Continuous IL-10 Therapy Prevents Liver Damage in Preclinical Model of Autoimmune Hepatitis

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Introduction: Autoimmune Hepatitis

➢ Autoimmune hepatitis (AIH) results from a breakdown in immune tolerance leading to production of pro-inflammatory cytokines by autoreactive T-cells and subsequent hepatocyte destruction.

➢ While AIH patients benefit from immunosuppressive agents such as prednisolone and azathioprine, the chronic nature of this disease requires life-long systemic administration often resulting in serious adverse effects and associated morbidities.

➢ Immunomodulatory cytokines, such as IL-10, are well established preclinically as a way to treat autoimmune diseases including AIH.

➢ However, while these cytokines have high potency, they have an extremely short half-life, making it challenging to treat with the protein therapeutic.
Shielded Living Therapeutics™ Platform

- **Non-viral, cell-based, modular platform** was designed to address two major challenges of allogeneic cell therapy:

  - **Cell-to-cell interaction and rejection**
  - **Pericapsular fibrotic overgrowth (PFO)**

**Physical shield (2-compartment, modified alginate sphere)**

- **Inner Compartment:**
  - Genetically modified allogeneic cells expressing therapeutic protein
  - Modified alginate designed to optimize cell function

- **Outer Layer:**
  - Modified alginate chemically linked to small molecule to minimize PFO

**Small-molecule conjugated alginate in outer layer**

1.5 mm

Bright field microscope image of a typical sphere
Allogeneic Cells Shielded by the Two-Compartment Alginate Spheres Are Immunologically Silent

**Two-Compartment Sphere Architecture Preserves Cellular Viability In Vivo**

**Allogeneic Cells in Two-Compartment Spheres Do Not Invoke Any Inflammatory Responses**

Because the SLTx platform is immunologically silent, it provides an ideal solution for the treatment of autoimmune diseases.

Allogeneic Balb-3T3 cells encapsulated in SLTx spheres and implanted in immunocompetent C57Bl/6 mice for 7 weeks.

SLTx platform shields allogeneic cells from immune system, as indicated by No changes in immune cell number and in cytokine levels between the groups Balb 3T3 spheres, empty spheres and sham surgery.

[Graphs and images showing cell viability and immune response]
The Innovative Platform Can Overcome Pharmacokinetic Barriers Preventing Therapeutic Use of Cytokines

Genetically engineered cells

Encapsulation

Intraperitoneal administration

Sustained Production of mIL-10 by SLTx Encapsulated Genetically Engineered Balb 3T3 in Plasma of C57Bl/6 Mice

Mouse cell

Nutrients

Therapeutic proteins

Fast Fact:
10,000 to 80,000 cells fit into one sphere. Each sphere is 1.5 mm in diameter.

Protein secretion and bioactivity are tested at every step

SLTx platform provides durable production of therapeutic concentrations of IL-10, obviating the need for frequent administrations
Sustained Controlled Administration of IL-10 Can Restore Immune Homeostasis

Sustained production of mIL-10
- Therapeutic levels at disease proximal sites

Sustained intraperitoneal administration of IL-10 protects from inflammatory liver diseases

Drivers of Inflammation:
- Con-A
- Balb 3T3-mIL10

Encapsulation of mIL-10-expressing cells

Antigen Presentation

Proinflammatory Cytokines
- IFNγ
- TNFα
- IL-2

CD4+ T Cells

Macrophage

MHCI

CD86

↓ IL-6

↓ TNFα

↑ CD206

Dendritic Cells

MHCI

CD86

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Sustained IL-10 Administration Protects Mice from Concanavalin-A Induced Liver Inflammation

**Liver Histology (H&E)**

- **Control - Saline**
- **Control – ConA**
- **mrl10 – ConA**
- **IL-10 Spheres – ConA**

**Plasma ALT Levels**

- **Concanavalin A (ConA)**
- **-**
- **+**
- **++**
- **+++**

**Liver Necrosis**

- **Control - Saline**
- **Control – ConA**
- **mrl10 – ConA**
- **IL-10 Spheres – ConA**

**Liver Necrosis Score (0-4)**

- **-**
- **+**
- **++**
- **+++**
Sustained IL-10 Administration Limits Concanavalin-A Induced Pro-Inflammatory Immune Responses

**Plasma Cytokine Levels**

- **IL-10**
  - Saline
  - Control
  - rmIL10
  - 3T3-rmIL10

- **IFN-γ**
  - Saline
  - Control
  - rmIL10
  - 3T3-rmIL10

**Peritoneal Macrophages Modulation**

- **CD206**
  - Saline
  - Control
  - rmIL10
  - 3T3-rmIL10

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Non-Confidential
Our innovative modular platform **shields the genetically modified allogeneic cells** from the immune system and foreign body response.

The encapsulated engineered cells produce a **sustained level of functional IL-10**.

IL-10 produced by cells:

- **restores immune homeostatic level** by modulating peritoneal macrophages towards an anti-inflammatory phenotype.
- **suppresses the production of proinflammatory cytokines** even when Con-A induces their upregulation.

Finally, sustained IL-10 production results in **protection of mice from acute liver injury** induced by Con-A.

Sustained controlled administration of IL-10 using this modular platform could provide a **functional cure to immune mediated liver inflammatory diseases**.
Thank you for your attention!

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