CANCER PROGRAM
Children's Memorial Hospital's Cancer Program takes a multidisciplinary approach to research and treatment. The following entities play a vital role in achieving our mission:

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CANCER COMMITTEE MEMBERS

Morris Kletzel, MD  
Head and Meryl Suzanne Weiss Endowed Professor of Hematology, Oncology and Stem Cell Transplant; Director, Stem Cell Laboratory and Pheresis Program; Professor of Pediatrics, Northwestern University's Feinberg School of Medicine

Marleta Reynolds, MD  
Head, Division of Pediatric Surgery; Director, Extracorporeal Membrane Oxygenation; Co-medical director, Institute for Fetal Health; Lydia J. Frederickson Professor in Pediatric Surgery; Professor of Surgery, Northwestern University's Feinberg School of Medicine

Ellen Benya, MD  
Attending physician, Medical Imaging (Radiology); Program director, Pediatric radiology fellowship; Assistant professor of Radiology, Northwestern University's Feinberg School of Medicine

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Head, Anatomic Pathology, Pathology and Laboratory Medicine; Director, Pediatric pathology fellowship program; Professor of Pathology, Northwestern University's Feinberg School of Medicine

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Nursing director, Hematology, Oncology and Stem Cell Transplantation (Nursing)

Maryanne Marymount, MD  
Director, Pediatric Radiation Oncology; Co-director GAMMA Knife Radiosurgery Program; Assistant professor of Radiation Oncology, Northwestern University's Feinberg School of Medicine

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Yolanda Santiago, CCRP  
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Jean Schwab, LCSW  
Social Work

Heidi Thomalla, CCLS  
Certified child life specialist

Tadanori Tomita, MD  
Division head, Neurosurgery; Medical director, Falk Brain Tumor Center; Yeager Professor of Pediatric Neurosurgery; Professor of Neurological Surgery, Northwestern University's Feinberg School of Medicine

Grady Wade, PhD  
Senior analyst, Process Improvement

Linda Ward, BHA  
Quality facilitator, Process Improvement
MESSAGE FROM THE CANCER COMMITTEE CHAIR

This has been a very exciting year for our Cancer Program.

Not only have we added new faculty in oncology and stem cell transplantation, but we have also increased the volume of patients we serve. As we prepare to move into our new facility in 2012, we will continue to increase research efforts and further strengthen faculty development, all of which will enable us to incorporate new technologies that will benefit our patients.

I am very excited about the construction of the Ann & Robert H. Lurie Children’s Hospital of Chicago, as it will move us closer to Northwestern University’s Feinberg School of Medicine and the Lurie Cancer Center. The proximity will enhance our ability to increase collaboration with other professionals, and offer us direct access to scientists who are already doing fabulous research.

We have been working with the architects and planners to ensure that our new facility is the best it can be. While the new space will afford us many improvements, our program must continue to grow and expand. Therefore, we must continue to focus on developing our outreach programs at both Central DuPage and Northwest Community hospitals. These outreach programs will increase our presence in the suburban areas, allowing some patient families to be seen closer to home.

I want to take this opportunity to thank all of the members of the hospital who help make the Cancer Program successful, and hope that you continue with the same enthusiasm in the upcoming years.

Morris Kletzel, MD
Chair, Cancer Committee; Head Hematology, Oncology and Stem Cell Transplantation; The Meryl Suzanne Weiss Professor in Hematology, Oncology; Professor of Pediatrics, Feinberg School of Medicine, Northwestern University
**WHAT’S NEW**

**13th International Symposium on Pediatric Neuro-Oncology**
Childrens Memorial Hospital is pleased host the 13th International Symposium on Pediatric Neuro-Oncology (ISPNO). Under the direction and leadership of Stewart Goldman, MD, and Tadanori Tomita, MD, this worldwide consortium of members will present 483 abstracts on epidemiology, current trends, treatment, management and care of children with central nervous system tumors including medulloblastomas, infant tumors, low-grade and high-grade gliomas, ependymomas, brain stem gliomas, PNET, ATRT, neuro-imaging, neuropathology, molecular biology, neuro-oncology nursing, outcomes and quality of life.

Diverse and multidisciplinary approaches taken by different cooperative groups will be examined in a series of panel debates, seminars, oral presentations and poster discussions. A pre-symposium day includes educational seminars on the basics of pediatric neuro-oncology. In addition, the meeting includes family day activities focusing on the importance of familial partnerships with the medical care team in addition to discussions on survivorship, transitions to adulthood and an “ask the expert panel.” The meeting will run concurrently with the Société Internationale d’Oncologie Pédiatrique (SIOP) meeting and will be held at the Chicago Marriott on Michigan Avenue from June 29-July 2, 2008. For more information, please visit www.ispno.com.

**Minimally invasive surgery**
Children’s Memorial is on its way to becoming the regional referral center for neonatal minimally invasive surgery, which uses small incisions to correct congenital anomalies of the chest and abdomen in newborns as tiny as four pounds. For babies born with a malformed lung, a hole in the diaphragm or other anomalies, this means less pain, minimal scarring and faster recovery. In 2007, the hospital opened two state-of-the-art minimally invasive surgery suites and recruited pediatric surgeons, Katherine Barsness, MD; Anthony Chin, MD; and David Rothstein, MD, who are trained in advanced minimally invasive techniques.

**New MRI scanner**
In March 2008, the Department of Medical Imaging introduced a new MRI scanner at the Children’s Memorial Outpatient Center in Lincoln Park. Using the latest technology, it will scan patients for MR procedures while accommodating the most complex scanning protocols. The new equipment will also allow us to provide sedation services based on patient needs.

**Beads of Courage: Patients’ symbols of emotional and physical journeys**
They are the hospital’s latest accessory trend for the young people who create and wear them, and for nurses and family members as well. They are called Beads of Courage. More than 220 patients have begun to strand together a meaningful and integral, personal symbol of their cancer treatment, since the Beads of Courage program’s inception at the hospital in September 2006. Gwendolyn Possinger, a child life specialist, was responsible for beginning this program at Children’s Memorial, creating a supportive outlet that helps patients cope with cancer and ongoing treatments.

The strands of beads that patients create are not just a distraction; they are a symbol of courage and of patients’ emotional and physical journeys. Possinger says, “The strands represent something tangible for cancer patients to hold on to and to symbolize all that they have been
through, are going through, or will experience during treatment. The beads aren’t just jewelry; they tell a very personal story.”

Each bead is representative of a procedure or treatment. For instance, a child will receive a glow-in-the dark bead for each radiation treatment or a purple heart for the completion of chemotherapy. All milestones, procedures and stages of cancer treatments are recognized through a variety of beads.

The Beads of Courage program is also helping families come together during a difficult time. Often, the beads will help initiate conversations with newly diagnosed patients and families and create a way to cope and talk about something that is overwhelming. Nurses and staff are also creating strands. “As caregivers, nurses and staff walk much of the treatment path alongside the patient. The beads are a meaningful symbol to reflect their work and the triumphs and challenges along the way,” says Possinger.

Beads of Courage became a very personal way to tell of a courageous fight for Jenny Nadoff and her daughter Chaya, who recently lost her battle with an aggressive brain tumor. Nadoff remembers, “Chaya was so proud of her beads. It was really exciting for Chaya and for all of us to see in such a tangible way where Chaya had been, how much she had gone through and accomplished, as well as for others to see it and understand her story.”

During Chaya’s treatment, the beads she collected and strung together not only represented her strength and her journey, but connected her with another young patient at Children’s Memorial. “Being able to compare their necklaces, the two girls really bonded. The little girl even created a special bead for Chaya’s necklace,” Nadoff continues “When Chaya passed away, Gwendolyn helped the girl pick out a bead for losing a special friend. Chaya will be a part of her necklace as well.”

Cancer Program phone numbers

Chief, Division of Hematology, Oncology and Stem Cell Transplantation: 773.880.4562

Hematology, Oncology and Stem Cell Transplantation (8 a.m. - 5 p.m.): 773.880.3004
• Appointments: Press 5
• Dial known party’s extension at any time: Press 2
• Medication refills: Press 4
• Urgent issues requiring MD attention: Press 1

Stem Cell Transplantation: 773.868.8046
• Ambulatory Stem Cell Unit: Press 4
• Dial specific team member: Press 3
• General questions: Press 6
• Urgent issues requiring MD attention: Press 0, ask operator to page physician on call

The STAR (Long-term follow-up) Program: 773.880.4584

Friends of the Family Coordinator: 773.880.3680
Our laboratory started the year under the guidance of Bernard L. Mirkin, PhD, MD. Unfortunately; we lost our mentor in August. He brought us together from many walks of life to work on understanding the behavior of neuroblastoma. This was a passion for Dr. Mirkin and has become a passion for all of us in the laboratory. It is in his memory that we continue our work.

Overview
The primary thrust of our research team has focused on studies to identify the basic biological processes that regulate adaptation of malignant tumor cells to stressful environments, such as those produced by anti-cancer drugs, and thereby permit their survival in the presence of agents that would normally kill them. Understanding these processes will help cancer researchers develop novel chemotherapeutic strategies. Our group has directed its attention to tumors that predominate during early childhood, such as neuroblastoma, but these principles apply to all cancers.

Lastly, a new area of investigation has been undertaken in the laboratory by an additional investigator. Growth factors have long been known to have an effect on tumor behavior, and the therapeutic implications of growth factor pathway manipulation have been well established [e.g., Epidermal Growth Factor (EGF) and breast cancer]. Previously, we have investigated the effect of EGF on neuroblastoma behavior. Currently, we are investigating the nerve growth factor (NGF) pathway and its effect on neuroblastoma survival and behavior.

Individual projects
1. Suppression of Midkine Reverses Cytoprotection in Human Neuroblastoma Drug-Sensitive Cells
Resistance to cytotoxic agents is a major limitation for their clinical use to treat human cancers. Tumors become resistant to chemotherapy when a subset of cells undergoes molecular changes leading to overexpression of drug transport proteins, alterations in drug-target interactions or reduced ability to commit apoptosis. In such tumors, a cytoprotective relationship may exist between drug-resistant and neighboring drug-sensitive cells. Early studies of midkine revealed that this molecule was able to exert a survival function in a variety of cellular systems and against various stimuli, suggesting that it could be associated with drug resistance. Overexpression of midkine in doxorubicin-drug-resistant human neuroblastoma cell lines confirmed this assumption and suggested that it may play a role as a cytoprotective signal between drug-resistant and drug-sensitive cells.

Co-culture experiments showed that doxorubicin-resistant cells can protect wild-type human neuroblastoma cells from cell death when doxorubicin is added to the medium. When
the midkine expression was suppressed by siRNA, the protective effect was lost, strongly suggesting that midkine is the cytokine in the medium that makes drug-sensitive cells resistant.

2. Efflux Transporters and Function in Multidrug-Resistant Neuroblastoma Tumor Cells

There have been significant advances in the diagnostic techniques and therapeutic modalities available for the treatment of neuroblastoma. However, the survival rate of patients who are classified in the high-risk subgroup is 40 percent or less. Chromosomal anomalies are present in this high-risk subgroup but another factor underlying this poor prognostic outcome is the development of multi-drug resistance (MDR) to a wide variety of anti-neoplastic agents. Efflux transporters have been identified in MDR cells, which decrease the uptake and efficiency of specific chemotherapeutic drugs. P-glycoprotein (P-gp), a 170kD membrane localized efflux transporter, multi-drug resistant protein (MRP-1), a 190kD protein residing in the plasma membrane, and proteins associated with the nuclear pore complex have all been shown to play a role in drug resistance. The expression of active efflux transport systems in malignant cells that become resistant to anti-neoplastic agents represents a biologically significant adaptive response to stressful environments. This investigation was designed to quantitatively characterize the relationship between cellular uptake, nuclear localization and cytotoxic potency of chemotherapeutic drugs in human neuroblastoma cells.

This study has demonstrated the presence of P-gp in cell extracts and nuclei prepared from human neuroblastoma cells that are resistant to doxorubicin (SK-N-SH-rDOX6) and etoposide (SK-N-SH-rETOP5), but not 5-fluorouracil (SK-N-SH-r5FU4). Treatment of SK-N-SH-rDOX6 and SK-N-SH-rETOP5 cells with verapamil, which blocks P-gp, resulted in increased uptake of doxorubicin in these cells. In addition, there was a dose-dependent increase in cytotoxic potency in cells treated with doxorubicin. The multi-drug resistance protein (MRP-1) was also detected in whole cell homogenates of wild-type and all drug resistant SK-N-SH cell lines. Finally, studies using leptomycin B to block the nuclear pore signal receptor, CRM1, induced a dose-dependent accumulation of topoisomerase II alpha and histone deacetylase 4 in the nucleus of neuroblastoma cells. As a result of these changes, cellular response to chemotherapeutic drugs was significantly enhanced.

3. Cytotoxicity Study of Neuroblastoma Cell Lines with Doxorubicin-Conjugated Polymer Nanoparticles (PNPs)

Anthracylane derivatives such as doxorubicin are frequently used in the treatment of numerous human malignancies, including neuroblastoma. However, the therapeutic efficacy of this relatively insoluble small-molecule drug is limited by its low bioavailability and short-plasma half-life. In addition, the often life-threatening side effects that accompany the administration of doxorubicin, including cardiotoxicity and the development of secondary cancers, make this an undesirable chemotherapeutic treatment. To remedy these shortcomings, the packaging of a high density of doxorubicin into nanoscale vessels may allow the drug to be preferentially delivered to tumor sites without causing side effects to healthy tissues. In addition, the poly(ethylene glycol) shells of our PNPs are well-known to mask the particles against the efflux pumps such as P-glycoprotein and multi-drug resistance proteins that export anti-neoplastic agents from their intracellular location to the extracellular space. This should also increase the bioavailability of doxorubicin. Finally, the slow release of doxorubicin, through acid-labile linkages, inside acidic tumor tissues and endosomes appeared to give our PNPs a selective edge over the free drug.
We have demonstrated through in vitro cell studies that doxorubicin-containing PNPs can be viable chemotherapeutic agents for cancer. Not only is the polymer platform non-cytotoxic, the PNPs can be readily taken up by the cells and their drug contents sustainably released inside the cellular environment over a long period. SK-N-SH wild-type cells exhibited a dose-dependent cytotoxic response to DOX-PNPs, albeit at a higher concentration than free doxorubicin alone, consistent with a gradual uptake and release mechanism. Most importantly, SK-N-SH-rDOX6 (doxorubicin-resistant cells) exhibited similar responses to both free doxorubicin and DOX-PNPs, suggesting that doxorubicin must be the active cytotoxic agent in the latter case. In addition, inhibition studies revealed that the growth of SK-N-SH wild-type cells was not only significantly inhibited upon incubation with DOX-PNPs, but also led to a decrease in total cell population over 7 days. Similar findings were shown in SK-N-SH-rDOX6 cells.

4. The Role of Histone Deacetylases in Regulating the Drug Resistance of Neuroblastoma Tumor Cells

Epigenetic modifications, particularly acetylation and covalent histone modifications, play an important role in regulating chromatin dynamics, and therefore have a significant impact on gene expression. The transcriptional expression of critical genes relies on two opposing enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs). An imbalance in the equilibrium of histone acetylation has been associated with carcinogenesis and cancer progression. Intriguingly, the selective inhibition of chromatin remodeling pathways has provided a new therapeutic window in cancer biology. Currently, more and more evidence has shown that chromatin remodeling by HDACs might be implicated in the development of cancer chemotherapeutic drug resistance. This project directly targets the role of HDACs in the regulation of drug resistance in neuroblastoma cells.

We have previously demonstrated that Sirt1 (Silence information regulator 1), a class III histone deacetylase, was up-regulated in many different cancer cells selected for resistance to doxorubicin, and was also a positive regulator of the multidrug resistance gene, MDR1. Further, we have found that continuous exposure of neuroblastoma SK-N-SH cells to trichostatin A (TSA), a HDAC inhibitor, results in resistance not only to this drug, but also to other stressors, such as SAHA, doxorubicin, cisplatin and H2O2. These findings provide further support for the hypothesis that modification of chromatin structure by HDAC inhibitors plays a key role in generating drug resistance.

5. Differential Effects of Nerve Growth Factor Receptors, P75 and Trk A, on the Biological Response of Human Neuroblastoma (SK-N-SH) Cells to Nerve Growth Factor (NGF)

Since neuroblastoma tumors are derived from neural crest cells, they have many of their characteristics and respond to neuronal growth factors, most significantly, nerve growth factor (NGF). Perturbations in the expression of Trk A have been shown to influence the clinical behavior of neuroblastoma tumors. Neoplasms lacking Trk A receptors (due to chromosome 1 deletions) are more aggressive. Previous investigations have demonstrated that neuroblastoma cells transfected with the Trk A receptor and incubated with NGF undergo differentiation, leading to slower growth and a less aggressive phenotype. In addition to the high-affinity Trk A receptor, NGF also exerts its cellular effects through the low-affinity p75 receptor. Neuroblastoma cells expressing an elevated level of the p75 receptor showed a high degree of apoptosis (programmed cell death). This effect was inhibited when Trk A was transfected into these cells. The clinical implications of manipulation of the NGF cascade are currently being studied in a phase I clinical trial of a pan-Trk receptor inhibitor.

Using a retroviral vector, the human NGF gene (generously provided by Dr. X.O. Breakefield) was transfected into the human SK-N-SH neuroblastoma cell line. SK-N-SH/NGF cells, when compared to the wild-type SK-N-SH cells, were slower growing, developed more neurites and expressed the neuronal differentiation marker, neuron specific enolase (NSE). In addition, expression of the NGF receptors, p75 and Trk A, was determined in the SK-N-SH/NGF cells and compared to their wild type (SK-N-SH) counterparts. P75 expression was significantly increased in the SK-N-SH/NGF cell line.

Since p38 activation has been associated with apoptosis, its activation and downstream effectors were analyzed. Our findings indicated that expression of activated p38 was increased in SK-N-SH/NGF cells treated with NGF and that apoptosis, demonstrated by DNA laddering, occurred more readily in these cells. To discern whether this effect was due to the p75 receptor, both immunoprecipitation and SiRNA studies were undertaken. The results confirm that the effects seen were mediated via the p75 receptor and not the Trk A receptor.
Research publications

Presentations (2007 only)


Full length manuscripts (referred Journals, 2006-2007)


Book chapters
The Cancer Registry is a data collection system that analyzes and stores information on diagnosis, site, treatment, extent of disease and follow-up information for all cases seen at Children’s Memorial Hospital. Cases are separated into two categories: analytic and non-analytic.

Analytic cases are those patients who are diagnosed and/or received any of their first part of treatment at Children’s Memorial Hospital.

Non-analytic cases are patients who have already been diagnosed and the entire first course of treatment was completed elsewhere. This includes patients who are receiving subsequent treatment, patients diagnosed prior to our reference date of January 1, 1991 or those diagnosed at autopsy.

The registry maintains a lifetime follow-up on management and progress of each analytic case. This data is utilized in tracking treatment trends in the hospital and can be compared with state and national data. Our follow-up rate is maintained at 93% for patients diagnosed within the last five years and an 80% follow-up rate is maintained for all eligible analytic patients from the cancer registry reference date.

Since our reference date, 2,940 cases have been accessioned into the database. In 2006, 202 analytic and 21 non-analytic cases were abstracted. The gender distribution for analytic cases was slightly higher with 128 males and 95 females. The five major sites of analytic cases seen at Children’s Memorial in 2006 were tumors of the central nervous system (inclusion of benign tumors), bone marrow (leukemia), lymph nodes, endocrine tumors and connective soft tissue tumors. There was a higher incidence of CNS tumors than seen in the state and nationally. Leukemia, lymphoma, sarcomas incidence at Children’s Memorial fell in-between state and national figures and had a slightly lower incidence of neuroblastomas and Wilms tumors.

The Cancer Program software, ERS, continues to the provide the registry with support and compliance with the National Cancer Data Base submission and the ever changing Illinois State Cancer Registry and American College of Surgeons Guidelines. In December 2001, the Cancer Program was awarded a three-year approval by the American College of Surgeons accreditation as a Pediatric Teaching Hospital Cancer Program. We have recently undergone re-accreditation.

Bonnie Okamura, BS, CTR
Cancer Registrar,
Hematology/Oncology Services

### 2006 distribution by incidence
Children’s Memorial Hospital compared to state and national percentages

<table>
<thead>
<tr>
<th>Histology</th>
<th># of Cases</th>
<th>CMH%</th>
<th>IL%</th>
<th>US%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>63</td>
<td>31%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>52</td>
<td>26%</td>
<td>22%</td>
<td>32%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>20</td>
<td>10%</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>10</td>
<td>5%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Sarcoma-Soft Tissue</td>
<td>18</td>
<td>9%</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Wilm’s Tumor</td>
<td>5</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>17%</td>
<td>21%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Since its inception in 1992, the Stem Cell Transplantation Program at Children’s Memorial Hospital has performed approximately 750 hematopoietic stem cell transplants. Located on the hospital's fourth floor with the hematology/oncology unit, the program features six heparfiltered positive pressure rooms with state-of-the-art monitoring equipment, an ambulatory stem cell unit and an Apheresis Center. The program has three major components:

Clinical program
Within the past few years, several innovative programs have been developed and/or expanded:
- Expanded options and gained experience for reduced intensity conditioning regimens for malignancies and non-malignant disorders. These treatments focus on suppressing the recipients' immune system while promoting donor cell engraftment without the use of toxic, high-dose chemo-radiotherapeutic treatments. This approach can enable “outpatient transplants” with reduced hospitalization time and expenses
- Enhancement of the quality management program to assess clinical and laboratory proficiencies, facilitate improvements and reduce potential for complications
- Expansion of Apheresis Program for stem cell collection, photopheresis and other therapies
- Completion of a four-bed Apheresis Center enhancing the number of patients able to receive apheresis procedures and improve their experience during the sometimes lengthy procedures
- Chronic GVHD Program multi-specialty clinic established and multi-institutional development of assessment tools proceeding
- Development of a program and clinic for immunodeficiency patients receiving transplants
- Enhanced application of electronic record/data entry software

Laboratory program
This component of our program has made major advances in support of the activities of the clinical program and includes:
- A molecular immunogenetic laboratory to assess chimeric status of engraftment in the allogeneic transplant recipients by the use of VNTR (variable number of tandem repeats). This has enabled better assessment of engraftment in reduced intensity conditioned patients and allowed for interventions that will promote engraftment/hinder relapse
- A minimal residual disease laboratory for malignancies (including leukemia and neuroblastoma)
- A molecular HLA typing laboratory to support the activities of the clinical program

Transplants performed in calendar year 2006

**Stem Cell (63 total)**

**Allogeneic transplants** n=44

- Stem Cell sources:
  - Matched siblings: 23 (Peripheral blood stem cells 18, marrow 5)
  - Mis-matched relatives: 4 (Peripheral blood stem cells)
  - Unrelated Adult Donors: 13 (Peripheral blood stem cells 12, marrow 1)
  - Umbilical Cord Blood: 4, (3 unrelated)

- Conditioning regimen:
  - Myeloablative: 17
  - Reduced Intensity: 27

- 32 Patients with malignancies
  - 17 Acute Lymphoblastic Leukemia
  - 8 Acute Myeloblastic Leukemia
  - 5 Lymphoma (Hodgkins or Non-Hodgkins)
  - 2 Myelodysplasia/Chronic Leukemia

- 12 patients with non-malignant conditions
  - 8 immune deficiencies
  - 1 congenital metabolic disorder
  - 3 Severe Aplastic Anemia

**Autologous transplants** n=19

- 7 neuroblastoma
- 6 central nervous system tumors
- 1 lymphoma
- 5 other solid tumors
Children's Memorial Hospital is participating in clinical trials sponsored by:

- Children's Oncology Group (COG), a National Cancer Institute-sponsored group formed by the merger of the Pediatric Oncology Group, the Children's Cancer Group, the National Wilms Tumor Study Group and the Intergroup Rhabdomyosarcoma Study Group
- Institutional trials
- Industry trials (Pharmaceutical)
- New Approaches to Neuroblastoma Therapy (NANT)
- Pediatric Brain Tumor Consortium (PBTC)

During 2006 and 2007, there were 157 registrations on therapeutic trials and 178 on ancillary (laboratory classification, tumor biology, and epidemiology) protocols. The table below is a breakdown of these registrations by diagnosis.

### Oncology clinical research associates

- Jennifer Dino, BS
- Lauren Evans, BS, CCRP
- Molly Fouts, BS, CCRP
- Adrienne Gerhardt, BS
- Carrie Kempler, MPH, CCRP
- Lauren Pernicka, BS
- Yolanda Santiago, CCRP

### Protocol registration

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Therapeutic</th>
<th>Ancillary</th>
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<tbody>
<tr>
<td>Leukemia</td>
<td>36</td>
<td>55</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>81</td>
<td>55</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Wilm's tumor</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other (non-malignant)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>157</strong></td>
<td><strong>178</strong></td>
</tr>
</tbody>
</table>
Data from the Surveillance, Epidemiology and End Results Program reveal 22 percent of cancers in children less than 15 years of age are of primary Central Nervous System (CNS) origin.

In 1997, 23 percent of newly diagnosed cancer patients presented at Children’s Memorial Hospital had primary CNS tumors. Since then, the numbers of patients with CNS tumors seen at Children’s Memorial has increased. In 2006, 31 percent of the cancer patients had primary CNS tumors.

In 2002, The Neuro-oncology Program at Children’s Memorial was awarded placement in the Pediatric Brain Tumor Consortium (PBTC). This NCI-sponsored consortium consists of 10 institutions and the pediatric branch of the NCI, whose purpose is to rapidly develop and institute innovative treatments in phase I and phase II trials. Membership in the PBTC allows children throughout the Midwest access to these research trials.

This year, patient enrollment on IRB-approved CNS tumor protocols continued its annual increase. The advancement in enrollment was due to the increased number of national and limited institutional trials open to patients at Children’s Memorial.

In late 2000, the Medical Research Institute Council (MRIC) funded development of the first photon intrabeam program in pediatrics, called the INTRABEAM™ System. This intraoperative radiation is now underway in a Phase I Study opened only at the Children’s Memorial Neuro-oncology Program.

The care of patients with primary CNS tumors necessitates a multidisciplinary approach. Neurosurgery, oncology, radiation oncology as well as the disciplines of neurology, endocrinology, otolaryngology, audiology, occupational and physical therapy and neuro-psychology are extremely important for the present and future management of these patients.

The locations of these tumors and the therapies necessary to control these diseases pose significant challenges. The primary goal for the children’s care is not only to eradicate and prevent recurrence of their disease, but also to do so in a manner that leaves them with the least amount of long-term sequelae. The best possible care is, therefore, given in a multidisciplinary setting that is coordinated through our Brain Tumor Board and the multidisciplinary Brain Tumor Clinic. Concerns over education, neurologic, neuroendocrine and neuropsychiatric issues are held equal to the importance of tumor surveillance.

It is through the work of this team that we continue to make progress toward innovative therapies that maximize survival while minimizing the sequelae faced by these patients and their families.

Stewart Goldman, MD
Neuro-oncologist, Hematology, Oncology and Stem Cell Transplantation
The Radiation Oncology division is located in the Galter Pavilion of Northwestern Memorial Hospital. This state-of-the-art, 250,000-square-foot facility houses three linear accelerators, two simulators (one for computerized tomography), a Gamma Knife unit, a high dose rate (HDR) brachytherapy unit and deep Superficial BSD hyperthermia unit.

We have two inverse planning intensity modulated radiation therapy (IMRT) systems that are very critical for treating tumors in challenging locations close to critical organs like the eyes, brain stem and spinal cord. We also have an active pediatric brachytherapy program and the total body radiation therapy (TBI) program.

Each year, we treat close to 100 children with a variety of primary and recurrent pediatric tumors on in-house and Children’s Oncology Group (COG) protocols.

In 2000, in partnership with the Division of Neurosurgery, we began using the novel intra-operative irradiation using the Photon Radiosurgery System (PRS) for children with primary and recurrent brain tumors. We have an active phase I/II clinical protocol, the first of its kind in the world, to determine the maximum tolerated dose (MTD) of irradiation with this device. Thus far we have not had any major complications. In parallel with this clinical study, we have an active neuro-oncology translational research program that will determine the MTD of irradiation with this PRS system in normal rabbit brains. We are also testing brain tolerance of this irradiation in combination with chemotherapy in this animal model. We hope that the results of these animal trials will allow us to use similar treatment strategies in clinical studies.

We are also studying the use of nanoparticles to deliver intracellular hyperthermia and chemotherapeutic agents to animal brain tumor models. For this project we are collaborating with radiologist, Gayle Woloschak, MD and Vinayak Dravid, MD, director of the Northwestern Center for Nanotechnology. This study will initially use a rabbit tumor model and we hope to initiate a clinical phase I study in the future. We hope to use such adjunctive therapies to improve the local control rates in children with brain tumors, specifically brain stem gliomas.

During the last year, we have presented several papers at national and international meetings, published several manuscripts in international radiation oncology journals, and co-authored several text book chapters on pediatric oncology.

Maryanne Marymont, MD
Director, Pediatric Radiation Oncology

John A. Kalapurakal, MD
Co-director, Pediatric Radiation Oncology
Hematology, Oncology, and Stem Cell Transplantation

Children who require an inpatient stay for cancer and blood diseases are admitted to the 4-West Unit at Children’s Memorial Hospital. This 22-bed specialty unit is designed, staffed and equipped to deliver the most sophisticated level of treatment to children of all ages. To assist with infection control, the unit maintains its own water and air filtration system.

Of the 22 beds, six are devoted to stem cell transplantation and feature positive pressure rooms, which provide protection for children who are significantly immunosuppressed related to the transplantation process. Hemodynamic monitoring is available to accommodate critical care needs as necessary.

A comprehensive, primary care team approach is used to coordinate the treatment of patients and their families. Inpatient care is planned by the attending and resident physicians, advanced practice nurses, clinical educators, staff nurses, case managers, pharmacists and dieticians. All team members specialize in the care and treatment of childhood cancers, diseases of the blood, and patients undergoing stem cell transplantation. In addition to the clinical team, social workers, child life specialists and chaplains are involved on a daily basis to provide patients and families with the psychosocial support systems required to support families coping with cancer. A playroom on the 4-West Unit is staffed by dedicated child life specialists and volunteers who coordinate playroom activity, individualized visits and interactive television.

During 2006, care shifted more to the outpatient setting, resulting in a decline of inpatient volume. The length of stay (LOS) remained relatively stable.

### 4-West inpatient report

<table>
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<th>January-December</th>
<th>2005</th>
<th>2006</th>
<th>Change</th>
</tr>
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<tbody>
<tr>
<td>Patient days</td>
<td>5875</td>
<td>5596</td>
<td>(5%)</td>
</tr>
<tr>
<td>Average LOS</td>
<td>4.8</td>
<td>4.6</td>
<td>(4.3%)</td>
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As inpatient stays decrease, comprehensive ambulatory services become more essential. Children’s Memorial’s primary sites for acute outpatient therapy in the Division of Hematology, Oncology and Stem Cell Transplantation are the Ambulatory Care Center, the Day Hospital (DH), the Ambulatory Stem Cell Unit (ASCU) and the Apheresis Center. By design, these areas are located proximal to the inpatient unit to facilitate continuity of care delivery from the inpatient to outpatient settings.

### Hematology, Oncology and Stem Cell Transplantation Ambulatory services

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<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>Change</th>
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<tbody>
<tr>
<td>Day Hospital</td>
<td>4930</td>
<td>4710</td>
<td>(5%)</td>
</tr>
<tr>
<td>Ambulatory Stem Cell Unit</td>
<td>1643</td>
<td>1902</td>
<td>16%</td>
</tr>
<tr>
<td>Clinic</td>
<td>8696</td>
<td>8801</td>
<td>1%</td>
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<tr>
<td>Star Late Effects</td>
<td>275</td>
<td>285</td>
<td>4%</td>
</tr>
<tr>
<td>Apheresis procedures</td>
<td>NA</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

The Ambulatory Care Center features a family-friendly atmosphere designed so families may receive assessment and treatment by a multidisciplinary team in one location. Services are provided by a dedicated group of attending physicians, fellows, advanced practice nurses, nurse clinicians, child life specialists and social workers who provide consistent, comprehensive medical follow-up for children and families. The center’s playroom is staffed by trained child life specialists, volunteers and a ParentWise™ coordinator, who supervise activities while children wait for test results. This area experienced a modest 1 percent increase in volume primarily related to growth in our neuro-oncology / brain tumor population.

The Day Hospital—adjacent to the Ambulatory Care Center—provides treatments such as chemotherapy, transfusions, intravenous fluids and other medications, thus reducing the need for children to be hospitalized for these therapies. In 2006, the Day Hospital volume increased 5 percent as more oncology therapies shifted to the outpatient setting.

The Ambulatory Stem Cell Unit experienced a significant volume increase of 16 percent, as more patients received outpatient stem cell transplantation using reduced intensity conditioning.

The Apheresis Center began plans to build a new four-bed unit, expected to open in 2007.

In addition to the acute-care services provided for patients with cancer and those requiring stem cell transplantation, Children’s Memorial’s Survivor Program provides long term follow-up and counseling for the effects of cancer and transplantation treatment. Additional resources were added in 2006 to increase follow-up for children who have been transplanted.

Jane Kilian, RN, MS
Director operations, Hematology, Oncology and Stem Cell Transplantation
FAMILY SERVICES

The Family Services staff works to help children and their families adjust emotionally, socially, spiritually and developmentally to life with cancer. The multidisciplinary team consists of four licensed clinical social workers, a resource specialist, two certified child life specialists, one chaplain, one parent volunteer coordinator, a Beads of Courage program coordinator, one music therapist and one art therapist.

A wide variety of support services
The families and children within the oncology population are given access to a variety of services designed to complement each unique family situation. Patients receive developmentally appropriate preparation for procedures from Child Life professionals, which may include medical play targeted to a child’s treatment protocol and interests. Patients are also offered activities and coping techniques geared toward helping them manage the stress of illness. Various expressive arts are used in play areas and inpatient settings to facilitate coping. Siblings are encouraged and welcome to participate in activities and may receive individualized intervention from various team members.

Educational assistance is coordinated through the school services coordinators and their volunteers who provide tutoring and homework help for children during their hospital stay and beyond.

Parents receive a broad range of supportive services including proactive referrals for concrete resources and financial assistance. An ever-increasing number of families live far from Children’s Memorial and need alternate housing during treatment. They may also have significant income changes due to one or both parents leaving work to remain at the bedside or attend clinic appointments. Many families stay at the Ronald McDonald House®, located within walking distance of the hospital. Kohl’s House, a home-away-from home for transplant patients and their families, is operated by Children’s Memorial and houses families for extended periods of time at a very modest fee. Within the hospital’s Janice and Kimberly Brown Family Life Center, inpatient families have access to books, games, computers, organized events and more. Parents have access to a business center with computers and Internet access, books and games, “tune up” massages and haircuts.

Emotional and spiritual support
Emotional and spiritual support can take many forms and are crucial to the ultimate success of each child’s treatment regimen. Many parents find comfort through the ParentWISE™ Program, which connects individual families with parent volunteers who have also experienced pediatric cancer. These highly trained, supervised volunteers provide opportunities for peer support in clinics and inpatient hospital areas. Ongoing counseling is available for families in conjunction with both social workers and pastoral care staff.

The search for meaning in the face of a health crisis is explored through discussion, journaling, expressive arts and other parent groups and educational sessions. Special events targeting the emotional needs of our adolescent patients are also held several times during the year. The Family Services team celebrates with families at every opportunity. Birthdays, school accomplishments, developmental achievements, holidays and milestones in cancer treatment are all given the attention they deserve with special projects, staff recognition, parties and theme days.

Bereavement services
For families that experience the loss of a child due to cancer, there are bereavement services for both siblings and parents. These services are provided through the hospital’s Heartlight program. Families may participate in support groups and also receive materials that offer anticipatory guidance about issues of loss and grief. Staff and families may participate in our annual hospital-wide memorial service in the spring and “Remembrance Week” activities in the fall.

Family Services goal
The goal of the Family Services team is to provide comprehensive support for our patients and their families throughout treatment. We endeavor to alleviate stress, teach new coping and communication skills, and facilitate thoughtful communication between our patients, their families, their medical team and the community at large.

Jean E. Schwab, LCSW
Pediatric Oncology Social Worker
Children’s Memorial Hospital
Current treatment strategies result in approximately 75 percent of children diagnosed with cancer becoming long-term survivors. This success is a major feat of pediatric medicine, surgery and radiation oncology. As a result, we believe we have a responsibility to provide continued monitoring and care of the late effects of these diseases and treatments. Survivors have the right to expect an organized, systematic and comprehensive follow-up program, one that addresses both the physiologic and psychosocial effects of their treatment. This is the focus of the STAR Program at Children's Memorial Hospital and the Robert H. Lurie Cancer Center.

We have over 1,300 long-term survivors in our database and see approximately 360 patients annually. Patients are referred to our STAR Program five years after diagnosis if they have remained in full clinical remission. Barbara Lockart RN, PNP and Karina Danner-Koptik, RN, MSN share the program’s nursing responsibilities for patient evaluations and patient education. They also provide expertise to instruct nursing colleagues and participate in the research protocols of the STAR Program.

In 2004, we added Kimberley Dilley, MD, MPH as a full-time physician seeing patients in the STAR clinic and directing the development of an active research program. Meg Crum, LCSW also came on board as a dedicated social worker and is available in clinic to perform assessments and provide needed follow-up for families. The clinics are now held every Wednesday (morning and afternoon) at the Children’s Memorial Outpatient Center in Lincoln Park, enabling us to see as many as 700 patients annually. The team also offers clinics the second Tuesday of each month at the Children’s Memorial Outpatient Center in Arlington Heights.

During clinic visits, patients meet with an advanced practice nurse who specializes in the physiologic and psychosocial issues that face childhood cancer survivors, as well as an attending physician. A licensed social worker is also available during the clinic visit to discuss survivors’ various psychosocial, educational, insurance or employment needs. We consult other subspecialty physicians as warranted by the history and physical obtained during the visit. The input of these subspecialists provides optimal management of complications that could result in impaired growth and development, infertility, reduced bone density, dyslipidemia or cardiac toxicities.

We now refer patients who are approximately 20 years or older to Dr. Aarati Didwania, MD, an internist at Northwestern Memorial and medical director of the Adult STAR Program. Dr. Didwania follows adult survivors of childhood cancer. Karen Kinahan, MS, RN assists Dr. Didwania. This unique and exciting program for adult survivors of pediatric malignancies is supported by the Robert H. Lurie Cancer Center. Both pediatric and adult programs emphasize the same goals to provide patients with a smooth transition.

Research performed by the STAR team has been presented at a variety of national and international meetings, including the American Society of Pediatric Hematology-Oncology, the American Society for Bone and Mineral Research and the International Conference on Long-Term Complications of the Treatment of Children and Adolescents for Cancer.

In May 2006, the STAR Program hosted an educational symposium sponsored by the national Childhood Cancer Foundation. Additional outreach efforts, including a symposium held in September 2007, are facilitated via the STAR Program’s participation in the Chicago Pediatric Cancer Care Coalition.
STAR social work has spearheaded the training of young-adult survivors of stem cell transplantation to serve as peer mentors. An expansion to oncology survivors is also planned.

Further ideas and support for survivor services come from the generous participation of SurvivorVision, a not-for-profit organization that focuses on the needs of pediatric cancer survivors.

Our STAR Program liaison is Tricia Salicete. She continues to play an important role in clinic management, including scheduling appointments, coordinating referrals as well as organizing clinic flow and patient files. She has also provided critical input on developing a new database that will help in STAR research efforts.

As indicated in previous annual reports, our specific program goals are:
1. To provide a comprehensive, systematic evaluation of the potential medical, social and psychological risks which may be unique to survivors of childhood cancers as a result of their disease or treatment. Specifically, to identify “small” medical problems before they become “big” medical problems.
2. To address these health care needs through an established referral pattern to various medical providers, including but not limited to, endocrinologists, cardiologists, pulmonologists, neurologists, orthopedists and psychologists. And, to compile results in a systematic manner to provide vital early detection, prompt intervention and coordination of comprehensive care for our patients.
3. To educate survivors on their changing potential for new or different late-therapy complications. We must promote patient responsibility for awareness and identification of late complications as they progress from Children’s Memorial to the adult transition program at Northwestern Memorial Hospital.
4. To uphold our promise to remain current on the outcomes of various research studies related to survivors and to deliver clinically relevant results to our patient population. And, to develop and/or participate in research aimed at identifying potential complications that are not yet fully understood, which will improve quality of life for survivors.
5. To educate the community about the potential long-term effects of childhood cancers and their treatment.


Kimberley Dilley, MD, MPH
Director, STAR Program
Attending Physician, Division of Hematology, Oncology and Stem Cell Transplantation

Barbara Lockart, RN, PNP;
Karina Danner-Koptik, RN, MSN
Advanced Practice Nurses, STAR Program

Tricia Salicete
Liaison, STAR Program

Meg Crum, LCSW
Social worker, STAR Program

Accreditations
- AABB
- Children’s Oncology Group (COG)
- College of Surgeons
- FACT
- International Bone Marrow Transplant Registry (IBMTR)
- JCAHO
- National Marrow Donor Program (NMDP)
- Pediatric Blood and Marrow Transplant Consortium (PBMT)

Member of:
- COG
- IBMTR
- NANT
- NMDP
- PBMT
- Pediatric Brain Tumor Consortium

Member of:
The patients, families and staff of Children’s Memorial Hospital are grateful to our many friends supporting cancer care and research through their generous gifts during fiscal years 2005, 2006 or 2007.

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CANCER PROGRAM DONORS


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