OX40L-Jagged-1-Fc chimeric fusion protein for the in vivo expansion of T-regulatory Cells

Bellur S. Prabhakar. MSc. PhD

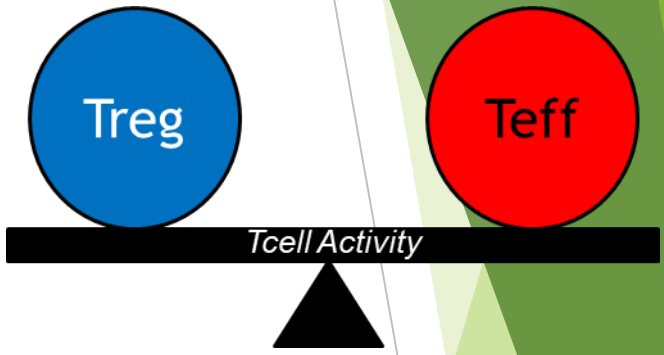
T-REGULATORY CELL (TREGS) DOWNREGULATION IN AUTOIMMUNE DISEASES

- T-regulatory cell (Tregs) downregulation has been implicated in the pathogenesis of many autoimmune diseases.
- The NIH estimates 23.5* million Americans suffer from autoimmune diseases (AARDA).
- Autoimmune diseases include but are not limited to:
  - Type 1 diabetes (T1D)
  - Rheumatoid arthritis
  - Hashimoto's Thyroiditis
  - Lupus
  - Allergic diseases
  - Transplant rejection

Source: Children's Hospital Los Angeles

Mechanism of Tregs downregulation in Autoimmune Diseases

- Tregs downregulation causes the self-reactive lymphocytes to escape natural control, thereby triggering the immune system to attack self.
- Current immunosuppressive therapies non-specifically suppress the body's defense/immune system, resulting in debilitating side effects and a very poor quality of life.
- Currently available approaches are not curative, are nonspecific, are non-targeted, and have a narrow therapeutic window (efficacy – toxicity trade-off).
- There is a dire need for a more targeted, safe & accepted approach.

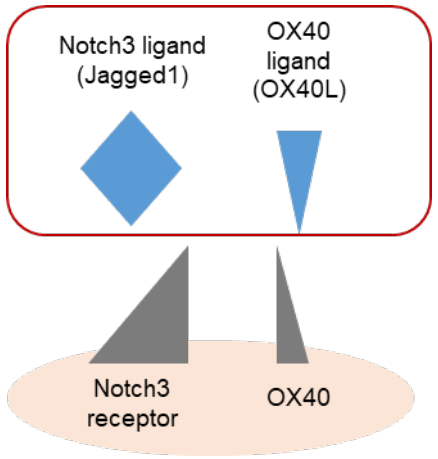


- T-reg cells protect the body from rogue T-eff cells that would otherwise attack the body (e.g., by killing insulin producing beta cells).
- The balance of activity between Treg and Teff is necessary to maintain a properly functioning immune system.
  - Treg > Teff = immunosuppression
  - Teff > Treg = autoimmunity

Targeting Two Receptors OX-40L & Jagged-1 (Notch3)

- Our therapeutic approach targets both Notch3 and OX40 receptors on Tregs
- Selectively expands functional Treg cells *in vitro* and *in vivo*
- 3 Potential Approaches to target both receptors

Combination therapy



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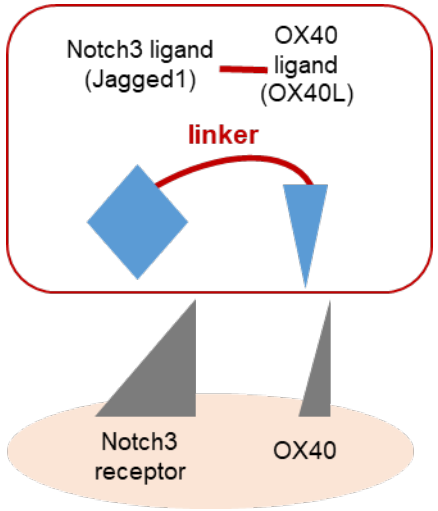
Single therapeutic (linked)



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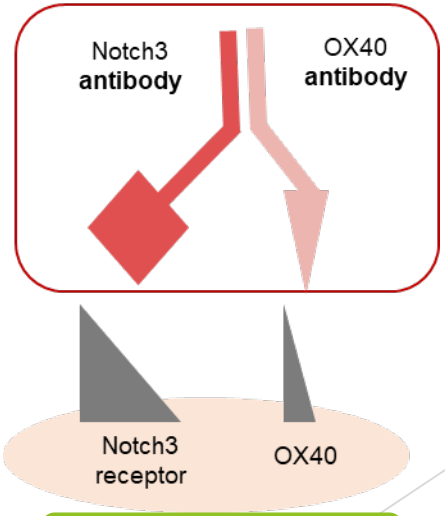
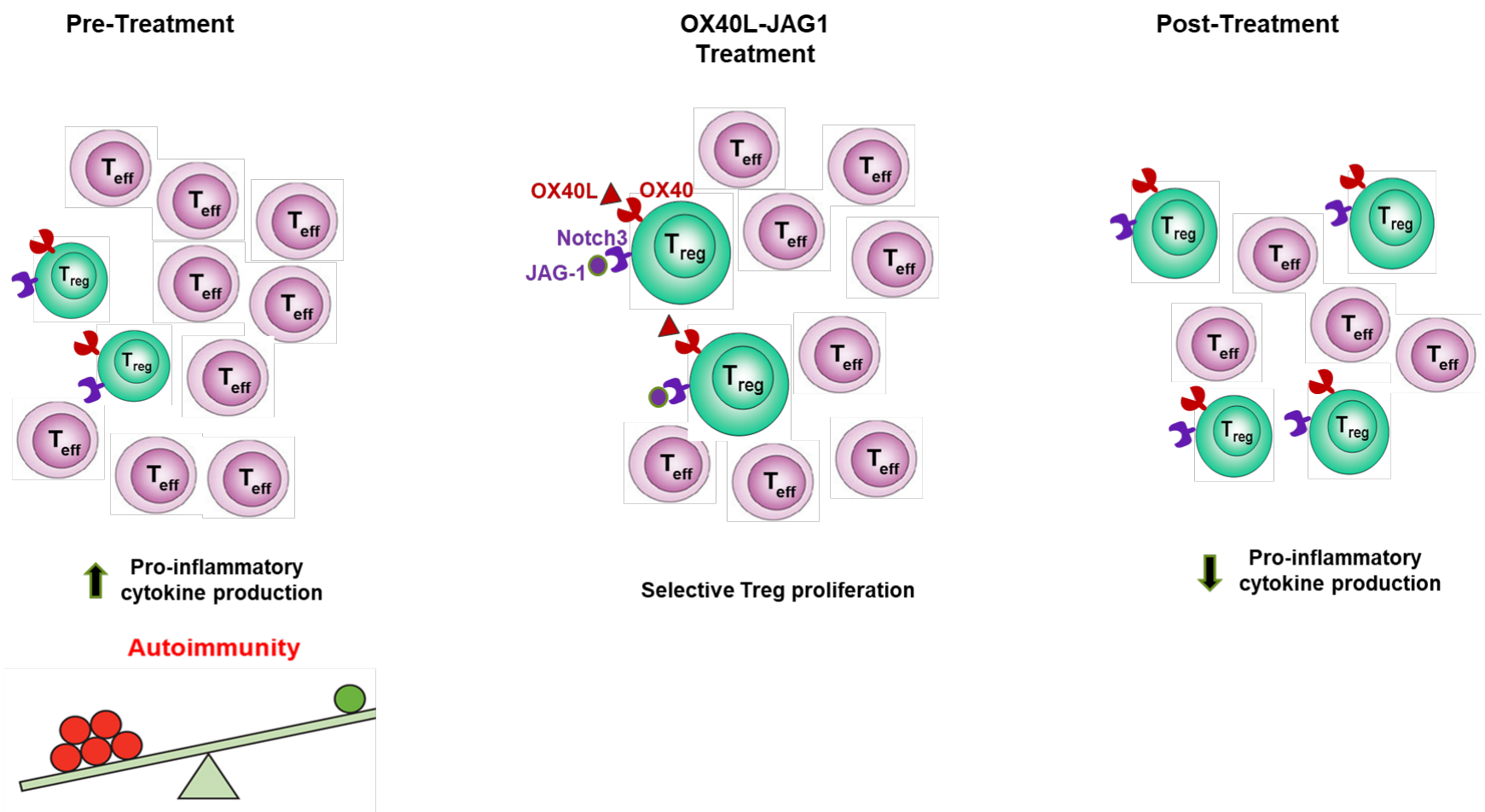
Bi-specific antibody



Future Product

Targeting Two Receptors (OX-40 & Notch3)



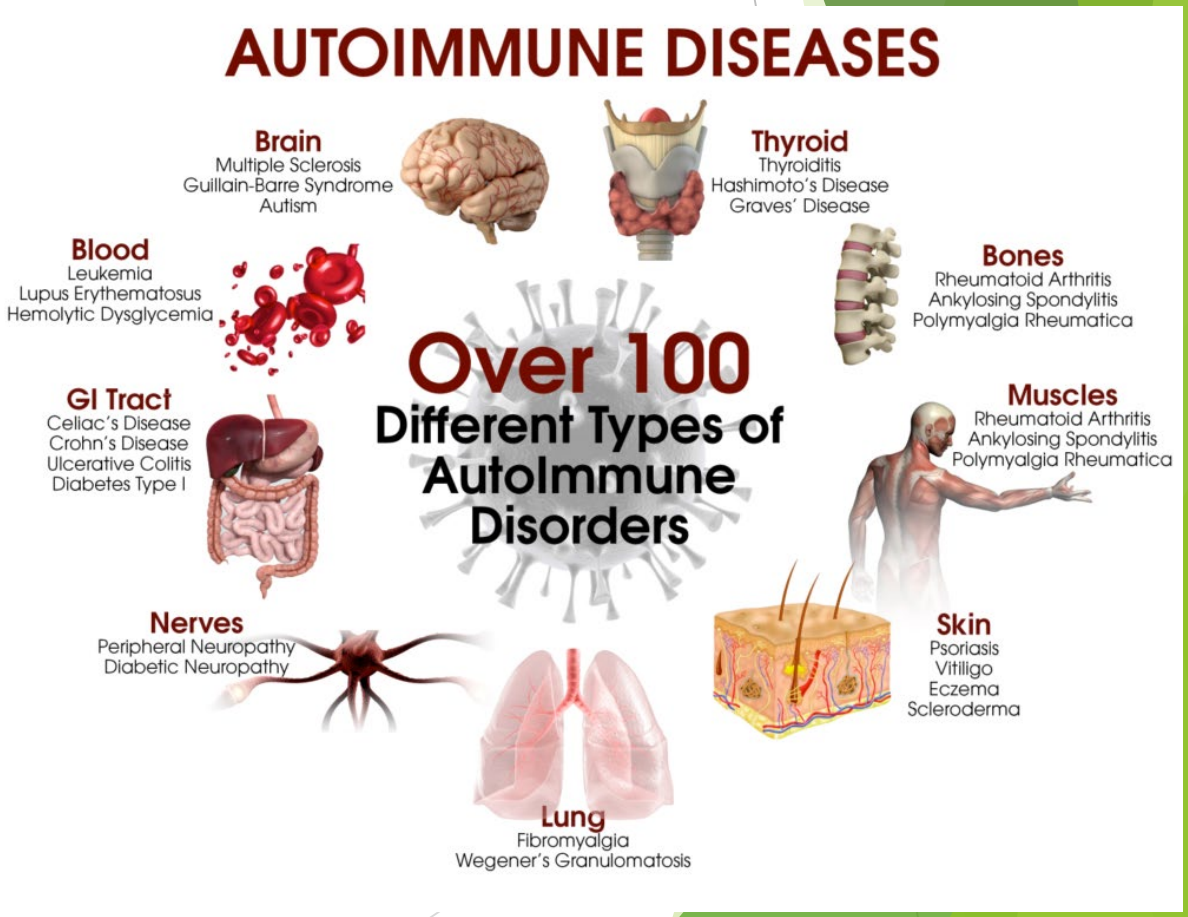
Our OX40L-JAG1 chimeric protein:

- Selectively expands Tregs, and not pathogenic T effector cells (Teff)
- Restores homeostatic balance to the immune system
- Does not cause general immune suppression
- Suppresses Autoimmune diseases (e.g. T1D and HT)

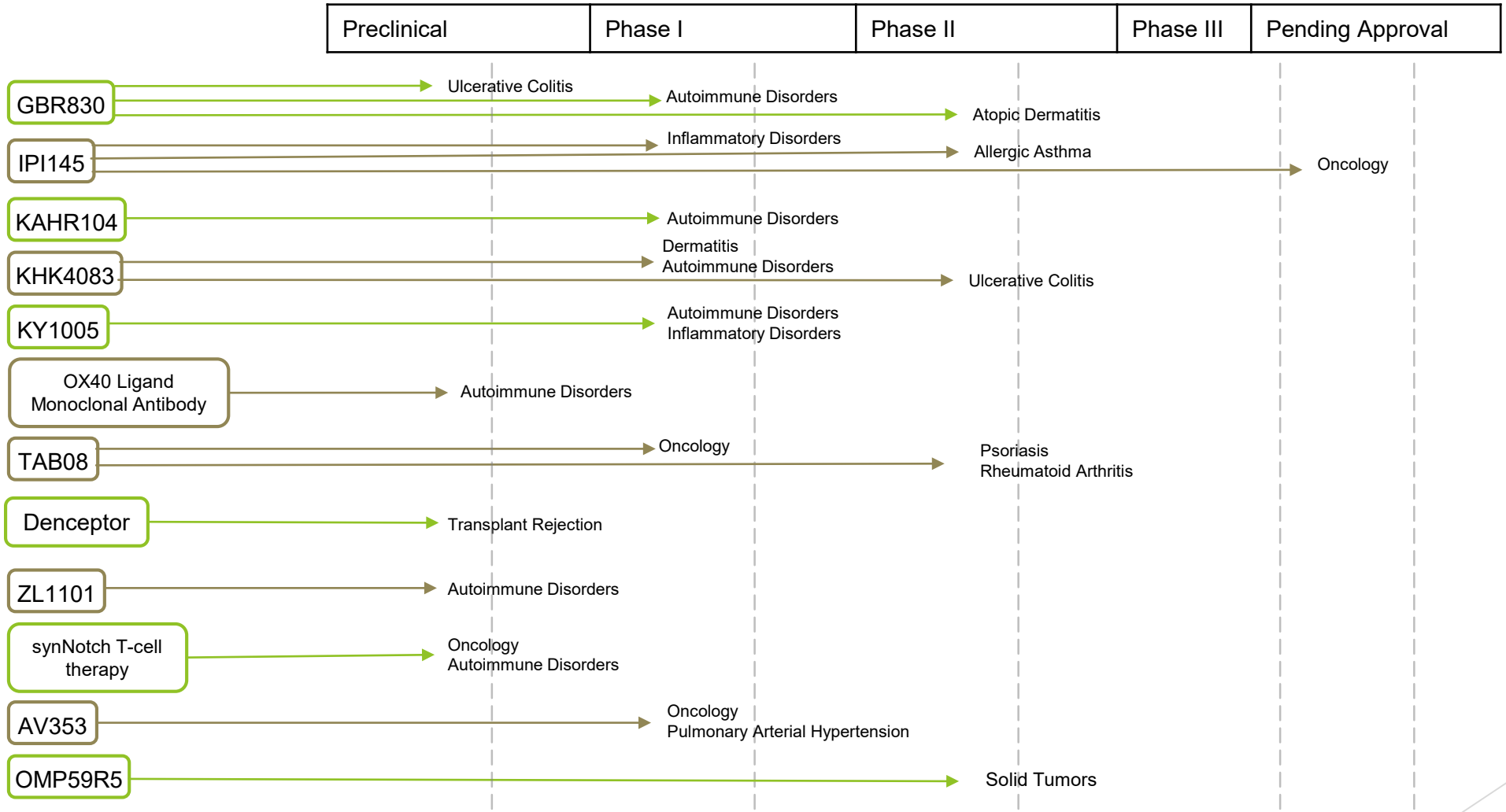
PROJECT SIGNIFICANCE

Autoimmune Diseases: no cure and only limited symptomatic relief

- Existing Treatments (anti-TNF alpha, anti-IL1β, anti-CD3, anti-B220, and anti-CTLA4):
  - Not curative
  - Non specific
  - Cause general immune suppression
  - Debilitating side effects
  - Poor quality of life
  - Increased risk of serious infections and malignancies
  - Narrow therapeutic window (efficacy – toxicity trade-off)



Competitive Advantage

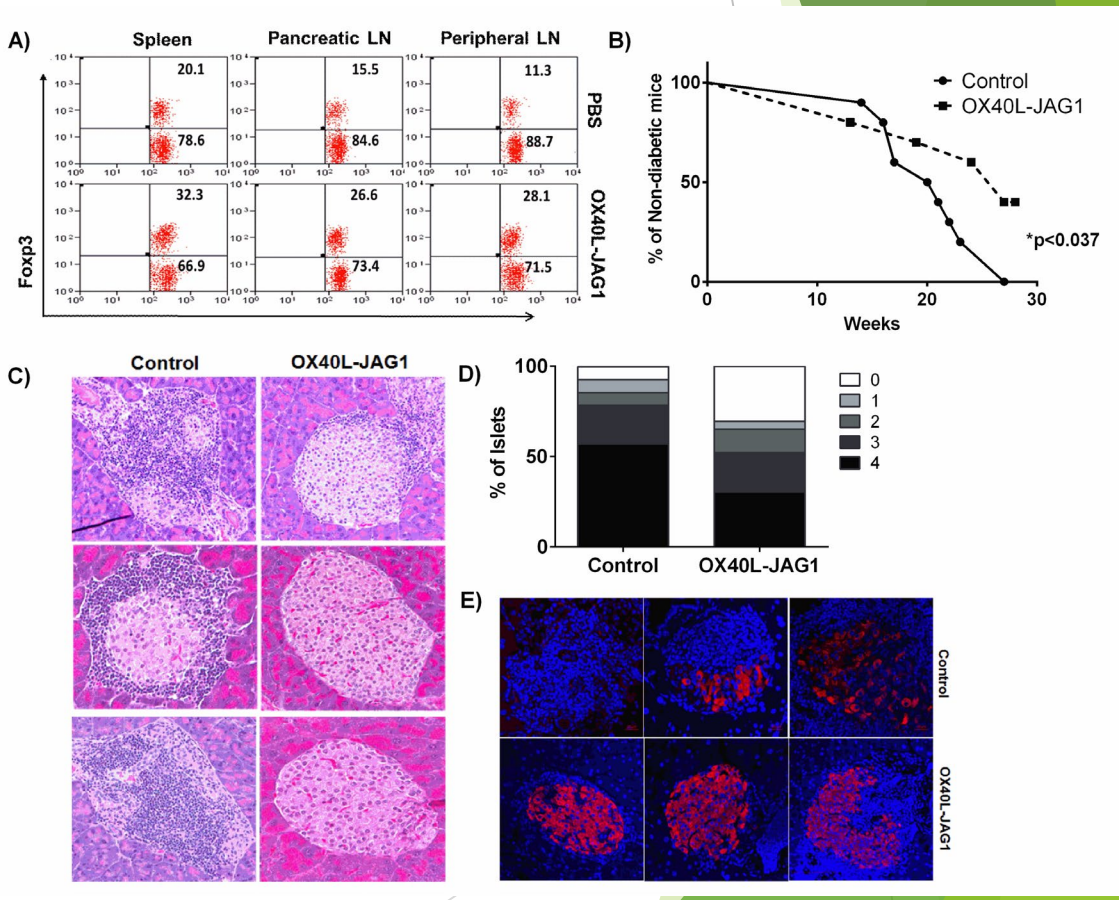


- Current research validates both OX40 and Notch3 as targets
- Current leads target either OX40 or Notch3 separately, but no other drugs targeting both
- Currently no therapies on the market for autoimmune disorders

Combination of OX40L and Jagged1 treatment: Preliminary diabetes results

1-NOD mice treated with soluble OX40L and Jagged1 (diabetes)

- Significantly delays the onset of diabetes
- Substantially reduces insulitis
- Arrests insulin producing islet beta cell destruction
- Increases anti-inflammatory cytokines (e.g., IL10, TGF-ß)
- Decreases pro-inflammatory cytokines (e.g., IL1ß, IFNγ)



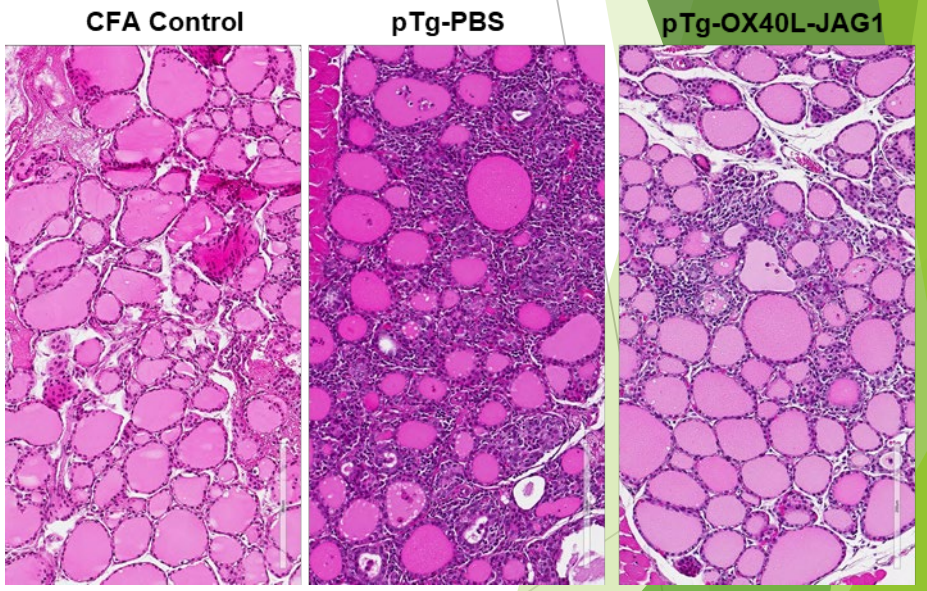
Combination of OX40L and Jagged1 treatment: Preliminary thyroiditis results

1-NOD mice treated with soluble OX40L and Jagged1 (thyroiditis)

- Significantly delays the onset of Thyroiditis
- Arrests Thyroid hormone producing thyrocyte destruction

Mechanism of action

- Increases the number of Functional Tregs
- Suppresses autoimmune response
- Increases anti-inflammatory cytokines (e.g., IL10, TGF-ß)
- Decreases pro-inflammatory cytokines (e.g., IL1ß, IFNγ)



Value Proposition

- **Scientific:**
  - Selective expansion of Tregs
  - Specific down regulation of effector T-cells
  - Increases suppressor cytokines
  - Decreases pro-inflammatory cytokines
  - Follows natural pathways of immune regulation
  - Restores homeostatic balance to the immune system
  - Avoids adverse effects of generalized immunosuppression
- **Protection and manufacturing**
  - Novel composition and method of action
  - Recombinant Proteins – product flexibility
  - Scale-Up
- **Regulatory**
  - Modest investment with multiple licensing opportunities
  - Several exit opportunities along the development pathway

DEVELOPMENT PLAN

- Determine primary market
- Determine pathway for product type (separate Notch3 and OX40 ligands, a linked Notch3-OX40 ligand, or Notch3-OX40 bi-specific antibody)
- Determine best regulatory path forward for indication (Investigational New Drug application to FDA)
- Investigate orphan drug opportunities (Myasthenia gravis and multiple sclerosis)
- Determine manufacturing possibilities
- Determine other potential issues

Summary

- Autoimmune diseases – Over 80 conditions that afflict millions: chronic, costly, and very high morbidity
- Current therapies are broadly immunosuppressive and non-specific
- OX40L and Jag-1 are already proven sufficient for selective Treg expansion *in vitro* and *in vivo*
- OX40L and Jag-1 are already proven sufficient to protect against development of Type-1 diabetes and Hashimoto's thyroiditis