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Geoffrey Beene Cancer Research Center: Research Retreat

On April 16 and 17, 2012, the Geoffrey Beene Cancer Research Center (GBCRC) held its fifth annual retreat at Skytop Lodge in Pennsylvania. The agenda of the two-day retreat focused on a wide array of innovative and groundbreaking translational research topics, which reflects the mission of the Geoffrey Beene Cancer Research Center. The retreat hosted more than 190 attendees including lab members and senior leadership from the Sloan-Kettering Institute's [Cancer Biology and Genetics Program \(CBG\)](#), the [Human Oncology and Pathogenesis Program \(HOPP\)](#) within Memorial Hospital, and faculty members from across Memorial Sloan-Kettering Cancer Center.

[Charles Sawyers](#), Chair of HOPP, kicked off the retreat by recognizing the efforts of G. Thompson Hutton, Trustee of the Geoffrey Beene Foundation, for his vital role in the creation and continued support of the Geoffrey Beene Cancer Research Center at Memorial Sloan-Kettering.

Following the opening remarks, GBCRC Chair [Scott Lowe](#), along with GBCRC grant recipients [Robert Klein](#) and [Michael Berger](#), presented research on genomic approaches to cancer gene discovery. Then [Kitai Kim](#), [Hans Guido-Wendel](#), and [Yu Chen](#), members of CBG and HOPP, discussed their work, which is related to epigenetics and transcription in cancer. The last session of the first day featured a talk delivered by guest speaker William Sellers, Vice President and Global Head of Oncology at the Novartis Institute of Biomedical Research, on the opportunities and challenges presented when studying the genetic basis of cancer therapy.

A cocktail hour and poster session included 46 poster presentations from trainees across Memorial Sloan-Kettering Cancer Center. Each year the GBCRC extends five poster awards to the presenters chosen by fellow trainees and faculty members. This year's award winners were [Yiyu Dong](#) of James Hsieh's laboratory, [Yoon Chi-Han](#) of Andrea Ventura's laboratory, [Thomas Kitzing](#) of Dr. Lowe's laboratory, [Ping Mu](#) also of Dr. Ventura's laboratory, and [Patrick Ward](#) of Craig Thompson's laboratory.

The following day, the retreat kicked off with a lively debate between Dr. Sellers and [Neal Rosen](#), of the Sloan-Kettering Institute's [Molecular Pharmacology and Chemistry Program](#), comparing the benefits and drawbacks of developing drugs in academia versus industry. The debate was followed by presentations from six investigators from HOPP and Memorial Hospital that focused on cancer imaging and targeted therapies. The speakers were Memorial Sloan-Kettering laboratory heads [Moritz Kircher](#), [Ingo Mellinghoff](#), [David Solit](#), and [James Fagin](#), as well as Michael Evans of [Jason Lewis's laboratory](#) and Margaret Callahan of [Jedd Wolchok's laboratory](#).

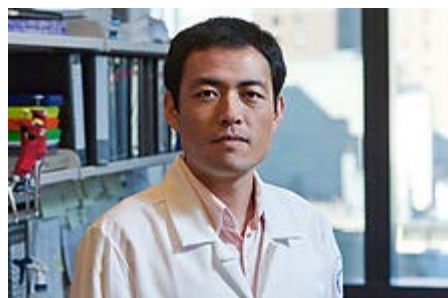
SLIDESHOW

2012 Geoffrey Beene Cancer Research Retreat



Because of the enthusiastic participation from faculty members and trainees across Memorial Sloan-Kettering, the annual retreat continues to be the most successful event for the Geoffrey Beene Cancer Research Center. The event promotes the mission of the GBCRC by focusing on translational research in both the clinical and lab setting and by bringing together faculty members from across the institution and fostering a collaborative environment. We are grateful to the Geoffrey Beene Foundation for its continued support of both the Geoffrey Beene Cancer Research Center and the Annual Retreat.

■ Poster Awardees and Abstracts

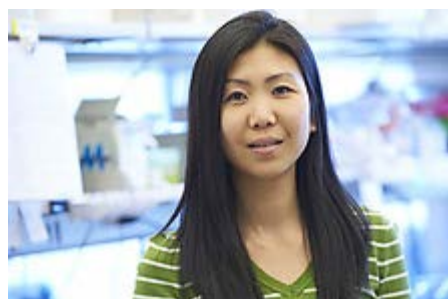


Yiyu Dong

Specific Protection against Her2/neu-Induced Breast Cancer by Taspase 1 Ablation in Vivo

Yiyu Dong, Brian Van Tine, Toshinao Oyama, Hoson Chao, Emily Cheng, and James Hsieh

Taspase1, a threonine endopeptidase, cleaves nuclear transcription factors to activate genetic programs and plays an important role in cancer cell proliferation. Inhibition of Taspase1 in MMTV-neu-driven breast tumors in mice using a small molecule Taspase1 inhibitor (TASPIN) effectively suppresses tumor growth. To further investigate the role of Taspase1 in breast tumorigenesis, we specifically deleted Taspase1 in the mouse mammary glands by generating MMTV-neu, MMTV-cre, T1F^{-/-} mice. We demonstrate a profound block of MMTV-neu-driven breast cancer initiation in the absence of Taspase1 in vivo. Mechanistically, loss of Taspase1 resulted in a failed accumulation of Cyclin E and A for cancer cell proliferation, accompanying a decreased S-phase population. Importantly, ablation of Taspase1 in mice had no effect on the development and the proliferative response to gestation of mammary glands. As our prior data indicated that Taspase1 cleaves MLL1 to regulate Cyclin E expression, MMTV-neu, MLL1^{nc/nc} mice were generated. Remarkably, these mice also exhibited impaired tumorigenesis, indicating that MLL is the primary proteolytic substrate of which cleavage is required for MMTV-neu-induced tumor formation. In total, Taspase1 cleaves MLL1 to enable the overexpression of Cyclin E induced by Her2/neu in the mammary gland, which constitute an essential axis for mammary gland tumorigenesis. Thus, Taspase1 plays a critical role in breast tumor formation and may serve as a therapeutic target for Her2-positive breast cancer.



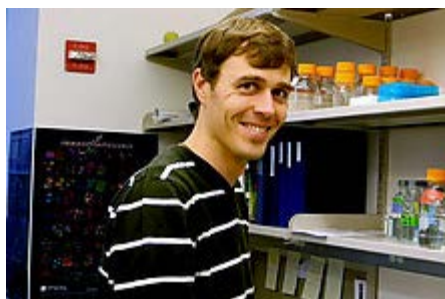
Yoon-Chi Han

Multidisciplinary Approach to Study the Oncogenic MicroRNA Cluster miR_17~92

Yoon-Chi Han, Ciro Bonetti, Ping Mu, Evelyn Yao, Joana A. Vidigal, Paul Ogdoroski, Christina Marney, Robert D. Darnell, Doron Betel, and Andrea Ventura

The oncogenic miR-17~92 cluster is a polycistronic microRNA often amplified or overexpressed in a variety of human cancers. It encodes six distinct

miRNAs that can be grouped into four “seed families” predicted to modulate largely non-overlapping gene sets. Interestingly, *in vivo* studies have also uncovered a role for this cluster in mouse development. As for the oncogenic role, miR-17~92 cooperates with c-Myc for the maintenance of c-Myc-driven B cell lymphomas as the deletion of the cluster leads to increased apoptosis. Surprisingly, among the six miRNAs in the cluster, only miR-19 family is necessary and sufficient to mediate the oncogenic activity in Myc-induced lymphomagenesis. This raised the important issue of determining the relative contribution of individual miRNAs in the miR-17~92 cluster in tumorigenesis and mammalian development. To address this question, we have generated an allelic series of six miR-17~92 knock-in (ki) mice harboring deletion of selective components of the cluster. These ki mice are a very useful tool that entails the systematic analysis of an entire cluster of the miRNAs in the mouse through loss-of-function experiment. We are taking a multidisciplinary approach to identify a set of genes whose expression is modulated by each family of miRNAs, which will allow us to dissect their oncogenic and physiological functions. Argonaute-HITS-CLIP combined with genome-expression profiling by RNA-Seq, and gene-expression profiling from wild-type, ki, and full ko mice begin to reveal the intricate interactions of these miRNAs and their targets.



Thomas Kitzing

Large Chromosome 8p Deletions Target Multiple Tumor Suppressor Genes That Cooperate in the Development of Hepatocellular Carcinoma

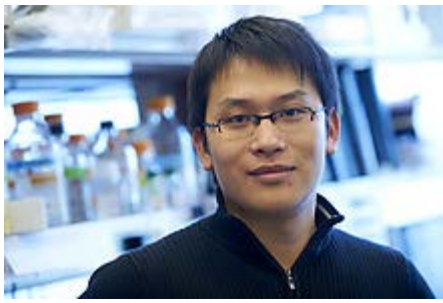
Thomas Kitzing, Wen Xue, Stephanie Roessler, Alexander Krasnitz, Nikolaus Schultz, Xin Wei Wang, Scott Powers, Michael Wigler, and Scott W. Lowe

The large heterozygous deletions that are hallmarks of cancer genomes are thought to arise as a “second hit” mechanism to inactivate a single tumor suppressor gene in the deleted region. Deletions of chromosome 8p frequently occur in various epithelial tumors, e.g., liver, breast, colon, and lung, commonly affecting the whole chromosome arm. Although different genes on

chromosome 8p have been implicated as candidate tumor suppressor genes, the driving tumor suppressor on 8p has not been identified.

Using *in vivo* RNAi-mediated gene suppression of the frequently deleted 8p22 and adjacent chromosome 8p regions in a hepatocellular carcinoma (HCC) mouse model, we tested an alternative hypothesis that such deletions can arise from selective pressure to attenuate the activity of multiple genes. Indeed, we functionally validated multiple chromosome 8p tumor suppressor genes and show that their co-suppression can synergistically promote tumorigenesis. Moreover, expression data from HCC patients indicates that combined loss of these genes is correlated with poor survival outcome.

Hence, our data suggest that such deletions can emerge from selective pressure to impair multiple signaling pathways and can produce phenotypes distinct from those arising through loss of a single tumor suppressor gene and, as such, should be considered and studied as distinct mutational events.



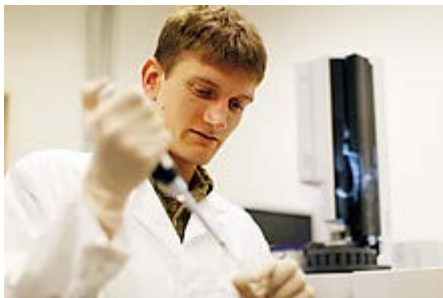
Ping Mu

Novel Role of miR-19 in Myc-driven B-cell Lymphoma and Prostate Carcinoma

Ping Mu, Yoon-Chi Han, Doron Betel, Brett Carver, Aleco D'Andrea, Carla Concepcion, Joana Vidigal, Ciro Bonetti, Evelyn Yao, Massimo Squatrito, Paul Ogradowski, Elisa de Stanchina, Chris Sander, Charles Sawyers, and Andrea Ventura

The *miR-17~92* cluster is frequently amplified or overexpressed in human cancers and is a bona fide oncogene. *miR-17~92* encodes six distinct miRNAs and is a direct transcriptional target of c-Myc. By using a conditional knockout allele of *miR-17~92*, we have previously shown that sustained expression of endogenous miR-17~92 is required to suppress apoptosis in Myc-driven B cell lymphomas. Furthermore, we have shown that among the miRNAs that are encoded by *miR-17~92*, miR-19a,b are absolutely required and largely sufficient to recapitulate the oncogenic properties of the entire cluster.

To further characterize the role of miR-17~92 cluster in tumor initiation, we have generated a series of knock-in mice carrying targeted deletion of individual miRNAs within the *miR-17~92* cluster and crossed them to E μ -Myc mice. Our data show that the deletion of miR-19a,b dramatically delays the initiation and progression of B cell lymphomas without impairing normal B cell development. In contrast to what is normally observed in E μ -Myc mice – mostly pre-B cell lymphomas – the lymphomas that eventually develop in miR-19-deficient mice usually originate from B cells that express a mature B cell receptor. Our data has also shown that deletion of miR-19 would decelerate the initiation and progression of Myc-driven prostate carcinomas as well. These results have implications for the treatment of lymphomas and possibly other Myc-driven human cancers.



Patrick S. Ward

IDH Mutations Producing the Most of the 2HG Oncometabolite Are the Most Tumorigenic

Patrick S. Ward, Alan Shih, Chao Lu, Justin R. Cross, Gary K. Schwartz, Ross L. Levine, and Craig B. Thompson

Most cancer-associated enzyme mutations cause either inactivation or inappropriate activation of an enzyme's normal biochemical function. However, we have previously reported that mutations in the IDH1 and IDH2 enzymes, which are prevalent in brain tumors, leukemias, and chondrosarcomas, represent an exception to this rule. The common feature of IDH1 and IDH2 mutations is the acquisition of a novel enzymatic activity producing an abnormal metabolite called 2HG. Here, we report that unresolved questions regarding why different types of IDH mutations associate with different cancer types and prognostic groups may be explained by factors that quantitatively determine the amount of 2HG produced in the tumor. We demonstrate that those IDH mutations associated with the worst prognosis in human leukemia have the biochemical ability to produce the most 2HG, and they also appear to drive the most severe and rapidly progressive disease in mouse models. Collectively, these data support the hypothesis that high levels of 2HG drive cancer development and that strategies to block 2HG production can be useful therapeutically in IDH mutant cancers.

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