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# Imagine

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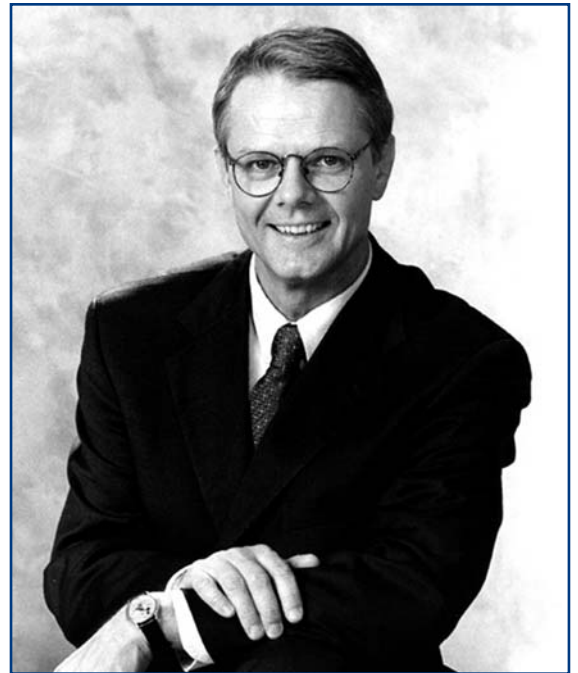
The Annual Scientific Report  
of The Arthur and Sonia Labatt  
Brain Tumour Research Centre  
at The Hospital for Sick Children



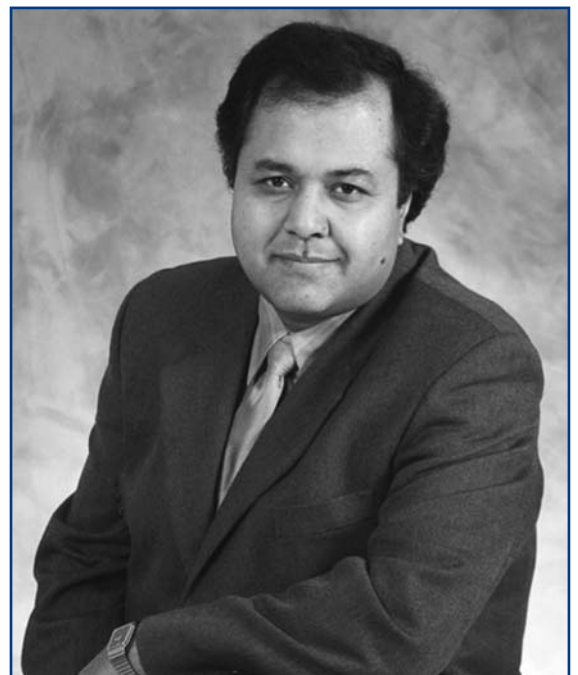
This past year has been characterized by many significant scientific advances in the field of brain tumour research.

We are pleased that some of these have been made within the Arthur and Sonia Labatt Brain Tumour Research Centre (BTRC). We now have powerful new mouse models of astrocytomas which enable us to test novel pharmacotherapeutics for this disease. Many of these mouse models have been developed and pioneered by Dr. Ab Guha in his laboratory. Several new protein: protein interactions have been identified in the laboratory of Dr. Jane McClade which help us understand the basic mechanisms of tumorigenesis. A novel tumour suppressor gene, Human Suppressor of Fused, was cloned and sequenced in the laboratory of Dr. Jim Rutka and reported in Nature Genetics July 2002. The discovery of this novel gene which works as a tumour suppressor in the Hedgehog Signaling pathway in human medulloblastoma offers new hope for therapy directed specifically against this target.

We are pleased to provide this summary of activities within the Labatt BTRC for the academic year 2002-2003. From the materials that are presented within, we hope you will share our enthusiasm for continued progress in this important field of research.



James T. Rutka, MD, Ph.D., *Co-Director*



Ab Guha, MD, MSc, *Co-Director*



Imagine

# Development of the BTRC

On September 22, 1997, Arthur and Sonia Labatt donated \$5-million to establish the University of Toronto Brain Tumour Research Centre (BTRC) at The Hospital for Sick Children and The University Health Network. This gift from the former President of Trimark Financial Corporation and his wife was the single largest contribution from a family in the history of The Hospital for Sick Children. The BTRC is a project that brings together scientists and clinicians studying the problem of human brain tumours from The Hospital for Sick Children and The University Health Network within the University of Toronto teaching hospitals system. The BTRC fosters excellence in brain tumour research, amalgamating the expertise of scientists, clinician-investigators, and physicians in a virtual laboratory environment at the University of Toronto. A stimulating research environment has been created allowing scientists to share ideas, resources and equipment in an atmosphere conducive to achieving excellence in molecular neuro-oncology research, scientific publications, and translational research.

Currently, the Arthur and Sonia Labatt BTRC is situated on the third floor of the Elizabeth McMaster Building at The Hospital for Sick Children. Approximately 3500 sq. feet of conjoined space has been renovated and remodeled to form the physical site. The space is comprised of state-of-the-art laboratory bench space fashioned in an "open concept" model.

A core-facility housing large equipment is shared and contains ultracentrifuges, freezers, scintillation counters, ovens, bacterialshakers, refrigerators, and vacuum pumps. Other important features of the laboratory include a walk-in cold room, separate cell culture facilities with 4 laminar flow hoods, and a designated area for work with radio-isotopes. Additional space on the same floor as the BTRC has been designated for offices for staff, study rooms for post-doctoral fellows, graduate students and students, lunch room, library and resource room, and seminar room.



## About the BTRC Logo

The Labatt Brain Tumour Research Centre Logo was created at the time of the grand opening of the Centre, January 1999. The logo depicts a dove, symbolizing hope, carrying a twig in its beak. The twig is actually a piece of double-stranded DNA representing molecular medicine. Hence, the logo symbolizes the mandate of the BTRC which is "Hope through molecular medicine".



**Laboratory Personnel:**

Stacey Ivanchuk Graduate Student  
 Mike Loreto Graduate Student  
 Todd Mainprize Graduate Student  
 Michelle Mastronardi Technologist  
 Soma Mondal Graduate Student  
 Aurelia Peraud Post Doctoral Fellow  
 Amit Ray Post Doctoral Fellow  
 Bodour Salhia Graduate Student  
 Shigeo Ueda Post Doctoral Fellow  
 Raafat Yahya Post Doctoral Fellow  
 Dong-Seok Kim Post Doctoral Fellow  
 John Kuo Post Doctoral Fellow

**Research Support:**

National Cancer Institute of Canada  
 Canadian Institutes of Health Research  
 Terry Fox New Frontiers Award  
 Brainchild  
 Katie's Kids for the Cure  
 Pediatric Brain Tumour Foundation  
 of the United States  
 Ontario Cancer Research Network

**Dr. James T. Rutka** *Co-Director Labatt BTRC, Principal Investigator*

Dr. Rutka's laboratory has been studying the cytoskeleton as a means to increase our understanding of the mechanisms by which astrocytoma cells grow, adhere to surrounding substrates, and invade normal brain tissue. Current studies are aimed at investigating how cytoskeletal matrix interactions lead to the profound cellular changes we have observed through a detailed analysis of cell cycle gene alterations, metalloproteinase and inhibitor secretion, and ultrastructural cytoskeletal relationships.

Recently, we have focused additional research interests on the childhood brain tumour known as medulloblastoma. We are studying the contributions of the sonic hedgehog (SHH) signaling pathway in the pathogenesis of medulloblastoma. We have recently shown that an inhibitor of SHH signaling, Human Suppressor of Fused, is mutated in patients with medulloblastoma. This gives us a new avenue to pursue treatment of children with this disease.

**Laboratory Personnel:**

Deepak Kamnasaran Post Doctoral Fellow  
 Zia Karim Research Technologist  
 Johann Micallef Graduate Student  
 Ajay Pandita Research Associate  
 Baoping Qian Technician  
 Nesrin Sabha  
 Assistant Research Technician  
 Qingxia Wei Post Doctoral Fellow  
 Gelareh Zadeh Post Doctoral Fellow  
 Cindy Zhang Off-Site Worker

**Research Support:**

National Cancer Institute of Canada  
 Canadian Institutes of Health Research  
 National Institutes of Health, USA  
 Physicians Services Incorporated  
 Heart and Stroke Foundation  
 American Cancer Research Society  
 NSERC  
 Ontario Ministry of Health  
 Ontario Cancer Research Network

**Dr. Ab Guha** *Co-Director Labatt BTRC, Principal Investigator*

Dr. Guha and colleagues have shown that activated Ras is functionally relevant in human astrocytomas. Blockade of Ras signalling leads to decreased glioma growth. This activation is not only found within human gliomas, but also peripheral nerve tumours. Ras and other signalling pathways are activated by aberrant growth factor receptors in gliomas, such as the epidermal growth factor receptor (EGFR). Using state-of-the-art technologies, in collaboration with MDSProteomics, Dr. Guha's lab is investigating Ras and other signaling pathways utilized by these receptors to promote growth of gliomas. It is hoped that drugs being investigated in the Guha lab to inhibit these receptors or their signaling pathways, will be ultimately efficacious in the clinic.

Another area of interest for the laboratory is the study of angiogenic factors. Brain tumours remain among the most angiogenic tumours known to man. In particular, vascular endothelial growth factor (VEGF) and Angiopoietins and their receptors are angiogenic specific and aberrant in human gliomas and peripheral nerve tumors. Dr. Guha's laboratory is studying how VEGF and Angiopoietins stimulate and interact to promote angiogenesis, how they are regulated in normoxia and hypoxic conditions, as well as pharmaceutical inhibition in pre-clinical models to determine if they are relevant clinical therapeutic targets.





**Dr. Jane McGlade** *Senior Scientist, Principal Investigator*

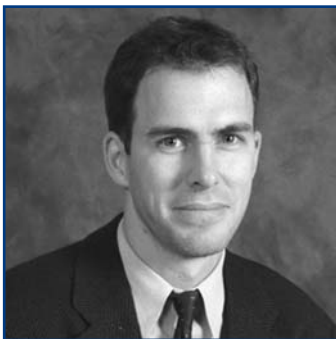
Dr. McGlade's research is directed towards understanding the molecular changes which occur during the process of malignant cell transformation. Work in the lab involves several aspects of signal transduction and the identification and characterization of novel signaling molecules. Recently Dr. McGlade has focused specifically on one class of cytoplasmic adapter molecules and the role they play in the localization, integration and co-ordination of signaling cascade components within two distinct signaling paradigms. It is hoped that this work will have broad implications in terms of understanding temporal and spatial organization of mitogenic signal transduction pathways, as well as the process of asymmetric cell division, and epithelial cell polarity in mammals. The long term goal of this work is to define the molecular processes which regulate the formation and activation of signaling complexes and how disruption of this regulation can lead to cell dysfunction and malignant disease.

**Laboratory Personnel:**

- Sally Benn Post Doctoral Fellow
- Donna Berry Research Technologist
- Sascha Dho Research Associate
- Melanie McGill Graduate Student
- Jenny Nie Post Doctoral Fellow
- Ben Pakuts MSc Graduate Student
- Nancy Silva Post Doctoral Fellow
- Dan Simoncic Graduate Student
- Christian Smith Graduate Student

**Research Support:**

- National Cancer Institute of Canada
- Canadian Institute of Health Research
- Cancer Research Society
- Leukemia Research Fund



**Dr. Peter Dirks** *Scientist, Principal Investigator*

The long-term goal of Dr. Peter Dirks' research program is to determine if a normal neural stem cell or progenitor cell is transformed into a brain tumour. Two approaches are being used to study this question. One approach involves a study of primary human brain tumours to determine if stem cell populations exist in brain tumours. Our question is: are there a small population of cancer cells in a brain tumour that uniquely has the ability to maintain the tumour? Dr. Dirks' lab has recently isolated and characterized a repopulating cell from human brain tumours of different phenotypes that expresses neural stem cell markers and has stem cell-like behaviour in vitro. This subpopulation of tumour cells could be considered as cancer stem cells, because they share properties with normal stem cells and because they are necessary for maintaining tumour growth in vitro. The second approach involves a study of the key determinants of proliferation and self renewal in normal neural stem cells. We focus on the sonic hedgehog signalling pathway, as it is perturbed in primary human brain tumours (medulloblastomas), and because it has been shown to be critically important for normal brain development. Our preliminary studies suggest that different SHH pathway members play important and distinct roles in neural stem cell proliferation and self renewal. A better understanding of how this pathway functions in normal neural stem cells may help us to better understand brain tumour proliferation and self renewal.

**Laboratory Personnel:**

- Ian Clarke PhD  
Technician & Assistant Scientist
- Victoria Bonn  
Master's Graduate Student
- Sheila Singh Graduate Student
- Takuichiro Hide Post Doctoral Fellow

**Research Support:**

- National Cancer Institute of Canada
- Research Institute,  
Hospital for Sick Children
- Rob and Wendy Durigon honouring their daughter Jessica Marie Claire Durigon





**Dr. Mark Bernstein** *Scientist, Principal Investigator*

Dr. Bernstein's laboratory and clinical research focus addresses the understanding of the biology of and improving the treatment of primary malignant brain tumours. Using a small animal model of brachytherapy developed in his laboratory, Dr. Bernstein has studied the radiobiology of focused radiation, and the use of lazarooids, or 21-aminosteroids, to protect the brain against radiation injury. Concurrently in the clinic, Dr. Bernstein has studied innovative image- and function-guidance techniques for the surgery of patients with brain tumours culminating in the development of a prototype operating MRI system, and of awake craniotomy as a standard surgical approach. Dr. Bernstein has also been co-principal investigator in a TWH/ Princess Margaret Hospital randomized study of iodine-125 brachytherapy for de novo glioblastoma which has established the lack of significant benefit of this modality and helped resolve the controversial issue of dose-escalation in the battle against glioblastoma. Dr. Bernstein was co-principal investigator in phase II and phase III studies of HSV-TK/ganciclovir gene therapy for the treatment of recurrent and de novo glioblastoma respectively.

**Laboratory Personnel:**

Jennifer Glenn Research Associate

**Research Support:**

Foster Hewitt Foundation  
Princess Margaret Hospital/Ontario Cancer Institute Foundation



**Dr. Annie Huang** *Scientist, Principal Investigator*

The newest member to join the Labatt BTRC, Dr. Huang is studying the mechanisms of growth of human neuroblastomas and subtypes of medulloblastomas using cDNA microarray analyses. Genes that are up-regulated or down-regulated in these tumours will be further corroborated by RNA and protein analysis. Altered genes from this analysis will then provide important clues as to the key mechanisms involved in the growth of neuroblastomas and medulloblastomas.

**Research Support:**

HSC Research Institute  
Cancer Care Ontario/Eli Lilly Translational Research Award

Dr. Huang's research focus is in the molecular biology of medulloblastoma, a pediatric cerebellar tumour. Her studies are directed at identifying biologic/genetic features of medulloblastoma that correlate with disease outcome, and in delineating the role of poor biologic prognosticators in the molecular pathogenesis of medulloblastoma. One of her current studies utilizes the microarray technology to establish genomic and expression profiles of infant medulloblastoma, a group with particularly poor clinical outcomes. In a related project she is investigating how c-myc, an oncogene associated with an aggressive variant of medulloblastoma, interacts with different cellular genes to specify malignant cell transformation. The long-term goals of these studies are to refine current treatment stratification of children with medulloblastoma, and to gain insights into novel molecular pathways that may be targeted for therapy in medulloblastoma.



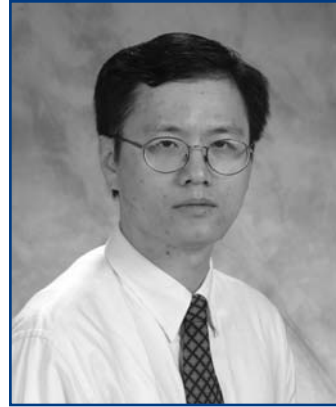
# Visiting Post Doctoral Research Fellows



**Dr. Michael Carter**  
England



**Dr. Takuichiro Hide**  
Japan



**Dr. John Kuo**  
USA



**Dr. Aurelia Peraud**  
Germany



**Dr. Amit Ray**  
Wales



**Dr. Shigeo Ueda**  
Japan



**Dr. Raafat Yahya**  
Lebanon



**Brain Tumour  
Research Centre**



**Michelle Mastronardi**  
USA

Michelle Mastronardi  
Visiting Technician from  
Henry Ford Hospital,  
in Detroit, Michigan  
Her supervisor  
in Michigan is  
Dr. Irene Newsham

# 2003 BTRC Visiting Lectureship *Dr. Luis Parada*



## Annual Arthur and Sonia Labatt Brain Tumour Research Centre Academic Lecture

Each year in January, an academic lectureship is hosted by members of the Labatt BTRC to bring a scientist of international acclaim to The Hospital for Sick Children to deliver a lecture on the topic of research in human brain tumours. Dr. Luis Parada, University of Texas at Dallas, was the invited guest lecturer. Dr. Parada delivered his lecture on "A Role for NFI as a Tumor Suppressor in the Central Nervous System".

### Previous BTRC Academic Guest Lecturers

- 1999 Dr. Robert Martuza, Professor and Chairman, Department of Neurosurgery, Massachusetts General Hospital, Harvard University
- 2000 Dr. Gregory Cairncross, Professor of Neurology, Director, London Regional Cancer Centre, University of Western Ontario
- 2001 Dr. David Kaplan, The Montreal Neurological Institute McGill University
- 2002 Dr. Charles Stiles of the Dana Farber Cancer Institute at Harvard Medical School



# Advisory Board

Arthur and Sonia Labatt Benefactors

Alan Hudson CEO, Cancer Care Ontario

Alan J. Gayer CEO, The Hospital for Sick Children

John Wedge Surgeon-in-Chief, The Hospital for Sick Children

Manuel Buchwald Director, The Research Institute,  
The Hospital for Sick Children

Dianne Lister President, The Hospital for Sick Children Foundation

Tom Clossen CEO, UHN Foundation

Charles Tator Division of Neurosurgery, Toronto Western Hospital

Christopher Paige Director, UHN Research Institute

Robert J. Birgeneau President, The University of Toronto

David Naylor Dean, Faculty of Medicine, The University of Toronto

Helen and Joe Berman Benefactors

Dr. David Berman Scientific Advisor



## Dalton McGuinty visits the Labatt BTRC:

This year, Liberal Premier Dalton McGuinty paid a visit to the Labatt BTRC to learn more of the research that is being conducted within the Centre.

Mr. McGuinty was very interested in knowing how the research was being performed and funded. He is seen here in this photograph speaking to Dr. Rutka, with HSC President and CEO Alan Gayer, and Cathy Seguin in the background.

# Affiliated Scientists

Cameron Ackerley Ph.D.

Sylvain Baruchel MD

David Kaplan Ph.D.

Normand Laperriere MD

Warren Mason MD

Paul Muller MD

James Perry MD

Michael Schwartz MD

Eric Bouffet MD

Jeremy Squire Ph.D.

Cynthia Hawkins Ph.D. MD



# The Year in Review

## Highlights from the BTRC (2002/03)

- Dr. Guha is a recipient of an NCIC Award on "Development and Characterization of Transgenic Mouse Models of Astrocytomas"
- Dr. Guha and Dr M. Moran received a grant from the Ontario Cancer Research Network on the "Characterization and identification of oncogenic receptor protein tyrosine kinase signaling complexes in malignant astrocytomas"
- Dr. Guha received a grant from the Cleveland Clinic Foundation on "Finding Cures for Glioblastomas: Characterization of a Mouse Transgenic Astrocytoma Model as a Therapeutic"
- Dr. Ray and Dr. Hawkins received the Grant Miller Cancer Research Grant from The University of Toronto Faculty of Medicine on the "Tissue Microarray for Paediatric Medulloblastoma"
- Dr. Rutka received a grant from The Ontario Cancer Research Network on "The Role of Gli2 in medulloblastoma"
- Dr. Rutka received a grant from the Pediatric Brain Tumor Foundation of the United States on "Gli2 as a treatment for Medulloblastoma"
- Dr. C. Jane McGlade received a grant from Canadian Institute of Health Research on "Role of adaptor proteins in hematopoietic cell signaling"
- Dr. James Rutka and Dr. Cynthia Hawkins received a grant from B.R.A.I.N.child for "Tissue Microarray for pediatric medulloblastoma"
- Dr. Peter Dirk's novel research on stem cells in human brain tumours was published in the September 2003 issue of Cancer Research and quoted by Science the same month.

## Promotions

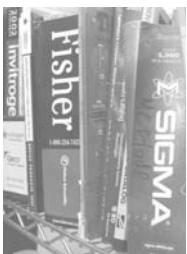


### Promoted to Full Professor, The Department of Medical Biophysics, The University of Toronto

Dr. C. Jane McGlade was promoted to full professor in July 2003.

Dr. McGlade has been at The University of Toronto since 1995 as both an assistant and an associate professor in the Department of Medical Biophysics. She also holds cross appointments in the Departments of Medicine and Surgery.

Congratulations Dr. McGlade!



# Awards to BTRC Students and Post Doctoral Fellows

## DR. RUTKA'S LAB

BODOUR SALHIA HSC RESTRACOMP,  
U of T Open Fellowship

STACEY IVANCHUK NCIC Travel Award

TODD MAINPRIZE NREF, HSC RESTRACOMP,  
Warren Ho Memorial Scholarship

## DR. DIRK'S LAB

SHEILA SINGH

2003 Gallie Bateman 1st prize research in the  
University of Toronto Surgeon Scientist  
Research Competition

1st prize basic science research The Hospital for Sick  
Children Surgical Services Research Competition

Acceptance into The Hospital for Sick Children  
Scientist Training Program

University of Toronto Thomas P Morley  
Neurosurgical Resident 2nd prize

2002 NREF Award presented by the AANS  
Chrisholm Memorial Fellowship, University of Toronto  
Miriam Neveren Memorial Award, University  
of Toronto

## DR. GUHA'S LAB

GELAREH ZADEH

McKenzie Award, First Place, Basic Science Research  
in Neurosurgery

Morley Prize, First Place, Basic Science Research in  
Neurosurgery University of Toronto

Postgraduate Medical Education Award, University  
of Toronto

National Cancer Institute of Canada (NCIC), Research  
Fellowship Award

Clinician Scientist Training Program, Hospital for  
Sick Children

JOHANN MICALLEF HSC RESTRACOMP

QINGXIA WEI ABTA: Post Doctoral Fellowship

AJAY PANDITA ABTA for the term July 2003 - June 2004

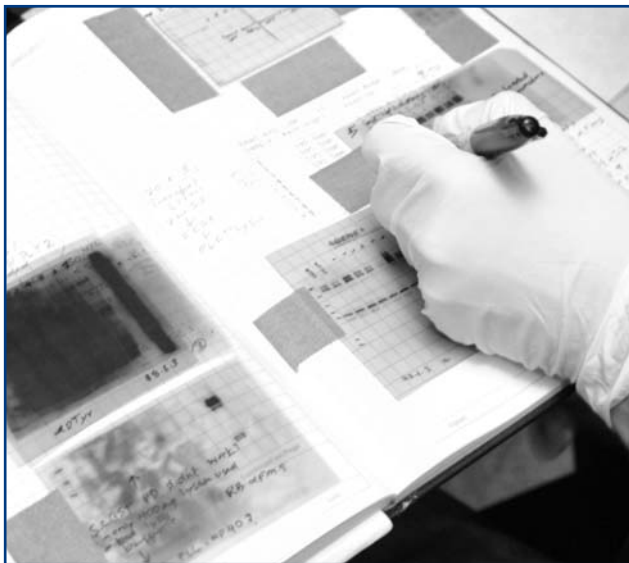
## DR. McGLADE'S LAB

NANCY F. SILVA HSC Restracom

MELANIE MCGILL AND CHRISTIAN SMITH Terry Fox  
Studentship (NCIC)

BEN PAKUTS NSERC (PGSA)

Last year's recipients of the NCIC Terry Fox Studentship  
are Dan Simoncic and Jenny Nie who continue  
their work.



*Congratulations to all students and fellows for their  
outstanding accomplishments this year!*

# Major Gifts

The Labatt BTRC's initiatives are further strengthened by a community of donors who support research, education and equipment needs – making possible a culture of discovery and care that gives hope to children and families.

We gratefully acknowledge the following endowment funds which provide support in perpetuity for programs and research initiatives at the Labatt Brain Tumour Research Centre:

**Laurie Berman Fund** for Brain Tumour Research established in 2002 by Helen and Joe Berman in memory of their son Laurie. This fund provides ongoing support for graduate students post-doctoral research fellows, lab equipment and supplies. The fund also enables neurosurgical nurses to attend the annual Canadian Congress of Neurological Sciences meeting.

**The Wiley Fund** in Brain Tumour Research established in 2001 by Averil and Joe Wiley in honour of their son Andrew who was cared for by Dr Rutka. This fund supports the ongoing research projects of two PhD students, and two post-doctoral research fellows.

**Bequest from the Estate of Eric Yolles** This year a bequest was received from the estate of Eric Yolles to be used for furthering research in the Arthur and Sonia Labatt Brain Tumour Research Centre.

**Jack Michael Baker Fund** Brian and Erin Baker have established a fund to further our work on cancer stem cells in brain tumors. This donation is in honour of their son Jack Michael Baker.

**Rochelle Sherwood Fund** for Brain Tumour Research. Judy Stein-Korte and Carl Korte gave generously to establish a fund to support research in the Brain Tumour Research Centre in honour of Judy's sister Rochelle who was diagnosed with a brain tumour. This endowment fund will be used to support ongoing research projects on esthesioneuroblastoma, medulloblastoma and primitive neuroectodermal tumours.

**Maritimes Brainchild in Halifax, Nova Scotia** has once again generously provided ongoing support for research projects at the Labatt Brain Tumour Research Centre.

## Annual Fund Raising Events:

**5th Annual BUNZL for Brainchild Golf Tournament:** Each year, BUNZL Canada organizes a golf tournament where the proceeds go to support Brainchild through the Rigatoni for Research Dinner and Auction (see below). This year's golf tournament raised over \$125,000 thanks to the efforts of Mary Lombardi, Carrie Boss, and BUNZL president, John Howlett.

**Rigatoni for Research Dinner & Auction,** organized by Kathy Douthart, is one of Sick Kids' largest third-party events. The fundraising efforts of the Douthart family, close friend Judy Collaton, the Carlan family and the Wolski family, and the Rigatoni for Research committee have helped give hope to children living with brain tumours and their families. The 5th annual dinner, this year, raised over \$125,000 for research at the Labatt Brain Tumour Research Centre. A bowl-a-thon held by Javelin Technologies and the Swinging for Kee Kee golf tournament both raised significant funds in support of Rigatoni for Research efforts this past year.

**BRAINCHILD** is a group of parents, families and friends who have shared the common experience of caring for a child with a brain tumour. Formed in 1993, this volunteer organization provides support and education to other parents, patients as well as public education on the importance of early detection and the special needs of children with brain tumours.

Brainchild is also a major donor to the Labatt Brain Tumour Research Centre, raising money in the community for research into the causes, treatment, and cure of brain tumours. This year, a golf tournament organized by Gary Kisiloski, raised over \$52,000 in support of Brainchild's objectives to help find a cure for paediatric brain tumours.

*Thank you, to everyone for each contribution. They all help us continue our work for you.*



# Publications 2002/2003

## Rutka

Langlois A, Lee S, Kim D, Dirks P, Rutka JT: p16ink-4a and Retinoic Acid Modulate rhoA and GFAP Expression During Induction of a Stellate Phenotype in U343 MG-A Astrocytoma Cells: *Glia* 2002 40: 85-94

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Sakai K, Kurimoto M, Tsugu A, Hubbard SL, Trimble WS, Rutka JT: Expression of Nedd5, a mammalian septin, in human brain tumors: *J Neurooncol* 2002 57(3): 169-77

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McDonald P, Matouk C, Papsin B, Rutka JT: Clival osteoblastoma in a child Case Illustration: *Journal of Neurosurgery* 2003 98: 25

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Weiss W, Israel M, Cobbs C, Holland E, James D, Louis D, Marks C, McClatchey A, Roberts T, Van Dyke T, Wetmore C, Chiu I-M, Giovannini, M, Guha A, Higgins R, Marino S, Radovanovic I, Reilly K, Aldape K: Neuropathology of genetically engineered mice: consensus report and recommendations from an international forum: *Oncogene* 2002 (21) 7453-7463

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Ding H, Shannon P, Lau N, Roncari L, Wu X, Gutmann D, Nagy A, Guha A: Astrocyte-specific expression of activated p21 ras and constitutively active form of EGFR results in malignant oligodendroglioma formation: *Cancer Research* 2003 63: 1106-1113

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Siomin V, Willinsky R, Shannon P, Guha A: Metaplastic Bone Formation in a Low Grade Conus Glioma: Case Report and Review of the Literature *J NeuroOncology* 2003 62(3): 275-280

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