HMRI news

Huntington Medical Research Institutes ◆ Pasadena, California ◆ May 2005

Microchip Electrodes Will Improve DBS For Treatment of Parkinson's Disease

Martin Han, PhD, of HMRI's Neural Engineering Laboratory is developing an advanced system of electrodes that may improve deep brain electrical stimulation for patients with Parkinson's disease (PD) and other movement disorders.

The new electrodes will be etched from iridium-coated silicon using a powerful ion beam. The beam will cut out tiny picket-shaped probes that safely penetrate into the brain and stay in position for a lifetime. Another shallow-cutting step in the manufacturing process will remove most of the iridium, leaving a microchip-like pattern of neuron-contact dots and insulated connecting lines.

Photo by Robert Olson

Martin Han of the Neural Engineering Laboratory examines an electron-beam evaporator which is used to make microchip electrodes. Using high-energy electron beams to evaporate (melt) precious metals such as gold and platinum, this particular deposition system coats silicon wafers with thin layers of the metals in a vacuum environment, one of multiple steps involved in the silicon probe fabrication process.

Deep brain stimulation (DBS) is FDA approved for symptoms of PD and essential tremor and currently is being evaluated as a treatment for other neurological conditions. Electrical stimulation in the subthalamic nucleus (STN) — a group of cells about the size of a pea located deep in the human brain — can improve all the symptoms of PD, including bradykinesis, rigidity and tremors.

However, stimulation has so far been delivered through macroelectrodes that are quite large, resulting in side effects such as unwanted muscle contraction and speech and vision disturbances. Han and laboratory director Douglas McCreery, PhD, also a biomedical engineer, believe that by developing new microelectrode arrays they achieve greater selectivity and precision of stimulation.

For more than 25 years the HMRI neural prosthesis team has been meeting the daunting challenges inherent in designing implantable electrodes. They have already developed a prototype electrode array for deep brain stimulation, as well as an apparatus for implanting the array. The HMRI arrays are safe to implant, have functioned safely for several years, can deliver controlled-current stimulation for many hours each day, and are made of materials that can withstand the chemical environment of the human body. The new devices will add more electrode sites, be capable of

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New Studies Aim to Find Early Cancer Biomarkers

Biochemist James Riggins, PhD, joined the Molecular Neurology Laboratory in December 2004, launching a new project in HMRI's ongoing studies of disease at the molecular level. With laboratory director Dr. Michael Harrington and Drs. William Corey and Myron Tong of the HMRI Liver Center, he is developing a way to find early biomarkers for liver cancer.

Riggins earned an undergraduate degree in biochemistry, *magna cum laude*, from McDaniel College in Maryland and his PhD in chemistry from Vanderbilt University. He brings a strong background in data analysis, mass spectroscopy, and related technologies such as 2-D gel electrophoresis to HMRI's current proteomic studies. "I've been interested in how protein and DNA changes may signify disease for the majority of my scientific career," he said recently. "I look forward to working with this specific disease here at HMRI."

Photo by Ryan Beck

Dr. James Riggins removes tissue and serum samples from a freezer for use in his search for biomarkers of liver cancer. Dr. Myron Tong of the HMRI Liver Center has collected these archival materials during 25 years of treating patients with liver disease.

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ALF Honors Dr. Myron Tong For Advances Against Liver Disease

The Greater Los Angeles Chapter of the American Liver Foundation (ALF) honored Myron J. Tong, MD, at its 6th Annual Gala Recognition Dinner. Tong, Medical Director of the HMRI Liver Center, is one of the world's leading hepatologists, specializing in diseases of the liver, including cancer, for more than 25 years. He discovered that Hepatitis B is one of the primary causes of liver cancer.

Dr. Ron Busuttil, Professor and Executive Chairman of UCLA's Department of Surgery, and head of the Pfleger Liver Center and the Dumont-UCLA Transplant Center, said in presenting the ALF Medical Award to Tong, "Myron and his colleague, Dr. William Corey, have cared for thousands of patients with liver diseases of all types. He is a world expert in therapy of

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Considering the Potential of Stem Cells

By Chuck Champlin

California voters in November expressed their excitement about stem cell research by passing the California Stem Cell Research and Cures Initiative. Over the next ten years, the state will sell $3 billion in bonds to fund many research projects, hoping to tap the potential of these special cells that are so pivotal in human development.

Like the moon program of the 1960s, there is a goal – curing disease with new stem cell technology. Unlike the moon program, the goal is very broad and there is a lot of uncertainty about how to get there. Recently, researchers at HMRI talked about their ideas and experiences relative to the potential of stem cell research.

"It doesn't take a rocket scientist to understand that if a stem cell can make any kind of cell in the body, you can make a new cell to replace a bad cell," said Marylou Ingram, MD, of the Tissue Engineering Laboratory. "The hitch is that it's very complicated to know what message to give to a stem cell to tell it to make another cell. A lot of people are trying to understand what the molecular messages are, how and when to apply them, and how to turn them on and off. It's a huge problem, but the general nature of the questions that have to be answered is pretty clear."

According to Michael Harrington, MD, of the Molecular Neurology Laboratory, "The good news is, there is tremendous scientific expertise in California. The experts on the initial panel are world leaders in science. I'm optimistic that they'll come up with a good strategy and plan. The major benefit from stem cell research will be learning how cells are regulated and regenerated – how they become organs. If we know these things, we can begin to envision remedies for all sorts of diseases."

What is a stem cell?

The term "stem cell" suggests the stem of a plant or a tree, which branches out into the leaves, the flowers, the pollen, the fruit, the seeds and acorns.

Human stem cells come in two major classes. The embryonic stem cell has been the major focus. These cells make up the inner cell mass of the embryo in its early development. They are key because they evolve and differentiate into every tissue of the body as the embryo grows into a fetus. Because of this unique power to become any cell, they are called *pluripotent* stem cells. They only exist for a brief time in the evolution of a human body; however, when isolated in tissue culture they have the capacity to keep proliferating indefinitely.

A second major category of stem cells includes progenitor cells or tissue stem cells that exist in the adult body. Further along the chain of differentiation, these adult stem cells are called *multipotent* because each one can evolve into a limited set of functional cells within their tissue type. There are scores of these different adult progenitor stem cells in the tissues of the body, but they are relatively few in number, hard to identify and hard to collect and grow.

"The truth is that every tissue has these adult stem cells," said Dr. Ingram. "Skin has stem cells. The liver has stem cells. The pancreas has stem cells, and so on. In fact, the current thinking is that in most cases cancers represent abnormalities in the functioning of tissue stem cells."

These cells serve as a cell production system in the tissues of the body to help maintain, repair and regenerate the cells within their tissue type. After the progenitor divides to produce a red blood cell progenitor, for example, that new cell divides repeatedly to maintain the proper level of specialized cells in the body.

Stem Cells for Blood

In her work on blood, cancer and tissue growth, Ingram has learned a lot about bone marrow stem cells, called the *hematopoietic* stem cell, literally "blood producing." This cell resides in bone marrow and produces both red and white blood cells and other cells of the blood. When a hematopoietic stem cell gets a signal to divide, it will make two daughter cells, she explains. One of those will be another stem cell, which will just sit there. The other cell will become a more differentiated progenitor cell (red or white blood cell or platelet), which will proliferate to produce a large number of specialized cells in the blood. Pretty soon you have a small pot of stem cells and large masses of differentiated cells. "Many people think this is where cancer can come from, in a division from a tissue stem cell that produces abnormal daughter cells," she said.

Bone marrow stem cells were among the first stem cells to be isolated in reasonably substantial numbers for experiment. The potential of these multipotent cells to become a variety of other specific cells is still being explored. "You can take these bone marrow stem cells and entice them to produce cells of other tissues," Ingram said. They can make liver cells, for example. They probably can make myocardial (heart muscle) cells. In fact, some researchers are injecting bone marrow into myocardial infarct (heart attack) patients. There is reasonably good evidence that these cells can transform into new myocardial cells. Thus, these multipotent stem cells can respond to different messages and divide into several different kinds of functional cells. There is even some evidence that bone marrow stem cells can make new brain cells. People are asking, "Just how plastic are these adult tissue stem cells?"

Ingram points out that there may be real potential if we can learn how to nudge adult tissue stem cells to become certain kinds of needed cells. "If you knew how to manipulate these cells directly from a patient, you wouldn't have to worry about transplanted tissue rejection, which is the big problem with anything that you put in from an embryo. It would be wonderful to get the stem cell from the tissue that you want in the first place and know it would match. That, I believe, may be more realizable in the foreseeable future," she said.

Looking at Brain Function

Dr. Harrington is studying changes that occur in brain chemistry during various brain malfunctions. While he says that his work does not relate directly to stem cell research, his investigations could potentially fit in at any time. They may help shed light on the molecular changes that are so important to stem cell evolution.

Harrington's team is working with patients who have severe headaches, schizophrenia, depression, Alzheimer's and Parkinson's disease. They are asking the question: What's different at the molecular

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Cell Therapy at HMRI

Stem cell therapy is an emerging 21st century phenomenon, but cell therapy is not new. In this photo, research assistant Laszlo Csernohorszky processes a patient's immune cells that were stimulated and cultured, following a procedure developed at HMRI, in preparation for implantation into the patient's brain after neurosurgeons removed a malignant tumor. The patient was one of nearly 200 with malignant brain tumors who were treated using the HMRI cellular immunotherapy procedure in an FDA-approved clinical trial between 1985 and 1992.

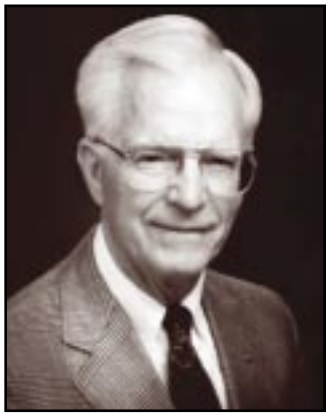
Clinical applications of cell therapy in general, and stem cell therapy in particular, will require significant advances in isolation and culture of the cells themselves. We must have a much greater understanding of the complex molecular signals that control the cells' survival, specialization, migration and their capacity to interact appropriately with other cell types. All these factors determine the success with which they can be integrated into the vital economy of the living organism. ◆

Incumbents Are Re-elected

Hezlep and Higgins Join HMRI Board

The HMRI Board of Directors elected Herbert Hezlep III and Thomas E. Higgins to membership on January 26, 2005. President Roger Engemann was pleased with their addition to the Board, saying, "Men of Tom and Herb's stature and community involvement will make a big impact on the future of HMRI."

Seven incumbent directors were elected to additional three-year terms. They are Michael C. Doyle, James T. Helsper, MD, R. William Johnston, CL Keedy, Robert J. Mackin, Jr., PhD, Harold J. Meyerman and John H. Richards, PhD. In addition, all incumbent officers were re-elected to one-year terms: Roger Engemann, president, Michael Doyle, vice-president, John Russell, secretary, and Harold Meyerman, treasurer. William Opel, PhD continues to serve as executive director (CEO).



Herbert Hezlep III

Herbert Hezlep was born in Pittsburgh, attended Pasadena public schools, including Pasadena City College, and received a BS in Business Administration from the University of California, Berkeley.

After working three summers for the Yellowstone Park Company he joined his family's hardware manufacturing company, Acme General Corporation, where he served in various capacities, eventually becoming president, chairman and CEO. He took Acme public and later performed a leveraged buyout and sold the company to The Stanley Works, from which he retired in 1988.

Hezlep has served as a member of the session, the board of trustees and as chair of the investment committee of the Pasadena Presbyterian Church. He chaired the building committee and served as president of the Santa Anita YMCA, as well as president of the Pasadena YMCA, where he received the Y's Man of the Years award. He has been treasurer and chairman of the finance committee of the Pasadena City College Foundation. In the Monrovia Rotary Club he has been president and has been active at the District level, largely in group study and youth exchange programs.

He also established the Hezlep Family Foundation, serves on its board, and has directed contributions to HMRI's capital projects over the last few years, including the new electron microscopy suite.

"I have known of HMRI's good work for a number of years and am honored to be joining the Board," he said. "I look forward to helping in any way I can." He and his wife Liz live in San Marino and have traveled extensively, with over 900 days at sea and visits to 125 countries. They have a son, three daughters and four grandchildren.

Thomas E. Higgins

Thomas Higgins is a businessman with a longstanding interest in medicine and medical research. He is chairman of Higgins, Marcus & Lovett, Inc., a business valuation organization in Los Angeles.

He earned a Bachelor's degree from the University of Southern California and an MBA from Pepperdine University, where he has been on the finance faculty and the University Board. He completed courses in securities analysis through the New York Institute of Finance, as well as in finance, tax, securities analysis and accounting through USC and UCLA.

"My professional life has been spent largely among business people, so I'm excited about this increased exposure to the world of medicine and medical research," said Higgins. "HMRI is truly on the cutting edge of medical discoveries that are changing and improving people's health and quality of life."

Higgins started his career as an account executive and securities analyst with McDonnell and Company. He then moved to the appraisal business, where he became vice president of Valuation Research Corporation, analyzing value and depreciation of businesses, including their property and fixed assets. He was a founder of Higgins, Marcus and Lovett, Inc., which does corporate valuation studies and provides expert testimony, including participation in settlement hearings with the IRS. He is a member of the commercial panel of arbitrators for the American Arbitration Association, has lectured widely on business valuation to legal, finance, academic and civic organizations, and made radio and television presentations.

He is a former board member and past president of the Jonathan Club and belongs to the Los Angeles Yacht Club. He and his wife Karen live in Pasadena and are supporters of the Pasadena Symphony. They spend most weekends at their mountain retreat in Idyllwild, where he has been active on the Board of Governors of the Idyllwild School of the Arts. They have a son and two grandchildren.

HMRI Executive Director William Opel, PhD, said, "Herb Hezlep and his family have been longtime generous donors to HMRI. Tom Higgins has a deep interest and family history in medical research. Both have potential to help enhance our ongoing development of new medical knowledge and technology that will help restore health to many people." ◆

Cancer Biomarkers *continued from page 1*

In his studies Riggins will use samples of blood serum from archival materials collected and preserved by Dr. Tong during more 25 years of treating patients with liver disease. His goal is to develop a blood surveillance method for patients that would indicate a liver tumor is starting to grow, allowing doctors to treat it early. "These specimens could unlock secrets about the molecular characteristics of hepatitis, which often leads to hepatocellular carcinoma (HCC)," said HMRI Executive Director Dr. William Opel. "These study samples are invaluable in terms of what they can do for humanity."

The research involves measuring thousands of proteins and protein changes in the serum of patients with HCC, hepatitis B and C, and from normal controls, in order to detect abnormal proteins that occur specifically in those conditions. The noted changes would be considered biomarkers of liver disease. Designed as a long-term study, the project will produce a "mosaic" of protein changes in all types of chronic liver disease.

Eventually, Riggins will apply these biomarker studies to develop a clinical assay that physicians can use to help monitor and treat their patients. One known biomarker for HCC — alphafetoprotein (AFP) — increases in the blood of some, but not all, HCC patients. Also, it lacks the reliable sensitivity needed for early detection. "We hope to find definite, consistent pre-cancerous markers sensitive enough for surveillance so that clinicians can have more options for treatment and patients have better chances of beating the disease," said Dr. Harrington.

Dr. Corey, Research Director of the Liver Center, said, "If we can identify a specific protein in serum unique to liver cancer, we'll have a new tool for early detection, leading to better outcomes. We were hoping to find a scientist such as Dr. Riggins to participate in these studies."

The epidemic occurrence of hepatitis B and C, especially in Asian populations, makes these studies important to hundreds of thousands of people in southern California. Many who received the virus through blood transfusions before screening was required have unknowingly carried latent disease, which finally appears as advanced liver disease or HCC. ◆

Microchip Electrodes *continued from page 1*

delivering localized stimulation to many locations within the target nucleus, and will be compatible with the arrays now in clinical service. Of great importance will be their ability to stimulate and record the activity of individual neurons — in the STN or other target sites in the brain — via the same set of microelectrodes.

Before arriving at HMRI, Han knew of HMRI's expertise in electrode design and fabrication. He was familiar with the book "Neural Prostheses" by William Agnew and Doug McCreery and made contact with HMRI scientists during scientific meetings in 2002 and 2003. He was subsequently invited to present a lecture on his PhD thesis work on microelectrode arrays and joined the Neural Engineering Laboratory in 2003. "The capabilities that Martin brings to our group will allow us to develop neural prostheses that are state-of-the-art in every sense," says McCreery.

Han had previous experience with semiconductor manufacturing technology during his PhD studies, when he helped develop microchips to replace damaged areas of the hippocampus, a part of the brain involved in learning and memory. He is an expert in photolithography (the science of making microchips) and is familiar with state-of-the-art technologies such as deep-reactive ion etching. In his new endeavor, he welcomes HMRI's extensive experience working with the biological environment of implanted electrodes. "It is unusual to have both these capabilities within the same group," he said.

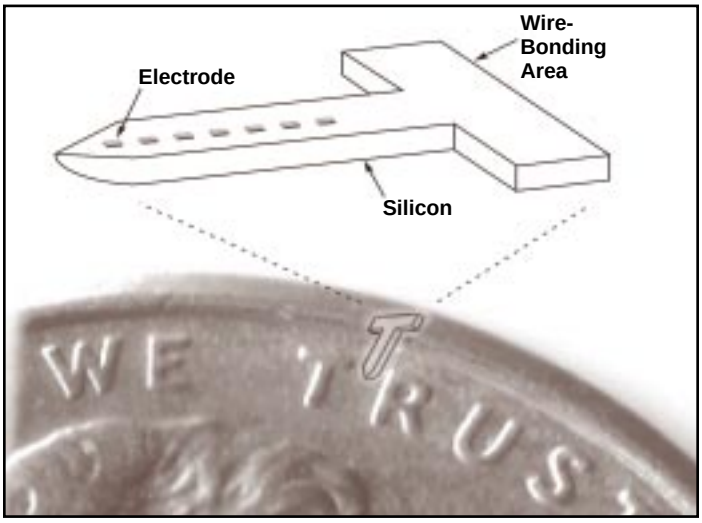


Illustration: Martin Han, PhD

Schematic shows a silicon-based microelectrode array to be fabricated by HMRI bioengineer Martin Han, PhD, using photolithographic techniques. The overall dimension of the array device is approximately the same as the letter "T" on a penny.

In the study's first phase he will work in a micromachining laboratory with a clean room for semiconductor fabrication. Making the microelectrodes will be a multi-step process. He will use solid sheets of silicon, which has the physical and chemical properties amenable to photolithography, and will work with small devices in micron scale. "Making the first one is the biggest challenge," he says. "After that, it's like using a cookie cutter."

Once a suitable device is developed for implantation, a corporate partner will provide the electronics required to interface with the electrode array. HMRI will then seek clinical partners so physicians will have an effective therapy to offer their patients.

Over the horizon, "smart stimulators" could monitor the pattern of neuronal activity in and near the implant sites deep in the patient's brain throughout the patient's life and make adjustments to the stimulation. By requiring less frequent intervention by a neurologist, they would also reduce ongoing costs and inconvenience to the patient.

"DBS will likely always be costly and carry some risks," McCreery says, "but so far it is the best alternative for patients with advanced Parkinson's disease whose medications have become ineffective. We believe our proposed system will greatly improve and preserve quality of life for a number of years for persons with PD and other movement disorders." ◆

Invitation to "A Tuscan Sunday"

Photo by Florence Photography

"A Tuscan Sunday" co-chairs Julie Manning (left) and Marie Darr prepare to relax and enjoy the Altadena Guild's May 1st Home Tour to benefit HMRI.

The Altadena Guild will offer an afternoon in Italy at the 54th annual home tour, "A Tuscan Sunday," on May 1. The tour benefits HMRI's research programs. Co-chairs Marie Darr and Julie Manning and Guild members are preparing beautiful homes and gardens for visitors, anchored by an open *piazza* filled with market umbrellas, strolling musicians and rustic carts.

Tour hours are 10:00 a.m. to 4:00 p.m. At a garden café, situated on a gently rolling lawn with graceful palms, complimentary coffee and dessert will be offered beginning at 11:00. Handmade boutique items will be available for sale from market carts in the colorful *piazza* as will "street art" from Guild members' original creations.

Three stately Altadena houses built in 1922, 1926 and 1927 will be featured on the tour. Renovations have retained original architectural features and have been done with sensitivity to the historical significance of the structures. One home features extensive decorative painting and a garden and arbor designed by Frank Lloyd Wright, Jr.

Beautiful custom woodwork is prominent in an elegant Italian Period Revival home owned by the Balian family. Since 1955 it has been known throughout the area for extensive lights and decorations during the holiday season. This home has a special connection with HMRI's early history. Wine tasting in the garden here will be a new feature of the tour, at an extra cost of $8.

Guild members' specialty food items will be for sale at one of the houses, and a beautiful, handmade, queen-sized quilt is being offered as an "opportunity drawing" item. As always, floral arrangements prepared by Guild members will grace all the homes.

Guild president Kathy Klomburg invites everyone to enjoy this special day, saying, "We are excited to see our Altadena hills transformed to those of Tuscany for the benefit of HMRI."

Tickets cost $22 in advance and are available at Huntington Hospital Gift Shop, HMRI at 734 Fairmount and 99 N. El Molino, the Altadena Webster's Shopping Center in the Pharmacy, and at Mofit, 1389 E. Washington Blvd. in Pasadena. The day of the tour they can be purchased for $25 at the corner of Allen and Mendocino in Altadena.

For additional information call 626.304-4678 or visit www.altadenaguild.org. ◆

Peggy Rinderknecht

HMRI extends sincere condolences to the family of Peggy Rinderknecht, long-time member of the Altadena Guild, who passed away on January 2, 2005.
The family suggests memorial donations to HMRI, 734 Fairmount Avenue, Pasadena, CA 91105.

Dr. Tong Honored *continued from page 1*

Hepatitis B and C, diseases that often attack healthy individuals and rob lives. His work has such tremendous importance and effect."

Busuttil described Tong as having unique and formidable abilities. "He's a brilliant clinician, a healer with a gentle manner and extraordinary empathy; he's a gifted scientist, has laser focus, a hunger for knowledge and the ability to find answers in complexity; and he's a world-class teacher — articulate, unselfish — and role model. Every single day of his career, he's made life better for his patients, for his students, and for his colleagues," he said. "When future medical historians chronicle the story of hepatology in our time, Myron Tong is going to be a key figure."

Lori and Dr. Myron Tong

Currently, Drs. Tong and Corey are testing new medications for treatment of hepatitis B and C in clinical trials. In a new research program with HMRI's Dr. James Riggins, Tong is seeking protein markers in the blood that would indicate early liver tumors. Besides his ongoing role at HMRI, Tong was recently named Director of Clinical Hepatology at the UCLA Dumont Liver Cancer Center.

William Opel, PhD, HMRI Executive Director, said, "We join Dr. Tong's patients, colleagues and friends in congratulating him for his great accomplishments in research and his outstanding clinical care of patients with hepatitis and liver cancer." ◆

Janet Rich spoke at the recent American Liver Foundation banquet honoring HMRI's Dr. Myron Tong. A former patient of Dr. Tong and a new member of the Board of the American Liver Foundation, she said appreciatively, "I feel so fortunate. As a result of Dr. Tong's dedication to liver disease treatments and cures, today I am healthy and hepatitis free. I am grateful to Dr. Tong and his fine team at the HMRI Liver Center. May the research continue!"

Photos by Debra Lex

Stem Cells *continued from page 2*

compositional level when someone is healthy versus when they are sick? They employ techniques to look at many of the important molecules in their patients – their DNA, proteins, lipids, for example. "These molecules are what we're made of," Harrington said. "The same molecules are going to be the ingredients and influencers in cells as they progress from their omnipotent stem cell state down to their ultimate, differentiated state.

"It's a pretty loose conceptual connection between our work and stem cells, but we have worked with Dr. Marylou Ingram on neural progenitor cells. The idea there was to understand the molecular components of those cells as they differentiated down a path. We would use the same technology approach that we use in our current studies to look at stem cells. Meanwhile, we're making some good progress understanding both migraines and Alzheimer's disease."

Would Harrington's team take on stem cell research? He says that right now they have their hands full with current work and would be cautious about taking on a project that is a distraction, just because the funding is there. "You don't spread yourself all over the map just to get funding," he said.

Nonetheless, he will follow the developments in the molecular dissection of how stem cells learn to develop and differentiate. His research team will watch for any connections that may fit in with the changes they are finding in brain disease. "I think it will work beneficially both ways," said Harrington. "We will find changes in the chemical pathways related to brain disease. This might shed light on molecular messages you could use with stem cells and their biochemical machinery."

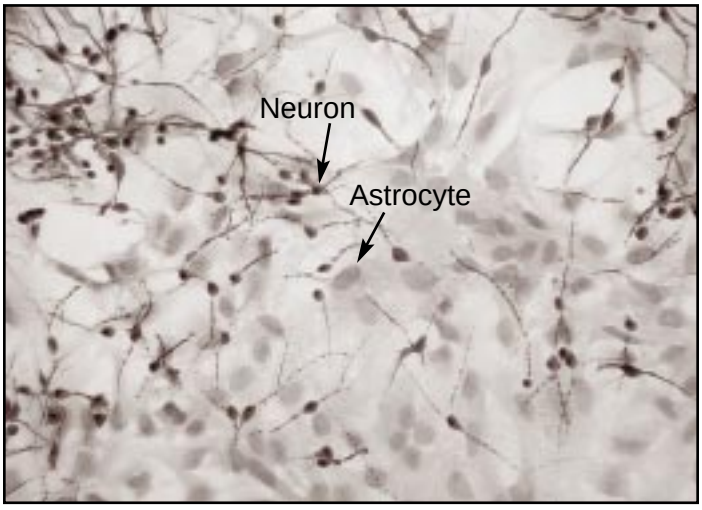
Engineering Nerve Growth

Douglas McCreery, PhD, runs the Neural Engineering Lab at HMRI. In the past, he and his team have produced devices to generate electrical signals in the brain and nerves – for example, to control seizures. He sees potential for stem cells to produce beneficial results in the nervous system.

McCreery says that research in the past 20 years has shown that the adult nervous system has more ability to rewire itself (plasticity) than was previously thought. Stem cell research that could lead to neural grafts, if they could make the proper connections, could potentially lead to restoration of brain or nerve tissue. An example of this would be to restore the part of the brain that degenerates in Parkinson's disease. The disease causes the cells to stop producing needed dopamine.

The first step, characteristic of all stem cell research, would be to induce stem cells to grow into the proper cell type that could once again produce dopamine. The tissue would be surgically implanted in the brain. But there would be a second problem – inducing the nerve cells to form the proper relationship with the other cells. The new cells have to be integrated both physically and functionally into the existing tissue. "I believe it might be possible," McCreery said, " – and there is evidence from related studies that it might be possible – that electrical stimulation could be used to guide the electrical connections in the cells."

He would capitalize on a principle in the nervous system that helps lead to the right electrical contacts during development of the brain and nervous system. The principle is summarized in a catchy phrase: "Neurons that fire together, wire together." He believes that by inserting tiny electrodes into both the new and existing tissues, synapses could be encouraged to grow across the gap. This has already been demonstrated in an auditory nerve channel, and McCreery said it might also hold promise for spinal cord injuries, but would be a more difficult problem. "It seems quite possible that electrical stimulation, and arrays of electrodes within the nervous system, could capitalize on



HMRI's Marylou Ingram, MD, and Michael Harrington, MD, have studied human neuroprogenitor (a kind of stem cell) cells such as these in culture to understand how they differentiate. The cells were immunostained to demonstrate the presence or absence of two specific marker molecules that identify them as either dopaminergic neurons (the small dense cells that express both markers) or astrocytes (the larger, lighter cells with oval nuclei that do not contain the markers). Neurons and astrocytes are two major cell types in the brain.

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Golf 2004

Lynn Smith Tourney Scores Generous Gift

Photo by Penny Gill

At its December 3rd meeting the Altadena Guild presented HMRI with a check for $44,269.77, the proceeds from the October 18th Lynn Smith Memorial Golf Tournament. Pictured, left to right, are 2005 golf chair Carole Lambert, 2004 golf chair Deborah Smith, HMRI Board president Roger Engemann, Altadena Guild president Kathy Klomburg and John Howe, golf sponsor and Golf Committee member. ◆

Stem Cells *continued from page 5*

the principle of neuronal organization and help neural grafts grow into place. That's how I think our neural prostheses might ultimately tie in to stem cell research. The electrical stimulation will help model and integrate new nerve tissue that has been developed from stem cells."

A key issue, however, is what would happen to the patient's persona following a neural graft. In the higher centers of the brain such as the cerebral cortex, neural cells, their synapses and interactions are what determine who we are as a person. "It's precisely these areas of the brain that are affected by Alzheimer's disease – which is why Alzheimer's is so destructive to the persona," McCreery said. "If you were to replace those diseased cells with good healthy cells, you would have a different person, one who would be alive but who wouldn't remember anything of his past. On the other hand, the brain would probably be able to learn again. Also, it's worth remembering that in many cases information is preserved on both the left and right sides of the brain.

"There are other parts of the brain that learn and become shaped in response to environmental stimuli, but they do not contain the persona. The part of the brain damaged in Parkinson's disease is a very important part of the brain, but there is no indication that you would have a different person if it were replaced."

Conclusion

So what is the main promise of stem cell research? Perhaps it's the possibility of growing a new lung or liver for cancer patients, and other miracles of that sort. The sky's the limit when it comes to imagining the possibilities. That's a concern for Marylou Ingram, who said, "It's too bad they got advertising people in the picture so early. They are all well-meaning people, and they are all heartfelt advocates. But it's really been hyped. There is so much fundamental work to be done before it's ready to be anything. Maybe the sheer numbers of researchers at work plus the voice of the populace will make a difference."

Most likely, the developments will be more subtle but still profound. "I think the prominent area will come as we discover how cells develop and grow and are activated into healing processes," said Mike Harrington. "Then we can promote those activities as they are needed. If you need extra tissue, you could promote it. Obviously if that were done without control, you would have cancer, or something akin to it, so this is not an area that will be simple at all. Once we learn how those steps can be taken – how to regulate the progression from primitive stem cells to established tissue cells – from that knowledge can come a lot of therapy." ◆

HMRI Spectroscopy Team Teaches 20th Successful Clinical MRS Course

By Alex Lin

For the 20th time since 1995, Huntington Medical Research Institutes offered our popular Clinical Magnetic Resonance Spectroscopy Course March 11-14, 2005. More than a dozen radiologists, neurologists and radiology technologists came to Pasadena for this session, which was led by Dr. Brian Ross and his MRS staff. In the fall of 2004 the course was presented in Shanghai, China.

HMRI Executive Director Dr. William Opel hosted a welcome banquet with opening lectures at Pasadena's Valley Hunt Club. During the next four days, the MRS students were taught everything they would need to establish successful spectroscopy practices at their own radiology centers, at major hospitals such as Children's Hospital Pittsburgh, or at academic sites such as the University of Utah.

They learned the basic physics of spectroscopy; MRS of brain tumors, Alzheimer's disease, pediatric disorders and metabolic diseases; high-field (3T+) spectroscopy; reimbursement; and spectroscopy outside of the brain. Lectures were held at Huntington Memorial Hospital and hands-on demonstrations given at the MR scanner at 10 Pico Street, where the first HMRI radiology courses were begun by Dr. Ross' predecessor, Dr. William Bradley.

We proudly presented two lectures in memory of HMRI's co-founders, neurosurgeons C. Hunter Shelden, MD, and Robert H. Pudenz, MD. In the Shelden Memorial Lecture, Dr. Edward Helmer of Kaiser-Permanente Sunset, LA, spoke about how MRS changed his practice of radiology. (The course is held at the 10 Pico Street Magnetic Resonance Laboratory named after Shelden.) Dr. Gordon McComb of Children's Hospital Los Angeles presented the Pudenz Memorial Lecture, marking the first time a neurosurgeon has given a talk about MRS at our course. Pudenz invented the hydrocephalus shunt at HMRI and was a long-time supporter of the MRS program.

Corporate support was again provided by General Electric Healthcare, which recognizes this course for its importance and excellence in spectroscopy education by providing full scholarships for six attendees. Specialists from all major equipment manufacturers were represented at this course, providing full technical support to our attendees.

One of this year's attendees, Dr. Marc Bintner, traveled a record-setting distance of 11,455 miles across the world from Reunion Island, just east of Madagascar.

Continuing Medical Education credits were sponsored by Huntington Memorial Hospital. In comments made via anonymous CME surveys, attendees gave all instructors excellent scores. One stated: "This is one of the best, if not the best CME course I have ever taken. It met or exceeded every expectation I had for the weekend." ◆

Former Student Travels From Japan To Honor His Friend and Mentor

When HMRI's Dr. Richard Bing was honored at a recent benefit, "Forever Young," sponsored by the Huntington Hospital Senior Care Center, his friend Dr. Kinji Ishikawa traveled from Osaka, Japan, to attend. Ishikawa did cardiac metabolism research studies in Dr. Bing's Experimental Cardiology Laboratory at HMRI in 1972-73. He is now Director of Kinki University Hospital at the Kinki University School of Medicine. ◆

Huntington Medical Research Institutes
Publication List 2004

HMRI scientists communicate and permanently record research results in books and journals circulated to colleagues and libraries worldwide. Editorial boards comprised of other experts carefully examine the experimental procedures, data and interpretations by HMRI scientists before accepting any article for publication. In each of the following entries, authors' names are followed by titles of papers, and the names of journals are printed in italics.

Cardiology

Bing RJ. Advances in heart health. Cardiac Research – Past, Present and Future. *CV Network* 3(2):16, 2004.

Bing RJ. Paul Ehrlich and his magic bullets, *Heart News and Views* 12(2):4-6, 2004.

Bing RJ. The endless river. *Heart News and Views* 12(1):3-5, 2004.

Bing RJ. Past Truth and Present Poetry. The Nobel Prize and its history. *Heart News and Views* 11(3):3-4, 2004.

Gene Therapy

Saha B, Zhang N, Naritoku WY, Tsao-Wei DD, Groshen SL, Carlsson G, Larsson L, Gustavsson B, Chaiwun B, Taylor CR, Imam SA. LEA 135 expression: Its association with a lower risk of recurrence and increased overall survival of patients with lymph-node positive primary invasive breast cancer. *Anticancer Research* 24:2391-2400, 2004.

Liver

Blatt LM, Tong MJ. Epidemiology of chronic hepatitis viruses: Hepatitis B virus and Hepatitis C virus. *Hepatitis Prevention and Treatment*, Colacino JM and Heinz BA, eds. Birkhauser Verlag/Switzerland, 2004.

Lung

Glovsky MM, Ward PA, Johnson KJ. Complement determinations in human disease. *Annals of Allergy, Asthma and Immunology* 93:513-523, 2004.

Taylor PE, Flagan RC, Miguel AG, Glovsky MM. Release of respirable allergens into the outdoor air. In: *Allergy Frontiers and Futures.* Allergy and Clinical Immunology International – Journal of the World Allergy Organization. Supplement 1. Proceedings of the 24th Symposium of the Collegium Internationale Allergologicum. Eds: Bienenstock JB, Ring T, Togias AGT. Hogrefe and Huber Publishers, USA, p 15-16, 2004.

Taylor PE, Flagan RC, Miguel AG, Valenta R, Glovsky MM. Birch pollen rupture and the release of aerosols of respirable allergens. *Journal of Clinical Experimental Allergy* 34:1591-1596, 2004.

Taylor PE, Jonsson H. Thunderstorm asthma. *Current Allergy and Asthma Reports* 4:409-413, (Invited Review), 2004.

Magnetic Resonance Spectroscopy

Haseler LJ, Lin AP, Richardson RS. Skeletal muscle oxidative metabolism in sedentary humans: 31P MRS assessment of O2 supply and demand limitations. *Journal of Applied Physiology,* 2004. Sept:97(3):1077-81. Epub May 07, 2004.

Kanamori K, Ross BD. Quantitative determination of extracellular glutamine concentration in rat brain, and its elevation in vivo by system A transport inhibitor, alpha(methylamino)isobutyrate. *Journal of Neurochemistry* July:90(1):203-10, 2004.

Molecular Neurology

Davidsson P, Harrington MG. Human cerebrospinal fluid. In: *Biomedical Applications of Proteomics*. Sanchez, Hochstrasser, Corthals, Eds. Wiley-VCH, Germany, pp 341-353, 2003.

Fonteh AN. An outline of arachidonate remodeling and its biological significance. In *Arachidonate Remodeling and Inflammation*. Fonteh AN, Wykle RL, eds. Birkhauser Verlag Basel, Switzerland, pp 1-11, 2004.

Marion CR, Fonteh AN. Enzymatic and receptor mediated effects of secretory phospholipase A2 on the pathophysiology of inflammatory disease. In *Arachidonate Remodeling and Inflammation*. Fonteh AN, Wykle RL, eds. Birkhauser Verlag Basel, Switzerland, pp 37-60, 2004.

McAlexander AM, Barham BJ, Johnson M, Fonteh AN. Control of long chain polyunsaturated fatty acid levels and the role of inhibitors of incorporation and remodeling on the biosynthesis of lipid mediators. In *Arachidonate Remodeling and Inflammation*. Fonteh AN, Wykle RL, eds. Birkhauser Verlag Basel, Switzerland, pp 89-113, 2004.

Fonteh AN and Harrington MG. Remodeling of arachidonate and other polyunsaturated fatty acids in Alzheimer's disease. In *Arachidonate Remodeling and Inflammation*. Fonteh AN, Wykle RL, eds. Birkhauser Verlag Basel, Switzerland, pp 145-167, 2004.

Molecular Oncology and Genetics

Eggerding FA. The Oligonucleotide Ligation Assay, in *Medical Biomethods Handbook*, Rapley R and Walker J, eds, Humana Press, Totowa, NJ, Chapter 22, pp 293-303, 2004.

Neural Engineering

Cogan SF, Guzelian AA, Agnew WF, Yuen TGH, McCreery DB. Overpulsing degrades activated iridium oxide films used for intracortical neural stimulation. *Journal of Neuroscience Methods* 137:141-150, 2004.

Lossinsky AS and Shivers RR. Structural pathways for macromolecular and cellular transport across the blood-brain barrier during inflammatory conditions. Review. *Histology and Histopathololgy* 19:535-564, 2004.

Manoonkitiwongsa PS, Schultz RL, McCreery DB, Whitter EF, Lyden PD. Neuroprotection of ischemic brain by vascular endothelial growth factor is critically dependent on proper dosage and may be compromised by angiogenesis. *Journal of Cerebral Blood Flow and Metabolism* 24: 693-702, 2004.

McCreery D, Pikov V, Lossinsky A, Bullara L, Agnew W. Arrays for chronic functional microstimulation of the lumbosacral spinal cord. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 12:195-207, 2004.

McCreery D. Tissue Reaction to Electrodes: The problem of safe and effective stimulation of neural tissue. In: *Neuroprosthetics: Theory and Practice*, pp 592-611. Horch KW, Dhillon GS, eds. Singapore: World Scientific Publishing Co., 2004.

Pikov V. Spinal Plasticity. In: *Neuroprosthetics: Theory and Practice*, pp 302-316. Horch KW, Dhillon GS, eds. Singapore: World Scientific Publishing Co., 2004.

Pikov V, McCreery DB. Mapping of spinal cord circuits controlling the bladder and external urethral sphincter functions in the rabbit. *Neurourology and Urodynamics* 23:172-179, 2004.

Torres Memorial Golf Tournament Will Benefit Cancer Research at HMRI

Friends and family of 2nd Lt. Andrew Torres will hold a golf tournament in his memory on April 18th to benefit cancer research at HMRI. It will take place at the beautiful La Canada Flintridge Country Club, with dinner following for golfers, guests and supporters. Silent and live auctions will add to the festivities.

2nd Lt. Andrew Jacob Torres, USMC

The day will begin with a putting contest in the morning and a barbecue lunch for the players, accompanied by mariachi music. Rusnak Chrysler Jeep & Dodge of Pasadena is offering a beautiful Chrysler 300C as a Hole-in-One prize, and many businesses and individuals in the area have contributed to the event.

Andrew Torres, who lived in La Canada, was a graduate of the U.S. Naval Academy in Annapolis. He was 23 years old and on active duty in the Marine Corps at the time of his death in April 2004. Many of his high school friends from the Flintridge Prep Class of 1998 were active on the tournament organizing committee, carrying out his wish that they help find a cure for liver cancer. Classmate Noelle Ito said, "We wanted it to be a community event to celebrate Andrew's life and help find a cure for cancer."

The proceeds will support studies by HMRI's Dr. Myron Tong and Dr. James Riggins to develop a biomarker for hepatocellular carcinoma. (See story on page one.) Dr. Tong said recently, "An accurate blood test for liver cancer is sorely needed, because liver cancer is a silent disease that often goes unnoticed until it's too late. We're very grateful that the Torreses are putting on this tournament to help us conduct this research."

Andrew's mother Anita Brenner Torres said recently, "We are pleased that HMRI is doing this research that will hopefully benefit patients with solid tumors." She added, "This will be an annual event."

More information about Andrew Torres and the tournament is available at www.andrewtorres.org, and by calling 792-3175.

HMRI extends its appreciation to the Torres family, the hard working golf committee, Andrew's friends and classmates, and the generous sponsors and players who are taking part in this very special event.

Special thanks to the following individuals, organizations and foundations for major gifts November 2004 through February 2005

Dr. John B. Baldeschwieler and Marlene R. Konnar		Lucile Horton Howe & Mitchell B. Howe Foundation	
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Mr. and Mrs. Roger Engemann	Liver research	Robert H. Pudenz & Rita Coveney Pudenz	
Joan A. Fritz	MRS 4T Project	Advised Fund of the Greater Cincinnati Foundation	
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Maralou and Jerry Harrington	Golf Tournament, Rhodamine Project and General research	Peggy and John Russell	
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Herbert Hezlep III		Slavik Family Trust	
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Jacobs Engineering Foundation	2005 Golf Major Sponsor	Judy and Bob Spare	
Bill and Pat Johnston		Alan Stock	Epilepsy research
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Major Gifts are listed on page 8

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HMRI also received a number of gifts from donors who wish to remain anonymous.

In Memoriam

Contributions in memory of the following individuals were received from November 2004 through February 2005

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