Learning for Life Lecture Series, Northwestern University
October 26, 2022

"Public Health's Transforming Human Genetic Disease Outcomes"

Speakers

Dr. Ali Shilatifard is the Robert Francis Furchgott Professor and Chair of the Department of Biochemistry and Molecular Genetics, and a Professor of Pediatrics, at Northwestern University Feinberg School of Medicine. He is also the Director of the Simpson Querrey Institute for Epigenetics. Dr. Shilatifard received his PhD from the University of Oklahoma. Research from his laboratory is leading to the development of promising, epigenetic target-specific drugs for childhood leukemia and other forms of cancer. The epigenetic inhibitors developed in the laboratory are currently being tested to treat childhood leukemia, brain cancer, and other solid tumors.

Dr. Shana Kelley is the Neena B. Schwartz Professor at Northwestern University and a member of the Departments of Chemistry, Biomedical Engineering, and Biochemistry & Molecular Genetics. Dr. Kelley received her Ph.D. from the California Institute of Technology and was a NIH postdoctoral fellow at the Scripps Research Institute. The Kelley research group works in a variety of areas spanning biophysical/bioanalytical chemistry, chemical biology and nanotechnology, and has pioneered new methods for tracking molecular and cellular analytes with unprecedented sensitivity.

Moderator

Dr. Eric G. Neilson, MD, is the Vice President for Medical Affairs and the Lewis Landsberg Dean at Northwestern University Feinberg School of Medicine. A medical graduate of the University of Alabama in Birmingham, he trained in internal medicine and nephrology at the Hospital of the University of Pennsylvania. After 23 years at the University of Pennsylvania as the C. Mahlon Kline Professor of Medicine, chief of the Renal-Electrolyte and Hypertension Division, and director of the Penn Center for Molecular Studies of Kidney Diseases, he moved to the Vanderbilt University School of Medicine to serve for 13 years as the Hugh Jackson Morgan Professor and Chairman of the Department of Medicine. He has made important contributions to understanding the cell fate of fibroblasts in fibrogenesis, the expression of the nephritogenic immune response, and the biochemical characterization of nephritic antigens.

Michael H. Schill took office as Northwestern's 17th president on Sept. 12, 2022. He also serves as a professor in the Northwestern Pritzker School of Law.

He previously spent seven years as president of the University of Oregon (UO), where he raised the university's profile in teaching, research, innovation, student access and diversity. Under Schill's leadership, UO built the Phil and Penny Knight Campus for Accelerating Scientific Impact, increased its four-year graduation rates by 10 percentage points and launched the Ballmer Institute for Children's Behavioral Health in a new campus in Northeast Portland. Schill also led the extension and historic close of the university's fundraising campaign in 2021, which exceeded its goal with $3.2 billion total raised.

Schill is a nationally recognized expert in property, real estate and housing law and policy. He is the author or co-author of three books and more than 40 scholarly articles. His work includes studies of the determinants of value in condominium and cooperative housing, the impacts of housing programs on property values, the enforcement of Fair Housing laws, mortgage securitization and the effects of housing market regulation. His casebook, "Property," co-authored with James Krier and Greg Alexander, is one of the most widely adopted casebooks in American law schools.

He served as dean and professor at the law schools of the University of Chicago and UCLA, and also held tenured faculty positions at New York University and the University of Pennsylvania.

In 2004, Schill founded NYU's Furman Center for Real Estate and Urban Policy, which has become one of the nation's leading research centers on housing and the built environment.

He has served on several nonprofit boards and civic bodies, including Argonne National Laboratory, ITHAKA, the Chicago Innovation Exchange, and the Housing Preservation Compact of Chicago.

Promising Epigenetic Treatments for Human Cancer

Dr. Ali Shilatifard

Over the last few decades, Professor Shilatifard's research has been inspired by one of his early discoveries – a link between a gene involved in the regulation of gene expression and human leukemia.

Interestingly, this work is related to that of Chicago-native, Professor Janet Rowley who was the first to link chromosomal translocation and leukemia.

Useful Background information:

DNA: A polymer that encodes the genetic information for life

Transcription: The copying of a segment of DNA into RNA

Translation: Process by which proteins are synthesized after transcription

Nucleosomes: DNA wrapped around a group of proteins. (Nucleosomes packed together make up our chromosomes.)

The story is complex – more and more research highlights that DNA is not our destiny. Epigenetics ("above" genetics) plays an important role.

Some early scientists whose work pointed to epigenetics are

Jean-Baptiste Lamarck (1744-1829) who argued that organisms could pass on traits based on what happens to us in life ("Lamarckism")

C. H. Waddington (1905-1975) – who investigated the inheritance of characteristics

The field of epigenetics has exploded. Professor Shilatifard's highly cited paper from 2009, "An Operational Definition of Epigenetics" sets out a consensus definition as "an epigenetic trait is a stably heritable phenotype (observable trait) resulting from changes in a chromosome without alterations in the DNA sequence." It is now widely accepted that the environment impacts how DNA is understood by our cells.

Epigenetics and Cancer

- Professor Shilatifard motivated the importance of epigenetics and cancer with a graph showing the incidence of cancer as a function of age – highlighting the lower incidence among children versus older adults, indicating the possible effect of our environment. (Epigenetics is being investigated in a wide range of areas from neurodegenerative disease to aging. This talk focuses on the effects in cancer.)

- To understand the possible ramifications for cancer, we need to understand epigenetic signals. Central to this understanding is the realization that chromosomes are not isolated entities, they exist with other chromosomes. Professor Janet Rowley was the first to show that chromosomes can exchange arms, a process called **translocation**. By studying the chromosomes of patients with leukemia, she found that many exhibited a similar translocation. She was able to tie specific translocations to specific types of leukemia.

- Leukemia is characterized by the hyperproliferation of white blood cells (WBCs). This hyperproliferation leads to infiltration of large amounts of these WBCs into tissues or organs causing malfunction. The outlook for patients with pediatric leukemia is still dire. Of 100

children who are diagnosed, within five years 70 will die. Treatment has not changed or improved in decades.

- Professor Shilatifard's research focuses on finding potential therapies by first focusing on the basic biology, replicating cellular processes in a test tube. To set the stage, he compared the typical composition of blood (45% red blood cells (RBCs), 1% WBCs, and remaining plasma) to the composition in children with leukemia. Their blood will be composed of 80% WBCs and 10x lower than normal amounts of RBCs leading to problems of severe anemia and associated problems of hyperproliferation of WBCs.

- To replicate transcription in a test tube, Professor Shilatifard's lab looks at the effects of nuclear extract on DNA and the enzyme that synthesizes RNA. By observing that the process of transcription is much faster in the presence of nuclear extract and with subsequent studies, his lab identified a **super elongation complex (SEC)**, central to the processes of transcription and translocation.

- To find ways to get rid of the SEC, Professor Shilatifard's lab undertook a structural-based strategy to computationally screen compounds that could interact with the SEC. They began with 10 million compounds, filtered down to 160 hits, and finally to two compounds.

- These compounds demonstrated, for the first time, the ability to slow down the process of transcription. In a mouse model, his lab extended the life expectancy by 50% and demonstrated significant tumor shrinkage. Work is continuing to optimize these compounds with the hope that they can be in the clinic in 5-10 years.

- His lab is also looking at pediatric brain tumors (diffuse intrinsic pontine glioma (DIPG)), a condition with no therapy where 99% of patients perish. (Radiation therapy helps only 1% of patients.) Sequencing indicated that epigenetics was playing a central role and the lab was able to develop an effective therapy.

- The lab is also looking at the epigenetic balance of promoting versus inhibiting gene expression and the implications on cancer. In these studies, they have developed an approach that is in an NCI trial for the treatment of bladder cancer.

- Epigenetics also plays a large, central role in solid tumor cancers. The Shilatifard lab focused on lung cancer and found through a CRISPR screen, that an existing drug (a metabolic inhibitor) was effective in mouse models of lung cancer.

- The lab is also extending its scope to metastasis.

Professor Shilatifard closed by emphasizing the importance of basic research to finding new therapies.

Finding Cells that Cure Cancer,
Professor Shana Kelly

Professor Kelly focused on new ways to deliver cell therapies for cancer.

- Cancer is challenging. Because of metastasis, treatment often is required throughout the body. Many approaches have been developed including surgery, radiation, hormone therapy, chemotherapy, and immunotherapy. Additionally, there are several modalities to deliver therapies – small molecules, antibodies, or by administering cells. One of the attractions of cell therapy is that it is potentially curative.

- Professor Kelly's focus is on immunotherapy and particularly cytotoxic T-cells. Cytotoxic T-cells are surveying cells that can find cells affected by disease, infected by virus, or may be cancerous. These T-cells can give off chemicals or biological factors to kill the appropriate cells.

- Giving cancer patients a "new immune system" can be effective treatment. For example, bone marrow transplants for blood cancers have been used for 50 years. This approach does have pluses and minuses as there can be side effects, the treatment is not tailored, and not effective against all cancers.

- Over the last decade, tailored cell therapies, particularly CAR-T have been developed. In this approach, T-Cells are harvested from the patient, isolated, and then programmed with a CAR (a biochemical construct that lets it recognize tumor cells) to produce engineered cells that can be administered back into the patient. This treatment has been shown to be quite effective even in pediatric patients. Developed at University of Pennsylvania, two of the primary researchers were Carl June and Michael Karlos.

- While successful with blood cancers, CAR-T had not seen the same success with solid tumors which are more prevalent in general population. Blood tumors are dispersed in circulation and therefore easier to access. Solid tumors, on the other hand, are masses of cells and are difficult for CAR-Ts to access.

- However, T-Cells exist in solid tumors, so we should be able to take them out and develop therapies. Dr. Steven Rosenberg of the NIH showed that these T-cells could kill tumor cells in a petri dish. Initial trials with this approach failed but later studies which grew large numbers of these cells (200 billion!) found success in advanced melanoma.

- The approach has now been used in many types of melanomas, breast cancer, and other cancers. However, the therapy is still not mainstream due to difficulties in implementing in the clinic - - tissue must be removed and the manufacturing of **tumor infiltrating lymphocytes (TILs)** is complex compared to other modalities.

- In addition, the FDA does not like TIL-therapy. There are many different kinds of cells in a dose – some are non-reactive, some are exhausted, and then some are the "just right" cells desired for therapy. The FDA wants clarity on the profile and ideally only the "just right" cells.

- Professor Kelly's group is focused on how to find the cells that are "just right." Her paper "Efficient recovery of potent tumor-infiltrating lymphocytes through quantitative immunomagnetic cell sorting" published last year (and featured on NPR!) established a powerful platform to find the optimum cells.

    - Professor Kelly's lab specializes in looking at large collections of cells very quickly. Her lab has developed Magnetic Ranking Cytometry, a method that uses magnetic nanoparticles to bind to TILs and a microfluidic device to separate the TILs into chambers based on whether they are non-reactive, exhausted, or "just right." With this method and device, Professor Kelly's lab was able to isolate "Goldilocks" cells and demonstrate in mouse models significant improvements in tumor shrinkage and sometimes even complete disappearance.

    - More recently, they are looking to see if the TILs can be isolated from the blood rather than requiring extraction from the tumors. Studies showed how to identify the TILs in the blood stream, isolate, and multiply them. These circulating TILS (control cells) are excitingly demonstrating efficacy in mouse models of melanoma and lung cancer.

- With this platform, Professor Kelly has founded CTRL Therapeutics, located in Chicago at Portal Innovations, to pursue this powerful approach to immunotherapy. Michael Kalos (one of the primary researchers in the first breakthroughs of immunotherapy) has joined the company as Chief Scientific Officer.

Questions:

For Professor Shilatifard: What is future of in-vivo CRISPR?

Next generation of CRISPR should do this next decade. The big advance will be to look at tumor type by genetic phenotype rather than characterizing as lung, blood, etc.

For Professor Kelly: What about immunotherapy for pediatric osteosarcomas?

Immunotherapy is typically late for pediatric conditions and we are not aware of any current approaches, but will check.

How do nanoparticles help your approach?

Our nanoparticles help recognize the cells. We need their small size to help with recognition.

Do we have to wait to have the tumor, or for it to metastasize? Is there a preventive approach?

We are looking at earlier and earlier – in principle, our approach should be compatible with earlier and earlier detection.