BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Cho, Yoon-Jae	Assistant Professor, Department of Neurology and Neurological Sciences, Stanford University
eRA COMMONS USER NAME (credential, e.g., agency login)	
yoon-jaecho	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Rice University, Houston, TX	B.A.	08/1990-05/1993	Chemistry, Anthropology
Oregon Health & Science University, Portland, OR	M.D.	06/1994-062002	Mol. & Medical Genetics

A. Personal Statement

I am a physician-scientist who specializes in Pediatric Neuro-oncology. My lab focuses on the functional annotation of genomes/epigenomes of childhood brain tumors, with a particular emphasis on medulloblastoma and pediatric high-grade glioma (pHGG), two of the most lethal types of brain tumors in children. We utilize a mix of computational, genomic and chemical biology approaches to 1) understand the molecular and cellular basis of brain tumors, 2) generate new treatment strategies for patients diagnosed with these diseases and 3) inform the current and next generation of clinical trials. Current projects include combining genome-wide RNAi with chemical biology and chemical genomic screens to systematically identify vulnerabilities in *MYC*-amplified medulloblastoma. Additionally, we completed an in-depth survey of somatic and germline events in medulloblastoma using whole exome sequencing and have identified a number of previously unreported mutations, many of which affect genes encoding epigenetic modifying enzymes and RNA helicases. We are characterizing these mutations further to determine whether they carry significance in terms of prognosis, treatment response or potential for targeted therapy.

In addition to my lab activities, I serve as co-Chair of the Biology Committee within the Pediatric Brain Tumor Consortium. With co-Chairs Dr. Ian Pollack (Pittsburgh) and Dr. Will Parsons (Texas), we direct the overall direction of correlative biological studies for clinical trials run through PBTC and our goal in this capacity is to increasingly integrate molecular and genomic studies for each clinical trial moving forward. This occurs at all stages of trial development including the establishment of biological rationale, in patient selection or stratification, and in informing post-hoc analyses of treatment response as studies mature. In addition to helping guide the overall tenor of the Biology Committee, I have established a preclinical working group focused on high-risk medulloblastoma. The goal of this highly collaborative, multi-institutional effort is to integrate high-throughput screening campaigns performed at various sites to identify the most promising 'hits' and move them to concept then clinical trial as efficiently as possible. This collaborative effort supports the exchange of data and resources such as orthotopic xenograft models and genomic data within PBTC sites.

B. Positions and Honors

Positions and Employment

2002-2003 Intern, Pediatrics, Children's Hospital of Pittsburgh / UPMC, Pittsburgh, PA
2003-2004 Resident, Pediatrics, Children's Hospital & Research Center Oakland, Oakland, CA
2004-2007 Resident, Neurology, Children's Hospital Boston, Boston, MA
2007-2008 Neuro-oncology Fellow, Children's Hospital Boston/Dana Farber Cancer Institute, Boston, MA
2008-2011 Instructor in Neurology, Harvard Medical School, Boston, MA
2008-2011 Assistant in Neurology, Children's Hospital Neurology Foundation, Inc., Boston, MA
2008-2011 Consultant in Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA
2008-2011 Affiliate, Broad Institute of Harvard and MIT, Cambridge, MA
2010-2011 Associate Member, Dana-Farber/Harvard Cancer Center, Boston, MA

2011-present Assistant Professor, Departments of Neurology and Neurosurgery, Stanford University, Palo Alto, CA
2011-present Associate Member, Stanford Cancer Institute, Stanford, CA
2011-present Member, Bio-X, Stanford University, Stanford, CA
2012-present Member, Child Health Research Institute, Stanford University, Stanford, CA
2012-present co-Chair, Biology Committee, Pediatric Brain Tumor Consortium

Honors

1991-1993 Jones College Fellow in Chemistry, Rice University
1992 American Association of Clinical Chemistry Summer Research Fellowship
1990-1993 President's Honor Roll, Rice Univ, Fall '90, '91, '92, Spring '93
1994-2002 Oregon Medical Research Foundation Laurel MD-PhD Scholar
2002 Fred and Mary Brauti Scholarship, Oregon Health & Science University
2003 Finalist, Gold Foundation Resident Teaching Award, University of Pittsburgh School of Medicine
2007 Young Investigator Award, Pediatric Brain Tumor Foundation
2007 Young Neuroscientist Award, Childhood Neurobiological Solutions
2009, 2010 Faculty Development Award, Shore Program for Scholars in Medicine, Harvard Medical School
2011-2014 St. Baldrick's Foundation, Scholar Award
2011- Beirne Faculty Scholar in Pediatric Neuro-oncology, Stanford University School of Medicine
2012 Philip R. Dodge Young Investigator Award, Child Neurology Society

C. Selected peer-reviewed bibliography with annotation (16 of 40 peer-reviewed papers listed)

1) Contributions to the genomic characterization of medulloblastoma and its use in risk-stratification

a. Cho YJ, et al. Integrative genomic analysis of medulloblasotma identifies a molecular subgroup that drives poor clinical outcome. ***J Clin Onc.*** 2011 Apr 10;29(11):1424-30. PMC3082983
b. Tamayo P and Cho YJ, et al. Predicting relapse in medulloblasotma patients by integrating evidence from clinical and genomic features. ***J Clin Onc.*** 2011 Apr 10;29(11):1415-23. PMC3082982
c. Pugh TJ, et al. Medulloblasotma exome sequencing uncovers subtype-specific somatic mutations. ***Nature.*** 2012 Aug 2;488(7409):106-10. 2012 Aug 2;488(7409):106-10. PMCID3413789
d. Northcott PA and Shih DJH, et al. Subgroup-specific structural variation across 1,000 medulloblasotma genomes. ***Nature.*** 2012 Aug 2;488(7409):49-56. PMC3683624

Medulloblastoma have long been known to be heterogeneous, clinically, histologically and at the molecular level. This collection of manuscritps represents some of the large scale genomic profiling my lab has performed on primary medulloblastoma samples. These studies utilized gene expression profiling, copy number analysis using SNP arrays, and whole exome/whole genome sequencing. The publicly available data generated in these studies has served as a reference database for the medulloblastoma research community and has had a significant impact on how we approach medulloblastoma, diagnostically, prognostically and therapeutically.

2) Contributions to our understanding of general mechanisms of tumorigenesis in medulloblastoma

a. Pei Y, et al. Dysregulation of c-MYC and p53 transforms cerebellar stem cells into large cell anaplastic medulloblastoma. ***Cancer Cell.*** 2012; 21 *(2): 155-67*. PMC3285431
b. Wu X, et al. Genetic divergence of medulloblastoma due to clonal selection. ***Nature.*** 2012 Feb 15;482(7386):529-33. PMC3288636
c. Weeraratne SD, et al. Pleiotropic effects of miR-183~96~182 converge to regulate cell survival, proliferation and migration in medulloblastoma. ***Acta Neuropathol.*** 2012 Apr;123(4):539-52.
d. Dykhuizen EC and Hargreaves DC, et al. mSWI/SNF (BAF) Complexes Facilitate Decatentation of DNA by Topoisomerase IIa. ***Nature.*** 2013 May 30;497(7451):624-7. PMC3668793

Building on the genomic chracterization of medulloblastoma that my lab has directly contributed to, this collection of work demonstrates our ability to utilize this data to inform studies aimed at understanding mechanisms of tumorigenesis in medulloblastoma and in cancer in general. These studies range from

generation of autochthonous models of medulloblastoma in the mouse to understanding how specific mutations in medulloblastoma contribute to genetic instability and metastasis in certain subtypes of medulloblastoma.

3) Contribution to our understanding of SMARCB1/SNF5/INI1 pathobiology in ATRT

a. McKenna ES and Sansam CG, et al. Loss of the epigenetic tumor suppressor Snf5 leads to cancer without genomic instability. ***Mol Cell Biol.*** 2008 Oct;28(20):6223-33. Epub 2008 Aug 18. PMC2577431
b. Wilson BG, et al. Epigenetic antagonism between Polycomb and SWI/SNF complexes during oncogenic transformation. ***Cancer Cell.*** 2010 Oct 19;18(4):316-28. PMC2957473
c. Jagani Z, et al. Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog-Gli pathway. ***Nature Medicine.*** 2010 Dec;16(12):1429-33.
d. Mora-Blanco EL, et al. Activation of b-catenin/TCF targets following loss of the tumor suppressor SNF5. ***Oncogene.*** 2013 Feb 25.

Deletion/mutation of *SMARCB1/SNF5/INI1* is the hallmark of aggressive malignant rhabdoid tumors, including ATRT. I was the first to observe the absence of genomic copy number alterations, with the exception of focal ch. 22 deletions at the *SNF5* locus, and approached Dr. Charlie Roberts with this finding. We subsequently initiated a productive collaboration looking into the genetic/epigenetic mechanisms driving these tumors. This body of work has led to a much deeper understanding of rhabdoid tumors and of 'epigenetically-driven' tumors in general.

4) Contributions to the genomic characterization of pediatric low grade glioma

a. Jones DTW, et al. Recurrent *FGFR1* hotspot mutations represent a novel therapeutic target in childhood astrocytoma. ***Nature Genetics.*** 2013 Aug;45(8):927-32.
b. Ramkissoon LA, et al. Genomic analysis of diffuse pediatric low-grade gliomas identifies recurrent, oncogenic MYBL1-truncating rearrangements. ***PNAS.*** 2013 May 14;110(20):8188-93. PMC3657784

Pediatric low grade gliomas (WHO Grades I/II) are a substantial percentage of the patients we see in the childhood brain tumor clinic, yet their behavior is often unpredictable, with some rather indolent and others more aggressive and refractory to treatment. Following on the identification of duplication and fusion lesions involving the *BRAF* gene, these studies characterize further, the genetic lesions that contribute to pediatric gliomagenesis and identifies additional driver genes that could be useful as predictive biomarkers for current therapy or candidate therapeutic targets.

5) Contributions to our understanding of FGFR pathobiology

a. Su WC, et al. ***Nature*** 1997 Mar 20;386(6622):288-92.
b. Cho J, et al. Defective lysosomal targeting of activated FGFR3 in achondroplasia. ***PNAS.*** 2004 Jan 13;101(2):609-14. PMC327195
c. Guo C, et al. Sprouty 2 disturbs FGFR3 degradation in thanatophoric dysplasia type II: a severe form of human achondroplasia. ***Cell Signal.*** 2008 Aug;20(8):1471-7. PMC2675614

Activating mutations in fibroblast growth factor receptors (FGFR) were identified in several syndromic dwarfing conditions in the mid-1990's. As part of my graduate school thesis research at OHSU, I hypothesized that activation of these receptors not only occurred through direct regulation of the kinase domain, but additionally through defective receptor turnover/degradation. It is now well regarded that signaling pathways in development and cancer are intricately regulated by protein turnover through the ubiquitin/proteasome pathway and serves as a therapeutic target in diseases such as cancer. My specific role(s) in this project was the conception of the original hypotheses, generation of reagents for the studies, performing the wet bench experiments, writing (or contributing to writing) of the manuscripts.

D. Research Support

ACTIVE

Scholar Award (Cho) 09/01/2011-08/31/2014 2.4 cal
St. Baldrick's Foundation $330,000
Title: Functional annotation of the medulloblastoma genome
The goal of this project is to perform genome-wide shRNA-mediated knockdown in MYC-amplified medulloblastoma cells to identify genetic factors that these tumors depend on for growth and survival. These potential therapeutic targets will then be validated using mouse orthotopic xenograft models.
Role: PI

Large-Scale Applied Research Project (Taylor, Malkin) 07/01/2011-06/30/2014 0.6 cal
Genome Canada $9,856,814
Title: Stratifying and Targeting Pediatric Medulloblastoma Through Genomics
The goal of this multi-institutional collaboration is to perform RNAseq on a large cohort of medulloblastoma samples (estimated 2000) to better define subgroups within this disease, molecular markers predictive of prognosis and genetic lesions or pathways amenable to more effective therapeutic strategies.
Role: Co-Investigator

Research Scholar Grant (Tran) 7/01/2012-06/30/2016 1.2 cal
American Cancer Society $142,937
Title: Twist1 structure-function studies of Kras-induced senescence inhibition
The goal of this project is to identify through human and mouse models of Kras-induced lung carcinogenesis, the structural domains of Twist1 that inhibit Kras-induced senescence and the global differences in Twist1 occupancy of genomic loci that occur between senescent and tumorigenic states. My specific role on this project is to provide bioinformatics support for Twist1 ChIP-seq/ChIP-chip studies.
Role: co-Investigator

Phil R. Dodge Young Investigator Award (Cho) 10/1/2012-9/30/2014 .024 cal
Child Neurology Society $20,000
Title: Genetic and pharmacological manipulation of the medulloblastoma genome
The goal of this project is to perform and then merge RNAi, chemical biology and chemical genomic screening to identify cross-platform consensus of putative therapeutic targets in medulloblastoma.
Role: PI

1U01CA176287-01 (Weiss, Balmain, Cho) 05/01/2013-03/31/2015 1.2 cal
NCI/Cancer Target Discovery and Development Network ~$250,000
Title: Genetic network analysis of cancer targets
The goal of this project is to integrate genomic screening of human medulloblastoma tumors with mouse coexpression networks to identify both new medulloblastoma targets, and novel roles for pathways with existing therapeutics. This project is intended to provide collaboration and resource sharing through the Cancer Target Discovery and Development network at NCI.
Role: co-PI

PENDING

Application for R01 funding anticipated during the 2013-2014 academic year.

OVERLAP

There are no overlaps between the Aims of the projects listed above and those proposed in this Conquer Cancer Now Award proposal.