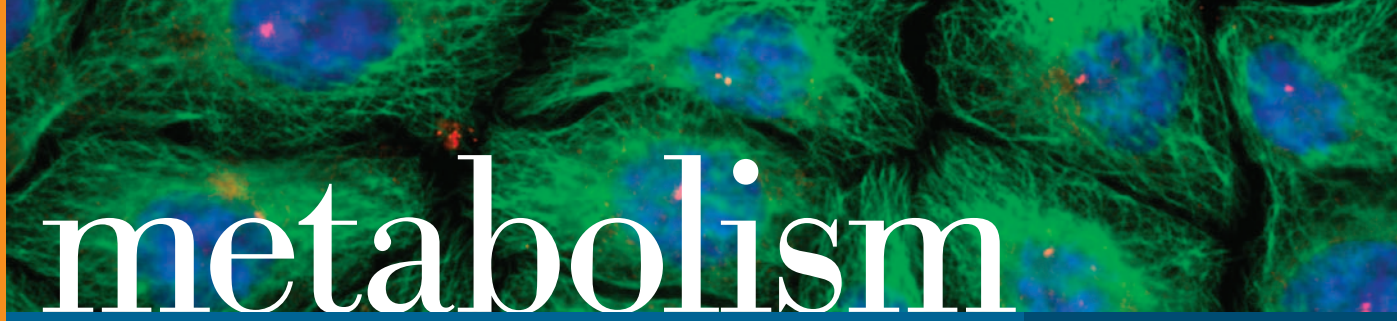
From the Bench



metabolism

CURRENT RESEARCH AT THE SALK INSTITUTE SPRING 2008

THE PREVALENCE OF OBESITY HAS INCREASED AN alarming 75% since 1980, rendering a third of all men and women obese in the U.S. With the increase in body weight comes a slew of metabolic disorders, including: glucose intolerance (high sugar), insulin resistance (high insulin), high cholesterol (high fat), hypertension (high blood pressure), atherosclerosis ("hardening" of blood vessels).

These are all established risk factors for cardiovascular disease and type II diabetes. Obesity and diabetes also increase the risk for prostrate, breast and colon cancers. Genetic studies of aging identified nutritional programs that, when optimally tuned, dramatically extend healthful life. But how metabolic changes are linked to cancer and aging remains unclear.

To get to the bottom of these puzzling connections, the Salk Institute recently started a Metabolism Initiative that brings together different disciplines to build a link between the disparate fields of diabetes, cancer biology and aging research. The newly established metabolism center will enable Salk scientists to work together across disciplines to understand the metabolic changes associated with cancer and aging, as well as type I and type II diabetes, and to accelerate the development of new therapies and disease-prevention strategies.

Faced with an over-abundance of food, little physical activity combined with a middle- age reduction in metabolism, even the most robust regulatory mechanisms break down resulting in— on average —one additional pound per year.

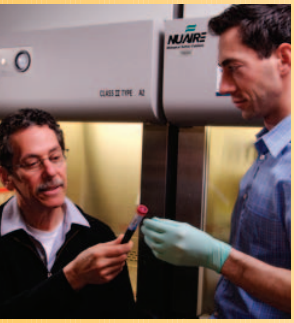
The affected network is key to our understanding of obesity and will be critical for the development of future anti-obesity drugs. **Tony Hunter, Professor, Molecular and Cell Biology Laboratory, Salk Institute**

When exercise comes naturally

THE EQUATION SOUNDS DECEPTIVELY SIMPLE: PEOPLE GAIN WEIGHT WHEN their energy intake in the form of food exceeds their energy expenditure. But scientists, parsing the intricacies of how the body regulates appetite, stores fat, and burns flab, have discovered that the body's energy balance is controlled by a complex network of brain signals, dozens of hormones and physiological mechanisms. **Tony Hunter** and his team discovered that shutting down two genes that modulate the body's energy balance turns mice into lean and mean exercise aficionados even though they chomp down like there is no tomorrow.

Turning fat on fire

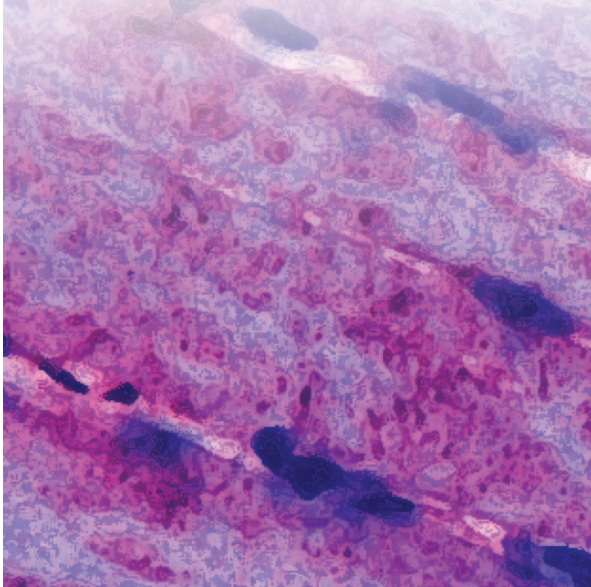
RONALD EVANS PROBES THE MOLECULAR CONNECTION BETWEEN obesity and diabetes. In particular, he studies a family of genes that controls the storage and burning of fat. Among those genes, he discovered the molecular target of the new multi-billion-dollar drugs Actos and Avandia, which belong to the newest generation of anti-diabetic medications. The target, a genetic switch called PPAR gamma, regulates the storage of surplus glucose as fat. However, when PPAR gamma is stimulated by a drug, the body's response to insulin improves, lowering levels of circulating glucose.



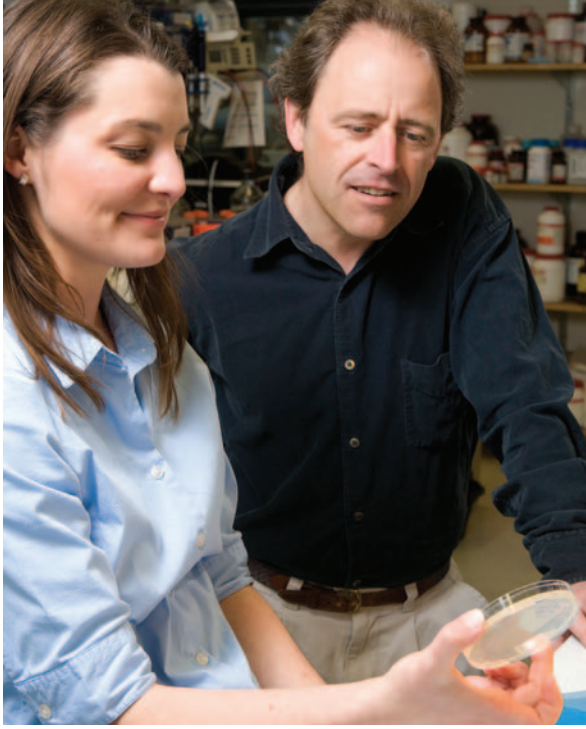
Its sibling gene switch, PPAR delta, controls the ability of cells to burn fat. When Evans and his team artificially turned on PPAR delta in muscle, the resulting mice became marathon runners, leaving their cage-mates in the dust. In addition to turning into super-endurance athletes, the altered mice were resistant to weight gain, even when fed a high-fat diet that caused obesity in ordinary mice. Three companies are already developing oral drugs that activate PPAR delta in humans, which could lead to treatments for diabetes and obesity. The discovery could also be good news for people who are confined to a wheelchair or suffer from muscle-wasting diseases like AIDS or muscular dystrophy.

An old standby in a new light

METFORMIN (GLUCOPHAGE), THE most commonly used oral drug for lowering blood glucose in the U.S., was known to block glucose production by the liver in patients with type II diabetes, but how it worked was unknown. **Reuben Shaw,** in collaboration with **Marc Montminy,** found that glucophage shuts down glucose production in diabetes by turning off the CRTC2 switch in the liver. Having identified a molecular target for this drug, new, more active drugs will be much easier to develop.



Alternative fuels



JUST LIKE A FLEX-FUEL VEHICLE that can run on either gasoline or ethanol, the human body can switch between different types of fuel; during the day the body mostly burns glucose, and during the night or prolonged fasting, it primarily burns fat. But neither flex-fuel engines nor human brains can run on ethanol or fat alone—a little bit of gasoline or glucose needs to be thrown into the mix to keep either one of them humming.

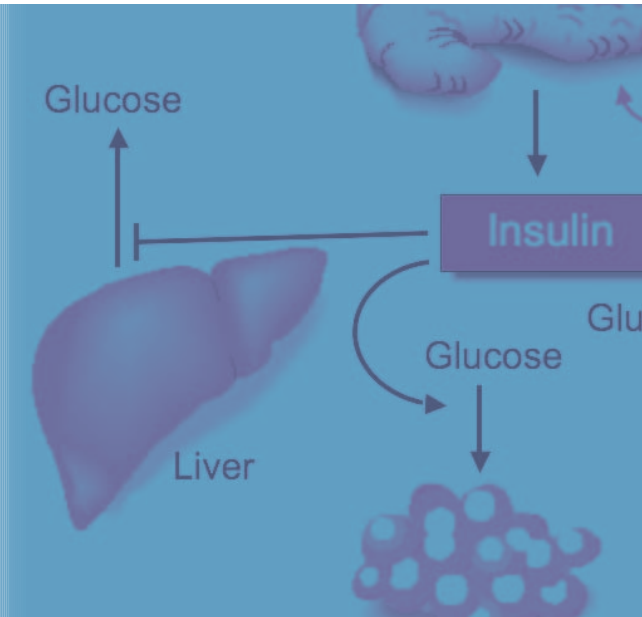
Marc Montminy discovered a, "fasting switch", called CRTC2 that flips on glucose production in the liver when blood glucose levels run low during the night. In many patients with type II diabetes, however, CRTC2 is on all the time, and as a result, the liver acts like a sugar factory on overtime, churning out glucose throughout the day. His latest study revealed that the vicious circle gets rolling when out-of-control blood sugar levels permanently lock the fasting switch in the "on" position. Initial experiments suggest that drugs, which prevent CRTC2 from getting stuck, might be useful for lowering glucose levels in diabetic individuals and reducing long-term complications associated with the disease.

The bitter side of sugar

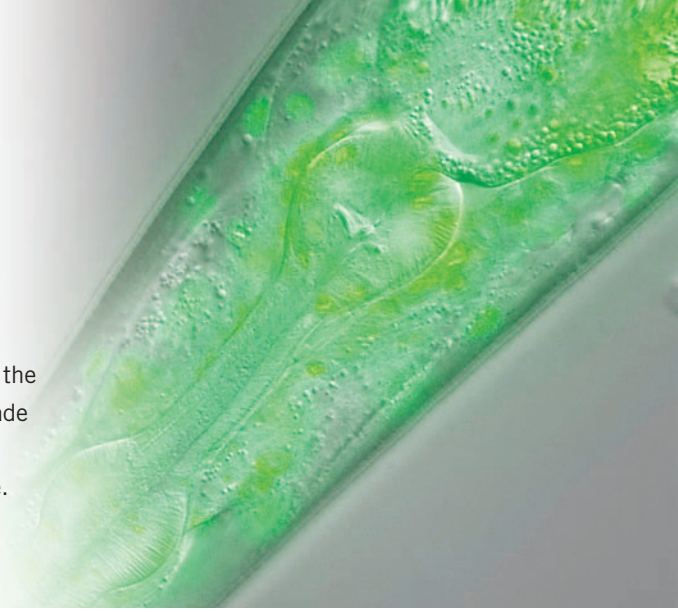
DIABETIC INDIVIDUALS HAVE A significantly higher risk of developing Alzheimer's disease but the molecular connection between the two remains unexplained. In their latest study, **David Schubert** and his team discovered that the blood vessels in the brain of young diabetic mice are damaged by the interaction of elevated blood glucose levels characteristic of diabetes and beta amyloid, a peptide that clumps to form the senile plaques riddling the brains of Alzheimer's patients. Although the damage takes place long before the first plaques appear, the mice suffer from significant memory loss and an increase in inflammation in the brain. Ongoing work in Schubert's lab centers on a new family of drugs that has shown promise for preventing Alzheimer's disease and perhaps the vascular damage associated with diabetes.

Boosting production capacity and output

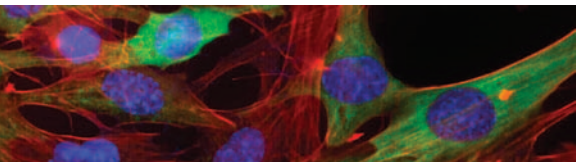
KEY TO THE DEVELOPMENT OF EITHER TYPE I OR TYPE II DIABETES IS THE inability of the pancreas to produce enough insulin, either because the number of insulin-producing islet cells is too low (type I) or because the body is insulin resistant and the pancreas cannot keep up with demand (type II). **Wylie Vale's** and **Paul Sawchenko's** research teams have discovered a new hormone— known as urocortin 3 —that was shown by Vale postdoctoral fellow **Chien Li** to be produced and act in the pancreas. It can increase both islet cell proliferation and insulin production making it a promising target for the development of drugs treating type I and type II diabetes.

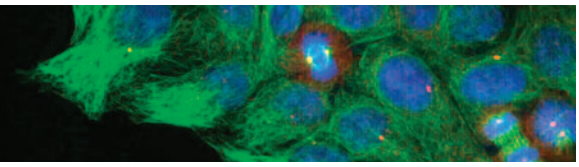


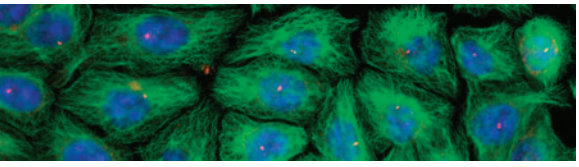
Eat (much) less, live longer

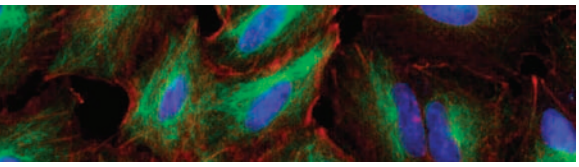


SUPERIMPOSED ON THE METABOLIC REGULATORS' MINUTE-TO-MINUTE effects on energy balance and metabolism are long-lasting changes that impact lifespan and survival. In studies going back to the 1930s, mice and many other species subsisting on a severely calorie-restricted diet have consistently outlived their well-fed peers by as much as 40 percent. **Andrew Dillin** recently discovered the first molecular switch that specifically links calorie restriction to longevity. He made his discovery in a small laboratory worm called *C. elegans* and is currently strengthening this connection by studying how the switch regulates aging in mice.









Cutting off the supply

WHEN A NORMAL CELL HAS LOW energy levels it won't divide. But, in some cases, cancer cells can override the built-in shut-off. **Reuben Shaw** discovered that cells with a defect in the tumor suppressor LKB1, one of the most commonly mutated genes in sporadic lung cancer, fail to activate a key metabolic switch when intracellular energy stores run low. They just keep dividing. Now, he is trying to connect the dots to identify the critical components of this particular biochemical route through which nutrients regulate cell growth. Such intersections between cancer and metabolism embody critical intervention points for future therapeutics.

This issue of *From the Bench* is the first in a series of updates on key areas of scientific research conducted at the Salk Institute for Biological Studies. Our goal is to keep you informed of Salk researchers' most recent findings in areas such as stem cells and regeneration, vision, plant biology, neuroscience, behavior, and more. We would love to receive feedback from you regarding this update.

For more information, or to share your comments, please contact Judy Hodges at the Institute's Office of Development at 858.453.4100 ext. 1882 or email hodges@salk.edu.

Rebecca Newman
Vice President, Development

Gina Kirchweger
Director, Scientific Communications
Editor

SALK INSTITUTE
FOR BIOLOGICAL STUDIES

10010 North Torrey Pines Road
La Jolla, California 92037-1099

Post Office Box 85800
San Diego, California 92186-5800

From the Bench