Diabetes In Control.com

THE CURE FOR DIABETES? *Or Too Good to be True!*

Part 2

Diabetes and INGAP

How would this new treatment affect Type 1and possibly Type 2 diabetes?

The key organ that is affected in the development of diabetes is the pancreas. Inside the pancreas there are a small group of cells known as Beta Cells. These cells are responsible for producing insulin, the hormone that controls the transfer of glucose into energy. Without insulin your body cannot store or deliver the energy you need to survive.

In Type 1 diabetes, there is an insult on the pancreas that affects the beta cells' genetic susceptibility, the development of antibodies, and the viral assault. There is a progressive destruction of the pancreas' ability to make insulin and a reduction of beta cell mass until only about 2% of beta cells remain, and diabetes develops.

In Type 2 diabetes, a person may start with resistance to the action of insulin, but over time the capacity to make insulin is lost. Type 2 diabetes is usually never diagnosed if the pancreas can make enough insulin to compensate for insulin resistance.

Prospective studies in the United Kingdom have taught us, on the day that a person is diagnosed with Type 2 diabetes, they probably have been developing the condition for at least 8 -12 years and possibly have already lost up to 50% of beta cell function and have complications from diabetes. Beta cell loss continues at approximately 3.5% - 5% per year, often culminating in a loss of all beta cell function within ten years from diagnosis.

Both Type 1 diabetes and Type 2 diabetes exhibit defective pancreatic beta cell function. It has therefore been proposed that beta cell regeneration could potentially be a treatment for people with people with Type 1 and Type 2 diabetes.

There is a curvilinear relationship between how much insulin a person's pancreas needs to make depending upon how sensitive the body is. If either the pancreas does not make enough insulin or the body becomes resistant to its action, diabetes then develops.

The objective of most research programs is to take people who have fallen off the curve and enable them to make more insulin or to help them become more sensitive to the insulin.

The most well-known research vehicle to make this possible is islet transplantation. A process fully backed by the American Diabetes Assoc. and the Juvenile Diabetes Research Foundation. In the past year this process has been highly publicized by the islet transplantation success of the research group at the University of Alberta in Edmonton, Canada. They have stated that they can improve on islet isolation, they can include larger islet doses immediately after islet isolation, and they can use the appropriate drugs so that the islets are not rejected.

Can this be a truly successful program for millions hoping for a cure? Through this process, scientists will

So what's the ideal answer?

Regenerating islets from endogenous adult stem cells in one's own pancreas. These islets could express the full complement of the hormones that were needed – insulin and glucagon – so that in a person's system, blood sugar could be lowered as well as raised. There would be no need for immunotherapy, and we could use benign drugs. This approach could treat both Type 1 and Type 2 diabetes. There would be sufficient insulin production to combat the diabetes as well as the resistance to insulin. Insulin secretion would be regulated. The effect would persist beyond the treatment period. The treatment would not be associated with any toxicity whatsoever. And we would target only the adult pancreatic stem cells. Is it possible? It is now on it's way to possibly becoming a reality.

In Part one we explained how the research all began, now lets see where the research is and where it is going.

The beginning of this new line of research demonstrated that the cellophane wrapping reversed streptozotocin-induced diabetes in hamsters. From there, they were able to identify an active protein called "ilotropin". Years were then spent working on that protein, trying to isolate it to its pure form so that they could administer it to animals made diabetic and later to people with diabetes. The nature of ilotropin eluded the researchers. So they decided to change the process around.

They decided to look within the pancreas that was growing again for a protein that was capable of stimulating new growth. A new technology became available that enabled them "shake the genetic haystack" and watch the needles, or proteins, drop out. The researchers found the genetic message and then went after the gene itself. In doing that, they discovered INGAP (Islet Neogenesis Associated Protein). It was shown that the protein product was capable of stimulating islet neogenesis and lowering blood glucose levels. This finding was published in 1997 in the *Journal of Clinical Investigation*. The protein was created by recombinant (molecular biologic) techniques. Investigations were begun to determine if this new construct could treat and reverse diabetes in animals.

This recombinant form of INGAP was given to animals made diabetic with streptozotocin. Several things happened. It stimulated pancreatic duct proliferation; it turned out to be the major component of ilotropin; and antibodies to natural INGAP could neutralize its effect. They then looked to see if INGAP caused the formation of new islets. Low and behold, it did. After looking for 15 years for the active ingredient, it turned out that this gene encodes a protein that is buried in the ilotropin protein mixture and is doing exactly what they wanted it to do.

Their work with diabetic hamsters revealed that for every log dose increase of INGAP, there was a progressive reduction in blood glucose concentration. Each dose that they gave dropped the blood glucose 35 mg/dl translating into about a 1% drop in blood hemoglobin A1c. and by repeating the process, they were able to reverse diabetes 30 – 40% of the time.

Investigation ensued to determine if there was a protein fragment that could successfully duplicate the action of the whole INGAP protein. They cut up the protein into little pieces and eventually isolated a smaller protein, actually a peptide made from a string of 15 amino acids that yielded the same results.

They synthesized this new INGAP Peptide in vitro and began further testing to see if the INGAP Peptide would reach its target and stimulate islets in the normal hamster.

They used the C57BL/bt black mouse. When made diabetic, this mouse gets inflammation of the pancreas, and the cells look exactly like a person with Type 1 diabetes. They investigated if increasing the dose could attain a greater effect. The answer was, yes. In a small study with eight animals, the animals that received salt water, the diabetes remained. In the animals that received INGAP Peptide, the diabetes was reversed.

The next step was to ascertain how the INGAP Peptide reversed diabetes. With the animals that received saline treatment, the blood glucose remained elevated. With those that were treated with INGAP Peptide, the blood glucose started coming down. After the INGAP Peptide was discontinued, the blood glucose stayed down. This seemed to indicate that INGAP does more than cause the pancreas to make insulin. INGAP Peptide possibly had a biological effect that went beyond just making insulin. The Peptide seemed to have a biological effect to create new cells in the body that make insulin – new cells that the body recognized as its own.

In 2000 EVMS licensed the INGAP technology to GMP Companies, Inc. with one interest in mind - to make INGAP into a drug to treat diabetes. They formed a relationship to work together to design and conduct studies to test dose, safety, efficacy, route of administration, and the possibility of human use. Together they would meet the Food and Drug Administration's requirements.

The Companies and People involved in the INGAP program:

Scott Mohrland, Ph.D. is Senior Vice President, Therapeutics Division for GMP Companies, Inc. As Senior

Vice President he manages and directs the acquisition, development and commercialization of pharmaceuticals and other therapeutic modalities within GMP's Therapeutics Division. Prior to joining GMP Companies, Inc., Dr. Mohrland spent more than 21 years with Pharmacia Corporation (formerly Pharmacia and Upjohn), most recently as Vice President of Scientific, Professional and Government Operations.

Dr. Mohrland shared with us that INGAP fits well within GMP Companies, Inc.'s mission of *Helping Medical Discoveries Help People™ Worldwide*.

INGAP will be able to take advantage of GMP's comprehensive product development infrastructure". "GMP's innovative approach reduces the organizational, administrative and financial burdens on individual business units, freeing innovators to concentrate on their research activities." "Using our "cradle to commercialization" approach we make best efforts to ensure that every aspect of the process is shepherded by experts in each functional area, which we believe increases our probability of success."

GMP Endotherapeutics, Inc. is the business unit of GMP Companies, Inc. whose efforts are dedicated to developing treatments for diabetes mellitus. So far this relationship has worked well as GMP was instrumental in helping get the Phase 1 / 2a Clinical Study initiated rapidly.

GMP has established a collaborative agreement with Procter & Gamble Pharmaceuticals on the project. (More on Procter & Gamble Pharmaceuticals' involvement next week)

"This is an exciting time for us even though we know it will be a while before we can answer the many questions that each phase of the research will tell us."

"What makes this research so exciting is that we could have answers that will not only help those with Type 1 diabetes but also those who have Type 2 diabetes that require daily Insulin injections."

GMP Companies successfully completed Stage 1 of the study and entered into Stage 2 of the study. The second stage is examining the safety and tolerability of approximately one month of daily treatments in a planned 32 patients.

This initial clinical trial is not designed to answer whether the drug is effective for the long term, but is assessing the safety and tolerability of single and repeat administration of INGAP Peptide. The Phase 1/2a clinical trial is expected to run towards the end of the year (2002).

If the results of the Phase 1/2a clinical trial indicate that INGAP Peptide is safe and tolerable in humans, and GMP Companies is given regulatory approval to move forward, there are plans for further studies. The next clinical trial will begin after all of the evaluations for the initial clinical trial are completed and reviewed.

At this time, the study sites for the next phase have not been selected.

For information on participation in the INGAP human trials,
Contact: GMP Companies, Gisele Galoustian 954-745-3537

To View Part 1 of this feature, CLICK HERE

For more information on INGAP and islet regeneration, please visit the Diabetes Institutes Foundation's website at www.dif.org or contact the Foundation at difcure@aol.com.

Please visit http://www.jci.org/cgi/content/full/99/9/2100 to read the entire research article
To review the Abstract please visit http://www.evms.edu/diabetes/ingap_abstract.html
To review other collaborations between Dr.Vinik and Dr. Rosenberg please visit http://www.evms.edu/diabetes/research-pubs-abstracts2.html and http://www.evms.edu/diabetes/research-pubs-abstracts1.html