A Novel Immune Approach to Fight Neurodegeneration
Two Sides of the Same Coin

Immune Response is Critical, yet Opposite in these Disorders
Immune Systems Role in Disease

**Oncology**
- *Genetic* aberrations & *environment* lead to incorrect cell cycle development
- Tumor growth unchecked
- Immune system does not recognize tumor cells as foreign
  - *i.e.* underactive cancer-targeting mechanisms

**Neurodegeneration**
- *Genetic* aberrations & *environment* lead to incorrect protein production
  - Limited GWAS
- Alternative disease triggers are likely
- Immune system does incorrectly recognize neurons as foreign
  - *i.e.* overactive autoimmunity
Disease Progression & Treatment

Genetic Predispositions

Pre-Diagnosis/Early Onset

Alzheimer’s, Parkinson’s, ALS, MS

Immune Health

Environmental Triggers

Preventative Measures or Treatments

Wellness

Neurotransmitter Modulation

FMT

Young blood transfusion

DBS

Clearing Plaques Has not Worked

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Immunology Strategies for Targeting Neurodegeneration

CNS Plaque & Tangle Inhibitors
Traditionally viewed as cause of degeneration

Target Innate CNS Immune Cells

Pro-Inflammation  
Plaque Clearance

Modulate Peripheral Immune Response

Pro-Inflammation  
Anti-Inflammation  
T cell Function

Degenerating Neuron

Pro-inflammatory

Glial Cells

T Cells

CNS Peptides & Biologics

Sm. Molecules & Abs

BBB

PERIPHERY
Immunology Strategies for Targeting Neurodegeneration

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Target Innate CNS Immune Cells

Modulate Peripheral Immune Response
A DIFFERENT APPROACH: TARGET T CELLS DIRECTLY

Rebalance Immune System *without* Immunosuppression
Autoimmunity in Parkinson’s Disease: 
α-Synuclein & the Adaptive Immune Response...

1. Direct Neuronal Death
   - Pro-inflammatory Factors
     - IFN-γ, IL-17, TNF-α, IL-1β, IL-6, ROS

2. Indirect Neuronal Death
   - Glial Cells
   - CNS
   - BBB
   - PERIPHERY

Direct & indirect neuronal death pathways induced by Tresps

References:
- Sulzer et al. Nature 546, 656–661 (29 June 2017)
- Abad & Tan J Mol Neurosci 2018) 66:102–113
...Modulating Peripheral Immune System is Protective


Shifting T cell profiles from Tresp to Treg is neuroprotective

VPAC$_2$ Receptor

Cytotoxic / Responder T cell (Tresp)

Regulatory T cell (Treg)


Sulzer et. al. Nature 546, 656–661 (29 June 2017)

Abad & Tan J Mol Neurosci 2018) 66:102–113
LBT-3627 Increases Peripheral Treg Function & Protects Neurons In Vivo

Peripheral Immune Function

- Tresp:Treg
- % Inhibition ± SE
- PBS
- VIP
- LBT-3393
- LBT-3627

* p<0.05 PBS, VIP

* p<0.05 PBS, VIP

Neuroprotection

- Neuron number ± SD
- MPTP
- No MPTP
- Dopaminergic (TH+)
- Non-dopaminergic (TH-)

- PBS
- MPTP
- VIP
- LBT-3393
- LBT-3627

* p<0.05

Dopaminergic Neuron Survival
- n=8

Treg Enhancement = A New Paradigm for Neuroprotection

Olson et al. J Neuroscience 2015 - Mouse MPTP Model with splenocyte adoptive transfer
VIP: Vasoactive Intestinal Peptide, LBT-3393: VPAC1 selective, LBT-3627: VPAC2 selective
## LBT-3627 Efficacy To Date

### Preclinical

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<th>6-OHDA rat</th>
<th>AAV A53T (α-syn)</th>
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### Clinical

- LBT-3627 restores immune function → Paralleled by neuron survival in multiple preclinical Parkinson’s models
- Currently working to apply this strategy to other neurodegenerative disorders
Parkinson’s Immune Biomarker Study: Identify & Stratify for Intervventional Trial

- Multiple panels of protein markers by cell type
- In vitro cytokine profiling
- In vitro Treg function
- UPDRS exam
- History & Health Qs
- Standard labs
- Real time collection
- Quantitative analysis
- Novel protein analytes

1) Clinical diagnostic
2) Evaluation of immune function
3) I/E tool for clinical trials

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