Interactive International Neuroblastoma Information Network

Due to the rarity of neuroblastoma, research in this field has been hampered, especially among the "high-risk" subset of patients that still experience long-term survival rates of less than 40%. Multi-institutional, cooperative group clinical trials are needed to enroll sufficient numbers of patients for prospective randomized clinical trials, and it has become increasingly apparent that greater international collaboration is needed to conduct research on this rare pediatric cancer to improve survival rates and minimize treatment-related toxicities. Dr. Susan Cohn and her neuroblastoma research colleagues around the world have a long-standing commitment to international collaboration as demonstrated by the recent development of the International Neuroblastoma Risk Group (INRG) Classification System.

To facilitate comparison of clinical trials performed in different regions of the world, Drs. Cohn and Pearson, in collaboration with colleagues across North America, Australia, New Zealand, Europe and Japan, developed the International Neuroblastoma Risk Group (INRG) Classification System. This classification system is based on the statistical analyses of 35 potential prognostic factors in a cohort of 8,800 neuroblastoma patients enrolled on cooperative group studies and is being used to define uniform risk-groups across these geographical areas to ensure the results of clinical trials conducted in different regions of the world can be directly compared.

With Dr. Cohn as co-Chair, the INRG Task Force also developed a mechanism for investigators from around the world to mine the INRG database to advance research with meaningful populations. To date, 20 neuroblastoma research projects have been approved by the INRG Executive Committee, resulting in several abstract presentations, publications, and our improved understanding of the disease. To facilitate expansion of the INRG database and to have the ability to perform analyses with more complex data, from multiple datasets, there is a need for the development of technologies to support and expand the access, management, organization, analysis, and dissemination of these data.

To date, the INRG Task Force has collected data on roughly 11,500 children diagnosed with neuroblastoma between 1980-2002. A number of Society for International Pediatric Oncology Europe Neuroblastoma (SIOPEN) and Children's Oncology Group (COG) cooperative group studies have recently been completed, and we anticipate adding data from over 4,000 new patients treated on these studies within the next two years. This database contains by far, the largest number of neuroblastoma patients ever collected, and significant discoveries have already been made in data mining projects using this unique resource. Although the data mining studies have led to a number of seminal discoveries, the current application housing the INRG database has a number of limitations.

VISION

Our goal is to harness the outstanding computational infrastructre and expertise at the University of Chicago to develop technology that will facilitate international, multi-institutional, interdisciplinary research in childhood neuroblastoma. Over the long term, this technology will accelerate research efforts for a better understanding of the epidemiology of this disease, the genetic mechanisms that contribute to tumor behavior and development, the long-term consequences of treatment, and new strategies for tumor treatment and prevention.

We are working to create a system, the Interactive International Neuroblastoma Information Network (IININ), which will provide physicians, scientists, and other members of the INRG community with access to high-quality health and research related information resources and services. We intend to integrate data from multiple datasets pertaining to childhood neuroblastoma, including biological data, phenotypic measures, and clinical outcomes. By leveraging the current data collection and sharing procedures developed by the INRG community, we will be positioned to expand the connections to additional datasets, introduce tools for facilitating data requests and data sharing, and create interfaces for data visualization and basic statistical analysis. This infrastructure is likely to provide a distinctive advantage to scientists involved in neuroblastoma research and thus enable new perspectives, collaborations and knowledge. The specific aims of the proposed 2-year project are:

1. To assess the information needs of researchers, biostatisticians, and clinicians. We will use an adaptation of the Critical Incident Technique and survey instruments to analyze and understand the information and data needs of researchers in the INRG Task Force. These studies will explore issues related to data governance, data sharing, and application functionality.

2. To develop an architecture for the IININ database. We will develop database models and web applications to support research in neuroblastoma. We will evaluate the INRG data set and additional clinical, biological, genomic, outcomes, imaging, and survivorship data. We will leverage the interaction of clinicians, researchers, and biostatisticians to clarify and refine the models and applications.

3. To assess the ease-of-use of the application in a pilot study. We will use a pilot study and standardized instruments to measure the perceived ease of use, usefulness, functionality and satisfaction of the application. We will conduct usability studies to analyze the process of users performing a task, and the ease with which they can do this. These studies will be instrumental for guiding our future developments.

HOW

The IININ will be an internet-based initiative designed to stimulate research and accelerate progress on epidemiology, prognosis, treatment, and outcome of neuroblastoma in children. The main goal is to serve as the international resource for researchers in the neuroblastoma community, providing an environment that would include phenotypic, genotypic, and environmental data from patients of multiple backgrounds, gender, race and ethnicity. A secondary goal is to facilitate local, regional, and international collaboration among researchers, clinicians, research institutes, and national organizations.

To ensure that we have the ability to collect more complex patient data and that investigators have access to high-quality health and research related information resources, we plan to develop technologies to support the INRG database's expansion into the IININ. The IININ will provide unparalleled opportunities for investigators focused on studying this rare cancer, and we anticipate this research will ultimately direct us to a better understanding of neuroblastoma genomics, epidemiology, therapeutic strategies, and long-term outcome. We anticipate that this technology will also serve as a paradigm for other pediatric cancer registries.

- Drs. Susan Cohn, Eneida Mendonca, and Wendy London co-direct this project because their expertise is synergistic. Dr. Cohn is a pediatric oncologist who has devoted her career to the care of children with NB and to understanding the molecular pathogenesis of the disease through the investigations of her laboratory.

- Dr. London has expertise in both statistical methodology and neuroblastoma and serves as the lead statistician in the Children's Oncology Group (COG) Neuroblastoma Disease Committee. She is also the Chair of the INRG Statistical Subcommittee and has worked closely with the INRG co-Chairs Drs. Cohn and Pearson in developing the INRG Classification System and the current INRG database.

- Dr. Mendonca is Board-certified in pediatrics and intensive care with a doctoral degree in biomedical informatics. A member of the University of Chicago Computation Institute, she has expertise in user needs assessment and the development and evaluation of clinical and research systems. Her research interests lie in using computational methods and informatics techniques to analyze large biomedical data sources for patterns and new knowledge. As Director of Informatics for the New York-Presbyterian Hospital from 2002-2007, Dr. Mendonca lead the development of a web-based registry which currently includes more than 140,000 children has been used by inpatient and outpatient clinics associated with both the Weill Medical College at Cornell University and Columbia University.

IMPACT: ONE EXAMPLE

Less than 5% of localized neuroblastomas are *MYCN* amplified, a genetic marker that is strongly associated with aggressive behavior and poor outcome in advanced-stage disease. Because of the rare nature of this finding in localized disease, it has been difficult to develop an evidence-based therapeutic strategy for this group. Because of the large numbers of patients included in the current INRG database, it presents a unique opportunity to study rare subgroups of patients, including those with unusual combinations of clinical and biological features. Our current database includes 87 patients with low-stage, *MYCN* amplified neuroblastomas, more than 3-fold the number of patients ever previously reported with these clinical and biological features.

Although tumor cell genetics was associated with outcome in this cohort of patients, more modern genome-wide molecular studies are likely to reveal the genes and cellular pathways that distinguish the tumors that will be cured from surgery alone from the ones that will require additional treatment. This is an intriguing set of tumors to analyze because by definition, they all have *MYCN* amplification, yet only a subset behave aggressively, suggesting that the *MYCN* targets are not universally activated. Genome-wide molecular studies of neuroblastoma tumors are being conducted in laboratories around the world, and these data are largely available to the public. Linkage of the clinical and biological data in the IININ database with publicly available genomic data will provide an unprecedented resource for analyzing neuroblastoma biology and determining risk. Our long-term goal is to improve the outcome for all children with neuroblastoma using an evidence-based approach. For rare cohorts of patients such as those with *MYCN*-amplified localized neuroblastomas, large databases, like the proposed IININ database, with detailed clinical and biological information are essential.

International Interactive Neuroblastoma Information Network system architecture