New Center to map hidden pathways of critical cellular processes

Professor Andrew Emili, a leader in systems biology and molecular interaction networks recently recruited to Boston University, directs a state-of-the-art research laboratory and the new Center for Network Systems Biology. This multi-disciplinary research Center aims to map the myriad of protein interactions present inside healthy and diseased cells and tissues that have fundamental mechanistic significance, by developing and deploying innovative 'functional proteomic' methods.

Human health and development depend on an extensive network of dynamic physical and functional interactions between the many thousands of proteins encoded by our genome, but the identity and composition of most of the multiprotein assemblies that support critical cellular processes are still largely unknown. In normal cells and tissues, these macromolecular networks act in harmony, whereas this balance is disrupted in disease states, leading to pathology.

Yet despite immense progress in genomic sequencing over the last decade, it remains unclear which proteins associate together normally in different human cells and tissues during development, or which subnetworks go awry in common disorders like cancer, neurodegeneration or cardiovascular disease.

Professor Emili has developed and applied innovative proteomics methods to identify hundreds of previously unknown protein complexes in eukaryote model organisms (whose cells contain a nucleus) as well as in simpler prokaryotic bacteria. In doing so he and his collaborators have uncovered previously unknown physical connections that form essential links between proteins critical for cell viability and growth, giving a much clearer picture of how these vital macromolecular assemblies perform the higher order functions essential to multicellular life.

NEW INSIGHTS REQUIRE NEW TECHNIQUES

The new Center (or CNSB) will utilise the latest technology in protein isolation and analysis to achieve their goal. In recent Cell and Nature publications, Professor Emili and colleagues described new approaches they have developed in which traditional biochemical fractionation is combined with quantitative precision mass spectrometry and computational 'machine learning' to comprehensively identify which animal proteins associate stably together to perform essential functions such as DNA replication and RNA transcription.

Tandem mass spectrometry is a technique for ionising large molecules with minimal fragmentation. In this method, the purified protein samples are digested with a protease, typically trypsin, and then electrosprayed into a high-performance mass spectrometer, where their relative mass is determined using an ultra-sensitive detector. These data are then analysed to identify the exact chemical composition of each of the many thousands of peptides present in a mixture, using state-of-the-art computational analysis pipeline, from which the team are able to infer the underlying molecular associations between the protein species that are observed.

This iterative process enables the researchers to identify a wealth of vital associations between many of the most highly conserved proteins existing across virtually all animal species. The most conserved proteins were found to be the most well connected. This core interactome is enriched for macromolecular assemblies critical to normal multi-cellular development and human diseases, like cancer, displaying uncontrolled growth. This paints a picture of the vital importance of these network relationships to the function of an individual protein, to an entire cell, and to life in general.

The CNSB is making maps which can further the understanding of protein networks across species”

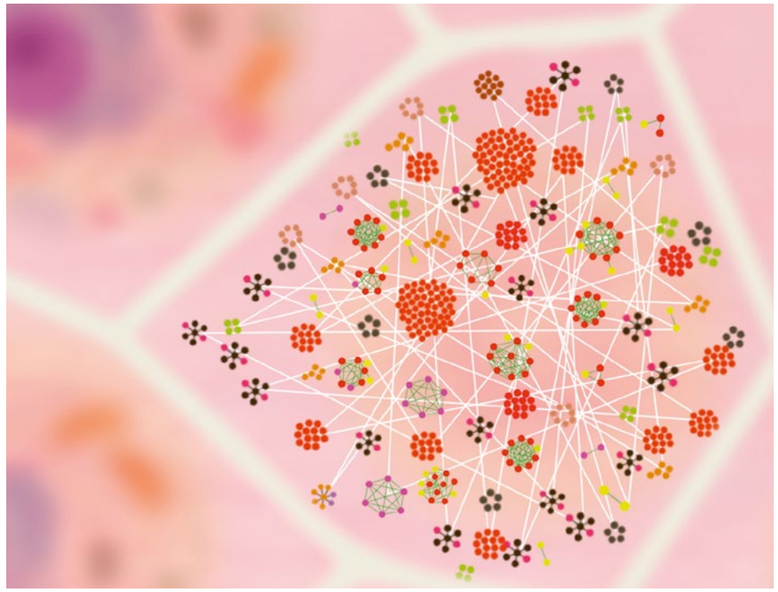
CONNECTIONS ARE KEY

Professor Emili began this research programme whilst at the University of Toronto, where he was a founding member of the Donnelly Centre for Cellular and Biomolecular Research. Drawing on his experiences as a Damon Runyon/Walter Winchell Research Fellow with the Nobel Laureate Leland Hartwell at the Fred Hutchison Cancer Research Center in Seattle, and his training in protein mass spectrometry with John Yates III, a pioneer in the field, at the University of Washington, Professor Emili has now created a laboratory at Boston University that will continue to build on his groups innovative, high impact track record in cutting-edge proteomics analyses.

NETWORKS AND HUMAN HEALTH

The long-term goal of this research is to understand the significance of multi-protein complexes for the correct functioning of human cellular processes, and how these networks go awry in pathological states such as diabetes, heart disease, cancer and neurodegeneration. To this end, the CNSB plans to analyse thousands of biochemical fractions from human, mouse and other animal specimens. By applying a global integrative profiling approach that combines high resolution fractionation, precision mass spectrometry and the latest developments in computational filtering, such as deep learning, the team aims to identify those protein complexes present in different cell types and tissues that have eluded detection before.

In creating high-quality interaction networks from these data, the team predicts there will be a strong overlap between these maps and other existing sources of diverse functional attributes, such as memberships in biochemical signalling pathways, roles in metabolism, and genomic variants and single cell mRNA expression datasets, helping to bridge these fields together. The main difference is that the Center will define specific functions to previously unreported physical entities. This leads Professor Emili to conclude that, "To our knowledge, these resources will generate the largest experimentally derived catalogues to date of human protein complexes beyond standard transformed cell culture systems. By measuring protein interaction networks in a more pathophysiologically relevant setting using a standardised workflow, we will build the first reliable draft reference maps of the basic physical wiring diagram present in each of the many different human cell types and tissues."



Protein networks are central to all cellular systems, and are essential for virtually every biochemical process. Therefore, knowledge of the global architecture and dynamic regulation of protein networks is critical for understanding the mechanistic basis of human biology, development and disease. Using innovating methods and cutting-edge technology, the CNSB plans to discover this fundamental information in an unprecedented manner.

The importance of this resource should not be underestimated. Many diseases relate to the loss or alteration of one or more specific protein complexes, either through congenital or acquired mutations or via environmental perturbations. Identifying how the subunits of these affected complexes interact with each other and with other protein assemblies provides valuable insight into the course of the disease, and that of related pathologies, offering potential targets for new diagnostics and therapies.

SOCIAL NETWORKING FOR PROTEINS

Following this research, each dataset generated by the Center will be made publicly accessible to other researchers via a dedicated web portal, allowing multidisciplinary research to flourish based on the findings of Professor Emili, the CNSB's rapidly expanding team of associates, and other researchers associated with the Center.

This highly collaborative, multi-disciplinary approach is key to how Professor Emili and the CNSB will operate, forging new links with motivated skilled researchers across both BU campuses, the greater Boston area, and the world.

By harnessing the great potential of this team and their cutting-edge techniques to identify previously unreported molecular relationships, Professor Emili and the CNSB's talented researchers will make global maps which can further mechanistic understanding of cellular systems as they relate to human cell biology and development. By exposing the underlying networks of connections, which are often hidden from view but conserved across vast evolutionary timescales, they will shed light on the fundamental principles governing essential cellular processes. As the Center for Network Systems Biology drives forward with its ground-breaking work at Boston University, the road ahead looks bright, open and inviting.

To our knowledge, this resource represents the largest experimentally derived catalogue to date"

Q&A

What do you hope the new Center for Network Systems Biology will achieve?

Physical protein-protein interactions are instrumental to all biological processes, and by extension, to human health, development and disease. While advances in genomics are providing valuable information about gene function and their links to pathology, a key challenge is to understand how genetically-encoded proteins actually work together inside cells and how their interactions become perturbed in disease. My research vision for the Center is to characterise the protein interaction networks and macromolecular complexes present in the various cells and tissues of the human body in different pathophysiological contexts.

How does your work to date feed into that goal?

While mutations and pathophysiological stresses are understood to affect human protein interactions, we still do not know which proteins work together normally in the various different cell types and tissues of our body, nor do we know which interactions are altered in many major illnesses such as cancer, neurological impairments and cardiovascular disorders like heart failure – knowledge critical for developing more effective diagnostics and treatments. Through our many discoveries, the Center will generate valuable data resources and tools, important new biomedical findings, and promising candidate targets for new diagnostics and therapeutics relevant to the broader biomedical research community.

What have you learnt so far about the importance of interaction networks?

As a pioneer in network systems biology, my research group has reported thousands of protein interactions for classical model organisms like yeast, fly and worm, including the largest map of protein complexes conserved across animals. Our work addresses fundamental biological questions: How are protein interactions normally organised inside different cells and organs? What are the general features and properties of these networks? What are the regulatory principles that guide their dynamic formation and disruption? We have only just begun to scratch the surface into these important problems, and are now increasingly turning our attention to humans with all the complexity and diversity that entails, so there remains much to be discovered.

What are the impacts for human health and disease?

Networks are central to human health and disease at all levels. Why do some patients with the same disease have a more complicated course and others a milder outcome? Which networks are disrupted in common diseases like neurodegeneration, heart disease or cancer? How can we exploit this knowledge to improve human health? Our Center aims to break new ground by documenting the protein interaction networks of sick cells and tissues – which has never truly been done before. Our overarching goal is to identify macromolecules critically important to human pathobiology, with ramifications for the early diagnosis and treatment of human disease, with the long-term goal of translating this knowledge into more effective 'theranostics'.

How do you envisage the Center working with other researchers across disciplines?

Our work is inter-disciplinary, itegrating technology from various fields (e.g. analytical chemistry, medicine, biochemistry, computation) and we have established the only platform currently capable of directly mapping native protein assemblies in human tissues. By working closely with renowned biology, clinical and industry partners, the Center will generate molecular 'connectivity' diagrams of unprecedented quality, scope and utility. By charting new directions at the forefront of functional proteomics, we will push the boundaries in network systems biology. By translating our findings into high-impact papers, resources and tools, the Center will foster skilled trainees who will become leaders in biomedical research.

Detail

RESEARCH OBJECTIVES

The CNSB uses bioinformatic technologies to generate ground-breaking molecular 'connectivity' maps.

FUNDING

Multiple funding sources in Canada and the US have contributed to the success of the Emili lab and the CNSB.

COLLABORATORS

Researchers across North America, Europe and Asia.

BIO

The founding director of the CNSB, Professor Andrew Emili, a leader in systems biology and molecular interaction networks, was recruited to Boston University in 2017, through the Provost's Senior Faculty Hiring Initiative, where he directs a state-of-the-art research laboratory and the new Center for Network Systems Biology (or CNSB). He is dually-appointed in the Departments of Biochemistry and Biology where he mentors skilled and motivated young researchers, such as the graduate student Ben Blum (left) engaged in ambitious forward looking discovery projects probing the fundamental molecular basis of human health and disease.

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