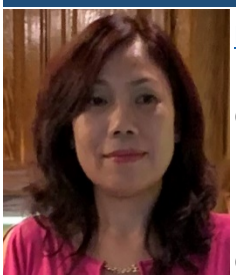
Newsletter: Issue December 2020

Kimonis Laboratory

2020 Research Update

Dear Research Patients and Friends,
My lab has focused on rare genetic diseases with the goal of understanding the underlying mechanism and generating novel treatments since the discovery of VCP as the gene for Inclusion Body Myopathy, Paget, Frontotemporal dementia, and ALS. The number of patients who have contacted me recently has grown and the number of families affected by VCP disease has grown to over 100 for this disorder, for which there is no treatment to prevent early demise resulting from muscle weakness, respiratory failure, and dementia.

Lab Personnel Projects



Lan Weiss, MD., PhD., Project Scientist

Medical school: Hue University, Vietnam
Graduate: Nagasaki University, Japan
Research interest: Developing therapies for rare diseases such as HSPB8, VCP, and Pompe disease using the two generated preclinical platforms: patient iPSC-derived myoblasts and mouse models.
Hobbies: Nature, flower arrangement. She is also passionate about training the next generation of doctors and scientists.

Her work has focused on discovering the pathological mechanism in the hereditary Inclusion Body Myopathy with mutations in Valosin Containing Protein (VCP) genes and Heat Shock protein B8 (HSPB8), and performing translational studies of different treatments in myoblasts and knock in mice. 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, VCP inhibitors and HSPB8 modifiers. Lan has successfully made muscle cells from induced pluripotent stem cell (iPSC)-derived from patient skin derived myoblasts which provide a reliable powerful platform to test the drugs. After identifying the efficacy and doses, the candidate drug is then tested in our engineered knock-in mouse models. Studies with mice with the most common VCP R155H mutation have shown that (1) The high fat diet can slow down the progression of muscle weakness and rescue the lethality (2) One of the drugs used to down regulate the gain of function VCP 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. Studies in the c.515dupC HSPB8 mice show that the mice are a useful model of the disease and can be used for therapeutic strategies such as treatments tp modify HSPB8 expression.
She is finishing off a pre-clinical study using antisense oligonucleotide (ASO, from IONIS) in Pompe mice with a promising result. The lab is expanding this therapeutic strategy to VCP and potentially the HSPB8 mouse models.

Alyaa Shmara, MBChB, Specialist
Medical school University of Baghdad college of medicine
Research focus: VCP and HSPB8 inclusion body myopathy.
To highlight the importance of *VCP* mutations in cancer development, we are publishing a paper that presents cases of unusual tumors in patients with classic features of *VCP* associated disease. These tumors include malignant peripheral nerve sheath tumor, anaplastic pleomorphic xanthoastrocytoma, malignant thymoma as well as common cancers. This is the first paper that expands the phenotype of VCP disease to potentially include unusual cancers.

Cheng Cheng, Ph.D.
Undergraduate: Knox College
Graduate: Washington University in St. Louis
Research interest: Therapeutic strategies of genetic neuromuscular and neurodevelopmental disorders.
Hobbies: Travelling

We are interested in investigating the therapeutic strategies for a rare neuromuscular disease caused by genetic mutations in VCP. This year, we have completed the preclinical testing of a VCP inhibitor, CB-5083 in treating animal models of VCP disease. We found that muscle pathology is ameliorated upon drug treatment. In particular, the pathological markers including phosphorylated TDP43, damaged lysosomal markers as well as elevated autophagy markers and the gross muscle morphology is improved. In collaboration with Dr. Henri Leinonen, a vision scientist, we further investigated CB-5083's off-target effect on PDE6. Despite transient targeting of PDE6 by CB-5083, we found that chronic treatment of CB-5083 does not alter retinal structural or function, indicating the CB-5083 could be safe for the visual function with long-term regimen.
Currently, in collaboration with Ionis Pharmaceuticals, we are exploring antisense oligonucleotides as well as gene therapy as additional strategies to treat this devastating disorder.
This year Cheng received the Uplifting Athletes/Cure VCP Award 2020, for her preclinical studies in myopathy with VCP inhibitors and VCP antisense oligonucleotides (ASOs), in addition to the 2020 WSPR Mead Johnson Travel Award.

IBM Publications from the Kimonis Laboratory: Please let us know if you would like a copy.

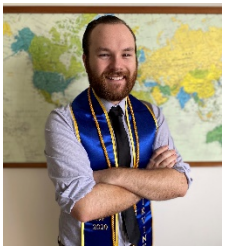
1. Plewa J, Surampalli A, Wencel M, Milad M, Donkervoort, Vincent J. Caiozzo VJ, Goyal N, Mozaffar T, Kimonis V. A cross-sectional analysis of clinical evaluation in 35 individuals with mutations of the valosin-containing protein gene. Neuromuscular Disorder. Sep;28(9):778-786. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6490182/
2. Surampalli A, Nalbandian A, Donkervoort S, Khare M, Wang A, Castellani R, Yin H, Rubio A, Patel P, Weiss J, Mozaffar T, Kimonis VE. A Clinicopathologic Case Report of a Female with Valosin- Containing Protein (VCP) Gene Mutation Related Disease. Int J Neurodegener Dis 2018, 1:006 Volume 1 | Issue 1 https://www.clinmedjournals.org/articles/ijnd/international-journal-of-neurodegenerative-disorders-ijnd-1-006.php?jid=ijnd
3. Al-Tahan S, Weiss L, Yu H, Tang S, Saporta M, Vihola A, Mozaffar T, Udd B, Kimonis V. A New Family with HSPB8 Associated Autosomal Dominant Rimmed Vacuolar Myopathy. Neurology Genetic. 2019;5:e349. https://ng.neurology.org/content/5/4/e349
4. Cheng C, Weiss L, Ta L, Kimonis V. Expression level of R155H mRNA in the knock-in mouse model. Biochem Biophys Res Commun. 2020 Mar 19;523(4):985-986. doi: 10.1016/j.bbrc.2020.01.021. Epub 2020 Jan 20 https://www.sciencedirect.com/science/article/abs/pii/S0006291X20300504?via%3Dihub
5. Nguyen M, Plewa J, Sweetman D and Kimonis V. A Natural History Study of VCP Associated Vacuolar Myopathy in a Patient with the Common R155H Mutation. Clinical and Experimental Investigations. 2020. https://www.sciencerepository.org/articles/a-natural-history-study-of-vcp-associated-vacuolar-myopathy-in_CEI-2020-1-101.pdf
6. Korb M, Kimonis VE, Mozaffar T. Multisystem proteinopathy: where myopathy and motor neuron disease converge. Muscle Nerve. 2020 Nov 3. doi: 10.1002/mus.27097. https://pubmed.ncbi.nlm.nih.gov/33145792/
7. Weiss L, Jung K-M, Nalbandian A, Llewellyn K, Yu H, Ta L, Chang I, Migliore M, Squire E, Ahmed F, Piomelli D, Kimonis V. Ceramide contributes to pathogenesis and may be targeted for therapy in VCP inclusion body myopathy. Human Molecular Genetics (In press).

Platform and Poster presentations from the Kimonis Laboratory:

1. Kimonis.V. VCP inhibitor CB-5083: a potential treatment for VCP inclusion Body Myopathy, Small Molecules & Therapeutic Antibodies: Experimental, Preclinical, Clinical, MDA Clinical and Scientific Conference, Jun 19, 2020. Virtual conference

2. Cheng C, Weiss L, Ta L, Ton T, Do TA and **Kimonis V** (CC: WSPR Mead Johnson Travel Award Winner). VCP inhibitor CB-5083: a potential treatment for VCP Inclusion Body Myopathy. 2020 (WSPR) Western Medical Research Conference. January 23-25, 2020, Carmel, California.

Recommended Evaluations in Individuals with VCP associated Inclusion Body Myopathy and/or Paget Disease of Bone and/or Frontotemporal Dementia https://www.ncbi.nlm.nih.gov/books/NBK1476/



Ryan Mahoney

Clinical Studies. We continue to recruit patients with VCP disease. We have more than 100 families and aware of 170 patients with VCP disease. To date >50 mutations have been identified in patients across the globe and have recently identified new VCP mutations. We are in the process of completing the analysis of clinical studies that several of you have contributed at UC Irvine or at Boston Children's Hospital in addition to the CORDS registry. Ryan Mahoney will be sending out surveys to those who have participated in the UC Irvine research studies through REDCAP. Please contact Ryan at rpmahone@hs.uci.edu if you have not received a survey invitation.

If not already enrolled please contact me if you are interested in participating in our research studies. We are interested in collecting information on any echo, DEXA, bone scans. MRI, X-rays, muscle biopsies, neuropsychological studies etc. that has been obtained on you in addition to treatments that you are currently taking. A consent/HIPAA/medical release form can be completed by docusign (Link for medical records release: https://drive.google.com/file/d/1D0DEiN3F0ts369wXHSlntJ_6VN-k7M7H/view?usp=sharing)

New Study: Benefit of Remote Exercise Training in Familial Myopathy.

I am excited to announce that I will be starting a clinical trial (remotely) of a respiratory resistance training study in patients with myopathy or muscle disease. We will be studying the effects of a respiratory resistance exercise training in improving lung function, in addition to muscle strength and function. We are looking to recruit 25 individuals to make the study statistically significant. You will be provided a training device and a guage to measure respiratory pressures. You will be involved in a breathing exercise that you can do at home twice daily. No travel is required to participate in this study. The study duration is 40 weeks. https://drive.google.com/file/d/1XH9SDR-Y0xBkqAuwoq_8y5Msn1Y1vbps/view?usp=sharing

Participants will receive a $200 gift card and a CureVCP Disease Inc. T-shirt, or cap and upon completion of the study. The true reward will be improvement in the respiratory function and sense of well being.
Please contact me on **vkimonis@uci.edu** if you are interested in participating in the study.

Cure VCP Disease, Inc., https://www.curevcp.org/ has also done a fantastic job with establishing the CoRDs registry. A major goal of the registry is to track the rate of progression of VCP disease. We currently have little longitudinal data in the registry, and the data you enter each year is very helpful to monitor the progression of the disease. If you have not done so, please register for the CoRDs registry through the website and update the information regularly. If you have any questions you can contact: Nathan Peck curevcpdisease@gmail.com or Jeannie Macaluso jeannie.macaluso@gmail.com

University of Maryland Brain and Tissue Bank
A Brain and Tissue Repository of the
NIH NeuroBioBank
Facilitating Research and Creating Awareness

If you are interested in donating your body for research please contact me by email or cell. Further information is available at https://www.medschool.umaryland.edu/btbank/

Federal funding is always a challenge 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.

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 Carley Fox (Director of Development) foxc@uci.edu
Gifts can also be made online at: https://give.uci.edu/inclusionbodymyopathy
All donations are Tax deductible

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