Drug Research, Innovation, Validation & Evaluation (DRIVE): A CVRI/FoMD core faciliy

Summary: DRIVE is a proposed CVRI/FoMD core facility focussed on drug design/synthesis and animal/human phenotyping. DRIVE will integrate existing CVRI facilities with newly created "first in Canada" research units and partner with other U of A core facilities to create a much-needed novel platform of translational research, filling an institutional and national gap in drug development and translational research. DRIVE will allow drugs, along with companion biomarkers, to be discovered through *in silico* modeling through artificial intelligence (AI)-enabled drug discovery pipelines, chemically synthesized, and validated using cutting-edge animal and human tissues phenotyping units, with the ultimate goal of advancing them to early-phase clinical trials. DRIVE would be the first of its kind in Canada and will be open to all investigators from the U of A, as well as from Canadian and international universities and industry. This timely comprehensive approach will accelerate the U of A research progress in identifying drug targets (e.g., new cryo-EM unit), AI and clinical trials (NACTC, SPORE), positioning the U of A as a national leader in translational research and accelerated drug development. The focus of DRIVE will include, but not restricted to, cardiovascular/stroke, aging, obesity, diabetes and cancer research, all established or emerging research priorities at the U of A and Alberta. DRIVE will evolve towards a financially self-sustainable core and eventually, through partnership with other academic and industry leaders, to a profitable national hub of drug development and translational research. U of A researchers will use DRIVE to enhance their competitiveness in tri-council grants, further improving our institution's national standing in research.

Institutional Need

A) There is no comprehensive drug design and synthesis core facility at the U of A or anywhere in Canada. Discovery of novel drugs and their companion biomarkers is the cornerstone of innovation in medical research, and this gap significantly compromises academic translational research and opportunities for spin-off companies. Pharmaceutical companies increasingly rely on academic centers that have the ability to design, evaluate and validate new drugs. The U of A should be such a center.

B) Comprehensive human phenotyping is not available at the U of A and is publicly available in very few sites in Canada, mainly in BC and Quebec. An increasing number of academia or industry-driven clinical trials now require genetic and molecular phenotyping of their subjects through OMICs studies to select best optimal candidates (precision medicine). Centers that can do that, have a much higher chance to be the drivers of such large international studies. The U of A should be such a center, not only for the careers of its investigators but also for its branding and the large financial benefits as well.

C) The U of A lacks an integrated comprehensive animal phenotyping core. These are now more critical than ever for drug development and translational research. This is because, in contrast to the past, the impact of a drug in multiple organs (over and above its primary target and disease) is required prior to approval, to predict adverse effects. In addition, the complete phenotype of transgenic animals is required prior to their utilization in drug validation. This requires cores that can evaluate multiple parameters in a treated or transgenic animal, including cardiovascular, CNS, liver, kidneys bone marrow and metabolism. DRIVE will fill these 3 critical gaps.

Components of DRIVE

I. Drug Discovery and Synthesis Unit (DDSU): Proprietary and existing AI platforms will be applied to identify drugs that target critical disease-modifying proteins, also using AI-enhanced robotic surface plasmon resonance (SPR) high-throughput screening (HTS) and molecular modeling. Screening will involve both small-molecule libraries and AI-generated analogs that mimic naturally occurring ligands. Then, drugs will be synthesized chemically in house at purity adequate for biological experiments, using the equipment proposed. Lastly, binding profiles/sites and predicted mechanisms of action will be identified *in silico* to guide molecular and in vivo validation experiments in the animal phenotyping unit of DRIVE. The unit will be directed by Dr. Tabatabaei, a drug design expert and junior faculty from the FoPPS. It will include Dr. Zhao, a medicinal chemist from the Dept of Medicine. Additional expertise in

structural biology will be sought as the program grows. Over the past 3 years, the DDSU has designed 3 novel small molecules that show promising cardiovascular, cancer, diabetes and anti-ageing benefits and are currently being validated by several CVRI members. This CFI award will massively accelerate the proses of design, synthesis and validation of new drugs. In partnership with the Drug Development & Innovation Centre (DDIC) core of the FoPPS, formulation, delivery modes, pharmacokinetics and regulatory support will also be established. The CFI award will also allow hiring chemists and technicians to create an efficient pipeline, open to academic and industry scientists. Space is available within the CVRI, which recently integrated with the CVRC.

II. Comprehensive Animal Phenotyping Unit (CAPU): Drugs synthesized in the DDSU will be tested and validated at the cellular and animal level in the CAPU, essentially a small animal hospital. The unit will integrate existing units in the CVRI (funded by several prior CFI awards that have cutting edge equipment, some of which need to be updated through this CFI award). These include a rodent PET/MRI, echocardiography/vascular ultrasound, metabolic chambers, body composition assessment unit, rodent catheterization and surgery, telemetry, exercise treadmills, blood chemistry point-of-care, and cognitive/memory assessment units. These stations can assess the full impact of drugs, as well as the full phenotype of relevant transgenic animals in several diseases, including cardiovascular/stroke, cancer, obesity, diabetes and ageing. The CAPU will collaborate with the U of A transgenic core facility. Equipment will also be provided for the FoMD transgenic core to ensure all knockout and transgenic animals can be cryopreserved following phenotyping. The CAPU will be particularly critical for ageing research where multiple organs and functional states need to be assessed simultaneously over time. The unit will be directed by Drs. Dyck (Pediatrics) and Ussher (FoPPS), who will be joined by CVRI scientists (many of them CRCs) that have published expertise in the molecular biology, pharmacology and physiology of all these diseases, including Drs. Sutendra, Michelakis, Oudit, Kassiri, Jickling, Freed, Nagendran. This team will be enriched by many others from several faculties, departments and institutes from the U of A, that will bring additional expertise in cancer, nutrition, stroke, transplantation, cardiac surgery, liver and kidney disease.

III. Comprehensive Human Phenotyping unit (CHPU): The U of A has many strengths in clinical and outcomes research (e.g., NACTRC, SPORE, a unique province-wide electronic medical record) but has not reached its potential as it lacks a core for high throughput OMICS in human blood/tissues (genomics, transcriptomics, proteomics, epigenomics from the same patient). This phenotyping is now essential for most academic and industry trials that assess drugs and biomarkers. The simultaneous assessment with multi-OMICS is essential not only for the eventual approval of drugs and their companion biomarkers, but also for their mechanistic understanding and interpretations. The CHPU will fill this gap and allow the U of A to assume a leadership role in clinical trials at the national and international level. The CHPU will also be essential for ageing/longevity research. The Dept of Medicine and the CVRI are planning a large longevity study of 10,000 subjects for which multi-omics are essential (the Alberta Ageing Project ALP, led by Dr. Michelakis). At this point the only way to do that would be by shipping blood to one of only 2 centers that can reliably do this in BC and Quebec, causing a significant increase in cost and compromise in efficiency/speed. Similar needs exist in the Alberta-wide clinical heart failure program (Alberta HEART study, led by Dr. Dyck) as well as province-wide stroke studies (led by Dr. Jickling). Similar needs exist in many ongoing U of A cancer, transplantation and diabetes trials. The CHPU will be directed by Drs Michelakis and Sutendra, a clinician scientist and a basic researcher with published expertise in mechanistic early-phase trials in CV disease and cancer.

Research Supported by DRIVE

DRIVE will support any novel drug for any disease, but priorities will include: **a) Ageing/longevity research**, a global priority that is also the top priority for the CVRI, the Dept of Medicine, and an emerging priority at the CHS and AHS. Ageing and longevity research is one of the fields that needs DRIVE the most, since there is an explosion of need for anti-ageing drugs and longevity research, which

involves all organs and biology systems. **b) CV disease**, including heart failure and acute coronary syndromes, the focus of most CVRI members and many other faculty in several departments and institutes and a recognized strength of the FoMD both at the basic science and clinical research and outcomes research. The strengths of the U of A in clinical CV disease fields (NACTRC, provincial electronic medical record, VIGOUR, SPORE) will elevate to a level of international leadership if the clinical trials/outcomes research will be supplemented by novel drugs and multi-OMICs profiles of Alberta patients. One can envision databases of molecularly phenotyped patients merged with their clinical phenotype drawn by the EMR and the SPORE unit. Such comprehensive databases will be unique and highly sought after by academia and industry outside the U of A.

c) Ischemia-reperfusion (IR) injury that compromises the use of most offered solid organs for transplantation (hearts, lungs, livers, kidneys). The U of A is one of the largest transplant centers in the world (lungs, hearts, islets, kidney, liver). Some of the drugs already synthesized by the DDSU team (e.g., SNAP) inhibit IR injury in normal organs and can be directly translated in clinical trials where CVRI transplant clinician scientists (e.g. Drs Freed, Nagendran) conduct pioneering work in heart and lung transplants. A partnership has been established between CVRI and ATI and it is projected that many anti-IR injury drugs developed by DRIVE for CV disease will have applications in transplant medicine.

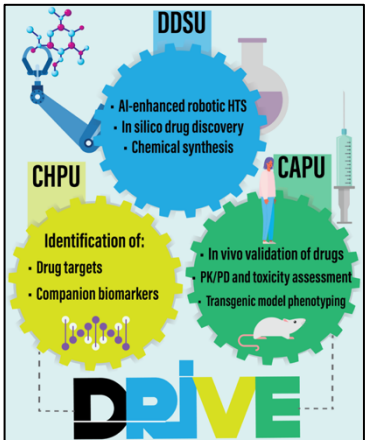
d) Stroke research, a recognized strength of the U of A. Several clinician scientists like Dr. Jickling, run provincial networks or stroke outcomes with a great need to link them with multi-OMICs data. The CHPU will be of significant help to Dr. Jickling, who was recently awarded a large Genome Canada grant to phenotype stroke patients at the population level.

e) Diabetes, an established strength of the U of A. Novel diabetes drugs are prime examples of drugs developed for one disease, but during clinical trials it became apparent that they have unexpected benefits for seemingly unrelated diseases like dementia or even ageing (e.g. metformin, Ozempic, SGLT2 inhibitors). Had they been tested in a unit like DRIVE, this would have been realized much earlier. All 3 drugs developed by the DDSU have anti-diabetes effects and the PIs that developed them (Dyck, Ussher, Sutendra, Michelakis) are CVRI members with expertise in both metabolism and CV disease.

f) Cancer: CVRI members that developed novel drugs through the DDSU, also have strong presence in the cancer field (Michelakis, Sutendra, Dyck) and remarkably, these drugs, in addition to longevity and diabetes, have anti-cancer benefits (like metformin). Cancer scientists will benefit from DRIVE tremendously. One of the most exciting developments in translational cancer research is the conduction of co-clinical trials, where a drug is tested in real time simultaneously in animals and patients. Only a unit like DRIVE will offer U of A scientists the ability to conduct them.

Operational Components of DRIVE

A steering committee (clinical/basic researchers, administrators) will be set to prioritize the drugs tested in DRIVE, from CVRI and other institutes. It will oversee DRIVE's vision and expansion. Members from U of A spin off companies will be added to the committee in time. A business plan has been set in terms of fees paid to DRIVE from UofA investigators or out-of-UofA academics and industries and is attached. All contracts including IP issues will be approved by the U of A legal department. The supervision of finances will be under the Dean's office of the FoMD. Beyond cost recovery, profits will be reinvested in DRIVE to cover repairs and hiring additional HQPs. DRIVE will be featured in the CVRI and FoMD core facilities web sites. It will be supplemented by a graduate training program in Translational Medicine (currently under the Dept of Medicine that will be expanded into the CVRI) as well as a robust program of visiting professors sponsored by the CVRI and the Dept of Medicine in partnership with other institutes.



A summary vision of the flow of knowledge within DRIVE's components: Disease targets will be identified in the CHPU. Drugs for these targets will be designed and synthesized in the DDSU and then validated and developed in animal disease models in the CAPU. These targets can also lead to generation of transgenic mice that would also be comprehensively phenotyped in the CAPU.