck M, Pinto D, Deveau AP, Gunja SM, Boonyawat B, Coombs AJ, Mucciolo M, Marozza A, Buoni S, Turner L, Li H, Jarrar A, Sabanayagam M, Kirby M, Shago M, **Berman JN**, Scherer SW, Virtanen A and Dror Y. Poly(A)-specific ribonuclease (PARN) is required for normal hematopoiesis. *J Med Genetics* 2015 Nov;52(11):738-48.
21. Deveau AP, Forrester AM, Coombs AJ, Wagner GS, Grabher C, Chute I, Leger D, Mingay M, Alexe G, Rajan V, Liwski R, Hirst M, Stegmaier K, Lewis S, Look AT and **Berman JN**. Epigenetic therapy restores normal hematopoiesis in a zebrafish model of *NUP98-HOXA9*-induced myeloid disease. *Leukemia*, 2015 Oct;29(10):2086-97.
22. El-Naggar AM, Veinotte CJ, Tognon CE, Corkery DP, Cheng H, Tirode F, Grunewald TGP, Kyle AH, Baker JH, Mathers J, Somasekharan SP, LePard NE, McKinney S, Bennewith KL, Minchinton AI, Delattre O, Wang Y, Dellaire G, **Berman JN**, and Sorensen PH, Translational activation of HIF1a by YB-1 promotes sarcoma metastasis. *Cancer Cell*, 2015 May 11;27(5):682-97.
23. Prykhozhij SV, Rajan V, Gaston D, and **Berman JN**, CRISPR MultiTargeter: a web tool to find common and unique CRISPR single guide RNA targets in a set of similar sequences. *PLoS One*. 2015 Mar 5;10(3):e0119372. doi: 10.1371
24. Liu Y, Asnani A, Zou L, Bentley VL, Yu M, Wang Y, Dellaire G, Sarkar KS, Dai M, Chen HH, Sosnovik DE, Shin JT, Haber DA, **Berman JN**, Chao W, and Peterson RT. Visnagin protects against doxorubicin-induced cardiomyopathy through modulation of mitochondrial malate dehydrogenase. *Science Trans Med*. 2014 Dec 10;6
25. Bentley VL, Veinotte CJ, Corkery D, Pinder J, Leblanc MA, Bedard K, Weng AP, **Berman JN\***and Dellaire G.\* Zebrafish Xenotransplantation and Focused Chemical Genomics: A Preclinical Therapeutic Model For T-Cell Acute Lymphoblastic Leukemia. *Haematologica*. 2015 Jan;100(1):70-6 \*Co-corresponding authors
26. Tang Q, Abdelfattah NS, Blackburn JS, Moore JC, Martinez SA, Moore FE, Lobbardi R, Tenente IM, Ignatius MS, **Berman JN**, Liwski RS, Houvras Y, and Langenau1, DM. Optimized cell transplantation using hypomorphic *rag2* mutant zebrafish. *Nat Methods*. 2014 Aug;11(8):821-4. doi: 10.1038/nmeth.3031. Epub 2014 Jul 20.
27. Veinotte CJ, Dellaire G, and **Berman JN**. Hooking the Big One: The Potential of Zebrafish Xenotransplantation to Reform Cancer Drug Screening in the Genomic Era. *Dis Mod Mech* 2014 Jul;7(7):745-54.
28. Balci TB, Prykhozhij SV, Teh EM, Da'as SL, McBride E, Liwski R, Chute IC, Leger D, Lewis SM, and **Berman JN**. A transgenic zebrafish model expressing KIT-D816V recapitulates features of aggressive systemic mastocytosis. *Br J Haematol* 2014 Oct;167(1):48-61. doi: 10.1111/bjh.12999. Epub 2014 Jul 2.
29. Prykhozhij SV, **Berman JN**. The progress and promise of zebrafish as a model to study mast cells. *Dev Comp Immunol* 2014 Sep;46(1):74-83.
30. Wu Z, Macneil AJ, Junkins R, **Berman JN**, and Lin TJ. Calcineurin-Rcan1 interaction contributes to stem cell factor-mediated mast cell activation. *J Immunol*, 2013 Dec 15;191(12):5885-94.
31. Steele SL, Prykhozhij SV, **Berman JN**. Zebrafish as a model system for mitochondrial biology and diseases. *Transl Res.*, 2014 Feb;163(2):79-98.

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32. Daugaard M, Nitsch R, Razaghi B, McDonald L, Jarrar A, El-Naggar A, Rotblat B, Li L, Castillo-Lluva, Malliri A, **Berman JN**, Penninger JM, and Sorensen PHB. The Hace1 tumor suppressor is an integrated component of the oxidative stress response that regulates NADPH oxidase. *Nat Commun.*, 2013;4:2180.
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38. Berman JN, Payne E, Hall C. The zebrafish as a tool to study hematopoiesis, human blood diseases and immune function. *Adv Hematol*; Epub 2012 Oct 3.
39. Da'as SI, Coombs AJ, Balci TB, Grondin CA, Ferrando AA, and **Berman JN**. The zebrafish reveals dependence of the mast cell lineage on Notch signaling *in vivo*. *Blood*, 2012 Apr 12; 119(15):3585-94.
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44. Corkery D, Dellaire G, **Berman JN**. Leukemia xenotransplantation in zebrafish - chemotherapy response assay *in vivo*. *Br J Haematol*., 2011 Jun;153(6):786-9.
45. **Berman JN**, Gerbing RB, Alonso TA, Ho PA, Miller K, Hurwitz C, Heerema NA, Hirsch B, Raimondi SC, Lange B, Franklin JL, Gamis A, Meshinch S. Prevalence and clinical implications of NRAS mutations in childhood AML: a report from the Children's Oncology Group. *Leukemia*, 2011 Jun;25(6):1039-42.
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47. Da'as S, Teh EM, Dobson JT, Nasrallah GK, McBride ER, Wang H, Neuberg DS, Marshall JS, Lin TJ, and **Berman JN**. Zebrafish mast cells possess an Fc $\epsilon$ RI-like receptor and participate in innate and adaptive immune responses. *Dev Comp Immunol.*, 2011 Jan; 35(1):125-34.
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**BOOKS/JOURNAL ISSUES:**

1. Cancer Genomics: From bench to personalized medicine. (2014) Eds. Graham Dellaire, **Jason N. Berman**, Robert J. Arceci. Elsevier. ISBN-10: 0123969670
2. Zebrafish as a tool to study hematopoiesis, human blood diseases and immune function. (2013) Eds. Hall C, Payne E, **Berman JN**. *Advances in Hematology*. Hindawi Journals.

**BOOK CHAPTERS (trainees are underlined):**

1. Rajan V, Dellaire G and **Berman JN** (2016). "Modeling leukemogenesis in the zebrafish using genetic and xenograft models." *Methods in Molecular Biology*, Humana Press.
2. Wertman J, Veinotte CJ, Dellaire G, **Berman JN** (2016). The zebrafish xenograft platform: evolution of a novel cancer model and preclinical screening tool. *Cancer and Zebrafish: Mechanisms, Techniques, and Models*. Springer Science, Advances in Experimental Medicine and Biology Series.
3. Lubek JE, Shihabi A, Murphy LA, **Berman JN** (2015). Hematopoietic Neck Masses. Atlas Oral Maxillofac Surg Clin North Am.
4. Cochrane DR, Lin D, Dellaire G, Halvorsen EC, **Berman JN**, Wang, Y, Huntsman DG, and Bennewith KL (2014). Animal Models of Metastasis. Genomic Instability and Cancer Metastasis. Springer Science.

5. **Berman JN** and Look AT. (2014) Myeloid Leukemia, Myelodysplasia, and Myeloproliferative Disease in Children. Nathan and Oski's – Oncology of Infancy and Childhood – 8<sup>th</sup> Edition. Saunders Elsevier.
6. Da'as SI, Balci T, Berman JN. (2014) The zebrafish as an *in vivo* tool to study mast cell development and function. Mast Cells - Methods in Molecular Biology. Humana Press.
7. **Berman JN**, Chiu PPL, and Dellaire G. (2014) "Preclinical Animal Models for Cancer Genomics" in Cancer Genomics: From bench to personalized medicine. Eds. Graham Dellaire, Jason N. Berman, Robert J. Arceci. Elsevier. ISBN-10: 0123969670
8. Arceci RJ, **Berman JN**, and Meshinchi S. (2014) "Acute Myeloid Leukemia" in Cancer Genomics: From bench to personalized medicine. Eds. Graham Dellaire, Jason N. Berman, Robert J. Arceci. Elsevier. ISBN-10: 0123969670
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1. Prykhozhij SV, Steele SL, Cloney K, Veinotte C, Razaghi B, Blake K, Shlien A, Malkin D, **Berman JN.** Enhancing functional efficiency of CRISPR/Cas9-mediated genomic engineering for rare disease modelling in zebrafish. 7<sup>th</sup> Strategic Conference of Zebrafish Investigators. Asilomar, CA.
2. Prykhozhij SV, Steele SL, Veinotte CJ, Razaghi B, **Berman JN.** Effective allele-specific PCR assay facilitates genotyping and enrichment of zebrafish with CRISPR/Cas9-mediated knock-ins of defined point mutations Genome Engineering (A2), Keystone, CO.

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3. Prykhozhij SV, **Berman JN.** A rapid and effective method for screening, sequencing and reporter verification of engineered frameshift mutations in zebrafish. 12th International Conference on Zebrafish Development and Genetics @TAGC. Orlando, Florida.
4. Wilson ER, Brodersen LE, Zehentner BK, Menssen AJ, Voight AP, Pardo L, Wells DA, Hitzler J, **Berman JN**, Alonso TA, Kahwash SB, Meshinchi S, Loken MR. Down Syndrome AML Is Unique in Phenotype Both at Diagnosis and in Post Chemotherapy Regeneration. Blood 2016 128:1687. 58th Annual Meeting of the American Society of Hematology, San Diego, CA.
5. Garshot D, Melong N, Sarker TT, Xi Y, Brownell A, Callahan M, **Berman JN**, Fribley A. The Novel Sulfonamidebenzamide ML291 Activates Apoptotic UPR Signaling in Pediatric Leukemia. Blood 2016 128:3523; 58th Annual Meeting of the American Society of Hematology, San Diego, CA.

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6. Rajan V, Melong N, Campbell CJV, Dellaire G, **Berman JN.** A Humanized Zebrafish Transplant Model Expressing CXCL12 Provides an Enhanced In Vivo Therapeutic Screening Platform for T-ALL. 57<sup>th</sup> Annual Meeting of the American Society of Hematology, Orlando, Florida.
7. Deveau AP, Coombs AJ, Dhanraj S, Wagner G, Dror Y, **Berman JN.** The Zebrafish Provides Mechanistic Insights into the Role of Poly (A)-Specific Ribonuclease (PARN) in Hematopoietic Stem Cell (HSC) Homeostasis and Bone Marrow Failure. 57<sup>th</sup> Annual Meeting of the American Society of Hematology, Orlando, Florida.

- Early tumor detection and prevention in Li-Fraumeni Syndrome Berman, Jason
8. Filiaggi C, Deveau AP, Prykhozij S, Dellaire G, **Berman JN**. Fishing with a Transgenic Line: Using Zebrafish to Elucidate Mechanisms and Therapeutics in NUP98-NSD1 AML. 57<sup>th</sup> Annual Meeting of the American Society of Hematology, Orlando, Florida.
9. Dhanraj S, Gunja S, Deveau AP, Nissbeck M, Boonyawat B, Coombs AJ, Renieri A, Mucciolo M, Marozza A, Buoni S, Turner L, Li H, Jarrar A, Sabanayagam M, Kirby M, Shago M, Pinto D, **Berman JN**, Scherer SW, Virtanen A, Dror Y. Bone marrow failure and developmental delay caused by mutations in poly(A)-specific ribonuclease. 57<sup>th</sup> Annual Meeting of the American Society of Hematology, Orlando, Florida.
10. Wertman JN, Razaghi B, Prykhozij S, Dellaire G, Sorensen PHB, Irwin M, **Berman JN**. Investigation of the role of the HACE1 tumor suppressor in high risk pediatric neuroblastoma. Canadian Cancer Research Conference, Montreal, QC.
11. Arumuggam N, Too CKL, **Berman JN**, Rupasinghe V. Phloridzin docosahexaenoate (PZ-DHA), a novel polyphenolic derivative shows cytotoxic effects against human leukemia cells. Canadian Cancer Research Conference, Montreal, QC.
12. Deveau AP, Filiaggi C, Forrester AM, Coombs AJ, Wagner GS, Mingay M, Alexe G, Stegmaier K, Hirst M, **Berman JN**. Preclinical determination of the efficacy of epigenetic therapy in pediatric and adult high-risk myeloid disease using the zebrafish model. Canadian Cancer Research Conference, Montreal, QC.
13. Corkery DP, Gebremeskel S, Johnston B, **Berman JN**, Dellaire G. PRP4K: a mediator of chemoresistance and ascites development in ovarian cancer. Canadian Cancer Research Conference, Montreal, QC,
14. Holly AC, MacDonald M, Corkery DP, **Berman JN**, Dellaire G, Zoubeidi A. Zebrafish Xenograft: A model for Prostate Cancer. Canadian Cancer Research Conference, Montreal, QC.
15. Pringle ES, Coombs AJ, Veinotte C, Robinson C-A, Ha MN, Dellaire G, **Berman JN**, McCormick C. A zebrafish model for primary effusion lymphoma. Canadian Cancer Research Conference, Montreal, QC.
16. Rajan V, Prykhozij S, Pandey A, Rainey J, Dellaire G, **Berman JN**. Development of novel cell-based and zebrafish transgenic strategies to screen for KIT dimerization inhibitors. Canadian Cancer Research Conference, Montreal, QC.
17. Veinotte CJ, Melong N, El-Nagger A, Crompton B, Dellaire G, Stegmaier K, Sorensen PHB, **Berman JN**. Using zebrafish to investigate molecular players influencing Ewing sarcoma proliferation and metastasis. Canadian Cancer Research Conference, Montreal, QC
18. Steele SL, Cloney K, Stoyek M, Smith F, Blake K, **Berman JN**. Direct visualization of gastrointestinal morphology and motility changes associated with chd7 loss of function in a zebrafish (*Danio rerio*) model of CHARGE syndrome. 12th International CHARGE Syndrome, Chicago, IL.
19. Porter R, Cummings E, Coombs AJ, Kelly M, **Berman JN**. "Using a Zebrafish Model to Screen the in-vivo Cell-Specific actions of Cannabinoid-2 Receptor Ligands in Systemic Inflammation," International Cannabinoid research Society Conference, Wolfville, Nova Scotia.
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25. Taub JW, **Berman JN**, Hitzler JK, Sorrell AD, Lacayo NJ, Mast K, Head DR, Raimondi SSC, Hirsch BA, Gerbing RB, Alozno TA, Capmana D, Coustan-Smith E, Mathew P, Gamis AS. "Improvement in Treatment Outcome and Identification of a New Prognostic Parameter in Down Syndrome Acute Myeloid Leukemia (DS-AML): Results of the Children's Oncology Group (COG) Phase III AAML0431 Trial," Oral Abstract #278 American Society of Hematology Annual Meeting, San Francisco, CA, Blood December 06, 2014; 124
26. Deveau AP, Forrester AM, Coombs AJ, Wagner GS, Grabher C, Chute I, Leger D, Lewis S, Mingay M, Hirst M, Look AT, **Berman JN**, "Preclinical Determination of the Efficacy of Epigenetic Therapy in High Risk Myeloid Disease Using the Zebrafish Model" Oral Abstract #436 American Society of Hematology Annual Meeting, San Francisco, CA, Blood December 06, 2014; 124
27. Veinotte CJ, Crompton B, Melong N, Fraser K, Sorensen PB, Dellaire G, Stegmaier K, **Berman JN**. "Using Zebrafish Xenotransplantation to Evaluate Anti-Cancer Drug Efficacy: Examining the Impact of Focal Adhesion Kinase Inhibition on Ewing's Sarcoma Cell Proliferation and Metastasis" Poster 11th International Conference on Zebrafish Development and Genetics, Madison, WI.
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29. Razaghi B, Steele SL, McDonald L, Lin W, Daugaard M, Scott IC, Sorensen PHB, **Berman JN**, "Hace1 influences oncogenesis and vertebrate cardiac development via ROS-dependent mechanisms" Poster 11th International Conference on Zebrafish Development and Genetics, Madison, WI.
30. Bentley VL, Veinotte CV, Corkery DP, Pinder JB, LeBlanc MA, Bedard K, Weng AP, **Berman JN**, Dellaire G. "Zebrafish xenotransplantation identifies a targetable NOTCH1 mutation in a child with T-cell acute lymphoblastic leukemia" Poster Zebrafish Disease Models 7, Madison, WI.
31. Prykhozhij SV, Rajan V, **Berman JN**. "CRISPR MultiTargeter in zebrafish: a bioinformatics tool to find common and unique CRISPR guide RNA targets of any type in a set of similar sequences" Poster 11th International Conference on Zebrafish Development and Genetics, Madison, WI.
32. Steele SL, Prykhozhij SV, Nasrallah GK, Poon PP, Coombs AJ, Robinson CA, McMaster C, **Berman JN**. "The zebrafish pycr1/2 knockdown model of autosomal recessive cutis laxa, a disease affecting proline biosynthesis" Poster Zebrafish Disease Models 7, Madison, WI.

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34. Rajan V, Prykhozhij SV, **Berman JN**. "Development of Novel Cell-based and Zebrafish Transgenic Strategies to screen for KIT dimerization inhibitors" Poster 11th International Conference on Zebrafish Development and Genetics, Madison, WI.
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37. Razaghi B, Steele SL, McDonald L, Lin W, Daugaard M., Scott IC, Sorensen PH, **Berman JN**. "Hace1 influences oncogenesis and vertebrate cardiac development via ROS-dependent mechanisms". Canadian Zebrafish Conference, Mont-Tremblant, QC.
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42. Prykhozhij SV, Fernandez-Murray P, Nasrallah G, Dufay N, Fernandez CV, Jarrar A, Coombs AJ, McMaster C, **Berman JN**, "A combination of glycine and sodium folate strongly ameliorates the anemic phenotype of the zebrafish Congenital Sideroblastic Anemia model induced by slc25a38a and slc25a38b knockdown" Poster 8th European Zebrafish Meeting, Barcelona, Spain.
43. Prykhozhij SV, Nasrallah GK, Poon PP, Coombs AJ, Robinson C, McMaster C, **Berman JN**, "Characterization of zebrafish lacking pycr1 and 2 as a model of cutis laxa, a disease of proline biosynthesis, reveals metabolic and developmental defects as well as specific p53-mediated cell death" Poster 8th European Zebrafish Meeting, Barcelona, Spain.
44. **Berman JN**, Veinotte C, Corkery D, Bentley V, Thompson A, El-Naggar A, Weng A, Sorensen PB, Dellaire G, "From Fins to Pharma: The zebrafish as an emerging preclinical model to personalize childhood cancer therapy" Invited Abstract Paediatric Cancer Research at the Interface, Vienna, Austria.

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53. **Berman JN**, Corkery D, Veinotte C, Balci TB, Forrester AM, Thompson A, Sorensen PB, Weng A, Dellaire G. "A zebrafish xenograft platform as an in vivo tool for drug screening and personalized cancer therapy" Poster Personalized Cancer Care: Risk prediction, early diagnosis, progression and therapy resistance, Oslo, Norway.
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63. Veinotte CJ, El-Naggar A, Corkery D, Dellaire G, Bernstein ML, Sorensen PHB, **Berman JN**, "Zebrafish and murine renal sub-capsule xenografts identify a role of Y-Box binding protein (YB-1) in the metastasis of Ewing family tumors." Abstract Translational Pediatric Cancer Genomics Meeting, Scottsdale, AZ.
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67. Forrester AM, Grabher C, Look AT, **Berman JN**. "NUP98-HOXA9 drives high-risk myeloid leukemia in zebrafish – a platform to study  $\beta$ -catenin and perform drug discovery." Abstract 7th European Zebrafish Genetics and Development Meeting, Edinburgh, Scotland.
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78. Da'as S, Ferrando A, **Berman JN**, "Notch signaling is required for mast cell development in the zebrafish." Abstract The 9th International Conference on Zebrafish Development & Genetics, Abstract #181, Madison, WI
79. Da'as S, Balci TB, McBride ER, Klein LR, Teh EM, Ferrando A, **Berman JN**, "Notch Signaling is required for mast cell development in the zebrafish and may represent a novel therapeutic strategy in systemic mastocytosis. Platform Presentation" Abstract Zebrafish Disease Modeling III: Cancer, Blood and Immune responses. Boston, MA
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82. **Berman JN** Gerbing RB Sung L Miller K Pollard JA Ho P Stirewalt D Radich J Hurwitz CA Heerema NA Hirsch B Raimondi SC Lange B Gamis AS Franklin JL Alonso TA Meshinchi S, "Prevalence and clinical implications of N-RAS mutations in childhood AML - A report from the Children's Oncology Group." Abstract 51st Meeting of the American Society of Hematology, New Orleans, LA
83. Forrester AM, Boyd ER, Grabher C, McBride ER, Da'as S, Kai FB, Look AT, **Berman JN**. "NUP98-HOXA9 reprograms embryonic myelopoiesis, suppresses cellular apoptosis, and causes malignant tissue infiltrates in transgenic zebrafish." Abstract 51st Meeting of the American Society of Hematology, New Orleans, LA
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85. Abbott LS, Price VE, Deveeska M, Barnard D, Fernandez CV, Yhap M, Fitzgerald C , Dix D, **Berman JN**, "The impact of prophylactic fresh frozen plasma and cryoprecipitate on the incidence of CNS thrombosis and hemorrhage in children with acute lymphoblastic leukemia receiving asparaginase." Abstract International Society of Thrombosis and Haemostasis Meeting, Boston, MA.
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88. Da'as SI Rygier L Ferrando A **Berman JN**, "Notch signaling is required for mast cell development in the zebrafish." Abstract 6th European Zebrafish Genetics and Development Meeting, Rome, Italy
89. Henry H **Berman JN** McBride ER Barnard D Dickey L Gao J Price VE, "The use of the platelet function assay (PFA) to assess bleeding risk in a pediatric population." Abstract International Society of Thrombosis and Haemostasis Meeting, Boston, MA
90. Da'as SI Rygier L Ferrando A **Berman JN**, "Notch Signalling is required for mast cell development in the zebrafish." Abstract 6th European Zebrafish Genetics and Development Meeting, Rome, Italy
91. Reaume LM Erickson T Forrester AM **Berman JN** Waskiewicz AJ, "The HOX cofactors Pbx and Meis1 act upstream of gata1 to regulate primitive erythropoiesis." Abstract 6th European Zebrafish Genetics and Development Meeting, Rome Italy
92. Da'as SI Teh EN Dobson JT Neuberg DS Marshall J Lin TJ **Berman JN**, "Zebrafish mast cells possess an Fc#RI-like receptor and participate in innate and adaptive immune responses." Abstract 6th European Zebrafish Genetics and Development Meeting, Rome, Italy

2008

- Early tumor detection and prevention in Li-Fraumeni Syndrome Berman, Jason
93. Forrester AM, Grabher C, Kai F-B, Da's S, Look AT, and **Berman JN**. Transgenic Zebrafish Models of HOXA9-Mediated Acute Myeloid Leukemia Demonstrate Protection Against IR-Induced Cellular Apoptosis, Abstract#205, The 8<sup>th</sup> International Conference on Zebrafish Development & Genetics, June 2008.
94. Teh E, Kichler S, Hrytsenko O, Pohajdak B, Wen X-Y, Lin T-J, and **Berman JN**. Zebrafish Mast Cells Share Functional Similarities to Their Mammalian Counterparts, Abstract# 582, The 8<sup>th</sup> International Conference on Zebrafish Development & Genetics, June 2008.

2007

95. **Berman JN**, Seibert J, Dobson JT, Crosby A, Fraser R, Gritsenko O, Pohajdak B, Lin TJ. The Identification and Characterization of Zebrafish Mast Cells, Abstract#34, The 5<sup>th</sup> European Zebrafish Genetics and Development Meeting, July 2007.
96. Higgs JR, Sadek I, Neuman PE, Ing V, **Berman JN**, Renault, N and Greer W. Familial Essential Thrombocythemia Showing Spontaneous Megakaryocyte Colony Formation and Aquired Jak2 Mutations Without a Germline Mutation in C-Mpl or Tpo, Abstract#4655, Blood 110, Nov 2007.
97. **Berman JN**, Greer WL, Loh M, Riddell C, Morash B, Dumas N, Fernandez CV and Ludman M. A Rare Case of Jak2 V617f Positive Polycythemia Vera In A Child With Neurofibromatosis Type 1, Abstract#4661, Blood 110, Nov 2007.
98. Simpson DC, Gao J, Fernandez CV, Yhap M, Price VE and **Berman JN**. Bone Marrow Examination in the Initial Evaluation of Pediatric Hodgkin's Disease: The Canadian Perspective, Abstract#2326, Blood 110, Nov 2007.
99. **Berman JN**, Seibert J, Dobson JT, Teh E, Daas S, Fraser R, Paw B, and Lin TJ. The Identification and Characterization of Zebrafish Mast Cells, Abstract#2405, Blood 110, Nov 2007.

2006

100. **Berman JN**, Seibert J, Crosby A, Fraser R, Lin TJ. The Characterization of Zebrafish Mast Cells and Their role in Myeloid Leukemic Progression. Abstract #225, The 7<sup>th</sup> International Conference on Zebrafish Development & Genetics, June 2006.
101. Grabher C, **Berman JN**, Hsu K, Liu T, Deng M, Kanki J, Look AT. A Zebrafish Model of Myeloid Leukemia Mediated By Human And Murine Oncogenes, Abstract #174, The 7<sup>th</sup> International Conference on Zebrafish Development & Genetics, June 2006.
102. **Berman JN**, Seibert J, Crosby A, Fraser R, Lin TJ. The Characterization of Zebrafish Mast Cells and Their role in Myeloid Leukemic Progression, Abstract#166, Experimental Hematology, 34, number 9, September 2006.
103. **Berman JN**, Seibert J, Dobson JT, Crosby A, Fraser R, Gritsenko O, Pohajdak B, Lin TJ. The Characterization of Zebrafish Mast Cells and Their role in Myeloid Leukemia, Abstract #1664, Blood, 108, November 2006.

2004

104. Heinrichs S, **Berman JN**, Ortiz TM, Kornblau SM, Neuberg DS, Estey EH, Look AT. CD34+ cell selection is required to assess HOXA9 expression levels in patients with myelodysplastic syndrome. Abstract #4733, Blood, 104, issue 11, November 16, 2004.

Early tumor detection and prevention in Li-Fraumeni Syndrome

Berman, Jason

105. **Berman JN**, Hsu K, Liu TX, Deng M, Langenau D, Kanki J, Look AT. A Transgenic Zebrafish Model of Hoxa9 and Meis1 Mediated Myeloid Leukemias., Abstract #236, The 6th International Conference on Zebrafish Development and Genetics, July 2004.
106. Hsu K, Traver D, Kutok JL, Hagen A, Liu TX, Paw B, Rhodes J, **Berman JN**, Zon LI, Kanki JP & Look AT. The pu.1 promoter drives myeloid gene expression in zebrafish. Abstract #403, The 6th International Conference on Zebrafish Development and Genetics, July 2004.
107. Heinrichs S, **Berman JN**, Ortiz TM, Kornblau SM, Neuberg DS, Estey EH, Look AT. CD34+ cell selection is required to assess HOXA9 expression levels in patients with myelodysplastic syndrome. Abstract #4733, Blood, 104, issue 11, November 16, 2004.
108. **Berman JN**, Wang M, Berry W, Neuberg D, Guinan EC. Herpes zoster infection in the post-hematopoietic stem cell transplant pediatric population may be preceded by transaminitis. Abstract #3167, Blood, 104, issue 11, November 16, 2004.

**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

FULL NAME:	Ran Kafri		
POSITION TITLE:	Scientist		
INSTITUTION:	Hospital for Sick Children		
FULL ADDRESS:	PGCRL, 686 Bay Street, Room 18.9708, Toronto, Ontario M5G 0A4 Canada		
TELEPHONE :	(416) 813-7654 x 309092	EMAIL:	ran.kafri@sickkids.ca
WEB-ADDRESS:	<a href="http://www.kafrilab.com/">http://www.kafrilab.com/</a>		

**ACADEMIC BACKGROUND**

Degree Type	MM/YY	Discipline/Field/Specialty	Institution & Country
Postdoctoral Fellow	7/2006 - 7/2010	Department of Systems Biology	Harvard Medical School, Massachusetts, USA
PhD	7/2002 – 6/2006	Department of Molecular Genetics	Harvard Medical School, Massachusetts, USA
MSc	7/2002 – 6/2006	Department of Chemistry	Weizmann Institute of Science, Rehovot, Israel
BSc	9/1996 – 6/1999	Department of Chemistry and Biophysics	Ben-Gurion University, Beersheba, Israel

**WORK EXPERIENCE**

Position, Organization	Department/Division	Start Date	End Date
Scientist	SickKids Hospital, Program in Cell Biology	9/2013	Present
Assistant Professor	University of Toronto, Department. of Molecular Genetics	11/2013	Present
Lecturer	Harvard Medical School, Department of Biology	9/2010	6/2013

[expand tables as required]

**A. Personal Statement (max one page)***Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.*

When I first began my research on cell size, literature was conflicted not on how size of animal cells is specified but on whether it is specified at all! Significant authors including Martin Raff and Alison Lloyd have repeatedly argued that, unlike yeast, “animal cells do not need, and probably do not have, cell size checkpoints”. But, animal cells do have cell size checkpoints – a fact that was definitely shown for the first time by my 2013 publication in *Nature*. Over the past four years, our work has established the first evidence of signal transduction pathways that communicate information on cell size to regulate both the length of cell cycle (G1) and the rate of cell growth. Not only that, but in more recent work, we have now identified the specific signaling pathways that communicate information on cell size – bringing us one step closer to the elusive cell size sensor. My work on cell size has been published in top journals including *Science*, *Nature* and *Cell*. More recently, our research proposals on cell size have been recognized by CIHR and NSERC, resulting in two multi-year grants. In addition, I have been awarded two Garron Family Foundation grants and a Tier 2 Canada Research Chair in Cell Size and Uniformity. These funds have secured my research program and will allow us to reach our goals and potential.

A pioneering aspect of my work has been to introduce the question of size uniformity into the subject of cell size. While cell growth has been the subject of many investigations, these studies have been exclusively focused on identifying signaling, such as mTOR, that promote or repress growth in cell size. However, these studies have overlooked two fundamental questions: (1) how do a common set of signals (including mTOR) specify a different and distinct size for each of the different animal cell types? (2) When considering cells of a given type, how are numerous individual cells in the tissue regulated to have the same exact size? The unique

aspect of these two questions is not that they have not yet been answered but rather – that they have not yet been asked.

To answer the questions posed above, we developed innovative new approaches to examine multivariate single cell measurements. In 2013, I published ergodic rate analysis - an original approach to extract information on cellular dynamics from static measurements of single cells. Since then, we have been continuously innovating analytic methods that are routinely used in our lab to exploit single cell variability to make inference onto the signaling that controls reporter targets. Our innovations in analysis are also the premise for the collaboration with the pharmaceutical giant, Novartis, and our current proposal to the TFRI.

In addition to new methods of analysis, by collaborating with Novartis, we have established the first comprehensive pharmacological library of drugs that affect cell size. Specifically, my lab has identified numerous compounds that increase cell size, compounds that decrease cell size and compounds that disrupt cell size uniformity in culture and in animal tissues. These compounds are a priceless resource and tool for investigating the mechanisms of size control in animal cells.

In science, recognition is awarded to those who pose new fundamental questions that have not been previously conceived, or, to those who come up with new approaches to answer questions that have not yet been solved. My research encompasses both these qualities. We have identified questions that have not yet been asked: i.e. what is the mechanism for cell size uniformity. Our work has identified phenomena that have not yet been observed: size sensing in animal cells. Last, we have established new tools and pharmacology to answer the questions that we addresses, and made important productive collaborations to ensure international recognition in the field.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (*max four pages*)**

*In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).*

**Invited Lectures:**

- 2017 Molecular Mechanisms of Size Sensing in Animal Cells. Mechanisms of Cell Division with Special Emphasis on Cancer. Cell Growth & Proliferation, Gordon Research Conference, West Dover, Vermont, USA, July 9-14, 2017
- 2017 How animal cells sense their size? - Evidence and mechanisms of size sensing. University of Texas Southwestern Medical Center, Dallas, Texas, May 21-23, 2017
- 2017 Mechanisms controlling cell size in animal cells. Program in Systems Biology at the University of Massachusetts Medical School, Massachusetts, United States
- 2017 Size regulation in animal cells. Distinguished Scientist Lecture Series, Montreal, Quebec, January 30, 2017
- 2017 Size regulation in animal cells. Program in Systems Biology, University of Massachusetts Medical School, January 19, 2017
- 2016 Invited to host and mediate a debate on “Is there cell size sensing in animal cells?” EMBO meeting on cell size., Joachimsthal, Germany, September 14 – 18, 2016
- 2016 Size regulation in animal cells. Program in Systems Biology, University of Massachusetts Medical School, Boston, Massachusetts, United States
- 2016 Negative feedbacks coordinate growth and cell cycle progression to maintain size uniformity in animal cells. Institute for Advanced Studies (IIAS), Jerusalem, Israel
- 2016 Invited to present on “how to articulate scientific material”. 2016 Winter q-Bio (Quantitative Biology) Meeting. San Diego Center for Systems Biology, Oahu, Waikiki, February 14 18, 2016

- 2015 Size specification in animal cells. Donnelley Seminar Series, Toronto, Canada
- 2014 Targeting the messenger: using cell labeling for development of novel approaches in cancer pharmacology. Cell Signaling Technology, Danvers, United States
- 2013 Specification of cell size and control of size heterogeneity by mTOR-dependent modulation of growth rate. Gordon Research Conferences: Cell Growth & Proliferation, West Dover, United States
- 2013 Specification of cell size and control of size heterogeneity by mTOR-dependent modulation of growth rate. Computational Cell Biology: The Interplay between Models and Experimentation, Cold Spring Harbor, United States
- 2013 Feedbacks linking growth and proliferation in animal cells. Cell Biology Program Special Seminar, Toronto, Canada

**Collaborations:**

- Collaboration with Novartis – Development of a high throughput assay for temporal signaling from measurements on fixed cells
- Collaboration with Novartis – Screening compounds with known mechanism of action for their joint effects on the coordination of cell growth and cell division
- Collaboration with Dr. William Trimble from the Hospital for Sick Children on studying p38 in the context of cell size
- Collaboration with Dr. Yuval Dor from Hebrew University on studying size regulation of pancreatic beta cells

**Supervisory/Mentoring Activities**

- 11/2013 - **Nish Patel**, PhD  
Sr. Research Associate  
Role: Supervisor
- 2/2016 **Miriam Ginzberg**, PhD  
Research Fellow  
Project Title: Mammalian cell-autonomous size control.  
Role: Supervisor
- 9/2015 - **Eden Fussner - Dupas**, PhD  
Research Fellow  
Project Title: Cells sense size: Investigating the signaling and biophysics by which Dyrk2 mediates cell size sensing in animal cells.  
Role: Supervisor
- 2/2016 - **Shixuan Liu (International)**  
Degree: Ph.D., Department of Molecular Genetics, University of Toronto  
Project Title: Investigating the Cross-talk Between Cell Growth and Division in Mammalian Cells.  
Support: Supervisor's grant  
Role: Supervisor
- 01/2017 - **Ceryl Tan (International)**  
Degree: Graduate Student  
Department of Molecular Genetics, University of Toronto

	Early tumor detection and prevention in Li-Fraumeni Syndrome	Kafri, Ran
	Project Title: Studying feedback mechanisms in oncogenic pathways using single cell imaging and mathematical modeling for data analysis.	
5/2015 - 8/2016	Summer Student Role: Supervisor	
9/2016 -	<b>Dale Wong</b> Degree: Graduate Student Department of Molecular Genetics, University of Toronto Project Title: Evolution of the NF-κB mediated inflammatory response. Role: Co-Supervisor	
9/2015 -	<b>Bosco Leung</b> Degree: Graduate Student Department of Molecular Genetics, University of Toronto Project Title: Investigating the role of p38 in animal cell size regulation.	
5/2015 - 8/2015	Summer Student Role: Co-Supervisor	
5/2017 -	<b>Justin Sing</b> Degree: Undergraduate Research Student Department: Bachelor of Technology, McMaster Project Description: Investigating the effects of steroid drugs on cell size cycle. Role: Supervisor	
9/2016 - 8/2017	<b>Jing Yi Yuan</b> Degree: Undergraduate Research Student Department of Molecular Genetics, University of Toronto Project Title: Investigating the novel interaction between two cell-size sensing pathways: The oncogenic kinase LKB1 and the stress-stimulated kinase p38 pathways.	
6/2016 - 8/2016	Summer Student Role: Supervisor	
5/2017 – 8/2017	<b>Annie Herman</b>	
6/2016 – 8/2016	Queen's University Project Description: Elucidating the role of the stress response p38 pathway in cell size regulation. Summer Student Role: Supervisor	
5/2017 – 8/2017	<b>Daniel Han</b> University of Toronto Project Description: Investigating the role of LKB1 in cell size sensing. Summer Student Role: Supervisor	
5/2017 – 8/2017	<b>Alex Mendell</b>	
5/2016 – 8/2016	McGill University Project Description: Screening for the pathways underlying cell size control. Summer Student Role: Supervisor	
5/2017 – 8/2017	<b>Heather D'Souza</b> University of Waterloo	

Project Description: Mammalian cell-autonomous size control.

Summer Student

Role: Supervisor

9/2016 - 3/2017	<b>Shula Diena</b> Position: Research Student
5/2016 - 8/2016	Summer Student Role: Supervisor
5/2017 - 8/2017	<b>Alex Mendell</b>
5/2016 – 8/2016	Summer Student Degree: Completed 2nd year of Bachelor of Engineering (Civil) at McGill University Project Title: Image Processing of Broad Institute Data Role: Supervisor
4/2014 - 5/2015	<b>Loen Hansford</b> , Research Associate SickKids Hospital Present Position: Research Fellow Role: Co-Supervisor

### C. Honours & Awards

*List any honours and personal awards in chronological order.*

#### Awards, Honours, and Distinctions:

10/2016 – 9/2021	<b>Canada Research Chair (Tier II)</b> Award: \$478,585 CDN
4/2016 – 3/2021	<b>Early Researcher Awards (ERA)</b> Award: \$140,000 CDN
7/2010 – 6/2012	<b>Charles A. King Trust Postdoctoral Research Fellowship</b> , Harvard Medical School Award: \$92,000 USD
4/2007 – 9/2010	<b>Human Frontier Science Program Organization, HFSP Fellowship</b> Award: \$160,688 USD
1/2006	<b>Dean's Honor Award</b> Weizmann Institute of Science Distinction
1/2005	<b>Dean's Honor Award</b> Weizmann Institute of Science Distinction

### D. Overview & Details of Research Support

*Provide an overview of your current areas of research focus including supports of your research / laboratory (max one page). Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.*

**Current Research Support**

Funding Source & Program Name: Engineering Medicine Hospital (EMH) Seed Program

Project Title: Challenging the dogma: Cell size regulation in embryonic wound repair.

Total Award: \$15,000

Term: 2017/1 - 2017/12

Main Objective and Outline of Methodology: The goal of the project is to investigate the roles of p38-mediated cellular hypertrophy in embryonic wound repair. To this end, we will 1: investigate the growth-promoting functions of p38 during wound repair; 2: establish the signals that selectively activate p38 at the wound periphery. We will use genetic and pharmacological means to perturb signaling via p38 MAPK and identify the signals that activate this pathway at the wound periphery and whether they are involved in wound repair of the epidermis of Drosophila embryos.

Budget Details: Salary support for 1 MSc graduate student

Relationship to 2017 PPG application: 0% overlap

Funding Source & Program Name: Canada Research Chairs

Project Title: Identifying the mechanisms that specify cell size in animal cells.

Total Award: \$478,585

Term: 2016/10 - 2021/9

Main Objective and Outline of Methodology: To decode the cell size sensing machinery that regulate the uniformity in cell size. We combine systems pharmacology and genetic perturbations to identify the molecular signals that communicate information about cell size to the cell size sensor.

Budget Details: Salary support for the PI and 2 FTEs as well as research related expenses.

Relationship to 2017 PPG application: 0% overlap

Funding Source & Program Name: Ministry of Research and Innovation -  
Early Research Awards (ERA)

Project Title: Cell size specification in normal populations

Total Award: \$140,000

Term: 2016/4 – 2021/3

Main Objective and Outline of Methodology: With the research described in current proposal we will take the next step to identify the elusive sensor of cell size and uncover its' role in normal and malignant cell biology. We examine whether p38 activity communicates information on cell size to selectively promote growth of small but not large cells, consequently increasing uniformity in cell size. We combine systems pharmacology and genetic perturbations to identify the molecular signals that may constitute the cell size sensor.

Budget Details: Salary support for 1 postdoctoral fellow and 5 undergraduate summer research students

Relationship to 2017 PPG application: 0% overlap

Funding Source & Program Name: Natural Sciences and Engineering Research Council of Canada  
(NSERC)

Project Title: Size regulation in animal cells.

Total Award: \$195,000

Term: 2015/9 – 2021/8

Main Objective and Outline of Methodology: The goal of this proposal is to identify the mechanisms that specify a cell's particular and definite size. Specifically, we will focus, not on mechanisms of cellular enlargement, but mechanisms that specify one cell size over another. In this proposal we will try to understand how rates of cell growth are regulated and coordinated with cell size and cell cycle. We will build a system to experimentally manipulate cell size in order to further investigate the mechanisms of size control. Lastly, we will attempt an unbiased search for new regulators of cell size.

Budget Details: Salary support and research-related expenses for 2 graduate students

Relationship to 2017 PPG application: 0% overlap

Funding Source & Program Name: Canadian Institutes of Health Research (CIHR)  
 Project Title: Mechanisms of cell size specification and their role in cancer pathology.

Total Award: \$723,978

Term: 2015/10 – 2020/9

Main Objective and Outline of Methodology: We aim to further define the upstream and downstream components of the p38 MAPK pathway regulating the growth of small cells, and examine how this pathway goes awry in pleomorphic cancers. We combine systems pharmacology and genetic perturbations to identify the mechanisms that distinguish cell-size regulation of cancer cells from normal cells – and rely on these mechanisms to suggest novel targets for cancer pharmacotherapy for pleomorphic models of breast cancer.

Budget Details: Salary support and research related expenses for 2 postdoctoral fellows

Relationship to 2017 PPG application: 0% overlap

Funding Source & Program Name: Garron Family Cancer Centre (GFCC)

Project Title: RAS: Is it possible to drug the undruggable?

Total Award: \$77,000

Term: 2015/7 – 2018/6

Main Objective and Outline of Methodology: In this study we ask whether we can develop a more informative compound screening strategy, which like the single-target approach is centered on a specific mechanism, but unlike single-target approach success is not dependent on a small number of targets that may be undruggable? We aim to implement an inference method to identify cross talk between Ras and apoptosis from two-color single cell imaging. Using this inference as a readout, we will screen for compounds that target not only Ras activity, but also the specific molecules that relay or perturb its oncogenic influence.

Budget Details: Salary support for 1 FTE with expertise in computational biology

Relationship to 2017 PPG application: 0% overlap

Funding Source & Program Name: Garron Family Cancer Centre (GFCC) Pitblado Discovery Grant

Project Title: Confronting the mechanisms and roles of cell enlargement in tumorigenesis

Total Award: \$50,000

Term: 2014/7 – 2015/6

Main Objective and Outline of Methodology: To identify the role and mechanisms responsible for the observed enlargement of cell size in tumors. We will use systems pharmacology and genetic perturbations to identify the molecular signals that govern cell size enlargement in clones of human mammary epithelial cells (HMLER).

Budget Details: Salary support and research-related expenses for 0.5 FTE

Relationship to 2017 PPG application: 0% overlap

## E. List of Publications

*Provide a full list of all your scientific publications.*

### Publications:

1. Liu S, Ginzberg MB, Patel N, Hild M, Leung B, Chen Y, Chang N, Wang Y, Trimble W, Wasserman L, Jenkins J, Kirschner MW, **Kafri R**. Size uniformity of animal cells is actively maintained by a p38 MAPK-dependent regulation of G1-length. *eLife* 2017, Manuscript No: 17-03-2017-SR-eLife-26947 (under review)
2. Ginzberg MB, Chang N, **Kafri R**, Kirschner MW. Cell size sensing in animal cells coordinates growth rates and cell cycle progression to maintain cell size uniformity. *eLife* 2017, Manuscript No.: 17-03-2017-RA-eLife-26957 (under review)
3. Ginzberg MB, **Kafri R**, Kirschner MW. (2015). Cell biology. On being the right (cell) size. *Science*. 2015 May 15;348(6236):1245075. doi: 10.1126/science.1245075. Review. PMID: 25977557
4. **Kafri R**, Levy J, Ginzberg MB, Oh S, Lahav G, Kirschner MW. Dynamics extracted from fixed cells

reveal feedback linking cell growth to cell cycle. *Nature* 2012; 494 (7438): 480-3. PMID: 23446419

5. Karanam K, **Kafri R** (equal contribution with Karanam), Löwer A, Lahav G. Quantitative live cell imaging reveals a gradual shift between DNA repair mechanisms and a maximal use of HR in mid S phase. *Mol. Cell* 2012; 47 (2): 320-9. PMID: 22841003
6. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza AL, **Kafri R**, Kirschner MW, Clish CB, Mootha VK. Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science* 2012; 336 (6084): 1040-4. PMID: 22628656
7. Juang YT, Peoples C, **Kafri R**, Kyttaris VC, Sunahori K, Kis-Toth K, Fitzgerald L, Ergin S, Finnell M, Tsokos GC. A systemic lupus erythematosus gene expression array in disease diagnosis and classification: a preliminary report. *Lupus* 2011; 20 (3): 243-9. PMID: 21138984
8. **Kafri R**, Markovitch O, Lancet D. Spontaneous chiral symmetry breaking in early molecular networks. *Biol. Direct* 2010; 5: 38. PMID: 20507625
9. Tzur A, **Kafri R** (equal contribution with Tzur), LeBleu VS, Lahav G, Kirschner MW. Cell growth and size homeostasis in proliferating animal cells. *Science* 2009; 325 (5937): 167-71. PMID: 19589995
10. **Kafri R**, Springer M, Pilpel Y. Genetic redundancy: new tricks for old genes. *Cell* 2009; 136 (3): 389-92. PMID: 19203571
11. **Kafri R**, Dahan O, Levy J, Pilpel Y. Preferential protection of protein interaction network hubs in yeast: evolved functionality of genetic redundancy. *Proc. Natl. Acad. Sci.* 2008; 105 (4): 1243-8. PMID: 18216251
12. **Kafri R**, Levy M, Pilpel Y. The regulatory utilization of genetic redundancy through responsive backup circuits *Proc. Natl. Acad. Sci.* 2006; 103 (31): 11653-8. PMID: 16861297
13. Shenhav B, Bar-Even A, **Kafri R**, Lancet D. Polymer GARD: computer simulation of covalent bond formation in reproducing molecular assemblies. *Orig. Life Evol. Biosph.* 2005; 35 (2): 111-33. PMID: 16010993
14. **Kafri R**, Bar-Even A, Pilpel Y. Transcription control reprogramming in genetic backup circuits. *Nat. Genet.* 2005; 37 (3): 295-9. PMID: 15723064
15. **Kafri R**, Lancet D. Probability rule for chiral recognition. *Chirality* 2004; 16: 369-78. PMID: 15190582
16. Rosenwald S, **Kafri R**, Lancet D. Test of a statistical model for molecular recognition in biological repertoires. *J. Theor. Biol.* 2002; 216 (3): 327-36. PMID: 12183121
17. Segré D, Shenhav B, **Kafri R**, Lancet D. The molecular roots of compositional inheritance. *J. Theor. Biol.* 2001; 213 (3): 481-91. PMID: 11735293
18. Kolusheva S, **Kafri R**, Katz M, Jelinek R. Rapid colorimetric detection of antibody-epitope recognition at a biomimetic membrane interface. *J. Am. Chem. Soc.* 2001; 123 (3): 417-22. PMID: 11456543

**TERRY FOX RESEARCH INSTITUTE****BRIEF CURRICULUM VITAE**

(Use 11 pt font, single spacing, no more than 51 lines per page, and half-inch margins throughout)

FULL NAME: GANG ZHENG	
POSITION TITLE: SENIOR SCIENTIST	
INSTITUTION: UNIVERSITY HEALTH NETWORK – PRINCESS MARGARET CANCER CENTRE	
FULL ADDRESS: 101 College St. Suite 5-354	
TELEPHONE: 4165817666	EMAIL: <a href="mailto:gang.zheng@uhnres.utoronto.ca">gang.zheng@uhnres.utoronto.ca</a>
WEB-ADDRESS: <a href="http://zhenglab.utoronto.ca/">http://zhenglab.utoronto.ca/</a>	

<b>ACADEMIC BACKGROUND</b>			
Degree Type	MM/YY	Discipline/Field/Specialty	Institution & Country
B.A.Sc.	1988	Chemistry	Hangzhou University (now Zhejiang University), China
Ph.D.	1999	Medicinal Chemistry	State University of New York, Buffalo, USA
Postdoc.	2000	Photodynamic Therapy	Roswell Park Cancer Institute, Buffalo, NY

<b>WORK EXPERIENCE</b>				
Position, Organization	Department/Division	Start Date	End Date	
Full Professor	Medical Biophysics (Primary), Institute of Biomaterials & Biomedical Engineering, Department of Pharmaceutical Sciences (x-appointment), University of Toronto	2012	Present	
Senior Scientist	Joey and Toby Tanenbaum/Brazilian Ball Chair in Prostate Cancer Research, Ontario Cancer Institute, University Health Network (UHN)	2006	Present	
Scientific Lead	Nanotechnology & Radiochemistry, Techna Institute, UHN, Canada	2011	Present	
Scientist (cross-appointment)	Joint Department of Medical Imaging, Mount Sinai Hospital, University Health Network, and Women's College Hospital	2015	Present	
Adjunct Professor of Radiology	University of Pennsylvania	2006	June 2016	

[expand tables as required]

**A. Personal Statement (max one page)**

Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.

Throughout Dr. Zheng's academic career, he has been focused on developing clinically translatable technology platform to combat cancer. His lab discovered porphysome nanotechnology (Nature Materials 2011) that opened a new frontier in cancer imaging and therapy, which is the center focus of this program project proposal. His lab also discovered an ultrasound-induced mechanism for microbubbles to nanoparticle conversion that could open the door for bypassing the enhanced permeability and retention effort that dictates how nanoparticles are accumulated in tumors (Nature Nanotechnology 2015). Dr. Zheng is an Associate Editor for the Bioconjugate Chemistry and a Fellow of the American Institute of Medical and Biological Engineering (AIMBE). During the last 5 years (since 2011), he has published 85 peer-reviewed papers, given 82 invited lectures and had 5 issued patents and 8 patent applications. During the same period, he has also supervised 8 research staffs, 29 graduate students (graduating 9 PhD and 7 MSc), 9 postdocs and more than 30

## B. Selected Research / Technology Development Contributions Over the Past Five Years (*max six pages*)

### Most significant contributions during the last 5 years

Dr. Zheng's most significant contribution in this period is his discovery of porphysome nanotechnology that opens new frontiers in cancer imaging and therapy, which won him the UHN Inventor of the Year Award in 2012. This discovery along with his pioneering work on activatable photosensitizers for photodynamic therapy were cited as the reasons for his recent election to the College of Fellows of The American Institute for Medical and Biological Engineering (AMIBE).

Porphysomes are self-assembled porphyrin bilayers that leverage the densely packed porphyrins to effectively convert light of specific wavelengths to heat with extremely high efficiency, given them ideal photothermal and photoacoustic properties that are unprecedented in organic nanoparticles (Nature Materials 2011, cited 429 times). Named as one of the "Top 10 Cancer Breakthroughs of 2011" by the Canadian Cancer Society, this patented discovery (USP 9, 072,774 and 9,017,974) also allows low background fluorescence imaging and activatable photodynamic therapy. Metal ions can be directly incorporated into the porphyrin building blocks of the preformed porphysomes, unlocking their potential for PET and MRI applications. As a result, the simple yet all encompassing nature of the porphysome represents a new paradigm in nanomedicine.

Beyond porphysomes, Dr. Zheng also developed HDL-like porphyrin nanoparticles (~20nm), porphyrin shell microbubbles (~2um), giant porphyrin vesicle (~100um) and hybrid porphyrin-gold nanoparticles, all of which led to new cancer applications. Recently, Dr. Zheng discovered high-ordered porphyrin supramolecular assemblies in both nano and microstructures by mimicking light harvesting systems, which led to the discovery of the ultrasound-induced microbubbles-to-nanoparticle conversion (Nature Nano 2015). This opens the door to the EPR-independent nanoparticle delivery, thus addressing a fundamental challenge in cancer nanomedicine. This paper won the "Till and McCulloch Paper of the Year (Translational)". In addition, a novel class of self-regulated photothermal agents was discovered based on high-ordered porphyrin assemblies to overcome the inherent limitations (overheating and narrow ablation depth) of all existing photothermal agents (Angewandte 2016 Very Important Paper). Furthermore, by "expanding" the 4-coordination state of porphyrins to the 5-coordination state of texaphyrin-lipid building blocks with stable chelation of 18 metals (Mn, Fe, Co, Y, Cd, In, Re, Bi, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu) (Angewandte Chemie 2016), Dr. Zheng introduced the nanotexaphyrin family, unleashing the metal chelating power of texaphyrins for a wide array of nanomedicine applications.

Since its inception in 2011, 42 peer-reviewed papers (most in top journals) were published with total citations >1200. This has laid the foundation for the field of porphyrin nanomedicine, which is now blossoming.

### Selected Service (Last 5 Years):

Co-Chair Personalized Cancer Medicine Conference, Princess Margaret Cancer Center (Feb 1-2, 2016)

Associate Editor: *Bioconjugate Chemistry* (2014-)

Advisor: Technical Group of Molecular Probes and Nanobio-optics, Optical Society of America (OSA)  
(2014-2017)

Member, Executive Committee, Princess Margaret Cancer Center (2015-)

Feature Issue Editor: Combined Issue of Biophotonic Materials and Applications for OSA journals, *Optical Materials Express and Biomedical Optics Express* (2016)

Editorial Board: *Bioconjugate Chemistry* (2010-2013); *Theranostics* (Founding member, 2011-present); *Journal of Innovative Optical Health Science* (2007-present), *Photonics and Laser Medicine* (2011-present); *American Journal of Nuclear Medicine and Molecular Imaging* (2011-present); *Frontiers in Biomedical Physics* (2013-present); *Biophysics Report* (2014-); *Nanotheranostics* (Founding member, 2016-present).

Panel Chair: Discovery Grant Review Panel C, Prostate Cancer Canada, May 2013 & May 2014

NIH review: Nanotechnology Study Sections (06/2011, 10/2011, 06/2012, 05/2013, 02/2014, 06/2015)

NIH Review: Program Project (P01) panel (Oct 2013, May 2014), Academic-Industry Partnership R01 Panel on In Vivo Imaging (02/2011, 06/2011, 10/2011);

DOD review: BCRP (10/2012, 11/2013); PCRP (04/2011, 06/2012, 07/2013, 10/2014)

CIHR review: "Fellowships - Post-PhD" committee (2013-2016)

Early tumor detection and prevention in Li-Fraumeni Syndrome Zheng, Gang  
Other review: China (2011, 2013, 2014, 2015, 2016); France (2011), Netherland (2011), Israel (2011, 2012, 2014, 2015), Switzerland (2012, 2013), Portuguese (2012, 2014), Hong Kong (2013, 2014, 2015)  
Member/Ad-hoc Chair: Ontario Cancer Institute Animal Care Committee (2010-present)  
Co-Founder: DLVR Therapeutics, Inc. (2011)  
Member Scientific Advisory Board, European Society for Photobiology (2008-2014)  
Member Scientific Advisory Board, International Photodynamic Association (2012-2014)  
Member Advisory Committee, School of Engineering Sciences, Huazhong University of Science & Technology (HUST) (2015-2017)  
Reviewer for tenure/promotion:  
Harvard Medical School, Stanford University, Washington University in St Louis, University of Colorado at Boulder, University of Wisconsin at Madison, University of Texas at Dallas, University of Toronto, NIH, University of Maryland, National University of Singapore (Singapore), Peking University, Northwestern University, Northeastern University, University of North Carolina at Chapel Hill, University of Missouri, University of Buffalo, Yonsei University (Korea) and POSTECH (Korea)

#### **Issued Patents:**

**Zheng G**, Lovell JD, Porphyrin Nanovesicles, US Patent 9, 072,774 (Issued on July 7, 2015)  
**Zheng G**, Lovell JF, Method for the Synthesis of Porphyrin-Phospholipid Conjugates, *US Patent 9,017,974* (issued on April 28, 2015)  
**Zheng G**, Zhang Z-H, Corbin I, **Chen J**, High-Density Lipoprotein-Like Peptide-Phospholipid Scaffold ("HPPS") Nanoparticles, Japanese Patent 5,658,568 (issued on Dec 5, 2014)  
**Zheng G**, Glickson, JD, Chance B. Delikatny EJ, Stefflova K, Chen J, Activatable Photodynamic Therapy Agents, *US Patent 8,133,482* (issued on March 13, 2012)  
**Zheng G**, Glickson JD, Antineoplastic Agents Targeted via GLUT Transporters, *US Patent 7,943,586* (Issued on May 17, 2011)

#### **Patent Applications:**

**Zheng G**, Keca JM, Texaphyrin-phospholipid conjugates and methods of preparing same, PCT application, (4.16.2016) (US Provisional Patent Application No. 62/148,839)  
**Zheng G**, **Chen J**, Harmatys K, Ng K, Takada M, Nanovesicle with porphyrin-lipid conjugate core, US provisional patent application #62310108 (3.18.2016).  
**Zheng G**, Ng K, **Weersink R**, **Wilson B**, US Prov. Appl., The method of improving heat delivery in photothermal therapy using temperature-responsive auto-regulating photothermal (TRAP) agents, Dec 2014  
**Zheng G**, Chen J, Liyang Cui, US Prov. Appl. No. 62/014,964, Ultrasmall Porphyrin Vesicles (6.20.2014)  
**Zheng G**, Ng KK, Huynh E, Shakiba M, **Weersink R**, **Wilson BC**, J-aggregate Forming Nanoparticles, US Prov. Appl. No. 61/757,750 (Jan 29, 2013), PCT filed.  
**Zheng G**, Tam N, WO/2013/159185 – Porphyrin-Lipid Stabilized Nanoparticles for Surface Enhanced Raman Scattering Based Imaging (10.31.2013), PCT/CA2013/000372  
**Zheng G**, Huynh E, Lovell J, WO/2013/082702 – Giant Porphyrin-Phospholipid Vesicles (6.13.2013), PCT/CA2012/001122  
**Zheng G**, Huynh E, Lovell J, WO/2013/053042 – Porphyrin-Phospholipid Conjugate Microbubbles and Their use as Contrast Agents (4.18.2013), PCT/CA2012/000937

#### **Notable trainee award received during the last 5 years:**

National Science Fund for Distinguished Young Scholars (2016) Zhihong Zhang  
NIH Director's Early Independence Award 2013 (Jonathan Lovell)  
Biomedical Engineering Society Young Investigator Award 2015 (Jonathan Lovell)  
CIHR Postdoctoral Fellowship (Tracy Liu), ranked #1 in the nation (1 out of 1119)  
Vanier Canada Graduate Scholarship (Maneesha Rajora)  
US Army BCRP Predoctoral Award (Tracy Liu)  
Knudsen Postdoctoral Fellowship 2015 (Christina McCaughlin)  
CIHR Banting/Best Award (Elizabeth Huynh, Kenneth Ng, Tracy Liu, Arash Farhadi)  
NSERC PhD Scholarship (Ben Luby)  
NSERC CRD Postdoctoral Fellowship (Neeshma Dave)  
Harvard Medical School Medical Physics Residency Training Award (Elizabeth Huynh)

## List of Publications

1. Rajora M, Zheng G, Targeting SR-BI for cancer diagnostics, imaging and therapy, *Frontiers in Pharmacology*, 2016, 8: 796–813. Featured as Front Cover
2. Song QX, Song HH, Xu JR, Huang JL, Hu M, Gu X, **Chen J**, Zheng G, Chen HZ, Gao XL. (2016). Biomimetic ApoE-Reconstituted High Density Lipoprotein Nanocarrier for Blood-Brain Barrier Penetration and Amyloid Beta-Targeting Drug Delivery. *Molecular Pharmaceutics*. DOI: 10.1021/acs.molpharmaceut.6b00781 Publication Date (Web): October 4, 2016
3. \*MacLaughlin CM, Ding LL, Jin CS, Cao PJ, Siddiqui I, Hwang DM, **Chen J, Wilson BC**, Zheng G, Hedley DW, Porphysome nanoparticles for enhanced photothermal therapy in a patient-derived orthotopic pancreas xenograft cancer model, *J Biomed Optics*, 21(8):84002. Highlighted by the Feature Article by Cynthia Keen, “Nanoparticles boost photothermal therapy” published in MedicalPhysicsWeb on Oct 17, 2016. <http://medicalphysicsweb.org/cws/article/research/66639>.
4. \*Valic M, Zheng G, Rethinking translational nanomedicine: Insights from the “bottom-up” design of the Porphysome for guiding the clinical development of nanomaterials, *Current Opinion in Chemical Biology*, 2016, 33, 126-134.
5. \*Charron DM, **Chen J**, Zheng G, Nanostructure-Dependent Ratiometric NIR Fluorescence Enabled by Ordered Dye Aggregation, *ChemNanoMat*, 2016, 2, 430–436.
6. \*Keca JM, **Chen J**, Overchuk M, **Muhanna N**, MacLaughlin CM, Jin CS, Foltz WD, **Irish JC**, Zheng G, Unleashing the Metal Chelation Power of the Texaphyrins for Nanomedicine: One-Pot Synthesis and Nanoassembly of Manganese Texaphyrin-Phospholipids for MRI, *Angewandte Chemie*, 2016, 55, 6187-91.
7. \*Ng KK, **Weersink R**, Lim SL, **Wilson BC**, Zheng G, Controlling spatial heat and light distribution using photothermal enhancing auto-regulated liposomes (PEARL), *Angewandte Chemie* 2016, DOI: 10.1002/anie.201605241R1, designated as a Very Important Paper (VIP).
8. Huynh E, Rajora M, Zheng G, Multimodal Micro, Nano and Size Conversion Ultrasound Agents for Imaging and Therapy, *Wiley Interdiscip Rev Nanomed Nanobiotechnol*, 2016, doi: 10.1002/wnan.1398.
9. Burgess L, **Chen J**, Wolter N, **Wilson BC**, Zheng G, Topical MMP Beacon Enabled Fluorescence-Guided Resection of Oral Carcinoma, *Biomed Opt Express* 2016, 7, 1089-1099. Featured in Spotlight of OSA journals.
10. \*Ng KK, Takada M, Harmatys K, **Chen J**, Zheng G, Chlorosome-inspired synthesis of templated metallochlorin-lipid nanoassemblies for biomedical applications, *ACS Nano*, 2016, 10: 4092-101.
11. \*Jin CS, Cui LY, Overchuk M, **Wilson BC**, Bristow RG, **Chen J**, Zheng G, Nanoparticle-enabled selective destruction of prostate tumor using MRI-guided focal photothermal therapy, *The Prostate*, 2016, doi: 10.1002/pros.23203.
12. Jin CS, Wada H, Anayama T, McVeigh PZ, Hu S, Hirohashi K, Nakajima T, Kato T, Keshavjee S, Hwang D, **Wilson BC**, Zheng G, Yasufuku K, An integrated nanotechnology-enabled fluorescence-guided transbronchial photothermal therapy of peripheral lung cancer, *Cancer Research*, in press.
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14. Huang M, Hu M, Song QX, Song H, Huang J, Gu X, Wang X, **Chen J**, Kang T, Feng X, Jiang D, Zheng G, Chen HZ, and Gao XL, GM1-Modified Lipoprotein-like Nanoparticle: Multifunctional Nanoplatform for the Combination Therapy of Alzheimer's Disease, *ACS Nano*, 2015, 9, 10801-16136.
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21. \***Muhanna N**, Cui LY, Chan H, Burgess L, Jin CS, Huynh E, Wang F, **Chen J, Irish JC**, Zheng G, Multimodal Image-Guided Surgical and Photodynamic Interventions in Head-and-Neck Cancer: From Primary Tumor to Metastatic Drainage, *Clinical Cancer Res*, 2016, 22:961-970 (Featured as the Issue Cover).
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23. \*Ng KK and Zheng G, Molecular Interactions in Photonic Organic Nanoparticles: Principles and Theranostic Applications, *Chemical Reviews* 2015, 115: 11012-42.
24. Cui LY, Lin QY, Jin C, Jiang WL, Huang H, **Muhanna N, Irish JC**, Wang F, **Chen J**, Zheng G, A PEG-free Biomimetic Porphyrin Nanoplatform for Personalized Cancer Theranostics. *ACS Nano*, 2015, 9: 4484-95.
25. \*Ng KK, Takada M, Jin C, Zheng G, Self-Sensing FRET-Porphysomes for Fluorescence-Guided Photothermal Therapy, *Bioconjugate Chem*, 2015, 26: 345-51.
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28. Huang H, Cruz W, **Chen J**, Zheng G, Learning from Biology: Synthetic Lipoproteins for Drug Delivery, *WIREs Nanomed Nanobiotechnol* 2015, 7: 298-314.
29. Huynh E, Helfield BL, Leung BYC, Shakiba M, Gandier JA, Jin C, Master ER, **Wilson BC**, Goertz DE, Zheng G, In Situ Conversion of Porphyrin Microbubbles to Nanoparticles for Multimodality Imaging, *Nature Nanotechnology*, 2015, 10: 325-332. Research highlighted in *Nature Nanotechnology* 2015, doi:10.1038/nnano.2015.61, 8: 370-371 “Theranostic Agents: From Micro to Nano in Seconds”, and *Nature Nanotechnology* 2015, 10: 301-302, “In the Class Room: From Nano to Micro, and Back”, *Nature Nanotechnology* 2015, 10: 380.
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## Editorial, Proceedings and Book Chapters

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2. Lin QY, Huang H, **Chen J**, Zheng G, “Using fluorescence imaging to track drug delivery and guide treatment planning in vivo”, in *In Vivo Fluorescence Imaging: Methods and Protocols* (Editor: Bai MF), by Springer, 2015
3. van Hest J, Lavik EB, Smith BC, Zheng G, Rotello V, “Editorial”, *Bioconjugate Chemistry*, 2015, 26: 163-5.
4. Cui LY, **Chen J**, Zheng G, “Porphyrin Nanoparticles for Cancer Imaging and Phototherapy”, in *Porphyrins in Cancer Imaging and Photodynamic Therapy* (Editors: Pandey RK, Kessel D, Dougherty T), by World Scientific.
5. Charron DM, **Chen J**, Zheng G, “Theranostic Lipid Nanoparticles for Cancer Medicine”, in *Nanotechnology-based precision tools for the detection and treatment of Cancer*, Mirkin C, Meade TJ, Petrosko S, Stegh A (Eds.). *Cancer Research and Treatment Series* 166(1) pp. 103-127, Springer New York, NY, 2015.
6. Farhadi A and Zheng G, “Porphyrinoid and Porphyrin-Lipid Nanocomplexes: Shifting the Paradigm for Photonic Nanomedicine”, in *Perspective in Micro and nanotechnology for biomedical applications*,
7. Luby B, Farhadi A, Shakiba M, Charron D, Roxin A, Zheng G, Research Highlights: Highlights from the latest articles in nanomedicine. “Spherical Nucleic Acids: Crossing the uncrossable to drug the undruggable”, “Nanoworms shed synthetic urinary biomarkers to aid the detection of thrombin activity”, “Resolving the paradox of rapid clearance and effective tumor targeting”, “Shaking up lipoprotein for nanocrystal-based imaging and therapy”, “The “GO chip” goes beyond efficient circulating tumour cell capture”, *Nanomedicine (Lond)*. 2014 Apr;9(4):385-8.
8. \*Shakiba M, **Chen J**, Zheng G, “Chapter 26: Porphyrin Nanoparticles in Photomedicine”, in *Applications of Nanoscience to Photomedicine*, by Chandros Publisher.
9. Liu TW, Huynh E, MacDonald TD, Zheng G, “Porphyrins for Imaging, Photodynamic Therapy and Photothermal Therapy”, in *Cancer Theranostics*, by Elsevier/Academic Press.
10. Lo P-C, Lovell JF, Zheng G, “Photodynamic Molecular Beacons” in “*HANDBOOK OF BIOPHOTONICS*”, John Wiley & Sons, 2011.

**C. Honours & Awards***List any honours and personal awards in chronological order*

- 2016 Fellow, the American Institute of Medical and Biological Engineering (AIMBE)  
 2016 The Sullivan Lecturer, 18<sup>th</sup> Annual Wharton/Elia Day with the Sullivan Lecturer, May 27, 2016  
 2016 Till and McCulloch Paper of the Year (Translational)  
 2012 "Top 10 Cancer Breakthroughs of 2011" by the Canadian Cancer Society  
 2011 Travelling Lectureship, Optical Society of America  
 2011 Inventor of the Year (University Health Network)

**D. Research Support***List current – followed by completed – research support (grants and contracts) held over the past five years from all sources. Identify any proposals for research support that are under review with an (R) and awarded with an (A) in the R/A column in the table below.***Laboratory overview (maximum one page)**

We develop new platform technologies to more effectively diagnose and treat cancer. We primarily develop molecular imaging and phototherapy agents as well as nature-inspired theranostic nanomedicines, with a focus on creating clinically translatable technologies.

**Current Research Support**

Funding Source & Program Name: TFRI Program Project Grant - Zheng (Program Leader, PL) Co-PLs: B Wilson/J Irish

Project Title: Porphysome Nanoparticle-Enabled Image-Guided Cancer Interventions

Total Award: 7,315,000

Total Award to You: 3,625,000

Start Date: 07/2017

End Date: 06/2022

Main Objective: . The goal is to create a translational research program to develop porphysome nanotechnology from bench to bedside, to apply them for image-guided therapy of prostate and thyroid cancer, and to perform pilot clinical trials.

Outline of Methodology:

Budget Details: Salaries: 1,901,000 Supplies and expenses: 1,724,000

Relationship to and overlap with 2017 PPG application: There is no overlap

Funding Source & Program Name: CCSRI Innovation Grant

Project Title: Nature-inspired smart nanoparticles for spectral-modulated photothermal and photodynamic therapy of cancer

Total Award: \$200,000

Total Award to You: \$200,000

Start Date: 08/2016

End Date: 07/2018

Main Objective: We mimic the most efficient light-to-chemical energy conversion known in nature to create novel porphyrin nanoparticles to transform the efficacy and safety of PDT with curable intent for these patients.

Outline of Methodology:

Budget Details: Salaries: 110,000 Supplies and expenses: 90,000

Early tumor detection and prevention in Li-Fraumeni Syndrome  
Relationship to and overlap with 2017 PPG application: There is no overlap

Zheng, Gang

Funding Source & Program Name: CIHR Project Scheme Grant

Project Title: A new treatment platform for glioblastoma: Ultrasound-mediated *in situ* conversion of porphyrin microbubbles to theranostic nanoparticles

Total Award: \$707,164.00

Total Award to You: \$707,164.00

Proposed Start Date: 07/2016

End Date: 06/2021

Main Objective: The major goals of this project are: 1) optimize the pMB formulation and conversion parameters to minimize pNP size and polydispersity; 2) establish optimal MB/FUS exposure parameters and pMB dose for BBB disruption; 3) use 64Cu-labelled pMBs to quantify porphyrin distribution *ex vivo* and validate tumor-selective pNP accumulation following pMB/FUS; 4) deliver dose-ranging PDT and measure tumor responses and collateral brain tissue damage; and 5) evaluate the therapeutic efficacy of combined PDT + SDT *in vivo*.

Outline of Methodology: develop a novel BBB-crossing photodynamic therapy paradigm for brain tumors

Budget details: Consumables: 311,000 Salaries: 515,000

Relationship to and overlap with 2017 PPG application: There is no overlap

Funding Source & Program Name: PMCC Collaborative Translational Grant

Project Title: Personalized Porphysomes

Total Award: \$ 300,000

Start Date: 8/01/15

End Date: 7/31/17

Main Objective: This goal is to perform preclinical toxicology and early phase assessment of porphysomes in ovarian and H&N cancers.

Outline of Methodology: We will enlist a Health Canada-approved CRO to perform the preclinical GLP toxicity studies and we will also develop clinical trial applications for the 1st-in-patient studies of porphysomes

Budget Details: Toxicology studies \$ 200,000 Clinical trials \$ 100,000

Personnel Details: n/a

Relationship to and overlap with 2017 PPG application: There is no overlap

Funding Source & Program Name: PMCC Innovation Accelerator Fund

Project Title: Scale up production of porphysome

Total Award: \$250,000

Total Award to You: \$ 250,000

Start Date: 10/06/15

End Date: 10/5/16

Main Objective: This fund will support the scale up and synthesis of drug substance and product to enable pre-clinical GLP toxicology and Phase I clinical trial.

Outline of Methodology: Transfer lab SOP for porphyrin-lipid synthesis to CRO to complete the 400g batch synthesis

Budget Details: entire budget for paying an external contractor

Personnel Details: n/a

Relationship to and overlap with 2017 PPG application: There is no overlap

Funding Source & Program Name: NSERC Discovery Grant

Project Title: New Chemistry of Making Porphyrin Nanostructures

Total Award: \$370,000

Total Award to You: \$370,00

Start Date: 04/01/15

End Date: 03/31/20

Main Objective: Develop new chemistry, structure and function of lipid nanoparticles and greatly expanded the utility of lipid nanoparticles from conventional delivery systems to novel functional materials.

Early tumor detection and prevention in Li-Fraumeni Syndrome

Zheng, Gang

*Outline of Methodology: Synthesis and physical characterization of novel porphyrin-lipid structures (shape, size, morphology)*

*Relationship to and overlap with 2017 PPG application: There is no overlap*

*Funding Source & Program Name CIHR Operating Grant*

*Project Title: : Improving cure rate of early stage lung cancer with personalized nanomedicine*

*Total Award: \$695,000*

*Total Award to You: \$695,000*

*Start Date: 02/01/14*

*End Date: 01/31/19*

*Main Objective: This is a multidisciplinary proposal that will test novel approach and using patient-derived XG models for increasing the efficacy of chemotherapy against NSCLC, with the ultimately goal of increasing the cure rate for this disease.*

*Outline of Methodology: develop an image-guided drug delivery approach based on a HDL-like paclitaxel core-loaded porphyrin nanoparticle*

*Relationship to and overlap with 2017 PPG application: There is no overlap*

*Funding Source & Program Name: CFI Innovation Grant*

*Project Title: Targeted Biologics - Molecular Diagnostics and Therapeutics*

*Total Award: \$ 8,939,425*

*Total Award to You:*

*Start Date: 11/2015*

*End Date: 10/2020*

*Main Objective: This equipment will be used by a multidisciplinary pool of Principal Investigators, Post-Doctoral Fellows, and graduate students in the many laboratories at the Faculty that conduct groundbreaking oncology research.*

*Outline of Methodology:*

*Relationship to and overlap with 2017 PPG application: There is no overlap*

*Funding Source & Program Name: Canadian Cancer Society Impact Grant*

*Project Title: Ultra-minimally invasive multi-modal image-guided therapeutics of lung cancer*

*Total Award: \$1,250,000*

*Total Award to You: \$250,000*

*Start Date: 01/ 2016*

*End Date: 12/2021*

*Main Objective: The major goals of this project are: Our final goal is to achieve a highly sensitive and precise ultra-minimally invasive localization system and treatment modality that can be translated to both surgical and non-surgical lung cancer patients*

*Outline of Methodology: This project is a continuation of the early CIHR grant (PI: Zheng) but to take a step further to make the transition from bench to bed side*

*Relationship to and overlap with 2017 PPG application: There is no overlap*

*Funding Source & Program Name: CFI Leaders Opportunity Fund*

*Project Title: : Science Operating Room Extension (ScORE)*

*Total Award: \$1,597,680*

*Total Award to You: \$1,597,680*

*Start Date: 01/2013*

*End Date: 12/2017*

*Main Objective: The mayor goals of this project are: The requested infrastructure for ScORE will enable research to develop and de-risk agents for image-guided surgery, pathology and diagnosis. These agents will improve the treatment of cancer for Canadians by better diagnosing and classifying tumors so that the treatment can be personalized and guiding surgery to ensure complete resection of malignant tissue.*

*Outline of Methodology: see above*

*Relationship to and overlap with 2017 PPG application: There is no overlap*

**Pending Research Support**

*Funding Source & Program Name: CIHR Foundation Grant*

*Project Title: Porphyrin Nanomedicine for Cancer Imaging and Therapy*

*Total Award: \$ 3,750,000*

*Total Award to You: \$ 3,750,000*

*Start Date: 09/2017*

*End Date: 10/2024*

*Main Objective: The goal of my Foundation Program is to rationally expand the scope of porphysomes to generate novel classes of intrinsically multifunctional nanomaterials that address current challenges in phototherapy, drug delivery and cancer medicine.*

*Outline of Methodology:*

*Relationship to and overlap with 2017 PPG: There is no overlap*

**TERRY FOX RESEARCH INSTITUTE****CURRICULUM VITAE**

(Use 11 pt font, single spacing, half-inch margins throughout)

<b>FULL NAME:</b> Trevor John Pugh	
<b>POSITION TITLE:</b> Scientist, Princess Margaret Cancer Centre  Assistant Professor, Department of Medical Biophysics, University of Toronto	
<b>INSTITUTION:</b> University Health Network / University of Toronto	
<b>FULL ADDRESS:</b> TMDT 9-305, 101 College Street, Toronto, ON M5G 1L7	
<b>TELEPHONE:</b> 416-581-7689	<b>EMAIL:</b> trevor.pugh@utoronto.ca
<b>WEB-ADDRESS:</b> <a href="http://www.uhnresearch.ca/researchers/profile.php?lookup=59885">http://www.uhnresearch.ca/researchers/profile.php?lookup=59885</a>	

<b>ACADEMIC BACKGROUND</b>			
<i>Degree Type</i>	<i>MM/YY</i>	<i>Discipline/Field/Specialty</i>	<i>Institution &amp; Country</i>
B.Sc.	05/04	Biochemistry, Chemistry, Minor in Commerce	University of British Columbia, Canada
Ph.D	11/09	Medical Genetics	University of British Columbia, Canada
Clinical Laboratory Fellowship	03/12	Clinical Molecular Genetics (ACMG)	Harvard Medical School, USA
Post-Doctoral Fellowship	06/13	Cancer Genomics	Dana Farber Cancer Institute/Broad Institute of Harvard & MIT, USA

<b>WORK EXPERIENCE</b>			
<i>Position, Organization</i>	<i>Department/Division</i>	<i>Start Date</i>	<i>End Date</i>
Director and Associate Scientist, Translational Genomics Laboratory	Ontario Institute for Cancer Research	Jan. 2016	n/a
Scientist and Lead Clinical Genomics Program, University Health Network	Princess Margaret Cancer Centre	Sept. 2013	n/a
Assistant Professor, University of Toronto	Medical Biophysics	Sept. 2013	n/a
Consultant, Bioinformatics Developer, Brigham and Women's Hospital	Center for Advanced Molecular Diagnostics	May 2013	June 2013
Assistant Laboratory Director (Part Time), Partners Center for Personalized Genetic Medicine	Laboratory for Molecular Medicine	Apr. 2012	Apr. 2013
Genomics Technologist (Part Time), BC Cancer Agency	BC Genome Sciences Centre	Sept. 2003	Aug. 2004
Co-op Student, BC Cancer Agency	BC Genome Sciences Centre	Jan. 2003	Aug. 2003
Co-op Student, University of British Columbia	Dept. of Physics & Astronomy	May 2002	Dec. 2002
Co-Founder, Head of PC Technical Services, Quicktech Computer Consulting Inc.	PC Technical Services	Nov. 1999	Nov. 2002

**A. Personal Statement (*max one page*)**

*Briefly describe why your experience and qualifications make you particularly well-suited for your role in the application.*

My research seeks to enable application of genome sequence analysis as a routine clinical test, particularly as modern cancer treatments are increasingly predicated on genetic information. I am interested in genome analysis of serial biopsies and circulating tumour DNA collected during clinical trials (particularly immunotherapies), as well as genetic relationships amongst tumour subclones and metastatic sites suggestive of effective combination therapies. As a board-certified molecular geneticist (ABMG), I support clinical test development using a next-generation sequencing platform within University Health Network (UHN) Laboratory Medicine Program. By participating in clinical and research activities across UHN, I am well-suited to lead a multidisciplinary team to translate novel discoveries into clinical practice. While I am now based at an adult cancer hospital, I have published landmark genome studies of several pediatric solid tumours and have continued this work a principal investigator in the NCI TARGET Initiative (<https://ocg.cancer.gov/programs/target>) and as a member of the StandUp2Cancer Cancer Stem Cell Dream Team characterizing pediatric ependymomas and glioblastomas ([www.standup2cancer.ca/en/dream\\_teams/view/cancer\\_stem\\_cell\\_dream\\_team](http://www.standup2cancer.ca/en/dream_teams/view/cancer_stem_cell_dream_team)). I am also a Terry Fox New Investigator mentored within Dr. David Malkin's PROFILE Translational Cancer Research Project.

In September 2013, I established a clinically-oriented cancer genomics research program at the Princess Margaret Cancer Centre, with the goal of using DNA, RNA, and epigenetic sequence analysis in clinical studies of cancer patients treated at Princess Margaret and other hospitals. In support of this effort, I received competitive infrastructure funding from the Canada Foundation for Innovation and the Ontario Ministry of Research and Innovation that I used to strategically house core equipment with the Princess Margaret Genomics Centre ([www.pmgenomics.ca](http://www.pmgenomics.ca), PMGC) for use by the broader community. I am appointed Scientist and Lead, Clinical Genomics Program at the Princess Margaret Cancer Centre (PM), and am appointed as Assistant Professor in the Department of Medical Biophysics at the University of Toronto. Here, I lead an academic laboratory (10 trainees and 5 staff), provide scientific oversight of the PM Genomics Centre (PMGC, 6 staff), and am Director of the Translational Genomics Laboratory (4 staff), a new joint initiative between the Princess Margaret Cancer Centre and Ontario Institute for Cancer Research to facilitate clinical translation of genome technologies.

I have received \$796,800 in infrastructure awards from the CFI Leaders Opportunity Fund and ORF Research Infrastructure Program to purchase equipment that enable cancer genome discovery projects such as this one. We have strategically placed much of this equipment in the PMGC to support genomics research across our institute, including three laboratory robotics systems (Hamilton STAR and STARlet, QIAsymphony), a high-throughput DNA shearing device (Covaris LE220), Fluidigm C1 and Access Array systems, and a newly purchased 10X Genomics Chromium system. The PMGC also maintains next-generation sequencing platforms from Illumina (2x HiSeq2500s, 2X NextSeq500s) and Life Technologies (Ion Proton). Dedicated equipment in my laboratory includes a Thermo Microm Cryostat, Leica DMI6000B imaging microscope, 3 Biological Safety Cabinets, an Agilent TapeStation, Qubit fluorometer, Nanodrop 2000c, vacuum manifold for circulating tumour DNA extraction, cell culture incubator, dedicated fume hood, plus multiple thermocyclers and centrifuges.

For computational analysis, my laboratory utilizes a shared compute resource maintained by a bioinformatics lead (Carl Virtanen) and 4 bioinformaticians. The compute cluster houses 500 CPU cores and ~1 PB of storage space, plus my group's dedicated server for interactive jobs and web services. This system brings together lab members from across PM, to develop a common set of tools and share a controlled, local mirror of public genomics data. To support storage and reanalysis of publicly available data sets, I have recently purchased a 114 terabyte storage server dedicated for my group's use. We currently have local access to RNAseq data from >3,200 non-cancer tissue specimens analyzed by the Genotype-Tissue Expression project; exome, genome, and RNAseq data from >1,500 tumours analyzed by The Cancer Genome Atlas (TCGA); and exome, RNAseq, and targeted sequencing data from >750 pediatric cancers analyzed by the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative. As our bioinformatics activities grow, we will migrate our tools to the HPC4Health platform ([www.hpc4health.ca](http://www.hpc4health.ca)). This will provide another 1,444 CPU cores with 256 GB of memory per node, and an additional 1.2 PB of storage, thereby ensuring we have sufficient, scalable capacity for expanded analytic requirements for this program.

**B. Selected Research / Technology Development Contributions Over the Past Five Years (max four pages)**

In this section provide your most significant contributions to research / technology (peer-reviewed articles, reports, books, intellectual property, products, services, trainees and other forms of research output).

**Cell-free DNA sequencing for non-invasive monitoring of tumour and immune cell populations**

Recently, my lab developed a circulating tumour DNA (ctDNA) sequencing assay, termed Liquid Biopsy Sequencing (LB-Seq) that combines a hybrid-capture method with a novel bioinformatics algorithm to enable full-length sequence analysis of all exons in genes of interest, rather than mutation hotspots (Kis et al. *Nature Communications* 2017). In collaboration with Dr. Suzanne Trudel, we initially developed LB-Seq as part of MYELSTONE (“MYELOma STOp NEedle”), a study of patients with multiple myeloma to assess whether sequencing of cell-free DNA (cfDNA) circulating in blood plasma was comparable to the current clinical standard of analyzing tumour cells isolated from painful bone marrow needle aspirates. Applying LB-Seq to 59 cfDNA specimens, we used hybrid capture to isolate all exons from 5 genes (*KRAS*, *NRAS*, *BRAF*, *EGFR* and *PIK3CA*), followed by ultra-deep (>25,000X) DNA sequencing and filtering of mutation calls using a novel algorithm that enabled detection of tumour-derived fragments at concentrations as low as 0.4%. Comparing 42 cfDNA specimens with matched bone marrows collected within 1 hour of the blood draw, LB-Seq detected 42/44 somatic mutations and called one mutation not detected in bone marrow tumour cells (96% sensitivity, 99% specificity). The single mutation found in cfDNA but not detected in bone marrow DNA was found in serial blood draws from this patient and was not seen in any other cases, suggesting this may be derived from a clone not captured by the bone marrow aspirate and that the specificity may be even higher than estimated. Analysis of 17 cfDNA specimens from patients without usable matched bone marrow aspirates (typically 15% of multiple myeloma patients) uncovered actionable mutations in 53% of cases that otherwise would have no molecular profiling result. Hence, this approach represents a significant advance for molecular profiling of patients with multiple myeloma and is likely translatable to solid tumours as well. We have now been funded to deploy this test within the CAP/CLIA/OLA certified molecular lab within UHN (Dr. Suzanne Kamel-Reid).

Stemming from our work with immunotherapy clinical trials at Princess Margaret Cancer Centre, we have adapted developed our cfDNA sequencing method to target functional V, D, J regions within T-cell receptor (TCR) sequences corresponding to tumour infiltrating lymphocytes (TIL) within tumours and circulated in blood. Due to the diversity of TIL populations and presence of non-T-cells in tissues and blood, we require highly targeted sequencing data to adequately sample rare clones that may expand upon re-activation by immunotherapy. Therefore, my lab has developed a TCR sequencing assay based on hybrid capture (IDT xGen Lockdown probes) followed by ultra-deep Illumina sequencing. This method is amenable to low quantities of fragmented DNA such as cell-free DNA in plasma and cerebral spinal fluid, and is not subject to size bias seen in other PCR-based methods. Our data demonstrate base-level resolution of polyclonal, enriched, and monoclonal T cell populations, including explicit enumeration of each TCR population. We have also applied this method to peripheral blood mononuclear cells isolated from patients receiving TIL infusion products from an adoptive cell therapy trial, illustrating the ability to track T-cell populations in blood. We are now optimizing probes against the immunoglobulin loci to enable profiling of B-cell populations, should this become an important population arising from the single cell analysis in cancers described in this proposal. We patented this method in 2016.

**ii. Discovery of oncogenic mechanisms in pediatric cancer genomes**

From 2010–2013, I was a postdoctoral fellow with Dr. Matthew Meyerson at the Dana-Farber Cancer Institute, and a part of the Cancer Genome Analysis group of the Broad Institute of Harvard and MIT. Here, I led three major cancer genome discovery projects characterizing pediatric solid tumours: medulloblastoma (brain), neuroblastoma (nervous system), and pleuropulmonary blastoma (lung pleura). In these studies, we used exome and genome analysis to identify significantly mutated genes encoding mechanisms commonly disrupted in each cancer.

Our analysis of 92 medulloblastomas (Pugh et al. *Nature*, 2012) found twelve genes altered at significant frequency that implicated WNT, hedgehog, histone methyltransferase, and nuclear co-repressor (N-CoR) complexes within specific molecular subtypes of this disease. Our approach also nominated the RNA helicase *DDX3X* as a novel component of pathogenic beta-catenin signaling—a finding confirmed by subsequent functional studies. Through the NCI TARGET consortium, our analysis of 240 neuroblastomas (Pugh, Morozova et al. *Nature Genetics*, 2013) uncovered relatively few recurrently mutated genes beyond known entities *ALK*, *PTPN11*, *ATRX*, *MYCN*, and *NRAS*. Instead, mutations were dispersed across many genes, challenging therapeutic strategies reliant upon single, frequently mutated targets. Within

this flat landscape of somatic mutation, we observed frequent mutation of RAS/MAPK components as well as germline loss-of-function *BARD1* variants, consistent with a recent genome-wide association study. I also performed an analysis of clinically-associated germline variation from NCBI's ClinVar database to nominate pathogenic germline variants in *ALK*, *CHEK2*, *PINK1*, *TP53*, and *PALB2*.

In contrast to neuroblastoma and medulloblastoma, mutations in pleuropulmonary blastoma were highly recurrent, as nearly every case harbored two *DICER1* variants: a predisposing loss-of-function germline allele and an oncogenic somatic point mutation with the RNase IIIb domain (Pugh et al. *Oncogene*, 2014). Our analysis of mutation clonality suggests that these events are initiating and subsequently synergistic with biallelic loss of *TP53* as the disease progresses from cysts to tumours. Mutation frequencies in pleuropulmonary blastoma were closer to adult cancers (median 32 exonic mutations) than pediatric malignancies studied by our group (median 14 in medulloblastoma, 18 in neuroblastoma).

Together, these three studies illustrate a diversity of oncogenic mechanisms apparent in relatively simple pediatric cancer genomes, and identify several new avenues for genome, functional, and clinical study. In recognition of these effects, I received trainee scholar awards from the American Association of Cancer Research in 2011 (neuroblastoma), 2012 (medulloblastoma), and 2013 (pleuropulmonary blastoma).

### **iii. Building collaborative genomics platforms**

Since joining PM in 2013, my group has been a catalyst for collaborative cancer genomics projects. To date, we have analyzed 480 exome, 443 RNA-seq, 1371 targeted panel, 510 cell-free DNA, 24 targeted Methyl-seq, 51 ATAC-seq, and 12 single cell-RNAseq libraries we derived from patient specimens. In addition to projects I lead, my group has collaborated and published with 7 other laboratories to uncover molecular mechanisms underlying 6 cancers and several purified immune cell populations. Collaborative cancer genomics projects include discovery of near-genome-wide copy neutral loss of heterozygosity in pancreatic neuroendocrine tumours (Quevedo et al. submitted), discovery of somatic recovery of BRCA1/2 function as a mechanism of resistance to olaparib (Lhereux et al. *JCO* 2017), analysis of cells demonstrating viral mimicry after treatment with DNA demethylating agents (Roulois et al. *Cell*. 2015), analysis of lung cancers with *ALK* rearrangements missed by immunohistochemistry but found by FISH (Shi et al. *J Thorac Oncol*. 2016), verification in primary breast cancer specimens of non-coding somatic variants that modulate ESR1 expression (Bailey et al. *Nat Genet*. 2016), elucidation of the risk of risk SNPs in modulating long noncoding RNA expression (Guo et al. *Nat Genet*. 2016), and discovery and targeted sequencing of a recurrent in-frame SH3PXD2A-HTRA1 in schwannoma, a peripheral nerve sheath tumour (Agnihotri et al. *Nat Genet* 2016).

Independent of our research labs, Dr. Ken Aldape and I recently founded the [PM-OICR Translational Genomics Laboratory](#) to standardize our exome, RNA-seq, and methylation platforms to support clinically-oriented cancer genomics projects. We have engaged >15 PIs from 5 institutions to profile tumours from patients with rich clinical annotations. These projects often center around patients with unusual clinical or molecular features such as exceptional response or resistance to immunotherapies, lack of any actionable mutations despite extensive panel testing, rare tumours of unknown etiology (particularly brain tumours), or challenging clinical specimens such as lung primary/brain metastasis pairs. Since September 2016, we have analyzed >200 exome, RNA-seq, methylation array data sets and deployed a local instance of cBioPortal to share mutation and copy number data with our collaborators.

As Scientific Director of the [PM Genomics Centre](#), I have overseen the deployment of four complementary single cell transcriptome analysis platforms: flow sorting cells into plates, a Fluidigm C1, a custom Drop-Seq device, and a 10X Genomics Chromium. The availability of these new technologies has driven a local boom in single cell RNA-seq analysis including analysis of planaria, zebrafish, mouse cancer and non-cancer models, and human cancer and non-cancer primary tissues. These platforms are now used by >30 PIs at 9 different institutions across North America and Europe including USA, Germany, Norway, Switzerland, and Canada.

### **Invention disclosures**

1. Hybrid-capture sequencing for determining immune cell clonality  
Patent, Filing Date: 2016-04-15
2. Liquid Biopsy Sequencing (LB-Seq) Method for non-invasive profiling of tumour-specific genetic mutations

Disclosed, Filing Date: 2015-11-26

3. Clinical Trials App: A mobile app that helps select an appropriate and relevant clinical trial for a patient by filtering on biomarkers and clinical history information  
Disclosed, Filing Date: 2015-11-05
4. A secure, web-based, auditable framework for clinical data collection and sharing  
Disclosed, Filing Date: 2015-02-02

**COMMITTEES**

Genomics of MPNST Consortium, Scientific Advisory Committee	Member	2017/4 – Present
Cancer Genomics Consortium Plasma Cell Disorder Working Group	Chair	2016/8 – Present
BC Cancer Agency Personalized OncoGenomics Scientific Advisory	Member	2016/4 – Present
Terry Fox Research Institute ASM Scientific Organizing Committee	Member	2015/11 – 2016/5
Canadian Clinical Trials Group, CSTB Scientific Advisory	Member	2016/4 - Present
American Association for Cancer Research, GENIE Project	Member	2013/7 – Present
U of Toronto, Dept. Medical Biophysics Executive Committee	Member	2015/12 – Present
U of Toronto, Dept. Medical Biophysics Curriculum Committee	Member	2015/1 – Present
HPC4Health Steering Committee	Member	2014/6 – Present
Cancer Care Ontario Molecular Oncology Test Advisory Committee	Member	2014/1 – Present
Ontario Cancer Institute Animal Care Committee	Member	2014/3 – Present
Princess Margaret Cancer Genomics Program Executive	Member	2013/9 – Present
Princess Margaret Circulating Tumor Biomarker Committee	Chair	2013/9 – Present

**PROFESSIONAL ASSOCIATIONS**

American Association for Cancer Research	Associate member	2010 – Present
American College of Medical Genetics and Genomics	Fellow	2013 – Present

**GRANT REVIEWS & PANELS**

Israel Cancer Research Fund	Grant Reviewer	4/2017
Vanier Canada Graduate Scholarships – U of T MBP	Grant Reviewer	10/2016
Seeds4Hope, Windsor Essex County Cancer Centre Foundation	Grant Reviewer	9/2016
Prostate Cancer Canada Discovery Grants Review Panel B	Grant Reviewer	2016/6
Ontario Graduate Scholarship – U of T Medical Biophysics	Grant Reviewer	2016/5
Princess Margaret Personalized Medicine Collaborative Team	Grant Reviewer	2016/5
Mitacs, Accelerate Research Grants	Grant Reviewer	2015/9, 2017/8
Garron Family Cancer Centre, Hospital for Sick Children	Grant Panel Reviewer	2015/6
Canadian Cancer Society Research Institute, Travel Awards	Grant Panel Reviewer	2015/3-2015/11
Multiple Myeloma Research Foundation	Grant Reviewer	2014/7, 2017/8

**JOURNAL MANUSCRIPT REVIEWER**

Nature Medicine, Nature Communications, Genome Medicine, Oncotarget, Annals of Oncology, BMC Medical Genomics, BMC Cancer, Bioinformatics, PLOS Medicine, Laboratory Investigation, Genetics in Medicine, Journal of Clinical Oncology, Cancer Research, BMC Genomics

**MENTORSHIP****Postdoctoral fellows**

Samah El Ghamrasni, PhD (joint with Mathieu Lupien)	1/2016 - Present
David Mulder, PhD	2/2015 – Present
Soroush Samadian, PhD	1/2015 – Present
Olena Kis, PhD	11/2014 – 6/2017
Jeff Bruce, PhD	6/2014 – 5/2016

**Graduate Students**

Danielle Croucher, MSc (joint with Suzanne Trudel)	9/2016 - Present
Leslie Oldfield, BSc	1/2016 - Present
Laura Richards, BSc	1/2016 - Present
Nina Tingting Wang, BSc (joint with Scott Bratman)	1/2016 - Present
Signy Chow, MD	10/2015 - Present
Cindy Yang, BSc	8/2014 - Present
Rene Quevedo, BSc (joint with Benjamin Haibe-Kains)	9/2014 - Present

**Undergraduates**

Harold Hodgins – Summer student (Laurier, MBP Summer Scholar)	5-8/2017
Emily Hutchings - Summer student (Queen's, MBP Summer Scholar)	5-8/2016
Joseph Song - Co-op student (Waterloo)	5-8/2015
Michael Li - Co-op student (Waterloo)	9-12/2014, 5-8/2015
Maya Schonbach - Co-op student (Waterloo)	9-12/2014, 5-8/2015
Rene Quevedo - Co-op student (Seneca College)	5-8/2014
Mark Mansour - Summer student (McMaster, MBP Summer Scholar)	5-8/2014
Jessica Liu - Summer student (Queen's University)	5-8/2014, 5-8/2015
Andrew Reid - Summer student (Queen's University)	5-8/2014

**TEACHING**

Module Coordinator, U of Toronto MBP1001Y, Quantitative Cancer Genomics	1/2017
Lecturer, U of Toronto MBP1007Y, Fundamentals in Medical Biophysics	10/2014, 10/2015
Lecturer, U of Toronto LMP1530, Next Generation Genomics in Clinical Medicine	2/2014
Lecturer, Harvard Medical School Genetics Training Program	10/2012

**C. Honours & Awards**

List any honours and personal awards in chronological order.

3/2011-05/2013	CIHR Postdoctoral Fellowship (deferred 1 year due to clinical training program)
4/2011	Partners HealthCare Partners in Excellence Team Award (Clinical sequencing platform)
4/2011	AACR-GlaxoSmithKline Outstanding Clinical Scholar Award
2/2012	CureSearch Travel Award (Pediatric Cancer Translational Genomics)
4/2012	AACR-Aflac Incorporated Scholar-in-Training Award
4/2013	AACR-GlaxoSmithKline Outstanding Clinical Scholar Award

**D. Overview & Details of Research Support**

*Provide an overview of your current areas of research focus including supports of your research / laboratory (max one page). Include a list of the current and pending research support (grants and contracts) from all sources. For each research support, clearly describe the main objective and provide a brief outline of the methodology and budget details including staff requirements. Explain any relationship, difference or overlap (scope or financial) between this application and all other research support (current or pending) held by the applicant. If applicable, explain any perceived duplication in funding or how this application complements research funded by other sources.*

The Pugh lab is focused on the application of genome sequence analysis as a routine clinical test, particularly as modern cancer treatments are increasingly predicated on genetic information. I am particularly interested in genome analysis of serial biopsies and circulating tumour DNA collected during clinical trials; genomic predictors of immunotherapy through integrated analysis of tumour, stromal and immune cells; subclonal genetic relationships amongst metastatic sites suggestive of effective combination therapies; and oncogenic mechanisms underlying rare tumours of unknown etiology. I also spend part of my time supporting diagnostic testing as a clinical molecular geneticist through the CLIA-certified Advanced Molecular Diagnostics Laboratory at the Princess Margaret Cancer Centre.

Cancers arise due to changes in genetic sequence and structure that alter the biology of normal cells. Large-scale studies have uncovered differing mutation rates across cancer types, with the lowest rates found in pediatric (Pugh et al. Nature. 2012, Pugh et al. Nat Genet. 2013) and hematologic malignancies (Wang et al. N Engl J Med. 2011) and the highest rates in environmentally associated cancers, such as lung cancer (smoking, Imielinski et al. Cell. 2012) and melanoma (sun exposure, Berger et al. Nature. 2012). Recurrent somatic alterations of cancer genomes have been found within and across cancer types, leading to the identification of new biological subtypes and an understanding of mechanisms disrupted in tumours regardless of tissue site. This observation emphasizes a need to transition from an anatomical- to a molecular-based classification of tumours and reveals opportunities for use of targeted and/or immuno-therapies across tumour types, if strong genotype/phenotype associations are known.

To begin linking genomic genotypes to clinical phenotypes, our laboratory seeks to enable comprehensive genomic profiling of consistently ascertained and treated cancer specimens. Specifically, we are conducting high-resolution examinations of tumour DNA, RNA and epigenetic marks from primary tumour biopsies; examinations that are now feasible due to continued advancements in DNA sequencing technology. Termed "next-generation sequencing" (NGS), advanced DNA sequencing methods have enabled routine analysis of all genetic content (whole genome sequencing, WGS), all annotated genes (whole exome sequencing, WES), all expressed genes (RNA sequencing, RNA-Seq) and regulators of gene expression (e.g. epigenetic marks, histone binding sites, and DNA/protein interactions) in tissues and, more recently, single cells. These data types are highly complementary and analysis of one large-scale data set greatly informs another. Therefore, we are developing laboratory and computational approaches to extract multiple sources of genome variation from suboptimal tumour specimens, and to integrate these data types into cohesive portraits of individual tumour biology. Part of our work focuses on translation of these findings into clinical practice through nomination of clinically-informative markers for targeted testing and development of bioinformatics tools to support clinical laboratory workflows.

<b>Funding Source &amp; Program Name</b>	Canadian Institutes for Health Research – Program Grant
<b>Project Title</b>	<b>Non-invasive monitoring of liver cancer recurrence following surgery using circulating tumour DNA sequencing</b>
<b>Total Award</b>	\$1,331,100
<b>Total Awarded to Me</b>	\$1,331,100
<b>Start Date</b>	April 1, 2017
<b>End Date</b>	March 31, 22
<b>Main Objective</b>	Our goal is to improve outcomes of surgical intervention for hepatocellular carcinoma (HCC) by developing a non-invasive blood-based assay for monitoring of disease after liver resection or transplant.
<b>Outline of Methodology:</b>	We will achieve this goal by integrating clonal genomic structure in tumours from 120 patients followed by assessment of whether these alterations can be detected in circulating tumour DNA in serial blood draws as a marker of recurrence following surgery. In patients with recurrent disease, we will compare the clonal composition of biopsies at relapse with the original surgical specimen.
<b>Budget Details</b>	Personnel, Supplies
<b>Personnel Details</b>	Support for Grad Student, Post Doc Fellow, Research Technician, research coordinator
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Terry Fox Research Institute – New Investigator Award
<b>Project Title</b>	<b>Single cell dissection and non-invasive monitoring of childhood cancer and immune systems during treatment</b>
<b>Total Award</b>	\$449.942
<b>Total Awarded to Me</b>	\$449,942
<b>Start Date</b>	April 1, 2017
<b>End Date</b>	March 31, 2020
<b>Main Objective</b>	We seek to understand how the balance of cancer and immune cells in pediatric tumours may dictate the efficacy of a new class of drugs that activate the immune system to combat cancer. We will also assess whether the response of tumour and immune cells to immunotherapy may be tracked using analysis of simple blood draws rather than invasive surgery or tissue biopsy.
<b>Outline of Methodology:</b>	We propose to use single cell RNA sequencing methods to analyze which genes are expressed by each of thousands of cells from serial collections of tumours from children with cancer. We will also examine the DNA of immune cells that infiltrate tumours to understand how they recognize tumour cells. To assess whether these patterns can be monitored using non-invasive blood tests, we will apply a new liquid biopsy sequencing technology to track immune and tumour response in serial blood samples over time.
<b>Budget Details</b>	Personnel, supplies, services
<b>Personnel Details</b>	Post-doctoral fellow
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Leukemia and Lymphoma Society – Specialized Center of Research Program (SCOR)
<b>Project Title</b>	<b>Therapeutic implications of altered epigenetics and DNA damage responses in hematologic disorders</b>
<b>Total Award</b>	\$3,416,645
<b>Total Awarded to Me</b>	\$187,500
<b>Start Date</b>	Jan. 1, 2017
<b>End Date</b>	Jan. 1, 2022
<b>Main Objective</b>	Our objectives are 1) to enable systematic genome and proteome characterization of single cells that will underpin all projects in our program; 2) to enable exploration and cross-fertilization of these data by investigators across the program, augmented by complementary publicly available genomic data sets; and 3) to extend our current single cell transcriptome platform towards high-throughput assays amenable to detection of rare cell types within complex populations.
<b>Outline of Methodology:</b>	Currently, single cell manipulation is well-supported through a commercial microfluidics platform, the Fluidigm C1. This instrument can isolate up to 96 or 800 single cells that can be imaged, qualified and processed via whole genome or whole transcriptome amplification for downstream analysis (full-length transcripts from 96 cells or end-tags from 800 cells). This material can then be used for single cell RNA-seq; targeted RNA-seq; ATAC-seq; targeted DNA sequencing; whole genome sequencing; and/or qPCR. Using our current deep, single cell RNA-seq configuration (>2 million reads/cell), we can assay ~20,000 annotated protein-coding genes in 96 cells for expression level, isoform usage, somatic mutations, and fusion transcripts. Core A will have access to two Fluidigm C1 instruments, and has already generated high quality data from mouse hematopoietic samples.
<b>Budget Details</b>	Personnel, Supplies, Services
<b>Personnel Details</b>	Partial Support for 2 research associates
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Terry Fox Research Institute – Translational Research Program
<b>Project Title</b>	<b>The Terry Fox Pan-Canadian Multiple Myeloma Molecular Monitoring (M4) Cohort Study</b>
<b>Total Award</b>	\$5,000,000
<b>Total Awarded to Me</b>	\$150,000
<b>Start Date</b>	July 1, 2016
<b>End Date</b>	June 30, 2021
<b>Main Objective</b>	We will collaboratively apply leading edge technologies for myeloma characterization and monitoring towards improving patient care and outcomes in a more personalized fashion. Our objectives are: 1) To determine the optimal integration of ultrasensitive molecular methods of monitoring myeloma disease burden into clinical practice; 2) To identify and implement strategies for making better myeloma patient management decisions based on the results of ultrasensitive disease monitoring; and 3) To explore novel methods of characterizing and monitoring the biology of the myeloma clone being developed in Canadian laboratories for their potential to further individualize therapy.

<b>Outline of Methodology:</b>	We will evaluate the optimal application of the most well developed new methods of minimal residual disease monitoring – FDG PET scanning, multiparameter flow cytometry and next generation immunoglobulin gene sequencing – including the development of treatment protocols in which patient management decisions are directly informed by the test results in conjunction with baseline risk stratification parameters. We will explore novel approaches to myeloma characterization and monitoring – circulating tumour DNA, mechanisms of drug resistance, and drug-resistant myeloma progenitor populations – for their potential value in patient care. We will evaluate the impact of the implementation of these novel technologies on patients' disease control, survival, and quality of life, and the economic impact of the implementation of these new technologies on the Canadian health care system. By applying these leading edge technologies to the development of more personalized treatment strategies, we expect to maintain or improve patient outcomes while avoiding the costs and toxicities of ineffective or unnecessary therapies.
<b>Budget Details</b>	supplies, services
<b>Personnel Details</b>	None
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Terry Fox Research Institute - Translational Cancer Research Projects program
<b>Project Title</b>	<b>immunoTherapy NeTwork (iTNT): Targeting ovarian cancer</b>
<b>Total Award</b>	5,414,068
<b>Total Awarded to Me</b>	\$549,150
<b>Start Date</b>	July 1, 2016
<b>End Date</b>	June 30, 2021
<b>Main Objective</b>	To provide insights into the basic immunobiology of High Grade Serous Ovarian Cancer and use this knowledge to develop rational combination clinical trials in cancer immune therapy.
<b>Outline of Methodology:</b>	The major deliverables from this network include: 1) A comprehensive understanding of the impact of PD-1 targeted checkpoint blockade and standard chemotherapy on the immune profile and tumor microenvironment. 2) Potential identification of new signatures and biomarkers to guide subtype-directed immunotherapies. 3) Ranking of key inhibitory mechanisms in relation to the genetic and molecular subtypes of HGSC. 4) Potential identification of novel target antigens for cancer vaccines and adoptive T cell therapy. 5) Establishment of a Canadian network for T cell-based therapies. The impact of these findings will be realized with the development of novel clinical trials for HGSC, providing new hope for HGSC patients. We will achieve these deliverables using the following approaches: 1) Patient samples from a clinical trial of PD-1 blockade (to reverse immune suppressive signals) will be extensively surveyed at multiple time points using genomic, bioinformatic, and immunological approaches to evaluate biomarkers and signatures of response. 2) Samples from patients undergoing standard chemotherapy will be interrogated at multiple time points using genomic, bioinformatic, and immunological approaches to understand changes in the immune response and tumor microenvironment over time. 3) Tumor infiltrating lymphocytes from patients' tumors will be used to identify antigens that are natural targets of the immune response. Approaches will include mass spectrometry and predictive algorithms to identify relevant target peptides for T cell-based therapies.

<b>Budget Details</b>	supplies, services, personnel
<b>Personnel Details</b>	graduate student
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	BioCanRx, Enabling Studies Program
<b>Project Title</b>	<b>Development of predictive companion biomarkers and therapeutic monitoring for hypermutant cancers to immune checkpoint inhibition</b>
<b>Total Award</b>	\$744,996
<b>Total Awarded to Me</b>	\$100,00
<b>Start Date</b>	Oct. 14, 2016
<b>End Date</b>	Sept. 30, 2019
<b>Main Objective</b>	To determine molecular determinants of response and resistance to immunotherapies in hypermutant tumours
<b>Outline of Methodology:</b>	We will infer the presence and shifts in infiltrating immune cells in these tumours through RNA sequencing analysis of serial or multi-site surgical tumour tissues. We will assess the clonal structure of infiltrating immune cells through ultra-deep sequencing of the T-cell receptor in tissues and compare these patterns over time in serial tissues
<b>Budget Details</b>	supplies, services, personnel
<b>Personnel Details</b>	Bioinformatician
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	American Association for Cancer Research (Philadelphia, PA) SU2C Canada Cancer Stem Cell Dream Team
<b>Project Title</b>	<b>Targeting brain tumour stem cell epigenetic and molecular networks</b>
<b>Total Award</b>	\$10,577,947
<b>Total Awarded to Me</b>	\$332,000
<b>Start Date</b>	Oct. 1, 2015
<b>End Date</b>	Sept. 30, 2019
<b>Main Objective</b>	To focus our attention on the worst prognosis brain tumours, glioblastoma (GBM) of adults and children, and posterior fossa subtype A (PFA) ependymomas of infants, with a goal of finding new treatments.
<b>Outline of Methodology:</b>	To define the position of BTSCs within the subclonal genetic architecture within primary brain tumours, we will use deep (250X) whole genome sequencing to detect and stratify clonal and subclonal somatic mutations in coding and untranslated regions of the GBM (n=50) and PF ependymoma (n=20) primary tumour genomes. To stratify somatic mutations and structural alterations into specific subclonal populations, we will use the PyClone and PhyloWGS algorithms to assign absolute cancer cell fraction values to each mutation, copy number, and rearrangement call, accounting for overall tumour content of the biopsy, tumour purity, and allele-specific copy-number profiles derived using the Sequenza algorithm. As these populations reflect fractions of the tumour population, there is a strong possibility that BTSCs harbour distinct genomic changes from the overall patient sample, apparent as subclones with a core set of shared somatic alterations across brain tumours. To nominate BTSC subclones, we will perform a comparison of somatic alterations across subclonal populations within each tumour, as well significance analysis of alterations frequent in subclonal populations across patients. A genome-wide approach is needed to survey

	sufficient numbers of mutations to enable robust subclonality assignments, and to define mutations outside protein coding regions that might be drivers of abnormal epigenetic states. As a functional read-out of these alterations, we will also generate matched RNA-seq data to quantitatively determine expression level of candidate genes altered in BTSC subclones and noncoding RNA fractions that are associated with the stem cell subpopulations from these glial tumours.
<b>Budget Details</b>	Personnel, supplies, services
<b>Personnel Details</b>	Grad Students
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Canadian Institutes of Health Research – Terry Fox New Frontiers and Terry Fox Research Institute, Program Project Grant
<b>Project Title</b>	<b>Delineating therapeutic opportunities in Triple-Negative Breast Cancer</b>
<b>Total Award</b>	\$2,249,997
<b>Total Awarded to Me</b>	\$320,000
<b>Start Date</b>	July 1, 2016
<b>End Date</b>	June 30, 2019
<b>Main Objective</b>	To identify targeted therapeutic approaches to improve outcome in triple negative breast cancer patients
<b>Outline of Methodology:</b>	Our program consists of complementary research projects inclusive of basic and clinical research on immuno- (Project 1), epigenetic (Project 2) and metabolic (Project 3) therapies to identify effective precision medicines against TNBC. Furthermore, we propose a personalized Patient- Derived Xenografts (pPDX) avatar project (Project 4) set in the context of a clinical drug development program to improve patient matching to therapies. These projects will be supported by a Genomics Core to develop technologies improving biomarker identification and a Patient-Derived Model Core to provide physiologically relevant models for preclinical validation of new therapeutic strategies.
<b>Budget Details</b>	Supplies, Services
<b>Personnel Details</b>	n/a
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Canada Foundation for Innovation, Cyberinfrastructure Program
<b>Project Title</b>	<b>Distributed Infrastructure for Genomics Data Sharing and Analysis</b>
<b>Total Award</b>	\$3,920,000
<b>Total Awarded to Me</b>	\$375,000
<b>Start Date</b>	Apr. 1, 2016
<b>End Date</b>	Mar. 31, 2019
<b>Main Objective</b>	To enable exchange and common analysis of large-scale data across research and clinical genomics programs within cancer
<b>Outline of Methodology:</b>	Our proposal is organized around four main Activities. In Activity 1, we will develop a broad Canadian data sharing framework, using the APIs that we and others are developing under the auspices of the GA4GH. These APIs will link the data at our sites using the high-throughput network connecting our respective Compute Canada nodes, and will allow trusted users to run computation directly at the sites where the data is stored. In Activity 2, we will continue the development of GenAP: a computational gateway for data analysis in life sciences that is configured to take advantage of Compute Canada infrastructure. We will

	make improvements to the GenAP portal in order to increase security, stability, and monitoring, and oversee its implementation at additional Compute Canada nodes. In Activity 3, we will build a data-sharing platform that will allow for the collection of standardized clinical data, dynamic definition of cohorts, and performance of genome analytics across datasets that are being stored on various Compute Canada nodes. The platform will also support “matchmaking” of rare disorder patients, rare cancers, and between cancer patients and clinical trials. To enable genome-guided clinical trials across Canada, in Activity 4 we will establish the Canadian Molecular Profiling in Cancer Trials (CAMPACT) Interchange. Cancer patients with tumours harbouring rare clinically actionable mutations occur too infrequently at any one institution, but combining patient data across Canada will help power trials. This Activity will also extend our distributed infrastructure into clinical practice by enabling a new form of distributed, genome-guided clinical trials that would not be otherwise possible. Together, the four Activities will utilize Compute Canada infrastructure to build a distributed and secure computational framework for the analysis of genomic datasets relevant to human diseases and beyond.
<b>Budget Details</b>	Equipment
<b>Personnel Details</b>	None
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Canadian Cancer Society Research Institute – Innovation Grant
<b>Project Title</b>	<b>Non-invasive monitoring of multiple myeloma disease burden by cell-free circulating tumour DNA</b>
<b>Total Award</b>	\$200,000
<b>Total Awarded to Me</b>	\$180,000
<b>Start Date</b>	Feb. 1, 2016
<b>End Date</b>	Jan. 31, 2019
<b>Main Objective</b>	To use Ig VDJ sequencing of cfDNA for monitoring of tumour burden in patients with MM
<b>Outline of Methodology:</b>	We hypothesize that detection of cfDNA encoding the VDJ gene segments of clonal, rearranged Ig receptor genes of MM can be used as a minimally invasive assay to detect minimal residual disease (MRD) and sequentially track disease. The proposal encompasses the following aims: 1. To develop a highly sensitive VDJ rearrangement sequencing assay based on hybrid capture of cfDNA fragments followed by deep Illumina sequencing. 2. To conduct a pilot study to address the utility of cfDNA in monitoring disease burden in MM pts receiving upfront high dose chemotherapy.
<b>Budget Details</b>	supplies, services
<b>Personnel Details</b>	none
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Susan G. Komen Career Catalyst Research Grant
<b>Project Title</b>	<b>Delineation and mutational analysis of open chromatin regions in breast cancer</b>
<b>Total Award</b>	\$449,996 USD
<b>Total Awarded to Me</b>	\$449,996 USD
<b>Start Date</b>	June 1, 2015

<b>End Date</b>	May 1, 2018
<b>Main Objective</b>	To uncover non-coding driver mutations can reveal the molecular mechanisms favorable to breast cancer development and progression, as well as reveal new biomarkers to better tailor personalized/precision cancer medicine through 1) Delineation of functional elements across the genomes of primary luminal breast cancers, 2) Identification of significantly mutated regulatory elements and their targets in primary tumours, and 3) Characterization of the effect of regulatory element mutations on expression of associated genes
<b>Outline of Methodology:</b>	In Aim 1, we will map nucleosome positions and open chromatin using “assay for transposase-accessible chromatin using sequencing” (ATAC-seq) in up to 30 freshly collected breast tumor tissues. In Aim 2, regions of open chromatin from Aim 1 will be ascribed to specific genes using Intercellular Feature Correlation and gene structures will be extended to include regulatory elements active in luminal breast cancers. We will then design a targeted DNA sequencing assay capturing these extended genic regions. In Aim 3, we will perform unbiased, random-primed RNA-seq to assess allele-specific expression of genes under the influence of mutated open chromatin region in luminal breast cancers. We will examine whether somatic mutations in regulatory elements skew allele-specific expression in its target gene or whether other trans regulatory effects are imposed. These assays will be applied to RNA extracted from up to 120 breast tumours and allelic expression levels compared to test for significant differences between tumours with a putative driver mutation from those without such mutations. As all samples are derived from patients on active clinical trials, we may eventually nominate validated sets of functional mutations for correlation with clinical outcome in larger, focused cohorts.
<b>Budget Details</b>	Personnel, Supplies, Equipment
<b>Personnel Details</b>	Post-Doctoral Fellow
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Medicine By Design, University of Toronto, Canada First Research Excellence Fund
<b>Project Title</b>	<b>Regulatory network control of neural stem cells for endogenous repair</b>
<b>Total Award</b>	\$3,053,789
<b>Total Awarded to Me</b>	\$423,491
<b>Start Date</b>	Sept. 1, 2016
<b>End Date</b>	Aug. 31, 2019
<b>Main Objective</b>	We propose a transformative discovery approach to understanding these inter- and intra-cellular regulatory networks that will provide new insights into normal and pathological development and aging, help develop drugs that activate stem cells for tissue repair, and enable the growth of pure populations of specific cell types potentially useful for replacing damaged tissue.
<b>Outline of Methodology:</b>	We will infer intra- and inter-cellular regulatory networks and comprehensively define cell types and lineages using single cell genomic data we collect using a variety of platforms including the Drop-Seq and 10X Genomics platforms. Data mining and simulation of these networks and lineages will identify cell states, state transitions and critical points that we will target with the aim of controlling stem cell fate for therapeutic use.
<b>Budget Details</b>	Personnel, supplies, sequencing services
<b>Personnel Details</b>	Partial support for a scientific associate

<b>Relationship to and overlap with 2017 PPG Application</b>	None
<b>Funding Source &amp; Program Name</b>	Princess Margaret Cancer Foundation Personalized Medicine Team Grant
<b>Project Title</b>	<b>MYELSTONE: replacing bone marrow aspirates with circulating tumour DNA analysis of multiple myeloma (multiple myeloma stop needle)</b>
<b>Total Award</b>	\$299,849
<b>Total Awarded to Me</b>	\$114,827
<b>Start Date</b>	Aug. 1, 2015
<b>End Date</b>	July 31, 2017
<b>Main Objective</b>	To deploy a clinical laboratory platform for non-invasive monitoring of multiple myeloma DNA circulating in blood
<b>Outline of Methodology:</b>	In Aim 1, we will evaluate two ctDNA sequencing protocol modifications to enable detection of minimal residual disease in MM patients following treatment. Specifically, we will compare single-strand-consensus and Duplex sequencing methods with barcode modifications to enable efficient ligation and multiplex sequencing. For Aim 2, Implementation of ctDNA protocols in the Advanced Molecular Diagnostics Laboratory (AMDL) will require coordinated deployment of laboratory and bioinformatic protocols. Research protocols will be modified to suit the AMDL laboratory configuration and entered into UHN's controlled document management system. Should Aim 1 not be complete or neither Duplex nor SSC methods yield an appreciable increase in sensitivity, we will deploy our current ctDNA protocol without modification. In Aim 3, we will perform prospective testing of MM patients enrolled on clinical trials of novel drugs directed against specific MM genomic abnormalities. Patients are recruited into biomarker positive (NRAS, KRAS or BRAF mutated) or biomarker negative study groups; 2) a Phase II multi-center clinical trial of JNJ-42756493, a selective fibroblast growth factor receptor (FGFR) inhibitor for the treatment of relapsed myeloma expressing wild-type or mutated FGFR3 to be opened in the second quarter of 2015; and 3) an umbrella trial of several different drugs in patients with relapsed MM, with treatment assignment guided by genomic studies. Within this activity, Dr. Jeremy Lewin will conduct a cost effectiveness analysis by capturing direct costs associated with profiling of BM aspirates and ctDNA, as well as indirect costs associated with patient health, trial enrollment, supportive care, and treatment following testing. We will also assess each patient's level of pain and overall experience following collection of BM and ctDNA through a questionnaire immediately after each procedure. We will also assess whether similar clinical decisions would have been made using ctDNA analysis alone compared to current BM-based profiling.
<b>Budget Details</b>	Personnel, supplies, services
<b>Personnel Details</b>	Grad student
<b>Relationship to and overlap with 2017 PPG Application</b>	None

**Pending Research Support**

<b>Funding Source &amp; Program Name</b>	Canada Research Chair
<b>Project Title</b>	<b>Canada Research Chair in Translational Genomics</b>
<b>Total Award</b>	\$500,000

<b>Total Awarded to Me</b>	\$500,000
<b>Proposed Start Date</b>	April 2018
<b>End Date</b>	April 2023
<b>Main Objective</b>	Dr. Trevor Pugh will lead a collaborative and clinically-integrated research program to understand how the balance of cancer and immune cells in tumours may dictate the efficacy of immunotherapy--a new class of drugs that activate the immune system to combat cancer.
<b>Outline of Methodology:</b>	Using state-of-the-art genomic approaches, his program will create molecular tests to predict and monitor immunotherapy efficacy. His work will also reveal new strategies to help the immune system destroy cancer cells. This program will provide unique training opportunities at the interface of basic and clinical research, and will deliver tangible socioeconomic benefits to Canada and beyond.
<b>Budget Request</b>	\$500,000
<b>Personnel Request</b>	Technician, travel, supplies
<b>Relationship to and overlap with 2017 PPG Application</b>	None

<b>Funding Source &amp; Program Name</b>	Cancer Research Society, Operating Grant
<b>Project Title</b>	<b>Functional architecture of retained zygosity amidst near-global loss-of-heterozygosity in pancreatic neuroendocrine tumours</b>
<b>Total Award</b>	\$120,000
<b>Total Awarded to Me</b>	\$120,000
<b>Proposed Start Date</b>	9/2017
<b>End Date</b>	9/2019
<b>Main Objective</b>	The objective of this project is to understand the functional architecture conferred by a striking pattern of near-global, copy neutral loss of heterozygosity (CN-LOH) we recently discovered in pancreatic neuroendocrine tumors.
<b>Outline of Methodology:</b>	To determine which genes retain critical functionality on a background of CN-LOH in PNETs, we will: 1) Validate our finding of restricted regions of heterozygosity within near-global copy neutral LOH using shallow whole genome sequencing 2) Determine whether paternal or maternal alleles are preferentially subject to CN-LOH in PNETs 3) Perform functional lethality screens of genes that are not subject to CN-LOH and candidate genes with skewed paternal inheritance in regions of LOH in PNETs.
<b>Budget Request</b>	services, supplies
<b>Personnel Request</b>	none
<b>Relationship to and overlap with 2017 PPG Application</b>	none

<b>Funding Source &amp; Program Name</b>	NIH PAR-15-333 - Sustained Support for Informatics
<b>Project Title</b>	<b>The cBioPortal for Cancer Genomics</b>
<b>Total Award</b>	\$2,500,000 USD
<b>Total Awarded to Me</b>	\$618,840 USD
<b>Proposed Start Date</b>	1/2018
<b>End Date</b>	1/2023

Main Objective	
<b>Outline of Methodology:</b>	<p>We are now establishing a multi-institutional software development network, which will coordinate and drive the future development of the software and associated data pipelines. This group will focus on four main areas:</p> <p>New analysis and visualization features, including:</p> <ul style="list-style-type: none"> <li>1) Improved support for cross-cancer queries and cohort comparisons.</li> <li>2) Enhanced clinical decision support for precision oncology, including an improved patient view with knowledge base integration, patient timelines and improved tools for visualizing tumor evolution.</li> <li>3) New data pipelines, including support for new genomic data types and streamlined pipelines for TCGA and the International Cancer Genome Consortium (ICGC).</li> <li>4) Software architecture and performance improvements.</li> <li>5) Community engagement: Documentation, user support, and training.</li> </ul>
<b>Budget Request</b>	Personnel
<b>Personnel Request</b>	Software engineer
<b>Relationship to and overlap with 2017 PPG Application</b>	None

## E. List of Publications

Provide a full list of all your scientific publications.

\* = co-authorship

1. Rheinbay E, Parasuraman P, Grimsby J, Tiao G, Engreitz JM, Kim J, Lawrence MS, Taylor-Weiner A, Rodriguez-Cuevas S, Rosenberg M, Hess J, Stewart C, Maruvka YE, Stojanov P, Cortes ML, Seepo S, Cibulskis C, Tracy A, **Pugh TJ**, Lee J, Zheng Z, Ellisen LW, Iafrate AJ, Boehm JS, Gabriel SB, Meyerson M, Golub TR, Baselga J, Hidalgo-Miranda A, Shioda T, Bernards A, Lander ES, Getz G. Recurrent and functional regulatory mutations in breast cancer. *Nature*. 2017 Jul 6;547(7661):55-60. doi: 10.1038/nature22992. Epub 2017 Jun 28. PubMed PMID: 28658208.
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**TERRY FOX RESEARCH INSTITUTE**  
**CURRICULUM VITAE**

<b>FULL NAME:</b> Anita Villani	
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<b>ACADEMIC BACKGROUND</b>			
<i>Degree Type</i>	<i>MM/YY</i>	<i>Discipline/Field/Specialty</i>	<i>Institution &amp; Country</i>
MSc	11/2015	Genetics and Genome Biology	Institute of Medical Science, University of Toronto, Canada
MD	05/2007		Faculty of Medicine, University of Ottawa, Canada
BSc	04/2003	Biology	Faculty of Science and Engineering, York University, Canada

<b>WORK EXPERIENCE</b>			
<i>Position, Organization</i>	<i>Department/Division</i>	<i>Start Date</i>	<i>End Date</i>
Associate Staff Oncologist, The Hospital for Sick Children	Haematology/Oncology	09/2016	
Assistant Professor, University of Toronto	Department of Paediatrics	09/2016	
Locum Consultant Paediatrician and Paediatric Oncologist, Southlake Regional Health Centre	Department of Paediatrics	06/2016	09/2016
Locum Consultant Paediatric Oncologist, Southlake Regional Health Centre	Department of Paediatrics	10/2014	08/2015
Part-time Staff Physician, The Hospital for Sick Children	Division of Emergency Medicine, Department of Paediatrics	10/2011	07/2013

#### A. Personal Statement

I have a longstanding clinical and research interest in the management of patients with Li-Fraumeni Syndrome (LFS). Together with Dr. David Malkin, I run the Cancer Genetics Clinic at The Hospital for Sick Children, which sees the largest volume of patients with various cancer predisposition syndromes in Canada. This rich experience has allowed me to develop specific expertise in the unique aspects of surveillance and cancer treatment for patients with Li-Fraumeni Syndrome, including the key challenges and opportunities for great impact in these areas. I have established an international reputation for the development and evaluation of an effective clinical surveillance protocol for patients with LFS (described below). The “Toronto Protocol” has been adopted at numerous centres around the world, and serves the basis for consensus international surveillance recommendations for pediatric patients with LFS.

To compliment this clinical experience, I completed a Master’s of Science degree at The University of Toronto in Genetics and Genome Biology, during which time I investigated the role of specific genetic modifiers in determining the cancer phenotype of patients with LFS. This training, supported by a CIHR graduate scholarship, was characterized by rich mentorship in the use and application of genetic research technologies. Accordingly, I have become well-positioned to execute translational clinical studies, based on a solid understanding of genetic research methodologies and applications.

## Early tumor detection and prevention in Li-Fraumeni Syndrome

Villani, Anita

I have demonstrated proficiency in translating genetic/genomic findings into clinical care through my leadership roles in our local and national precision oncology programs. I am a lead co-investigator in The Hospital for Sick Children's comprehensive cancer genomic sequencing research program ("KiCS") and I am the clinical site lead at The Hospital for Sick Children for the national "PROFYLE" precision oncology program, as well as a key contributor to many subcommittees. The broad objective of these programs is to evaluate the impact of next generation sequencing technologies on clinical oncology care (that is, to evaluate the contribution of comprehensive somatic and germline sequencing to clarifying diagnoses, prognoses, identifying unique treatment targets, assessing response to treatment, and understanding etiology of cancer/cancer predisposition). In these roles, I have developed frameworks for classifying and reporting variants with respect to clinical actionability/utility, synthesized pertinent genomic findings with clinical impact from our local Sickkids sequencing efforts, and have identified challenges and solutions to the application of these technologies to the genomic interrogation of certain subgroups of pediatric oncology patients. Many of our translational efforts for the KiCS program have been adopted by the national PROFYLE program. Our preliminary findings on the clinical applicability of somatic and germline genomic data has also led to the development of a number of important specific translational research projects.

These experiences make me particularly well-suited to bridge novel findings of various projects of this program into the clinical realm; namely, the development of a tumor profiling program for patients with LFS (**Project 1**), and the evaluation of novel imaging technologies and circulating tumor DNA for surveillance and early tumor detection (**Project 4**).

### B. Selected Research / Technology Development Contributions Over the Past Five Years

As a young investigator, it is noteworthy that while my research contributions to date may appear to be relatively few in number, they have been important and impactful studies. In 2011, I led a prospective observational study exploring the role of surveillance for patients with Li-Fraumeni Syndrome (LFS; Villani et al, 2011). As the first study to demonstrate the feasibility and efficacy of a comprehensive surveillance program for patients with LFS, this study was published in *The Lancet Oncology*, and I was recognized with the CIHR Institute of Genetics Lap-Chee Tsui Publication Prize. We demonstrated that a surveillance protocol detects tumors at an early stage and grade, and that this early detection translates into a survival advantage for patients with LFS. This study has received international attention in the form of meeting presentations, has resulted in a practice change/widespread adoption at a large number of institutions worldwide, and has been referenced in National Comprehensive Cancer Network (NCCN) guidelines. Importantly, this work has spurred an impressive influx of further clinical studies on surveillance in LFS around the world. I contributed key expertise to a multi-institutional analysis of the use of whole-body MRI for surveillance of patients with LFS, to be published in *JAMA Oncology* (Ballinger et al, *in press*). Further to this, I successfully published our updated evaluation of the "Toronto Protocol" (11 year follow-up) in a second *Lancet Oncology* publication (Villani et al, 2016). These publications have clearly been influential and have placed me as a widely recognized leader in this field. Accordingly, I was invited by the American Association for Cancer Research (AACR) to be a member of a working group whose goal was to develop consensus recommendations for surveillance for a large number of pediatric cancer susceptibility syndromes. Notably, these contributions have also resulted in a number of impactful publications (Wasserman et al, 2017, Villani et al, 2017, Rednam et al, 2017, Kratz et al, 2017). Ultimately, I aim to bridge genetic and genomic data to the personalization of surveillance strategies and study the integration of genetic analysis of circulating tumor DNA into surveillance protocols. I shared my perspectives on the application of next generation sequencing technologies to the care of patients with cancer predisposition syndromes in a recent publication in *Nature Reviews Clinical Oncology*, as a co-first author (Samuel et al, 2016).

I have also engaged in successful collaborations with genomic scientists, resulting in an influential publication in *Clinical Cancer Research* (Merino et al, 2015). This study explored the genomic landscape of choroid plexus carcinoma, and identified mutant TP53 copy number as a prognostic indicator. My efforts to integrate the results of genomic analysis with clinically-relevant data helped to provide meaningful output for this work. The application and integration of genomic technologies into clinical oncology care ("precision oncology"; see section A and D) has risen to the forefront of my research program, and will be the focus of a series of studies and publications in the next year.

### C. Honours & Awards

**INTERNATIONAL**

Received

- 2016      Publication recommended in F1000Prime as being of special significance in its field by F1000 Faculty Member Ygal Haupt (Villani et al, Lancet Onc, 17(9), 2016)

**NATIONAL**

Received

- 2016      Canadian Cancer Society's Top 10 Society-funded research stories of 2016  
(Villani et al, Lancet Onc, 17(9), 2016)

**Student/Trainee Awards**

**NATIONAL**

Received

- 2014-2015      Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarship. \$17,500 CAD  
2011      CIHR Institute of Genetics – Lap-Chee Tsui Publication Prize. \$1,000 CAD  
2010      Selected to represent The Hospital for Sick Children at the National Paediatric Resident and Fellow Research Competition in Winnipeg  
2002, 2003      NSERC (Natural Sciences and Engineering Research Council) Undergraduate Student Research Award. \$4,500 CAD  
1999-2000      Governor General's Academic Award: Bronze Medal

**LOCAL**

Received

- 2015      Institute of Medical Science (University of Toronto) Academic Development Award. \$200 CAD  
2014, 2015      Clinician Scientist Graduate Scholarship, Postgraduate Medical Education, University of Toronto. \$8,257; \$16,329 CAD  
2013-2014      Clinician Investigator Program, University of Toronto (Acceptance & Award). \$76,210 CAD  
2008      The Hospital for Sick Children Department of Paediatrics Research Day: 2nd place award. \$500 CAD  
2007      University of Ottawa, Faculty of Medicine Silver Medal for academic achievement  
2007      Ward Family Scholarship for Paediatric Medicine. \$1,500 CAD  
2006      Association of Professors of the University of Ottawa Student Award.  
                \$1,000 CAD  
2004      University of Ottawa Merit Scholarship  
2003      University of Ottawa Entrance Scholarship. \$3,666.66 CAD  
2003      York University Faculty of Science and Engineering Gold Medal for Academic Excellence

**D. Overview & Details of Research Support**

My research program is broadly set in the field of cancer genetics and is divided into two main areas of focus. The first is based on patients with cancer predisposition syndromes. I have an interest in developing and studying practical and effective surveillance protocols for early tumour detection in this population, and have embarked on number of studies to demonstrate efficacy, patient/parent experience and economic impact. My longer-term goals include rationalizing/tailoring approaches to surveillance based on patient-specific modifiers and to translate emerging technologies (circulating tumor DNA, advanced functional imaging) into the clinical setting, for surveillance of individuals with LFS. I am also seeking to better understand unique aspects of the management of cancer in patients with LFS. I am currently launching and seeking grant support to lead a multi-institutional study investigating the contribution of radiation and cytotoxic therapies to second malignant neoplasm risk in patients with LFS. The use of preventative therapeutics in the LFS population remains a long-term interest as well.

My second area of research is the translational implementation of genomic technologies into clinical oncology care. I am a lead co-investigator of the Precision Oncology research program at The Hospital for Sick Children, whose broad objective is to improve the care of oncology patients through investigation of the tumor and normal genome using next-generation sequencing technologies. I am exploring a) the clinical utility of these findings with respect to diagnosis, prognostication, treatment considerations and assessment of etiology/evolution of cancer, b) the stakeholder experience (patient and family psychosocial and behavioural outcomes), and c) germline cancer predisposition genes, including novel genes and pathways underlying pediatric cancer susceptibility and genetic modifiers of cancer predisposition syndromes.

**Current Research Support**

*Funding Source & Program Name: Garron Family Cancer Centre, KiCS Program*

*Project Title: SickKids Cancer Sequencing (KiCS) Program*

*Total Award: \$1,750,000 (Canadian)*

*Total Award to You: \$1,750,000*

*Start Date: September, 2015*

*End Date: September, 2018*

*Main Objective: To develop and implement a precision medicine program for molecular target identification and enrollment on basket, umbrella, n-of-1 or other clinical trial for all young people with refractory, relapsed or metastatic cancer at SickKids Hospital.*

*Outline of Methodology:*

*Budget Details: ~\$1 milion for personnel, and \$750K for sequencing and informatics*

*Personnel Details: supports 1 bioinformatician, 0.5 genetic counselor, 1.0 information coordinator*

*Relationship to 2017 PPG application: No overlap*

**E. List of Publications****1. PEER-REVIEWED PUBLICATIONS****Journal Articles**

1. Wasserman JD, Tomlinson GE, Druker H, Kamihara J, Kohlmann W, Kratz CP, Nathanson KL, Pajtler KW, Parareda A, Rednam SP, States LJ, **Villani A**, Walsh MF, Zelley K, Schiffman JD. Multiple Endocrine Neoplasia and Hyperparathyroid-Jaw Tumor Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood. *Clin Cancer Res* July 2017; 23:13; doi: 10.1158/1078-0432.CCR-17-0548. Co-Author
2. **Villani A**, Greer MLC, Kalish JM, Nakagawara A, Nathanson KL, Pajtler KW, Pfister SM, Walsh MF, Wasserman JD, Zelley K, Kratz CP. Recommendations for Cancer Surveillance in Individuals with RASopathies and other Rare Genetic Conditions with Increased Cancer Risk. *Clin Cancer Res* June 2017; 23:12; doi: 10.1158/1078-0432.CCR-17-0631. Primary Author
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#### Book Chapters

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## 2. SUBMITTED PUBLICATIONS

#### Journal Articles

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