Statement of Habib Zaghouani

J. Lavenia Edwards Endowed Chair in Pediatrics

Professor, Department of Molecular Microbiology and Immunology, Department of Child Health, and Department of Neurology.

The University of Missouri School of Medicine, Columbia, MO

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Chairman Collins, Ranking Member McCaskill, and members of the Special Committee, I am delighted to be here and thank you for the invitation to appear before you today. My name is Habib Zaghouani. I am a professor and the J. Lavenia Edwards Endowed Chair in Pediatrics at the University of Missouri School of Medicine. Let me state that the views expressed here today are my own and are not given on behalf of the University of Missouri or its Curators.

My research focuses on determining why and how the immune system reacts against our own tissues and organs to cause autoimmune diseases such as type 1 diabetes (T1D) and multiple sclerosis (MS). Also, my laboratory is devoted to developing approaches to halt such adverse reactions and cure these diseases. Other research in my laboratory is focused on studying immunity in newborns and how the function of neonatal immunity impacts the development of pediatric vaccines. My testimony today focuses mostly on a new approach we recently developed that cures T1D in mice and on the perspectives for translation of this approach to humans.

The first part of the testimony describes our clinical trial, which successfully cured T1D in mice. The second part highlights the challenges the field of T1D faces. The third part defines the opportunities for translational research, and the last part highlights the importance of NIH funding.

Introduction

T1D is a chronic condition that usually occurs in children and young adults when cells of the immune system attack the insulin producing beta (β)-cells of the pancreatic islets. Researchers have always thought that halting the immune attack of β-cells would help overcome the disease. This proved feasible for prevention of T1D in animal models, however curing the disease in humans has proven difficult to achieve.

Combination therapy successfully cured T1D in mice

In recent years my laboratory developed a protein based drug referred to as Ig-GAD2, which prevented progression of disease in pre-diabetic mice (1). We learned from this initial trial that Ig-GAD2 was able to rid the pancreatic islets of pathogenic immune cells. Additionally, we discovered that new insulin-producing β-cells were formed. This is crucial information indicating that the pancreas can generate new insulin-producing β-cells.

In humans, T1D is diagnosed when the disease is already established. Thus, in order to cure T1D, the drug has to be effective after diagnosis of the disease. The logic then was to carry out a trial with Ig-GAD2 when the mice have established or overt T1D in the hope that formation of new insulin-producing β-cells will occur and support recovery from the disease. The trial with Ig-GAD2 in overtly diabetic mice was performed but recovery from T1D was not achieved (2). This was intriguing, as pathogenic immune cells were no longer found in the pancreas (2).

The conclusion that was drawn from this failed trial was that new insulin-producing β-cells could not form perhaps because there was not a sufficient number of residual β-cells or stem cell precursors to reproduce β-cells from.

The logic, then, was to infuse the sick mice with bone marrow cells from healthy donors during treatment with Ig-GAD2 in the hope of enriching the recipients with stem cell precursors for β-cells. A clinical trial was then performed in which the sick mice were given Ig-GAD2 and bone marrow stem cells from healthy donors. The results were successful, as the sick mice were cured from T1D (2). After this trial, it was discovered that the bone marrow cells were giving rise to endothelial cells, the cells that form the walls of blood vessels. This conclusion was confirmed by the observation that infusion of the sick mice with endothelial stem cell precursors from adult healthy donor mice during treatment with Ig-GAD2 can substitute for infusion with bone marrow cells and repair islets' vascular networks. This facilitates the formation of new insulin-producing β-cells and thus recovery from overt T1D.

The knowledge gained from these trials suggests that the immune attack in the pancreatic islets destroys the insulin-producing β-cells and causes collateral damage to the blood vessels forming the islets' vascular network. The lack of insulin causes loss of function in endothelial cells and their precursors so that the mice cannot repair their islets' vascular network.

In conclusion, to cure T1D, the therapeutic strategy has to be able to modulate the immune attack and repair the islets' vascular network in order for insulin-producing β-cells to reproduce and thrive.

Exhibits A, B and C below represent schematic illustrations of the Ig-GAD2 and stem cells combination therapy.

Exhibit A. Shows a sick mouse that received adult endothelial stem cells from a healthy donor and the drug Ig-GAD2. The mouse recovered from disease and regained a normal lifestyle. The reason for the recovery is that the mouse, which had very little insulin (brown spot) before treatment, regained production of normal amounts of insulin.

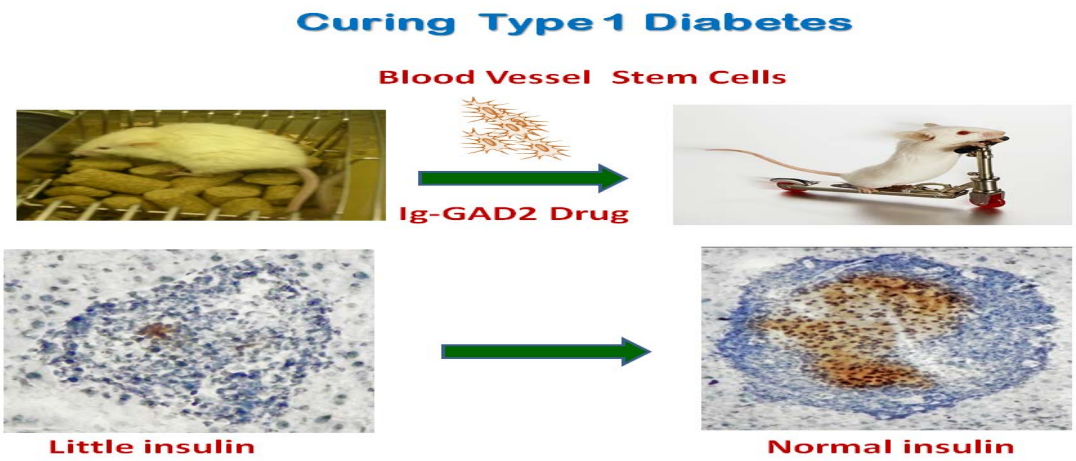


Exhibit B. Activated pathogenic immune system cells (bugs) destroy insulin-producing β-cells (black flowers) and cause collateral damage to tiny blood vessels in pancreatic islets (water pipe).

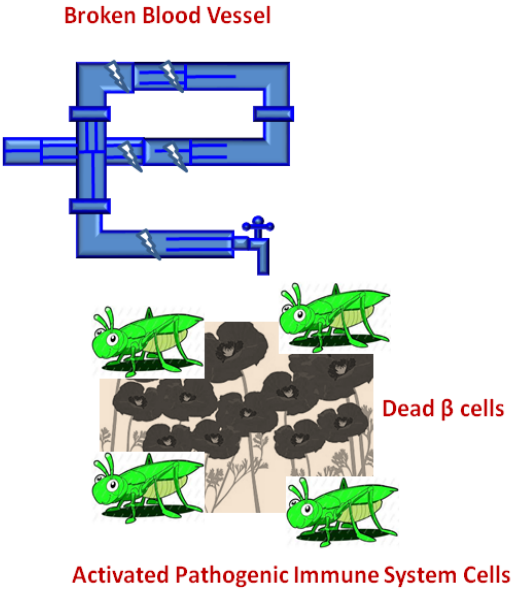
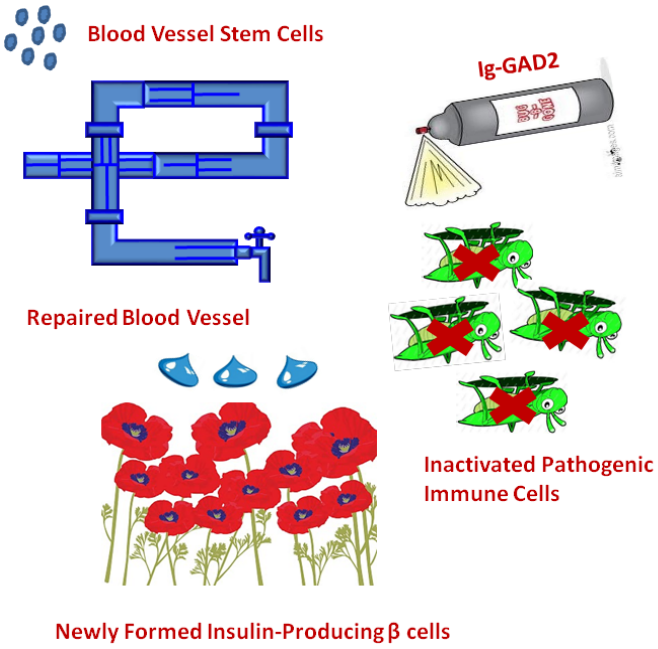


Exhibit C. Ig-GAD2 **(**spray can**)** inactivates pathogenic immune system cells (dead bugs), and the blood vessel stem cells repair the tiny blood vessels in pancreatic islets (repaired water pipe), leading to formation of new insulin-producing β-cells.



References

1. Jain et al., 2008. Journal of Experimental Medicine. 205:207-218.

2. Wan et al., 2013. Diabetes. 62:2879-2889.

Challenges the field of T1D research faces

In my opinion, meeting the challenges listed below is likely to foster progress toward a cure for T1D.

- The disease involves the endocrine system, the immune system, and now the vascular system. Collaborative efforts among researchers in the fields of endocrinology, immunology, and vascular biology will provide the multidisciplinary knowledge this disease demand and ensure better progress toward finding a cure for T1D.

- Development of humanized T1D animal (preferably mouse) models will certainly facilitate research that cannot be performed in humans and foster progress toward finding a cure for T1D.

- Focusing research on stimulation of beta cell proliferation and differentiation of their stem cell precursors is likely to foster progress toward developing a cure for T1D.

- Fostering the concept that more than one drug is needed to cure T1D will likely focus the research in a bidirectional path and ensure better progress toward finding a cure for T1D.

- Encouraging young and fresh minds to pursue careers in research in T1D research will ensure continued progress toward finding a cure for T1D and toward improving and adapting futures cures.

Challenges to translational T1D research

Research findings so far suggest that islet transplantation, which is associated with great limitations, may not be the major avenue for the cure of T1D. In order to achieve progress toward the cure with the alternative approach that I put forward, however, we must meet certain challenges.

- Fostering trials for combinatorial drugs.

- Fostering trials involving drugs and stem cells.

- Founding of specialized centers for large-scale production of drugs and for toxicology studies.

- Engaging the pharmaceutical industry in progressive clinical trial design and consideration of combinatorial therapeutics.

NIH funding and investment in T1D research and drug development

In my opinion, the challenges facing T1D fundamental and translational research will only be met by boosting availability of funds, optimizing access to these resources, and devising strategic programs for fund allocation.

- Enhancing the budget for T1D research and clinical translation is the principal requirement for progress toward a cure for T1D.

- Developing cross institute funding programs to meet the multidisciplinary requirement for progress in T1D research and translation. Joint programs by the NIAID, NIDDK and NHLBI will meet the need for expertise in immunology, endocrinology and vascular biology.

- Developing collaboration and developing a targeted funding program with foundations and charitable organizations is key for progress toward a cure for T1D.

- Developing programs that support collaboration with the pharmaceutical industry is likely to foster progress in translation and in the development of a cure for T1D.