The Problem
Humans are built to hunger for fat but when deluged by foods rich
in fat and sugar coupled with a sedentary lifestyle, the modern
waistline often far exceeds the need to store energy for lean
times. The result has been an epidemic of diabetes, heart disease
and other obesity-related problems, including cancer. Although
exercise and calorie restriction are known to be effective at
preventing and treating diabetes, the obesity epidemic continues
to grow and new drugs to treat the problem are desperately needed.

The Approach
Ronald Evans is an authority on hormones, both their normal
activities and their roles in disease. A major achievement in
Evans’ lab was the discovery of a large family of molecules, called
nuclear hormone receptors, which respond to various steroid
hormones, vitamin A and thyroid hormones. These hormones
help control sugar, salt, calcium and fat metabolism, affecting
our daily health as well as treatment of disease. The receptors
Evans discovered are primary targets in the treatment of breast
cancer, prostate cancer, pancreatic cancer and leukemia, as well
as osteoporosis and asthma.

In addition, Evans’ studies led to a new class of PPAR delta
drugs called exercise mimetics, which promote the benefits of
fitness without the need to train. Exercise mimetics represent an
important advance in addressing problems arising from excess
weight and obesity, such as frailty, muscular dystrophy and
type 2 diabetes.

The Innovations and Discoveries
• Evans’ team developed two innovative approaches for
potentially treating diabetes. The group identified the missing
link in the regulation of the activity of insulin—a protein known
as fibroblast growth factor 1 (FGF1), which reboots glucose
metabolism. Evans also developed a new type of diet pill that
tricks the body into thinking it has consumed calories, causing
it to burn fat. The compound effectively stopped weight gain,
lowered cholesterol, controlled blood sugar and minimized
inflammation in mice.

• Two receptors found on the nuclei of mouse and human
cells, known as REV-ERB-α and REV-ERB-β, are essential
for synchronizing normal sleep and metabolic cycles. Evans’
findings describe a powerful link between circadian rhythms
and metabolism and suggest a new direction for treating
disorders of both systems, including jet lag, sleep dysfunction,
obesity and diabetes.

• Evans’ lab discovered that a chemically modified form of
vitamin D might offer a new approach to the treatment of
pancreatic cancer. The vitamin D derivative makes tumor
cells vulnerable to chemotherapy and more sensitive to the
body’s immune system. With clinicians at the University of
Pennsylvania, Evans’ team launched a clinical trial to test this
drug in cancer patients.

For more information, please visit:
www.salk.edu/scientist/ronald-evans