



# The U54 Vanderbilt Center for Cancer Systems Biology Presents:

## 2020 TUMOR PLASTICITY VIRTUAL THINK TANK MEETING

December 18, 2020

### Who We Are:

Our Center addresses a fundamental issue in oncology: the pervasive and ubiquitous occurrence of phenotypic heterogeneity in any cancer, at all stages of progression. The overarching goal of the Center is to produce a quantitative understanding of plasticity and dynamics of cancer cell phenotypes in a tumor, as we believe this knowledge holds the promise of major advances in treatment. Both genetic and epigenetic factors contribute to tumor heterogeneity. Furthermore, multidirectional interactions of distinct tumor cell phenotypes amongst themselves and with host cells shape the evolutionary trajectory of a tumor, including its metastatic properties. Thus, heterogeneity is a complex, multi-scale problem (from genes to molecules to cells to tissues), intrinsically unsuitable to reductionist approaches. Rather, we consider a systems-level approach to current challenges, which include: 1) identifying useful quantitative metrics of a tumor phenotypic space; 2) defining deterministic and stochastic components of heterogeneity at molecular and cellular levels; 3) deriving emergent tumor phenotype dynamics from single-cell behavior; and 4) designing effective treatment strategies based on this system-level knowledge. To tackle these challenges, we frame tumors as complex adaptive systems and apply concepts from dynamical systems theory. Furthermore, we resolved to focus a multitude of theoretical and experimental approaches on one single cancer type, Small Cell Lung Cancer (SCLC), which at the moment is a disease with dismal outcomes and no improvement in treatment approaches for over half a century.

<https://lab.vanderbilt.edu/ccsb/>

### Agenda (Central Time)

**10:00 AM** *Welcoming Remarks – Dr. Amanda Linkous*, Vanderbilt University

**10:05 AM** *Center Introduction – Dr. Vito Quaranta*, Vanderbilt University

**10:20 AM** Q&A

**10:30 AM** *Heterogeneity in Breast Cancer – Dr. Kornelia Polyak*, Dana-Farber Cancer Institute, Harvard Medical School

**10:45 AM** Q&A

**10:55 AM** *Musings on Plasticity, Cell State, Multicellular Attractors, and Context – Dr. Leonard Harris*, University of Arkansas

**11:10 AM** Q&A

**11:20 AM** – *Thinking about Plasticity from a Control Perspective* – **Dr. Arthur Lander**, University of California, Irvine

**11:35 AM** Q&A

**11:45 AM** *Damage as a Source of Cellular Plasticity in Human Tumorigenesis* – **Dr. Ken Lau**, Vanderbilt University

**12:00 PM** Q&A

**12:10 PM** *Break for Lunch*

**1:00 PM** *Towards Quantifying and Forecasting Tumor Evolution* – **Dr. Christina Curtis**, Stanford University

**1:15 PM** Q&A

**1:25 PM** *Predicting Drug Response and Synergy Using a Deep Learning Model of Human Cancer Cells* – **Dr. Trey Ideker**, University of California, San Diego

**1:40 PM** Q&A

**1:50 PM** *Quantifying Plasticity of Single Cells in Small Cell Lung Cancer* – **Sarah Groves**, Vanderbilt University

**2:05 PM** Q&A

**2:15 PM** *Break*

**2:30 PM** *New Single-cell Technologies to Dissect Reprogramming and Development* – **Dr. Samantha Morris**, Washington University School of Medicine

**2:45 PM** Q&A

**2:55 PM** *Group Discussion*

**3:40 PM** *Concluding Remarks* – **Dr. Vito Quaranta**

## Meet the Speakers



**Amanda Linkous, Ph.D.**, previously served as the Director of the Starr Foundation Cerebral Organoid Translational Core at Weill Cornell Medicine (New York, NY). She completed her postdoctoral training in the Neuro-Oncology Branch at the National Cancer Institute (Bethesda, MD). She has extensive expertise in cancer stem cell biology and the molecular signaling that promotes tumor progression. She established a novel, ex vivo 3D system to study the interactions and molecular cross-talk between tumor cells and a miniature model of the human brain—a finding that was published in *Cell Reports* and *Cancer Discovery* and featured on *CNN Pioneers* and in a special edition of *Science*. Dr. Linkous is currently the Scientific Center Manager for the NCI's Center for Cancer Systems Biology at Vanderbilt University (Nashville, TN), where she is developing similar 3D model systems to study the biology and refractory nature of small cell lung cancer.



**Vito Quaranta, M.D.**, is the Director of the Quantitative Systems Biology Center, and Professor of Biochemistry and Pharmacology at Vanderbilt University School of Medicine. Having studied cancer and the tumor microenvironment for most of his career, he implements cutting-edge interdisciplinary efforts melding mathematics, engineering, computation and biology to solve the problem of cancer invasion and metastasis. He has co-developed multiscale mathematical models that predict tumor aggressiveness based on the physical properties of extracellular matrix and adhesive properties of cancer cells. Dr. Quaranta has established single-cell techniques to quantify the rate of proliferation of single cells in response to perturbations (e.g., Fractional Proliferation), which can be applied in high-throughput fashion to measure the dynamics of cancer cell response to drugs. To explore the roots of differential cell behavior and tumor heterogeneity, Dr. Quaranta studies the dynamics of transcription factor and signaling networks that define and maintain cell identity, and ultimately contribute to forming the phenotypic landscape of the tumor microenvironment.



**Kornelia Polyak, M.D., Ph.D.**, is a Professor of Medicine at Dana-Farber Cancer Institute, Harvard Medical School and is an internationally recognized leader of the breast cancer research field. Dr. Polyak's laboratory is dedicated to the molecular analysis of human breast cancer with the goal of improving the clinical management of breast cancer patients. Her lab has devoted much effort to develop new ways to study tumors as a whole and to apply interdisciplinary approaches. Using these methods, Dr. Polyak's lab has been at the forefront of studies analyzing purified cell populations from normal and neoplastic human breast tissue at the genomic scale and *in situ* at single cell level and to apply mathematical and ecological models for the better understanding of breast tumor evolution. She has also been successful with the clinical translation of her findings including the testing of efficacy of JAK2 and BET bromodomain inhibitors for the treatment of triple-negative breast cancer in clinical trials. Dr. Polyak has received numerous awards including the Paul Marks Prize for Cancer Research in 2011, the 2012 AACR Outstanding Investigator Award for Breast Cancer Research, and the Rosalind Franklin Award in 2016. She was elected as a Fellow to the AAAS in 2019 and to the

AACR Academy of Fellows in 2020. She is also a 2015 recipient of the NCI Outstanding Investigator award and is a recipient of the 2020 Distinguished Alumna Award from Weill-Cornell.



**Leonard A. Harris, Ph.D.**, is an Assistant Professor of Biomedical Engineering at the University of Arkansas. He received his PhD in Chemical Engineering from Cornell University and did postdoctoral training in Computational & Systems Biology at the University of Pittsburgh and in Biochemistry at Vanderbilt University. He was recently awarded an NCI Transition Career Development Award to study the molecular networks underlying non-genetic tumor heterogeneity and their role in treatment avoidance and resistance. In collaboration with experimental biologists, Dr. Harris' lab builds computational models of intracellular signaling pathways and cell-cell interactions to understand the behaviors of single cells and cell populations to external perturbations, such as drug treatments. Dr. Harris maintains official roles within the NCI-funded Vanderbilt Center for Cancer Systems Biology and the Quantitative Systems Biology Center at Vanderbilt. He is also affiliated with the Interdisciplinary Program in Cell & Molecular Biology at the University of Arkansas.



**Arthur Lander, M.D., Ph.D.**, is the Donald Bren Professor of Developmental & Cell Biology at UC Irvine, where he holds joint appointments in the Departments of Biomedical Engineering and Logic & Philosophy of Science. He received his B.S. in Molecular Biophysics and Biochemistry from Yale, followed by an M.D. degree and a Ph.D. in neuroscience from the University of California, San Francisco. After postdoctoral research in neurobiology at Columbia University, he joined the faculty of the Massachusetts Institute of Technology in 1987, where he received tenure just prior to moving to UC Irvine in 1995. At UCI, Dr. Lander founded and directs the Center for Complex Biological Systems, designated a National Center for Systems Biology by the NIH, to foster interdisciplinary research, training, and outreach at the interface between biology and the physical, computational, and engineering sciences. He also co-directs UCI's U54 Cancer Systems Biology Center, and is an Associate Director of the NSF-Simons Center for Multi-scale Cell Fate Research. Dr. Lander's research has focused on the systems biology of morphogenesis and growth. Using diverse model systems, as well as mathematical and computational modeling, he has pursued questions about stem cells, pattern formation, tissue and organ size control, and the origins of syndromic and non-syndromic birth defects.



**Dr. Ken Lau** was born in Hong Kong and grew up in Toronto, Canada, where received his Bachelors of Science and his Ph.D. in Proteomics and Bioinformatics (2008) from the University of Toronto. After a joint postdoctoral fellowship at MIT and Massachusetts General Hospital, he was recruited to the Vanderbilt Epithelial Biology Center and the Department of Cell and Developmental Biology as a tenure-track in 2013, and was promoted to Associate Professor with tenure in 2019. Dr. Lau's laboratory applies data-driven systems biology approaches to understand cellular specification and function in the gut. His lab develops and utilizes single-cell technologies and data science algorithms to study cellular networks. His lab is broadly interested in the interactions between epithelium and the microbiome, cell states in stem cell and development, and the origins of cancer.



**Christina Curtis, Ph.D., M.Sc.**, is an Associate Professor and Endowed Faculty Scholar in the Departments of Medicine and Genetics at Stanford University where she leads the Cancer Computational and Systems Biology group and serves as Co-Director of the Molecular Tumor Board at the Stanford Cancer Institute. Dr. Curtis' laboratory leverages multi-omic data coupled with computational modeling and iterative experimentation in order to define the molecular determinants and dynamics of tumor progression and to identify robust biomarkers. Her research has helped to redefine the molecular map of breast cancer and led to new paradigms in understanding how human tumors progress. Dr. Curtis is the recipient of the awards from the V Foundation for Cancer Research, STOP Cancer, the AACR and is a Kavli Fellow of the National Academy of Sciences. She received the National Institutes of Health Director's Pioneer Award in 2018 and was named a Komen Scholar in 2020. Dr. Curtis is the principal investigator of a NCI Center for Cancer Targets Discovery and Development (CTD<sup>2</sup>), a Center for Excellence in Genomic Sciences (CEGS), and a Department of Defense funded biomarker-driven clinical trial, amongst other awards. She serves on the editorial boards of numerous journals and as a scientific advisor to both industry and academic institutes.



**Trey Ideker, Ph.D.** is a Professor in the Departments of Medicine, Bioengineering and Computer Science at UC San Diego, and Director or co-Director of three NIH-supported research centers: the NIGMS National Resource for Network Biology, the NCI Cancer Cell Map Initiative, and the NIMH Psychiatric Cell Map Initiative. Dr. Ideker received Bachelor's and Master's degrees from MIT in Electrical Engineering and Computer Science and his Ph.D. from the University of Washington in Molecular Biology under the supervision of Dr. Leroy Hood. Dr. Ideker is a pioneer in using genome-scale measurements to construct network models of cellular processes and disease and has founded software tools including the Cytoscape ecosystem for biological network analysis, which has been cited >13,000 times. Dr. Ideker serves on the Editorial Boards for *Cell*, *Cell Reports*, *Molecular Systems Biology*, and *PLoS Computational Biology* and is a Fellow of AAAS and AIMBE. He was named a Top 10 Innovator by *Technology Review* and was the recipient of the Overton Prize from the International Society for Computational Biology. His work has been featured in news outlets such as *The Scientist*, *San Diego Union-Tribune*, *Forbes magazine*, *NPR*, and *The New York Times*.



**Sarah Maddox Groves** received her B.S. in Physics and Mathematics from the College of William and Mary. She was accepted into the Quantitative & Chemical Biology Program at Vanderbilt University in 2016. As a predoctoral student in the laboratory of Dr. Vito Quaranta, Sarah studies the phenotypic heterogeneity of Small Cell Lung Cancer. Her current work focuses on how plasticity can be quantified for single cells using dynamical information from RNA velocity and Markov chain modeling. She includes this quantification method in a novel pipeline for characterizing SCLC phenotypes. Using a combination of single cell subtyping, transcription factor network analysis, and plasticity quantification, she hopes to find strategies for directly targeting plasticity to overcome SCLC's ubiquitous ability to acquire resistance to therapy.



**Dr. Samantha Morris, Ph.D.**, is an Assistant Professor of Genetics and Developmental Biology at Washington University in St. Louis. Her laboratory studies the mechanisms of cell reprogramming, focusing on how transcription factors drive gene expression, epigenetic, and functional changes in cell identity. To enable these studies, her group develops novel, open-source single-cell experimental and computational approaches to longitudinally record lineage and gene regulation during directed reprogramming. With her team, Dr. Morris aims to engineer clinically relevant cell populations, translating new insights in cell fate specification into better models of disease and development. With clinical collaborators, her laboratory uses their genomic technologies to dissect mechanisms of pediatric gastrointestinal disease, such as Short Gut Syndrome and

Hirschsprung's Disease, with a long-term goal of developing novel regenerative therapies. Dr. Morris trained as a Developmental Biologist at the University of Cambridge. In Magdalena Zernicka-Goetz's group, she investigated mechanisms of cell fate decision-making in the earliest stages of development. She then joined the laboratory of George Daley at Harvard Medical School, where she focused on the analysis of gene regulatory networks to dissect and engineer cell identity. In 2015, she established her independent research group. In 2017, Dr. Morris was named a Vallee Foundation Scholar. In 2019, she was awarded the St. Louis Academy of Science Innovation Award and was named an Allen Distinguished Investigator, and in 2020 a Sloan Research Fellow and a New York Stem Cell Foundation Robertson Investigator. She sits on the Board of Directors of the Society for Developmental Biology, serves on the editorial boards of *Development*, *Cell Systems*, *Developmental Cell*, and *Cell Stem Cell*, and is an Associate Editor at *Development*.