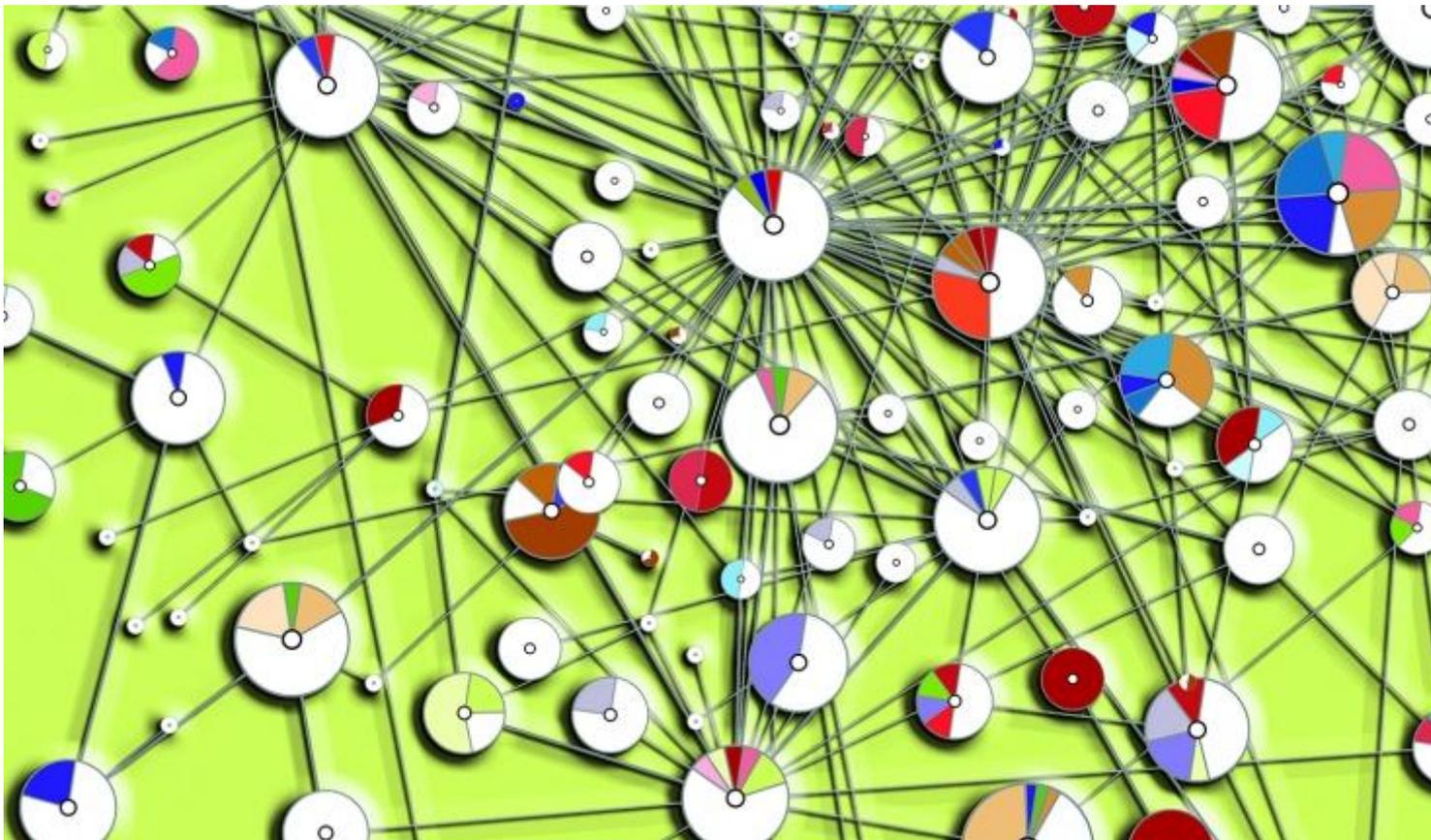


Cell mapping initiatives aim to uncover hidden pathways of disease

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Based on an article by Nicholas Weiler and Bennett McIntosh | Originally published on UCSF News [1]



Researchers believe mapping the connections between genes and proteins in many human cell types could hold the answers to understanding diseases from tuberculosis to cancer to autism. *[Illustration by Nevan Krogan Lab/QBI]*

Nevan Krogan, PhD [2], is a mapmaker, but the object of his exploration is not any newfound continent or alien world. Instead, he and his colleagues map cells. Rather than cities, towns and interstates, these maps show proteins, genes, and the shifting, convoluted network of interactions between them.

Learning to read these maps, Krogan believes, is key to the future of precision treatments for diseases from tuberculosis to Tourette disorder.

?At the cellular level, I see no distinction between being infected with HIV and having cancer. It?s just a set of proteins that are behaving badly to put the cell in a disease state,? said Krogan, who is director of the Quantitative Biosciences Institute [3] (QBI) and a professor of cellular and molecular pharmacology at UC San Francisco and a senior investigator in the academically affiliated Gladstone Institutes [4].

Krogan?s insight is that nearly all diseases are fundamentally mechanical problems at the level of our genes and the microscopic protein machines they produce and regulate. The challenge is that the vast number of genes and proteins in human cells can influence one another in complex, hard-to-predict ways.

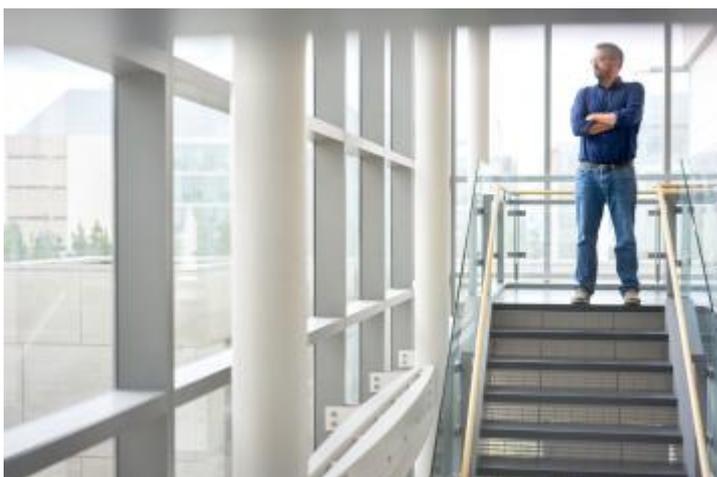
Currently, researchers tend to study the genes and proteins responsible for disease in isolation, but they are missing the big picture, Krogan believes.

Armed with complete maps of how genes and proteins interact in human cells, researchers could finally see how dozens of seemingly unrelated genes and proteins involved in a disease are in fact all part the same interconnected biological pathway. What?s more, increasing evidence suggests that the same defective biological pathways may be involved in disorders as different as autism and cancer.

Based on this unifying framework for understanding human disease, researchers at QBI, under Krogan?s leadership, along with colleagues at UC San Diego and UC Berkeley, have founded three ambitious map-making initiatives that aim to reshape three major pillars of human medicine: infectious disease, cancer and psychiatric disorders.

From the Human Genome Project to precision medicine

The drive to map cells grew out of the successes ? and the shortcomings ? of the Human Genome Project. Completed in 2003, the project sequenced every gene in our genome, but fell short of hopes that the purpose and function of each gene would become immediately clear.



Nevan Krogan, PhD, is at the forefront of mapping proteins, genes, and the network of interactions between them that may lead to diseases and disorders. *[Photo by Steve Babuljak]*

?What the Human Genome Project gave us is like the first page of an IKEA manual. It only

lists the parts," said Trey Ideker, PhD, a professor of medicine at UC San Diego and co-director with Krogan of the Cancer Cell Map Initiative [5] (CCMI). "How these genes and gene products, the proteins, are tied together is the rest of the manual — except there's about a million pages worth of it. You need to understand those pages if you're really going to understand disease."

At the time the Human Genome Project was rushing toward its finish, Krogan was a graduate student at the University of Toronto studying brewer's yeast, *Saccharomyces cerevisiae*, an easy-to-grow organism beloved by geneticists. Over the course of his PhD, Krogan developed and used techniques for systematically measuring how proteins physically and functionally interact with one another. With these techniques in hand, Krogan realized that generating maps of protein interactions could be a key first step toward writing the rest of the cell's genetic instruction manual.

"The proteins are the functional unit of the cell," said Krogan. They provide structure, pass signals, and control metabolism and development. Measuring how proteins and genes interact means gaining a direct view of the current state of a cell. "We now have powerful mass spectrometry technology and CRISPR/Cas9-based genetic tools to generate maps of how these proteins interact in mammalian cells."

Krogan came to UCSF in 2006 as a Sandler Faculty Fellow, intent on using his new techniques to map out how HIV infection changes how proteins interact within immune cells, work which was carried out in the context of the NIH-funded HIV Accessory and Regulatory Complexes (HARC) Center [6], which Krogan leads. Cancer was an obvious next target for cell mapping, characterized as it is by the systematic failure of genetic pathways that control cells' growth and death. Cancer's mutations also vary over time, often becoming resistant to initial therapies, so being able to find the best possible treatment the first time would be a boon to physicians.

Opening the black box of psychiatric disorders

Most recently, Krogan has teamed up with Jeremy Willsey, PhD [7], an assistant professor with the UCSF Institute for Neurodegenerative Diseases [8], and Matthew W. State, MD, PhD [9], professor and chair of psychiatry at UCSF, to found the Psychiatric Cell Map Initiative [10] (PCMI).

The PCMI immediately faces several challenges in mapping gene pathways in psychiatric disorders — these disorders are numerous and diverse; they can develop over many years or even decades; and they involve the human brain, which is arguably the most complex object in the universe.

"One of the challenges in psychiatric disorders is that there's little agreement over what the underlying pathological mechanisms are, which complicates diagnosis and development of effective therapeutics," Willsey said. "Protein and genetic interaction mapping could open that black box to find how genetic risk factors actually cause psychiatric disorders, potentially revealing therapeutic targets."

Willsey and State, both members of the UCSF Weill Institute for Neurosciences [11], have already made rapid progress unraveling the genetic basis of psychiatric disorders including autism and Tourette Disorder by looking for extremely rare mutations presented in affected children but not unaffected relatives. These mutated genes act as a starting point from which

to explore what other related cell systems and pathways may play a role in the disease.

“Having these precise maps of how these genes and proteins fit into larger cellular networks allows us to make predictions about which pathways treatments should target, and then test these predictions in a targeted manner in model systems,” Willsey said.



UCSF researchers (from left) Jeremy Willsey, PhD; Matthew State, MD, PhD; and Nevan Krogan, PhD, teamed up to found the Psychiatric Cell Map Initiative, which aims to map gene pathways in psychiatric disorders. *[Photo by Gina Nguyen]*

Like the other initiatives, PCMI researchers benefit from the mapping research in other labs across all three mapping initiatives.

“Seeing overlap between disorders will help in understanding why a given mutation might lead to schizophrenia in one case or autism in another,” Willsey said. “We already see that a lot of autism genes are cancer genes. We don’t know what that means, but the more genes we map the better we can understand that overlap.”

For Ideker, the overlap is the point of the initiatives. His lab produces computer models to predict how cells will respond to disruptions — from cancer-causing mutations to viral attacks. For these models to make sense of the data, they require ever more complex contextual data about how different cellular components are interrelated.

From genes to protein complexes to cell-spanning signaling networks, the layers of data Ideker feeds the models help them predict how cells will react more and more accurately. “We want to capture all the cellular interactions that we’re finding in these initiatives, and everything else that’s out there,” he said. “We’ll model the entire cell, at every level.”

Recently the three cell mapping initiatives held their first annual Cell Mapping Symposium, featuring scientists from all three initiatives and hundreds of guests, who overflowed the lecture hall at the Gladstone Institutes and spilled over into satellite rooms. Krogan was ecstatic at the response.

“Ultimately this whole project is about making connections — not only making connections between genes and proteins, but also between people,” he said. “We’re learning we’re all more connected than we thought we were.”

About UCSF Psychiatry

The UCSF Department of Psychiatry ^[12] and the Langley Porter Psychiatric Institute are among the nation's foremost resources in the fields of child, adolescent, adult, and geriatric mental health. Together they constitute one of the largest departments in the UCSF School of Medicine and the UCSF Weill Institute for Neurosciences, with a mission focused on research (basic, translational, clinical), teaching, patient care and public service.

UCSF Psychiatry conducts its clinical, educational and research efforts at a variety of locations in Northern California, including UCSF campuses at Parnassus Heights, Mission Bay and Laurel Heights, UCSF Medical Center, UCSF Benioff Children's Hospitals, Zuckerberg San Francisco General Hospital and Trauma Center, the San Francisco VA Health Care System and UCSF Fresno.

About the UCSF Weill Institute for Neurosciences

The UCSF Weill Institute for Neurosciences ^[11], established by the extraordinary generosity of Joan and Sanford I. "Sandy" Weill, brings together world-class researchers with top-ranked physicians to solve some of the most complex challenges in the human brain.

The UCSF Weill Institute leverages UCSF's unrivaled bench-to-bedside excellence in the neurosciences. It unites three UCSF departments—Neurology, Psychiatry, and Neurological Surgery—that are highly esteemed for both patient care and research, as well as the Neuroscience Graduate Program, a cross-disciplinary alliance of nearly 100 UCSF faculty members from 15 basic-science departments, as well as the UCSF Institute for Neurodegenerative Diseases, a multidisciplinary research center focused on finding effective treatments for Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and other neurodegenerative disorders.

About UCSF

UC San Francisco (UCSF) ^[13] is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. It includes top-ranked graduate schools of dentistry, medicine, nursing and pharmacy; a graduate division with nationally renowned programs in basic, biomedical, translational and population sciences; and a preeminent biomedical research enterprise. It also includes UCSF Health, which comprises top-ranked hospitals — UCSF Medical Center ^[14] and UCSF Benioff Children's Hospitals in San Francisco ^[15] and Oakland ^[16] — and other partner and affiliated hospitals and healthcare providers throughout the Bay Area.

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