



## **Hyundai Hope on Wheels Hyundai Scholar Research**

**Dr. Jeffrey R. Andolina**  
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Dr. Andolina is currently a second year pediatric hematology/oncology fellow within the hospital's Division of Hematology, Oncology and Stem Cell Transplantation. Prior to this, he received his medical degree from the University of Virginia School of Medicine and went on to complete his residency in pediatrics at Children's Memorial.

Our hospital's rigorous three-year training program places young physicians like Dr. Andolina on dual tracks by emphasizing the development of top-notch clinical expertise as well as the hypothesis-driven investigative skills necessary for a career in academic medicine. In their second and third years, fellows dedicate a significant amount of time to advance laboratory or clinical research of their choosing, which is a demanding undertaking that depends on talent, creativity and critical thinking. The third year of training is also a time when fellows prepare research abstracts for presentation at scientific meetings and manuscripts for publication in peer-reviewed journals.

While our seasoned physicians and scientists are dedicated to guide, teach and inspire those who seek out their knowledge, they too look to these emerging young physicians with great hope that one day they will uncover answers to some of medicine's most challenging questions. Hyundai's continued support will help ensure the professional development of pediatric physician-scientists such as Dr. Andolina who will care for childhood cancer patients today well into the future.

### **Current Research Project**

Dr. Andolina is currently leading a research study entitled, "Abnormal Receptor Expression in Pediatric Acute Myeloid Leukemia." This study is being conducted under the mentorship of Seth Corey, MD, MPH, a nationally-renowned physician scientist who came to Children's Memorial's from the University of Texas M.D. Anderson Cancer Center where he served as chief of pediatric leukemia and lymphoma. With guidance from this accomplished senior level researcher, Dr. Andolina will develop a strong foundation in basic research which may one day have a significant

impact on the lives of children who suffer from cancer. The various aspects of his research, for which we request support from Hyundai, are summarized below.

## **Background**

Although there have been significant strides in the treatment of pediatric leukemias, significant challenges remain. Acute myeloid leukemia (AML) is the second most common type of leukemia in children. Unfortunately, this disease has multiple subtypes, is poorly understood, is increasing in frequency and does not have effective therapies. The overall survival for children diagnosed with AML is only approximately 50%. There is a desperate need for novel therapies. All cells have multiple receptors (protein molecules that bind with other substances) on their surface for different molecules called cytokines. Many of these cell receptors are critical for cell signaling, and often are important in the signaling pathways that lead to cell growth and cell differentiation (process by which a cell becomes more specialized). Pediatric leukemias represent conditions in which these signaling pathways have gone awry. It is our hope that further understanding of these receptors and pathways will lead to new therapies to better treat children diagnosed with leukemia. One cell receptor which Dr. Andolina and his colleagues are studying in the lab is called the granulocyte colony-stimulating factor receptor (G-CSF-R). Granulocytes are a type of white blood cell that fight infection. However, due to poorly understood genetic changes, there are times when these granulocytes lose their normal ability to die (apoptosis), and develop abnormal, infinite capacity for growth and self-replication. The G-CSF-R is a cell receptor protein which is composed of 813 amino acids, and is critical to the function of granulocytes/neutrophils (a type of granulocyte).

The human form of the G-CSF-R occurs in multiple forms, although only the class I and class IV forms are clinically detectable. The class I form is the normal form, and represents >95% of the total receptors in normal individuals. The class IV form is a shortened protein which is normally present in very small amounts. In certain types of AML, there may be an increase in relative percentage of the aberrant class IV G-CSF-R. G-CSF is a cytokine that is present in normal bone marrow. However, this molecule has been made into a recombinant form, and is used clinically to treat patients with cancers who have very low white blood cell counts. The administration of GCSF may affect the different forms of the receptor differently.

**Hypothesis:** Dr. Andolina and his colleagues believe that the abnormal class IV G-CSF-R plays a significant role in the development of pediatric AML. They believe that this receptor makes cells more likely to reproduce and less likely to undergo normal cell death.

**Specific Aim 1:** They plan to determine the relative amounts of the class I and class IV G-CSF-R

in multiple types of leukemia cells. First, they have preliminary data in a human leukemia cell line, which is an immortalized group of cells that can be easily studied in the laboratory. They have treated these cells with a medication called ATRA (all-trans retinoic acid), which causes the cells to change, undergo normal cell differentiation, and eventually undergo cell death. They then harvested genetic material called mRNA from these cells, and performed a method called PCR (polymerase chain reaction) which allows them to quantify the amount of genetic material or protein in a cell. So far, they have determined that as cells progress and differentiate normally, the relative percentage of the abnormal class IV decreases.

They have multiple other experiments that they hope to perform in the laboratory. First, they would like to further define the relative amounts and absolute numbers of the G-CSF-R in leukemia cell lines. In addition, using pediatric patient leukemia samples from Children's Memorial (regulatory approval has been obtained for this), they would like to study the G-CSF-R and both the class I and class IV in these pediatric patient samples.

**Specific Aim 2:** As mentioned above, G-CSF is a cytokine that is known to bind to and activate the G-CSF-R. Dr. Andolina and his colleagues are interested in testing the response of leukemia cells to the administration of this medication. They have developed additional cell lines which express only the class I or class IV receptor. In preliminary experiments, they have shown that cells that harbor the class IV receptor may have a faster rate of growth than cells that harbor the normal class I receptor. They plan to perform multiple experiments comparing and contrasting the growth rates and cell behavior following administration of G-CSF.

Cell signaling is also critical to understanding more about leukemia cells. They have been able to identify molecules which are activated during the cell signaling cascade present in the G-CSF-R. There are plans to perform multiple experiments examining different proteins that are activated and inactivated during the signaling activated when the molecule G-CSF binds to the G-CSF-R. They also hope to further delineate any unknown signaling in the abnormal class IV G-CSF-R.

The laboratory in which Dr. Andolina works requires significant resources to continue to study the pathogenesis of pediatric leukemias. Grant money obtained from Hyundai will be used to fund many of the experiments, as there are significant costs associated with obtaining leukemia cells, growing the cells in liquid culture, treating the cells with medications/cytokines and performing experiments on the cells to better understand the mechanisms that lead from normal cell growth and differentiation towards the devastating progression to leukemia. Hyundai's support for this project would facilitate research time and a significant portion of the needed research supplies.