



National Institute of  
Diabetes and Digestive  
and Kidney Diseases

# Extramural Autoimmune Disease Research Supported by NIDDK

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Diabetes and Digestive  
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# Background

- The National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK's) Mission: to conduct and support medical research and research training, and to disseminate science-based information on diabetes and other endocrine and metabolic diseases; digestive diseases, nutritional disorders, and obesity; and kidney, urologic, and hematologic diseases, to improve people's health and quality of life.
- Autoimmune disease research is funded by all three divisions, KUH (Kidney, Urologic, and Hematologic), DDN (Digestive Diseases and Nutrition, and DEM (Diabetes, Endocrine, and Metabolic Diseases)

# NIH Reporter Active Awards

Type 1 Diabetes

Autoimmune Thyroid Disease

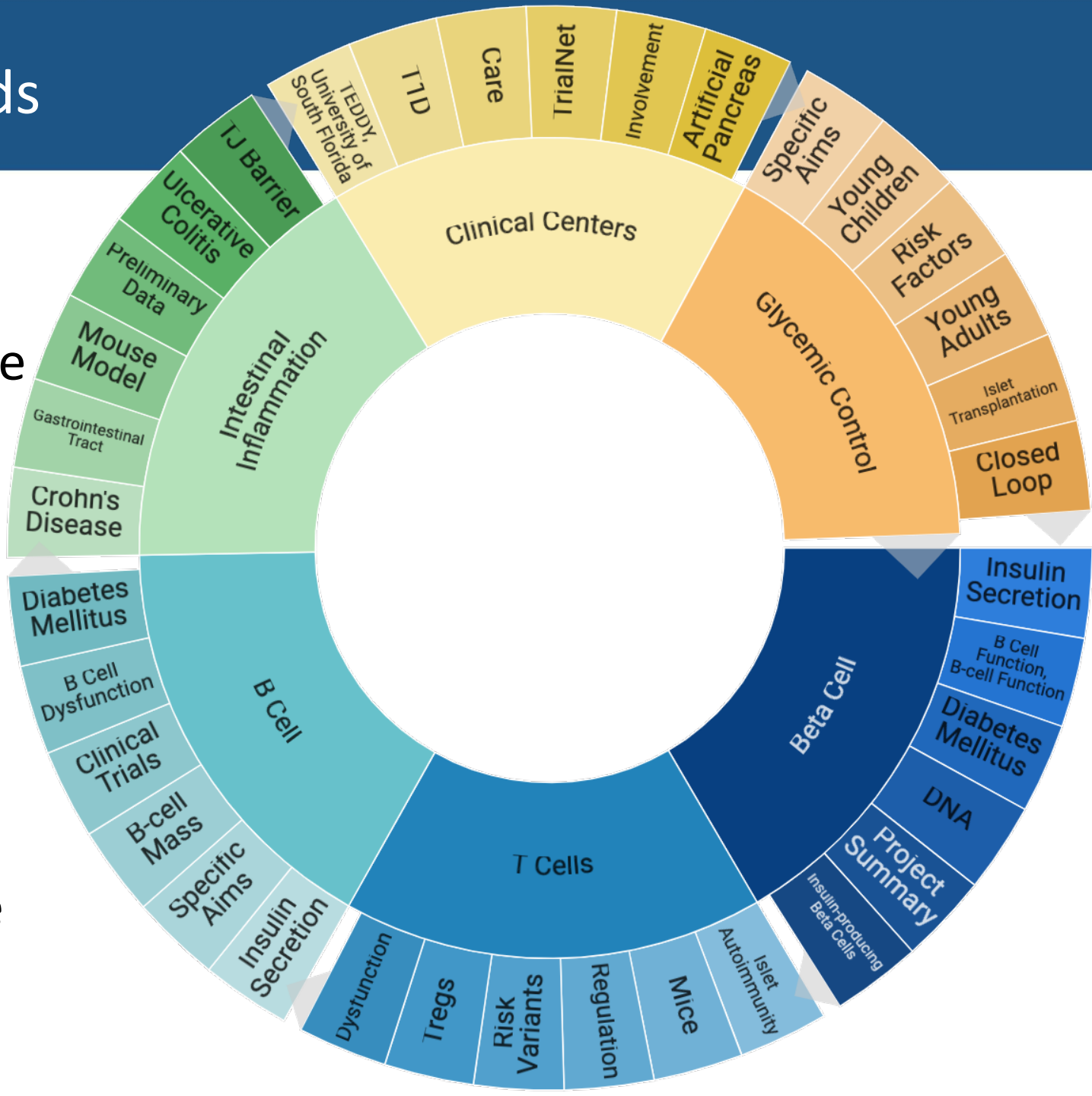
Celiac Disease

Crohn's Disease

Ulcerative Colitis

Inflammatory Bowel Disease

Glomerular Disease



# NIDDK's Initiative Development Process

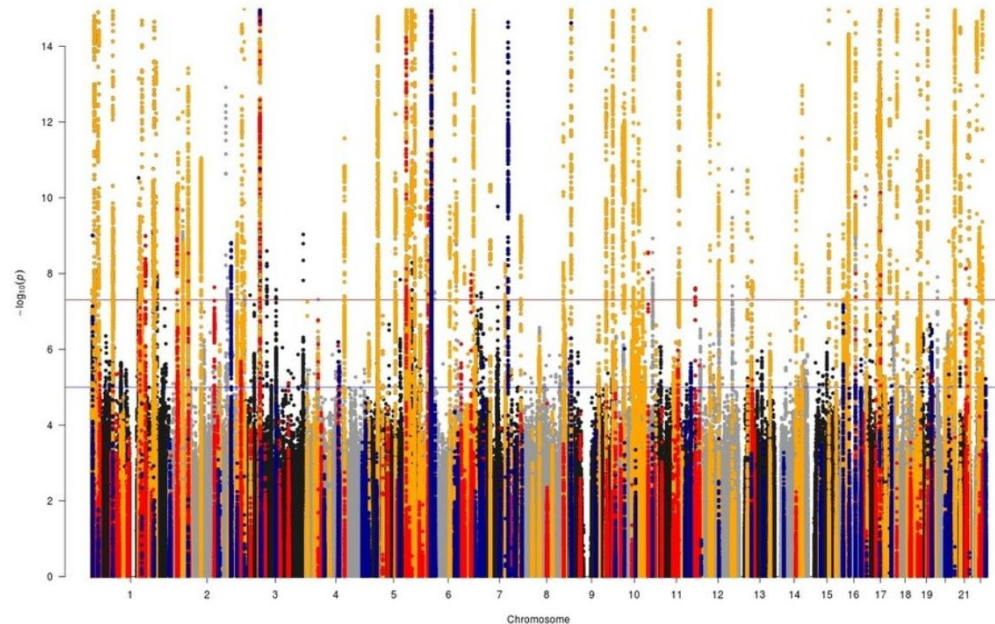
- NIDDK identifies research funding needs and scientific concept areas with input from the external scientific and lay communities (e.g., at scientific workshops, meetings with advocacy groups and societies, trans-NIH working groups like the Autoimmune Disease Coordinating Committee, etc.).
- NIDDK's leadership prioritizes initiatives to align with NIDDK's Strategic Plans (new version currently in development).
- NIDDK obtains feedback from its National Advisory Council, a diverse body whose members are drawn from the broad research community and the public.
  - Development and publication of Funding Opportunity Announcement
  - Receipt of applications, review, and award

# Division of Digestive Diseases and Nutrition

- Examples of research interests related to autoimmunity:
  - Inflammatory bowel diseases
    - Crohn's disease
    - Ulcerative colitis
  - Celiac Disease
  - Primary biliary cholangitis
  - Primary Sclerosing Cholangitis
  - Autoimmune hepatitis
  - Autoimmune pancreatitis

# Genetics of IBD: over 240 associations

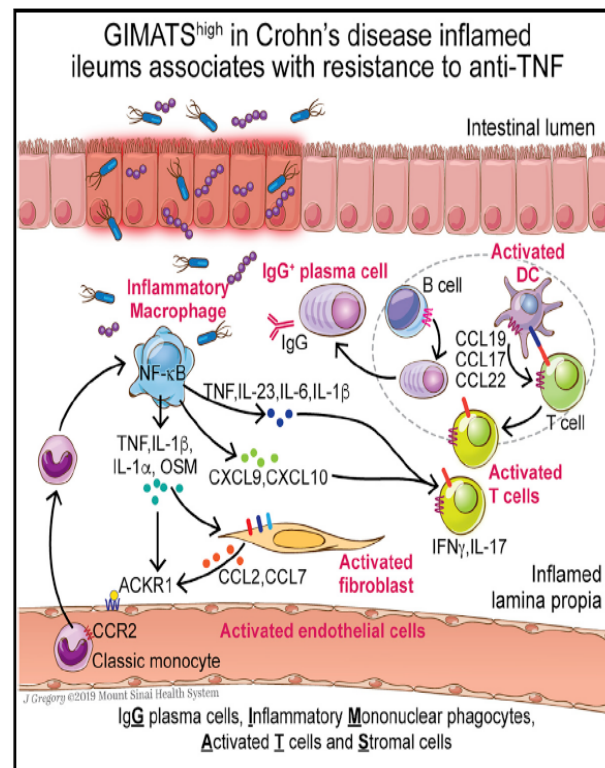
Manhattan plot of genes associated with IBD, Crohn's disease and Ulcerative Colitis



Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nature Genetics* volume 49, pages 256–261(2017)

# Towards Combination Therapy

## Graphical Abstract



## Single-Cell Analysis of Crohn's Disease Lesions Identifies a Pathogenic Cellular Module Associated with Resistance to Anti-TNF Therapy

Jerome C. Martin,<sup>1,2,3,18</sup> Christie Chang,<sup>1,2,3</sup> Gilles Boschetti,<sup>1,2,3</sup> Ryan Ungaro,<sup>4</sup> Mamta Giri,<sup>5</sup> John A. Grout,<sup>1,2,3</sup> Kyle Gettler,<sup>5</sup> Ling-shiang Chuang,<sup>5</sup> Shikha Nayar,<sup>5</sup> Alexander J. Greenstein,<sup>6</sup> Marla Dubinsky,<sup>7</sup> Laura Walker,<sup>8</sup> Andrew Leader,<sup>1,2,3</sup> Jay S. Fine,<sup>9</sup> Charles E. Whitehurst,<sup>9</sup> M Lamine Mbow,<sup>9</sup> Subra Kugathasan,<sup>10</sup> Lee A. Denson,<sup>11</sup> Jeffrey S. Hyams,<sup>12</sup> Joshua R. Friedman,<sup>13</sup> Prerak T. Desai,<sup>13</sup> Huaibin M. Ko,<sup>4,14</sup> Ilaria Laface,<sup>1,2,8</sup> Guray Akturk,<sup>1,2,8</sup> Eric E. Schadt,<sup>15,16</sup> Helene Salmon,<sup>1,2,3</sup> Sacha Gnjjatic,<sup>1,2,8,17</sup> Adeeb H. Rahman,<sup>1,8,15</sup> Miriam Merad,<sup>1,2,3,8,19,20,\*</sup> Judy H. Cho,<sup>5,18,\*</sup> and Ephraim Kenigsberg<sup>1,15,16,19,\*</sup>

Martin et al., 2019, Cell 178, 1493–1508

September 5, 2019 © 2019 Published by Elsevier Inc.

<https://doi.org/10.1016/j.cell.2019.08.008>

# Animal model of Celiac Disease

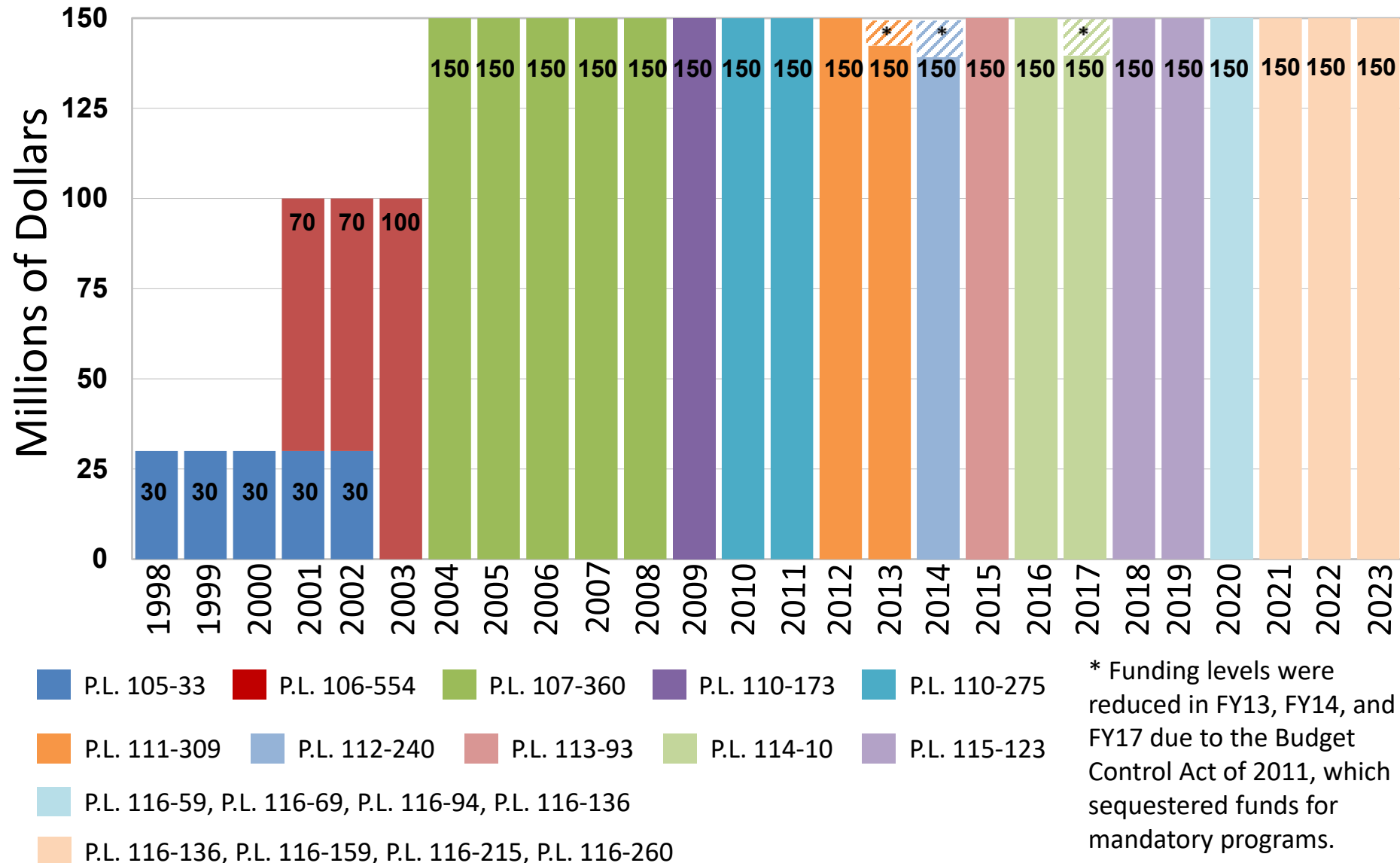
➤ [Nature](#). 2020 Feb;578(7796):600-604. doi: 10.1038/s41586-020-2003-8. Epub 2020 Feb 12.

## IL-15, gluten and HLA-DQ8 drive tissue destruction in coeliac disease

Valérie Abadie <sup># 1 2 3</sup>, Sangman M Kim <sup># 4 5 6</sup>, Thomas Lejeune <sup># 7 8</sup>, Brad A Palanski <sup>9</sup>,  
Jordan D Ernest <sup>4 5</sup>, Olivier Tastet <sup>10</sup>, Jordan Voisine <sup>4 5</sup>, Valentina Discepolo <sup>4</sup>,  
Eric V Marietta <sup>11 12 13</sup>, Mohamed B F Hawash <sup>10 14</sup>, Cezary Ciszewski <sup>4 5</sup>, Romain Bouziat <sup>4 5</sup>,  
Kaushik Panigrahi <sup>4</sup>, Irina Horwath <sup>11</sup>, Matthew A Zurenski <sup>4</sup>, Ian Lawrence <sup>4</sup>, Anne Dumaine <sup>10</sup>,  
Vania Yotova <sup>10</sup>, Jean-Christophe Grenier <sup>10</sup>, Joseph A Murray <sup>11</sup>, Chaitan Khosla <sup>9 15 16</sup>,  
Luis B Barreiro <sup>10 17 18</sup>, Bana Jabri <sup>19 20 21 22 23</sup>



# SDP: Laws Provide ~\$3.39 Billion Over 26 Years\*



# The Special Diabetes Program (SDP)



**\$150 M/Year**

- Supports ambitious, large-scale, high-risk, high-reward projects that would not otherwise be performed
- Enables stable, long-term investment in research

First FDA-authorized interoperable, automated insulin dosing controller, 12/13/19



Control-IQ Technology  
(Tandem Diabetes)

FDA-approved new soluble, stable glucagon formulation, 9/10/19



Glucagon Gvoke™ rescue pen  
(Xeris)

# Process for Development of SDP-funded Solicited Research Programs

- Collaborative process including other Institutes and Centers at NIH, the CDC, other federal agencies. Initiative development begins at least 2 years before release.
- Includes participation of non-federal stakeholders such as JDRF, ADA, Endocrine Society, and Helmsley Charitable Trust
- External Panel reviews progress and plans coordinated by the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC)
- NIDDK has obtained input from external experts at 10 External Evaluation Panel meetings in 19 years (2000-2019)
- The next Panel meeting will be April 2022

# Examples of Research Opportunities Responding to Panel Input

- ✓ **Develop strategies to facilitate maximal use of resources such as large clinical trials:** “Funding For Collaborative Clinical Research In Type 1 Diabetes: Living Biobank” RFA-DK-17-032
- ✓ **Expand artificial pancreas research:** “Clinical Trials to Test Artificial Pancreas Device Systems in Populations with Challenging to Manage Type 1 Diabetes (T1D)” RFA-DK-19-036
- ✓ **Support research to develop model systems that more closely represent human T1D:** “Human Islet Research Network - Consortium on Human Islet Biomimetics (HIRN-CHIB)” RFA-DK-18-011

# *Special Diabetes Program*

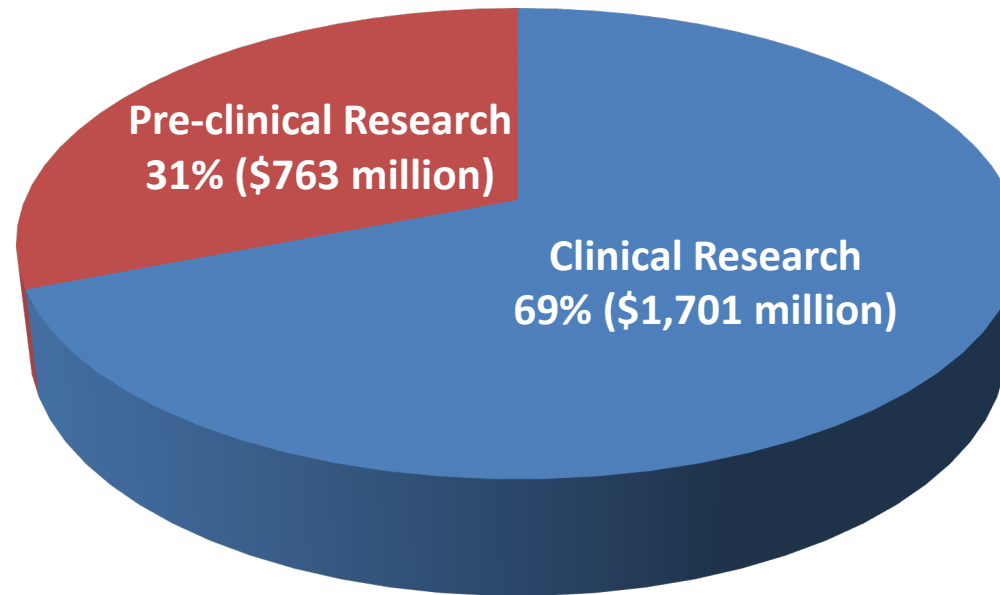
## Estimated Past Allocations (FY 98-18)

### Translational

- Animal Models
- BCBC
- HIRN/HPAP
- RAID

### Resources

- Islets for basic research
- CITR
- K12 (careers)



### Standardization

- A1C
- Antibodies
- C-peptide

### Etiology and Epidemiology

- TEDDY
- Genetics
- SEARCH

### Clinical Trials

- TrialNet
- ITN
- TRIGR
- CIT
- FL3X
- AP
- DirecNet
- DRCR.net
- PERL

# Examples of *Special Diabetes Program* Achievements in Pre-clinical/Translational Research



HPAP is using pancreata from cadaveric donors to perform a systematic and deep phenotyping of the human endocrine pancreas and its interaction with the immune system and other tissue compartments.

## Cell Metabolism

Resource

**Multiplexed *In Situ* Imaging Mass Cytometry Analysis of the Human Endocrine Pancreas and Immune System in Type 1 Diabetes**

Wang et al., 2019, *Cell Metabolism* 29, 769–783

## Cell Metabolism

Short Article

**SARS-CoV-2 Cell Entry Factors ACE2 and TMPRSS2 Are Expressed in the Microvasculature and Ducts of Human Pancreas but Are Not Enriched in  $\beta$  Cells**

Coate et al., 2020, *Cell Metabolism* 32, 1028–1040

## Immunity

Article

**Genetic Variation in Type 1 Diabetes Reconfigures the 3D Chromatin Organization of T Cells and Alters Gene Expression**

Fasolino et al., 2020, *Immunity* 52, 257–274

## Patterns

Descriptor

**Pancreatlas: Applying an Adaptable Framework to Map the Human Pancreas in Health and Disease**

Saunders et al., 2020, *Patterns* 1, 100120 November 13, 2020

# Examples of *Special Diabetes Program*

## Achievements in Genetics



- Type 1 Diabetes Genetics Consortium (T1DGC) has identified 50 additional loci that confer low to moderate risk of developing type 1 diabetes. ***This effort has made type 1 diabetes rare among polygenic diseases in that more than 80% of the genetic risk is accounted for by known loci.***
- Meta-analyses, fine-mapping and functional studies help identify causal variants, many shared across autoimmune diseases.
- Improved prediction for under-served populations.

### LETTERS

<https://doi.org/10.1038/s41588-018-0216-7>

nature  
genetics

**Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes**

Harm-Jan Westra<sup>1,2,3,4,5,20</sup>, Marta Martínez-Bonet<sup>4,20</sup>, Suna Onengut-Gumuscu<sup>6,7</sup>, Annette Lee<sup>8</sup>,

**Type 1 Diabetes Risk in African-Ancestry Participants and Utility of an Ancestry-Specific Genetic Risk Score**

*Diabetes Care* 2019;42:406–415 | <https://doi.org/10.2337/dc18-1727>



## UBASH3A Mediates Risk for Type 1 Diabetes Through Inhibition of T-Cell Receptor–Induced NF- $\kappa$ B Signaling

Yan Ge<sup>1,2</sup>, Taylor K. Paisie<sup>1,2,3</sup>, Jeremy R.B. Newman<sup>2,4</sup>, Lauren M. McIntyre<sup>2,4</sup> and Patrick Concannon<sup>1,2</sup>↑

## Targeted Deep Sequencing in Multiple-Affected Sibships of European Ancestry Identifies Rare Deleterious Variants in *PTPN22* That Confer Risk for Type 1 Diabetes

Yan Ge<sup>1</sup>, Suna Onengut-Gumuscu<sup>2,3</sup>, Aaron R. Quinlan<sup>4,5</sup>, Aaron J. Mackey<sup>2,3</sup>, Jocyndra A. Wright<sup>1</sup>, Jane H. Buckner<sup>6</sup>, Tania Habib<sup>6</sup>, Stephen S. Rich<sup>2,3</sup> and Patrick Concannon<sup>1,7</sup>↑

# Examples of *Special Diabetes Program*

## Achievements in Diabetes Control and Complications

- Clinical Islet Transplantation Consortium validated the process for islet cell manufacturing and showed that islet transplantation improved glycemic control and dramatically reduced hypoglycemia unawareness (with NIAID)
- New treatments for diabetic macular edema and diabetic retinopathy (**DRCR.net**) (with NEI)
- Early development or testing of FDA-approved devices, such as a hybrid artificial pancreas (**SBIR**), first CGM not requiring fingerstick calibration (**SBIR**), first implantable CGM, development of glucose-responsive SmartInsulin (**SBIR**)



# NIDDK- and SDP-supported Research Contributed to New Technologies for Treating Type 1 Diabetes

First FDA-approved “hybrid” artificial pancreas with finger-stick calibration, 9/28/16



MiniMed 670G (Medtronic)

First FDA-approved CGM without finger-stick calibration, 7/30/18



Freestyle Libre (Abbott)

First FDA-approved fully implantable CGM, 6/21/18



Eversense implantable CGM (Senseonics)

First FDA-approved integrated CGM system, 3/27/18



G6 iCGM system (Dexcom)

FDA-approved new soluble, stable glucagon formulation, 9/10/19



Glucagon Gvoke™ rescue pen (Xeris)

First FDA-authorized interoperable, automated insulin dosing controller, 12/13/19



Control-IQ Technology (Tandem Diabetes)

# Examples of *Special Diabetes Program* Achievements in Etiology and Epidemiology



## **nature**

**The human gut microbiome in early-onset type 1 diabetes from the TEDDY study**



**Plasma Metabolome and Circulating Vitamins Stratified Onset Age of an Initial Islet Autoantibody and Progression to Type 1 Diabetes: The TEDDY Study**

## **nature**

**Prospective virome analyses in young children at increased genetic risk for type 1 diabetes**



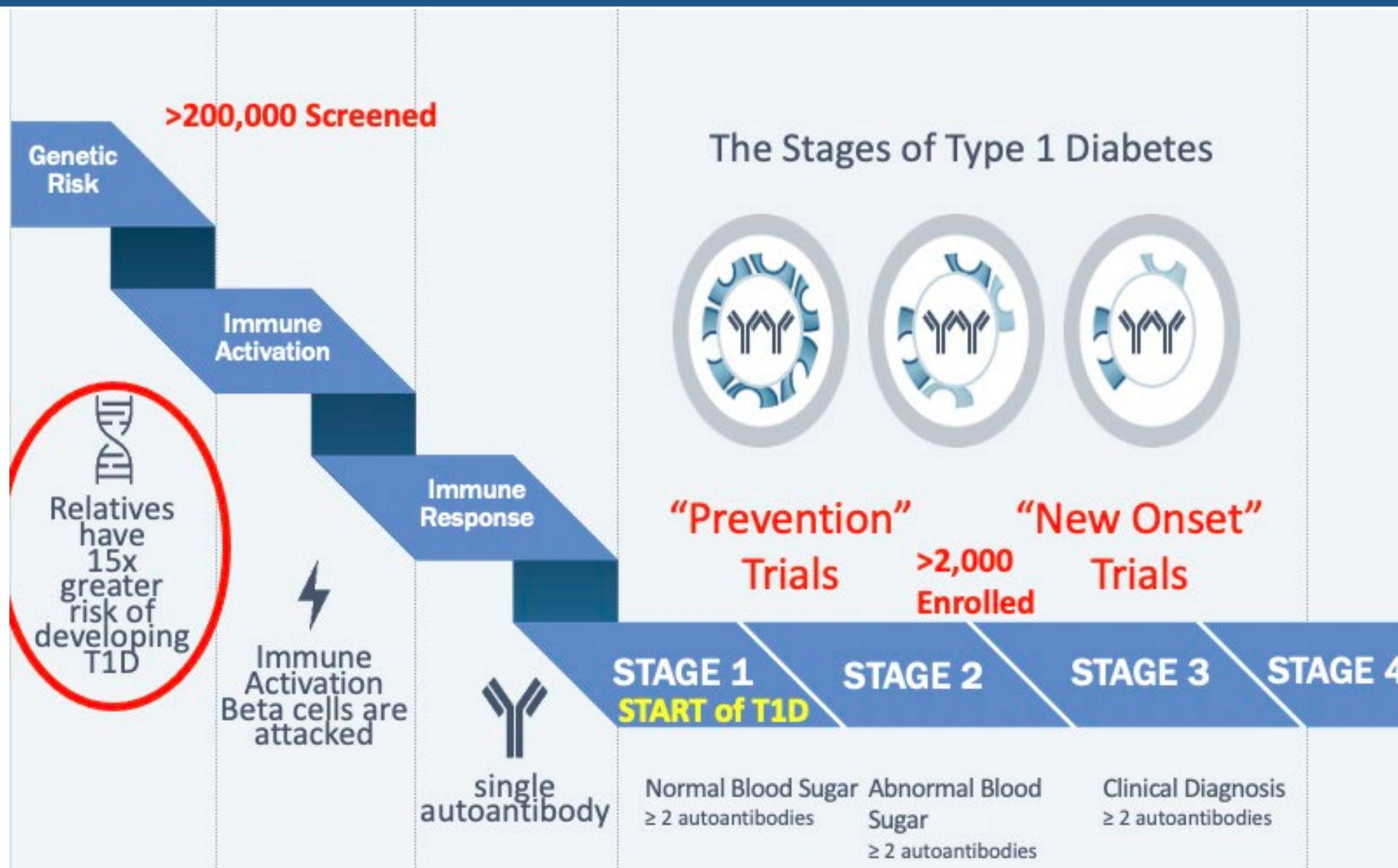
**Plasma 25-Hydroxyvitamin D Concentration and Risk of Islet Autoimmunity**

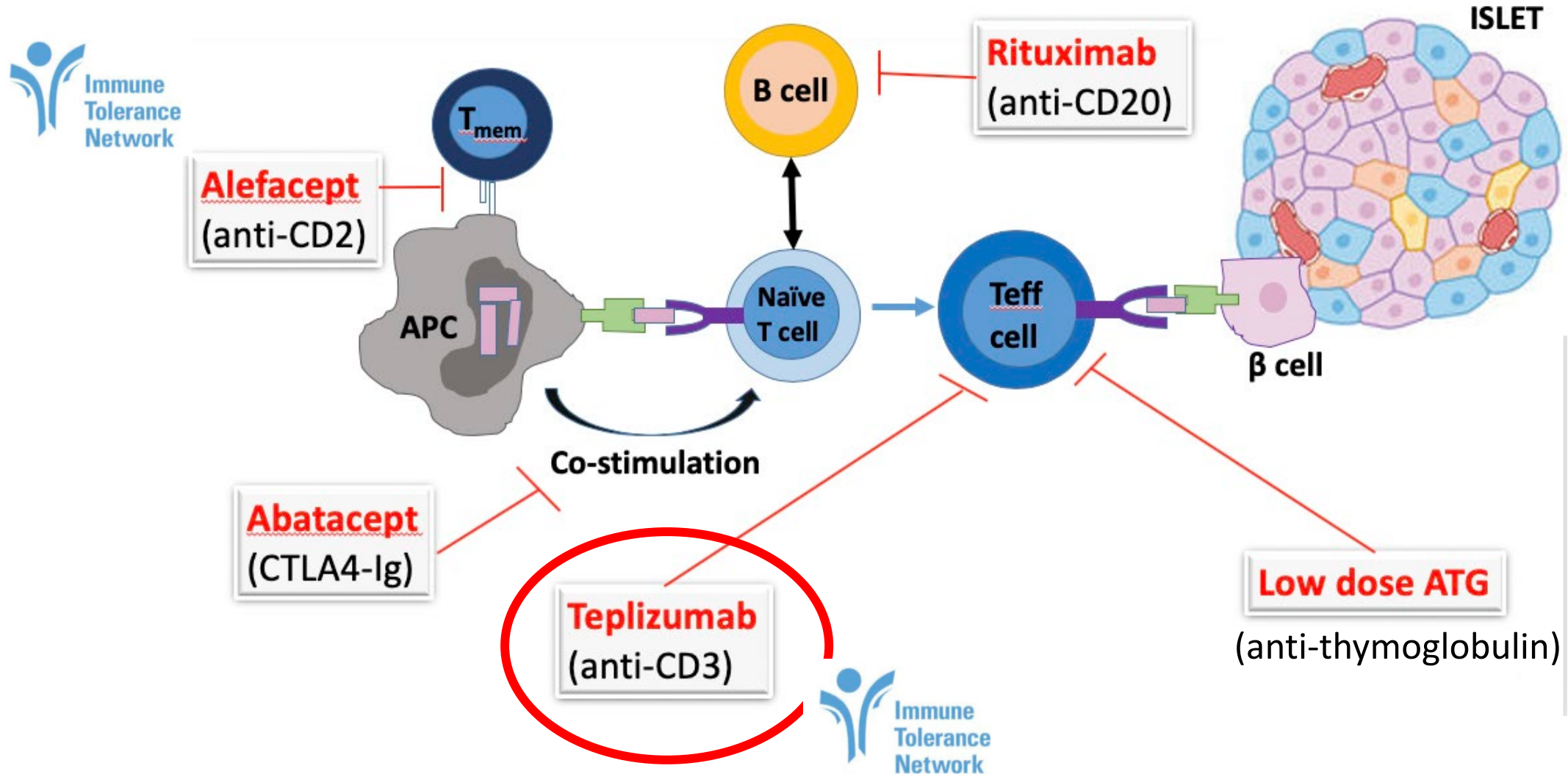
## **nature medicine**

**A combined risk score enhances prediction of type 1 diabetes among susceptible children**

# Examples of *Special Diabetes Program*

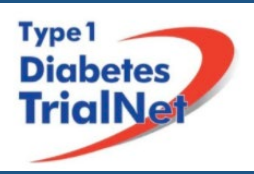
## Clinical Achievements: Type 1 Diabetes Is a Predictable Disease





# Examples of *Special Diabetes Program*

## Achievements in Disease-Modifying Interventions: Prevention



- First trial to robustly demonstrate that progression to clinical T1D can be delayed – by a median of 2 years
- Breakthrough therapy designation (ProventionBio)
- One of 2019's Top Advances: Endocrine Society and Nature Medicine



The NEW ENGLAND  
JOURNAL of MEDICINE

### ORIGINAL ARTICLE

#### An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

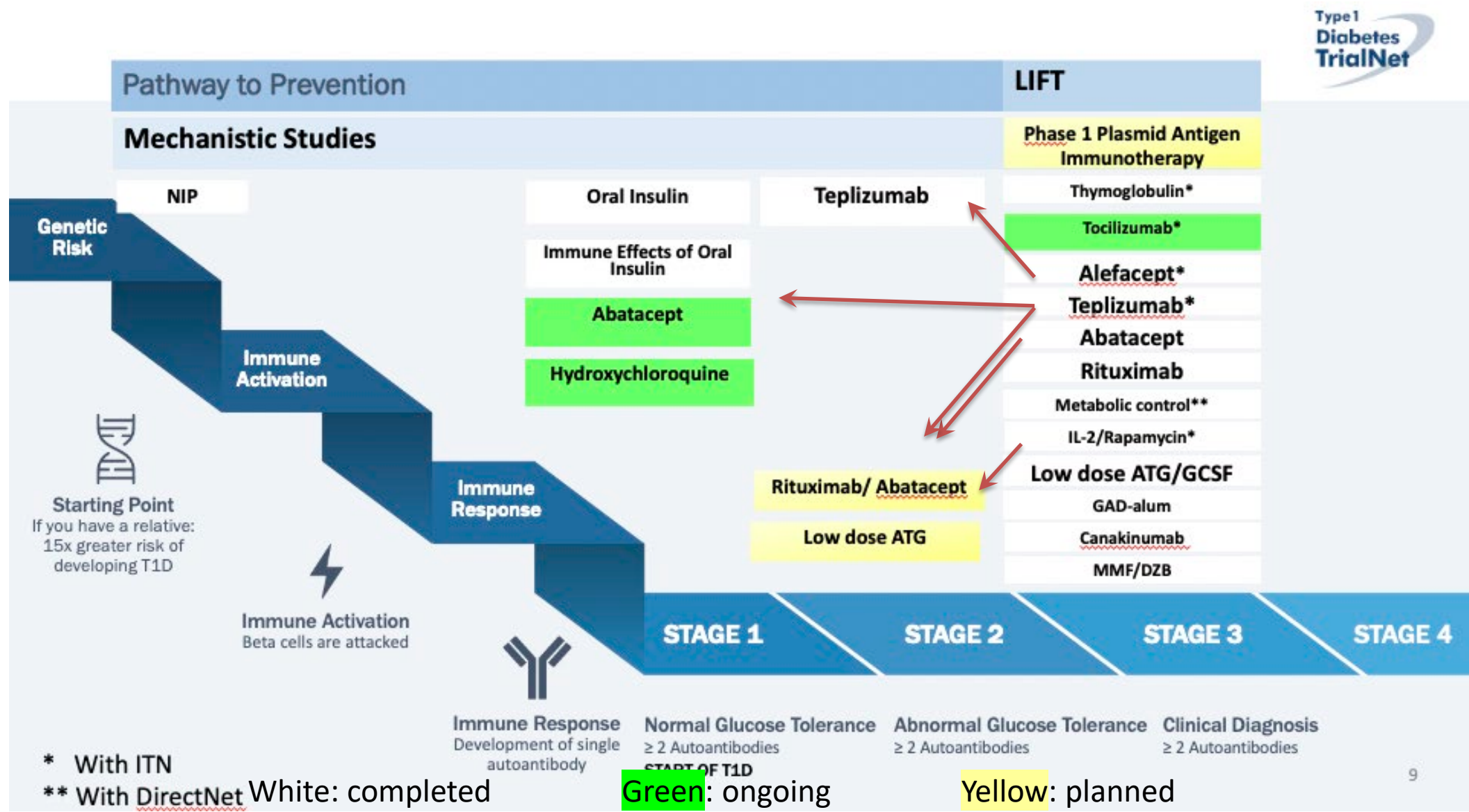
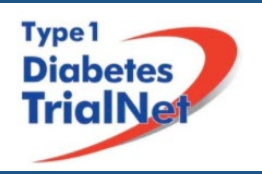
Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group.\*



K. Herold

# Examples of Special Diabetes Program

## Achievements in Disease-Modifying Interventions: TrialNet Clinical Trials





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