

CEM COMMUNIQUÉ

Center for Engineering in Medicine Newsletter

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From The Editor

Matthew Rosinski



It is our pleasure to offer this first issue of CEMcommuniqué. This new publication will serve to inform the CEM community of research advances, new fellows, facility updates and other exciting news.

We aim to produce this newsletter on a quarterly basis. We invite all of you to contribute to the newsletter by reviewing recent research breakthroughs, and introducing new fellows and faculty members, upcoming events, seminar series, research facilities, etc.

Microfabrication Facility

Octavio Hurtado
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An exciting state-of-the-art Clean Room laboratory and a class 1000 Bio-Measurement Room are now open for business in the CEM's new 5,500 square foot Charlestown Navy Yard facility. Located in the 1st floor of Building 114, a newly renovated structure in one of Boston's upcoming Health and Biotechnology Research Centers, the new lab also features tissue culture facili-

ties, open lab space, a cold room, a 135 seat auditorium and cafeteria. This laboratory supports the research of more than 250 scientists affiliated with Massachusetts General Hospital.



Biopreservation

Scope

Long-term storage of living cells or tissues is needed to ensure a readily available supply of cells and engineered tissue constructs to end-users including medical centers, hospitals, clinics, and physician offices. Effective preservation procedures are required at various steps in the production of engineered cells and tissues including: screening of source cells, cell banking, inventory control, quality control, product distribution and tissue banking.

The problem

When cells are removed from the body, changes in the external environment can not only result in cell damage but an inhibition or elimination of the natural repair and replacement processes. As isolated cells become damaged and die, the absence of replacement cells results in a gradual reduction in the biological activity of the system. The goal of biopreservation, therefore, is to preserve the viability and activity of cells, tissues and organ held outside the native environment for extended periods of time.

Possible solutions

Biopreservation can be categorized into four different areas based on the techniques used to stabilize the biological product and ensure a viable state following long-term storage. These include: tissue culture, hypothermic storage, cryopreservation and desiccation. Our group is focusing on making improvements to current freezing and drying techniques.

Cryopreservation

Cryopreservation is the process whereby biological function is maintained by freezing and storage at ultra-low subzero temperatures. At temperatures below -80°C , all metabolic and biochemical reactions cease and the cell is held in stasis. When cells are cooled below the solution freezing point ice forms in the extracellular space resulting in the concentration of extracellular solutes and the osmotic shrinkage of the cells. Cell

injury is related to cooling rate, with damage to cells caused by both intracellular freezing (rapid cooling) and exposure to high concentrations of solutes (slow cooling). The successful cryopreservation of a wide variety of cell types has been a result of the development of novel techniques using cryoprotectants to minimize both types of damage. Cryopreservation can be subdivided into two approaches based on the overall methodology, namely, slow freeze-thaw in the presence of 1-2 M cryoprotectants and vitrification using rapid cooling and much higher concentrations of cryoprotectants ($\sim 6-8$ M). Once a cell or tissue has been cryopreserved successfully it can be stored indefinitely until needed.

Several areas for improvement in cryopreservation exist. First, the high concentrations of chemical cryoprotectants used to cryopreserve cells have been shown to adversely affect transplant patients necessitating costly post-thaw removal. Second, there are a number of clinically important cell types from different species that have limited viability following cryopreservation including: hepatocytes, granulocytes, and oocytes. Similarly, the increased complexity of tissues adversely affects the utility of the current approach. Finally, the cryopreservation process itself is a costly procedure that requires highly trained technicians and specialized equipment for processing and storage. This is logistically prohibitive for routine use in a large-scale, or remote operations.

Desiccation

In natural systems, desiccation is used as a strategy to preserve biological activity through times of extreme environmental stress. Termed anhydrobiosis, the ability to survive in a dry state for extended times has been identified in a variety of organisms including plant seeds, bacteria, yeast, brine shrimp, fungi and fungal spores, and cysts of certain crustaceans. Extensive studies on these organisms

revealed that there are a series of complex molecular and physiological adaptations that permit these organisms to survive excessive water loss ($>99\%$). Central to this work has been the discovery that large amounts of mono- and disaccharides can act to protect biological structures during dehydration through the formation of a stable glass matrix and/or binding to sites previously stabilized by water. By incorporating sugars into the media, freeze-drying and ambient desiccation have been successfully used for the dehydration and storage of pharmaceutical agents, bacteria, yeast and liposomes. Current efforts are now focusing on the desiccation of mammalian cells.

For sugars to be maximally effective at protecting against the damaging effects of dehydration, they need to be present on both sides of the membrane. Mammalian cells do not naturally synthesize and are not permeable to desiccation-important polysaccharides. This is one of the key impediments to using these protectants for the dry storage of mammalian cells. A number of approaches have been used to load sugars, into mammalian cells including the genetic expression of sucrose and trehalose synthase genes, a metal-actuated switchable membrane pore, thermal and osmotic shock, and microinjection.

Early signs are promising and if successful, mammalian cell drying presents significant economic advantages over cryopreservation. Eliminating the need for costly toxic cryo-protectant removal before transfusion or transplantation is one benefit. Ambient temperature storage of desiccated cells and tissues is also possible representing significant savings over maintaining large scale inventories at subzero temperatures.

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Fellow Highlight Meindert Sossef, MD

CEM's expertise attracts participants from a great variety of countries. One of our visiting research fellows is Meindert Sossef MD, who joined the cryo-group July 2001 for a one year fellowship in his hometown Amsterdam, the Netherlands, Meindert most recently served as Chief Resident in Surgery and completed an extensive laboratory stint in partial fulfillment of his Ph.D. on bioartificial liver devices. Cooperation between the Amsterdam-group and the CEM with its vast experience in the field of cryopreservation resulted in his current project, the cryopreservation of hepatocytes for use in a bioartificial liver. His wife and two children of 2 and 4 join him in Boston, and help make this year a truly fabulous experience.



Fall 2002 Meetings

BMES

October 23-26, 2002
Houston, Texas
Papers due: April 5

Metabolic Engineering Meeting

October 6-11, 2002
Il Ciocco, Castelvechio Pascoli, Italy

The New Jersey Symposium on Biomaterials Science

October 17-18, 2002
Papers due: April 30

AIChE

November 3-8, 2002
Indiana, IN
Papers due: April 19

Materials Research Society

December 2-6, 2002
Boston, MA
Abstracts due: June 19

After Hours

As some of you now know, the initials C.E.M. also stand for "Center for Exploration of the Mountains", a roughly hewn group of individuals working at MGH and the Shriners Hospital who got together in the fall of 1998 for a weekend backpacking trip in the White Mountains of New Hampshire. Since then, we have organized a number of trips for the sole purpose of enjoying the great outdoors. Our main activity is hiking and backpacking, which we do in all four seasons. Other activities include sea kayaking, whitewater rafting, bicycling, rock climbing, and annual ski trips. All of our activities are low budget and take place within a driving distance from Boston, typically in northern New England and Southern Québec. A calendar of trips for 2002 is shown below. In general, a sign-up sheet is posted about 2 weeks before each trip on the door of room 265 at the Shriners Hospital. If you are interested to participate and wish further additional information about any of these trips, feel free to e-mail the appropriate contact person.



DATE	TRIP SUMMARY & CONTACT DETAILS
Jan. 26 - 27	Backpacking - Pemigewasset Wilderness, NH. Winter camping in a vast roadless area in the White Mountain National Forest.
Feb. 13 - 18	Annual Ski Trip - Le Massif, Québec, Canada. This ski area has the best snow, the best view, and the smallest crowds in the East.
Mar. 16	Day hike - Mt. Madison, NH. Winter climb of a major peak in the White Mountain National Forest. Atilles@pol.net
June 7 - 10	Backpacking - Adirondack State Park, NY. Summits in the High Peaks Region including Mount Marcy are on the menu. Vitolo@rci.rutgers.edu
Aug. 1 - 5	Sea kayaking - Tadoussac, Québec, Canada. The only place where you can do whale watching on a kayak. Fberthia@sbi.org
Aug. 23 - Sep. 2	Backpacking expedition - Mt. Groulx, Québec, Canada. The ultimate wilderness experience. No trails, just taiga and tundra. Fberthia@sbi.org
Sept.	Whitewater rafting - Gauley River, WV. With local guides, we will tame one of the most famous rivers in North America. Amacdona@sbi.org

Solid State Magnetic Resonance

Studies of Bone, Atherosclerotic Plaque and Synthetic Biomaterials

Magnetic Resonance Imaging (MRI) is well known for its ability to produce clear and diagnostically useful images of the soft tissues of the human body. However, conventional MRI does not work on solid materials such as bone or implanted devices composed of synthetic polymers or ceramics. A special form of MRI is being developed in our laboratory to study solid materials. This solid state MRI can measure true bone mineral density accurately and noninvasively, and furthermore is uniquely useful for characterizing the morphological and chemical properties of nonmetallic implanted devices within living organisms. It also shows promise in measuring bone matrix density, a feat not possible with existing noninvasive techniques. Bone matrix is the collagenous medium in which the mineral crystals of bone are embedded.

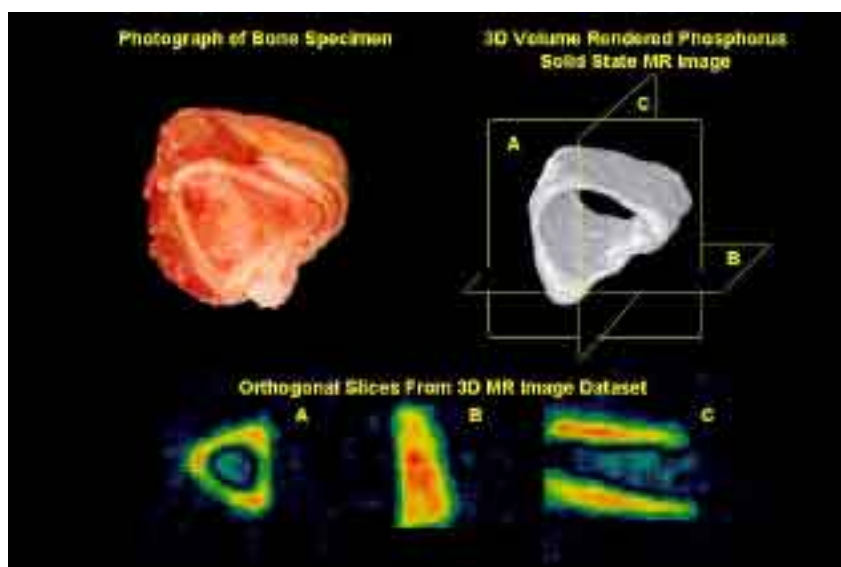
Solid state magnetic resonance spectroscopy (MRS, the mode of MR used as a tool of chemical analysis) can reveal critical details of chemical composition in specimens of bone, atherosclerotic plaque, and synthetic biomaterials. The combination of solid state MRI with solid state MRS constitutes a powerful technology for materials

science studies of biological systems. Our team has published an example of the combined chemical/imaging analysis of bone related materials in the Proceedings of the National Academy of Sciences (1999; 96: 1574-1578).

To study plaque most effectively by MR, tiny special intravascular radiofrequency coils (the pickup devices in MR scanners) can be surgically positioned directly within vessels just as interventional cardiologists use catheter based devices to diagnose and treat some cardiovascular conditions. In a new project we are developing novel high performance intravascular coils to identify and characterize so-called vulnerable plaques: those which are at high risk of triggering a heart attack or stroke.

Contributed by:

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Spring 2002 Seminar Series in Biomedical Science and Engineering

Shriners Burns Hospital, 4th Floor Conference Room,
8:30-9:30AM

April 2

Brian Seed, PhD
Genetics, Harvard Medical School
"New Approaches to Understanding Signal Transduction In Vivo"

April 9

Martha Gray, PhD
Division of HST, MIT
"Functional Imaging of Cartilage"

April 23

Jose Venegas, PhD
Anesthesiology, MGH
"Pulmonary Functional Imaging with PET"

See the Calendar of Events at <http://www.med.harvard.edu/> for new and upcoming seminars. Look under "Biomedical Science and Engineering Seminar Series"

If you have a story to tell or suggestions for this quarterly newsletter contact:

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Look out for the second issue in mid June.