BIOGRAPHICAL SKETCH

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NAME: Scott, Jacob G.

eRA COMMONS USER NAME (credential, e.g., agency login): scottjb

POSITION TITLE: Clinical Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
United States Naval Academy	B.S.	05/1998	Physics
Old Dominion University	M.S.	08/2003	Engineering Management
Case Western Reserve Univ School of Medicine	M.D.	06/2008	Medicine
Univ Hospitals of Cleveland, Case Medical Center	Intern	06/2009	Internal Medicine
H. Lee Moffitt Cancer and Research Center	Resident	06/2015	Radiation Oncology
Oxford University, Centre for Mathematical Biology	DPhil	05/2018	Applied Mathematics

A. Personal Statement

I am a veteran of the US Navy submarine force turned academic physician-scientist. My lab pursues research decomposing the complexity of cancer through mathematical modeling and the biological and clinical validation of these models. My background in physics, medicine, mathematics and engineering gives me a unique perspective on cancer and systems biology and I am able to communicate and collaborate with professionals across many disciplines. My role in the proposed work will be as Principal-Investigator. I have worked extensively on mathematical modeling of cancer evolution and treatment using a variety of models including Evolutionary Game Theory, cellular automata, differential equations and Markov chains. My DPhil thesis focused on the role of heterogeneity, both genetic and microenvironmental, on cancer evolution and radiation response, and my laboratory's focus is cancer evolution and therapy resistance. Since starting my own group, I have begun to diversify, and my lab now has a significant experimental component. We have been conducting experimental evolution in cancer cell lines as well as bacteria. The combination of mathematics, experimental evolution and a clinical focus makes my laboratory stand out as one of the most interdisciplinary in the field of translational cancer evolution, and I am eager to use my distinct perspective to help advance this field to help my patients.

B. Positions and Honors

Positions

1998 - 03 Junior Officer, US NAVY, Submarine Force, Kings Bay, GA
2003 - 04 Physics Teacher, Stanton College Preparatory School, Jacksonville, FL
2011 - DPhil student, Wolfson Centre for Mathematical Biology, Oxford University, Oxford, UK
2015 - 16 Clinical Instructor, Radiation Oncology & Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, FL
2015 - 16 Clinical Instructor, Department of Oncologic Sciences, Univ of South Florida, Tampa, FL
2016 - Associate Staff, Translational Hematology and Oncology Research and Radiation Oncology, Cleveland Clinic, Cleveland, OH
2016 - Assistant Professor, Center for Proteomics and Systems Biology, Case Western Reserve University School of Medicine, Cleveland, OH
2016 - Ad hoc Member of NCI Physical Science in Oncology Network U01 review panel

Awards

Landahl travel award, Society for Mathematical Biology, 2012
Roentgen Resident Research Award, 2011
NSF DMS-1135663, Travel Award, ECMTB Annual meeting, Krakow, Poland, July 2011
ASCO Cancer Foundation Merit Award, ASCO Annual meeting, June 2010
1st Annual National Cancer Institute Physical Sciences in Oncology Meeting, Poster award, 4/2010
Leonard Tow Humanism in Medicine award, 5/08
Samuel Packer Award for excellence in Medical Clerkship, 5/08
Irwin H. Lepow Medical Student Research Day, Poster award. 9 May, 2006
Merit Grant, Case Western Reserve University School of Medicine, Academic years 2004-2008

Honors Societies

Sigma Pi Sigma, ΣΠΣ– Physics honor society, elected 1998
Sigma Xi, ΣΞ– Scientific research society, elected 1998
Alpha Omega Alpha, AΩA– Medical honors society, elected 2008
Gold Humanism in Medicine Honor Society – elected 2008

C. Contribution to Science

1. The evolution of drug resistance represents the greatest unmet need in clinical oncology and infectious disease. Darwinian evolution is the driving force behind this process and is conserved across both fields. To tackle this problem, I have chosen two distinct approaches, the first of which is the direct study of the process of (epi)genetic mutation and selection. To study this issue we have used mathematical models on objects called hypercubes which represent the possible genotypes an organism or cancer cell can take, combined with directed experimental evolution. Our group is the first to show, in a manuscript published in *PLoS Computational Biology* that, in a theoretical model, **evolution can be steered** to suboptimal fitness peaks with rational sequencing of drugs. We have also shown, in a manuscript in revisions at *Nature Communications*, that the outcome of evolution, while stochastic, is predictable to first order, and have suggested a **novel method of reporting this: collateral sensitivity likelihood**. Working to apply these methods to cancer, we are the first group to perform experimental evolution under targeted therapies in lung cancer, and show, in a publication in *Scientific Reports*, that **there are evolutionary instabilities in collateral sensitivity during clinically relevant time scales**. We recently reviewed these and many other evolutionary concepts as applied to cancer in an *invited review in BBA-reviews on Cancer*.

    a. Nichol D, Jeavons P, Bonomo RA, Maini PK, Paul JL, Gatenby RA, Anderson ARA, **Scott JG**. "Exploiting evolutionary non-commutativity to prevent the emergence of bacterial antibiotic resistance." *PLOS Computational Biology* 2015:11(9),e1004493

    b. Nichol D, Rutter J, Jeavons P, Anderson ARA, Bonomo RA, **Scott JG**. "Antibiotic collateral sensitivity is contingent on the repeatability of evolution". *Nature Communications* 2019:10(1):334

    c. Dhawan A, Nichol D, Kinose F, Abazeed ME, Marusyk A, Haura EB, **Scott JG**. "Collateral sensitivity networks reveal evolutionary instability and novel treatment strategies in ALK mutated non-small cell lung cancer". *Scientific Reports* 7:2017

    d. **Scott JG**. and Marusyk A. Somatic clonal evolution: a selection-centric perspective. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, 1867(2), pp.139-150. 2017

2. Beyond (epi)mutational changes in individual clones, there is mounting evidence in cancer that ecological interactions, like those observed in other natural systems (e.g. cooperation, cheating and parasitism), can contribute to drug resistance. While standard genomic and other genotype:phenotype mapping experiments and models have a difficult time detecting these interactions, evolutionary game theory (EGT) is designed specifically to understand them. We have been using EGT for nearly a decade to probe, theoretically, the effect of these interactions in heterogeneous tumors. In *two publications in British Journal of Cancer*, we have **pioneered the use of these models to study treatment timing in prostate cancer and treatment ordering in an abstracted public goods game in lung cancer**. We have also made progress, in a publication in *Royal Society Interface*, in **understanding how spatial structure affects the payoff matrices** at the heart of EGT models. In an ongoing effort to map experimental co-evolution to this model formalism,

we have developed a first-in-class 'evolutionary game assay', which we present in a manuscript in press, *Nature Ecology and Evolution*.

a. Kaznatcheev, A., **Scott JG**, and Basanta, D. Edge effects in game-theoretic dynamics of spatially structured tumours. *Journal of the Royal Society: Interface.* 12(108), p.20150154. 2015

b. Kaznatcheev A, **Scott JG**, VanderVelde R, Basanta D. "Cancer treatment scheduling and dynamic heterogeneity in social dilemmas of tumour acidity and vasculature" *British Journal of Cancer*, 2017, 116(6):785-792

c. Basanta, D., **Scott JG**, Fishman, M.N., Ayala, G., Hayward, S.W. and Anderson, A.RA. Investigating prostate cancer tumour–stroma interactions: clinical and biological insights from an evolutionary game. *British journal of cancer*, 106(1), p.174. 2012

d. Kaznatcheev A, Peacock J, Basanta D, Marusyk A, **Scott JG**. "Cancer associated fibroblasts and alectinib switch the evolutionary games that non-small cell lung cancer plays." *Nature Ecology and Evolution,* 2019

3. While my laboratory's central focus is the emergence of drug resistance, in my clinical life I am a radiation oncologist. While our field has made amazing advances in imaging, and subsequently better targeting (both driven by medical physics), we have done little to advance our understanding of radiation dosing from a biological perspective - and we have been largely left behind from the perspective of personalized medicine. To remedy this, I worked together with Javier Torres-Roca to develop an algorithm for translating the information gleaned from any signature of radiation sensitivity into clinically actionable dosing information. This work, published in *The Lancet Oncology*, represents **the first steps towards personalizing radiation therapy**. Beyond this advance, which was born from my application of mathematics to the biology of cancer, in a publication in *PLoS Computational Biology*, **I have shown how the distribution of microvessels within a tumor affect radiation sensitivity**, and how this affects the way we should sequence drugs like bevacizumab together with radiation therapy. Continuing with my desire to improve the delivery of radiation, I have recently **patented a method by which to mathematically optimize the patio-temporal delivery of radiation** by considering the temporal evolution of normal tissue response - which is published in *Medical Physics*.

   a. **Scott JG** and Torres-Roca JT. "Systems and Methods for Providing Personalized Radiation Therapy" Serial #: U.S. Patent Application No. 62/157,245 Type: Provisional, filed 5/5/2015

   b. **Scott JG**, Berglund A, Schell M, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort study. *Lancet Oncology*, 16 December 2016

   c. **Scott JG**, Fletcher AG, Anderson ARA, Maini PK. Spatial metrics of vascular organization predict radiation efficacy in a computational model. *PLoS Comp Biol*

   d. López Alfonso, J.C., Parsai, S., Joshi, N., Godley, A., Shah, C., Koyfman, S.A., Caudell, J.J., Fuller, C.D., Enderling, H. and **Scott, J.G**., Temporally feathered intensity modulated radiation therapy: a planning technique to reduce normal tissue toxicity. *Medical physics.* 2018 June

4. Beyond the disease and therapy specific research mentioned above, I have long been interested in the application of network theory to cancer. My first work in this direction was to model metastasis on the network formed by the blood vessels, a formalism we first described in *Nature Reviews Cancer.* We first studied the relationship between primary tumors and metastases, and found that it is **unlikely that metastatic tumors promote primary tumor growth**. We then studied using data from patient CTCs and metastatic incidence in a paper in *European Journal of Cancer*, but more recently I have turned my attention to using networks as a surrogate for space. To this end, we have worked to use the new machinery of network theory to **derive analytical solutions to models of competition processes** of intra-patient variability in incubation dynamics for infectious disease and cancers, with a pair of publications in *Physical Review E* and *eLife*.

   a. **Scott JG**, Kuhn P, Anderson ARA. "Unifying Metastasis--Integrating intravasation, circulation and end organ colonization." *Nature Reviews Cancer* 12, 445-446, Jul 2012 PMCID: PMC4533867.

   b. **Scott JG,** Fletcher AG, Maini PK, Anderson ARA, Gerlee P. "A filter-flow perspective of hematogenous metastasis offers a non-genetic paradigm for personalized cancer therapy" *European Journal of Cancer*. 2014 Nov;50(17):3068-75 DOI:10.1016/j.ejca.2014.08.019

c. Ottino-Löffler B, **Scott JG**, Strogatz SH. "Takeover times for a simple model of network infection." *Physical Review E 96: 012313* (2017)

d. Ottino-Löffler B, **Scott JG**, Strogatz SH. "Evolutionary dynamics of incubation periods." *eLife* 2017;6:e30212

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/jacob.scott.1/bibliography/48563315/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing

K12CA076917 (Gerson) 07/01/2018 - 06/30/2020
Clinical Oncology Research Career Development Program
This mentored career development program supports physician investigators to gain skills in cancer research and clinical therapeutics that emphasizes innovative treatments and use of genomics to select proper and individualized treatments for cancer patients, increasing the likelihood that such treatment will be effective.
Role: Scholar - Paul Calabresi Award for Clinical Oncology

IRG-16-186-21 (Scott) 06/01/2018 – 05/31/2019
ACS IRG
Exploiting collateral sensitivities exposed during Ewings Sarcoma evolution
PI will serially treat, in various drug/radiation combinations, two Ewing Sarcoma (ES) cell lines, and assay their subsequent gene expression profiles. In this way, the PI hopes to identify treatments that confer sensitivities to other treatments.

Completed

Scott (PI) 09/01/2015 - 06/30/2017
Miles for Moffitt, Departments of Radiation Oncology and Integrated Mathematical Oncology award
"Evolution of Resistance"
The goal of this pilot project is the elucidate the changes in sensitivity to existing HSP-90 inhibitors, TKIs and chemotherapeutics after the evolution of resistance to first line therapies in ALK mutated NSCLC.