WHAT THE WEIZMANN INSTITUTE IS DOING

about Diabetes



Cover: Graphic presentation of an insulin molecule

"Just because Western science is motivated ideologically by the idea of progress and just because we may see increasing complexity, we must not assume that nature herself truly progresses. If there be any progress, it will have to be of our making."

Prof. Irun Cohen of the Weizmann Institute of Science in his book "Tending Adam's Garden"

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Introduction

Back in 1921 Dr. Frederick Banting and Charles Best of the University of Toronto made a discovery that would change the course of medical history. They had succeeded in obtaining a pancreatic extract that proved to have potent anti-diabetic characteristics when tested on dogs. Within a year, their team would purify the extract's key ingredient, a hormone known as insulin. The first human diabetes trial then began, extending the life of Leonard Thomson, a 14-year-old boy who lay dying in hospital, for 13 years.

Diabetes is a chronic metabolic disease associated with elevated blood sugar levels in which the body does not produce, or improperly uses insulin, a hormone that regulates blood sugar levels by signaling the body's cells to take up glucose, where it is converted into energy. Extensive research efforts have yielded dramatically improved, high-quality insulin as well as better delivery methods. These therapies, when complemented by a proper diet and adequate exercise, are helpful in controlling blood sugar levels. However, they merely combat the life-threatening nature of the disease. Diabetes patients remain insulin-dependent for life and are subject to serious complications, particularly as they age. Blindness, heart disease, stroke, neuronal damage, amputation and kidney failure are ever present threats. These complications generally result from the metabolic imbalance caused by high levels of blood glucose, which can damage both blood vessels and nerves. Abnormal retinal blood vessels, for instance, make diabetes the most prevalent cause of blindness in the Western world.

Recent data show that roughly 120 million people worldwide suffer from diabetes and the World Health Organization believes this number will skyrocket to 300 million by 2025, primarily due to an upsurge in obesity.

There are three major types of diabetes:

• Type 1 diabetes is an autoimmune disorder in which the immune system attacks the body's own insulin-producing pancreatic beta cells, reducing and ultimately leading to the complete absence of insulin.

Type 2 diabetes, affecting roughly
 90 percent of all patients, results from the body's inability to properly use insulin combined with inadequate insulin production.

■ **Gestational diabetes,** affecting roughly 4% of all pregnant women, is believed to be caused by hormones secreted to promote fetal development that impair insulin function in the mother's body.

At the Weizmann Institute

Long dedicated to battling diabetes, researchers at the Weizmann Institute of Science are studying all aspects of this complex disease - from its genetic causes and cellular processes, to new diagnostic techniques and prevention and treatment therapies. Institute scientists have developed the first successful vaccine to halt the progression of Type 1 diabetes, as well as a kit for its early diagnosis. Other Institute researchers are probing the complex chain of events in which insulin binds to its cellular receptors to trigger glucose uptake, while yet others hope to combat diabetes-related complications by achieving a better understanding of the cellular interactions that maintain the structural integrity of the body's blood vessels. Efforts are being made to establish a Center for Research on Diabetes and Related Metabolic Disorders. As in other Weizmann Institute endeavors, the hallmark of the Center will be an interdisciplinary approach, bringing together researchers from molecular biology, biochemistry and other fields to explore the multifaceted challenges of diabetes. Here's a look at what we are doing.

Prevention rather than replacement

Institute researchers have developed the first successful vaccine that halts the progression of Type 1 diabetes. The vaccine, which functions by blocking the destruction of insulin-secreting pancreatic cells, both prevents the onset of Type 1 diabetes and blocks its progression in patients whose cells have already begun to die.

Type 1 diabetes (also known as insulin-dependent or juvenile diabetes) usually results from an autoimmune disorder in which the immune system mistakenly attacks the body's own insulin-producing pancreatic cells, reducing and ultimately eliminating all insulin production. Affecting roughly 5% of all diabetes sufferers, Type 1 diabetes commonly begins during childhood or adolescence and leads to a total dependence on insulin supplementation. Nevertheless, insulin treatment is not a cure – it merely offers a replacement, helping to control blood sugar levels. A cure would stop the autoimmune destructive response, sparing the insulin-producing beta cells. The new vaccine currently in development, known as DiaPep277, has been shown to prevent the destruction of pancreatic cells through a unique process in which the immune system is "educated" to stop its destructive attack. The treatment, developed by a team led by **Prof. Irun Cohen** of the Immunology Department, is based on Cohen's earlier discovery that a key protein in pancreatic cells, known as HSP60, can act as an antigen, prompting the immune system's T lymphocyte cells to attack. Further investigation by Cohen and his group has revealed that injecting diabetic mice with a small peptide fragment of the HSP60 protein shuts down this immune response, preventing the progression of Type 1 diabetes.



DiaPep277 arrests beta cells destruction

Insulin production over 18 months (measured by C-peptide secretion)

Arrows: Treatment at 0, 1, 6 and 12 months Blue line: Treatment group – Preserved function of beta cells White line: Placebo – Progressive destruction of beta cells

Insulin's balancing act

Insulin works in several ways to keep blood sugar levels balanced. When glucose from a meal enters the bloodstream, insulin mediates its conversion into glycogen and fat, which are stored for later use. It also prevents gluconeogenesis (a process in which the stored fat is released and turned back into glucose) until it is needed. This double-valve process is a finely tuned balancing act that goes on minute by minute, ensuring that blood sugar levels are not subject to wild fluctuations.

Moving on to clinical trials, Cohen, in collaboration with researchers at Hadassah-Hebrew University Medical School and the Israeli biopharmaceutical company Peptor Ltd, found that three injections of the vaccine over the course of six months successfully blocked the progression of Type I diabetes in newly diagnosed patients without causing significant side effects. The researchers were able to trace the drug's effect to changes in the patients' T cells. Due to the success of initial trials, Aventis, one of the world's leading pharmaceutical companies, has recently purchased the exclusive right from Peptor Ltd. to develop, register and commercialize the DiaPep277 vaccine.

Developing a diagnostic kit

In a related development, Prof. Cohen has developed an approach that may make it possible to detect Type 1 diabetes early enough to salvage large numbers of insulin-producing cells. A major problem with Type 1 diabetes is that the autoimmune process that destroys the insulin-producing beta cells produces no symptoms. As a result, the disease is generally diagnosed only when the insulin shortage becomes apparent, by which time most beta cells have been irreversibly damaged.

In this approach, detection will be based on testing blood or urine samples for the presence of beta-cell debris released into the body fluids when these cells are mistakenly destroyed by the immune system. The method has been licensed for commercial development to Peptor Ltd.

Other scientists participating in the DiaPep277 study are: Professor Itamar Raz and Dr. Muriel Metzger of Hadassah-Hebrew University Medical School; and Dr. Dana Elias (now VP R&D at Peptor Ltd.), Dr. Ann Avron and Dr. Merana Tamir of Peptor Ltd. •

FIRST SUCCESSFUL VACCINE FOR TYPE 1 DIABETES



Prof. Irun Cohen holds the Helen and Morris Mauerberger Professorial Chair in Immunology

Reprogramming cells to produce insulin

Focusing on the properties that endow beta cells with the unique ability to manufacture insulin, Institute researchers hope to develop a new treatment for Type 1 diabetes, as well as a new method for its early diagnosis and prevention.

Among the key molecules involved in insulin production are transcription factors – proteins that determine which genes are switched on in a cell. A group led by **Prof. Michael Walker** of the Department of Biological Chemistry has shown that switching on the insulin gene in beta cells is a complex process involving at least four transcription factors.

Walker's group recently showed that these four proteins cooperate in switching on insulin production, thus explaining a large part of the previously mysterious ability of beta cells to produce this hormone. In collaboration with the Sheba Medical Center of Tel Hashomer Hospital, the researchers are currently implanting transcription factors into liver cells in the aim of activating the otherwise silent insulin gene. The approach of engineering cells taken from a patient to produce insulin may provide the basis for a cure for Type 1 diabetes. In a related project, Walker and colleagues have identified several previously unknown proteins produced preferentially in beta cells. Since the autoimmune attack in Type 1 diabetes is probably directed against a number of such proteins, the newly identified molecules may help reveal the precise protein fragments that serve as targets of attack (adding to the protein already identified by the Institute's Prof. Cohen). Working in collaboration with the Felsenstein Medical Research Center in Petah Tikva, Walker is seeking to determine whether antibodies from diabetic patients recognize these proteins. If so, this research may yield useful early markers for high-risk individuals.

One of the newly identified proteins is a membrane-bound receptor designated GPR40. Walker's team is using genetically modified mice to understand the role of GPR40 in the beta cell – a study that may lead to a better understanding of how beta cells become defective in Type 2 diabetics. \bullet

PROTEINS RESPONSIBLE FOR SWITCHING ON INSULIN PRODUCTION REVEALED



Prof. Michael Walker holds the Marvin Myer and Jenny Cyker Professorial Chair for Diabetes Research

The body electric

Hypoglycemia is a complication of Type 1 diabetes characterized by below-normal levels of glucose in the blood. Occurring when a diabetic takes too much insulin, hypoglycemia can lead to blindness, kidney disease, and, under severe circumstances, even death. Work by **Prof. Eitan Reuveny** of the Department of Biological Chemistry may help elucidate the process by which, under normal conditions, the body prevents too much insulin from flowing into the blood.

Reuveny is studying the electrical properties of insulin-producing beta cells in the pancreas. Using exciting new technologies from the worlds of biophysics and molecular genetics, Reuveny is able to do what was unthinkable just a few years ago: identify the tiny fluctuations of electrical potential that occur within a specific, living cell. His research has great significance for studying the hypoglycemia complication occurring in Type 1 diabetes.

As a postdoctoral researcher at the University of California at San Francisco, Reuveny was the first to identify and clone the gene coding for a gateway in the cellular membrane called the G-protein coupled potassium channel. Today, he is examining this channel to determine how fluctuations in its electrical activity trigger a "shut-down" response that controls insulin release. A number of laboratories worldwide are currently performing electrical recordings of pancreatic cells. However, Reuveny is the first researcher to combine such recordings with a specially bred transgenic mouse model. Using this model, beta cells can be easily separated from the mass of pancreatic islet tissue that has nothing to do with insulin production, thus dramatically increasing the accuracy and efficiency of research.

By characterizing the electrical process by which, under normal circumstances, the body prevents too much insulin from flowing into the blood, Reuveny hopes to establish the basis for a future hypoglycemia therapy.

NOVEL TECHNIQUE FOR PROBING THE ELEC-TRICAL ACTIVITY WITHIN A SINGLE LIVING CELL MAY LEAD TO HYPOGLYCEMIA DRUG



Prof. Eitan Reuveny

Type 2 diabetes: Probing insulin resistance

Type 2 diabetes, also known as adult-onset diabetes, is a metabolic disorder resulting from the body's inability to produce enough, or properly use, insulin. Affecting roughly 90% of all diabetes patients, this disorder usually sets in slowly after age 40 and mostly strikes overweight individuals. While its underlying roots are unknown, one of the causes of Type 2 diabetes lies in the process by which insulin sets off a chain of intracellular signals leading to nutrient absorption.

Normally, insulin binds with a receptor molecule on a cell membrane, rather like a ship docking, setting off signals that stimulate an array of events including the induction of glucose transport and cell growth. In Type 2 and sometimes Type 1 diabetes, this signaling system is inefficient, and the cell's ability to respond to insulin is impaired – a condition known as insulin resistance.

Three agents affecting insulin action have been identified: free fatty acids, TNF-alpha and a protein called leptin, first found to affect insulin function by **Prof. Menachem Rubinstein** of Weizmann's Molecular Genetics Department.

Leptin first made headlines in 1994, when scientists discovered that daily leptin injections cause genetically obese mice to eat less and lose weight. However, working with human liver cells, Rubinstein and colleagues **Drs. Batya Cohen and Daniela Novick** found that excessive leptin actually disrupts insulin function. The team found that when leptin binds to liver cells, the resulting biochemical cascade prevents a key insulin receptor from being phosphorylated (the process in which phosphate molecules attach to a protein). This failure results in impaired insulin performance – particularly affecting its ability to slow down the creation of new glucose in the blood, thus raising blood sugar levels in the body.

Unlike the much-publicized obese mice, which had a genetic mutation causing leptin deficiency, obese humans are known to have high blood leptin levels. Rubinstein's study may therefore explain why overweight people are five times more likely to develop diabetes than people of normal weight, as well as pointing the way toward new treatments. These findings also sound a warning bell regarding the use of leptin in weight-reducing drugs, since it may be an accelerating factor in the development of diabetes. •

LINK BETWEEN OBESITY AND TYPE 2 DIABETES REVEALED



Prof. Menachem Rubinstein holds the Maurice and Edna Weiss Chair of Cytokines Research



Prof. Yehiel Zick holds the Marte R. Gomez Professorial Chair

Short circuits and insulin resistance

In related research, **Prof. Yehiel Zick** of the Molecular Cell Biology Department has discovered that insulin resistance might be caused by protein blocking. Apparently, some of the effector proteins that relay messages from the insulin receptor to the glucose uptake machinery in cells undergo excessive phosphorylation, preventing their binding to the insulin receptor. This "short circuit" eliminates their ability to communicate messages to the cell's interior, rendering the cell insulin-resistant.

The new study by Prof. Zick adds to the contribution made by the Institute's Prof. Menachem Rubinstein in explaining the link between obesity, insulin resistance and diabetes. Zick found that two major culprits of inappropriate phosphorylation are free fatty acids and TNF - a molecule secreted by fat cells that is found at excessive levels in obese people. These findings may lead to future treatments for preventing insulin resistance by, for example, blocking the adverse effects of TNF.

Other research by Zick found that "sub-parts" of a cell's insulin receptor interact with different effector proteins to trigger different processes. For example, one receptor region interacts with the IRS-1 effector to control glucose absorption, while another interacts with the effector known as Shc, to control insulin's growth-promoting effects.

Zick is studying these interactions by developing peptide models of the regions and inserting them into cells. A better understanding of these reactions may form the basis for drugs that will improve the insulin signaling process.

SHORT CIRCUIT PREVENTS INSULIN RECEP-TORS FROM SENDING SIGNALS INTO THE CELL

Overcoming transport failure

Once absorbed, nutrients such as glucose and fat are directed toward specific sites inside a cell along set pathways. Defects in these pathways cause a large number of diseases, including diabetes.

Prof. Zvulun Elazar of the Biological Chemistry Department is studying the transport of molecules between different cell sites in order to understand what happens when this process goes awry, as in the case of Type 2 diabetes. He has identified three previously unknown proteins required for intracellular transport, and has recently isolated and cloned the gene for two of the proteins that take part in directing this process: "GATE-16"and "ERG30".

Understanding how the molecular mechanism is modulated may lead to new approaches for treating Type 2 diabetes by correcting defective intracellular transport. •

PROTEINS INVOLVED IN CELLULAR TRANSPORT ROUTES REVEALED



Prof. Zvulun Elazar

Seeking a backup system for insulin

Cells have a backup system that enables them to absorb glucose independently of insulin – as shown by **Prof. Yoram Shechter** of the Biological Chemistry Department. Shechter also found that vanadium, a metallic element present in minerals, activates this system and mimics virtually all the effects of insulin.

Based on this research, some vanadium compounds are already being tested in clinical trials in Europe and the United States to overcome insulin resistance. Such treatment would have two major advantages: First, unlike insulin, which needs to be injected into the bloodstream, vanadium can be given in pill form. Second, vanadium's molecular mode of action is distinctly different from that of insulin, rendering it valuable for insulin-resistant cases.

Shechter is now seeking more refined methods of "turning on" the vanadium-activated backup system. He has identified two proteins activated by vanadium that induce nutrient absorption by the cell. In the future, it may be possible to bypass insulin resistance by stimulating these activities. •

BACKUP COMPOUND ENABLES GLUCOSE ABSORPTION INDEPENDENTLY OF INSULIN



Prof. Yoram Shechter holds the Charles H. Hollenberg Chair of Diabetes and Metabolic Research

Plugs for drugs enhance insulin therapy

In parallel research, Prof. Shechter and colleagues developed a new technique that can affect how numerous drugs, including diabetic applications, are released into the body. The approach may prolong the action of these drugs, making it possible to administer them at much longer intervals without jeopardizing their effectiveness.

Immediately after it's taken, a drug's level in the blood normally surges – sometimes up to 100 times more than is needed. Such high levels are necessary to keep the drug in the blood long enough to do its job, but often produce damaging side effects. Then, within periods ranging from minutes to a few hours, the drug is cleared from the circulation, creating the need for a new dose.

The new technique, designed by Shechter, **Prof. Mati Fridkin** of the Organic Chemistry Department and **Dr. Eytan Gershonov** of both departments, is based on a molecular "plug" that attaches to and temporarily blocks the drug's action. Once the medication enters the circulation, the plug is gradually disconnected. This, the scientists believe, releases relatively low but steady quantities of the drug into the patient's bloodsream over a long period of time. The plugs for drugs approach showed promising results when tested with insulin. When diabetic rats were given "plug-modified" insulin, a single injection kept glucose levels at a normal level for two days. In contrast, a single injection of unmodified insulin produced the same effect for only 6-12 hours.

To commercialize the new method, Pamot Venture Capital Fund and the Institute's technology transfer arm, Yeda Research and Development Ltd., have recently set up a new start-up company, LAPID Pharmaceuticals Ltd. •

INSTITUTE DESIGNED MOLECULAR "PLUG" ENHANCES INSULIN DELIVERY

Diabetes – an unbalanced act

An imbalance in PFK, a key enzyme in glucose metabolism, might explain why Type 2 diabetics don't produce enough insulin. When glucose levels rise, PFK is believed to serve as a messenger, directing the pancreas to produce insulin. However, as Prof. Yoram Groner of the Molecular Genetics Department found, an imbalance in PFK composition may garble this directive.

PFK consists of three different sub-units. Working with Ph.D. student **Yael Weiss** and **Dr. Hilla Knobler** of Rehovot's Kaplan Hospital, Groner found that mice with abnormally high levels of the sub-unit known as PFK-L develop symptoms of Type 2 diabetes. The PFK-L gene is located on human chromosome 21, which may explain why children with Down syndrome – the genetic disorder characterized by an extra copy of chromosome 21 – are about 20 times more likely to develop diabetes than are normal children.

The fact that Down syndrome patients have three rather than two copies of this gene may trigger a PFK imbalance leading to impaired insulin production. These findings suggest that the activity level of PFK is important for controlling insulin secretion. \bullet



Prof. Mati Fridkin holds the Lester B. Pearson Professorial Chair of Protein Research

FAULTY PROTEIN MESSENGER MAY LINK TYPE 2 DIABETES AND DOWN SYNDROME



Prof. Yoram Groner holds the Dr. Barnet Berris Chair of Cancer Research

The good communication goal

In binding to receptors on the cell membrane, insulin triggers an array of events through which the body maintains proper energy levels as well as cell growth and proliferation. In the last few years, several insulin signaling mechanisms have been elucidated and shown to involve the sequential activation of enzymes known as protein kinase cascades. Each kinase cascade can be compared to an individual communication line within cells.

Signals are transmitted through the transfer of a phosphate group from one kinase to the next in a specific order, eventually activating an enzyme that initiates a given cellular process. In many of these kinase cascades, the transmission of signals is initiated by insulin; together, these cascades govern all insulin-dependent cellular processes. However, all the communication lines activated by insulin have not as yet been elucidated, including those that participate in regulating the rates of protein synthesis and blood glucose levels. **Prof. Rony Seger** of the Biological Regulation Department is working to identify the array of insulin-activated protein kinases. His preliminary results indicate that the stimulation of cells with insulin activates some well-known, as well as some previously unknown, communication lines. Seger is also studying the way in which signals are transmitted from the kinase cascades within the cell to the cell nucleus, where they trigger the activity of genes. The goal is to map the complete pathway of insulin signal transmission in the cell – knowledge that may eventually lead to drugs that would overcome malfunctions in the body's absorption of glucose. ●

STUDY TARGETS DRUGS THAT WOULD BYPASS MALFUNCTIONING INSULIN RECEPTORS



Prof. Rony Seger

Making transplants easier

Since diabetes is characterized by the increasing destruction of insulin-producing pancreatic beta cells, advanced diabetes may necessitate transplanting beta cells, the pancreatic islets where they are produced, or even the entire pancreas and a kidney. Transplants are risky, however, first requiring potentially lethal drug or radiation treatment to wipe out the patient's immune system and prevent transplant rejection. Even after such measures, a residual immunity sometimes causes rejection.

Working with bone marrow transplants for terminal leukemia patients, **Prof. Yair Reisner** of the Immunology Department has found a way to overcome residual immunity even in the case of transplants from unmatched donors. His method removes the main obstacles limiting the use of mismatched transplants – namely, graft failure and an adverse immunological reaction called graft-versus-host disease.

Normally, a donor and recipient are considered compatible when they are matched for all six immunological markers on their chromosomes – three inherited from the mother and three from the father. In Reisner's method, developed in collaboration with Prof. Massimo Martelli of Italy's Policlinico Monteluce, the donor and the recipient need to be matched for only three markers. Such a partial match is always found between parents and children, and there is a 75 percent chance of finding it between siblings. To date, hundreds of patients throughout Europe have been treated using this approach, yielding significant success rates, as reported in the *New England Journal of Medicine*, *Blood*, and other publications. Following these encouraging results, Phase 1 clinical trials are currently under way in major centers in the United States, and the European Bone Marrow Transplantation Society has recently launched a formal prospective study in 35 centers throughout Europe.

A key element of this method is the use of extremely large doses of donor marrow that literally overwhelm the recipient's rejection mechanism. The donated stem cells are "cleansed" to erase the characteristics contributing to rejection in mismatched transplants. But why does it work? How does bombarding the patient with a megadose of donor stem cells prevent transplant rejection?

A new study by Reisner and his team at the Weizmann Institute's Department of Immunology provides insights into this riddle. They have shown that certain stem cells, using a "veto" mechanism, are capable of protecting themselves against attack by the body's immune system. In addition to offering a possible explanation of how stem cells aid in preventing immune rejection, this finding may prove vital in targeting another longstanding research challenge – to lower the radiation dosages accompanying transplant therapies in a range of diseases, from advanced diabetes to leukemia.

HOPE FOR DIABETES PATIENTS FROM NOVEL TRANSPLANT THERAPY



Prof. Yair Reisner holds the Henry H. Drake Professorial Chair in Immunology

Maintaining blood vessel integrity

Diabetes-related complications – including blindness, stroke, kidney disease and even gangrene – are largely due to vascular defects. Research by Institute scientists aimed at studying the adhesion and motility of cells in blood vessels may help control these debilitating complications.

The normal function of blood vessels greatly depends on the dynamic properties of the endothelial cells that line the vessel. These cells are firmly attached to the underlying membrane as well as to their neighbors via specialized adhesions, which play a crucial role in regulating vessel formation (angiogenesis), stability and repair. When given a message by angiogenic factors, or following a pathological loss of cell-cell adhesion, endothelial cells extend flattened protrusions with motile properties, form new adhesions and migrate. This physiological response is essential for blood vessel maintenance.

This process can be simulated in the laboratory by an in vitro wound model, where cultured endothelial cells are allowed to migrate into and close a gap that has been artificially introduced into the endothelial layer. Under pathological conditions such as diabetes, the normal maintenance of blood vessels is severely disrupted, leading to increased fragility and malfunction of the vascular system. **Prof. Benjamin Geiger** of the Molecular Cell Biology Department is investigating the mechanisms regulating endothelial adhesion and motility. Current studies in his laboratory address the mechanisms underlying these dynamic processes, in healthy and diseased vessels. A better understanding of the molecular mechanisms underlying the generation of new blood vessels and wound closure may point toward possible targets for drug development.

In related research, the work of **Prof. Michal Neeman** of the Biological Regulation Department may help address the necrotic wounds in the extremities, characteristic of diabetes. Neeman is working on the use of quantitative magnetic resonance imaging (MRI) methods for the analysis of vascular growth in limbs deprived of blood supply. Her objective is to generate criteria for testing the efficacy of therapeutic approaches for blood vessel growth.

WOUND MODEL SHEDS LIGHT ON VASCULAR MALFUNCTION IN DIABETES



Prof. Benjamin Geiger holds the Prof. Erwin Neter Chair of Cell and Tumor Biology



Prof. Michal Neeman

Maternal diabetes and the fetal brain

Maternal diabetes is associated with an increased rate of spontaneous abortions, chromosomal aberrations and congenital anomalies in both humans and laboratory animals. Little information is available, however, regarding its impact on the fetal brain.

Using ¹³C stable isotopes and magnetic resonance spectroscopy **Prof. Aviva Lapidot** and her team in the Institute's Organic Chemistry Department have conducted pioneering studies showing how diabetes can affect the brain.

In particular, they were the first to demonstrate that diabetes in the pregnant mother has adverse effects on the brain of her fetus. It reduces glucose utilization and increases the uptake of other energy "fuels" known as ketone bodies, which are toxic to the fetus. Made of fatty acid degradation products formed in the liver of the diabetic mother, the ketone bodies are transported first from the maternal to the fetal circulation and then to the fetal brain, via the blood-brain barrier. Lapidot's research aims to clarify the origins of this toxicity and eventually help protect the fetus against it. Tight glycemic control during diabetic pregnancy has been shown to significantly reduce the occurrence of congenital malformations and other effects of maternal diabetes on the offspring. However, intensive insulin therapy often causes recurrent acute maternal hypoglycemia, which is harmful to the developing fetus.

Lapidot's team is currently examining the implications of poorly controlled, versus carefully controlled, maternal diabetes on both maternal and fetal brain glucose metabolism, including the potential for neonatal neurological complications.

STUDY AIMS TO PROTECT THE FETAL BRAIN IN DIABETIC MOTHERS



Prof. Aviva Lapidot

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Prof. Irun Cohen (p. 6) Research supported by: Minna James Heineman Stiftung Robert Koch Minerva Center for Research in Autoimmune Disease Mr. and Mrs. Samuel Theodore Cohen, Chicago, IL Prof. Cohen is the incumbent of the Helen and Morris Mauerberger Professorial Chair in Immunology

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Prof. Benjamin Geiger (p. 16)

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Prof. Eitan Reuveny (p. 9)

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Weizmann Institute of Science P.O.Box 26, Rehovot 76100, Israel Tel 972 8 934 3852 Fax 972 8 934 4132 E-mail: news@weizmann.ac.il http://wis-wander.weizmann.ac.il