UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE

Volume 14, Number 2
March-April 2011

Inside:

BioMET NOW

Center for Biomedical Engineering and Technology - University of Maryland School of Medicine
in conjunction with the Fischell Department of Bioengineering, School of Engineering, University of Maryland, College Park

Heart by the Numbers

In an age of difficult funding, few researchers are in the position of receiving large awards from NIH. BioMET's Acting Director Dr. W. Jonathan Lederer has done just that, being awarded a $5.5 million grant to model heart arrhythmias entitled "Calcium Entrained Arrhythmias." The proposal was in response to a special RFA (Request for Applications) at the National Heart, Lung, and Blood Institute to develop computational biology approaches to heart disease. The RFA supports development of computer models of heart function carried out with detailed biological experiments. Dr. Lederer's group proposed to target and advance research into the causes of abnormal heart rhythms, otherwise known as arrhythmias.

Much is unknown about the underlying causes of abnormal heart rhythms. Nevertheless some arrhythmias can be dramatically and effectively treated with incredible engineering wonders such as implantable electronic pacemakers and defibrillators. However, there are many others including some with dramatic names like "sudden cardiac death" where the causes are often poorly defined, the warning signs are few, and results often tragically lethal. Some of these include a number of genetic causes. The proposed work by Lederer and his colleagues seeks to investigate the molecular and cellular causes of sudden cardiac death. The proposed work seeks to investigate how these lethal arrhythmias can arise even when they have virtually no symptoms and to develop a new understanding of the molecular and cellular biology of the heart.

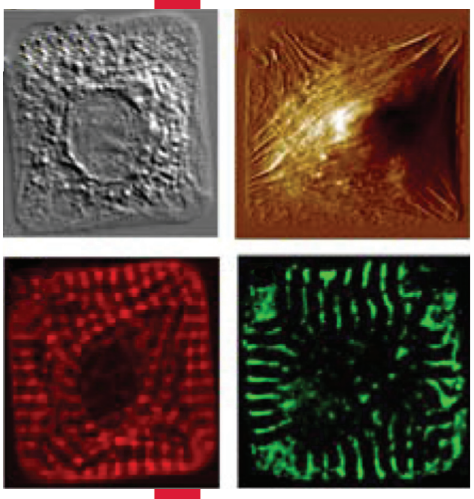

Figure 1; An engineered heart cell. A single heart cell is isolated and placed in a square chamber and allowed to grow. The same cell is imaged four difference ways: upper left, phase contrast; upper right, atomic force microscopy; lower left, immunostained for actinin; and lower right, immunostained for the sodium/calcium exchanger. (A. Ziman, K. K. Parker & W. J. Lederer, unpublished.)

The work combines computer modeling of cardiac calcium signaling and heart cell physiology with state-of-the-art cellular experiments involving high-speed high-resolution imaging and electrophysiology. The ambitious proposal starts with molecular function and organization within single heart cells and will be extended (over the five years of the funded work) to include larger regions of the heart and the whole heart itself. The work is made possible by novel computational methods invented by Dr. Lederer's colleague Prof. M. Saleet Jafri at George Mason University. This study is also enabled by critically important work done by Dr. Lederer's co-investigator Prof. Raimond Winslow at Johns Hopkins University. The grant thus brings together three powerful groups: Raimond Winslow's exceptional modeling group at the Johns Hopkins University, M. Saleet Jafri's superb computational biology group at George Mason University, and Dr. Lederer's internationally known molecular cardiology experimental laboratory. The real strength of the grant and the proposed investigation is considered to be the emphasis on the multiscale ***experimental*** data that is used to tightly constrain the parameters of the computer modeling. That is, the model parameters are limited by the experimental results, which are used to refine the model. The refined model then predicts another set of results that are tested experimentally. As the developing mathematical modeling expands, experimental tests of the predictive power of the model will lead to further

Equations

$$\frac{R_m}{\lambda^2}\frac{\partial^2 V^i}{\partial x^2} = C_m\frac{\partial V^i}{\partial t} + I^i_{gap} + \sum I^i_{ionic} \quad (eq\ 1)$$

$$\frac{\partial [Ca^{2+}]^i_{myo}}{\partial t} = D_{Ca}\frac{\partial^2 [Ca^{2+}]^i_{myo}}{\partial x^2} + J^i_{Cagap} + J^i_{leak} + J^i_{xfer} - J^i_{up} - J^i_{trpn} + \left(I^i_{Ca,b} - 2I^i_{NaCa} + I^i_{p(Ca)}\right)\frac{A_{cap}}{2V_{myo}F} \quad (eq\ 2)$$

Figure 2: Equations defining heart function. (M. S. Jafri, G. S. Williams & W. J. Lederer, unpublished).

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Partners' News

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Former Retreat Speaker, Dr. Bruce Yu from UMB's School of Pharmacy was in the news in March. He and Dr. Zygmunt Gryczynski, formerly of the Center for Fluorescent Spectroscopy housed in BioMET's building, are developing a new group of fluorescent dyes that can be targeted to specific tissues *in vivo*. While the original dye molecule was invented in Copenhagen, Dr. Yu will be responsible for the targeting and bio-enhancement of the dye. Dr. Gryczynski group, now at the University of North Texas, will be responsible for spectroscopy studies. See http://www.oea.umaryland.edu/communications/news/?ViewStatus=FullArticle&articleDetail=12615 for more details.

Congratulations to Drs. William Bentley and Gregory Payne who won the Regents Scholarship Collaboration Award for 2011. Dr. Bentley is Chair of the Fischell Department of Bioengineering and Dr. Payne is a professor in the same department. Both researchers are former members of the University of Maryland Biotechnology Institute. BioMET's Associate Director Dr. Joseph Kao with his long-time collaborator Dr. Gerald Rosen from the School of Pharmacy won the first ever Scholarship Collaboration Award in 2009.

Congratulations to BioMET Collaborator

Ever since she arrived in Maryland with a joint appointment between University of Maryland College Park and the now-defunct University of Maryland Biotechnology Institute (UMBI), Dr. Silvia Muro has been an enthusiastic collaborator and participant in BioMET activities. She collaborates with Associate Director Dr. Joseph Kao and has not missed a retreat since 2009, when she was asked to speak. She was looking forward to this year's retreat held on April 12 until she became a finalist in the inventor category at the Annual Experimental Biology Meeting held in Washington, D.C. We missed her presence, but she did send two members of her laboratory to attend the retreat.

While she did not win the Experimental Biology award, Dr. Muro has garnered another invention award. She and her student collaborator tied for first place in the University of Maryland's Office of Technology and Commercialization's Invention of the Year competition in the Life Sciences category for the invention of a novel drug carrier designed to target the cells that line the digestive tract. The carrier is designed to enter the cells, bearing its load, which is then released into the blood stream. The load is not limited to drugs, but can be used to deliver other biomolecules for imaging, tracking or sensing.

Dr. Muro has a joint appointment between the Fischell Department of Bioengineering and the Institute for Bioscience and Biotechnology Research (IBBR), formerly the Center for Advanced Research in Biotechnology at UMBI.

Congratulations to Dr. Muro from her BioMET colleagues.

Congratulations!

Dr. Mariusz Karbowski won a travel award to the upcoming Mitochondrial Biology Symposium entitled "Advances in Mitochondrial Dynamics and Mitochondrial-Cytosolic Communications." The symposium is sponsored by the National Heart, Lung and Blood Institute, National Institutes of Health and will be held May 16-17, 2011 in Bethesda, MD. Dr. Karbowski is an expert in mitochondrial dynamics.

That Time Again

Every four years, the Annual Biophysical Society Meeting comes to Baltimore. This was the year, and many local researchers and their laboratory personnel take advantage of the "cheap thrills" of a local meeting. For the Laboratory of Molecular Cardiology (LMC), headed by Dr. W. Jonathan Lederer, the Biophysical Society Meeting is *the* meeting to attend and it shows. The laboratory submitted 12 abstracts to the meeting. The abstracts are reviewed and sorted. The best abstracts are chosen for platform talks, while the rest are grouped into appropriate topics. This year, three abstracts were chosen for platform talks from the Lederer group. They are:

Brochet, D. X.P., Yang, D., Cheng, H., Lederer, W.J. Small Ca^{2+} Release Events in Rabbit Ventricular Myocytes.

Prosser, B. L., Ward, C, W., Lederer, W. J. Stretch-Dependent ROS Production and Ca^{2+} Signaling in Single Cardiomyocytes.

Zhao, G., Lederer, W.J. STIM1 in Rat Ventricular Myocytes.

They represent the wide range of ongoing projects in the LMC. The poster abstracts listed below are even more diverse, and include those put in by collaborators at other institutions, including Tel Aviv University (Boyman et al.), George Mason University (Hoang-Trong et al.), Johns Hopkins (Jafri et al.) and UMB's School of Nursing (Ward et al.).

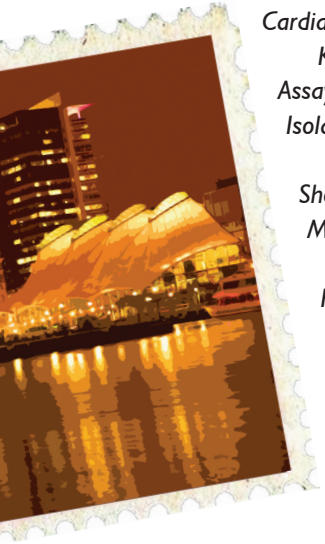
Boyman, L., Hagen, B. M., Hiller, R., Lederer, W. J., Khananshvili, D. The pH Sensitivity of the Cardiac Na^{+}/Ca^{2+} Exchanger Depend on Calcium Binding Domains (CBD) of NCX1.

Chikando, A., Kao, J. P.Y., Lederer, W.J. Effects of Mitochondrial Membrane Depolarization on Cellular Function in Cardiac Myocytes.

Hagen, B. M., Boyman, L., Kao, J. P.Y., Lederer, W.J. A Comparative Assessment of Fluo Ca^{2+} Indicators in Rat Ventricular Myocytes.

Hoang-Trong, T. M., Williams, G. S.B., Lederer, W.J., Jafri, S. GPU-Enabled stochastic Spatiotemporal Model of Rat Ventricular Myocyte Calcium Dynamics.

Jafri, M. S., Lederer, W. J., Williams, G. S.B., Greenstein, J. L., Winslow, R. L. Modeling the Mechanisms of Calcium-Mediated Cardiac Arrhythmias.



Khairallah, R.J., Prosser, B. L., Lederer, W.J., Ward, C.W. A Novel Assay of Muscle Energy Dynamics in Mechanically Loaded Enzymatically Isolated Adult Mammalian Skeletal Myocytes.

Riley, D. D., Chikando, A. C., Lederer, W.J. Glucose Provides Short-Term Protection to Mitochondria in Rat Ventricular Cardiac Myocytes.

Ward, C. W., Prosser, B. L., Greiser, M., Westerblad, H., Khairallah, R., Lederer, W.J. A Novel Assay of Mechano-Transduction in Single Muscle Cells.

Williams, G. S.B., Chikando, A. C., Lederer, W.J., Sobie, E. A., Tuan, H.-T. M., Jafri, M. S. Ca2^{+} Leak and Ca2^{+} Sparks in Mammalian Heart: Insights from a Computational Model.

Projects presented at meetings often represent relatively new work that may not yet be ready for full publication. Presenting at a scientific meeting garners feedback on the research, while giving young researchers a chance to hone their presentation skills.

Scientific meetings are critical to dissemination of results and networking. They also have career counseling, job openings and general information of what is happening in the areas covered by the Society. In an age where collaboration is absolutely necessary for success, they are a convivial and effective way to get together.

BioMET Happenings

Comings and Goings

Mary Graham, Accounting Associate, has left BioMET.

Publications

Neutzner A, Neutzner M, Benischke AS, Ryu SW, Frank S, Youle RJ, **Karbowski M.** A Systematic Search for Endoplasmic Reticulum (ER) Membrane-associated RING Finger Proteins Identifies Nixin/ZNRF4 as a Regulator of Calnexin Stability and ER Homeostasis. J Biol Chem. 2011 Mar 11;286(10):8633-43.

Pisciotta JM, Zou Y, **Baskakov IV.** Role of the photosynthetic electron transfer chain in electrogenic activity of cyanobacteria. Appl Microbiol Biotechnol. 2011 Apr 12. [Epub ahead of print]

Maruyama M, Li BY, Chen H, **Xu X,** Song LS, Zhu W, Yong W, Zhang W, Bu GX, Lin SF, Fishbein MC, **Lederer WJ,** Schild JH, Field LJ, Rubart M, Chen PS, Shou W. FKBP12 Is a Critical Regulator of the Heart Rhythm and the Cardiac Voltage-Gated Sodium Current in Mice. Circ Res. 2011 Mar 3. [Epub ahead of print]

Grants and Contracts

Dr. Bruce Vogel, NSF, Assembly and Composition of Elastic Fiber-like Structures in the Nematode *C. elegans*, $159,999, 3/1/2011, yr 4 of 4.

Dr. Mervyn Monteiro, NIH-NIGMS, Functional Studies of Ubiquilin, $307,500, 3/1/2011, yr 4 of 4.

Dr. W. Jonathan Lederer, Columbia University (NIH PPG), Molecular Basis of Sudden Cardiac Death, 4/1/2011, $354,274, yr 5 of 5

Dr. W. Jonathan Lederer, NIH-NHLBI, Calcium Entrained Arrythmias, 4/1/2011, $1,030,125, yr 1 of 5.

Talks and Travels

Dr. W. Jonathan Lederer, participant, Computational Biology Meeting, Cold Spring Harbor, NY, March 29-April 1, 2011,

Dr. Joseph Kao, Invited Speaker, "Targeted Delivery of Molecular Probes for In Vivo Electron Paramagnetic Resonance Imaging (EPRI)," Department of Physics, California Polytechnic University, Pomona, CA, April 15, 2011.

Dr. Joseph Kao, Invited Speaker, "Controlling Living Cells with Light and Photochemistry," Joint Science Department, Claremont Colleges, Claremont, CA, April 21, 2011.

Dr. Bruce Vogel, Invited Speaker, "Hemicentins: Ancient structural proteins with novel functions," Fischell Department of Bioengineering, University of Maryland College Park, April 29, 2011.

Heart, continued

constraints on the modeling. The work will not only inform us about how the heart works but it will also suggest and help investigate new therapies. The new award takes advantage of a unique combination of capabilities within the Lederer laboratory. The Lederer group has an extensive array of confocal microscopes equipped with state-of-the-art electrophysiological equipment that allows the measurement of electrical conductance of heart cells and also their ability to contract. These investigators also have the capability for manipulating and imaging of cells both temporally and spatially at near nanometer levels. In addition, this is one of the few laboratories in the country that can also engineer cells. This means that they can grow cells in a pre-defined shape. This allows the researchers to control the distances across a cell and between multiple engineered cells. This simplifies the testing of the models. Figure 1 shows one square cell imaged four different ways (developed with collaborator Prof. K. K. Parker of Harvard University). Heart cells are usually highly variable, elongated rectangles.

Researchers are usually limited on the amounts they can request. The maximum is usually $500,000/year direct costs. Most NIH grants are what are known as modular grants which have a maximum of $250,000 direct costs. Dr. Lederer's award is over $600,000/year direct costs for 5 years. To ask for this amount requires prior approval from the institute. In addition, in today's brutal funding environments most proposals will have their funding amount or number of years cut.

Besides this award, Dr. Lederer also just received a regular modular award, entitled "Stretch-Dependent Calcium Signaling in Heart." Congratulations to Dr. Lederer and his highly productive team.

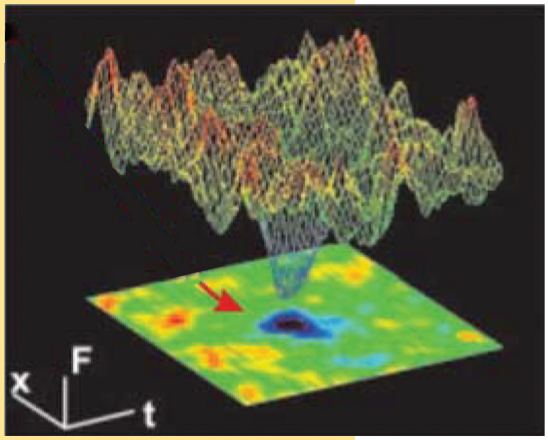


Figure 3: A calcium blink. Imaging measurements yield a picture of calcium movement within a heart cell. The dark area is an area of calcium depletion from an intracellular Ca^{2+} storage organelle. Calcium blinks, as well as other calcium signals such as calcium sparks, are the kind of measurements that must be accurately predicted by mathematical models of heart function. Changes in these signals are associated with arrhythmias. (Brochet, et al.(2005) Ca^{2+} blinks: Rapid nanoscopic store calcium signaling. Proceedings of the National Academy of Science, USA 102, 3099–3104)

Adobe CS5 Now Available

The Adobe suite of software packages are invaluable to the presentation of research data. BioMET recently invested in an upgrade to Creative Suite 5 from CS3. The package includes Illustrator, Photoshop, InDesign, Dreamweaver, Firewire, and Acrobat. Both Macs and PCs are supported. Since these are limited site licenses, anyone at BioMET can get a copy installed on their computer. For those who are not familiar with the software suite, Adobe has made the functions of individual software programs highly overlapping, so that the tools in one package are similar to the tools in another. Please see Mike Kelly, BioMET's IT Manager, for installation instructions. Questions with usage can be directed to Pamela Wright in the Director's office.