

## Title: Targeting the Hedgehog Pathway in Medulloblastoma



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**Speaker**



### **Nobuyuki Mizunuma, M.D.**

Director of Chemotherapy, Gastroenterology Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research (JFCR), Japan

**Chairman**

### **Tom Curran, Ph.D., FRS**

#### **EDUCATION:**

1978	BSc (Hons)	University of Edinburgh (Zoology)
1982	PhD	Imperial Cancer Research Fund Laboratories and University College London (Zoology and Anatomy)

#### **POSTGRADUATE TRAINING AND FELLOWSHIP APPOINTMENTS:**

1982-1984	Postdoctoral Fellow, Salk Institute, San Diego, CA
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## **FACULTY APPOINTMENTS:**

1991-1995	Associate Director, Roche Institute of Molecular Biology
1995-2006	Member and Chairman, Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN
1995-2006	Professor, Department of Anatomy and Neurobiology, The University of Tennessee, College of Medicine, Memphis, TN
2006-present	Professor of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine
2006-present	Deputy Scientific Director, Children's Hospital of Philadelphia, Research Institute
2007-present	Director, Basic Scientific Research, Center for Childhood Cancer Research, Children's Hospital of Philadelphia Research Institute
2008-present	Professor of Cell and Developmental Biology, University of Pennsylvania School of Medicine (Secondary)
2010-present	Member, Division of Cancer Pathobiology, CHOP

## **OTHER APPOINTMENTS:**

2006-present	Associate Director, Translational Genomics, Penn Genome Frontiers Institute (PGFI), University of Pennsylvania School of Medicine
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## **AWARDS, HONORS AND MEMBERSHIP IN HONORARY SOCIETIES:**

2000-2001	President, American Association for Cancer Research
2000-2005	National Cancer Institute Board of Scientific Advisors
2000	Highly Cited Scientist by Institute for Scientific Information (ISI) in three categories; Neuroscience, Molecular Biology & Genetics, and Microbiology
2001-2009	Javitz Neuroscience Investigator Award, National Institute of Neurological Disorders and Stroke, NIH
2001-2002	Past President, American Association for Cancer Research
2001	Presidential Address, American Association for Cancer Research, New Orleans, LA
2002	Peter M. Steck Memorial Award, Houston, Texas
2003	Martin Rodbell Lecture, Raleigh-Durham, NC
2004	LIMA International Award for Excellence in Pediatric Brain Tumor Research, Pediatric Brain Tumor FD, NY, NY
2005	Elected to The Royal Society, London, England, UK
2006	Marguerite Vogt Lecture Salk Institute, San Diego, CA
2006	21st Annual Colleen Giblin Memorial Lecture. Columbia University New York, NY
2009	W. W. Sutow Visiting Lecturer in Pediatric Oncology, University of Texas MD Anderson Cancer Center, Houston, TX
2009	Elected to the Institute of Medicine, of the National Academies
2012	Elected to the American Academy of Arts & Sciences, Cambridge, MA

## **BIBLIOGRAPHY:**

Research Publications, peer reviewed (print or other media):

1. Kimura H, Ng JMY, Curran T.: Transient inhibition of the Hedgehog pathway in young mice causes permanent defects in bone structure. *Cancer Cell* 13: 249-60, 2008.
2. Park TJ, Curran T: Alternative Splicing Disabled by Nova2. *Neuron* Page: 66(6): 811-3, June 2010. PMID: 20620865

3. Hallock Peter T, Xu Chong-Feng, Park Tae-Ju, Neubert Thomas A, Curran Tom, Burden Steven J: Dok-7 regulates neuromuscular synapse formation by recruiting Crk and Crk-L. *Genes & development* 24(21): 2451-61, Nov 2010. PMID: PMC2964755
4. Seidel Kerstin, Ahn Christina P, Lyons David, Nee Alexander, Ting Kevin, Brownell Isaac, Cao Tim, Carano Richard A D, Curran Tom, Schober Markus, Fuchs Elaine, Joyner Alexandra, Martin Gail R, de Sauvage Frederic J, Klein Ophir D: Hedgehog signaling regulates the generation of ameloblast progenitors in the continuously growing mouse incisor. *Development (Cambridge, England)* 137(22): 3753-61, Nov 2010. PMID: PMC3049275
5. Parsons D Williams, Li Meng, Zhang Xiaosong, Jones Siân, et al.: The Genetic Landscape of the Childhood Cancer Medulloblastoma. *Science (New York, N.Y.)* Dec 2010. PMID: PMC 3110744
6. Brechbiel Jillian L, Ng Jessica M Y, Curran Tom: PTHrP treatment fails to rescue bone defects caused by Hedgehog pathway inhibition in young mice. *Toxicologic pathology* 39(3): 478-85, Apr 2011.
7. Austgen Kathryn, Johnson Emily T, Park Tae-Ju, Curran Tom, Oakes Scott A: The adaptor protein CRK is a pro-apoptotic transducer of endoplasmic reticulum stress. *Nature cell biology* 14(1): 87-92, 2011. PMID: PMC3245775
8. George Britta, Verma Rakesh, Soofi Abdulsalam A, et al.: Crk1/2-dependent signaling is necessary for podocyte foot process spreading in mouse models of glomerular disease. *The Journal of clinical investigation* Jan 2012.
9. Romer J., Curran T.: Targeting medulloblastoma: small-molecule inhibitors of the Sonic Hedgehog pathway as potential cancer therapeutics. [Review] [23 refs] *Cancer Research* 65(12): 4975-8, Jun 15 2005.
10. Brumwell CL., Curran T.: Developmental mouse brain gene expression maps. [Review] [7 refs] *Journal of Physiology* 575(Pt 2): 343-6, Sep 1 2006.
11. Dellovade T., Romer JT., Curran T., Rubin LL.: The hedgehog pathway and neurological disorders. [Review] [115 refs] *Annual Review of Neuroscience* 29: 539-63, 2006.
12. Curran Tom, Ng Jessica M Y: Cancer: Hedgehog's other great trick. *Nature* 455(7211): 293-4, Sep 2008.
13. Curran Tom: Mouse models and mouse supermodels. *EMBO molecular medicine* 2(10): 385-6; author reply 386-7, Oct 2010.
14. Ng Jessica M Y, Curran Tom: The Hedgehog's tale: developing strategies for targeting cancer. *Nature reviews. Cancer* 11(7): 493-501, 2011.

Editorials, Reviews, Chapters, including participation in committee reports (print or other media):  
Curran T, Christen Y. Eds: Targeting Children's Brain Tumors: Development of hedgehog Pathway Inhibitors for Medulloblastoma. In *Two Faces of Evil: Cancer and Neurodegeneration; Research Perspectives in Alzheimer's Disease*. Springer, 1: 57-71, 2010.

**IAAO2012 Title of the Talk:**

**Targeting the Hedgehog Pathway in Medulloblastoma**

**ABSTRACT:**

Children's brain tumors are quite distinct from adult brain tumors but, because of the limited market potential, they have received relatively little attention from the pharmaceutical industry. Traditionally, treatments were first developed for adult brain tumors then introduced at a lower dose in clinical trials for pediatric brain tumors. Fifteen years ago, we embarked on a long-term program to develop new therapeutic approaches for children's brain tumors based on the identification of specific molecular targets. Initially, we focused on medulloblastoma, a peripheral neuroectodermal tumor that arises in the cerebellum. Approximately 30% of medulloblastoma exhibit activation of the Hedgehog pathway and in approximately half of these cases this occurs a consequence of the loss of Patched-1 (Ptch1), the receptor for Sonic Hedgehog (Shh). This results in excess signaling through the hedgehog pathway. We utilized mouse models of medulloblastoma to test novel inhibitors of the hedgehog pathway in preclinical trials. The results obtained indicated remarkable efficacy and encouraged the development of Smoothed inhibitors as potential therapeutics. Recently, the first inhibitor was approved for the treatment of advanced basal cell carcinoma and it is currently in clinical trials for a range of other tumors including pediatric medulloblastoma. I will discuss the trials and tribulations involved in shepherding a novel therapy from mice to young humans.