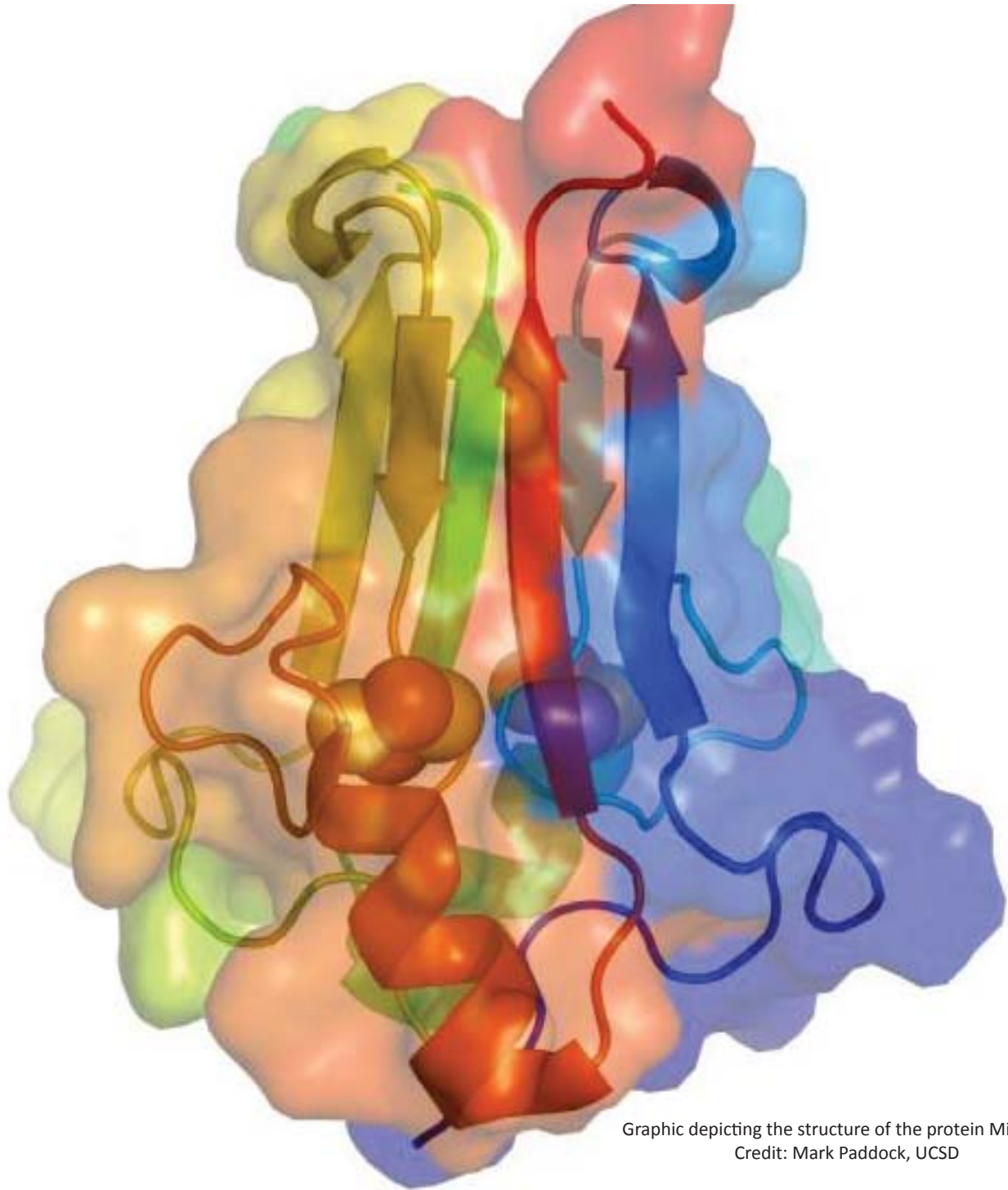


Diabetes 2009



Graphic depicting the structure of the protein MitONEET.
Credit: Mark Paddock, UCSD

**MitoNEET:
New Approach for
Designing Diabetes Drugs
SD2008-040**

BACKGROUND:

MitoNEET is an outer mitochondrial membrane protein that binds pioglitazone (Actos™), an insulin-sensitizing drug of the thiazolidinedione class used in the treatment of Type II diabetes. This protein has a unique dimeric structure where the two components interact to form a new fold not previously seen in any Fe-S protein structures or in any known protein. This new fold forms a binding domain between two acid labile 2Fe-2S clusters.

Defects in the ability of the MitoNEET protein to control assembly and transfer of Fe-S clusters typically result in mitochondrial dysfunction such as that found in Type II diabetes.

TECHNOLOGY:

The overall structure is described as a beta rich domain with a strand swap from opposite ends of the primary structure that forms a 'beta cap' domain. Crystallographic analysis was performed on isolated and truncated MitoNEET protein (AA33-108) to determine the precise structure of the novel fold. The Fe-S clusters are 16Å from each other, oriented close to the outer mitochondrial membrane.

Pioglitazone, a member of the thiazolidinedione class of insulin-sensitizing drugs has always been thought to work through the nuclear receptor PPAR-gamma by effecting lipid metabolism and oxidative capacity. Investigators at UCSD have demonstrated that it also binds to the 2Fe-2S binding site of MitoNEET.

ADVANTAGES:

The discovery of the MitoNEET fold provides another mechanism of action that may provide a new avenue for diabetes drug design. This finding opens new possibilities for studies of the mechanism of drug action and could lead to a method to optimize compounds in the thiazolidinedione class of drugs, which currently possess undesirable side effects such as weight gain and edema. Improved versions of drugs in this class based on the MitoNEET target fold could lead to new and better treatment options for patients with Type II diabetes.

PUBLICATIONS:

J. Biol. Chem. 2007 Aug. 17 282(33)::23745-9

The outer mitochondrial membrane protein MitoNEET contains a novel redox-active 2Fe-2S cluster
Wiley SE, Paddock ML, Abresch EC, Gross L, van der Geer P, Nechushtai R, Murphy AN, Jennings PA, Dixon JE.

Proc Natl Acad Sci U S A. 2007 Sep 4;104(36):14342-7. MitoNEET is a uniquely folded 2Fe 2S outer mitochondrial membrane protein stabilized by pioglitazone.

Paddock ML, Wiley SE, Axelrod HL, Cohen AE, Roy M, Abresch EC, Capraro D, Murphy AN, Nechushtai R, Dixon JE, Jennings PA

STATUS:

A PCT application has been filed

WEB SITE LINK: Diagram: <http://www.pnas.org/content/104/36/14342/F3.large.jpg>



UC San Diego is redefining the interplay of science and technology with the arts and culture. Our faculty has helped build biotech companies; earned Nobel Prizes in areas that include medicine, chemistry, and economics; and brought together digital technology and the visual arts to create new art forms. What happens here changes the world.

Method to Prevent Obesity and Diabetes by Modulating PARP-5 Activity

SD2007-115

BACKGROUND

Obesity is a growing epidemic affecting over 300 million people worldwide. It is a major risk factor for type 2 diabetes and other significant complications. A great deal of research is being directed to the identification of new targets and therapies that can address the needs of escalating numbers of obese and diabetic patients.

DESCRIPTION

The technology reported here from UCSD researchers describes a new target, PARP-5 (tankyrase-1), for obesity and diabetes treatment, unrelated to existing anti-obesity and anti-diabetic medications. PARP-5 is an ADP-ribose transferase in the cytosol that recruits protein substrates through its molecular scaffolding activity. In adipocytes, PARP-5 is known to associate with vesicles carrying the glucose transporter GLUT4 and to regulate the mobilization of these vesicles in response to insulin stimulation.

Using a mouse model of PARP-5 deficiency, it has been shown that modulation of PARP-5 activity can lead to upregulation of both GLUT4 and adiponectin, thereby increasing insulin sensitivity. Moreover, by heightening overall energy expenditure, PARP-5 deficiency in mice results in a lean phenotype despite increased food intake.

ADVANTAGES

PARP-5 has both catalytic and scaffolding domains, either or both of which may be useful targets to ameliorate obesity and diabetes. Potential approaches to modulate PARP-5 activity include:

*inhibiting the enzymatic activity of PARP-5 using small molecules that bind to the catalytic center.

*inhibiting the substrate recruitment of PARP-5 using hexapeptides that specifically bind to the scaffolding domain of PARP-5 and displace endogenous substrates.

*reversing PARP-5-mediated protein modification by activating PARG (poly-ADP-ribose glycohydrolase), which removes ADP-ribose from protein substrates.

STATUS

A provisional patent application has been filed

Additional information, including data on tankyrase KO mice studies is available under confidentiality.

Faculty Winners of the Nobel Prize

Currently, we have nine UC San Diego faculty members who are recipients of the Nobel Prize.

Year Won	Recipient	Department
2008	Roger Tsien	Pharmacology
2003	Robert Engle	Economics
2003	Clive Granger	Economics
2002	Sydney Brenner	School of Medicine
1995	Paul Crutzen	Scripps Institution of Oceanography
1995	Mario Molina	Chemistry and Biochemistry
1990	Harry Markowitz	Economics
1975	Renato Dulbecco	School of Medicine
1974	George Palade	School of Medicine

New Target for Cardiovascular Disease and Diabetes SD2005-165

UC San Diego Researchers have previously identified a protein which they have named PHLPP (ph domain leucine rich repeat protein phosphatase) which was disclosed in Case No. SD2004-088. The protein dephosphorylates Akt (protein kinase B) specifically at the hydrophobic motif and inactivates it.

In this disclosure, the inventors have shown that by inactivating PHLPP they could enhance Akt phosphorylation. Drugs or compounds that inhibit PHLPP, therefore, would be of therapeutic value in diseases such as diabetes or heart disease. Therefore, a potential drug would simply need to target PHLPP, thus inactivating it, for a therapeutic benefit to be observed. Preliminary experiments with others have shown that knock down of PHLPP increases glucose transport to the plasma membrane suggesting a significant role in diabetes. Additional studies are being planned to look at PHLPP and its effect on the heart.

An article published in Molecular Cell
<http://www.molecule.org/content/article/abstract?uid=PIIS1097276505011780>

Treatment for Type II Diabetes and Cancer by Regulating Glucose Transporter Levels SD2004-243

BACKGROUND:

UC San Diego researchers have discovered that a certain gene encoding a glycosyltransferase is able to regulate levels of glucose transporters on pancreatic beta cells. Over-expression of this gene in mice promoted glucose transporter activity on the plasma membrane, increasing glucose uptake and insulin secretion. When the expression of this gene was impaired, the mice developed type II diabetes.

INVENTION:

This invention provides methods to treat diabetes by controlling the expression of a gene encoding a glycosyltransferase. This glycosyltransferase might also be a promising target for cancer, since the increase in glucose transport resulting from this enzyme's activity contributes to the high metabolic rates found in cancer cells.



- UC San Diego's research engine generated over 300 innovations in each of the last 6 fiscal years.
- 1400+ technologies are available for licensing
- UC San Diego is credited with the formation of over 200 startups, of these, to date over 100 start-up companies were formed with licensed university innovations.
- Over 230 commercial products have been introduced to the market by licensed UC San Diego innovations.

Treatment for Diabetic Cardiomyopathy SD2004-071

Heart disease is the lead cause of mortality among diabetic patients in the United States. UCSD researchers have developed a method to treat diabetic cardiomyopathy by gene therapy using an enzyme specific for the removal of a single sugar molecule from proteins such as transcription factors. The researchers demonstrated that elevated extra-cellular glucose levels result in impaired calcium cycling in myocytes, leading to impaired cardiac contractility and poor myocardial performance, by a mechanism involving O-linked glycosylation of nuclear proteins. They found that these effects can be reversed by gene therapy with an enzyme, O-GlcNAcase, which can remove specific O-linked hexosamines from proteins. Delivery of viral vectors encoding O-GlcNAcase to myocytes from diabetic rats markedly improved calcium flux and contractile function.

Hydrogen Peroxide Sensing Electrode SD1998-014

DESCRIPTION:

A novel detection system and method for determining hydrogen peroxide (H₂O₂) levels in blood plasma and correlating those levels to essential (idiopathic) hypertension. As the hydrogen peroxide level is directly related to the level of reactive oxygen species in the plasma, this can be used as an accurate predictor of risk for hypertension. The system permits detection of oxidative stress in plasma of individuals with positive hypertensive family history but which do not yet have elevated blood pressure.

In addition, the possibility exists for assessing other diseases in which free radicals have been implicated (such as arthritis, atherosclerosis, cancer, diabetes, and ischemia), as well as assessing other contributors to oxidative stress such as biological and psychological stresses, smoking, and inappropriate diet among various other causes. Detection and/or quantitative assay of H₂O₂ may therefore be an indicator of these causes and suggest the course, timing, and extent of therapeutic intervention.

This technology provides a very early indicator of inflammation in many cardiovascular diseases and allows a direct measure for pharmacological intervention.

REFERENCES:: F. Lacy, D.T. OíConnor, G.W. Schmid-Schonbein, Journal of Hypertension 1998, 16:291-303. F. Lacy, M. T. Kailasam, D. T. OíConnor, G. W. Schmid-Schonbein, R. J. Palmer, Hypertension, November 2000.

Lacy, F., Gough, D.A., Schmid-Schonbein, G.W., Free Radical Biology & Medicine, 25:720-727, 1998.

Patents pending.



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Screening Method to Discover a New Candidate Therapeutic for Type II Diabetes SD2003-202

PROBLEM:

Pioglitazone (Actos®), Rosiglitazone (Avandia®), and Troglitazone (Rezulin®) are thiazolidinedione compounds (TZDs). They bind and activate the Peroxisome Proliferator-Activated Receptor, PPAR γ , which plays an important role in the regulation of glucose and lipid homeostasis as well as adipocyte differentiation. However, it is known that the response of patients to TZDs is variable. In fact, 20-30% of patients do not respond to TZDs and, of those that do respond, some may experience serious side effects. Therefore it is desirable to identify new therapeutics that function in a way that is similar to TZDs, but with fewer side effects. It is also desirable to develop more accurate methods that could predict a patient's response to TZDs.

SOLUTION/TECHNOLOGY DESCRIPTION:

UC San Diego researchers revealed the signature pattern of a panel of genes that are up- or down- regulated in cells expressing PPAR γ in the presence of its ligand. The technology allows for identification and optimization of novel PPAR γ compounds by using gene expression profiling. These signature profiles can be used to identify: (i) new TZD-like compounds that induce a similar expression pattern in adipocytes as the existing ones do; and (ii) new TZD-like compounds that are potentially more effective and have fewer side effects as predicted by their expression patterns.

BENEFITS:

- Fast and biological relevant screening method to identify good drug candidates.
- Identification of patients with a side-effect susceptibility profile

FEATURES:

- Expression profiling for genetic optimization of novel PPAR γ ligands

MARKETING POTENTIAL/APPLICATIONS:

In 2002, 18.2 million people had diabetes— thirteen million were diagnosed, and 5.2 million people were undiagnosed. Type II diabetes may account for approximately 90-95% of all diagnosed cases of diabetes. Diabetes was the sixth leading cause of death in the US in 2000. There are 1.3 million new cases diagnosed per year in people aged 20 years or older¹. The estimated market for Type II diabetes therapeutics in the US is currently estimated at \$5.5 billion and is expected to grow².

¹NIDDK/NIH ²Lead Discovery

LICENSING AND DEVELOPMENT STATUS:

This technology is available nonexclusively.

TECHNOLOGY-RELEVANT PAPERS AND WEBLINKS:

Hsiao, A, Worrall, D.S., Olefsky, J.M., and Subramaniam, S. Variance-modeled posterior interference of microarray data: detecting gene-expression changes in 3T3-L1 adipocytes. *Bioinformatics*, 20 (17), 3108-3127 (2004).
http://medicine.ucsd.edu/endo/Faculty/j_olefsky.htm

Novel, Validated Target for Type II Diabetes Drug Inhibitors SD2003-238

PROBLEM:

Insulin regulates glucose uptake into fat and muscle cells through glucose transporters (GLUT4) which are translocated from an intracellular membrane storage pool to the plasma membrane. A Type II diabetic either does not produce enough insulin or is resistant to insulin produced by the pancreas. Improperly metabolized glucose and increased serum glucose levels can trigger heart disease, kidney disease, blindness and limb amputations. Several oral medications can be prescribed to those who have been diagnosed with Type II diabetes and to those who are otherwise insulin resistant. Currently, there are two classes of oral anti-diabetic insulin sensitizers that can be used to treat Type II disease: biguanides (metformin, Glucophage®) and thiazolidinediones (rosiglitazone, Avandia® and pioglitazone, Actos®). However, there are side effects from these drugs which are especially acute in those whose kidneys or liver are not functioning normally. Also, although Type II diabetics can take oral drugs currently offered, over time most will need insulin injections to control their disease.

SOLUTION/TECHNOLOGY DESCRIPTION:

GRK2 is a novel target for insulin sensitizer development. The normal, endogenous function of this gene is to inhibit insulin signaling. Therefore, inhibition of the inhibitor, GRK2, should augment insulin action. This is demonstrated for both siRNA against GRK2 and an anti GRK2 antibody which increase insulin-stimulated insulin-responsive glucose transporter 4 (GLUT4) translocation in 3T3-L1 adipocytes.

BENEFITS:

- Very attractive for drug discovery to identify small molecule inhibitors rather than molecules which stimulate protein action.

FEATURES:

- Unique mechanism of action for an insulin sensitizer

MARKET POTENTIAL/APPLICATIONS:

- In 2002, 18.2 million people had diabetes— thirteen million were diagnosed, and 5.2 million people were undiagnosed. Type II diabetes may account for approximately 90-95% of all diagnosed cases of diabetes. Diabetes was the sixth leading cause of death in the US in 2000. There are 1.3 million new cases diagnosed per year in people aged 20 years or older¹.
- Insulin resistance affects more than 60 million Americans. One in four of them will develop Type II diabetes².
- The estimated market for Type II diabetes therapeutics in the US is currently estimated at \$5.5 billion and is expected to grow³. ¹NIDDK/NIH ²WebMD ³ Lead Discovery,

IP and DEVELOPMENT STATUS:

The invention is at a stage amenable to high throughput screening approaches to identify small molecule inhibitors. This technology is offered exclusively or nonexclusively for US and/or worldwide territories.

TECHNOLOGY-RELEVANT PAPERS AND WEB LINKS:

Usui, I., Imamura, T., Satoh, H., Huang, J., Babendure, J.L., Hupfield, C., and Olefsky, J.M. GRK2 is an endogenous protein inhibitor of the insulin signaling pathway for glucose transport stimulation. The EMBO Journal, 23, 2821-2829

[.http://biomedsci.ucsd.edu/faculty_descrip.asp?id=77](http://biomedsci.ucsd.edu/faculty_descrip.asp?id=77)

UC San Diego boasts top-rated programs at the School of Medicine, Jacobs School of Engineering, the Division of Biological Sciences, the Division of Physical Sciences, and Scripps Institution of Oceanography. Recently added programs include the School of Pharmacy and Pharmaceutical Sciences and the Rady School of Management.

The UC San Diego Technology Transfer Office (TTO) evaluates, patents, markets, and licenses UC San Diego-developed technologies for commercial applications in the global market. Our activities promote the economic development of the Greater Southern California region by out-licensing the fruits of UC San Diego research. The products of this research are also disseminated throughout the world. Companies from North America, Europe, Asia, and Australia license UCSD technologies to commercialize in their business ventures.

We, the Technology Transfer Office (TTO), organize the Pipeline Events Series, providing an educational outreach to the greater UC San Diego community on intellectual property issues. This series includes informative seminars, symposia, and workshops that foster innovation flow from the benchtop to the marketplace.

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Visit our website at <http://invent.ucsd.edu> for a listing of

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**Technology Transfer Office (TTO)
Mission:**

**Promote and facilitate the transfer of
UC San Diego innovations for the benefit
of the University community and the public.**

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