THE BENCH & BEYOND

Newsletter of San Diego BioMed

Giving Every Patient A Fighting Chance

Teamwork has been an important theme of the last two years, both globally and at San Diego BioMed, with communities around the world coming together to help us move forward while confronting the pandemic. Collaboration has proven necessary for both personal and professional growth. At San Diego BioMed, we have created an environment that allows our scientists to exchange ideas and strategies on how to best fight against disease, while working in safe conditions.

An environment of collaboration and respect has always been a goal of the institute and has been a driver of our growth. In 2022 we have continued to recruit scientists with different background and expertise to develop new ideas and strategies. We would like to officially welcome Bruno, Conti Ph.D. and Takanori Otomo, Ph.D. to the San Diego BioMed community!

RESEARCH AT SAN DIEGO BIOMED—TEMPERATURE AND THE BIOLOGY OF AGING

Dr. Bruno Conti is a biologist with training in molecular biology, immunology, pharmacology, and neuroscience. His laboratory uses a combination of genetic, pharmacological, and behavioral approaches to investigate the biology of aging and age associated diseases. Age is the main risk factor for the development of disease. By investigating the biology of aging, mechanisms can be identified and targeted to improve health and potentially prolong lifespan.

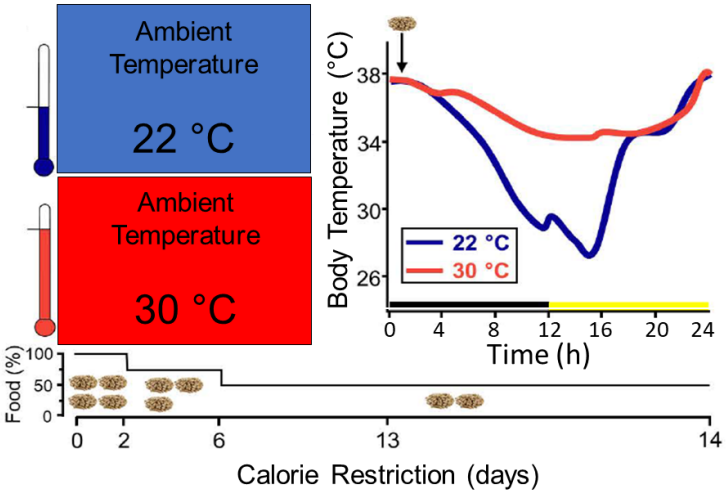
Aging was once thought of as an inescapable process influenced only by time. However, scientists have demonstrated that aging can be influenced by evolutionary mechanisms such as the regulation of metabolism and energy balance. One aspect of Dr. Conti's research is focused on understanding how temperature impacts the biology of aging with attention to the identification of genetic and biochemical pathways that regulate lifespan.

Diet is regarded as a pivotal regulator of health and aging. Indeed, a balanced reduction of calorie intake, known experimentally as calorie restriction, reduces the incidence of age associated disease and prolongs lifespan across several species. Dr. Conti's laboratory investigates the mechanisms that mediate the beneficial effects of calorie restriction. Since reducing calorie intake triggers a reduction of core body temperature, the Conti lab investigates the contribution that lowered temperature has on the biology of aging.

Temperature & Aging Continued

Experiments in the Conti lab have shown that even a modest (0.5° C) reduction of core body temperature promotes longevity and does so independently of calorie intake, indicating that diet is not the only factor regulating aging.

By investigating the mechanisms of the hypothermic response (temperature reduction) to calorie restriction, the Conti group has demonstrated that lowering body temperature is regulated in the brain by a protein called insulin-like growth factor receptor (IGF-1R), a known regulator of longevity. This discovery demonstrates that the main effectors of aging and lifespan are all components of the same pathways with body temperature being the main driver.



Calorie restriction promotes longevity by lowering body temperature. By housing specimens at different ambient temperature, the Conti lab separates the effects of nutrients from those of temperature. They use this strategy to identify the mechanisms by which lowered temperature increases lifespan.

Dr. Bruno Conti

How can lowered body temperature promote longevity? One mechanism is likely thermodynamics, i.e., the ability of temperature to affect the rate of chemical reactions in the body. However, research suggests the existence of other factors including the mediation of specific pathways which opens the possibility of "temperature mimetics" to treat aging and age associated disease. For example, the Conti lab performed an analysis of subjects in environmental conditions that allowed the group to measure the effects of lowered nutrients and temperature reduction separately. They found that many metabolic changes that occurred were not due to lowered nutrient intake, but rather, the extent of the hypothermic response. This could lead to the identification of mechanisms that contribute to the effects of temperature on aging and longevity which can lead to the development of "temperature mimetics".

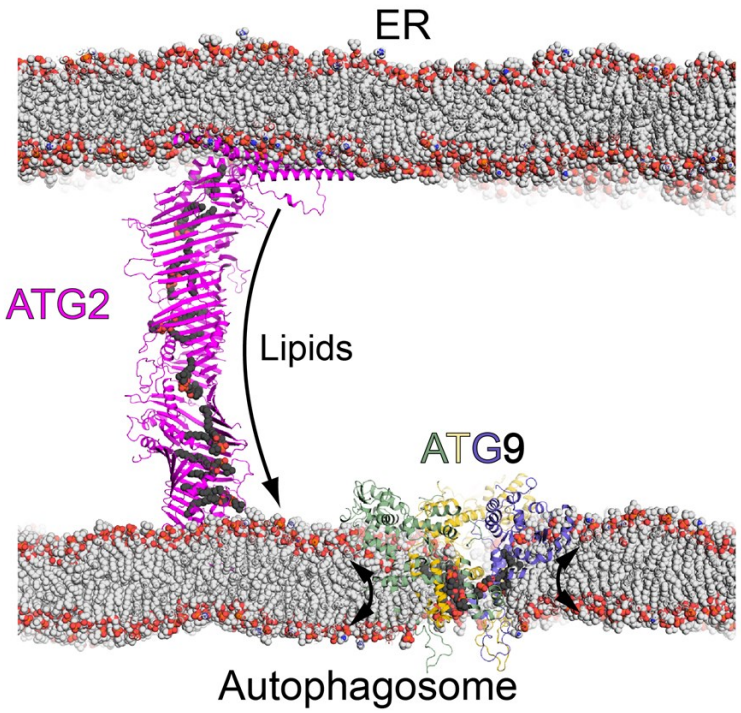
RESEARCH AT SAN DIEGO BIOMED—MAINTENANCE OF HEALTHY CELLS

Cells in our bodies eat internal parts of themselves to maintain their own health. This process, known as autophagy (spoken—aa-taa-fuh-jee), is essential for removing toxic material that causes diseases such as neurodegeneration and cancer. In autophagy, components inside cells are placed in a "trash bag" called the autophagosome which looks like a balloon. The process begins with a small membrane (a flexible wall) that grows into a cup-like shape that seals, making the "trash bag" ready for deposition. The autophagosome then fuses with the cell's incinerator to decompose the transported toxic material.

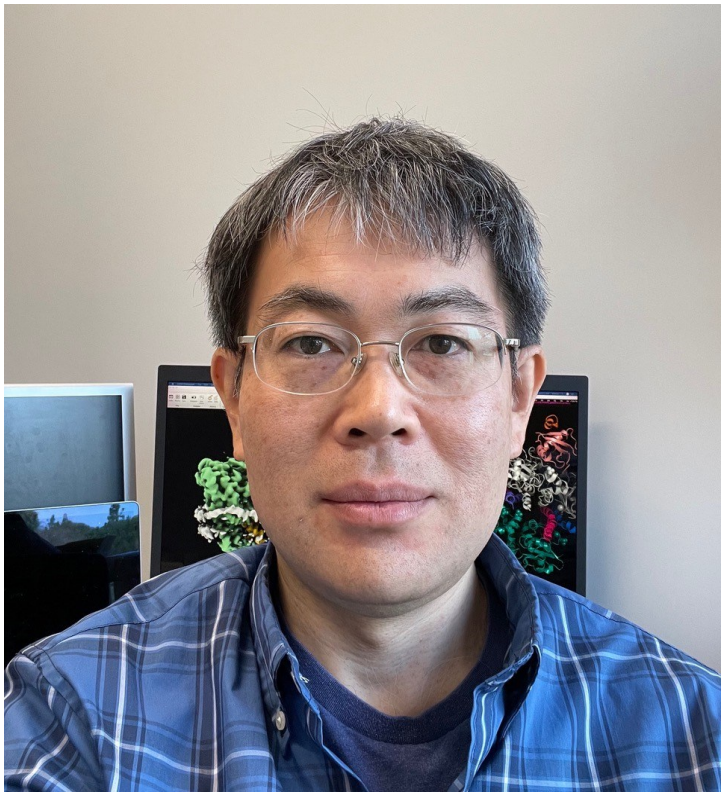
RESEARCH AT SAN DIEGO BIOMED—MAINTENANCE OF HEALTHY CELLS

Researchers have been working since the 1990s to find out how autophagosomes are made. While they have identified many proteins responsible for the process, the roles that the proteins serve is unclear, making it tough to understand the autophagy process. Dr. Takanori Otomo, uses biochemical and structural biology approaches to uncover the functions of the essential autophagy proteins with the goal of developing strategies to cure disease through autophagy interventions.

Recently the Otomo Lab characterized a protein called ATG2, which is located close to the initial autophagosomal membrane. The lab found that this protein can extract lipid molecules, the building blocks for membranes, from other membranes and transport them to the autophagosome, causing the membrane to form and grow. While this model was a milestone for the field, it raised another question.



The Autophagy Process



Dr. Takanori Otomo

The lipids that make up the autophagosomal membranes are called phospholipids, which have a water-soluble head and two oil-like tails. In water, phospholipids line up in two layers, with their heads facing water and tails meeting each other, forming a membrane. However, if lipids were transferred via the ATG2 protein, this would only add phospholipids to one layer of the membrane, making expansion impossible.

The Otomo lab also discovered that another protein, called ATG9A had a role in autophagy. Using a new technology called cryo-electron microscopy, the lab was able to reconstruct a 3-D shape of ATG9A, allowing them to see that the protein had large holes within it, a unique structure for a membrane protein. This structural feature gives ATG9A the ability to promote the growth of the autophagosomal membrane, a function that eluded the field for decades.

This discovery is critical to understanding how the autophagy process captures toxins, keeping our cells healthy. Dr. Otomo's work is a major contribution to the field, allowing for further research into interventions that might lead to novel treatments for disease.

San Diego BioMed is incredibly excited to welcome these two outstanding scientists and their groups to the Institute! With their help, we will continue our mission to create novel strategies to combat disease.