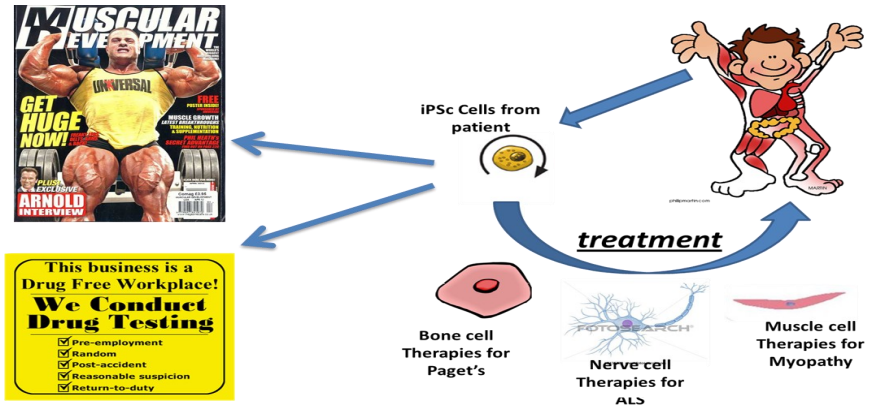
Stem Cells and iPS Cells

Stem cell therapy for genetic diseases is controversial and exciting. The controversy surrounding stem cells is based on when the cells are harvested, with many individuals ethically objecting to the use human embryos. Our laboratory has made stem cells (induced pluripotent stem (iPS) cells) from skin from the very first patient identified with VCP disease thereby bypassing any ethical concerns. Few discoveries in biology have as great a potential for altering modern medical research as induced iPS cells, as iPS cells give rise to every cell type in the human body. We have previously published our work in making iPS cells to neural cells that show



pathological similarities to VCP disease patients (Dec et. Al 2013).

Dr. Katrina Llewellyn has now made muscle cells from the iPS cells to study the mechanism of VCP disease and for the development of novel treatments. The differentiated cells show pathology mirroring the human disease, thus providing a reliable resource for these studies. Just this winter Dr. Llewellyn screened the effects of various autophagy-modifying compounds as a therapeutic strategy for VCP and related diseases. She found that some of these treatments did have a positive effect on the VCP pathology. She's now moving forward with more treatment experiments in our cell lines and mouse model in the hopes to one day provide a therapy for patients. ***Dr. Katrina Llewellyn, Ph.D.***

How You Can Help

There are many ways to support the groundbreaking research taking place in the Kimonis Laboratory at UC Irvine, including current gifts, planned gifts and organizing a fundraiser among your network. If you would like to learn more about how you can impact the development of cures for genetic disorders, please contact:

Valerie Amador (Senior Director of Development)
(949) 824-3950 or Valerie.amador@uci.edu or Dr. Kimonis
Gifts can also be made online at: http://www.uadv.uci.edu/VCP-Research
All donations are Tax deductible

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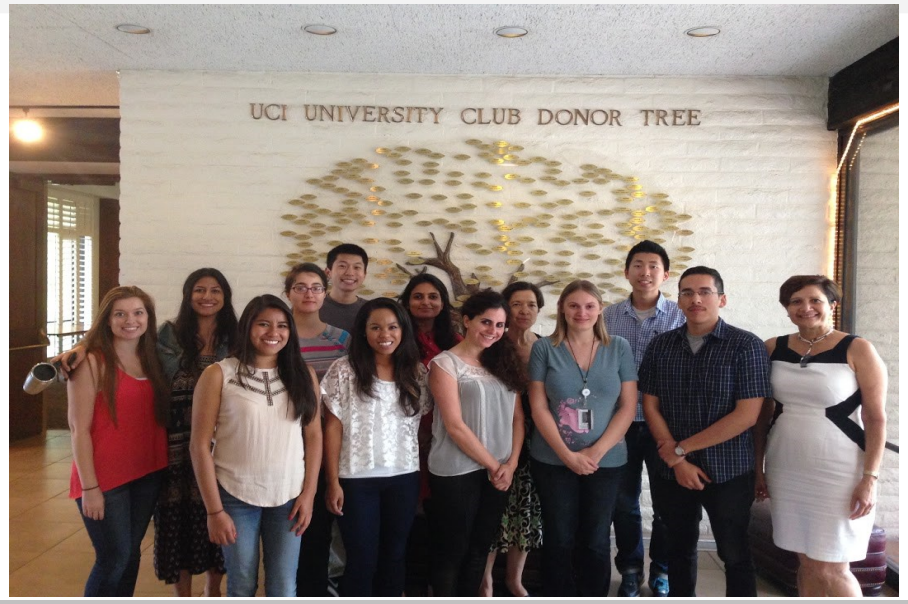
DEPARTMENT OF PEDIATRICS
UNIVERSITY of CALIFORNIA, IRVINE • SCHOOL OF MEDICINE

Kimonis Laboratory Newsletter
2015 Research Update



Lab Members Left to Right: *Arianna Gomez, Naomi Walker, Abhilasha Surampalli MBBS., Merit Milad, Kady Murphy, Angele Nalbanian PhD., Claudia Shambaugh, Katrina Llewellyn–Tanaka PhD, Daniel Weitz, Virginia Kimonis, MD, Ebaa Al-Obeidi, Josh Tan, Jesus Magallon, Alex Lew*

Brief Summary:

This is our seventh annual newsletter to our research patients and friends and the 11th anniversary of the discovery of VCP as the gene for the disease.

2015 has been a great year with several research breakthroughs as you see from the publication list. Specific strategies that look promising in cells/mouse model are: splicing strategies to remove the VCP mutation, manipulation of the autophagy pathway and a high fat diet that completely rescues the homozygous mouse. We have had discussions with 4 companies who are interested in developing novel treatments/drug trials in VCP disease. The most promising based on animal studies is a heat shock protein enhancer called arimoclomol. We are hopeful that a treatment will be available to slow the progression of the disease in the near future.

We had our first lab baby Emma born in January to Katrina and Tom. Abhilasha had a magnificent Indian wedding with groom riding on a white horse. Marie, and Katrina have secured great jobs and our students all graduated and moved on to excellent graduate programs. Angele will be offered an assistant professor position in the department. Virginia cohosted the first ever conference on VCP disease.

Federal funding is always a struggle and the support from the families is very important. This year the lab received a very generous donation from a patient to find the gene causing his family's inclusion body myopathy. The same strategies used for discovering VCP disease will be utilized. We are determined with your support to find a treatment for VCP and other rare genetic disorders we work on in the laboratory.

215th ENMC International Workshop: "VCP-related multi-system proteinopathy",

Dr. Kimonis co-hosted the first workshop in Heemskerk, Netherlands on November 13-15, 2015. Co-organizers were Teresinha Evangelista (UK); Hanns Lochmüller (UK); Conrad Weihl (USA); and Michael Hanna (UK).

Workshop attendees included a multidisciplinary group of 19 experts from 6 countries comprising both basic and clinical researchers and two patient representatives. During the workshop, the group discussed multiple aspects of the disease, such as current patient cohorts in four countries, the variability of genetic disorders related to the VCP disease and the expansion of the phenotypic spectrum to include sporadic disorders. The group also discussed the cellular and molecular aspects of VCP function and dysfunction in diseases, while reviewing the existing animal models and potential therapeutic targets, including VCP-specific therapies. In addition, the group considered patient diagnosis within rheumatology, neuromuscular and dementia clinics and the current clinical management of the three key phenotypes: myopathy, Paget's disease and dementia. Examples of patient registries, natural history studies and clinical trials in rare neuromuscular diseases also formed part of the discussion.

What were the outcomes of the workshop and how will they benefit patients?

1. Development of VCP-related clinical research projects based on collaboration between rheumatologists, cognitive neurologists, neuromuscular specialists and a research consortium with the aim of exchanging clinical results and research resources.
2. Improved understanding of the VCP disease's phenotypes and how to standardize clinical care through the multi-disciplinary clinical management of various specialists.
3. 10 additional mutations that cause the VCP disease were reported, expanding the number to 50.
4. Exchange of pre-clinical data from promising therapies applied in mouse models.
5. Open consortium to include other clinical groups with VCP patients
6. Form a working group to focus on clinical trial outcome measures, natural history and study design with the intent of preparing for future clinical trials.
7. Engage existing patient advocacy groups by providing workshop reports to MDA, ALS, FTD, Paget's and myositis associations.
8. Patient initiated social media site on the VCP disease.

Social media sites on VCP disease

I am very excited to begin creating two web based sites for VCP. One will be an independent website exclusive to VCP along with Facebook page with links to it and any other related sites. Any suggestions or comments are welcome. Keep you posted on progress but should be up and running in early 2016!!

Mahalo, Keith keithplimmer@sbcglobal.net

David Sweetman continues to offer support on the www.ibmpfd.com website

A note from one of our students who joined our team

I have been a part of the Kimonis Lab for two years before graduating in the summer of 2015, and have continued as a Research Assistant. My primary research focuses on experiments towards therapeutic strategies for VCP and related diseases.

My time in this lab grant me extensive experience with animal work consisting of mice care, physical assessment, tissue harvesting and preservation along with several molecular biological procedures ranging from extraction and quantification of protein from tissues, Western Blot assays, PCR, immunohistochemistry/immunocytochemistry, microscopy, and cell work.

During my undergraduate career, I have coauthored the publication *of papers i*n collaboration with Dr. Angéle Nalbandian and Dr. Katrina Llewellyn, our most recent work concerning the characterization of patient-specific inducible pluripotent stem cell (iPSC) is also ready for submission. This study hopes to demonstrate that patient-specific iPSC technology provides exceptional models linking clinical and bench research. After subjecting IBMPFD patient iPSC's to various autophagy-modifying drugs, these cells displayed effects similar to that of the mice models. Hence, by creating cellular mechanisms and pathways underlying IBMPFD via patient-specific iPSC technology, our team believes that this will advance our research in related diseases and in the development of future personalized regenerative cell therapies.

As an aspiring physician, I believe that research fuels the potency of our healthcare. Therefore, I hope that as I continue to proceed in academia, I can not only provide the benefit of good health, but also dedicate my career to scientific research.

Josh Baithang Tan

A note from one of our patients

"São Paulo is the largest city in Brazil and Latin America with a population in its metropolitan area at around 20 million. It is the largest economy of the country and industrial center, commercial and services. It is a cosmopolitan city, home to immigrants from around the world and working 24 hours a day.

I carry inclusion body myositis disease, as well as my older brother, my father and my uncle. In addition, we are also carriers of Paget's disease, except my father and my uncle who were not diagnosed at the time and died for many years ago. That IBM association with Paget's made me contact with his group in the UCI, where I was in January / 2015, submitting myself to various tests and medical evaluations.

My experience was surprisingly positive, as both Dra. Kimonis as her staff, were extremely welcoming, kind and understanding with my physical limitations and interested in provide a quality of life, discovering and studying new therapies. The UCI is a modern university, trained and, I'm sure, will be protagonist of great discoveries in the medical field."

Eduardo Freire Pinheiro

VCP Related Lab Publications in 2015. Please let us know if you would like the articles.

Nalbandian A, Llewellyn KJ, Nguyen C, Monuki ES, **Kimonis VE.** Targeted Excision of VCP R155H Mutation by Cre-LoxP Technology as a Promising Therapeutic Strategy for VCP Disease. Human Gene Ther Methods 2014 Dec 29.

Nalbandian A, Llewellyn KJ, Nguyen C, Yazdi PG **Kimonis VE**. Rapamycin and Chloroquine: the in vitro and in vivo effects of autophagy-modifying drugs show unexpected results in valosin containing protein multisystem proteinopathy. PLoS One. 2015 Apr 17;10(4)

Nalbandian A, Llewellyn KJ, Gomez A, Walker N, Su H, Dunnigan A, Chwa M, Vesa J, Kenney M and **Kimonis VE**. In Vitro Studies in VCP-Associated Multisystem Proteinopathy Suggest Altered Mitochondrial Bioenergetics. Mitochondrion. 2015 May;22:1-8

Llewellyn KJ, Walker N, Nguyen C, Tan B, BenMohamed B, **Kimonis VE,** Nalbandian A. A fine balance of dietary lipids improves pathology of a murine model of VCP-associated multisystem proteinopathy. PLoS One. 2015 Jul 2;10(7).

Katrina J. Llewellyn KJ, Nalbandian A, Khatib B, Tan B, **Kimonis VE**. Myogenic differentiation of VCP disease induced pluripotent stem cells: a novel platform for drug discovery (in press)