Stephen J. Weiss, MD  
Division Chief/Professor

Emeritus Faculty
George J. Brewer, MD (active)

Professor
Sally A. Camper, PhD  
Kathleen R. Cho, MD  
Eric R. Fearon, MD, PhD  
Thomas D. Gelehrter, MD, MA  
David Ginsburg, MD  
Jun-Lin Guan, PhD  
Randal J. Kaufman, PhD  
Yang Liu, MD, PhD  
Gilbert S. Omenn, MD, PhD  
Alan R. Saltiel, PhD

Associate Professor
Kathleen L. Collins, MD, PhD  
Colin S. Duckett, PhD  
Thomas M. Glaser, MD, PhD  
Stephen B. Gruber, MD, PhD, MPH  
John V. Moran, PhD  
Sean J. Morrison, PhD  
Elizabeth M. Petty, MD

Clinical Associate Professor
Stephanie Burns Wechsler, MD

Assistant Professor
Ezra Burstein, MD  
Zhe Han, PhD  
Cheng-Yu Lee, PhD  
Daniel E. Michele, PhD  
JoAnn Sekiguchi, PhD  
Deneen Wellik, PhD  
Xiaochun Yu, MD, PhD  
Yuan Zhu, PhD

Clinical Assistant Professor  
Jane M. Nicholson, MD

Research Assistant Professor  
Thomas L. Saunders, PhD

Research Investigator
Edward D. Allen, PhD  
Kevin B. Hotary, PhD  
Xiao-Yan Li, PhD  
Xuwen Liu, MD, PhD  
Farideh Sabeh, PhD  
Bin Zhang, PhD

A scanning electron microscope image of inguinal fat tissues. The cluster of fat cells are surrounded by collagen fibers.
Sharpening Our Knowledge of “Molecular Scissors”

Just below our skin lies a layer of fat cells, capable of stashing away energy in solid form. Evolutionarily speaking, our ability to store fat in the good times to get us through the lean times is crucial. But in this day and age, most of us have a lot more of this stored energy than we’ll ever possibly need—much to the delight of the weight-loss industry.

No matter how much of it we have, this “white adipose tissue” layer plays a key role in our growth from embryos to adults, our metabolism, and even our self image. A large amount of stored white fat is highly associated with diabetes, cardiovascular disease and other conditions, possibly because of the role it plays in regulating the amount of fat in the bloodstream, or because of the molecules that the adipose cells send out and receive.

But how do these adipose cells develop and manage to grow ever bigger? And how does insulin factor into the proper—or dysfunctional—storage of fat?

These questions form the focus of research by Tae-Hwa Chun, MD, PhD (near right), Alan R. Saltiel, PhD (far right), Stephen J. Weiss, MD (previous page), and their colleagues in Molecular Medicine and Genetics (MMG). Specifically, they have zeroed in on the importance of a molecule that could be thought of as a kind of “molecular scissors”—and that appears to allow fat cells to tailor their environment to fit their size.

This year, the team published an important paper in Cell, culminating several years of work on this molecule, called membrane-type 1 matrix metalloproteinase (MT1-MMP). The findings demonstrate that MT1-MMP is absolutely vital to white adipose tissue development—and that without it, fat cells cannot expand and store more fat.

To understand what MT1-MMP does, picture a fat cell as a person sitting down to a large meal wearing tight-fitting clothes and a belt. The clothes and belt represent the extra-cellular matrix, or ECM—the fibrous, thick gel of collagen and other substances that surround the cell and separate it from its neighbors and nearby blood vessels.

As the fat cell “eats” more and more stored energy, it needs to expand. But to do so, it needs to snip away at the ECM that “clothes” it. As the U-M team demonstrated this year, MT1-MMP acts as the scissors that does this snipping, digesting collagen and creating free space for the cell to expand into.

These results were based on their initial observation that mice that lacked the MT1-MMP gene, also called “knockout” mice, die early without gaining much weight.

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Cancer Genetics Supported by New Chair

In 2006, Stephen B. Gruber, MD, PhD was installed as the first H. Marvin Pollard Professor in Internal Medicine, made possible by a gift from the Shirley M. McLaughlin Trust. The endowment is named after H. Marvin Pollard, a graduate of the University of Michigan (MD 1931, Residency 1933), who devoted much of his research to cancer during his more than 50 years as a physician.

Dr. Gruber is director of the Cancer Genetics Clinic which specializes in caring for individuals and families with inherited susceptibility to cancer. Research in his laboratory focuses on identifying genetic factors that contribute to the development of cancer and understanding how environmental factors modify inherited susceptibility. Dr. Gruber’s clinic, combined with his research lab, serves as a model for translating advances in cancer genetics research into clinical practice.
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In other words, a cell that can’t modify its extracellular matrix in order to grow becomes as uncomfortable as a person at an all-you-can-eat buffet who can’t loosen his belt and collar. And no matter how much that cell wants to respond to the insistent signal of insulin—which, like a pushy waitress, tells it to store away more energy—it simply can’t.

After determining that MT1-MMP knockout mice had miniature white adipose tissue cells, but that these cells were unable to store fat, the researchers worked to determine the mechanism in culture. Strangely, the fat precursor cells isolated from the mice behaved almost normally when grown on top of a layer of collagen.

But then, the U-M team managed to grow them inside a three-dimensional simulation of the extracellular matrix—and the mysterious behavior of the knockout cells returned. The cell’s perturbed gene expression and lack of growth were the same as in the fat-free, knockout mice. And the cells refused to heed the call of insulin to store energy as fat.

Now, the team is working to determine which genes are expressed when cells use MT1-MMP to “remodel” their surroundings by altering the extracellular matrix, and how the physical rigidity of the matrix alters fat gene expression. They’re also looking at whether insulin resistance—the inability of cells to respond to insulin signals and store more fat—might be caused by inappropriate MT1-MMP activity.

At the same time, the U-M team is working with colleagues in Japan and North Carolina to find whether subtle changes in the MT1-MMP gene activity caused by single-nucleotide polymorphisms, or SNPs, might be linked to a predisposition for human obesity. They’re also looking for biomarkers of MT1-MMP that reflect its activity in fat tissue.

Finally, it is possible that drugs designed to decrease MT1-MMP’s activity could have a role in treating abnormal fat storage or problems associated with the regulation of fat metabolism. And many of us who have just a little too much of that white adipose tissue would celebrate that advance.
Stem Cells in the Spotlight

Most of the time, research scientists are content to stick to their laboratories and seminars, with the occasional foray into a national or international meeting to present their latest results. But once in a while, the times demand their presence on the public stage.

Such was the case this year for Sean Morrison, PhD (below), director of the University’s new Center for Stem Cell Biology and a member of the MMG faculty as well as the Life Science Institute and Howard Hughes Medical Institute.

With the debate over embryonic stem cells raging at the national and state level, Morrison jumped into the public-policy fray with both feet. Throughout the year, he could be found advising legislators and university officials, testifying before a committee of the state legislature, giving talks to groups of citizens and schoolchildren, writing newspaper opinion pieces and giving numerous interviews to reporters. He also helped create an online tutorial on stem cells and their potential uses, available to all on the University’s web site at www.umich.edu/news/stemcells/Windows.html.

In fact, these public-education efforts led to his selection as a 2006 Michiganian of the Year by the Detroit News.

The flurry of activity centered on two developments: A federal funding bill for embryonic stem cell research that passed the House and Senate with bipartisan support but was killed by President George W. Bush’s first-ever veto, and an unresolved state-level debate over whether to repeal a Michigan law that keeps scientists in the state from creating new lines of embryonic stem cells—no matter what their source of funding.

In the wake of both of these developments, the University has raised enough money to create a separate facility for embryonic stem-cell research using existing cell lines and private dollars from individual donors and private foundations. Further work will need to be supported by additional donations, since federal money can’t be used.

In addition to his efforts on behalf of the University’s stem-cell research community, Morrison has also become involved in public policy on a national and international level as an officer of the International Society for Stem Cell Research and a member of the public policy committee of the American Society for Cell Biology.

All the while, Morrison and his large laboratory team have continued to produce innovative findings in stem cell science, especially in the area of cells that give rise to blood and nervous system cells. But with the public clamoring to know more about this area of science, and policymakers deciding the future of the field, this was a year to be in the public eye as well as the lab.

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This image represents a metaphase spread of chromosomes from a leukemia cell superimposed upon a section through the spleen of a Pten-deleted mouse with leukemia. This is from a study which demonstrated that hematopoietic stem cells and leukemia-initiating cells differ in their dependence upon Pten. This knowledge can be therapeutically exploited to kill leukemia cells without harming normal stem cells. While this research was performed in mice, there are plans to initiate a clinical trial in patients at the U-M hospital in 2007.