The discovery of proteins that initiate the muscle wasting caused by tumors could lead to new treatments for this hard-to-treat and often fatal condition called cancer-induced cachexia or cancer cachexia, report scientists with UTHealth in a proof-of-concept study in the journal Nature Communications.

Cancer cachexia is a wasting syndrome that causes weight loss and inflammation and can reduce the effectiveness of cancer drugs while in turn increasing their harmfulness. Approximately half of all cancer patients will develop this condition, and about half of the patients with cachexia will die of it before their cancer treatment has a chance to kill the cancer.

The National Cancer Institute issued a “Provocative Question” to the scientific community several years ago: “What mechanisms initiate or sustain cancer cachexia, and can we target them to extend lifespan and quality of life for cancer patients?”

In an effort to answer this question, UTHealth researchers found that in mouse cancer models, when they blocked the activity of the proteins named Hsp70 and Hsp90 in the bloodstream, the development of cancer cachexia stalled. The researchers used antibodies to neutralize the proteins in one model and silenced the genes that create them in cancer cells in another.

“We are the first to link elevated serum levels of Hsp70 and Hsp90 to cachexia in mice, and show that these proteins drive both muscle wasting and inflammation,” said Yi-Ping Li, Ph.D., the senior author and a professor of integrative biology and pharmacology at McGovern Medical School. “These proteins are promising therapeutic targets for defeating cachexia.”

Cancer cachexia primarily occurs in solid tumors including lung, pancreatic, colorectal and gastric cancer. “We show that all of these tumor cells from humans release high levels of Hsp70 and Hsp90, which explains the previous clinical findings that patients with these tumors tend to have elevated serum levels of these proteins,” Li added.

The next step in the research will involve investigations on cancer patients to determine if these proteins are biomarkers of cancer cachexia in humans, Li said.

Li said their findings could help in the understanding of other conditions that cause muscle loss such as chronic obstructive pulmonary disease and congestive heart failure, where circulating Hsp70 is also elevated.

The paper, “Tumor induces muscle wasting in mice through releasing extracellular Hsp70 and Hsp90,” was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases grant (AR063786).

The paper’s first author, Guohua Zhang, Ph.D., is an assistant professor of integrative biology and pharmacology at McGovern Medical School. UTHealth coauthors include Yong Zhou, Ph.D.; Ka Wai Thomas Sin, Ph.D.; Zhiren Zhu; Rene Flores, Ph.D.; and Qingyun “Jim” Liu, Ph.D.

Liu is the Janice Davis Gordon Chair for Bowel Cancer Research at UTHealth, and is on the faculty of The University of Texas MD Anderson UTHealth Graduate School of Biomedical Sciences along with Li.
Facility Spotlight

UTHealth scientists help explain how dietary fat affects stem cell differentiation
Rob Cahill, Office of Public Affairs

You are what you eat when it comes to fat, report McGovern Medical School scientists in the journal Science Advances.
Dietary fats are converted into lipids, which make up the membranes that surround all living cells.
The type of fat a person consumes may determine whether stem cells are converted into bone cells or fat cells, said Ilya Levental, Ph.D., the study’s senior author and assistant professor of integrative biology and pharmacology at McGovern Medical School at UTHealth.

“The fats that we consume such as cholesterol, unsaturated fats and fish oil become robustly incorporated into the membranes of our cells and dramatically change the composition and function of those membranes,” said Levental, a Cancer Prevention & Research Institute of Texas (CPRIT) Scholar.

To test their theory, Kandice Levental, Ph.D., the study’s lead author and assistant professor of integrative biology and pharmacology at McGovern Medical School, measured the lipid content of mesenchymal (connective tissue) stem cells as they transformed into bone cells or fat cells.
The Leventals found that bone cell membranes had unique compositions, being particularly high in a type of dietary fat, omega-3 polyunsaturated fat. This fat is also called DHA and is the most abundant component of fish oil, a common dietary supplement. Most importantly, they found that adding such fish oil fats to mesenchymal stem cells pushed them to transform into osteoblasts (bone-forming cells) as opposed to adipocytes (fat-storing cells).

This fundamental research helps explain why fish oil might benefit people with osteoporosis, a bone weakening disorder. More broadly, it may provide insight into the many connections between dietary fats and a variety of clinical outcomes, including healthy aging and heart disease.

“Our investigations suggest a general mechanism by which dietary fats affect cellular physiology through remodeling of membrane lipidomes, biophysical properties and signaling,” the authors wrote.

UTHealth coauthors included Joseph Lorent, Ph.D.; Yong Zhou, Ph.D.; CPRIT Scholar Jeffrey Chang, Ph.D.; and John F. Hancock, M.B., BChir, Ph.D. Also contributing to the paper were Michael A. Surma, Ph.D., and Christian Klose, Ph.D., of Lipotype GmbH in Dresden, Germany, and Allison D. Skinkle, an undergraduate researcher from Rice University.

The study, titled “ω-3 polyunsaturated fatty acids direct differentiation of the membrane phenotype in mesenchymal stem cells to potentiate osteogenesis,” was supported by CPRIT (R1215), NIH/National Institute of General Medical Sciences (1RO1GM114282) and the Volkswagen Foundation (93091).

Chang, Hancock and Ilya Levental are on the faculty of The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences. Hancock is the John S. Dunn Distinguished University Chair in Physiology and Medicine at UTHealth.
Department News

Welcome Dr. Hyun-Eui Kim!

The Department of Integrative Biology and Pharmacology would like to introduce our newest faculty member, Dr. Hyun-Eui Kim.

Dr. Kim received her Ph.D. in the Department of Biochemistry at University of Texas Southwestern Medical Center in Dallas. As a graduate student under a mentorship from Dr. Xiaodong Wang, she delineated the molecular mechanisms of apoptosome formation that drive the mitochondrial-mediated cell death signaling cascade (Kim et al., PNAS, 2005). Concurrently, she also identified multiple key regulators of apoptosome formation and carefully pieced apart their biochemical functions during the stages of apoptosome assembly (Kim et al., Mol. Cell, 2008). Dr. Kim's graduate research findings gave the field an essential, comprehensive, and mechanistic insight into the regulation of the mitochondria-initiated apoptosis pathway and facilitated the development of multiple therapeutic strategies targeting the apoptotic pathway in various types of cancers.

After her Ph.D. training, Dr. Kim joined the laboratory of Dr. Andrew Dillin at The Salk Institute of Biological Studies (which has since relocated to University of California, Berkeley) to study the interactions between stress response activation and age-related protein misfolding disease. In this work, she was grateful to receive support from both the Jane Coffin Child's Memorial Foundation and through a grant from the California Institute for Quantitative Biology (QB3)-Calico alliance. Dr. Kim discovered a novel lipid-mediated communication between mitochondria and the cytosol that is capable of initiating a distinct mitochondrial stress response, the activation of which reshapes the protein folding landscape of the cytosol, protecting it from aggregate-prone toxic proteins. They named this novel pathway as Mitochondrial to Cytosolic Stress Response (MCSR) (Kim et al., Cell, 2016). These findings led her to uncover a metabolic link capable of transmitting stress signals between the subcellular compartments that is well conserved from C. elegans to mammalian cells.

As an independent researcher, taking advantage of cutting-edge technologies in C. elegans genetics, mouse genetics, molecular biology, and biochemistry, Dr. Kim’s research will focus on the role of mitochondrial-mediated, cross-compartmental communication in the maintenance of cellular homeostasis. In her lab, they aim to understand the connection between the mitochondrial metabolism, aging, and age-related diseases, which will be valuable to develop new strategies for treatment of many types of age-related protein misfolding diseases.

Dr. Kim has a visiting scholar in the lab from UC Berkeley: Nan Xin, PhD.

Nan studied Wnt signaling while pursuing her Ph.D. in Dr. Yashi Ahmed's lab at Dartmouth College. She used Drosophila as a model organism to investigate a transcriptional regulator of mitochondrial biogenesis for its novel function in context-specific Wnt signal transduction. She thereafter became interested in mitochondrial genetics and biochemistry, and later initiated her postdoctoral training with Dr. Andrew Dillin at UC Berkeley, where she studied the differential regulation of mitochondrial protein import upon cellular stress. Nan will continue her research in mitochondrial stress response and aging with Dr. Kim at UTH.

Lab webpage: KimLabUTHealth.wordpress.com
Department News

Dr. Rosenfeld Honored with Merrell Flair Award

Gary Rosenfeld, Ph.D. received the Group on Educational Affairs (GEA) 2017 Merrell Flair Award in Medical Education at the AAMC Annual Meeting, Boston, MA., 11/04/17

The Group on Educational Affairs (GEA) is one of the largest affinity groups of the Association of American Medical Colleges (AAMC). The Merrel Flair Award honors an individual who has made a major contribution over a significant time period to the process or administration or transmission of information regarding medical education in North America.

Dr. Bavencoffe Receives Grant

Dr. Alexis Bavencoffe was awarded last October a grant by the TIRR Foundation / Mission Connect for the 2017 call for Proposals in Spinal Cord Injury. The project is entitled: "Macrophage Migration Inhibitory Factor (MIF): a Novel Target for Reducing Chronic SCI Pain".

Chronic neuropathic pain afflicts more than half of people with spinal cord injury (SCI) and can have devastating effects on their quality of life. The mechanisms are poorly understood and treatments remain inadequate. Thus, defining novel molecular contributions to SCI pain may lead to new therapeutic targets. This multidisciplinary project will test the potential for a promising new molecular target, macrophage migration inhibitory factor (MIF), to reduce chronic pain after SCI and increase the effectiveness of glucocorticoid treatments for chronically painful effects of SCI. This work will be accomplished in close collaboration with Prof. Carmen W. Dessauer, Prof. Edgar T. Walters, Dr. Juan J. Herrera, Dr. Phillip G. Popovich (OSU Columbus, Ohio) and Dr. Sibani L. Biswal (Rice University, Houston).

New Members of the Team

Hyun-Eui Kim
Assistant Professor

Celine Kong
Research Assistant I
Dr. Lee

Junchen Liu
Postdoctoral Fellow
Dr. Hancock

Nan Xin
Visiting Scientist
Dr. Kim
On Friday March 16, 2018, Courtney Olsen participated in Match Day with 221 other graduating students from McGovern Medical School. Courtney matched with Stanford University with a specialty in General Surgery.

Congratulations Dr. Olsen!

Congratulations to the following students for successfully defending their thesis.

**Randi Fitzgibbon (left)**
Adviser: Dr. Rebecca Berdeaux

**Michael McCarthy (right)**
Adviser: Dr. Alemayehu Gorfe’s lab

**Courtney Olsen (below)**
Adviser: Dr. Agnes Schonbrunn & Dr. Jeffrey Frost lab
Sixteen proposals were submitted by the Department of Integrative Biology & Pharmacology in the first quarter of Fiscal Year 2018 by Drs. Berdeaux, Chang, Cheng, Cunha, Denicourt, Dessauer, Lee, Li YP, Li Y, Pochynyuk, Venkatachalam, and Zhu.

Six proposals were awarded this quarter. Faculty receiving new awards include Drs. Bavencoffe, Dessauer, Levental, Venkatachalam, and Walters.

### Proposals Submitted FY2018 1st QTR

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### Awards Received FY2018 1st QTR

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### New Awards

New Awards received during the first quarter of Fiscal Year 2018 include:

**Dr. Bavencoffe.** TIRR/Mission Connect. 
*Macrophage Migration Inhibitory Factor (MIF): a Novel Target for Reducing Chronic SCI Pain.*

**Dr. Levental.** NIH.  *Structural Determinants and Functional Consequences of Protein Partitioning to Ordered Membrane Microdomains.*

**Dr. Walters.** Drexel University/NIH.  *Regulation of Neuropathic Pain by Exercise: Effects on Nociceptor Plasticity and Inflammation.*
Proposals & Awards
Data provided by Deborah Brougher, Supervisor, Grants and Contracts Specialist

Thirty two proposals were submitted by the Department of Integrative Biology & Pharmacology in the second quarter of Fiscal Year 2018 by Drs. Chang, Cheng, Denicourt, Dessauer, Du, Frost, Gorfe, Lee, Li Y, Lichtenberger, Pochynyuk, Venkatachalam, Walters, Wong, and Zhu.

Fifteen proposals were awarded this quarter. Faculty receiving new awards include Drs. Berdeaux, Cheng, Dessauer, Frost, Gorfe, Hancock, Lee, Levental, Lichtenberger, Loose, Venkatachalam, and Zhu.

### Proposals Submitted FY2018 2nd QTR

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New Awards
New Awards received during the second quarter of Fiscal Year 2018 include:

**Dr. Berdeaux.** American Diabetes Associations. *Regulation of mitophagy by SIK1.*

**Dr. Dessauer.** NIH. *Regulation of Adenylyl Cyclase Signaling Pathways.*

**Dr. Berdeaux.** NIH. *Regulation of glucose utilization by skeletal muscle SIK1.*

**Dr. Levental.** University of Delaware / NIH. *Effects of Lipidomic Diversity.*

**Dr. Cheng.** Sanofi US Services, Inc. *Targeting Exchange Protein Directly Activated by (EPAC) for the treatment of Cardiovascular Diseases.*

**Dr. Venkatachalam.** University of Pennsylvania. *Targeting Endolysosomal Proteins to Treat RASopathies.*
Publications


Tomilin VN, Zaika O, Subramanya AR, Pochynyuk O. Dietary K\(^+\) and Cl\(^-\) independently regulate basolateral conductance in principal and intercalated cells of the collecting duct. Pflugers Arch. 2017 Nov 13. doi: 10.1007/s00424-017-2084-x. [Epub ahead of print].


IBP Calendar of Events

Administrative Staff Meetings, 2:30-3:30 PM, MSB 4.136
February 1, March 1, April 5, May 3, June 7

Faculty Coffee/Tea, 10-11 AM, MSB 4.100
January 3, 10, 17, 24, 31
February 7, 14, 21, 28
March 7, 14, 21, 28
April 4, 11, 18, 25
May 2, 9, 16, 23, 30
June 6, 13, 20, 27

Research-in-Progress Symposium, 12-1 PM, MSB 4.100
January 2, 9, 16, 23, 30
February 6, 13, 20, 27
March 6, 13, 20, 27
April 3, 10, 17, 24
May 1, 8, 15, 22, 29
June 29, 5, 12, 19, 26

Dates to Remember:
January 1: New Year’s Day
January 15: Martin Luther Kind Day — The University will be closed for Official Business.
February 2: Groundhog Day
February 14: Valentine’s Day
February 19: President's Day—The University will be closed for Official Business
March 11: Daylight Savings Time Begins
March 17: St. Patrick’s Day
March 20: First Day of Spring
March 30: Good Friday
April 1: Easter
April 1: April Fool’s Day
April 22: Earth Day
May 13: Mother’s Day
May 28: Memorial Day-The University will be closed for Official Business
June 17: Father’s Day
June 21: First Day of Summer
July 4: Independence Day-The University will be closed for Official Business