Checkpoint inhibitors and autoimmune endocrinopathies

FDA

December 1, 2017

Kevan C. Herold, MD

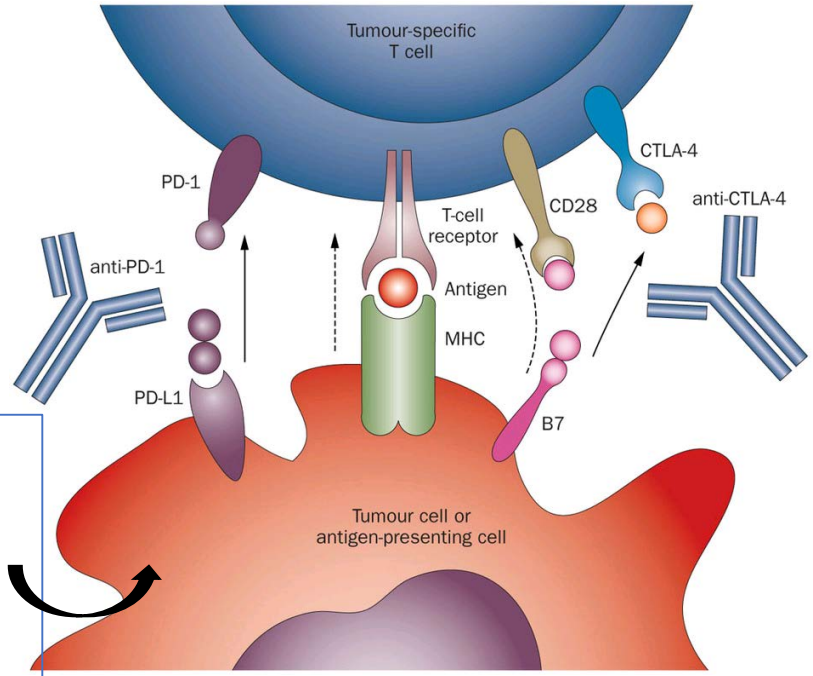
Department of Immunobiology

Yale University

Disclosures

- I have a patent application for a method to measure beta cell death in vivo
- I have consulted for Pfizer, BMS, Merck, Roche, Lilly, and Tiziana concerning treatment for Type 1 diabetes.
- I have no disclosures related to the material in this presentation

Immunotherapies targeting checkpoint inhibitors



Checkpoint inhibitors

CTLA-4 inhibitors
- Ipilimumab
- Tremelimumab

PD-1 inhibitors
- Nivolumab (FDA approved)
- Pembrolizumab
- Pidilizumab

PD-L1 inhibitors
- Atezolizumab
- BMS-936559
- Durvalumab
- Avelumab

Melanoma
NSCL
RCC
Urothelial
Ovarian
Head and neck
Hepatocellular
Lymphoma

This same mechanism of action would be expected to lead to immune related adverse events. Endocrine organs: pituitary, thyroid, adrenal, and β cells are prime targets for (auto)immune responses.

Cancer immunotherapy — immune checkpoint blockade and associated endocrinopathies

David J. Byun[1,2], Jedd D. Wolchok[1,2], Lynne M. Rosenberg[2] and Monica Girotra[1,2]

Table 1 | **Endocrine IRAEs in patients treated with ipilimumab**

Study	Cohort		Endocrinopathy					
	Age (range)	n	Hypophysitis	2° or other adrenal insufficiencies	2°or other hypothyroidisms	1° hypothyroidism	Thyroiditis	1° adrenal insufficiency
Total[§§]		2,938	184/2,017 (9.1%)	37/608[¶¶] (6.1%)	42/555[¶¶] (7.6%)	23/410 (5.6%)	9/283 (3.2%)	2/256 (0.8%)

Table 3 | **Endocrine IRAEs with PD1 and PDL1 antibodies**

Study	Cohort		Endocrinopathy					
	Age (range)	*n*	Hypothyroidism	Hyperthyroidism	Adrenal insufficiency	Hypophysitis	Other thyroid*	T1DM *
Total[#]		2,702	160/2,573 (5.9%)	71/2,153 (3.3%)	2/117 (1.7%)	10/1,658 (0.6%)	3/224 (1.3%)	3/766 (0.4%)

Totals with ipilimumab: 32.4%

Totals with PD-1 and PD-L1: 13.2%

<u>Overall rates from Barroso-Sousa et al (2017):</u>
Hypothyroidism: 6.6% (3.8-13.2%)
Hyperthyroidism: 2.9% (0.6-8.0%
Hypophysitis: 0.5% (0.4-6.4%)
1º Adrenal insuff and IDD: 0.7% and 0.2%

*There have been > 15 case reports of CPI induced diabetes

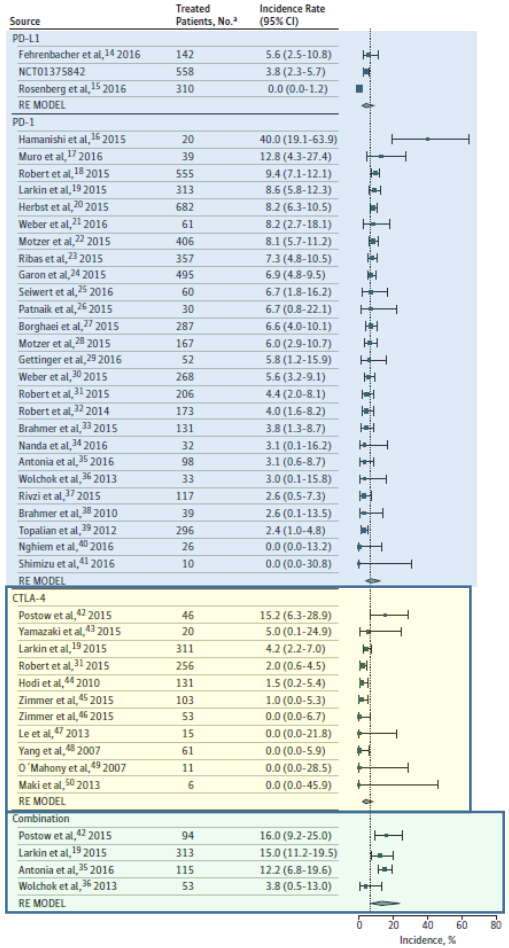
JAMA Oncology | Original Investigation

Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens

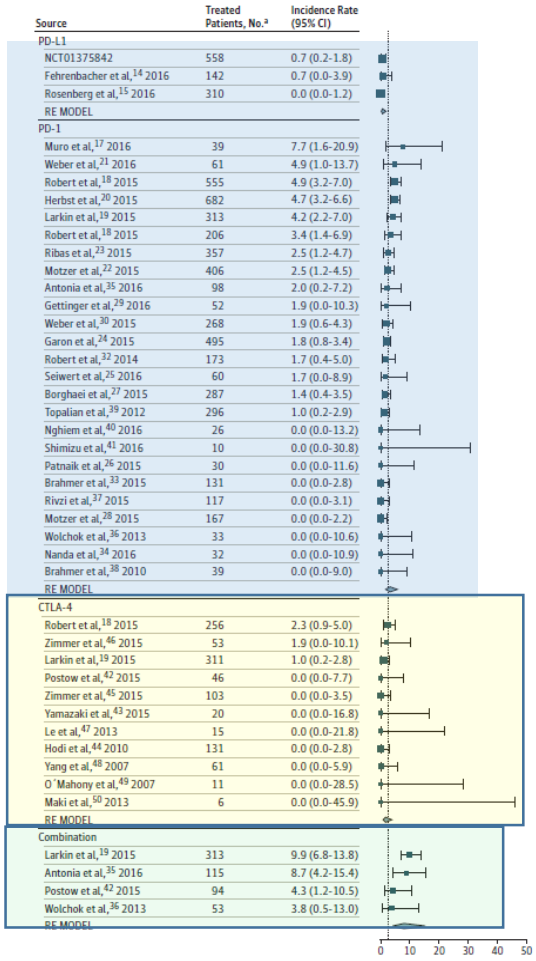
A Systematic Review and Meta-analysis

Romualdo Barroso-Sousa, MD, PhD; William T. Barry, PhD; Ana C. Garrido-Castro, MD; F. Stephen Hodi, MD; Le Min, MD; Ian E. Krop, MD, PhD; Sara M. Tolaney, MD, MPH (DFCI)

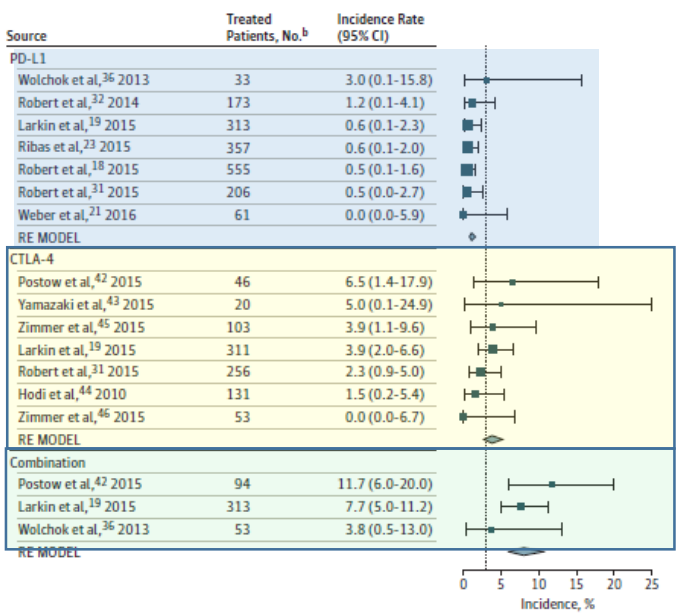
Hypothyroidism



Hyperthyroidism



Hypophysitis



The incidence of endocrine dysfunction was higher with combo vs ipi alone. The incidence of thyroid dysfunction and hypophysitis was highest with PD-1 inhibitors and ipi respectively.

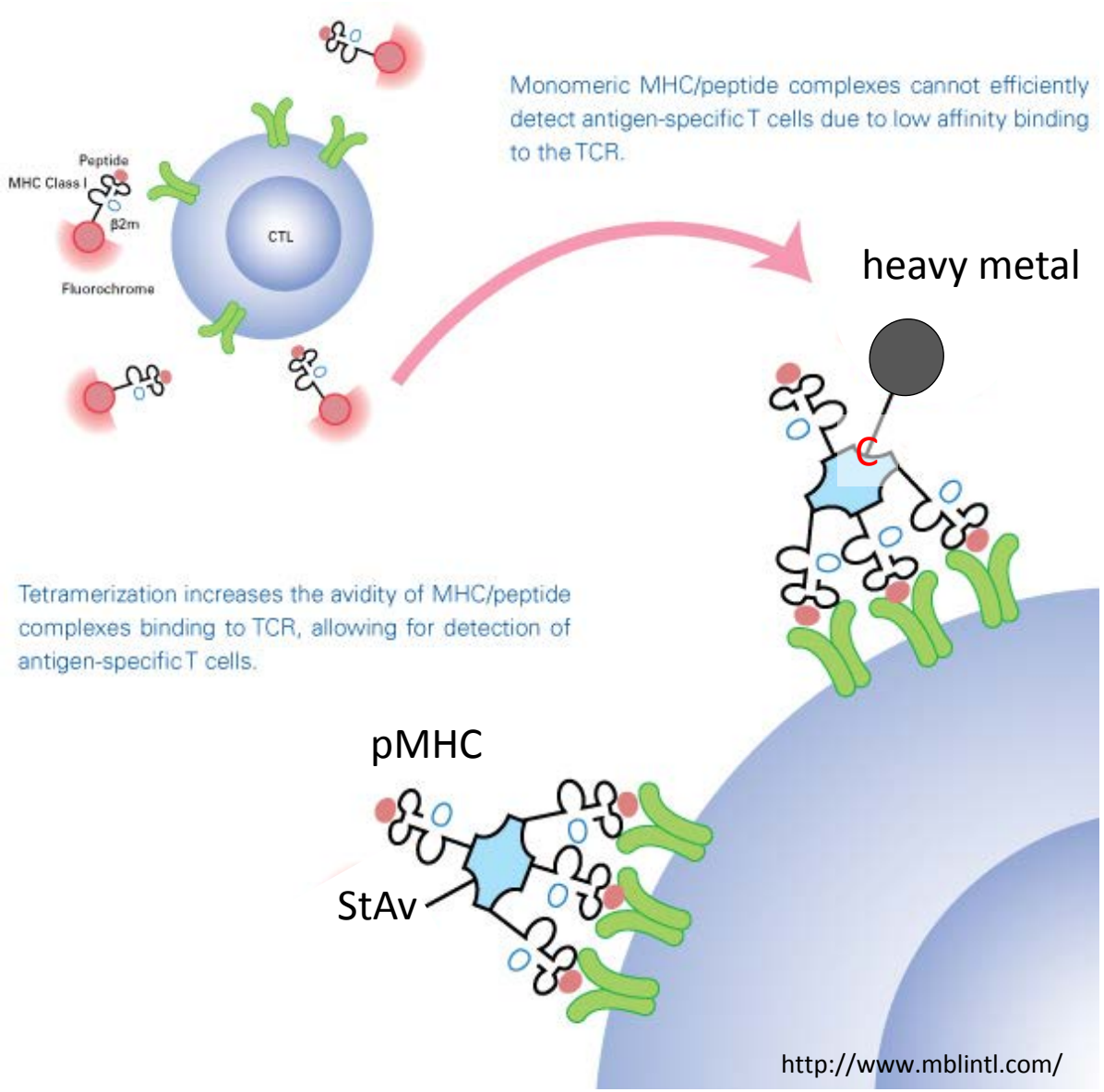
Potential mechanisms of immune related adverse events

- Activation of effector T cells: Are these cells affected by checkpoint inhibitor? Are they present before treatment?
- Disturbance of normal mechanisms of tolerance? Are changes restricted to T cells?
- Tissue responses?

Features of diabetes induced with check point inhibitors

- New onset of diabetes in elderly or dramatic increase in insulin requirements in a patient with known Type 2 diabetes.
- Time to dx: mean 10 mos w/o hx of DM but 3.5 mos with a hx of DM
- 7/17 present with diabetic ketoacidosis. Avg A1c=8.09%
- BMI=28.
- Both T1D associated (HLA-DR3,4) and protective alleles identified.
- May or may not have autoantibodies
- Triggers: incr px enzymes in 6/10, imaging c/w pxitis 2/6, infection 1/17; steroids in 4/17
- 4/17 with thyroid dysfunction, 1/17 with hypophysitis
- No FH of autoimmune diabetes but frequently a family history of autoimmune diseases
- Rapidly progresses to undetectable levels of C-peptide
- It does not appear that steroids will prevent complete loss of beta cell function
- Recovery is very uncommon
- Glucose lability is consistent with absolute deficiency of insulin.

Detecting Islet Ag-Specific T Cells in CyTOF



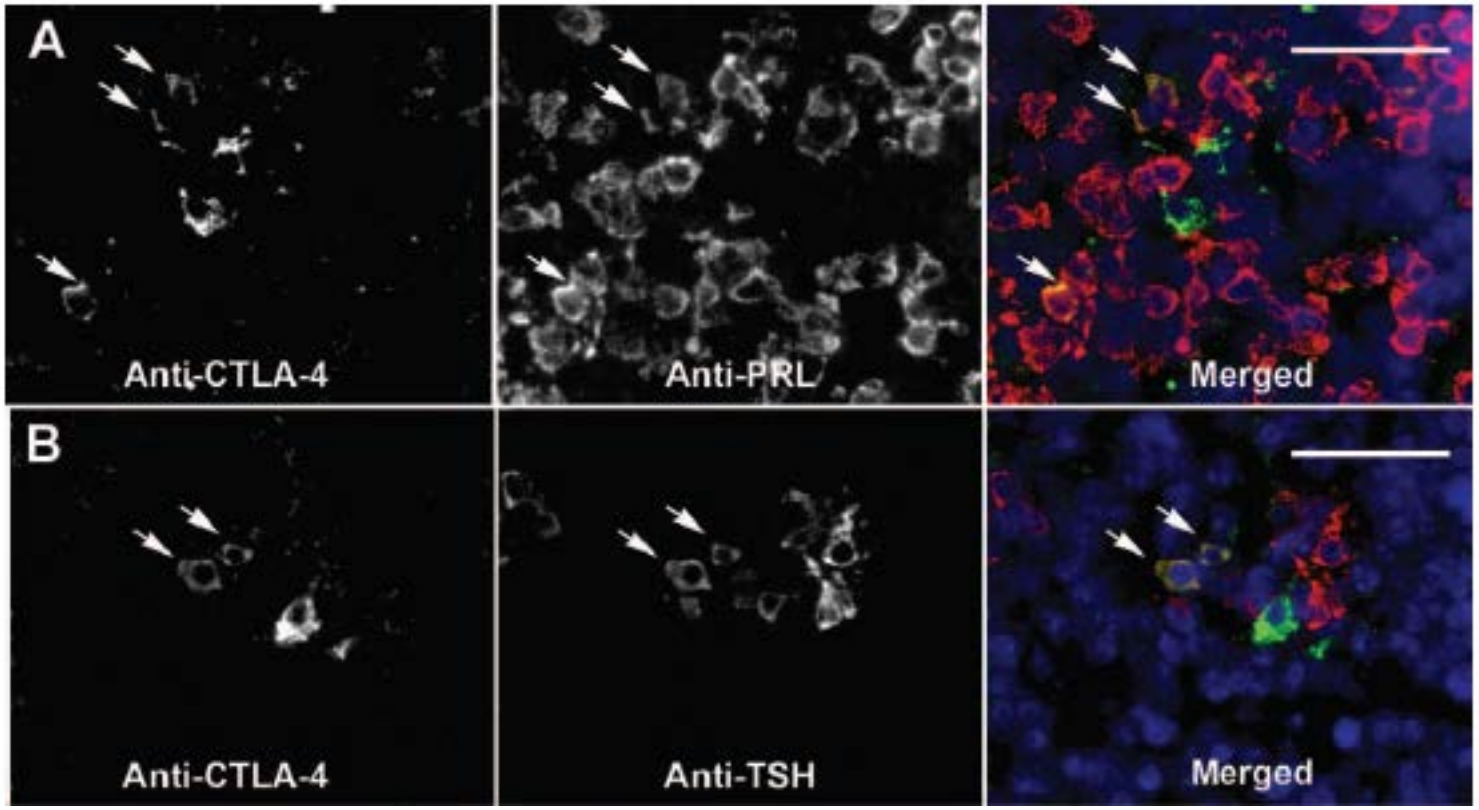
Direct heavy metal-conjugation on mutated streptavidin having cysteine residues (Newell EW et al., Nature Biotech 2013)

⇒ higher specificity with barcoding technology (and smaller sample size)

Tissue/drug interactions?

Pituitary Expression of CTLA-4 Mediates Hypophysitis Secondary to Administration of CTLA-4 Blocking Antibody

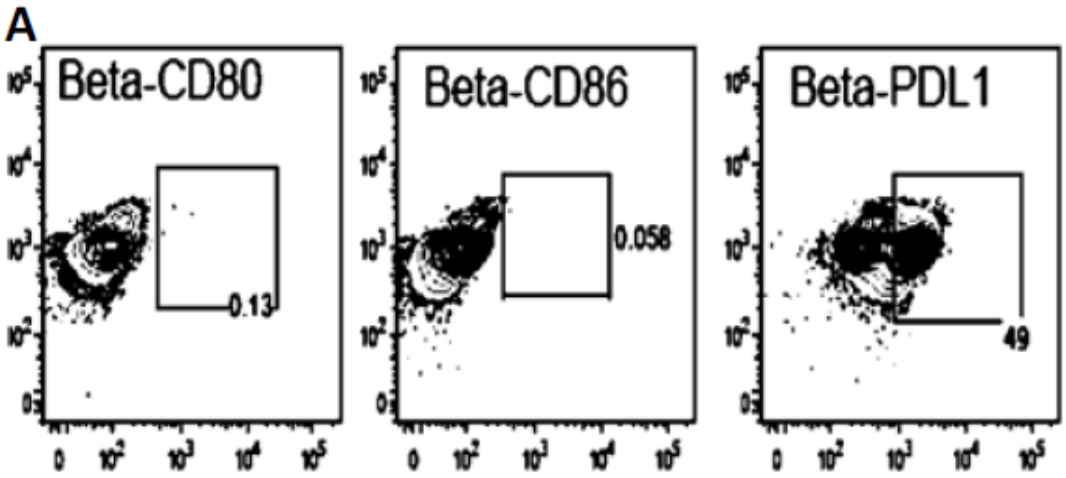
Shintaro Iwama,[1,2] Alessandra De Remigis,[1] Margaret K. Callahan,[3,4] Susan F. Slovin,[3,4] Jedd D. Wolchok,[3,4,5] Patrizio Caturegli[1,6]*

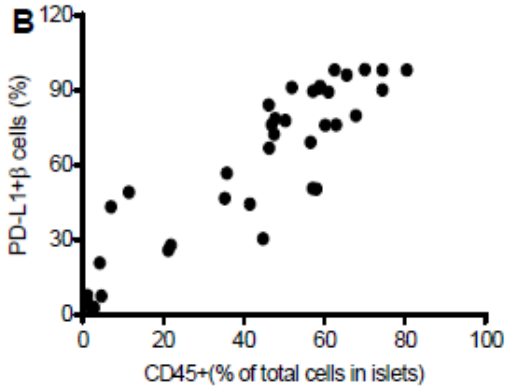


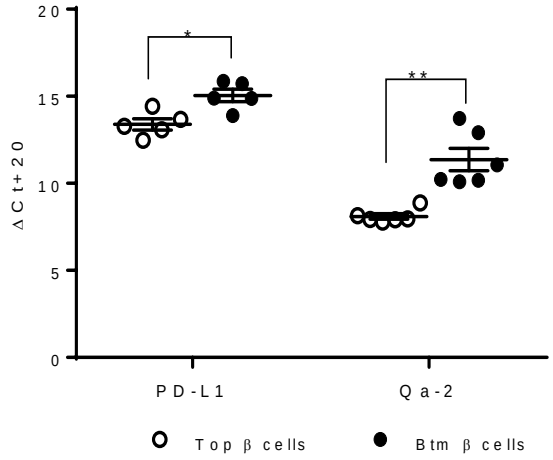
CTLA-4 staining was found on 2±1% of PRL-secreting cells and 3±2% of the TSH-secreting cells. It was not seen on GH, ACTH, FSH, or S100+ cells.

Why is autoimmune diabetes only seen with anti-PD-1/PD-L1 antibodies while thyroiditis is seen with PD-1 and CTLA-4 checkpoint inhibitors?

The new subpopulation has reduce expression of diabetes antigens and increased expression of immune inhibitory ligands







(Rui et al, Cell Metabolism, 2017)

Conclusions

- Autoimmune endocrine adverse events are common after checkpoint inhibitor therapies. They can result in considerable morbidity.
- The reasons why some but not others develop these adverse events require further studies:
  - There appears to be selection of target organs based on the checkpoint inhibitor – hypophysitis is more common with anti-CTLA-4 mAb, thyroid abnormalities are more common with anti-PD-1/L1 antibodies, and diabetes is exclusively with anti-PD-1/L1 antibodies.
  - Endocrine events are more common with combinations.
  - Changes in T, B cells and Tregs may be found but the relationship between these findings and risk or development of the adverse events will require further studies.
  - Tissue specific changes and associated inflammation may be important determinants of proclivity to immune attack.
- Understanding the pathogenesis of checkpoint inhibitor associated adverse events may shed light on normal immune tolerance and suggest ways to prevent autoimmunity in this setting or spontaneous disease.

Acknowledgements: The people who did this work :

- Ana Perdigoto, MD
- Angeliki Stamatouli, MD
- Harriet Kluger, MD
- Joyce Rui, PhD and Songyan Deng, MD
- Paula Preston-Hurlburt and Pam Clark
- Eric Meffre, PhD
- Collaborators at UCSF:
  - Zoe Quandt, MD
  - Mark Anderson MD PhD
  - Jeff Bluestone PhD

- Funding
  - ITN
  - TrialNet
  - NIDDK/HIRN
  - NIAID
  - JDRF
  - Brehm Coalition
  - Howalt family