Children's Cancer & Blood Disorders

AAMAC funded grant

Title: **ADP Signaling Defect as a Potential Cause for Aplastic Anemia**
Principal Investigator (PI): Dr. Kirk Schultz (BC Child and Family Research Institute)
Previous PI: Dr. Evan Shereck (currently at Oregon Health and Science University)

Funding: A total of $ 111,930 in 2008 & 2009.
Study to be completed in November 2014

Background Information: Aplastic anemia (AA) is a rare disease that can appear at any age but is most frequently diagnosed in children and young adults. An estimated 15 Canadian children are diagnosed with AA each year; 300 Canadian children have been diagnosed with AA in the past 20 years. People with AA do not make enough blood cells, including white blood cells (to fight infection), red blood cells (to carry oxygen), and platelets (to plug damaged blood vessels and stop bleeding). As a consequence, patients with AA may suffer from severe infections, lack of energy, and unusual bleeding and bruising.

Normally platelets circulate freely in the blood and do not stick to each other. If damage to a blood vessel is detected, platelets in the immediate area release a compound called ADP. In this process, ADP acts as a messenger. ADP attaches to specific "docks" on the outside of the platelet, and this docking stimulates the changes in the platelets that are required for clumping of the platelets and plugging of the damaged vessel. In some cases of AA, the platelets that are produced lack the ability clump, contributing to symptoms of bleeding and bruising. The ability of a patient's platelets to clump can be tested in a laboratory by exposing platelets from a blood sample to ADP, and watching how quickly and completely the platelets clump.

Defects in the immune system are thought to contribute to most cases of inherited or acquired AA. The goal of Dr. Kirk Schultz's research is to find out if there is a connection between immune system defects in children with acquired AA and defects in platelet clumping. To address this question, Dr. Schultz has been working with AA patients and families to acquire blood samples for research purposes.

Recruitment: Dr. Shultz's research is dependent on biological samples from AA patients, as well as healthy volunteers. Because AA is a rare disease, samples were collected from across Canada. Patient enrollment began at the BC Children's Hospital in January 2009, and 21 AA samples and 10 healthy control samples were been collected as follows.

- BC Children's Hospital (Vancouver): 13 AA patients and 10 healthy controls
- Alberta Children's Hospital (Calgary): 3 AA patients
- CancerCare Manitoba (Winnipeg): 2 AA patients
- McMaster Children's Hospital (Hamilton): 1 AA patient
- The Hospital for Sick Children (Toronto): 2 AA patients

Aplastic Anemia & Myelodysplasia Association of Canada

C17 strives to improve health outcomes and quality of life for children and adolescents in Canada with cancer and blood disorders, and to eliminate disparities in care and outcomes wherever they occur

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The AA patients ranged from 5 to 28 years of age at the time of biological sampling, with their AA diagnoses occurring at an average age of 6 years. The average age of the healthy volunteers was 26 years.

2013 (Year 5) Results: The research plan is made up of three main steps. The first two steps were completed in 2013, for both the AA and healthy control samples.

The first step was to determine how many children with acquired AA also have platelet clumping defects. This was done using the ADP-clumping test described above. Of the 21 patients tested, a total 14 displayed some type of platelet abnormality, including 7 with moderate clumping abnormalities and 5 with strong clumping abnormalities. In addition to clumping defects, 5 patients were found to have other types of platelet abnormalities.

In the second step, DNA from the blood samples was subjected to a genetic test called microarray analysis, which surveys how the patients' cells are interpreting and using their genetic information.

Research Plans for 2014: In the final step, three groups will be compared: i) AA patients with ADP-clumping defects, ii) AA patients without ADP-clumping defects, and iii) healthy controls. The Healthy controls are required to provide comparison and context for the research information generated from the AA patients. The goal of the comparison is to figure how these two AA patient groups are different at a genetic level—different from each other and from healthy controls. This genetic testing generates massive amounts of complex information. To identify the meaningful and interesting differences between these patient groups, the results are currently undergoing statistical analysis at Dr. Patrice Eydoux's lab at the Child and Family Health Centre in Vancouver.

Publication of the results from the platelet abnormality experiments is currently underway, and the results of the genetic comparison will be prepared for publication later in 2014.

Future Research Directions: This research is categorized as pilot study—exploratory research performed to point the way to interesting new research directions. The genetic differences discovered by Dr. Shultz will be confirmed next in a larger group of AA patients. Confirmed differences will then be used to direct the development of new AA therapies that are specific to the two different patient sub-groups, with a goal of improving treatment effectiveness for AA patients overall.

AAMAC competition—Round 2

AAMAC has partnered with C^{17} for a second time in 2014. Funds have been raised to support a new grant in the next round of the C^{17} competition. A total of $90,000 will be available over two years after C^{17} matched AAMAC funds .

A call for Scientific Medical Research in Pediatric, Adolescent or Young Adult Aplastic Anemia, Myelodysplasia (MDS) or Paroxysmal Nocturnal Hemoglobinuria (PNH) was sent out in September 2013. Results of the competition will be known in July, 2014.