The Bridge@USC

Understand the Human Body,
Improve the Human Condition
“The Bridge@USC draws on our university’s most stellar faculty members to revolutionize how we detect and treat human disease. I have no doubt that with this approach we will make Southern California an international hub of biomedical research.”

C. L. MAX NIKIAS PRESIDENT
University of Southern California

Great Minds, One Picture

To address “impossible” health challenges that have long eluded conventional approaches, the University of Southern California’s Dornsife College of Letters, Arts and Sciences has established The Bridge@USC. This initiative unites the best minds in chemistry, biology, medicine, mathematics, physics, engineering, and nanosciences — as well as experts in such areas as animation and cinematography — to build the first atomic resolution structure of man. Development of this dynamic model will accelerate the creation and implementation of novel therapies and cures for a host of intractable diseases and conditions.
A New Approach

Over the past century, the sciences, engineering and medicine have become progressively more specialized, each diverging into an array of sub-disciplines. While this divergent reductionist approach has led to significant increases in understanding human health, it has also resulted in silos of expertise that run deep and often remain isolated and inadequate in addressing society’s most urgent health problems.

It is time to disrupt conventional thinking — converging knowledge across disciplines to achieve radical progress in improving the human condition. The time has come for The Bridge@USC.

Building upon the university’s Convergent Bioscience Initiative, The Bridge@USC unites eminent professors across the entire university, including the USC Dornsife College of Letters, Arts and Sciences, the USC Viterbi School of Engineering and the Keck School of Medicine of USC, as well as animators and cinematographers in the USC School of Cinematic Arts and the USC Institute for Creative Technologies, and technology transfer experts in the USC Stevens Center for Innovation.

“...The Bridge@USC brings together scientists, engineers, clinicians and artists who are excited to assemble a functional atomic resolution model of the complete human body. Independently we can all do nice work, but together we can accomplish something truly impactful.”

RAYMOND C. STEVENS PROVOST PROFESSOR OF BIOLOGICAL SCIENCES AND CHEMISTRY AND DIRECTOR OF THE BRIDGE@USC
Leonardo da Vinci’s drawing of the Vitruvian man remains an icon of the Renaissance period. In a single sketch, he combined the mathematical, architectural, religious, philosophical and artistic principles of his time to provide us with a full map of the human body. “Man,” he wrote, “is the model of the world.”

More than 500 years later, we remain fascinated by the complexities of the human body. We have categorized most of the elements of man at the genetic, molecular and cellular levels, but have yet to integrate the different scales of data together. Until the gaps in these data are bridged, the most effective and efficient ways to develop new drugs and understand diseases will continue to elude us.

Google, for example, has embarked on a quest to create a fuller picture of the human brain hoping to pinpoint how diseases might be prevented rather than merely treated. While theirs is a top-down approach, we aim to do the reverse.

Working up from the molecule to the cell to the entire human body — The Bridge@USC will advance our understanding not only of precisely how biological systems function in both healthy and diseased states, but also how to manipulate those functions to dramatically improve human health.

By integrating and synthesizing such new knowledge holistically — across disciplines in the sciences, engineering, medicine and the arts, at multiple size and time scales — the institute will assemble a virtual model of the human body that can be used to create and explore new therapeutics and biomarkers.

This atomic resolution model of man will allow for the virtual test of drug candidates thereby dramatically increasing patient success rates and lowering drug development costs by avoiding failed clinical trials. The Bridge@USC will further the development of personalized treatment programs and medical devices for specific diseases affecting the brain such as autism, Alzheimer’s, Parkinson’s and addiction, and the rest of the body including cancers, and ensure that these breakthroughs reach the marketplace as quickly as possible to benefit patients everywhere.

The Bridge@USC’s core mission is to provide a nexus through which USC’s internationally renowned scientists, engineers and visual artists join forces with like-minded, trailblazing partners around the world in taking collective responsibility for transforming human health and integrating their translational research efforts at every step.

As a cornerstone of the new 190,000-square-foot USC Michelson Center for Convergent Bioscience, The Bridge@USC will provide a bold collaborative framework that underscores the building’s visionary design by further enabling affiliated faculty members to forge new pathways of discovery, to increase the rate and reduce the cost of innovation, and to cultivate new generations of researchers.

Los Angeles should become to medical research what Silicon Valley is to information technology. We owe it to the world. We owe it to L.A. We need to invest in this.”

GARY K. MICHELSON PHILANTHROPIST, RETIRED ORTHOPAEDIC SPINAL SURGEON AND USC DONOR

LEVEL III: BODY
Five orders of magnitude larger than a cell, the human body is one to two meters in height. When cells of the same type such as muscle cells congregate and perform the same function, a tissue is formed. Two or more kinds of tissues then work together to make an organ. The human body’s 78 organs each perform a specialized physiological function.

LEVEL II: CELLS
Five orders of magnitude larger than the chemical bond, each of the human body’s 70 trillion cells serve as its factories and boardrooms that manufacture and control all basic life processes.

LEVEL I: MOLECULES
The adult human body is made up of around 7 octillion atoms, with atomic bonds spaced 10⁻¹⁰ meters apart. These atoms combine to make different types of molecules that in turn form the body’s working parts, such as cells, as well as substances produced by some of those parts, such as hormones.
Level I: Molecules

Molecules — including proteins, nucleic acids, water, lipids, hormones, and carbohydrates — are formed when two or more atoms join together chemically. As the body’s fundamental elements, proteins and nucleic acids in particular are often the targets of medicines that treat human diseases. Raymond Stevens and Vadim Cherezov image molecules, particularly the proteins in the lipid membrane involved in cellular communication, to see how individual atoms bind with metabolites or drug candidates. Vsevolod “Seva” Katritch then uses computer modeling to infuse potential drug treatments into those protein-binding sites that Stevens and Cherezov have observed. Ultimately, all three collaborate with chemists to synthesize new compounds that most effectively target specific diseases.

Galloping Ahead

In 1886, Eadweard Muybridge and his experiments with motion photography proved that contrary to popular belief all four of a horse’s hooves do leave the ground at once when it gallops. More than a century later, Vadim Cherezov, associate director of The Bridge@USC and professor of chemistry, is applying a similar approach to see molecules in motion and observe changes in proteins as they occur. His work sheds light on the structure, stability and function of biological membranes. He has developed numerous novel instruments and technologies to enhance the biophysical characterization and crystallization of membrane proteins fostering a revolution in structural studies of G protein-coupled receptors (GPCRs), whose malfunctions often result in conditions such as Alzheimer’s, Parkinson’s, diabetes, cancer and heart disease. With nearly 1,000 members, GPCRs constitute the largest protein family in the human genome — and a key avenue to medical progress. These receptors are responsible for 80 percent of cell signaling, and some 40 percent of all pharmaceuticals act by binding to GPCRs. The therapeutic potential for patients with immune and metabolic diseases is vast, but Stevens expects the immediate impact of this work to be in diabetes, heart disease, cancer, embryonic development, and neurodegenerative diseases such as Alzheimer’s and Parkinson’s.

Modeling Treatment

Vsevolod “Seva” Katritch, assistant professor of biological sciences, develops and applies computational tools to study key biological phenomena, from DNA topology and chromatin folding to the molecular basis of drug action. He uses structural bioinformatics and integrative molecular modeling approaches to decipher the intricate mechanisms of G protein-coupled receptor (GPCR) signaling. This allows him to identify new venues to precisely modulate GPCRs by ions and small molecules leading to better medical treatments.

Signaling Medical Progress

The Bridge@USC Director and Provost Professor Raymond Stevens, Ph.D. ’88 is best known for his research in human cell signaling and for determining the structure of proteins. After a 20-year quest, Stevens, professor Vadim Cherezov and their research teams unlocked the biomedical potential of 6 protein-coupled receptors (GPCRs) by determining their structure. GPCRs serve as the cell’s gatekeepers and messengers, receiving and sending information in the form of light energy, peptides, fats, sugars, and proteins. Their signals mediate practically every essential physiological process, from immune system function to taste and smell to cognition to heartbeat.

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Led by The Bridge USCD Director Raymond Stevens (left), USC has joined with academic and industry leaders across the Pacific Rim to create a nonprofit organization that will generate high-resolution images of G protein-coupled receptors (GPCRs). Professors Vadim Cherezov (center) and Vsevolod “Seva” Katritch (right) will be among those contributing their expertise to help the consortium define the structures of at least 200 GPCRs. This will allow scientists to design pharmaceuticals that more effectively target diabetes, cancer, and mental disorders.
Level II: Cells

The building blocks of all living organisms, cells are composed of billions of molecules. Each cell acts as a “house” that organizes the molecules’ functions and determines how these will communicate with other cells to create tissues, organs and whole organisms. Therefore, when something goes awry on the molecular level, this ultimately affects the cells, which can impact the tissue, organs and whole body. Scott Fraser is a leading expert on imaging the fine details from the cellular level all the way to organs. He teams up with computational biologists to create models of how cellular structures are built and clinicians who rely on his imaging technology to deliver the best possible care for patients.

Imaging the Future

Provost Professor of Biological Sciences and Biomedical Engineering Scott Fraser collaborates with biologists, engineers and chemists to build new technologies for imaging biological structures and function. These state-of-the-art devices allow researchers to explore, in real time, the inner workings of such complex events as embryonic development and disease progression. By better observing the basic behaviors of cells, Fraser strives to improve regenerative, preventive and personalized medicine.

For example, he constructs microscopes that allow scientists to watch as cells interact with one another to form the heart muscle and valves. Understanding this process — how cells give off signals, respond and collaborate to build an embryonic heart — may offer keys to rebuilding heart valves in vitro.

Fraser and his research team have pioneered a technique that could enable a clinician to look into a patient’s undilated eye and identify the onset of diseases such as diabetic retinopathy and macular degeneration at an early stage. This way treatments can be administered when most effective — before the patient notices any symptoms or vision loss.

Fraser is also a leader in creating ultra-high-resolution magnetic resonance imaging (MRI) technologies that can visualize changes in the brain at the onset of diseases such as Alzheimer’s, Parkinson’s and multiple sclerosis. He and his collaborators use their imaging devices not only to detect the disease and monitor its process, but also to observe changes in cells that result from therapeutic agents. This provides new tools for designing the most effective treatment for each individual patient.
As director of the Translational Imaging Center at USC, Scott Fraser (left) helps fellow faculty members such as USC Dornsife Dean Steve Kay (right) accelerate their research by providing access to technologies for the intravital imaging of cells and cellular processes. In addition, USC is home to the Rare Cell Biology Center and the Structural Proteomics Center.
Level III: Body

The human body is made up of 78 organs and networks including the brain, heart, lungs and gastrointestinal tract. Steve Kay is investigating the human body’s circadian rhythms and how the body’s timing of the day/night cycle can influence the onset of diabetes and obesity. Peter Kuhn and James Hicks are examining the circulatory system and detecting how molecules move around the entire body to detect unwanted molecules or cells that might cause diseases such as cancer.

Resetting Our Biological Clocks

Scientists had long suspected that diabetes and obesity might be connected to problems with the body’s circadian rhythm, or biological clock. But it took a team headed by USC Dornsife Dean Steve Kay to discover the first biochemical link between circadian rhythm and diabetes. The researchers found that a key protein, cryptochrome — which regulates the biological clocks of plants, insects and mammals — also regulates glucose production in the liver. They observed that altering the levels of this protein could improve the health of diabetic mice. Like mice and other animals, humans have evolved complex biochemical mechanisms to keep a steady supply of glucose flowing to the brain at night, when we’re not eating or active.

More recently, Kay and his team discovered a much smaller molecule, KL001, which controls the intricate molecular cogs or timekeeping mechanisms of cryptochrome in a way that can repress the production of glucose. This finding opens potentially groundbreaking avenues for the development of drugs to treat diabetes and other metabolic disorders. The serendipitous discovery occurred during a parallel effort in Kay’s laboratory to identify molecules that lengthen the biological clock.

The team’s next step is to understand how KL001, and similar molecules that affect cryptochrome, function in living systems. The scientists plan to probe how such compounds affect other processes besides the liver that may tie the biological clock further to metabolic diseases. Their work holds promise not only for diabetes, but also for diseases such as asthma.

Finding a Needle in a Haystack

How cancerous cells gain the ability to exit tumors and populate distant organs is a fascinating yet poorly understood biological question of immense clinical importance. Working with oncologists, a mathematicians modeling group and single-cell genomics specialists including Professor (Research) of Biological Sciences James Hicks, The Bridge@USC Associate Director and Dean’s Professor of Biological Sciences Peter Kuhn set out to find that “needle in a haystack.” Their subsequent method for detecting cancer cells with just a blood sample has yielded a minimally invasive, inexpensive test that differentiates circulating tumor cells (CTCs) — which break away from the primary tumor to metastasize to other parts of the body — from ordinary blood cells using a digital microscope and image-processing algorithm. This next-generation, high-definition advance is expected to achieve results comparable to surgical biopsies without having to submit patients to the operating table. It also significantly enhances doctors’ abilities to detect, monitor and predict cancer progression at an earlier, more treatable stage.
Working with the Breast Cancer Research Foundation, professors Peter Kuhn (left) and James Hicks (right) use technology developed in their laboratories to compare information from DNA in the blood with information obtained from circulating tumor cells. This enables them to identify clinically useful biomarkers and to advance the use of the non-invasive fluid biopsy, which ultimately helps inform treatment decisions.
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Facilitating Progress

Pioneering facilities and programs will be paramount to accomplishing The Bridge@USC’s mission: uniting faculty and students across disciplines to build a virtual model of the human body at the atomic scale that can be used to test possible cures and treatments for a wide range of diseases and conditions.

The Bridge@USC will be located in the new 190,000-square-foot USC Michelson Center for Convergent Bioscience, which will support up to 24 principal investigators with laboratories employing hundreds of researchers and students.

A bold new collaboration between the USC Dornsife College of Letters, Arts and Sciences and the USC Viterbi School of Engineering, the center will feature state-of-the-art, flexible labs that accommodate the spectrum of scientific activities within the broad area of molecular science and engineering and can be reconfigured as needed to adapt to future discoveries. The Michelson Center — complete with a Translational Imaging Center, Rare Cell Biology Center, Structural Proteomics Center, Center for Electron Microscopy and Analysis, a nanofabrication facility, and a suite of microscopy imaging technology — will serve as a hub for researchers across USC’s University Park and Health Sciences campuses as well as commercial and industry partners.

The building is being designed to facilitate innovation through interaction among scientists and engineers at many levels. Such engagement will occur in the laboratories and seminar rooms as well as in plentiful informal collaborative spaces, which foster impromptu conversations that can lead to spontaneous insights and even crucial scientific breakthroughs.

The Bridge@USC faculty have already realized numerous achievements in fundamental scientific knowledge and technology. Combining their specialized skills with those of new junior- and senior-level faculty recruits will be essential to assembling the scope of expertise needed to create an atomic resolution model of man from the molecule to the cell to the entire human body.

To ensure these faculty members and their students represent a range of disciplines, departments and schools within USC and are freed from traditional academic confines, The Bridge@USC will establish a Catalyst Program. The program will provide seed funding that will allow faculty groups across the university to pursue promising research not yet viable to compete for external and government support.

In tandem with biotechnology and pharmaceutical industry partners as well as the USC Stevens Center for Innovation, The Bridge@USC is developing a vibrant start-up incubator for Southern California that will further fuel the progress of Catalyst Program teams. These efforts are expected to generate significant new intellectual property and technology transfers that will perpetuate a cycle of continuous scientific and medical advances.
Transcending Boundaries

The Bridge@USC has the unique opportunity to transcend academe’s silos and boundaries. Its cornerstones of creativity, community, collaboration and communication will reach throughout the university and far beyond to leverage knowledge and unite the most innovative minds across the sciences and technology to usher in a new era in biomedical research. Together researchers will merge their study of the molecular, cellular and human levels to create a single, never-before-imagined composite of the human body that will accelerate predictive insights and lead to pioneering advances. With the support of forward-looking partners, there is no limit to how far The Bridge@USC can extend for the benefit of humanity.

“Now is the time to advance biology and all life sciences from the descriptive to the predictive. The Bridge@USC is the foundry where solutions to complex human health challenges are forged.”

STEVE KAY
Dean
USC Dornsife College of Letters, Arts and Sciences