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Dear Mrs. Cuccione,

Business Plan for the Childhood Cancer Research Program of BC Children's Hospital and the Child and Family Research Institute

The following represents an overview of the current state of the Childhood Cancer Research Program (CCRP) of the BCCH and CFRI, in which we will outline the following: a) the current 3 areas of excellence in the group; b) the strategic plans to expand research capacity in each of the 3 areas; and c) how the Michael Cuccione laboratories will integrate within the overall strategic plans for the CCRP. It should be noted that we expect to expand the research efforts of the CCRP to include hematology, but such expansions are beyond the scope of the current strategic plan.

Summary of the three areas of research excellence:
We have three areas of excellence that form the foundation of the CCRP, including cancer biology, transplantation and tumor immunology, and clinical trials. All three areas are focused on identification of novel targets that can be used as both biomarkers and as potential therapeutic targets.

1. **Cancer Biology** and targeted therapeutics, including strengths in molecular pathology and basic biology of cancer signaling. The malignancies in which the group's research currently has an established internationally acknowledged reputation is as follows: breast (Dunn); sarcomas (Sorensen); and leukemia (Schultz). Areas in which researchers are developing established track records are as follows: breast (Sorensen); brain (Dunn); sarcomas (Pallen) gene polymorphisms in drug toxicity (Rassekh); and cancer and immune cell interactions with the microenvironment (Lim).
2. **Tumor and transplantation immunology,** including pre-clinical models of disease, biomarkers and drug development (Schultz). The diseases of focus are chronic GVHD (transplantation immunology) and ALL (tumor immunology).
3. **Clinical Trials,** including COG (Bond, Rogers, Dix, Schultz), PBMTC (Schultz), and local clinical trials (Strahlendorf, Pritchard, Rogers, Schultz).The areas of focus are trials in sarcoma, Wilms, ALL, BMT, GVHD, quality of life and apheresis.

The current laboratory-based research groups include the following senior scientists:

a. Kirk R. Schultz, MD - Professor of Pediatrics, Director of the CCRP, past CIHR/Wyeth Clinical Research Chair in Transplantation, Chair of the Pediatric BMT Consortium
b. Poul Sorensen, MD, PhD - Professor of Pathology and Laboratory Medicine, Endowed Johal Cancer Research Chair, Chair of the Biology and Translational Research Committee COG
c. Catherine Pallen, PhD - Professor of Pediatrics
d. Sandra Dunn, PhD - Associate Professor of Pediatrics

All 4 researchers are internationally known in their respective areas of research, functioning as expert speakers at national and international meetings, grant and paper reviewers, are well funded by grants, are extensively published in peer-reviewed journals and books; all have been heavily sought after by other centers in the past 5 years. All 4 investigators have turned down such recruitment efforts due to their belief in the excellence and future potential of the CCRP.

We recognize that the program has a predominance of well-established and well-known investigators primarily at the professor and associate professor level. In order to remain sustainable, it requires the addition of highly promising, young investigators with the potential to develop into internationally recognized researchers in childhood cancer.

Recent additions include:
a. Rod Rassekh - Clinical Assistant Professor Pediatrics, Clinician Scientist.
b. James Lim, PhD - Assistant Professor Pediatrics, Scientist.

Further recruitments are required for development of the group.

External relationships of the CCRP
The CCRP has a number of established research relationships with other productive groups with common funded grants, including the CMMT and BCCH (Bruce Carleton and Michael Hayden), PBMTC, CBMTG, BCCA (Mary McBride), Terry Fox Laboratories (Connie Eaves and Andy Weng) and CDRD. These local relationships are being supported and expanded.

Strategic Plan to Enhance the Research productivity of the CCRP

The oversight group of the CCRP unanimously approved a strategic plan for development of the CCRP in August 2007. The conclusion was that, in order to take the CCRP to a higher level of international achievement, a critical mass must be achieved in all three areas of excellence. We determined that:

1. Recruitment should be targeted to the areas that would synergize with the current and existing researchers and preferably would have a current research track record in the area of pediatric oncology, hematology, or BMT
2. That a "critical mass" could be achieved by having 5 - 7 researchers in each of the three areas.
3. We concluded that we already have a critical mass with the current clinician investigators who represent sufficient experience and expertise, but that the clinical research group is limited by insufficient infrastructural support.
4. Each of these three areas of focus should be developed in a proportional manner and not to the detriment of the other two.
5. Future plans were to create a fourth hematology laboratory research focus when sufficient funding became available and the building goals of the other three areas had been achieved.

FIVE YEAR PLAN

I. CCRP Program.
The clinical research program and laboratory plan were administratively merged under the leadership of the current CCRP director, Dr. Schultz. This allowed for the ability to expand and

provide an integrated administrative support structure and further the seamless development of bench-to-bedside-to-bench research efforts. Additional support personnel, administrative, and research meetings have been implemented. The groups is now beginning to focus on development of team grant applications to national and provincial funding agencies as the opportunities present themselves. As part of this merging administratively, we are beginning to partner clinicians with basic scientists for long term research projects, grant applications, and publications.

II. Development of the research groups

A. Clinical Trials

In order to achieve the goals of this group, an enhanced clinical trials structure with the addition of personnel and increased capacity has been created. This structure includes the following: a research program coordinator (Colleen Fitzgerald); CRA position; research nurse; part-time statistician; and part-time financial manager. In addition to these positions, participation in the program part of TACL (Therapeutic Advances in Childhood Leukemia) a phase I clinical trials network based in Los Angeles has been pursued. We have successfully applied and received approval from TACL for a study to use a drug based on preclinical data from the program laboratories with CpG ODNs for ALL relapse post BMT. This will be in collaboration with SBI Biotech, a company in Tokyo, Japan. A data management task force was created in January 2009 to identify the best system for management of trials based at BCCH with approval of the Dacima program that is supported by the CFRI and BCCH infrastructure. The task force identified the need for the development of both a tumor and normal tissue bank; this project was initiated in February 2009. Further, they will create a business and implementation plan and a budget for development of a biobank. The group hopes to link and leverage off of current biobanking initiatives at the BCCA.

Dr. Evan Shereck has the first program based clinical and correlative project evaluating the role for ADP signaling aplastic anemia; this project is funded by the C17 granting agency. In addition, the Research Oversight committee, responsible for development and management of the clinical trials unit, has been very active in integrating fellow research projects, overseeing current projects, and the development of new in-house BCCH derived studies.

Currently, the program is evaluating implementation of:

a. Continued submission for phase I program funding, development of the needed infrastructure, SOPs, and procedures for creation of a function phase I clinical trials unit.

b. The best data management system for the phase I clinical trials group and also for management of a biobank. Close evaluation of the Dacima system as the prime candidate.

c. Development and creation of a tumor tissue biobank starting with leukemia, brain tumors and followed by other solid tumors and normal tissues. Funding for the initiative has not yet been approved.

The CCRP has focused on two primary laboratory areas of research. One is to develop a critical understanding of the biology and mechanisms behind how childhood cancer cells develop and grow in children and to identify drug treatments targeted directly against the cancer cells. The second focus in the program is to develop therapies harnessing the immune system specifically against cancer cells.

B. Tumor and Transplantation Immunology
The tumor and transplantation immunology research program (TTIRP) includes pre-clinical models of disease, biomarkers and drug development. The diseases of focus are chronic GVHD (transplantation immunology) and ALL (tumor immunology). Previously, the TTIRP developed a new therapy for post transplantation rejection; this group is one of the leaders to identify biomarkers in immune rejection after blood and marrow transplantation. More recently, the program has and is currently using preclinical experimental models to test a novel immune therapy to treat childhood cancer. An additional priority of the program is collaboration with the clinical trials group, located at BCCH, that will perform phase I and II clinical trials exploiting the discoveries of the research groups.

The TTIRP although achieving success is currently limited in its ability to attain a higher level of international achievement due to a lack of a critical mass of researchers. It is proposed that we recruit two researchers holding PhDs in either tumor or transplantation immunology focused on pediatric leukemia and/or BMT: it is anticipated they will be junior level recruitments. An additional third recruitment of a clinician scientist is planned in the next three years. In order to develop this group the program will require expanded laboratory space and facilities. This was recently achieved with funding from the Commonwealth Insurance Company that will develop the needed laboratory space for the planned expansion of the tumor and transplantation research section of the pediatric CCRP.

The CFRI has one of the most productive concentrations of active immunology research in British Columbia and one of the most productive groups of immunology researchers focused on pediatrics in Canada. The TTIRP space will locate the developing group in close proximity to the currently active immunology core facilities of the Diabetes groups and the CUPIC group focused on the immunology of childhood infections: not only will this allow access to the state of the art core immunology infrastructure at the CFRI, but also the development of a productive and synergistic research environment by close interaction with immunology researchers working on the common biological mechanism related to diabetes, infection and tumor and transplantation immunology.

C. Cancer Biology
This group is the largest in the CCRP. Currently, the program has targeted funding from the Johal endowment for the Johal research chair, the only endowed chair in the CCRP at present. This chair is held by Dr. Sorensen. With Drs. Dunn, Pallen, and Sorensen, the group will be able to expand to create a critical mass in Cancer biology with the immediate recruitment of two additional MD, MD PhD, or PhD scientists and future recruitment of 2 additional PhD positions.

One weakness of the program has been a relatively low level of activity focused on childhood cancer. The balance between performing the outstanding science in cancer biology and maintaining a focus on childhood cancer can be difficult. When Drs. Pallen and Dunn were recruited, neither had a track record in childhood cancer specifically. Unfortunately, until two years ago, the program did not support the development of these scientists into childhood cancer specialists. Many pediatric oncology research programs have clinician scientists who are laboratory scientists who also perform patient care. Unfortunately, the only member who currently fits this category is Dr. Schultz. The Canadian system of training has only recently become supportive in the training of clinician scientists. Further, it is often difficult to obtain funding for those seeking to train as clinician scientists. Due to the worldwide shortage of high quality clinician scientists in pediatric oncology, the program has had a very difficult time in

recruiting such individuals. As the program continues to try to either train or recruit such individuals, we have adopted an alternative approach by linking clinician investigators, who are clinicians who perform between 25 - 50% research with each of our basic scientists. Dr. Dunn is now linked with Dr. Hukin, Dr. Lim with Dr. Schultz and potentially Dr. Shereck, and we hope to link Dr. Rassekh with a future recruitment.

D. Future research groups

It is the goal of the program to develop a fourth research focus in the laboratory in the area of hematology. Currently no funding exists for this initiative and can only be started when funding becomes available and the current goals for the other three research areas have been met. It is anticipated that this research node will closely collaborate and synergize with each of the other three research areas.

III. The Michael Cuccione Childhood Cancer Laboratory

The overall goal of this initiative is to build the Cancer Biology section of the CCRP. We have targeted the Michael Cuccione laboratory funding to further develop the program by recruitment of two researchers and provision of some needed infrastructure. The Michael Cuccione Childhood Cancer Laboratory will be targeted to recruit two outstanding young researchers. In addition, the laboratory will provide increased services to the current investigators of the CCRP at the CFRI. At present, there are five laboratory investigators in the CCRP.

Dr. James Lim has been recruited as the fifth laboratory investigator in the CCRP and is the first of two recruitments for the Michael Cuccione Laboratories. Dr. Lim will focus on tumor cell migration and its interaction with the microenvironment. He is an outstanding young scientist, who does not currently have a track record in childhood cancer. We will network him into the program to ensure that he has the appropriate access to samples and is linked with the right people to maximize his potential. We continue our recruitment efforts to identify a promising young scientist who will complement the program and balance the mixture of junior and senior scientists.

Respectfully submitted

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Professor Pediatrics, UBC