Treatment and Prevention of Type 1 Diabetes

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Type 1 Diabetes

- Approximately 1.25 million American children and adults (0.4%) have type 1 diabetes
- Predominant onset is in childhood
- 45% of children present before 10 years of age
- The body’s immune system attacks and destroys the Beta cells in the pancreas that produce insulin
- Patients require lifelong insulin to stay alive
Insulin

• Insulin is a hormone produced by the pancreas which sits behind the stomach.

• Insulin is released into the bloodstream where it travels throughout the body to help a sugar called glucose enter into cells to be used as energy.
Complications of Diabetes

• High glucose levels damage small and large blood vessels
• Diabetes is the leading cause of
  – Adult blindness
  – Kidney failure
  – Non-traumatic amputations
• Diabetes increases the risk of heart attacks and strokes 2-4 fold
Keeping Blood Glucose Levels Close to Normal will Largely Prevent Diabetes Complications
Type 1 Diabetes Management

- Teach patients to give insulin to blood match the body’s needs
- Insulin Injections
- Insulin pumps
- Fingerstick glucose measurements 4 or more times a day
  - Adjust insulin dosage based on glucose level
What Factors Influence How Well Glucose Levels are Controlled?

- Correctly estimating the amount of carbohydrates in the meal
- Giving insulin 15-20 before meals is best
- Recent exercise decreases insulin requirements
- Physical and psychological stress, or inactivity increase insulin requirements
- Insulin absorption is affected by the dose, depth of injection, skin temperature, injection site, smoking, scar tissue
Striving for Near-Normal Glucose Levels with Insulin Increases the Risk of Low Blood Glucose Levels (Hypoglycemia)
Severe Hypoglycemia

• A very low glucose reaction that requires assistance from another person
• Occurs in 25% of intensively controlled patients yearly
• Symptoms may take hours to fully resolve
• May lead to seizures
• Estimated to be the cause of death in 4-6% of type 1 diabetes patients
People Living with Type 1 Diabetes Have to Think about Their Diabetes all Day to Prevent Long Term Complications and Hypoglycemia
Fingerstick Glucose Measurement
Insulin Injections
Insulin pump therapy
What Diabetes Research Provides
What Patients with Type 1 Diabetes Want Most
Immunotherapy

- Prevent the onset or progression of autoimmune destruction of insulin-producing Beta cells
  - Block the destructive immune T cells
  - Support Regulatory cells which protect against autoimmunity
T Effector and Regulatory Cell Interactions
Determine Appropriate Immune Response

• Balance exists in normal immune response
• T effector cells kill viruses, bacteria and cancer cells
• Regulatory cells regulate the immune response

Misdirected T Effector Cells Orchestrate Cell Destruction in Autoimmune Type 1 Diabetes

- Normal proteins on the surface of Beta cells trigger an immune response
- T effector cells inappropriately destroy Beta cells by a number of mechanisms\(^1,^2\)
- Regulatory cell inhibition is ineffective\(^1\)

Preventive Treatments that Target T Effector Cells or the Destructive Cytokines they Release

- Azathioprine, Mycophenolate mofetil, Cyclosporine, Anti-CD3 antibodies, Teplizumab, Otelixizumab, Rituximab, Interleukin-1 antagonists

- Effective in mouse model of type 1 diabetes
- Commonly less effective in humans
- At higher doses that lead to better protection
  - Common effects: fever, headache, low blood pressure, rashes
  - Acute mononucleosis-like syndrome
- Concern over the risk of long term immune suppression
  - Infections
  - Cancer
Preservation of Regulatory Cells in New-onset Type 1 Diabetes

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Regulatory Cells

• Deficient in diabetic NOD mice and humans with type 1 diabetes

• We have confirmed that regulatory cells are destroyed by a Fas-FasL interaction between cells
  – The normal way that immune cells are down-regulated after increasing in number to fight an infection
  – This is pathway is turned on to destroy regulatory cells in mice and humans that develop type 1 diabetes
Blocking the Fas-FasL Pathway

• Through use of a FasL antibody
• Protects Regulatory cells from apoptosis (death) and prevents type 1 diabetes development in the NOD mouse model
Current and Future Studies

• Making humanized monoclonal FasL antibodies

• Identify and expand those with potent ability to block the activity of human FasL

• Plan to test their safety and immune effects in normal subjects

• Potential future use in type 1 diabetes prevention trials
  – As sole therapy
  – In combination with lower doses of drugs targeted to T effector cells and destructive cytokines
Thank you