2012

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• His lumbar puncture was inflammatory, and his symptoms progressed towards the inability to take anything by mouth, and deep encephalopathy
2012

- He was diagnosed with a presumed autoimmune disorder and was treated with immunotherapy
2012

- He was diagnosed with a presumed autoimmune disorder and was treated with immunotherapy

- He was subsequently diagnosed with anti-Tr autoimmune/paraneoplastic encephalitis
Autoimmune/Paraneoplastic syndromes

- Auto-antibody production is a hallmark of neurological paraneoplastic syndromes
- There are over 17 identified antibodies
- Usually these disorders are associated with a specific tumor type:
  - Ovarian teratomas in NMDAR
  - Testicular tumors in Ma2
  - Thymoma in MG
  - Hodgkin’s Lymphoma in Tr.
  - Ovarian cancer in Yo
  - Lung cancer in LEMS
  - No tumor in GBS
  - SCLC in Hu

Graus et. al., 1997
Bernal et. al. 2003

Dalmau, 2008
History of Tr

- In 1976 Trotter et al. described a staining pattern of sera of patients who had paraneoplastic cerebellar degeneration (PCD), 90% of whom had Hodgkin’s Lymphoma
- Anti-Tr named after Trotter

de Graaf, 2012
Anti-Tr

- There was one report identifying the target of Anti-Tr as DNER (de Graaff 2012)
Anti Tr antibodies are actually anti-DNER

HEK293 T cells were transfected to express DNER and immunostained with patient CSF (1:20; A) and a goat DNER antibody (B). Merged images show the patient CSF in red, the goat antibody in green and nuclei stained blue with DAPI (C). Note that patient CSF reacts strongly with DNER-expressing cells. Scale: 10 μM.

Greene, 2014
<table>
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<tr>
<th>Sera</th>
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Greene, 2014
Greene, 2014

**Labeling of Fixed Cells**

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**Labeling of Live Cells**

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Antibodies to Delta/Notch-like Epidermal Growth Factor-Related Receptor in Patients With Anti-Tr, Paraneoplastic Cerebellar Degeneration, and Hodgkin Lymphoma

Maxwell Greene, MD; Yongjie Lai, MD; Nicolle Baella; Josep Dalmau, MD, PhD; Eric Lancaster, MD, PhD
DNER

- Delta/Notch-like EGF related receptor
- Discovered in 2002
- Was reported to signal Notch 1

Eiraku 2002
Eiraku 2005
Rationale for investigating DNER

- DNER is CNS specific
- Eiraku et al. 2005 reports Notch 1 signaling
- Purkinje cells contain DNER while the adjacent cell type, Bergmann glia, contain Notch 1
- There is evidence in many other paraneoplastic neurologic syndromes that the antibodies are directly pathogenic (cell surface antibodies)
- The dysfunction in anti-Tr patients is due to Purkinje cell loss

Eiriku et. Al. 2002
What is Notch?

- Notch receptors and their ligands interact to signal apposing cells
- Widely present in metazoans to signal cell fate
- Notch implicated in blood cancers, arteriopathies (CADASIL), GVHD
What is Notch anyway?
What is Notch anyway?
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What is Notch anyway?
What is Notch anyway?
Eiraku 2005 evidence that DNER is a Notch ligand

- Myoblast differentiation assays
- Luciferase experiments
- Extracellular domain of DNER binds to Notch 1

- Cell surface binding of DNER to Bergmann glia
- DNER deficient mice have abnormal Bergmann glia
Structure of DNER

Kopan Review, 2009
Figure 1. Four separate luciferase experiments A-D.
Figure 2. HEK293T cells were transiently transfected to express Dll1 (A; red) or DNER (D; red) and then treated in culture with pre-clustered Notch-fc (B and E; green). Merged images, with nuclei of cells labeled with DAPI in blue, are shown in C and F. Scale 10 μM.
Thank you

- Warren Pear, MD, PhD
- Eric Lancaster, MD, PhD
- Will Bailis, PhD
- Kostandin Pajcini, PhD
- Yongjie Lai, MD
- Jon Aster, MD, PhD
- Steve Scherer, MD, PhD
- Joey and the Aster Lab
- Lanwei and everyone in the Pear Lab
- The Lancaster and Scherer lab