Initiative Against Diabetes and Obesity at The Scripps Research Institute
Hope for a Better Way

Americans are being swept up in a national epidemic of diabetes, obesity and related conditions. While diet and inactivity have contributed to this epidemic, a lack of fundamental understanding of the complexities of how humans use and store the energy that our cells need to survive has hampered the development of life-changing therapies.

Scientists at The Scripps Research Institute (TSRI) are focusing on uncovering this mystery and much more—how aging affects our metabolic rate, how junk food can become an addiction, how current therapies work in our body—information critical to the development of safer and more effective medicines.
Diabetes—a Leading Health Problem

- Diabetes is a family of diseases in which people have too much sugar (glucose) in their blood or cannot use that sugar properly—or both.
- Diabetes is a contributing factor in a range of health problems, including heart disease, stroke, hypertension, blindness and eye problems, kidney disease, nervous system damage, amputations and gum disease.
- Diabetes is the seventh leading cause of death in the US.
- Diabetes affects an estimated 8.3 percent (25.6 million) of Americans 20 years or older and an estimated 26.9 percent (10.9 million) of people 65 or older; a staggering 79 million Americans today are considered to be prediabetic.
- The cost associated with diabetes in this country has been estimated at $174 billion per year.
Obesity—a National Emergency

- Obesity is a serious condition affecting an increasing number of Americans—now over one third (35.7%) of adults and 12.5 million children (17%), according to the US Centers for Disease Control; according to the World Health Organization, obesity now affects at least 400 million people worldwide.

- Obesity is a major contributor to heart disease, stroke, type 2 diabetes and certain types of cancer, some of the leading causes of preventable death.

- Childhood obesity, now affecting 17% (or 12.5 million) of children and adolescents, increases risk of social and psychological problems, as well as health problems such as breathing issues (sleep apnea, asthma), fatty liver disease, gallstones and heartburn.

- The annual medical cost associated with obesity in this nation is estimated at $147 billion per year.
What We Know

- Diabetes and obesity are two related conditions affecting the body’s metabolism—the process by which your body converts what you eat and drink into energy.

- Metabolism, which relies on a complex network of hormones and enzymes, is influenced by age, gender, genetics and body composition (proportion of fat to muscle); it is also influenced by what and how much you eat and by physical activity—factors also affected by finely tuned feedback mechanisms.

- Normally, digestion breaks down food into glucose or sugar, which is then carried to the cells and used as fuel; the hormone insulin regulates glucose (sugar) levels in the blood.

- Sometimes, however, the body itself attacks cells in the pancreas that produce insulin, resulting in insufficient insulin levels and type 1 diabetes.

- In other cases, cells don't respond normally to insulin. This occurs in type 2 diabetes. The initiating factor in type 2 diabetes is insulin resistance, which can develop with age and increased body mass index.

- Diabetes and obesity can cluster together in “metabolic syndrome,” which can also include high blood pressure, high blood sugar levels, excess body fat around the waist and abnormal cholesterol levels.
Limited Treatment Options for Diabetes

Type 1
- Treatment for this autoimmune disease involves taking replacement insulin via injection or pump.
- While this therapy has drastically reduced fatality rates from type 1 diabetes, it is not a cure; people with type 1 diabetes need to closely monitor their blood sugar to avoid life-threatening health problems.

Type 2
- Type 2 diabetes (which accounts for 90 to 95% of diabetes cases) can be managed in part with lifestyle changes, including increased physical activity and a diet with limited amounts of sugar and refined carbohydrates.
- However, diet and exercise are often insufficient and many people take medication, insulin or both to stabilize blood sugar levels and try to prevent dangerous complications.
- Nonetheless, overall the risk for death among people with diabetes is about twice that of people of similar age without diabetes.
Limited Treatment Options for Obesity

- Diet and exercise are essential to controlling body mass index and the development of obesity.
- Unfortunately for many people, diet and exercise are not sufficient to prevent or reverse obesity; these patients are often desperate for additional help.
- Medical options include only a small number of prescription drugs—which don’t work for everyone and are often associated with unpleasant or toxic side effects—and bariatric surgery, which is a more drastic surgical procedure.
- Since factors leading to obesity are complex, the disease is difficult to treat and manage; most people who lose weight by dieting regain it within five years and a significant portion regain more than they lost.
While new effective and safe medications are needed for people struggling with these conditions:

- Almost all of the basic biomedical research is carried out in the academic sector, which relies heavily on funding from the federal government.
- Unfortunately, federal funding for basic biomedical research has been steadily declining in real dollars with no end in sight.
- The research funded by the National Institutes of Health (NIH) and the National Science Foundation (NSF) tends to be incremental and not sufficient to support development of new therapies. What is needed to achieve scientific breakthroughs are high-risk, high-reward endeavors.
- Pharmaceutical companies rarely invest in the basic biomedical research necessary to search for diagnostics and therapies.
The New Initiative at TSRI Offers a Path Forward

- TSRI proposes an organization that brings together varied scientific approaches to these critical problems in diabetes and obesity, funded aggressively to find breakthroughs in the shortest time feasible.

- The purpose is to find:
  - Novel therapeutic strategies.
  - Early disease diagnostics (biomarkers).
  - Effective new medications and other approaches to help affected individuals reclaim their health.

- This will be accomplished by assembling a critical mass of scientists, each contributing their specific expertise to an interdisciplinary approach, creating synergies and expanding the base of information needed to find solutions.
Why TSRI?

TSRI has:

- A track record of basic discoveries translated into new therapies, including treatments for arthritis, lupus, hemophilia and cancer.
- More than 50 companies launched from TSRI discoveries.
- More than 800 patents on innovative technologies.
- 30 pharmaceuticals currently in clinical development.
- Recognition as a leader at the intersection of biology and chemistry—ranked number one in the world in chemistry, number two in microbiology (ranked by Thomson Reuters, citations per paper over a decade).
TSRI Scientists at the Forefront

TSRI scientists have already shed new light on diabetes and obesity:

- Establishing a new class of anti-diabetic compound targeting a unique molecular switch.
- Identifying a natural product that increases sensitivity to insulin and reduces fatty liver in mice.
- Discovering a specific gene that plays an important role in keeping a steady balance between our food intake and energy expenditure.
- Creating the first comprehensive roadmap of the protein interactions that enable cells in the pancreas to produce, store and secrete insulin.
- Developing an anti-obesity vaccine that significantly slowed weight gain and reduced body fat in animal models.
- Discovering a catalytic antibody that degrades a known appetite stimulant, a potential treatment for obesity.
- Identifying a key regulator of fat cell development that may provide a target for obesity and diabetes drugs.
Some TSRI Scientists Tackling Questions in Diabetes and Obesity

- William Balch, PhD
- Roberto Baccala, PhD
- Anutosh Chakraborty, PhD
- Michael Conkright, PhD
- Bruno Conti, PhD
- Matthew Disney, PhD
- Martin Friedlander, MD, PhD
- Larry Gerace, PhD
- Patrick Griffin, PhD
- Scott Hansen, PhD
- Wendy Havran, PhD
- William Ja, PhD
- Kim Janda, PhD
- Theodore Kamenecka, PhD
- Oktay Kirak, PhD
- Douglas Kojetin, PhD
- Anastasia Kralli, PhD
- Philip LoGrasso, PhD
- Patricia McDonald, PhD
- Lindsey Miles, PhD
- Kerri Mowen, PhD
- Glen Nemerow, PhD
- Michael Oldstone, MD
- Amanda Roberts, PhD
- William Roush, PhD
- Enrique Saez, PhD
- Daniel Salomon, MD
- Peter Schultz, PhD
- Louis Scampavia, PhD
- Linda Sherman, PhD
- Supriya Srinivasan, PhD
- Roy Smith, PhD
- Charles David Stout, PhD
- Andrew Su, PhD
- Mark Sundrud, PhD
- Iustin Tabarean, PhD
- Luc Teyton, MD, PhD
- Dennis Wolan, PhD
- Eric Zorrilla, PhD
- Baoji Xu, PhD

For faculty bios, see www.scripps.edu
A Collaborative and Focused Effort

To make progress against diabetes and obesity, the initiative will:

- Marshal an organized and focused collaborative research effort, turning the best scientific minds loose on the problem.
- Recruit and retain talented young investigators working in the area and support their initial efforts in research.
- Create a collaborative, interdisciplinary, synergistic environment that expands scientific thinking about diabetes and obesity from many perspectives.
- Evaluate initiative-funded research aggressively on an annual basis to ensure that only promising pathways are pursued.
Supporting Innovative Research

Grants
- TSRI investigators submit requests for funding for innovative research.
- Accepted projects receive funding to develop new approaches that will be then competitive for National Institutes of Health/National Science Foundation funding to continue and expand the work.

Oversight
- A scientist-director, appointed by the TSRI president, holds an endowed chair to provide administration and scientific direction.
- An internal grant committee reviews the proposals and provides granting recommendations.
- A Scientific Advisory Board monitors the progress and research integrity of the center, reviews and evaluates work in progress, and issues recommendations concerning the continuation or discontinuation of projects.
Funding

The initiative will be funded by investments totaling $50 million.

Expenditure plan:

- $9 million—Endowed chairs for three senior investigators and a director
- $10 million—New cutting-edge equipment and scientific supplies
- $10 million—Training program for postdoctoral fellows
- $5 million—Seed money awarded on the basis of merit to fund innovative three-year projects
- $16 million—A ten-year term endowment to ensure resources are available to follow up on the most promising findings, for example with clinic trials
A Lasting Contribution

Your contributions will support world-class talent and fund innovative research projects to combat the epidemic of diabetes and obesity that is putting the health of people in this country, and increasingly other parts of the world, at great risk.

With your support, scientists at TSRI will unravel the mysteries of our metabolism and find answers that can lead to better treatments for those who suffer the most from these conditions today—and for generations to come.
Appendices
Appendix 1: Drugs Developed from TSRI Discoveries

- **Humira®** for rheumatoid arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis and other inflammatory conditions
- **Benlysta®** for lupus, a debilitating autoimmune disease
- **Leustatin®** for hairy cell leukemia, an unusual cancer of the blood
- Purification of **Factor VIII** for the bleeding disorder hemophilia
- **Vyndaqel®** for transthyretin familial amyloid polyneuropathy (TTR-FAP), a rare, progressive and fatal neurodegenerative disease
- **Surfaxin®** for infant respiratory distress syndrome, a life-threatening condition affecting pre-term infants
- **Cyramza®** for gastric and non-small cell lung cancer
- **Unituxin™** for the childhood cancer neuroblastoma
Appendix 2: Companies from TSRI Technology or Faculty

2014
- Aldabra Biosciences
- Padlock Therapeutics
- Transplant Genomics, Inc.

2013
- Blackthorn Therapeutics Inc.
- iGenomiX
- Sirenas Marine Discovery
- Zebra Biologics

2012
- Abide Therapeutics
- Cypher Genomics
- Vesper Biologics

2011
- RQx Pharmaceuticals

2010
- Ember Therapeutics
- Epic Science

2009
- Receptos Pharma
- Protix, Inc.
- Zyngenia

2008
- aTyr Pharma
- Curna

- Eyeceyte, Inc.
- Fate Therapeutics
- Proteostasis Therapeutics
- Sapphire Energy

2007
- Fabrus, Inc.
- Xcovery

2006
- Affinity Pharmaceuticals
- Calmune
- Viroime LLC
- Wittycell S.A.S.

2004
- Achaogen Inc.
- Motility, Inc.
- Promosome
- Rincon Pharmaceuticals (acquired by Sapphire Energy)

2003
- Ambrx Inc.
- FoldRx Pharmaceuticals
- Prion Solutions (acquired by Chiron)

2002
- CovX Research (acquired by Pfizer)
- NanoRX (acquired by Adaptive Therapeutics)
- VAXDesign (acquired by Sanofi Pasteur)

(continued)
Appendix 2 - continued

2001
- Kalypsys
- Phenomix
- Syrxx (acquired by Takeda)

2000
- ActivX Biosciences (acquired by Kyorin)
- Neurome

1999
- Geneformatics (merged with Structural Bioinformatics)
- Optimer Pharmaceuticals
- Prolifaron (acquired by Alexion Pharmaceuticals)

1997
- Epicyte (acquired by Biolex Therapeutics)

1996
- Digital Gene Technologies (purchased by Neurome)
- Discovery Labs (merged with Acute Therapeutics)
- Drug Abuse Sciences
- Sangamo Biosciences

1995
- PharMore
- Thrombosys

1994
- Apovia AG (formerly EVAX Technologies, originally Immune Complex Corp.)

- Applied Molecular Evolution (formerly Lxsys; acquired by Lilly, Inc.)
- CombiChem (acquired by Dupont-Merck Pharmaceutical and merged with Bristol-Myers Squibb)

1993
- Ciphergen Biosystems (acquired by Bio-Rad Laboratories)

1992
- Sequel Therapeutics (later acquired by Cytel, which was subsequently spun-out as Epimmune)

1989
- Avanir Pharmaceuticals (formerly Lidak)
- Corvas (acquired by Dendreon Corporation)
- UNASYN

1986
- MP Biomedicals (formerly Qbiogene and Bio101)
- NeoMPS (formerly Multiple Peptide Systems)

1984
- Stratagene

1982
- Synbiotics

1981
- Quidel
# Appendix 3
## Therapeutic Pipeline

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