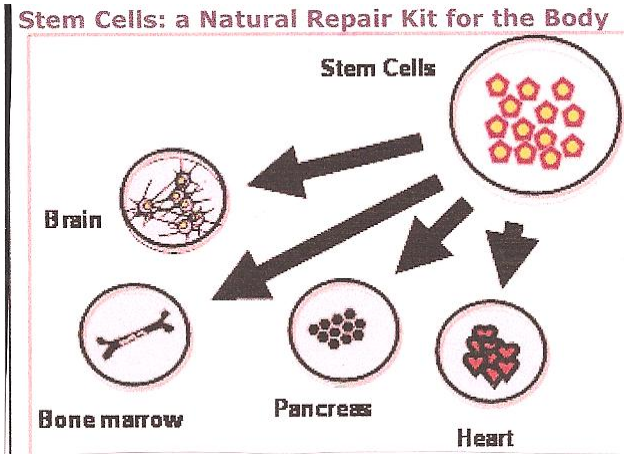
iPS Stem Cell Research for Curing IBMPFD

For some time, doctors have been using stem cells from bone marrow to cure some blood cancers, but using stem cells for other diseases is still very new in medicine. Stem cell research is very important as it can lead to new drugs and treatments for currently incurable diseases.

Stem cells are cells that can become any body part and can renew themselves indefinitely. Adult stem cells can only become certain cell types and are found in specific body parts. Embryonic stem cells are found in early-stage embryos and are "unspecialized"—they can become any type of cell. Genetic information and the environment during embryonic development control what type of cells they become.

The Kimonis Lab is currently working on making iPS cells from adult patients with IBMPFD. iPS cells are a form of adult stem cells that are derived from patient biopsies. They can be made to form cells that comprise muscle, nerve and bone tissue. We are currently working on one cell line with more planned in the future. Having these cells as raw material for studies will allow more research at a faster pace than with our current materials. Ample supplies of cells will enable us to test theories and assess the effectiveness of candidate treatments more quickly. In addition, in the future, these cells may themselves be a form of therapy.

Stem cells that come from an embryo can specialize into any type of cell as seen in this picture below. (Photo credit: http://stemcell.uci.edu/facts/basics.cfm).



Human embryonic stem cells come from early-stage embryos–blastocysts—which come from fertility treatment and are donated to science for research purposes. Donors must give informed consent to allow researchers to use the donated embryos for stem cell research. If those embryos were not used for research, they will be frozen indefinitely or be discarded. UCI follows all Federal and California laws for ethical reasons.

For more information about stem cell research visit: http://stemcell.uci.edu.

Mouse Model with IBMPFD developed by Kimonis and other scientists

Mouse models are used for research on genetic diseases because both mice and humans are mammals and thus respond similarly to genetic mutations. For example, a dominant genetic disease called Waardenburg Syndrome (WS), causes deafness, white hair, unique facial features and unique pattern of eye color. Scientists have developed mice with WS by putting the genetic mutation responsible for WS into the egg and fertilizing the egg with sperm. The resulting embryo is then put in the mother mouse which produces a mouse with WS. Mice are easy to use in research because they reproduce quickly and are low maintenance.

Dr. Kimonis and other scientists created a mouse model for Inclusion Body Myopathy Associated with Paget's disease of bone and Frontotemporal Dementia (IBMPFD) to understand how mutations cause symptoms and to find new therapies. Specifically, this model was developed to study how Valosin-Containing-Protein (VCP) mutations cause fALS. They created this mouse model—a knock-in mouse—by adding the most common mutation for IBMPFD, "R155H," a type of VCP mutation, through generations of breeding.

Scientists and Dr. Kimonis felt this is an excellent model for study purposes because of their discoveries of similar symptoms between IBMPFD patients and the knock-in mice. Therefore, mice are ideal for studying various diseases in people including IBMPFD.

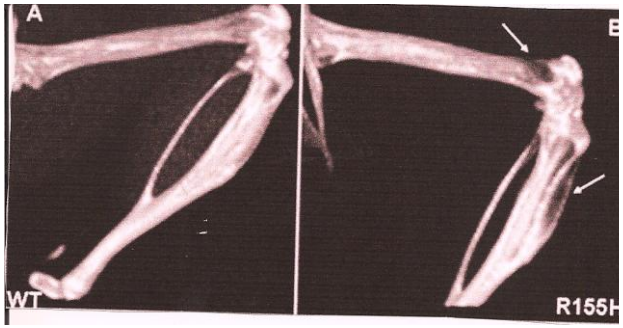
Scientists looked at how the R155H mutation affected mice by looking at their muscular, skeletal and brain tissues and symptoms. Mice with the R155H mutation show muscular weakness at 6 months of age. Their muscle cells show enlarged rimmed vacuoles, confirming that the R155H mutation causes IBMPFD.

Similarly, IBMPFD patients show the same characteristic in their muscle cells. Healthy, or wild-type (WT) mice without this mutation do not have enlarged rimmed vacuoles. Furthermore, both patients' and knock-in mice's muscle cells tested positive for high concentrations of specific proteins that are not present in high concentrations in healthy muscle cells. High concentrations of one of these—the TDP-43 protein—in muscle cells give the diagnosis of human muscle disease (myopathies). The knock-in mice also had brain cells with high levels of TDP-43 and ubiquitin proteins.

Bone:

Like IBMPFD patients, mice with the R155H mutation show lesions on the skeleton. These mice show a high proportion of "bone-eating cells" called osteoclasts compared to WT mice. Patients with Paget's disease also show skeletal cells with the same characteristic. On the other hand, knock-in mice did not show impaired memory like what is seen in IBMPFD patients. However, knock-in mice developed complex seizures at 15 months of age. This convinced scientists that they may find IBMPFD families affected with seizures. Seizures may be added to the symptom repertoire in these patients.

From studying the effects of the R155H mutation in mice, scientists have a positive outlook that the IBMPFD mouse model will help them understand how mutations in the VCP gene cause IBMPFD. They also hope to find cures by studying this mouse model.



WT stands for wild-type in Picture A on left, and Picture B on right shows bone in a mouse affected with IBMPFD, type of VCP disease. Bone in left is normal while degradation of bone is seen in the right. (Photo credit: PLoSone, October 2010 issue).

VCP Mutations and ALS

ALS affects motor nerve cells in the brain and spinal cord. When these cells die, the brain cannot control voluntary movement of muscles throughout the body anymore, and the muscles become weak and paralyzed.

ALS is very rare and strikes 1 or 2 out of 100,000 people every year. It is difficult to diagnose. Physicians look at symptoms and run tests to determine the diagnosis. Patients experience muscle weakness in the limbs during the early stages of disease, usually between the ages of 40 to 70 years. They may notice twitching, stiffness or pain in the muscles, especially in the limbs at first. Over time other muscles including the rib muscles weaken, often resulting in death.

The lifespan of ALS patients is around three years. There is no cure. Treatments for symptoms include physical therapy, speech therapy, and medications. Some medications like Rilutek could slow down the progression of ALS. 95% of cases are not genetic but 5% is. fALS is a dominant type of genetic disease; patients only need one copy of the mutation to develop fALS. Mutations in the genes SOD1, TDP-43 and FUS cause fALS. Scientists recently found a new mutation that could cause ALS—VCP (valosin-containing protein) mutations, also responsible for IBMPFD. These may be responsible for 1 or 2 percent of genetic cases of ALS. Like in IBMPFD, ALS patients show cells with high levels of TDP-43 and ubiquitin proteins. The discovery of genes that cause genetic ALS gave scientists a much clearer picture of how ALS develops. Scientists want to continue finding new genetic mutations that cause ALS.

Identifying mutations in ALS is not easy because only a small percentage of cases are genetic and because of the short lifespan of patients. However, scientists used a new method—whole exome sequencing—to find the VCP mutation in a multi-generational Italian family with four generations affected with ALS. They had a mutation called p.R191Q—the same mutation that caused IBMPFD. IBMPFD patients also have high levels of the TDP-43 protein. Additionally, scientists knew of one patient with a VCP mutation who had ALS. From this discovery of the p.R191Q mutation, scientists concluded that ALS patients also should be tested for IBMPFD and be screened for high osteoclast concentration. This approach may improve medical care for ALS patients.

Bone Fragility and Limb-Girdle Myopathy

Research has been conducted on an unusual family with an autosomal dominant limb-girdle type of myopathy and bone fragility. Clinical, biochemical, and radiological aspects were evaluated in eight living relatives and eight deceased individuals in this family. Elucidation of the novel molecular basis of this disorder may provide valuable links between bone, collagen and muscle, and targeted therapeutic options. Affected individuals in this family have various combinations of progressive muscle weakness, easy fracturing, and poor healing of long bones. Additional features include premature graying with thin hair, thin skin, hernias, and clotting disorders. We report genetic mapping of this disorder to chromosome 9p21-p22. A genome-wide scan for the disease locus obtained a maximal LOD score of 3.74 for marker GATA87E02 N (D9S1121). Haplotype analysis localized the disease gene within a 15 Mb interval flanked by markers AGAT142P and GATA5E06P. Identification of the gene will be necessary to understand the pathogenesis of this complex disorder.

Study Participation: It would be greatly helpful if more families participated in our studies. If you know of others who may be interested, please contact:
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Ms. Marie Wencel: (949) 824-0521

Funding: We have limited funding from the NIH and MDA. To be able to develop cures for genetic disorders, your help is essential. Please consider organizing fundraisers and donating to our research program at:
www.uadv.uci.edu/IBMPFDMyopathyPagetAndDementiaResearch
Please notify Dr. Kimonis when you have made a donation.

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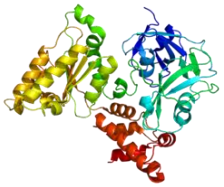

UC Irvine

From left to right: Dr. Virginia Kimonis, Dr. Katrina Llewellyn, Dr Angele Nalbandian, Raagav Mohankrishnan, Marie Wencel, Dr Eric Dec, Isabell Daye Chun, Dr Manaswitha Khare and Prachi Rana

I am happy to be sending you our third newsletter to update you on our research studies. Progress has been made in discovering genetic mutations that may cause ALS (amyotrophic lateral sclerosis), stem cell research for curing currently incurable diseases, and development of a mouse model for studying IBMPFD and fALS (familial ALS). We have also conducted research on generations of a family with a limb-girdle type of myopathy and bone fragility.