


BENAROYA RESEARCH INSTITUTE
UNLOCKING THE IMMUNE SYSTEM

BRING IT ON.

Type 1 Diabetes, treatment, prediction and prevention

Going to school



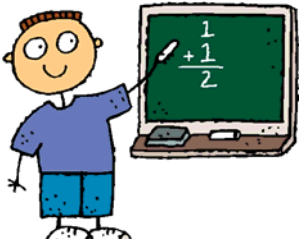
Carla Greenbaum MD
Director, Diabetes Program

BRING IT ON.

- Math
- History
- English
- Philosophy
- Civics

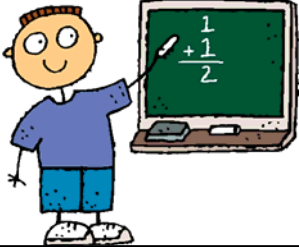
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MATH



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MATH: Absolute and Relative Risk




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Type 1 diabetes runs in families

TRUE or FALSE

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Raise your hand if you are a health care provider for someone with type 1 diabetes



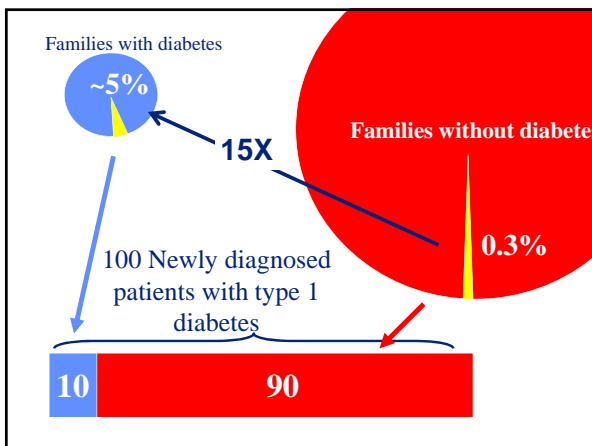
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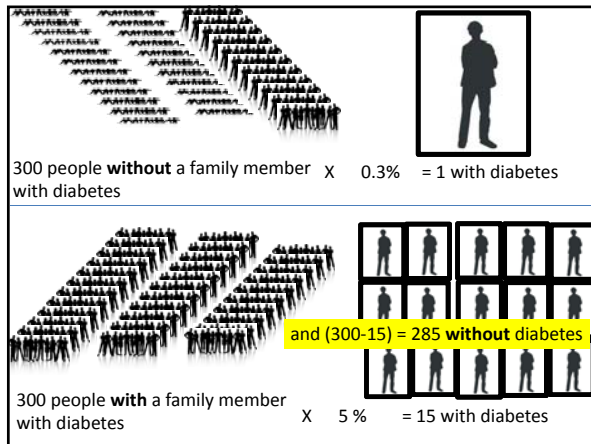
Keep your hand up if you are a health care provider to those with more than one family member with type 1 diabetes



Paradox? **BRING IT ON.**

How is it that most people do not have multiple family members with diabetes and yet, type 1 diabetes runs in families?





Risk summary


- About 0.3-0.5% or 3-5/1000 people have T1D.
 - This is the same as saying that the **absolute risk** of having T1D in the general population is 3-5/1000
- About 5% of those with a *family member* have T1D
 - This is the same as saying that the **absolute risk** of having T1D in families is 5/100 or 50/1000
- The **Relative Risk** of a family member is thus **15X** greater than someone in the general population.

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HISTORY

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HISTORY: Type 1 Diabetes and the immune system



Type 1 diabetes is a immune disease

“insulitis”

1970’s

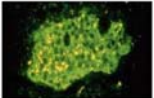


Normal islet Islet missing insulin producing beta cells
Lots of immune cells


2014’s Insulitis not seen in every islet

Type 1 diabetes is a immune disease

1980’s



Islet Cell Antibodies (ICA)



Insulin autoantibodies (IAA)

Jerry Palmer, University of Washington

ICA512 (IA-2); ZnT8 ab; GAD ab

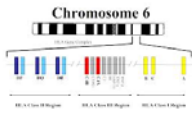
Type 1 diabetes is a immune disease

Risk Group	Type 1 diabetes
Population	1:300
Family members	1:20



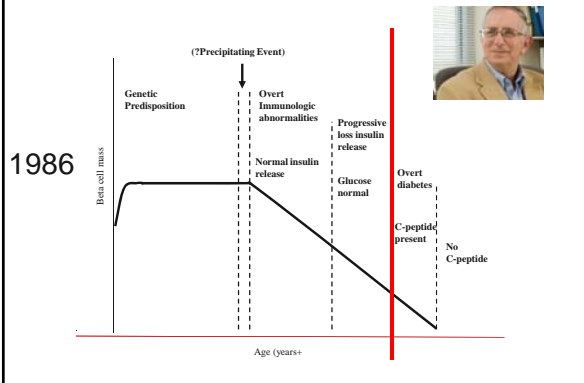
Jerry Nepom, MD, PhD
Benaroya Research Institute

1980's



Association with class II HLA type and HLA involves the immune system

Eisenbarth Model-T1D Natural History



1986

The modified model of disease: 2014

Its really complicated - when you get diabetes depends upon:

- Number of beta cells you start with
- When and how fast the immune system starts destroying beta cells
- Whether you slow or turn off the disease
- How much insulin you need to control glucose

Number of beta cells you start with

1. Each person who eventually develops T1D starts out with a variable amount of beta cell mass/function

Joe John
Jim

Number of beta cells you start with

1. Each person who eventually develops T1D starts out with a variable amount of beta cell mass/function
2. If the beta cells are destroyed at the same rate, they will get diabetes at different times

Beta cell function
Time

When and how fast the immune system attacks the beta cells

1. The rate at which the immune system attacks the cells also determines when you get diabetes

Beta cell function
Time

Whether you can turn off the immune attack

1. If you control or turn off the immune attack, you may delay or never get T1D

Beta cell function

Time

Joe

John

Jim

How much insulin you need to control glucose

1. Clinical Diabetes occurs when there is not enough insulin secretion to keep up with demand

Diabetes

No Diabetes

Even though it is complicated; we can predict who will get disease

Beta-cell mass

Age (years+)

Genetic Predisposition

(?Precipitating Event)

Overt Immunologic abnormalities

Normal insulin release

Progressive loss insulin release

Glucose normal


Overt diabetes

C-peptide present

No C-peptide

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ENGLISH



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ENGLISH: Determining Risk for T1D



Genetic Risk: HLA testing or Family History


Sensitivity: Proportion of people with disease who test positive:
$$\frac{\text{Number of people who have genetic risk who will get diabetes}}{\text{Number of people with diabetes}}$$

Specificity: Proportion of people without diabetes who test negative:
$$\frac{\text{Number of people without genetic risk and who do not get diabetes}}{\text{Number of people without diabetes}}$$

About 75% of people with Type 1 diabetes have high risk HLA, but 25% do not.
About 10% of people with type 1 diabetes have a family member with disease, but 90% do not

Genetic risk alone is neither very sensitive nor specific

Antibody testing

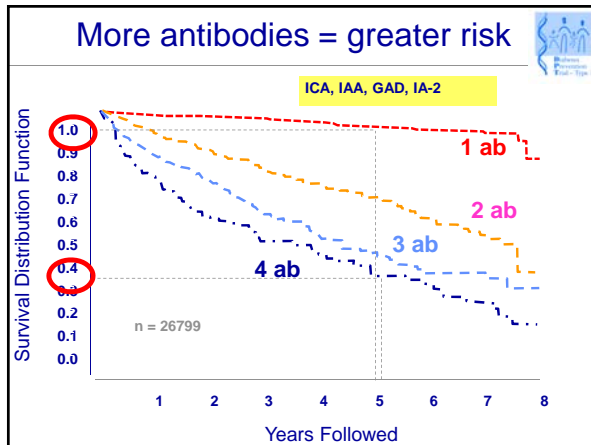


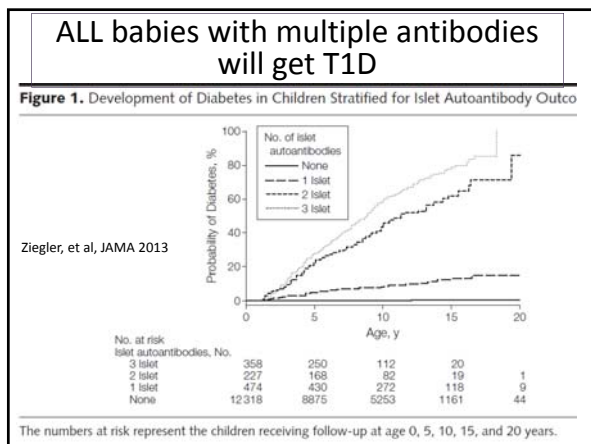
Antibody: Protein made by the immune system to identify and destroy foreign* objects (like infections)

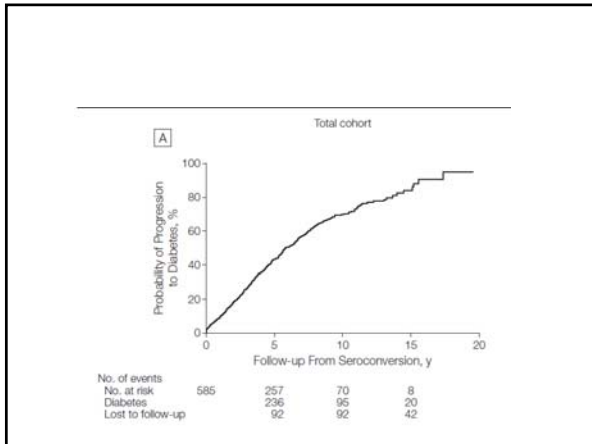
**in autoimmune disease the immune system makes a mistake and destroys "self" not foreign objects*

Risk of diabetes among those with genetic risk (family members)

	5 year risk	Longer term risk
No antibodies	Less than 1%	Likely less than 3%
One antibody	~3%	Likely less than 5%
Two antibodies	35%	Likely more than 90%
Two antibodies and abnormal glucose	85%	Likely almost everyone







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PHILOSOPHY

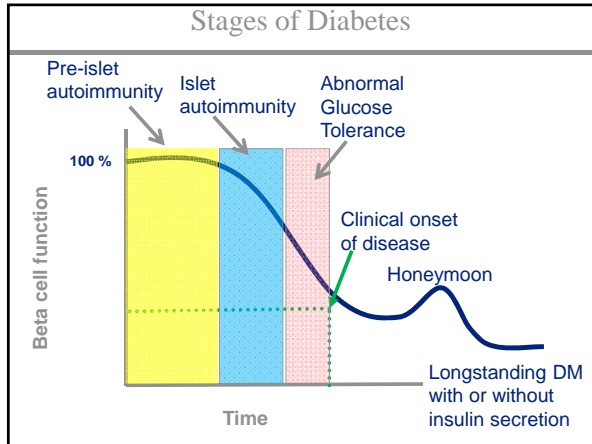


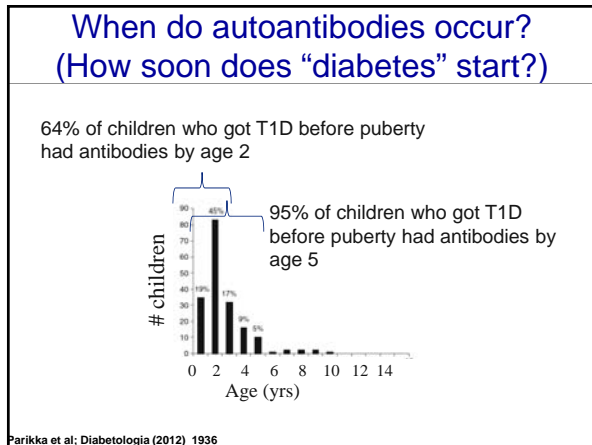
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PHILOSOPHY: When should we stop the immune attack?









Is having two or more antibodies a “disease”?

	5 year risk	Longer term risk
No antibodies	Less than 1%	Likely less than 3%
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Islet Autoimmunity



Is having two or more antibodies a "disease"?

Islet Autoimmunity  → 

Having islet autoimmunity has no symptoms, but it puts you at risk for getting diabetes

Hypertension (high blood pressure)

Having mild high blood pressure has no symptoms, but it puts you at risk for getting heart disease and stroke

 → 



PHILOSOPHY: Thought experiment

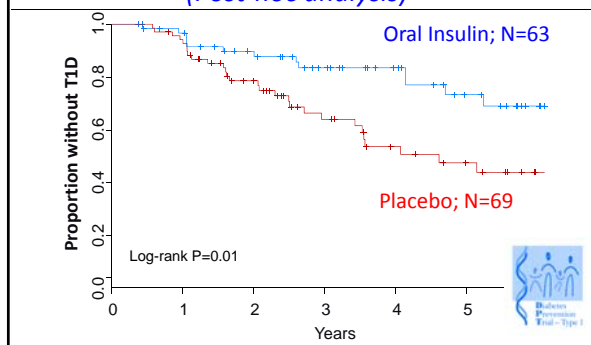
PHILOSOPHY: Thought experiment

Disease	Hypertension	Islet autoimmunity
Consequence within 4-5 years	~5/100 get coronary heart disease or stroke	35/100 get T1D

What therapy is being tested to treat islet autoimmunity?

- | | | |
|---------------------|-----------------------------------|--|
| Oral Insulin | Daily capsule
"oral tolerance" | <ul style="list-style-type: none"> • Age 2 or older • Two antibodies • One antibody is insulin autoantibody |
| Abatacept | Monthly IV infusion for 1 year | <ul style="list-style-type: none"> • Age 6 or older • Two antibodies, but not insulin autoantibody |
| Teplizumab | 14 days IV infusion just once | <ul style="list-style-type: none"> • Age 8 or older • Two antibodies and abnormal glucose |

4 year delay to diabetes onset in a subgroup of people treated with oral insulin
(Post-hoc analysis)

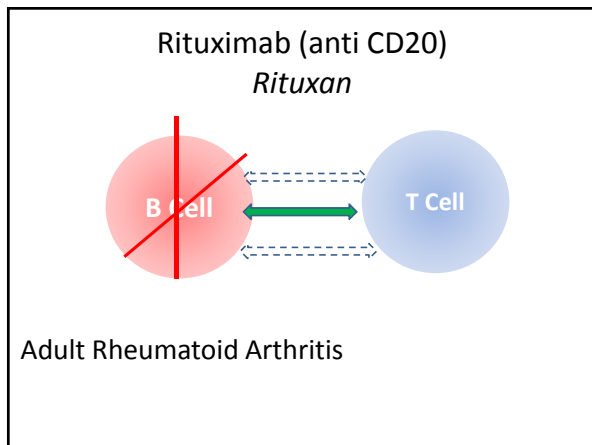


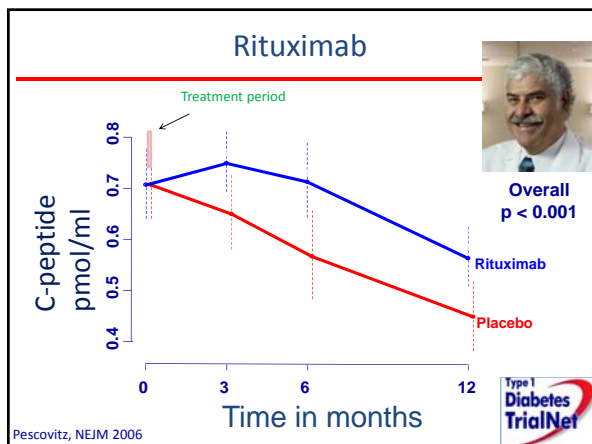
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Does immunotherapy scare you?

Immunotherapy is used to treat autoimmune disease.
 There are more than 80 million Americans with autoimmune disease
many of these are treated with immunotherapy

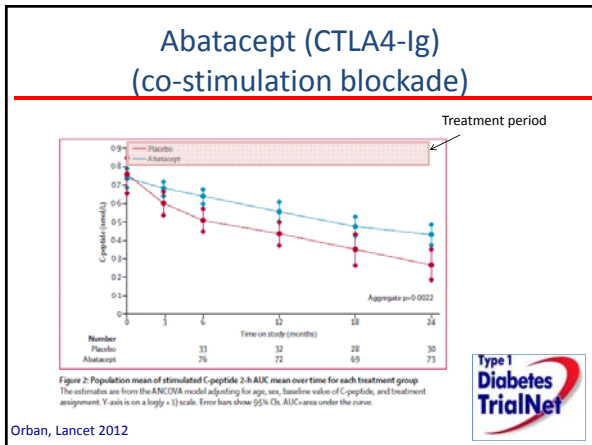
Alopecia	Myasthenia gravis
Ankylosin	Pernicious anemia
Addisons	Polyarteritis
Hemolytic	Polycy
Autoimm	Polym
Thrombot	Psori
Behcets disease	Rheu
Pemphigus	Scler
Crohns disease	Sjogren's syndrome
Dermatomyos	Stiff man syndrome
Lupus	Gia
Graves disease	Ulc
Hashimotos Th	Vas
Multiple sclerosis	Uve
	Viti



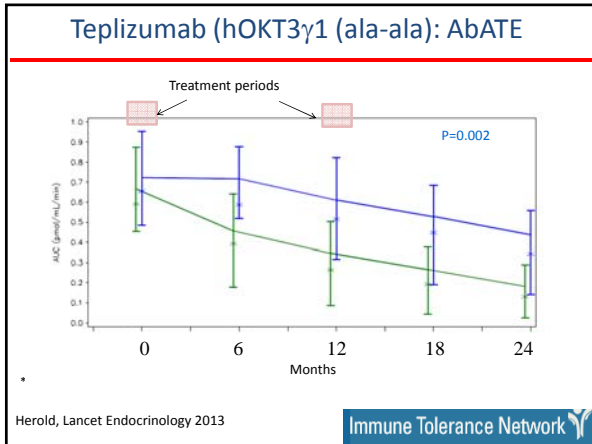


Abatacept (CTLA4 Ig)
Orencia

Adult Rheumatoid Arthritis
Juvenile Idiopathic Arthritis (JIA), age 6 or older

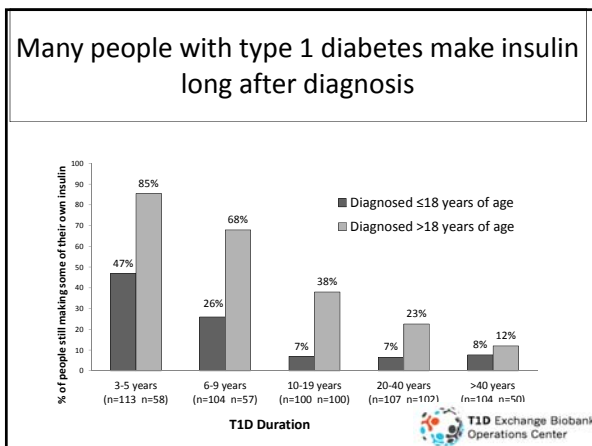


Teplizumab (anti CD 3)



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How does treating islet autoimmunity help people **with** type 1 diabetes?




It is common for adults with type 1 diabetes to still make insulin!!!!

Many people with type 1 diabetes make insulin long after diagnosis

Maybe the same therapies will be useful in people long after diagnosis as well

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- Math:
 - Family members have a 15 X increased risk of getting T1D
- History:
 - T1D is an immune mediated disease
- English:
 - Risk for diabetes can be accurately predicted
- Philosophy:
 - Having two or more antibodies IS a disease
- **Civics**



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Civics

Civics is the study of the great theoretical and practical aspects of citizenship, its rights and duties; the duties of citizens to each other as members of a political body and to the government

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New treatments will require more from the very people already burdened with type 1 diabetes

People with type 1 diabetes and their families are those that will need to participate in research

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Raise your hand if you encourage families to **participate in diabetes research**





Are you in compliance with ADA 2014 standards of care?

Standards of Medical Care in Diabetes—2014

Screening for Type 1 Diabetes

- Inform type 1 diabetic patients of the opportunity to have their relatives screened for type 1 diabetes risk in the setting of a clinical research study.

How to participate in research: families

- **Be a research ambassador –**
 - make sure that everyone you know with type 1 diabetes knows that it “runs in families”
 - Make sure that family members know they can be tested for risk (testing is “free”)
 - Let them know that they may be eligible for research trials to see if we can keep islet autoimmunity from becoming type 1 diabetes



How to participate in research: those with diabetes

- Join the **Benaroya Research Institute Diabetes (BRIDGE) Study:**
 - **Jointly** at BRI and Seattle Children's
- Join the T1D Exchange Biobank
 - Check with the BRI team



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How to participate in research: those recently diagnosed with diabetes

- **HOT NEWS!**
If someone is 18 to 35, and diagnosed with diabetes recently – there is a clinical trial enrolling now...with several more to come which will also include younger subjects

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JOIN THE FIGHT

BRING IT ON.

- **HAVE YOUR PATIENTS:**
- Sign up for our news
- Join a clinical study
- Join BRIDGE
- Visit our website at BenaroyaResearch.org



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