# The 2012 Andrew H. Weinberg Memorial Lecture

***Synopsis of the June 2012 Symposium***

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Dr. James R. Downing, Deputy Director and Scientific Director of St. Jude Children's Research Hospital, was the invited speaker at the 2012 Andrew H. Weinberg Memorial Lecture and presented *"Whole Genome Sequencing (WGS) of Pediatric Cancers: The Pediatric Cancer Genome Project"*.

*Dr. James R. Downing (Photo by Sam Ogden, Dana-Farber Cancer Institute)*

In January 2010, St. Jude Children's Research Hospital and Washington University School of Medicine in St. Louis announced an unprecedented effort to identify the key genetic changes that give rise to childhood cancers. The St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project (PCGP) is the largest investment to date aimed at understanding the genetic origins of childhood cancers. In his presentation, Dr. Downing, the leader of this outstanding effort, provided an update of the status of this initiative and discussed the implications of whole genome sequencing of pediatric cancers in our understanding and treatment of childhood malignancies.

The goal of this 3-year, $65-million privately funded initiative is to sequence at 30-fold haploid coverage the whole genome of 600 pediatric tumors and matched non-tumor germline samples (1,200 total genomes) and to define the landscape of somatic mutations that underlie major subtypes of pediatric cancer. Two years into the project, the effort has generated one of the largest highcoverage whole–genome DNA sequence databases in cancer.

Several important findings have emerged from these studies. First and foremost is the importance of using the WGS approach to identify mutations in pediatric cancers. Analysis of an aggressive subtype of pediatric ALL known as early T-cell precursor leukemia, identified complex structural variations, focal deletions and sequence mutations of genes encoding key hematopoietic regulators that act as driver lesions in these leukemias. The exceedingly complex nature of some of these structural alterations would make it impossible to accurately identify them using more targeted sequencing approaches, such as

exome or transcriptome sequencing. This observation has important implications for the application of next-generation sequencing–based assays in the clinic.

A second important lesson is that the spectrum of mutations that occur in pediatric cancers can be remarkably different than that seen in adult cancers, even in tumors with very similar histology. A specific example of this is afforded by a recent study from the PCGP on pediatric glioblastomas. In children but not adults, a substantial proportion of glioblastomas arise in the brainstem as diffuse intrinsic pontine gliomas (DIPGs). Of the DIPGs analyzed by the PCGP, 78% were found to have missense mutations in a key regulatory site of genes encoding 2 of the 16 different histone H3 isoforms.

This is the first demonstration of a cancer-associated mutation in a key histone modification site. Notably, the mutation was only detected in DIPGs and, at a lower frequency, in pediatric glioblastomas arising outside the brainstem, but not in any adult glial brain tumors, or in 252 other pediatric cancers of multiple histological subtypes. A variation on this lesson is that the frequency of a particular mutation can also vary within specific pediatric cancers as a function of the child's age. An example of this is provided in a recent PSGP study on stage 4 neuroblastoma. In this study, somatic mutations of *ATRX* were detected in 44% of adolescents and young adults, but were never seen in tumors arising in infants.

A third major lesson is the importance of integrating genome-level data with epigenetic and RNA expression data to fully explore the abnormalities that drive cancer. Unexpectedly, the PCGP found that retinoblastoma, a pediatric eye tumor characterized by inactivating mutation of RB1, had very few mutations across the genome. However, a detailed analysis of epigenetic and expression data revealed aberrant expression of *SYK*, encoding a cytoplasmic tyrosine kinase, in every retinoblastoma analyzed. Notably, inhibition of this kinase resulted in apoptosis of retinoblastoma tumor cells, both *in vitro* and *in vivo*, suggesting a possible new therapeutic approach. Because clear benefits can be achieved by combining whole-genome with transcriptome sequencing, going forward, the PCGP will perform transcriptome sequencing on all tumors from which sufficient RNA is available.

In summary, the detailed information emerging on the genomics of pediatric cancers will open a new era in cancer medicine, in which the definition and classification of diseases, as well as treatment paradigms, will be reaching a new level of complexity. Understanding the functional and clinical relevance of the identified mutations in cancer will require bringing together dedicated teams of genomic and computational experts, oncologists, pathologists, molecular and cellular biologists, chemists, pharmacologists and others in order to translate these descriptive data into effective clinical use.