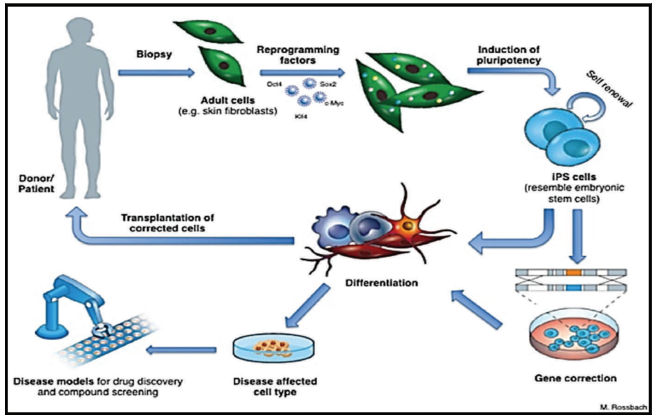
Stem Cells and iPS Cells

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. We do not use embryonic stem cells. In our laboratory stem cells have been made from skin from the very first patient identified with VCP disease thereby bypassing any ethical concerns. iPS cells can give rise to every cell type in the human body. Differentiating VCP disease-specific induced iPS cells into a myoblast lineage allows us to obtain an unlimited source of cells to investigate VCP-associated diseases and develop possible therapeutic treatments. I am now focusing on assessing the VCP disease phenotype in these differentiated iPS cells. My future studies will involve testing various drugs on these differentiated cells to test their therapeutic potential for VCP-associated disease and transplantation studies into muscles to assess whether these iPS cells have the ability recover muscle function. Few discoveries in biology have as great a potential for altering modern medical research as induced pluripotent stem (iPS) cells.

Dr. Katrina Llewellyn, Ph.D.



Applications of iPS cells *adult cells can be reprogrammed to produce induced pluripotent stem cells (iPS. The resulting iPS cells resemble embryonic stem cells and can be differentiated into any type of cell to study disease, test drugs or-after gene correction-develop future cell therapies*

Image from:
http://www.eurostemcell.org/factsheet/ips-cells-and-reprogramming-turn-any-cell-body-stem-cell
Dr M. Rossbach

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
Gifts can also be made online at: http://www.uadv.uci.edu/VCP-Research
All donations are Tax deductible

The Kimonis Laboratory
University of California Irvine
Division of Genetics and Metabolism
843 Health Sciences Rd., Room2038
Irvine, CA 92697-3940

Tel: (949) 824-0571 Direct Fax: (714) 456-5330, Pager (714) 506-2603
Email: vkimonis@uci.edu

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

Kimonis Laboratory Newsletter
2014 Research Update

Lab Members Left to Right: *Isabella Chan, Abhilasha Surampalli MBBS, Marie Wencel, Katrina Llewellyn– Tanaka PhD, Angele Nalbanian PhD., Andrew Dunnigan, Arianna Gomez, Jesus Magallon, Naomi Walker, Virginia Kimonis, MD*

Brief Summary:

This is our sixth annual newsletter to our research patients and friends that outlines our progress and efforts to better characterize VCP disease, solicit greater involvement by the research community that will help us develop better treatment strategies for our patients. It is also the 10th anniversary of the discovery of VCP as the gene for the disease.

In our last newsletter we described the positive results obtained in our work with "Lipid-enriched diet which rescued lethality and slowed down progression of the muscle disease in our VCP mouse model". We are continuing this study in order to narrow down which particular lipid(s) are improving symptoms in the mouse model and establish tolerated doses, for a translational study in patients.

Also mentioned was the work on exercise physiology that showed reversal in the skeletal muscle atrophy in the VCP mouse. In the study involving the "Targeted Excision of VCP R155H mutation by CreLoxP as a Therapeutic Strategy for VCP Disease" we had described some very promising results in the mouse model. Since then we have expanded the study to patient's fibroblast and stem cells, with some excellent preliminary results.

Inclusion Body Myopathy associated with Paget's disease of the bone and Frontotemporal Dementia is attributed to mutations in the Valosin Containing Protein (VCP) gene, mapped to chromosomal region 9p13.3-12. Affected individuals exhibit scapular winging and die from progressive muscle weakness, cardiac and respiratory failure typically in their 50s. Mutations in the VCP gene have also been associated with amyotrophic lateral sclerosis (ALS) in 10-15% of individuals with features of ALS noted in approximately 60% of individuals. Currently, there are no effective treatments for VCP-related myopathy or dementia. During the past year our lab was able to generate 13 publications in collaboration with other labs, which have proved to be a significant contribution to the literature and key to getting us a little closer to treatments for patients.

We were able to generate the required funding from the NIH, UC Irvine and generous donors amongst our patients and are continuing our efforts to find alternative sources of funding for these promising studies in our cells, VCP mice and in our volunteer patients.

Targeted Excision of VCP R155H Mutation by Cre-LoxP Technology as a Promising Therapeutic Strategy for VCP Disease

To determine the effects of targeted excision of the most common R155H mutation in VCP disease, we generated the Cre-ER^{TM}-VCP$^{R155H/+}$ tamoxifen-inducible model. We administered tamoxifen (0.12 mg/g body weight) or corn oil (placebo) to the pregnant mice by oral gavage and monitored the survival and muscle strength measurements of the pups until 18 months of age. In order to remove the VCP mutation. We confirmed efficient removal of exons 4 and 5 and the VCP mutation. We report that the Cre-ER^{TM}-VCP$^{R155H/+}$ mice demonstrated improved muscle strength and quadriceps fiber architecture, improved autophagy signaling pathway, reduced brain neuropathology, decreased apoptosis, and less severe Paget-like bone changes. The Cre-ER^{TM}-VCP$^{R155H/+}$ mouse model provides proof-of-principle that removal of the mutated exons could be beneficial to patients suffering from VCP disease, and serves as an excellent platform in understanding the underlying mechanisms and may serve as a promising therapeutic approach for patients with VCP-related neurodegenerative diseases. Our manuscript and proposal to the NIH is under review.

Rapamycin: The in vitro and in vivo effects of autophagy-modifying drugs show unexpected results in VCP multisystem proteinopathy

Patients show the presence of rimmed vacuoles and TAR DNA-binding protein 43 (TDP-43)-positive large ubiquitinated inclusion bodies in their muscles. The VCP$^{R155H/+}$ mouse model recapitulates the disease and also the impaired autophagy typically observed in patients with VCP disease. Autophagy is a basic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes. The breakdown of cellular components promotes cellular survival during starvation by maintaining cellular energy levels. Autophagy-modifying agents such as rapamycin at pharmacological doses have previously shown to alter the autophagic flux. Rapamycin treatment in 20-month old VCP$^{R155H/+}$ mice showed improved muscle performance, quadriceps histological analysis, and improvement of the ubiquitin, and TDP-43 pathology and defective autophagy as indicated by decreased protein expression levels of autophagy markers LC3-I/II, p62/SQSTM1, and optineurin. We are currently investigating the possibility of treating patients with rapamycin.

Global Gene Expression Profiling in R155H Knock-In Murine Model of VCP Disease

We have performed an analysis of genes in the muscle in the VCP disease mouse model. There were a total of 212 significantly dysregulated genes, several of which are involved in the regulation of proteasomal function and NF-κB signaling cascade.. This investigation reveals the importance of the the understanding of cellular and molecular mechanisms causing and in the discovery of novel therapeutic advancements and strategies for patients suffering with these debilitating disorders.

*Nalbandian A, Ghimbovschi S, Wang Z, Knoblach S, Llewellyn KJ, Vesa J, Hoffman EP, **Kimonis VE**. Global Gene Expression Profiling in R155H Knock-In Murine Model of VCP Disease. Clin Transl Sci. 2014 Nov 12. doi: 10.1111/cts.12241. [Epub ahead of print]*

VCP disease: Natural history study

We studied 41 individuals (24 affected, 5 presymptomatic carriers and 12 unaffected individuals; 18 males and 23 females, mean ages 51, 45, and 50 y. respectively) in 8 families harboring three missense mutations, R155H, R155C and R155P; 14 with myopathy, 8 with myopathy and Paget's disease and 2 also with dementia.

Average age of onset for myopathy and Paget's disease was 43 y. and 37 y. respectively. The respiratory muscle strength was evaluated using spirometry measurements; functional capacity by IBM Functional Rating Scale (IBMFRS), Fatigue Severity Scale (FSS), 6 minute walk test (6MWT) and peripheral muscular strength by handheld dynamometry and MRC (Medical Research scale) scores.

*The mean IBMFRS scores for **affected and unaffected** relatives was 28.4 versus 39.8 (P=.01); MRC scores for all muscle groups was 203 versus 279 (P=.01) and the fatigue scale score was 44 versus 25 (P=.03). Our results, therefore, provide some simple and inexpensive indexes of progression of respiratory and peripheral muscle involvement in VCP disease. These indexes will indirectly help through early intervention strategies (like night-time noninvasive ventilation) to help address concerns as soon as possible.*

The results are more meaningful when repeated at regular intervals. We are therefore requesting your help in regular questionnaire responses.

Diet and Exercise influence in VCP Disease

To investigate alternate therapies that may slow the progression of the disease and improve the quality of life in VCP patient population, we assessed data from the Quality of Life questionnaire in 30 individuals (mean age 50.86 years; range 27-65 years; 16 males, 14 females) that participated in the clinical study of Valosin Containing Protein (VCP) disease.

Eleven affected individuals consumed a high fat/sugar diet and 15 low fat/sugar diet of 4.0 and 1.5 servings/day respectively. Eleven individuals reported no exercise and 12 reported moderate exercise of 2.4 hours/week.

In this cohort, we found there was significantly higher mean physical health domain score for all those who exercised (P=.02) and surprisingly in those who had a high fat/sugar diet (P=.01). In the high fat/sugar diet group there was a significantly greater ability to walk; greater perceived muscle strength in arms and legs (P=.03; P=.02 and P= .02 respectively). We promote a healthy lifestyle with exercise training and a diet with polyunsaturated fats which may have a beneficial effect in affected individuals with VCP disease. Nevertheless, larger studies with further research are needed to confirm these preliminary studies before making clinical practice recommendations.

*Hamorsky K, Surampalli A, Wencel M, Khare M, **Kimonis VE**. The Influence of Diet and Exercise on the Physical Health of Affected Individuals with VCP Disease. International Journal of Biotechnology for Wellness Industries, 2014, 3.*