GENETIC NETWORKS

Focuses on mapping the biological networks that translate genomes into complex traits and on improving our fundamental understanding of biological systems to enable new treatments and preventive measures.

This year, the program was renewed for a two-year term, and program fellows published a number of influential discoveries. From the first full genetic interaction map of an organism, to the largest autism genetic sequencing project in the world available via open science, to new machine-learning methods and complementation assays for identifying human disease variants and genetic disorders, fellows have continued to develop our understanding of genetic networks and genotype-phenotype relationships. Transformative technologies — including rapid sequencing of whole genomes, CRISPR-Cas9 and machine learning — are contributing to the discovery of new breakthroughs in genetics research.

To foster new partnerships and collaborations with researchers and organizations abroad, both program meetings this year took place in international locations. The December 2016 meeting in Santa Cruz focused on recent progress in functionally annotating and interpreting variation in the human genome and highlighted new technological advances. Ten guest researchers from California institutes, including Stanford, University of California, Berkeley, University of California, San Francisco, University of California, Santa Cruz, and University of California, Los Angeles, were in attendance, along with others from around the United States. The meeting also included a Personalized Medicine Workshop with representatives from Helix and Invitae, two innovative genetic testing companies in the San Francisco Bay area.

The April 2017 meeting in Tokyo began with the workshop From Genetic Networks to a Cellular Wiring Diagram, sponsored by the University of Tokyo and RIKEN. Presentations from Japanese and international researchers alike focused on mapping genetic interactions, new computational methods and artificial intelligence technologies applied to analyzing genetic interactions, gene deletion and its effect on phenotypes and growth in organisms (specifically yeast and nematodes), and genetic factors and variants that affect human disease (including autism spectrum disorder). The program meeting that followed included presentations highlighting recent progress toward expanding the spectrum of genetic interactions, as well as the effect and influence of the environment on these interactions.

RESEARCH HIGHLIGHTS

Program members, together with a team of international researchers, published the first complete genetic interaction map of any organism. Fellows **Olga Troyanskaya** (Princeton University), **Brenda Andrews** (University of Toronto), **Philip Hieter** (University of British Columbia), **Chad Myers** (University of Minnesota) and **Charlie Boone** (University of Toronto) participated in a massive international study that identified almost one million pairwise interactions between about 6,000 genes (more than 90 per cent of all genes) in the yeast *Saccharomyces cerevisiae*. The results revealed a network of hierarchical relationships, with essential genes acting as network hubs. The global yeast genetic network should provide an important atlas for mapping analogous networks in more complex systems.

- Costanzo M et al. 2016. A global genetic interaction network maps a wiring diagram of cellular function. Science. 353(6306): aaf1420.

Identifying which coding variants disrupt the function of disease-associated genes remains an ongoing and pressing challenge. Program members **Fritz Roth**, **Charlie Boone** and **Brenda Andrews** (all University of Toronto) recently developed yeast-based complementation assays for about 60 different human disease genes. Despite a billion years of evolutionary divergence between yeast and human cells, the assays were able to identify disease-causing variants more accurately than any current computational methods.

- Sun S et al. 2016. An extended set of yeast-based functional assays accurately identifies human disease mutations. Genome Res. 26: 670-680.

AT A GLANCE

FOUNDED: 2005

MOST RECENT RENEWAL: 2017, for 2 years

PROGRAM DIRECTORS: Charles Boone, University of Toronto, and Frederick P. Roth, University of Toronto

FELLOWS, ADVISORS AND CIFAR AZRIELI GLOBAL SCHOLARS: 17

INSTITUTIONS REPRESENTED: 9, in 2 countries

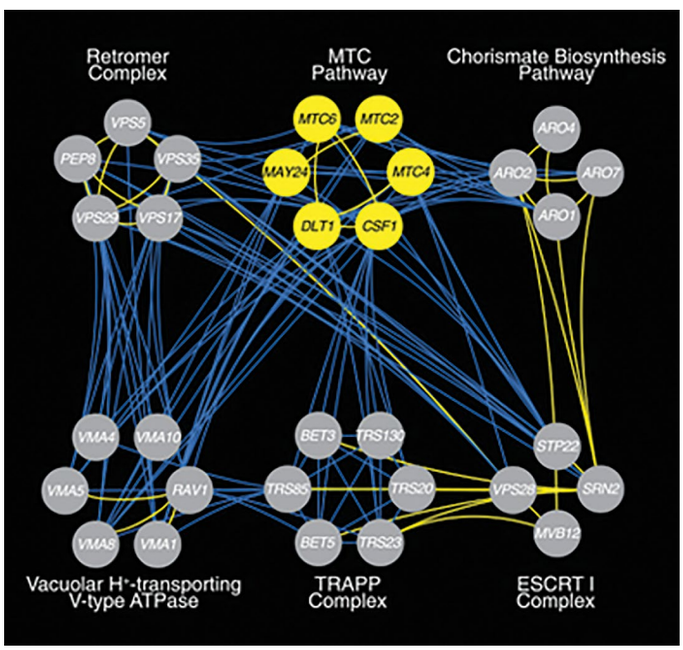
FIELDS AND SUBFIELDS REPRESENTED: genetics; biochemistry and molecular biology; computational biology and bioinformatics; cell, evolutionary and systems biology; pathology; immunology; biotechnology

MEETINGS: 2; in Santa Cruz, USA, and Tokyo, Japan

RELEVANT KNOWLEDGE USERS: human clinical geneticists; policy makers interested in the impact of genomic technologies and personalized genomic medicine; organizations managing patient medical records

TO LEARN MORE: www.cifar.ca/research/genetic-networks/

Tracing autism susceptibility genes and understanding the fundamental genetic factors underlying autism are key to developing precision medicine for these disorders. Senior Fellow **Stephen Scherer** (The Hospital for Sick Children) and a large international team of researchers recently undertook the MSSNG project, where they sequenced 5,200 samples from families with autism spectrum disorder (ASD). This is the largest such project in the world that is available via open science. The data will help subcategorize different phenotypes of ASD (i.e., the type of autism an individual has) in the hopes of helping individuals develop precision medical management plans. Computational work was also undertaken by the research group of Senior Fellow **Olga Troyanskaya** (Princeton University) to define a genome-wide prediction of autism risk genes. By using machine learning to analyze a human brain-specific gene network, the researchers were able to show that the large set of genes converges on a smaller number of key pathways that function within specific developmental stages of the brain.



An illustration of some of the genetic interactions important to cellular function uncovered by CIFAR Fellows Olga Troyanskaya, Brenda Andrews, Philip Hieter, Chad Myers and Charlie Boone. (Illustration courtesy of *Science*).

- Yuen RKC et al. 2017. Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder. Nat Neurosci. 20: 602-611.
- Krishnan A et al. 2016. Genome-wide prediction and functional characterization of the genetic basis of autism spectrum disorder. Nat Neurosci. 19: 1454-1462.

Other Notable Publications and Outputs

- van Leeuwen J, Myers CL, Andrews BJ, Roth FP, Boone C et al. 2016. Exploring genetic suppression interactions on a global scale. Science. 354(6312): aag0839.
- Payen C, Dunham MJ et al. 2016. High-throughput identification of adaptive mutations in experimentally evolved yeast populations. PLOS Genet. 12: e1006339.
- Hart T, Myers CL, Andrews B, Boone C, Moffat J et al. 2017. Evaluation and design of genome-wide GRISPR/SpCas9 knockout screens. In: BiorXiv. DOI: 10.1101/117341.

IDEAS EXCHANGE

The program hosted a workshop in Santa Cruz, California, called Genetic Networks in Human Medicine. The workshop brought together leaders in genomic medicine from academia, industry and the health care sector to explore the challenges and opportunities in dissecting the genotype/phenotype connection and how an understanding of genetic interactions could contribute to the field of personalized medicine. Based on the workshop, the program will develop a larger-scale conference that will take place in Toronto next year.

GLOBAL ACADEMY

Graduate students and postdoctoral fellows were integrated into program meetings by fellows. Trainees were also invited to present posters or talks. The program will appoint its first CIFAR Azrieli Global Scholars in Fall 2017.