To summarize will continue to recruit patients with VCP disease. At our last count we now have more than 200 patients with VCP disease and more than 70 families. To date >50 mutations have been identified in patients across the globe. We have recently identified 4 new mutations which we plan to publish.
Our lab continues to make advances on therapies for VCP disease which comprise of different methods to remove the mutation or silence the gain of function seen in VCP disease. Exon skipping has been shown to be very promising in the myoblasts. We are also studying another genetic method of silencing the VCP gene in the VCP mice which is looking promising.

Why VCP inhibitors would work in IBMPFD?
There is plenty of evidence that VCP mutations result in gain of function. Removing the VCP mutation in the mouse by Cre technology and downregulating VCP by other methods has improved the pathology seen typically in patient muscle cells and the mouse model of the muscle disease.

Goals for a pilot treatment study in VCP disease
I would like to conduct a small trial of a VCP inhibitor in a small group of patients to assess if there are any unexpected toxic effects and to look for possible improvement in muscle strength and function.

A note from one of our patients who has started a facebook group.
I encourage everyone to join. Together we can accomplish great things. Sarah Brumhard and her uncle participated in the first ever VCP conference. The publication that resulted is available at: https://*www.ncbi.nlm.nih.gov/pubmed/27312024 or from Dr.Kimonis.*

Dear all,
I've started a private Facebook group.
https://m.facebook.com/groups/1071177132997783?ref=bookmarks

The name is 'IBMPFD - Patients, Family and Friends' and I would enjoy to welcome you. The group is private. So everyone can see the members but only members can see the posts of others.
Best wishes
Sarah Brumhard [sarahbrumhard@web.de]

.....

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

Brian Jones has kindly donated funds to jumpstart a treatment trial and web domains.

We Need Your Help With Funding a Pilot Treatment Trial using VCP inhibitors in Patients

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:

Dr. Kimonis or Valerie Amador (Senior Director of Development)
(949) 824-3950 or Valerie.amador@uci.edu or
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
2017 Research Update

Lab Members Left to Right: Isabella Chang, Sanjana Ellur, Katherine Kolligian, Daniel Weitz, Dr. Virginia Kimonis, Paul Walker, Howard Yu, Caleb Bhatnagar, Jake Plewa, Dr. Lan Weiss (Lab Supervisor), Margaret Knight (Study Coordinator)

This is our eighth annual newsletter to our research patients and friends and the 13 th anniversary of the discovery of VCP as the gene for Inclusion Body Myopathy, Paget, Frontotemporal dementia, ALS and now also Parkinson's disease. The number of patients who have contacted me recently has grown and the number of families affected by VCP disease has grown to over 75.

The year 2017 has got us closer to a treatment for VCP disease using inhibitors. A recently published paper by Dr. Ming Guo who is a neurologist at UCLA shows conclusively that in a drosophila (fruitfly) model, the typical muscle pathology improved with the use of inhibitors

http://newsroom.ucla.edu/releases/ucla-research-potential-treatment-for-muscle-and-brain-degenerative-disease

Our lab is now planning on conducting experiments on patient myoblasts and VCP mice to help us understand more about efficacy, dosages and side effects of the drug prior to a patient trial. I have already met with the company who have licensed the VCP inhibitor . The company are willing to give the drug for free however, we do not have the necessary funding for the clinical trial as yet. We are writing grants to fund the preclinical along with a pilot study in patients and are hopeful that a treatment will be available to slow the progression of the disease in the near future. http://www.cleavebio.com/pipeline/p97.aspx

Federal funding is always a struggle and the support from the families is very important. We are determined with your support to find a treatment for VCP and other rare genetic disorders we are currently working on in our laboratory.

Important reports in the literature:

1. VCP plays a key role in ubiquitin-dependent protein degradation. VCP extracts proteins from membranes or macromolecular complexes to enable their proteasomal degradation. Dr. Deshaies's group demonstrated that normal VCP can unfold proteins however the mutant VCP unfolds substrate faster, suggesting that excess activity may underlie pathology. This finding of mutations causing gain of function has been shown in other studies and is the rationale for VCP inhibitors having potential benefit.

Blythe EE, Olson KC, Chau V, Deshaies RJ. Ubiquitin- and ATP-dependent unfoldase activity of P97/VCP•NPLOC4•UFD1L is enhanced by a mutation that causes multisystem proteinopathy. Proc Natl Acad Sci U S A. 2017 May 16. https://www.ncbi.nlm.nih.gov/pubmed/28512218

2. Dr. Ming Guo's group generated an IBMPFD *Drosophila* model which recapitulates the human disease. Mitofusin, which is required for outer mitochondrial membrane fusion. The authors show that common VCP disease mutants negatively regulates Mitofusin (MFN) more actively than normal VCP. VCP inhibitors however improved mitochondrial defects, muscle tissue damage and cell death associated with IBMPFD models in *Drosophila*. These inhibitors also suppressed mitochondrial fusion and respiratory defects in VCP patient fibroblasts. These results also suggest that VCP disease mutants cause IBMPFD through a gain -of-function mechanism, and that VCP inhibitors have therapeutic value.

Zhang T, Mishra P, Hay BA, Chan D, Guo M. Valosin-containing protein (VCP/p97) inhibitors relieve Mitofusin-dependent mitochondrial defects due to VCP disease mutants. Elife. 2017 Mar 21;6. pii: e17834. doi: 10.7554/eLife.17834.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360448/

Another interesting article by Papadopoulos C. et al. The EMBO Journal. 2017. 36, 135-15.
https://www.ncbi.nlm.nih.gov/pubmed/27753622
from Hemmo Meyer's group has identified the defect underlying VCP disease. They have shown that VCP (p97) cooperates with YOD1, UBXD1 and PLAA to drive clearance of ruptured lysosomes by autophagy. Ruptured lysosomes result in cell death and degeneration in VCP disease. This may be a therapeutic target to explore.

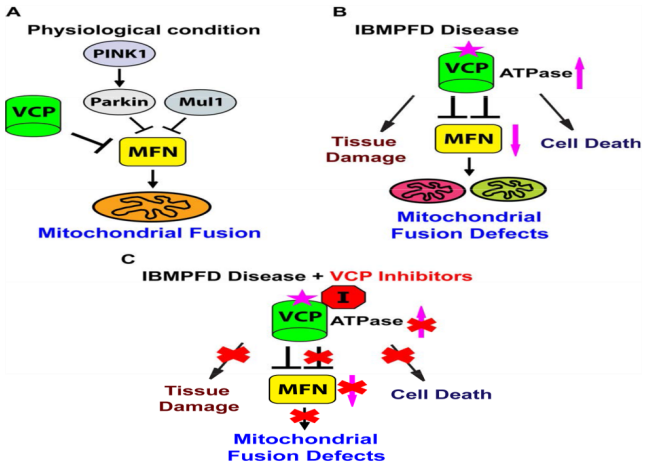

Figure: Proposed mechanisms of VCP disease mutants mediated mitochondrial defects and potential therapeutic role of VCP inhibitors.
MFN (mitofusin) has a role in maintaining mitochondrial structure. When VCP is overactive, MFN is downregulated and this leads to mitochondrial defects. By using inhibitors the VCP is downregulated and this restores the mitochondrial function. Treatment with VCP inhibitors resulted in improvement in the fruitfly VCP disease model.

A note from Dr. Lan Weiss, PhD., MD (post doc) who joined our team early 2016

A patient has asked Dr. Kimonis: "Will the treatment be available before I die?" What can we do? We have dedicated all our time and energy towards that question, finding a treatment that works. Different strategies have been studied in our lab such as gene modifications using exon skipping technology, drugs such as a natural compound in cancer treatment (Flavaglines), antioxidant molecule for mitochondrial respiratory chain disorders (Idebenone), high fat diet regimen and VCP inhibitor. Our induced pluripotent stem cell (iPSC)-derived VCP patient skin derived myoblasts have provided a reliable powerful platform to test the drugs. After identifying the efficacy and doses, the candidate drug is then tested in our knock-in mouse model engineered with the most common VCP R155H mutation. Result? (1) The high fat diet can slow down the progression of muscle weakness and rescue the lethality (2) One of the drugs used for down regulating the gain of function induced mutation, could recover VCP protein function with no toxic effect in VCP mouse model. Ever hopeful, there is now light at the end of the tunnel and patient treatment may soon prove to be a reality.

VCP Related Lab Publications in 2016– present from the Kimonis Laboratory:
Please let us know if you would like these articles.

1. Llewellyn KJ, Nalbandian A, Weiss L, Scarfone V, Khatib B, Tan B, Kimonis VE. Myogenic differentiation of VCP disease induced pluripotent stem cells: a novel platform for drug discovery (in press)
2. Nalbandian A, Khan AA, Srivastava R, Llewellyn KJ, Tan B, Shukr N, Fazli Y, Kimonis VE, BenMohamed L. Activation of the NLRP3 Inflammasome Is Associated with Valosin-Containing Protein Myopathy. Inflammation. 2016 Oct 11. [Epub ahead of print]
3. Walker P, Kimonis V. Transplantation of human iPSC (Human pluripotent stem cell derived myoblasts) in an animal model of VCP disease (Excellence in Research Program), Journal of Undergraduate Research, School of Biological Sciences, UC Irvine.
4. Al-Obeidi E, Al-Tahan S, Surampalli A, Goyal N, Wang A, Hermann A, Omizo M, Smith C, Mozaffar T, Kimonis V. Genotype-phenotype study in patients with VCP valosin-containing protein mutations associated with multisystem proteinopathy (In press)

Poster presentations from the Kimonis Laboratory: The following posters

American Society of Human Genetics, Vancouver, Canada Oct.18-20, 2016
American College of Medical Genetics, Phoenix, March 21 - 25, 2017, Advances in Skeletal Muscle Biology in Health and Disease. University of Florida, Gainesville, FL March 8-10, 2017. Neuromuscular Colloquium. Newport Beach May 12th 2017,UCI Undergraduate Research Symposium, UCI Student Center. May 20, 2017.
Translational Science Day, ICTS (Instit. of Clinical Translation & Science), UCI Jun 13, 2017

1. Al-Tahan S, Al-Obeidi E, Omizo M, Palmio J, Grafe M, Harati Y, Udd B, Kimonis V. Novel Valosin-Containing Protein (VCP) Mutations Associated with Multisystem Proteinopathy. Am College of Medical Genetics. 2017. Phoenix, AZ.
2. Kimonis V, Surampalli A, Al-Tahan S, Al-Obeidi E, Omizo , Udd B, Mozaffar T. Clinical Studies of Biomarkers in Autosomal Dominant Inclusion Body Myopathy.
3. Weiss L, Chan I, Llewellyn K, Nalbandian A, Wilton S, Kimonis V. Targeted exon excision therapeutics in iPSC-derived patients' myoblasts in vitro in VCP Inclusion body disease.
4. Weiss L, Llewellyn K, Nalbandian A, Chang I, Yu H, Daglian J, Jung K, Piomelli D, Kimonis V. Ceramide-mediated Pathogenesis may play a critical role in VCP inclusion body disease.
5. Ta LM, Ellur S, Weiss L, Kimonis V. Therapeutic Effects of Idebenone on Mice with VCP Inclusion Body Myopathy.
6. Koligian KM, Weiss L, Kimonis V. High fat diet helps prolong life and reverse effects in the VCP R155H+/+ knock in homozygotes mouse model of inclusion body myopathy.
7. Chan I, Walker P, Weiss L, Wilton S, Kimonis V. Targeted antisense oligonucleotides (ASOs) therapeutics in VCPR155H/+ Knock-In Mouse Model of VCP disease.
8. Le T, Nguyen A, Yu H, Weiss L, Kimonis V. Synthetic FL3 drug may ameliorate symptoms in a knock-in mouse model of VCP inclusion body disease.