THE DOSSIER

The Digest on CCR Staff Scientists and Staff Clinicians: Information, Employment and Research

December 2016 Issue 26

From the Editor

Welcome to the December issue of The Dossier, a newsletter dedicated to the Staff Scientists and Staff Clinicians (SSSC) of the CCR!

This issue contains important messages from the Director's Office, by Tom Misteli, Ph.D., and Darren Henderson, and a special article by Electron Kebebew, M.D. We feature Sohyoung Kim Ph.D., in the SSSC Corner, while the published work of Jianjian Zhu, Ph.D., is highlighted in our Author's Corner. Sikandar Khan, Ph.D. discusses the Society for Investigative Dermatology Annual Meeting in the Conferences Corner, and Cynthia Masison, Ph.D. gives an overview of important information for the 2017 SSSC Quadrennial Review.

We hope to continue to provide pertinent information to aid in the success of SSSCs. Please send your contributions, suggestions, and comments to budhua@mail.nih.gov.

Anuradha Budhu, Ph.D. (SS)
Editor-in-Chief
Laboratory of Human Carcinogenesis

In This Issue

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From the Office of the Director

*The CCR Director regularly invites senior staff members as guest columnists to expertly inform the SSSC community on diverse aspects of the CCR.

Space & Facilities Management in Support of CCR Science

CCR has scientific and administrative programs on three campuses: Bethesda, Frederick, and the Shady Grove facility. The Bethesda and Frederick campuses house our basic and clinical science programs while Shady Grove contains IT, computational, and clinical data support functions. With nearly 2,500 staff and more than 230 investigators located at these multiple locations performing an array of duties and operating diverse scientific programs, the management of space and facilities is a key part of supporting CCR's mission. As science and equipment needs evolve, CCR's operational space and facility needs must change as well. For this reason, the CCR Office of the Director has the Office of Research Support (ORS). This office is to facilitate these changes and provide CCR with the laboratory and administrative facilities it needs to succeed. The ORS realizes that space is essential to do great science.

The ORS is responsible for planning, managing, and overseeing all of CCR's space resources, renovation projects, and laboratory relocations on both the Bethesda and Frederick campuses. In addition, this office generates the space plans and summaries used in site visit reports. The ORS's goal is simply to provide the best laboratory and administrative facilities and infrastructure in support of CCR's research.

As buildings age and new scientific avenues are pursued, renovations are inevitably needed. This may range from electrical outlet installation to simple lab bench relocations to complete overhaul of large spaces. CCR also uses renovations and construction projects to align similar scientific programs and to consolidate laboratories to gain an economy of scale for large equipment usage and to foster synergy between groups. The ORS also manages several infrastructure systems that support the research enterprise. These include the scientific alarm systems that monitors your freezers and other important equipment, ensuring our buildings have bulk medical gases such as carbon dioxide and liquid nitrogen, and managing our Bethesda based bio-repository facilities located in Building 37, which actually houses NIH/Bethesda's first liquid nitrogen fueled -80 freezer system.

The staff in ORS mostly come from the laboratory environment themselves, having worked as technicians or laboratory managers. This gives the CCR scientist a unique advantage with laboratory design as ORS staff understand how the investigators operate and what their priorities and concerns are. This insight is used to build laboratories that meet the investigators needs and interests. ORS staff can translate these requirements into buildable designs and interface with the appropriate officials at NCI and NIH to accomplish projects so the investigators can spend the maximum amount of time on their research.

One larger renovation initiative you may recently have heard of is the Frederick Refurbishment Initiative. NCI senior leadership has decided to make a considerable investment to modernize and refurbish several large buildings on the Frederick campus. The scope of this project is vast and includes the design of open style labs, replacement of benches, lab cabinetry, shelving, lighting, and an upgrade of all the mechanical and electrical equipment most people never see. Total targeted areas for renovation approaches 120,000 square feet. When completed in 2021, these buildings will house an array of scientific programs as well as much needed animal vivarium space. These projects are so large they must be done in phases, and as such, will probably take around five years to complete, but the reward to our investigators will be worth the investment and wait! The new space will enable new research.

ORS is here to support CCR and facilitate science through better laboratories, please feel free to contact ORS with any questions or needs you may have with your CCR labs or offices!

Darren Henderson
Chief, ORS, CCR

Tom Misteli, Ph.D.
Director, CCR

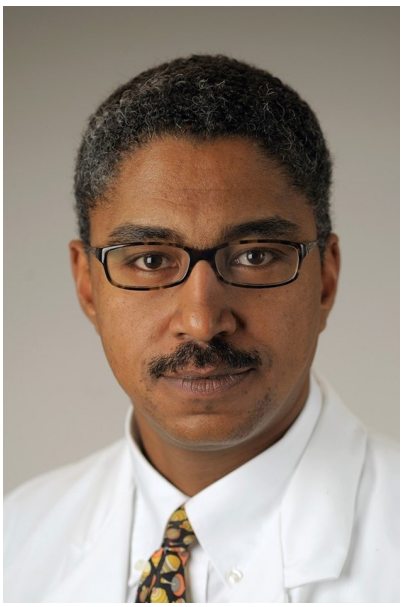
The PI Corner

Section Editor: Lakshmi Balagopalan, Ph.D. (*SS*)

As a Principal Investigator in the Endocrine Oncology Branch (EOB), I have found the work of our Staff Scientist and Staff Clinicians to be important for us to make progress towards our mission and scientific goals. The EOB is a small branch relative to others in the CCR, but we have accomplished so much in a relatively short time because of the dedication and talent of our Staff Scientist and Clinicians. It is often said that "team work makes the dream work" "but a vision becomes a nightmare when the leader has a big dream and a bad team" - John C. Maxwell.

In today's research environment, one won't be as successful or impactful if they don't collaborate or if they are not involved in "team science", putting together the unique skills of individuals working towards a common goal. This is especially true for EOB as our research focuses on relatively rare cancers that are fatal and neglected. Our former Staff Scientist, Lisa Zhang, Ph.D., led our effort to develop new therapeutic agents for endocrine cancers by establishing a fruitful collaboration with investigators at the National Center for Advancing Translational Sciences by 1) identify candidate anticancer agents using high-throughput drug screening, 2) developing an *in vivo* model that recapitulates endocrine cancers in humans, 3) deciphering their mechanism of action and 4) identifying biomarkers of response to these agents. Her work has led us to translate these preclinical studies into Phase I/II trials for rare and neglected endocrine cancers.

Our Staff Clinicians (Naris Nilubol, M.D., and Dhaval Patel, M.D.) provide outstanding patient care, perform complex surgical operations, and mentor and educate our clinical fellows. In addition to their clinical and educational responsibilities, they bridge the bench-to-bedside gap by conducting their own translational research focused on identifying and characterizing susceptibility genes in inherited endocrine cancer syndromes and by evaluating candidate molecular markers to stratify low-risk and high-risk endocrine cancers, using data generated from our integrated genomic and genetic studies in endocrine neoplasms. They have also initiated surgical clinical trials for pressing surgical management questions in patients with endocrine neoplasms. So the work of the EOB greatly depends on the commitment of its Staff Scientist and Clinicians.



Electron Kebebew, M.D.
Chief, Endocrine Oncology Branch

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The Conferences Corner

Section Editor: Majda Haznadar, Ph.D. (*SS*)

The Society for Investigative Dermatology Annual Meeting May 11-14, 2016, Scottsdale, AZ: An Amazing Opportunity to Explore Dermatological Innovations

The Society for Investigative Dermatology (SID) Annual Meeting provides a platform for skin researchers to present new scientific data covering insights into cutaneous biology, the molecular mechanisms of skin diseases and their clinical interventions. This year, the SID Annual Meeting was held at the Westin Kierland Resort in Scottsdale, Arizona, where about 1200 people from around the world had an opportunity to experience beautiful, sunny weather and a rich culture. The meeting began with a welcome reception, where attendees had the opportunity to meet each other in a relaxing environment. A social event was organized at the renowned Musical Instrument Museum the following evening, where scientists experienced the power of music, a universal art-form transcending cultural differences. However, the scope of the entire conference went far beyond simply creating a relaxing atmosphere, as the main purpose was to provide a forum for scientific innovation. The scientific program included concurrent mini-symposia, state-of-the-art plenary lectures, translational science symposia, poster sessions, as well as a resident retreat. The speakers presented scientific findings from basic to translational research that were both eye-opening and thought-provoking. The agenda of the meeting traditionally includes a dynamic forum for young investigators, which fosters professional growth in the research areas of interest.

There was strong representation of the NCI, NIH researchers at the SID Annual Meeting this year. Tom Misteli, Ph.D., the Director of the Center for Cancer Research (CCR), delivered the prestigious Herman Beerman Lecture, having been introduced by the SID President*, Mark C. Udey, M.D., Chief of Dermatology Branch and the Deputy Director of the CCR. The title of Dr. Misteli's talk was "Beyond the Sequence: Understanding the Genome in 3D." Among other important findings, he highlighted that the spatial location of genes in the nuclei of human cells is critical for their function. Dr. Misteli also talked about Hutchinson-Gilford Progeria Syndrome (HGPS), a human premature aging disorder caused by *de novo* mutation in the LMNA gene. His data supports that the disruption of the NRF2-mediated antioxidative pathway is the major contributor to the premature aging phenotype in the HGPS patients. Keisuke Nagao, M.D., Ph.D., from the CCR's Dermatology Branch, also delivered a plenary talk entitled "Hair follicles as regulators of immune homeostasis." His talk and several other interesting presentations are accessible on the SID website (http://www.sidnet.org/page/Recordedlectures).

In my laboratory, the DNA Repair Section of the Dermatology Branch (DB), our team works on human diseases with defective DNA repair, xeroderma pigmentosum (XP) and trichothiodystrophy (TTD), rare human autosomal recessive disorders. XP is caused by mutations in one of 8 nucleotide excision repair genes (*XPA* through *XPG*) or bypass polymerase eta (*POLH*). TTD is caused by defects in the DNA repair/transcription (*XPD*, *XPB*, *TTDA),* transcription (*GTF2E2*) and also in *TTDN1* or *RNF113A* genes with unknown function. While XP patients have a 10,000-fold increased risk for skin cancer development, TTD patients have a wide spectrum of clinical manifestations and developmental abnormalities that do not lead to skin cancer. We presented two posters at the meeting, which are related to our research interests. The first poster was entitled "Precision medicine interventions in xeroderma pigmentosum." Some Xeroderma pigmentosum group C (XP-C) patients have a premature termination codon (PTC) mutations, decreased *XPC* mRNA levels and no detectable levels of XPC protein. We found that some PTCs can be read-through by agents that disrupt ribosomal fidelity, including aminoglycoside antibiotics. As part of the pre-clinical basis for a precision medicine-directed XP treatment protocol, potential therapeutic compounds were tested on cell lines from XP-C patients. The second poster was entitled "Influence of paternal alleles on clinical outcome in trichothiodystrophy." This retrospective pilot study suggests that the outcome of pregnancy and mortality in TTD with defects in the *XPD* gene is influenced by the paternal allele. It is always an amazing experience to receive interesting questions during poster or oral presentation, and this year was just as fulfilling. Discussing our work with other scientists is a very beneficial experience in terms of scientific exchange that leads to increased knowledge-base and potentially

The Conferences Corner Con't

Section Editor: Majda Haznadar, Ph.D. (*SS*)

novel, innovative ideas.

From my personal experience, I can attest that the SID Annual Meeting plays an integral part in facilitating academic success and excellence among scientists as well as clinicians who have interests in dermatological research and innovations. Throughout the conference, we were able to catch up on cutting edge discoveries and inventions in the field of our research related to skin diseases. Conferences provide a platform for collaboration by promoting interactions among scientists who have common scientific research interests. This type of a healthy environment enlightens new discoveries and inventions that can improve human health.

Sikandar Khan, Ph.D. (SS)
DNA Repair Section
Dermatology Branch

Pictured are (from left) Sikandar G. Khan, Ph.D., Staff Scientist, DNA Repair Section, DB, CCR, NCI, NIH; Ms. Jennifer Pugh, Post Baccalaureate IRTA Fellow, DNA Repair Section, DB, NCI, NIH; Kenneth H. Kraemer, M.D., Chief, DNA Repair Section, DB, NCI, NIH. This photo was taken at the Westin Kierland Resort in Scottsdale, AZ, the site of the SID Annual Meeting.

** Dr. Mark Udey served as SID President as a private citizen, rather than as a federal employee.*

The Quadrennial Review Corner

The 2017 Quadrennial Review

Staff Scientists (SSs) and Staff Clinicians (SCs) are highly valued for the scientific knowledge, technical skills, leadership and mentoring ability and continuity they bring to their research group. These are time-limited, renewable positions that the NIH requires to be reviewed every four years. This is accomplished, in most cases, through the CCR Quadrennial Review (Quad Review) process. Quad Reviews form the basis for decisions about renewal and salary adjustments. Therefore, it is important for SSSCs to understand the process and the criteria used for these reviews.

In September, I contacted all SS and SC being reviewed in 2017 to allow them ample time to assemble their review packages. These packages are due to the CCR ARC by **December 12, 2016**. The Quad Review submission is composed of three parts: the recommending memo from the PI, the CV and at least two letters of recommendation from collaborators. The CCR Review Panels are asked to comment specifically on the SS's or SC"s accomplishments over the past four years in the areas of scientific productivity (publications, patents, clinical trials), scientific presentations (talks and posters), participation in the scientific community (i.e. interest groups, faculties, technology transfer, journal reviewer, grant reviewer, SSSC organization, poster judge for various CCR/NIH events), collaborations, mentoring/teaching, awards/honors and continuing education. In the case of SCs, the committee also evaluates performance with regards to patient care. All pertinent areas listed above should be clearly addressed in **both** the **recommending memo from** the SSSC's **PI/Supervisor** and in the SSSC's **CV**.

In most cases, a lower ranking can be attributed to a poorly prepared package. Your package should begin with a strong recommending memo from your PI/Supervisor that clearly conveys the role you play in their research program and in the greater scientific community. The memo would also be the place for your PI/Supervisor to address any setbacks or complications that possibly impacted your performance over the four-year period. The Reviewers only know what you tell them, so be sure to give **specific details**. For example, in your CV you are asked to list the

The Quadrennial Review Corner Con't

names of your mentees. However, you should provide details of how your mentoring affected their careers in terms of poster presentations, papers, educational opportunities and where they have gone since working with you are likely to have a higher impact. Pointing out specific roles that you have played in collaborations or as a participant in a special interest group allows the Reviewers to more fully appreciate your particular involvement. While scientific productivity is extremely important, the reviewers are looking for SSSC that actively contribute to the greater scientific community through their involvement, for example, as FARE judges, participants in interest groups, members of search committees, etc. Finally, ensure to request letters (at least two) from individuals who can comment directly on your accomplishments in the last four years.

This year 46 SSs and 4 SCs will undergo a Quad Review. New this year, to ensure consistency in the performance of all SS and SC, CCR will now be including Title 5/Title 38 and Commissioned Corps (CC) employees in the Quad Review. To note, PMAP or COER will remain the method that governs individual pay increases and/or promotions for Title 5/Title 38 and CC SS/SC. The Quad Review checklists and forms can be found on the CCR ARC website http://home.ccr.cancer.gov/intra/arc/documents/StaffScientistChecklistQuadReview.pdf http://home.ccr.cancer.gov/intra/arc/documents/StaffClinicianChecklistQuadReview.pdf.

If you have any questions, please contact me masisonc@mail.nih.gov or Geoff Kidd kiddg@mail.nih.gov.

Cynthia Masison, Ph.D.
Scientific Program Analyst,
Office of the Director

The SSSC Corner

Section Editor: Takashi Furusawa, Ph.D. (*SS*)

I first came as a Predoctoral Fellow in the Genomics and Bioinformatics Group, Laboratory of Molecular Pharmacology, headed by John Weinstein, M.D., Ph.D., as a 2nd year computational biology graduate student, which was the beginning of my long journey at NIH. After my graduation, I took another opportunity to pursue training in mathematical modeling of biological systems and bench work for live cell imaging. This was a collaborative effort between three laboratories, headed by Kurt W. Kohn, M.D., Ph.D., and Mirit I. Aladjem, Ph.D., at NCI, along with Geoffrey B. McFadden, Ph.D., at NIST. It was a precious experience that helped me understand biology and experimental procedures more in-depth. Later, towards the end of my fellowship, I wanted to take advantage of

The SSSC Corner Con't

Section Editor: Takashi Furusawa, Ph.D. (*SS*)

understanding biological systems based on the vast amount of genomic data generated from Next Generation Sequencing (NGS). Although most of my Postdoctoral training focused on mathematical modeling of systems and understanding single cell level dynamics of gene expression, as a bioinformatician or computational biologist, I thought that one should not be bound to a single approach to deal with biological issues, and NGS data was definitely next in line for me to conquer. Thankfully, I was able to join the Laboratory of Receptor Biology and Gene Expression, headed by Gordon L. Hager, Ph.D., to work on sequence data analysis to understand epigenetic features of cancer.

As a Staff Scientist, one of the projects I have been working on in Dr. Hager's lab is the Cancer Chromatin Profiling (CCP) project. In this project, we obtain biopsies from prostate cancer patients and survey genome-wide epigenetic features that may have the potential to indicate their risk of developing serious disease. This project requires the orchestration of the efforts from experts in diverse fields, including experimental/molecular biologists, computational biologists, statisticians, and medical doctors. The environment of NIH, whose campus is like a huge university full of closely related disciplines of medical science, has been tremendously beneficial to the project. When needed, it is not hard to find renowned world scientists in each specific field to consult, and I often find myself contacting them regularly to discuss this project. Of course, in the center of all these efforts, Dr. Hager has been very supportive of the collaboration to achieve the goal of project.

Outside the lab, I love spending time with my family, listening to music, reading, swimming, and solving the challenging Rubik's cube. I also love traveling, especially driving and exploring new places. I tend not to study too much on the area we plan to visit, initially due to time limitations in preparing for the trip, but later I started enjoying the unexpected welcome of a hidden gem. At the moment, due to the young age of my kids, we tend to take it easy in terms of where to explore, but I am very much looking forward to venturing into more rugged terrain once they are old enough to enjoy the experience together.

Pictured are Dr. Kim's family at Waikoloa beach on the big island of Hawaii.

Sohyoung Kim, Ph.D. (SS)
Laboratory of Receptor Biology
and Gene Expression

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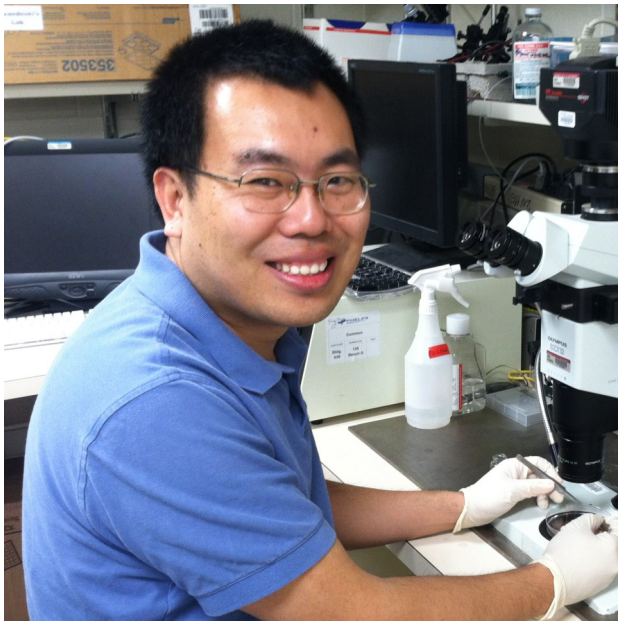
The Author's Corner

Section Editor: Cristina Bergamaschi, Ph.D. (*SS*)

Putative Oncogene Brachyury (T) is Essential to Specify Cell Fate but Dispensable for Notochord Progenitor Proliferation and Epithelial-Mesenchymal Transition

Jianjian Zhu, Kin Ming Kwan, and Susan Mackem. Proc Natl Acad Sci U S A. 2016 Apr 5;113(14):3820-5.



Embryonic development and cancer can be viewed as flip sides of the same coin. Many of the cellular processes involved in embryonic development, such as proliferation, adhesion, migration, and differentiation, are mediated by the actions of growth factors and transcription factors. In many cancers, these same growth factors and transcription factors frequently are abnormally expressed or are even mutated to form oncogenes. Understanding the functions of these factors in development will deepen our knowledge of the biology of cancer and ultimately will provide necessary insights for intervening with effective cancer therapies.

The notochord is the defining characteristic of chordates, serving both as a mechanical backbone for supporting the early embryo and as a signaling center for dorsoventral patterning of the adjacent neural tube and the somites. In the late stage of embryogenesis, the notochord is squeezed by the surrounding vertebrae into discrete segments and differentiates to form the nucleus pulposus of the intervertebral disks. This process can generate the notochord 'remnants' persisting within vertebral bodies in adults, which are thought to give rise to chordomas, a rare sarcoma of notochord cell origin. A major advance in understanding the pathogenesis of chordoma has been the discovery that *Brachyury* (*T* gene), which is highly expressed in these tumors, is duplicated in certain familial chordomas. T expression, which is pathognomonic for diagnosis of these sarcomas, has consequently become a major focus for therapeutic targeting in treatment of these cancers.

T is the founding member of the T-box gene family of transcription factors, and is highly conserved among species. During embryonic development, T is expressed in the notochord and primitive streak, and is essential for trunk/tail primary mesoderm formation and migration out of the primitive streak, which drives axis elongation. The embryonic role of T in epithelial-mesenchymal transition (EMT) of cells migrating from primitive streak has piqued interest that T, which is variably expressed in a number of common cancers in addition to chordoma, may play an important role in tumor progression promoted by EMT and following metastasis. A T deletion mouse mutant was first generated by X-ray-induced mutagenesis in 1927 and named after the characteristic short-tail phenotype in heterozygotes. However, homozygous T mutant embryos die at embryonic day E10.5 due to early axis truncation resulting from the loss of T in primitive streak, precluding definitive analysis of its role in notochord formation and maintenance. No conditional genetic approaches in mice have evaluated T's role in notochord development selectively. Therefore, a tissue-specific, conditional T-deficient mouse model is needed to address this important issue and potentially gain insights into its role in cancer.

Jianjian Zhu, M.D., Ph.D., a Staff Scientist in the Regulation of Vertebrate Morphogenesis Section headed by Susan Mackem, M.D., Ph.D. at NCI, have employed a conditional transgenic short-hairpin RNA (shRNA) approach to generate a Cre-regulated T-knockdown mouse line (T-shRNA). When activated using a notochord-selective Cre driver line absent from primitive streak mesoderm (ShhCre or Foxa2CreER), this transgene gives a highly efficient

T-knockdown in notochord progenitors while sparing other mesoderm progenitors, evidenced by complete loss of T transcripts and protein in the notochord by E10.5-11.5 (Fig 1). The extent of T protein loss correlates with the severity of observed skeletal defects, which ranges from the complete loss of vertebrae below the neck level to tail truncations. An examination on cell signaling pathways finds that expression of Sonic Hedgehog (Shh), a signal secreted from notochord and critical for inducing development of the vertebral column from somites, is lost in T-knockdown notochord, suggesting that sustained T expression is required for notochord maintenance. Using reporter genes to label and track notochord progenitor cells, we discovered that these cells survive in the absence of T, but form large epithelial tube structures and mesenchymal cell aggregates rather than normal notochord. Neural markers Nestin and Sox2 labeling of the tubular structures suggests that they have adopted a neural cell fate, consistent with a model that the notochord and neural tube arise from a common progenitor.

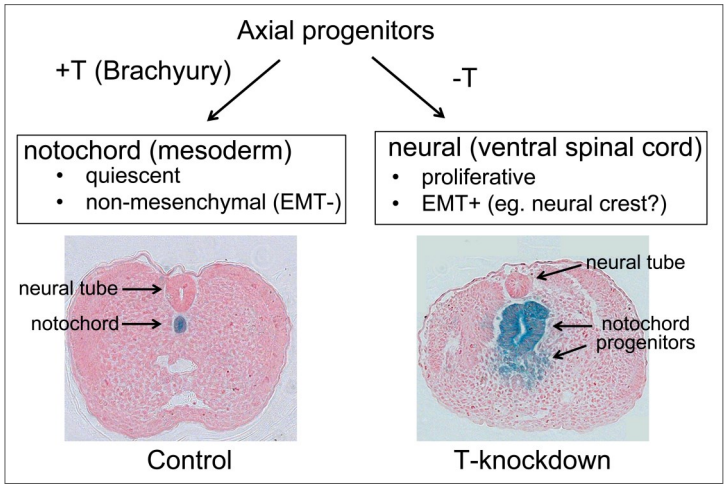


Figure 1. T regulates notochord vs. neural cell fate in pluripotent axial progenitors, but not cell survival, and is not required for EMT. Genetic labeling of notochord lineage by Cre-mediated RosaLacZ activation shows notochord progenitors in T-knockdown embryos form ectopic neural tubes and undergo EMT to become mesenchymal.

Now comes the fun part. Analysis on the proliferation of the T knockdown notochord progenitor cells reveals that these cells reproduce at more than twice the rate of control notochord. Nevertheless, notochord progenitor cells lacking T are also capable of adopting mesenchymal cell morphology and expressing the EMT regulator Twist-1, suggesting T is dispensable for notochord progenitor cell proliferation and EMT, a key feature associated with aggressive behavior in tumors. These results contradict expectations from previous studies associating T expression with oncogenesis, and reveal an essential role for T in notochord cell fate and function, but not in survival, proliferation, or EMT of notochord progenitors. Importantly, these data raise important questions about the value of therapeutic inhibition of T for cancer therapy in the context of tumor progression promoted by EMT. Understanding the role that T plays in cancer, particularly chordoma, will require further investigation.

Jianjian Zhu, Ph.D. (SS)
Regulation of Vertebrate Morphogenesis Section
Cancer and Developmental Biology Laboratory

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Dr. Jianjian Zhu is a Staff Scientist in the Regulation of Vertebrate Morphogenesis Section of the Cancer and Developmental Biology Laboratory, NCI. He plays a role in mentoring and training new students and fellows as well as participating in lab management. He carries on his own research within the lab, and is actively involved in establishing and maintaining collaborations within and outside NIH.

Announcements

Congratulations!

Our new SSSC Chairs and Vice-Chairs

Chin-Hsien Tai, Ph.D., Bethesda Co-Chair, Laboratory of Molecular Biology

Lakshmi Balagopalan, Ph.D., Bethesda Vice Co-Chair, Laboratory of Cellular and Molecular Biology

Yien Che Tsai Ph.D., Frederick Co-Chair, Laboratory of Protein Dynamics and Signaling

Krista Frankenberry Ph.D., Frederick Vice Co-Chair, HIV Dynamics and Replication Program

Baris Ismail Turkbey, M.D., Clinical Co-Chair, Molecular Imaging Program

Jennifer Kanakry Ph.D., Clinical Vice Co-Chair, Experimental Transplantation and Immunology Branch

Attend!

The 2017 NCI Intramural Scientific Investigators Retreat

Tuesday, January 10, 2017

National Institutes of Standard and Technology (NIST)

A Call for Content

We need your input! Send your articles or suggestions with subject title "The Dossier" to budhua@mail.nih.gov.

This newsletter is an avenue for you to express your ideas and thoughts on being a Staff Scientist or Staff Clinician at CCR and to make pertinent announcements.

Your contribution is very important to the success of The Dossier. Please send us your commentary, announcements, and suggestions for topics/subject matter and we will do our utmost to include your material in upcoming issues.

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