K-State Biochemistry
Molecular Biophysics
The Active Site

BMB Active Site News

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BMB's Brazilian Connections!

New relationships at Universidade de Sao Paulo and other Brazilian institutions

Phil Klebba and Sally Newton

Research in Dr. Klebba's laboratory. Research professor Sally Newton works in collaboration with her husband, department head Phil Klebba. She is a biochemist/molecular biologist who received her bachelor's and doctoral degrees from the Department of Chemistry at the University of Sao Paulo (USP), in Brazil. After post-doctoral study in Microbiology and Immunology at Stanford, she returned to Brazil as a professor in Microbiology at the Institute of Biomedical Sciences at USP. Her scientific career also took to her to other laboratories around the world, including Instituts Pasteur and Necker in Paris, before arriving in BMB. Her connections with the USP opened many doors for scientific collaborations here at K-State. Since her arrival in 2012, Dr. Klebba's lab hosted a graduate student (Heloise Balhesteros) and an undergraduate exchange student (Alexandre Viera), as well as the visit of Dr. Luis Carlos Ferreira, Head of the Microbiology at USP, to present a seminar on his vaccine research. His visit led to collaborations with Dr. John Tomich (see following) on the biotechnology of nanoparticles as vaccine tools.

Marilis Marques and Heloise Balhesteros

Dr. Balhestero's studies in the Klebba lab concerned the aquatic bacterium, *Caulobacter crescentus*. A few years ago, during visits to Microbiology at USP, we began to collaborate with Dr. Marilis Marques, an expert on *C. crescentus*, which is a Gram-negative bacterium. She wanted to study iron utilization by this organism, a process that Phil and Sally were well acquainted with from past work on *Escherichia coli* and other bacteria. Dr. Marques obtained a fellowship for her graduate student, Heloise Ballesteiros, to study under our supervision for a few months. That interaction opened new areas of research for our group, which led to a recently submitted article describing iron acquisition by *C. crescentus*, as well as the identifying of several genes involved in the process.

In Summer 2015 we were fortunate to host an energetic undergraduate student from Brazil, Alexandre Viera, who joined our laboratory for several months and worked together with graduate students to learn molecular cloning and the basic methodologies of iron biochemistry. His experiments were part of an effort to clone and express iron transport genes of pathogenic Gram (-) species, including *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumanni*. The goal is to find chemicals that block the process of iron uptake and thereby constitute novel antimicrobial agents.

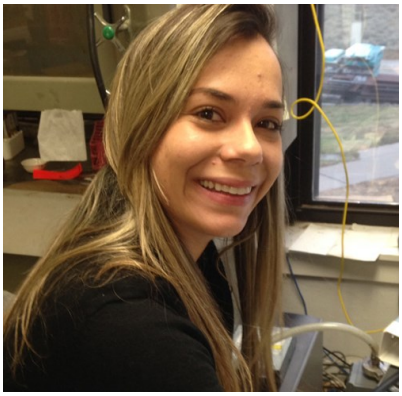
Raul Machado Neto and April Mason

International collaborations are positive experiences on many levels. In October of 2015, Provost April Mason; Dean of Arts & Sciences, Peter Dorhout; and a delegation of K-State faculty, including Drs. Newton and Klebba, traveled to Brazil. During the visit, USP professor Raul Machado Neto, Director of International Collaborations, and Provost Mason signed a memorandum of understanding for future interactions between our universities. We look forward to these academic activities and exchanges with our Brazilian colleagues!

Professor John Tomich's Lab

Dr. John Tomich

The second floor of Burt hall also developed a distinct "Latin flavor" over the past few years. BMB was a new research arena to several undergraduate and graduate students hailing from Brazil and other Spanish-speaking countries. The Tomich laboratory was the "home away from home" for seven such students. Among them, four visiting Brazilian natives were involved in collaborative projects with their home institutions supported through the Brazilian CAPES program. CAPES scholarships support the training of doctoral candidates, pre-doctoral short-term researchers, and post-doctoral scholars. In Dr. Tomich's lab it provided a year of support in the middle of their graduate programs. These students included Patricia Games and Aparecida das Dores Teixeira, both from the laboratory of José Eduardo Serrão in Cellular and Structural Biology at the Federal University of Viçosa. Patricia and Aparacida were defining the protein expression alterations that occur when honey bees move from one caste to another. For example, individual bees that once foraged for nectar to feed the hive can transition to a nurse caring for the immature bee larvae.



Patricia Games

Aparecida das Dores Teixeira

Adriana Avila and Luana R. M. M. Aps

A third student, Luana R. M. M. Aps is a student of Luis C.S. Ferreira in the Institute of Biomedical Sciences at University of São Paulo. Working with K-State's Adriana Avila, Ph.D., her participation led to a potential anti-cancer vaccine directed against a virus that causes a form of cervical cancer.

The fourth student, Sheila de Melo Barros was pursuing her doctoral degree in Biochemistry and Physiology at the Federal University at Pernambuco. Sheila worked on modifying the surface of the Branched Amphiphilic Peptide Capsules (BAPCs) that are under investigation in Dr. Tomich's lab, to include specific cell targeting ligands. BAPCs are readily taken up by cells and can stably encapsulate potent radioactive isotopes for use in cancer therapy. Her modifications to the BAPCs could lower the amount of radioactivity required for activity as well as protect non-cancerous cells from collateral damage.

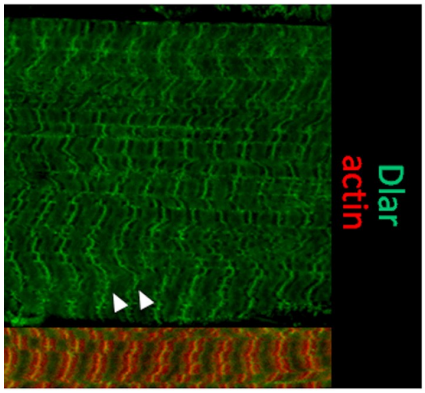
Sheila de Melo Barros

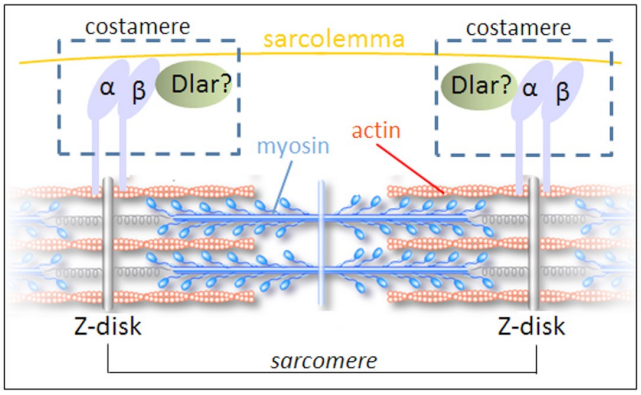
These collaborations across the Americas resulted in three Ph.D. theses and degrees to Aparecida das Dores Teixeira, Luana R. M. M. Aps, and Sheila de Melo Barros, as well as several publications. Two additional papers were already submitted for publication, and Dr. Barros will return to the lab in the new year as a postdoctoral fellow to continue her studies in BAPCs. K-State BMB was fortunate to profit from the energy and excitement for research that these outstanding young Brazilian scientists brought to Manhattan through the CAPES program.

Erika Geisbrecht and Collaborator pursue R21 grant.

The coordination of extracellular physical or chemical cues to elicit a response within a cell is called a signal transduction pathway. An example, the costamere complex, occurs in striated muscle. It relays mechanical stress signals from outside the cell to elicit intracellular signal transduction. The costamere also physically connects the muscle membrane to internal muscle architecture to allow synchronous muscle contractions. The costamere has been called the "Achilles' Heel" of striated muscle, as defects in key proteins lead to muscular dystrophies and cardiomyopathies.

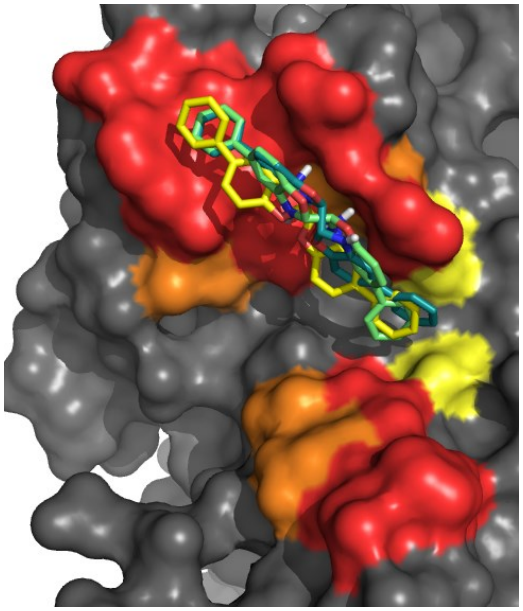
Erika Geisbrecht and Samuel Bouyain, her collaborator at the University of Missouri in Kansas City, are working on an NIH grant entitled "Protein tyrosine phosphatase signaling in muscle maintenance." This project focuses on how a transmembrane protein called Lar (Dlar), interacts with other proteins during signal transduction in the fruit fly muscle costamere. *Drosophila melanogaster* is a good model for these studies, as muscle structure and function are evolutionarily conserved from insects to vertebrates, and only a single Dlar protein exists in flies, compared to three Lar proteins in mammals, that have overlapping functions and expression. This work will provide a better understanding of the signaling pathways that support the integrity of muscle tissues, and may guide future studies towards treatments associated with muscle defects.

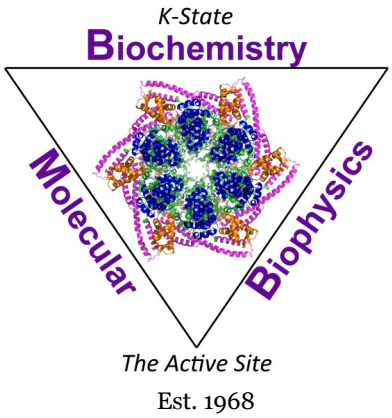




Cheminformatic Discovery of Alternative Pathway C3 Pro-Convertase Inhibitors.

The complement system is a cornerstone of human innate immunity, and as such helps our body fight off would-be infections from all types of microorganisms. However, there are certain situations that can result in either inappropriate or over-activation of complement against healthy cells and tissues within our body. Because of this, there has been a long-standing interest in developing complement-targeted drugs for treatment of a number of either acute or chronic diseases in humans. Unfortunately, very few drugs of this type have been shown to be effective enough to receive FDA approval for use in humans. To address this unmet medical need, our group has spent the last several years studying the structure/function relationships of naturally occurring virulence proteins from Staphylococcus aureus. These bacterial inhibitors potently block complement (AP) by disrupting formation of a multi-protein enzyme, called the AP C3 convertase, which is the main driving force behind complement-mediated inflammation. On their own, these proteins themselves are too antigenic to be used pharmacologically in human populations; however, preliminary studies from our group strongly suggest that small molecules which bind C3b sites known to be crucial for initial stages of AP C3 convertase assembly may mimic the useful function of these staphylococcal proteins. In this NIH-funded project, we are making use of emerging capabilities in cheminformatics to identify drug-like small molecules that bind C3b and disrupt formation and function of the AP C3 convertase. This work has the potential to discover entirely new classes of small molecule complement inhibitors, and therefore holds great promise for development of novel complement directed therapeutics.





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