

Therapeutic Treatments in VCP Disease

Our lab has a strong interest in how diet and exercise can effect disease progression. We have recently published multiple papers exploring how these treatments are helping the mouse model of VCP disease.

Lipid-enriched diet rescues lethality and slows down progression in a mouse model

The Kimonis laboratory uses a mouse model of VCP disease to study various treatment options. VCP mouse models carrying the common R155H mutation include several of the features typical of the human disease. In our previous investigation, VCP homozygous mice (two mutations) exhibited progressive weakness and very early death at 3 weeks of age. This was a problem because the mice would die before we had time to see the effects of a treatment. We recently published a paper reporting that feeding pregnant VCP heterozygous mothers (one mutation) with a lipid-enriched diet (LED) results in the reversal of the lethal phenotype in homozygous offspring. We examined the effects of this diet on homozygous and wild type mice from birth until 9 months of age. The LED regimen improved survival, motor activity, muscle pathology and autophagy cascade. A targeted lipidomic analysis of skeletal muscle and liver revealed elevations in tissue levels of non-esterified palmitic acid and ceramide (d18:1/16:0), two lipotoxic substances, in the homozygous mice. The ability to reverse lethality, increase survival, and ameliorate myopathy and lipids deficits in homozygous animals, suggests that lipid supplementation may be a promising therapeutic strategy for patients with VCP-associated neurodegenerative diseases.

We are currently conducting studies to determine which particular lipid(s) are improving symptoms in the mouse and what is the maximum tolerated dose.

Llewellyn KJ, Nalbandian A, Jung KM, Nguyen C, Avanesian A, Mozaffar T, Piomelli D, Kimonis VE. Lipid-enriched diet rescues lethality and slows down progression in a murine model of VCP-associated disease. *Hum Mol Genet.* 2013 Dec 3.

Exercise Training Reverses Skeletal Muscle Atrophy in the VCP mouse.

This study was done to examine the effects of uphill and downhill exercise training on muscle histopathology and the autophagy cascade in a VCP mouse model. The mice ran on a treadmill for 3 days a week for 6 weeks for 10-30 minutes per session. Each week the incline and speed of the treadmill and the duration of the exercise would change. The incline of the treadmill simulates uphill or downhill running. Sedentary mice were used as a control. We measured strength in the mice by measuring body mass, front paw grip strength, and a device called a Rotarod. Progressive uphill exercise in VCP mice revealed significant improvement in muscle strength and performance by grip strength and Rotarod analyses when compared to the sedentary mice. In contrast, mice exercised to run downhill did not show any significant improvement. Samples of the muscles were also analyzed. The uphill exercised mice had less muscle atrophy and an improvement in the Paget-like phenotype. The data highlights that uphill exercise training in VCP mice did not have any detrimental effects to muscle function. The therapeutic effects of exercise resistance and endurance training should be considered in the management of patients with diseases such as VCP.

Nalbandian A, Nguyen C, Katheria V, Llewellyn KJ, Badadani M, Caiizzo V, Kimonis VE. Exercise Training Reverses Skeletal Muscle Atrophy in an Experimental Model of VCP Disease. *PLoS One.* 2013 Oct 9: 8(10).

VCP Exercise Study

We are currently interested in volunteers for a study that will investigate the effect of exercise on muscle strength in VCP Disease. An exercise called knee extensors will be conducted 3 times a week over the course of 12 week at your local gym or your home with ankle weights. At each session you will do 3 sets of 10 knee extensors. Each week the amount of weight used will be increased. You will keep a log following each training program and rate your level of fatigue. At the start and end of the 12 weeks of training we will ask you to visit UC Irvine so we can conduct a battery of tests consisting of strength measurements, MRI, and muscle biopsy (optional).

Predictive Testing in IBMPFD

We did a study to assess how predictive genetic testing impacts an individual's psychological well-being. A total of 102 individuals with a 50% prior risk of inheriting IBMPFD mutation received an invitation and 33 individuals chose predictive genetic testing (32.3%). The baseline questionnaires were completed which assessed risk perception, reasons for accepting or declining genetic testing and an anxiety and depression Scale (HADS). 19 completed the post-test HADS questionnaire including 15 of the 18 who had tested positive. Baseline risk perception was 50.09% in the participants which matched their prior risk indicating that the participants and their families were aware of their empiric risk. Participants were equally concerned about myopathy as frontotemporal dementia. At baseline a quarter of the participants had high levels of anxiety but none had high levels of depression. Those who were anxious at baseline had a decrease at one year follow up indicating that performing pre-symptomatic genetic testing in a genetic counseling setting does not have a detrimental effect.

Surampalli A, Khare M, Kubrussi G, Wencel M, Tanaja J, Donkervoort S, Osann K, Simon M, Wallace D, Smith C, McInerney-Leo A, Kimonis V. Psychological Impact after the Disclosure of Genetic Testing Results in IBMPFD (in review).

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

IBMPFD is attributed to mutations in the VCP gene, mapped to chromosomal region 9p13.3-12. To determine the effects of targeted excision of the R155H mutation in VCP disease, we generated the Cre-ERTM-VCP^{R155H/+} Tamoxifen-inducible mouse model. We administered the pregnant dams with 0.12 mg/g body weight Tamoxifen or corn oil control by oral gavage and monitored the survival and muscle strength of the pups until 18 months of age. The Cre-ERTM-VCP^{R155H/+} treated mice demonstrated improved muscle strength and quadriceps fiber architecture, reduced expression of autophagy markers, reduced brain neuropathology, decreased apoptosis, and improvement of the Paget-like bone changes. The Cre-ERTM-VCP^{R155H/+} mouse is an excellent platform for understanding the underlying pathophysiological mechanisms and for therapeutic approaches for patients.

Nalbandian A, Llewellyn KJ, Nguyen C, Monuki ES, Kimonis V. Targeted Excision of VCP R155H Mutation by Cre-LoxP Technology as a Promising Therapeutic Strategy for VCP Disease. *Molecular Therapy – Methods and Clinical Development* (in review).

Cytokine Profiling in Patients with VCP-Associated Disease

We recently explored the idea that cytokines influence VCP disease (cytokines are proteins, peptides, or glycoproteins used for cell communication). Muscle wasting observed in VCP disease is suggestive of cytokine imbalance. We hypothesized that dysfunctional protein homeostasis caused by VCP mutations leads to cytokine imbalances thereby contributing to the muscle wasting symptoms. Study: Blood samples were taken from patients with VCP and control subjects. Plasma was isolated from the blood and multiple cytokines were measured to see if there was a difference between the disease and control patients. The cytokines we looked at were: interleukin-4 (IL-4), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF a) and epidermal growth factor (EGF). Results: TNF a and EGF were significantly altered in VCP disease as compared to control. TNF a was up-regulated, consistent with muscle wasting, and EGF levels were increased. No significant differences were observed in IL-4 and IL-6. Cytokine imbalances may be associated with VCP disease and may play a contributory role in VCP myopathy. Further understanding of how VCP dysfunction leads to aberrant protein homeostasis and subsequent cytokine imbalances may also aid in the understanding of other proteinopathies and in the development of novel treatments.

Dec E, Rana P, Katheria V, Dec R, Khare M, Nalbandian A, Leu SY, Radom-Aizik S, Llewellyn K, Benmohamed L, Zaldivar F, Kimonis V. Cytokine Profiling in Patients with VCP-Associated Disease. Clin Transl Sci. 2013 Oct 3.

Diet Questionnaire

We have been researching how diet affects IBMFPD and we would like to gather information from you. We have an online survey that will take 15-20 minutes. The survey will ask you what you ate and drank in the last 24 hours. It can be completed two separate times to collect two days' worth of diet info. If you chose to participate, please contact us and we will provide you with the link and login ID.

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>

Donations are tax deductible.

Donate Today!
We need your help to
continue this research!

If you wish to have your name removed from future Health Advancement fundraising requests, please email us at OptOutHealthAffairs@uadv.uci.edu or call our toll-free number at 855.824.3768.

Organ Donation

Our lab accepts organ donations to further our research in finding a cure. We understand that this is a very personal decision, and we want you to feel comfortable with your choice. Please feel free to contact us if you have questions or are interested in signing up to be a donor.

Study Participation

It would be very helpful if more families participated in our studies. If interested, please contact Study Coordinator **Marie Wencel**: (949) 824-0521 or mwencel@uci.edu.



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Newsletter

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From left to right: Dr. Abhilasha Surampalli, Marie Wencel, Dr. Angele Nalbandian, Dr. Virginia Kimonis, Dr. Katrina J Llewellyn, Andrew Dunnigan, Dave Ferguson

The Kimonis Lab would like to wish you



We are pleased to send you our Fifth Annual Newsletter as an update on our research studies. We hope these research efforts will help us develop novel treatment strategies for our patients.

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