Almost all cells in the human body have identical DNA sequences, yet there are 200-plus cell types with different sizes, shapes, and chemical compositions. Determining what parts of the genome are read to make protein and which are silenced is orchestrated by proteins called transcription factors. These regulate the availability of distinct stretches of DNA to be expressed as opposed to others that remain buried in tightly coiled structures called chromatin.

Researchers in the Perelman School of Medicine at the University of Pennsylvania, described last month in Immunity the role of a transcription factor called TCF-1 in targeting the condensed chromatin and regulating the availability of genome sequences in T-cell development. The new connection between TCF-1 and chromatin will aid in developing new therapies using epigenetic drugs to alter T-cell fate in cancer, autoimmune disorders, and infectious diseases.

Senior author Golnaz Vahedi, PhD, an assistant professor of Genetics, brings her multidisciplinary training in computational biology, epigenetics, and immunology to bear on the question of T-cell identity. She leads a multidisciplinary team integrating computational and experimental approaches to develop an understanding of gene regulation in immune cells. Vahedi is also a member of Penn’s Institute for Immunology and Epigenetics Institute.

She likens TCF-1 to an icebreaker ship that initially opens the ice (condensed, closed chromatin) and keeps a path available for other ships (other transcription factors that work in later stages of development) to steam through the now-open water (unwound chromatin). TCF-1 ultimately opens chromatin so that DNA can be read to make proteins, and it also keeps chromatin open so that subsequent factors can access DNA to make protein that guide a maturing T cell to its final identity.

Although the functional importance of TCF-1 in T cells has been known for more than 25 years, the mechanism by which this protein controls T-cell identity remained unknown. The team generated a profile of open and closed areas in eight stages of T-cell development and found an abundance of the transcription factor TCF-1 at regions along the genome that were open at the earliest stages of development.

“Our lab is interested in understanding how T-cell identity is established,” Vahedi said. “We chose to

Mutated KMT2D in Skin Cancer Plays Role in Skin Cell Renewal

Approximately once a month, our skin completely renews itself. If this highly coordinated process goes awry, it can lead to a variety of skin diseases, ranging from skin cancer to psoriasis. Cells lining such organs as skin and the gut, lungs, and many other organs (collectively called epithelial tissue) rely on a delicate balance of self-renewal, proliferation, and differentiation. However, disruption of this equilibrium may drive cancer and other disorders.

Researchers from the Perelman School of Medicine at the University Pennsylvania have shown for the first time that a key protein called KMT2D involved in the epigenetic regulation of gene expression guides this renewal. They published their work last month in Genes & Development. Epigenetics involves chemical modifications to DNA and its supporting proteins that affect the availability of genes to be “read” and made into proteins.

“We have known that KMT2D is one of the most frequently mutated genes in all of skin cancer, as well as other epithelial cancers such as those of the lung, esophagus, mouth, and throat,” said sen-
"Icebreaker" TCF-1

(Continued from page 1)

study T cells because of their all-important role in patrolling the body to clear it of germs and such other dangers as cancer cells."

They established the identity-making role for TCF-1 by deleting it in a mouse model and found that most open sites closed, becoming inaccessible in tightly wound chromatin. On the other hand, when they added TCF-1 to a type of common skin cell, it "broke the ice" and opened closed regions by removing chemical groups that tighten chromatin. The elongated fibroblasts reprogrammed to become more T-cell-like in shape and hundreds of T-cell genes were also expressed in these skin cells.

Using computational and epigenomic methods, the team found that TCF-1 behaved in a similar manner on the chromatin of individual T cells. Because of the consistency among many cells, they concluded that TCF-1 control of T-cell fate is fundamentally important in determining what a cell will become.

“We showed how TCF-1 controls T-cell fate through its ability to target closed chromatin and establish the identity of developing T cells,” Vahedi said. “TCF-1 is the focus of many immunology and oncology studies, especially those dealing with checkpoint inhibitors and sick immune cells. We think that the ‘ice-breaking’ ability of TCF-1 can be selectively harnessed to reset ‘old’ T cells to a ‘younger’ state so they can fight invaders again.”

Source: Penn Medicine Communications

Analysis Reveals Genetic Differences in Pediatric, Adult Tumors

Physician-scientists from Children’s Hospital of Philadelphia (CHOP) contributed crucial data and expertise to the first pan-cancer analysis of children’s cancer, published last month in the journal Nature. Pan-cancer analyses identify similarities and differences among the biological changes across diverse types of cancer, with the aim of discovering insights for improved care.

In this new study, the researchers found important differences in how cancers develop in children compared to how they develop in adults. For instance, they identified 142 genes that drive pediatric cancers, but only 45 percent of those genes match genes found in adult pan-cancer studies. This implies that precise treatments need to be better customized for children.

Co-authors from the Abramson Cancer Center lead the two largest datasets in the study, which analyzed DNA samples from nearly 1,700 patients from multiple centers across five groups of pediatric cancers: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), neuroblastoma, Wilms’ tumor and osteosarcoma. The study team, led by Dr. Jinghui Zhang of St. Jude Children’s Research Hospital, searched for mutations and other variations in DNA sequences. All the patients were in clinical trials sponsored by the Children’s Oncology Group, and the datasets came from the TARGET project of the National Cancer Institute.

Stephen P. Hunger, MD, CHOP’s Chief of Oncology and Professor of Pediatrics at PSOM, leads the TARGET team for acute lymphoblastic leukemia, (ALL). He explained, “As pediatric centers have developed precision medicine strategies, many have relied on diagnostic panels developed to detect mutations common in adult cancers. In contrast, CHOP has developed diagnostic panels specific to mutations common in pediatric cancers — many of which occur only rarely in adult cancers.”

CHOP’s John M. Maris, MD, also a Professor of Pediatrics at PSOM, who leads the neuroblastoma TARGET team, echoed the importance of the study, validating the need to focus on the unique attributes of pediatric cancers. “This collaborative project proves the concept that childhood cancers are not ‘small adult tumors.’ They show unique genetic changes. Thus, precision diagnostic and therapeutic strategies for childhood cancers will be very different than those being developed for common adult malignancies.”

Source: CHOP News
Seminars and So Forth

Tuesday 3/6/18  
12:00 pm  
Distinguished Lecture in Cancer Research  
CANCELLED  
BRB II/III Glen Gaulton Auditorium

Tuesday 3/6/18  
4:00 pm  
Immunology Colloquium  
“Force awakens the dark side of T cell autoimmunity.” Brian D. Evavold, PhD, Division Chief, Microbiology and Immunology; Professor, Pathology, University of Utah School of Medicine  
CRB Austrian Auditorium

Thursday 3/8/18  
9:00 am  
CCEB Seminar Series  
“Developing Better Treatments through Translational Science: Nicotine Dependence as a Model.” Rebecca Ashare, PhD, Assistant Professor, Center for Interdisciplinary Research on Nicotine Addiction; Senior Fellow, Center for Public Health Initiatives, PSOM  
JMB Class of ’62 Auditorium

Thursday 3/8/18  
12:00 pm  
Gastroenterology Seminar Series  
“Metabolism, epigenetics, and tumorigenesis.” Kathryn E. Wellen, PhD, Associate Professor of Cancer Biology, PSOM  
901 BRB II/III

Thursday 3/8/18  
12:00 pm  
Radiation Oncology Seminar Series  
“Redox Imaging Biomarkers for Breast Cancer Diagnosis/Prognosis: An Update.” Lin Z. Li, PhD, Research Associate Professor of Radiology, PSOM  
SCTR 8-146AB

Friday 3/9/18  
8:00 am  
The PAIR Center Monthly Meeting Series  
“Payment Reform and Practice Transformation: Implications for Serious Illness Care.” Matthew J. Press, MD, MSc, Associate Medical Director, Penn Medicine Primary Care Service Line Flyers/ 76ers Surgery Theatre (HUP)

Monday 3/12/18  
12:00 pm  
Pathology & Laboratory Medicine Grand Rounds  
“Precision Medicine for Humans and their Companions.” David B. Roth, MD, PhD, Simon Flexner Professor and Chair of Pathology and Laboratory Medicine, PSOM  
CRB Austrian Auditorium

Monday 3/12/18  
1:00 pm  
CHOP Normal and Malignant Hematopoiesis  
RAG Seminar Series  
“Metabolism, control of cell fate decisions, and hematopoietic renewal.” Keisuke Ito, MD, PhD, Associate Professor of Cell Biology/Stem Cell Institute & Medicine, Albert Einstein College of Medicine  
CTR 1100B (CHOP)

Monday 3/12/18  
4:00 pm  
Cancer Biology Special Seminar  
“Identification of Druggable and Redox Vulnerabilities in a Genetically Defined Cancer.” Liron Bar-Peled, PhD, Research Associate (Cravatt Lab), Scripps Research Institute  
CRB Austrian Auditorium

Tuesday 3/13/18  
12:00 pm  
Distinguished Lecture in Cancer Research  
“Identifying and Targeting Vulnerabilities in Triple Negative Breast Cancer.” Helen Piwnica-Worms, PhD, Vice Provost of Science and Professor of Experimental Radiation Oncology, MD Anderson Cancer Center  
Caplan Auditorium, 37th & Spruce Sts. (Wistar)

Tuesday 3/13/18  
4:00 pm  
CHOP CCCR Oncology Seminar Series  
“Clinical Genomics of Pediatric Brain Cancer.” Elaine R. Mardis, PhD, Co-Director, Genomics Institute, Nationwide Children’s Hospital  
CTR 1200B (CHOP)

Wednesday 3/14/18  
8:00 am  
Abramson Cancer Center Grand Rounds  
Ruben Carmona (Rad/Onc Fellow) and Dr. Jenna Yui (Heme/Onc Fellow) presenting on  
SCTR 8-146 A/B

Wednesday 3/14/18  
4:00 pm  
Cardiovascular Institute Seminar Series  
“Genome and Epigenome Editing to Treat Hemoglobinopathies.” Gerd Blobel, MD, PhD, Frank E. Weise III Professor of Pediatrics; Co-Director, Epigenetics Institute, PSOM/CHOP  
SCTR Rubenstein Auditorium

Thursday 3/15/18  
5:45 pm—8:30 pm  
Recent Advances in Oncology for the Primary Care Physician - Suburban Philadelphia West  
This CME/CNE activity will provide information on cancer screening, evaluation, treatment advances, and palliative care. Details and registration here.  
Sheraton Great Valley Hotel, Frazer, PA

Friday 3/16/18  
9:00 am  
Radiation Oncology Seminar Series  
“Radiation Therapy for the Treatment of Pediatric Brain Tumors.” Peter B. Nowell, MD, PhD, Associate Professor, Radiation Oncology, CHOP  
SCTR 8-146AB

Friday 3/16/18  
12:00 pm  
CCEB Seminar Series  
“Nutritional Therapy in Cancer.” Matthew J. Press, MD, MSc, Associate Medical Director, Penn Medicine Primary Care Service Line Flyers/ 76ers Surgery Theatre (HUP)
Funding Opportunities

PAR-18-681 Fundamental Mechanisms of Affective and Decisional Processes in Cancer Control (R01)
LOI: 30 days prior to application date
Application: 4/11/2018, 10/10/2018, more
The purpose of this FOA is to encourage projects to generate fundamental knowledge of affective processes. Basic affective science projects should have key consequences for single (e.g., cancer screening) and multiple (e.g., adherence to oral chemotherapy regimen) event decisions and behaviors across the cancer prevention and control continuum. The FOA is expected to encourage collaboration among cancer control researchers and those from scientific disciplines not traditionally connected to cancer control applications (e.g., affective and cognitive neuroscience, decision science, consumer science) to elucidate perplexing and understudied problems in affective and decision sciences with downstream implications for cancer prevention and control.

PAR-18-675/PAR-18-674 U.S. Tobacco Control Policies to Reduce Health Disparities (R01/R21)
LOI: 30 days prior to application date
Application: 6/13/2018, 10/11/2018, more
The purpose of these FOAs is to support observational or intervention research focused on reducing health disparities in tobacco use in the United States. Specifically, these FOAs are intended to stimulate scientific inquiry focused on innovative tobacco control policies. Applicants may propose projects in which the primary outcome of interest is on reducing tobacco use health disparities in vulnerable populations by utilizing tobacco prevention and control strategies. The long-term goal of this FOA is to reduce health disparities in health outcomes thereby reducing the excess disease burden of tobacco use within these groups.

PAR-18-677/PAR-18-678 Epidemiologic Research on Emerging Risk Factors and Liver Cancer Susceptibility (R01/R21)
LOI: 30 days prior to application date
Application: Standard dates apply
The purpose of these FOAs is to promote epidemiologic research investigating novel and innovative hypotheses on emerging risk factors (biological, environmental, and social) and their interplay with established risk factors (e.g., viral hepatitis) associated with the development of liver cancer (hepatocellular carcinoma and other histological subtypes) in the United States.

KMT2D Mutations

(Continued from page 1)

ior author Brian C. Capell, MD, PhD, an assistant professor of Dermatology and Genetics. “However, prior to this study, we had no idea how those mutations caused cancer or even what KMT2D did in these tissues. Now, armed with this knowledge, I envision in the near future we may be able to test the ability of novel epigenetic drugs to reverse these deleterious mutations.”

In the study, when the researchers depleted KMT2D from human skin cells, undifferentiated stem cells could not multiply normally, causing premature differentiation of the tissue into a more mature, differentiated state. As a result, when grown in three-dimensional cultures, the different layers of skin epidermis became thickened and disorganized.

“Our data suggests that KMT2D is critical for the proper coordination of our skin’s turnover process,” Capell said. “Because epigenetic changes are reversible, we hope that our ongoing studies in KMT2D mouse models will ultimately lead to identifying and testing new topical therapies preventing and treating skin cancer in people.”

Source: Penn Medicine Communications