

## **James Fund Research Report for 2008**

*The past year has been an exciting time for neuroblastoma research at SickKids and in Canada. The James Fund funds have enabled us to greatly increase the number of laboratories investigating new treatments for neuroblastoma, at SickKids and at other universities in Canada. These labs work together as a team, a unique and beneficial characteristic of research in Canada. The research funded by The James Fund has been recognized worldwide, and been the recipient of awards and prizes. Most importantly, we have begun in a short period of time to translate our findings in the laboratory to the clinic. On behalf of the James Fund investigators and funded laboratories, I thank you for your generous support that has enabled us to perform innovative and novel research that we hope will soon result in efficacious treatments.*

*Dr. David Kaplan, Senior Scientist  
The Hospital for Sick Children for the James Birrell Laboratory Investigators  
Toronto, Canada*

### **Clinical advances**

In January of 2008 we started a neuroblastoma clinical program at SickKids. Under the direction of Drs. Meredith Irwin and Sylvain Baruchel, all patients with newly diagnosed neuroblastoma as well as those with recurrent or relapsed disease are followed in a multi-disciplinary clinic. Through this program SickKids and other Canadian patients will have access to the latest clinical trials and novel therapeutics.

### **Clinical trials**

- . The drug discovery project funded by The James Fund has discovered rapamycin as a potentially potent agent for neuroblastoma. Rapamycin together with vinblastine is now being administered on a compassionate basis to patients at SickKids and the University of Vermont, and
- . another drug that works in a similar manner to rapamycin, temsirolimus, will be in a Phase I clinical trial together with vinblastine by the NANT clinical trials consortium, chaired by Dr. Sylvain Baruchel at SickKids. This trial will open in 2009.

### **Published papers, talks and prizes**

The following papers, published in leading cancer journals, report the results on potential neuroblastoma drugs squalene, cisplatin and nutlin.

- . Drs. Sylvain Baruchel, Herman Yeager, Paul Thorner:  
Das B, Antoon R, Tsuchida R, Lotfi S, Morozova O, Farhat W, Malkin D, Koren G, Yeger H, Baruchel S. Squalene selectively protects mouse bone marrow progenitors against

cisplatin and carboplatin-induced cytotoxicity in vivo without protecting tumor growth. *Neoplasia*. 2008, 10:1105-19.

- . Das B, Tsuchida R, Malkin D, Koren G, Baruchel S, Yeger H. Hypoxia enhances tumor stemness by increasing the invasive and tumorigenic side population fraction. *Stem Cells*. 2008, 26:1818-30. Bikul Das, a postdoctoral fellow who performed this work, was awarded the International Society of Paediatric Oncology (SIOP) Odile Schweisgutt 2008 award, the most prestigious award for a pediatric oncology trainee from this organization.
- . Tsuchida R, Das B, Yeger H, Koren G, Shibuya M, Thorner PS, Baruchel S, Malkin D. Cisplatin treatment increases survival and expansion of a highly tumorigenic side-population fraction by upregulating VEGF/Flt1 autocrine signaling. *Oncogene*. 2008, 27:3923-34.
- . Dr. Meredith Irwin: Lau LM, Nugent J, Zhao X, Irwin MS. HDM2 antagonist Nutlin-3 disrupts p73-HDM2 binding and enhances p73 function. *Oncogene* 2008; 27 (7): 997-1003.
- . Dr. David Kaplan: Leads the drug discovery project using neuroblastoma stem cells at SickKids, with the objective of finding new drugs and treatments. This research, led by Dr. Kaplan's postdoctoral fellows Drs. Kristen Smith and Loen Hansford, performed with Dr. Baruchel's postdoctoral fellow Dr. Libo Zhang, was awarded the Prize for "Best Paper" at the Advances in Neuroblastoma Research meeting in Japan, and was featured on the website of the American Society for Cancer Research. Dr. Kaplan presented seminars on this work in Sweden, and at the Memorial Sloan-Kettering Cancer Centre, New York University, University of Vermont, National Institutes of Health, University of Cincinnati, University of North Carolina, and at the American Society for Pediatric Oncology and Haematology. The drug discovery project investigators function as a team, with the other team members including Drs. Meredith Irwin (oncologist helping to lead the project), Paul Thorner (pathologist), Ted Gerstle (surgeon), and Herman Yeger.

### **New responsibilities/positions of James Fund scientists**

- . Dr. Meredith Irwin was named Associate Chair of Paediatrics (Research), SickKids, and Co-Director of the Neuroblastoma Program and Neuroblastoma Steering Committee and High-Risk Task Force leader for the Children's Oncology Group (COG).
- . Dr. Sylvain Baruchel was named Chair of the Advances in Neuroblastoma Research meeting to be held in 2012 in Toronto. This is the major forum for sharing results and findings in the neuroblastoma field. He was also named a Member of the International Neuroblastoma Registry Group to establish neuroblastoma tumor banking and treatment in under-privileged countries, and Chair of the Canadian Neuroblastoma Advance New Therapy Site Consortium.

### **New grants enabled by James Fund funding**

We are pleased that James Fund funding has enabled our team to receive neuroblastoma grants from:

- . Solving Kid's Cancer (U.S.A.)
- . the Ontario Institute of Cancer Research (to Dr. Kaplan)
- . The Terry Fox Cancer Institute (to Dr. Kaplan), and
- . the National Cancer Institute of Canada/Canadian Cancer Society (to Dr. Irwin).

These grants total approximately \$1.5 million, leveraged from projects initiated by \$30,000 James Fund seed grants. We are particularly grateful for the support of Solving Kids Cancer, a neuroblastoma parent-led foundation in New York City that is now partners with The James Fund in funded the cutting-edge neuroblastoma Drug Discovery Project at SickKids.

## Future funding and projects

This year, we anticipate funding “New Idea” neuroblastoma grants to the laboratories of:

- . Drs. Meredith Irwin, David Kaplan, Sylvain Baruchel, Paul Thorner, and Herman Yeger of the James Birrell Laboratories, and
- . laboratories at SickKids and University of Toronto that are new to the neuroblastoma field, those of Drs. Mike Moran, Jason Moffat (U. Toronto), Cliff Lingwood, and David Malkin.

The James Fund also plans to fund its first projects working together with research groups and clinicians at SickKids who study childhood brain tumors. Childhood brain tumors and neuroblastoma share many characteristics, but the clinicians, researchers, and patient-advocacy groups working on these important childhood cancers rarely work together.

In addition, The James Fund supports the following investigators in labs outside of SickKids for collaborative projects with SickKids scientists, either through direct funding or by providing matching funds for SickKids laboratories to perform projects with these laboratory directors:

- . Dr. Robert Korneluk (Children’s Hospital of Eastern Ontario)
- . Dr. Marco Marra (University of British Columbia)
- . Drs. Paul Beaudry and Steve Robbins (University of Calgary)
- . Dr. Carol Thiele (National Institutes of Health, U.S.A)
- . Dr. Tim Cripe (University of Cincinnati)
- . Dr. Frank Speleman (U. Ghent, Belgium)
- . Dr. Sven Pahlman (University of Lund, Sweden), and
- . Dr. Akira Nakagawara (Chiba University, Japan)

*The James Fund, in only a few years, is now funding some of the best neuroblastoma research worldwide, and through its funding initiatives, brought together a large international team and encouraged new laboratories to enter the neuroblastoma field.*