

Neuroblastoma

Research Update 2013

National Leadership

Cincinnati Children's is a leading national center for neuroblastoma research. Some of the first bone marrow transplants for neuroblastoma were pioneered here. Our investigators work to better understand the biology of neuroblastoma cells and develop new ways to treat the cancer, including sophisticated new drugs and combinations of drugs, safer and more effective approaches to bone marrow transplantation, and next-generation drug discovery.

Brian Weiss, MD, leads the nation's key clinical trial for high-risk neuroblastoma. He also serves in leadership role in the national Children's Oncology Group (COG) Neuroblastoma Committee and in the New Approaches to Neuroblastoma Therapy (NANT) consortium.

Daniel vonAllmen, MD is a national leader in neuroblastoma surgery. A member of the COG Neuroblastoma Committee, he has been instrumental in pursuing new techniques, including robotic surgery, to improve local control.

John Breneman, MD sits on the Steering Committee for the Radiation Oncology Committee of the COG and is active in protocol development and establishing standards for use of pediatric radiotherapy. In addition, he chairs the Pediatric Radiotherapy Committee for the American Board of Radiology.

Dr. Luke Pater specializes in the treatment of children with neuroblastoma and other tumors and is an active participant in several COG studies.

Research Highlights

New Drugs and Radiation Therapies

Cincinnati Children's is leading development of ¹³¹I-MIBG targeted radiopharmaceutical therapy for relapsed neuroblastoma. MIBG, a substance that



Clinical researchers Brian Weiss, MD, and John Perentesis, MD, FAAP

is absorbed by neuroblastoma cells more easily than normal cells, is chemically joined to ¹³¹I, a radioactive form of iodine. When this combination is given to neuroblastoma patients, the radioactive molecules are absorbed by neuroblastoma cells, killing them without causing too much damage to healthy cells nearby. To ensure the safety of patients, families and staff during ¹³¹I-MIBG therapy, Cincinnati Children's has built two specialized therapy suites shielded against radiation, and is building two new MIBG suites in 2013.

Cincinnati Children's investigator Brian Weiss, MD, is a national leader in the development of ¹³¹I-MIBG therapy and currently leads the national Children's Oncology Group pilot study examining the use of ¹³¹I-MIBG during induction therapy for newly diagnosed high-risk neuroblastoma patients. Dr. Weiss also leads an expanded access ¹³¹I-MIBG study at Cincinnati Children's, which makes experimental ¹³¹I-MIBG available to some patients for whom a national clinical study might not be appropriate. In addition, Dr. Weiss serves as the Cincinnati Children's principal investigator for the New Approaches to Neuroblastoma (NANT) Consortium, a group of researchers at children's hospitals across the U.S. and Canada working to develop the next generation of therapies for neuroblastoma.



High-throughput screening technology allows researchers to rapidly test thousands of potential drugs to find the most promising new leads

New Approaches to Bone Marrow Transplantation and Chemoprotection

For patients whose neuroblastoma cannot effectively be treated by surgery and standard chemotherapy, high-dose chemotherapy combined with a bone marrow transplantation can be an important tool against the disease. With more than 1,300 transplants performed overall, including more than 180 for neuroblastoma, Cincinnati Children's is one of the largest and most experienced pediatric bone marrow transplantation centers in the country and was one of the first to offer transplants for neuroblastoma patients.

Drug Development Center

Cincinnati Children's is the nation's leading center for new anticancer drug discovery and development in pediatric and young adult leukemia and solid tumors. In the laboratories of Drs. Yi Zheng, and Mohammad Azam, scientists have made remarkable progress and published new advances in the last year using sophisticated computer modeling techniques to design new selective drugs to target high risk pediatric cancers like neuroblastoma. In parallel, researchers in the Perentesis lab are screening new potential anticancer compounds and targeted drugs for their activity in killing otherwise drug resistant neuroblastoma.

The new drugs that show promise in these studies – called hits – are now being developed into treatments for patients with relapsed and drug refractory disease. These leading edge in advances in drug discovery at Cincinnati Children's are being integrated with our new center for personalized cancer therapy. We have learned through our research in the past year, that even to the same type of tumor from different patients are caused by

different genetic mutations. different genetic mutations. In this initiative, we are sequencing the DNA of tumors from individual patients to find their Achilles heel and Design unique treatment plans to target more effectively specific tumor.

Maryam Fouladi, MD, MSc, an internationally recognized expert in pediatric neural tumors, has led investigations in blocking growth factor pathways in neuroblastomas and other solid tumors. Growth factors are molecules inside cells that control how cells grow and divide. When cells produce too many of these molecules or become too sensitive to them, they grow and divide too rapidly.

Dr. Fouladi currently chairs a national COG Phase 1 clinical study examining whether blocking growth factors—in this case, the insulin-like growth factor and mTOR pathways—may slow or stop cancers that are not responding to standard chemotherapy. This study also includes sophisticated analyses of molecular signaling in patient samples in Cincinnati Children's laboratories to see if we can identify better ways to predict which patients will respond well to treatment and which may experience serious side effects.

Cincinnati Children's investigators will also lead a new Phase 2 study of a drug called fenretinide through the New Approaches to Neuroblastoma (NANT) Consortium. Researchers have shown that giving a drug called 13-cis-retinoic acid (RA) after high-dose chemotherapy and autologous stem cell transplant improves survival for some high-risk neuroblastoma patients, but some patients' neuroblastoma is resistant to RA. Fenretinide is another form of retinoic acid that appears to be effective in some resistant forms of neuroblastoma. The new study being developed by our researchers will test whether fenretinide can help patients for whom RA is not effective.

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