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Institute of Medical Research
DISCOVERIES FOR HUMANITY

Rethinking CD52: a therapy for autoimmune diseases

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CD52Fc A new therapeutic for autoimmune diseases

- **Unique immune checkpoint therapeutic CD52 fused with Fc with granted patent claims**
  - Inhibits T cell activity
  - Sequesters HMGB1 to reduce its pro-inflammatory activity
  - Immune homeostasis likely to have fewer side effects than immunosuppressives
- **Target validated in humans**
  - Diminished CD52Hi T cells in type 1 diabetes
  - Antibody to CD52 increases de novo onset of autoimmunity
- **Animal data supports efficacy in models** (more planned)
  - Type 1 diabetes
  - Multiple sclerosis
  - Sepsis
  - Arthritis

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Despite therapeutic progress, an unmet medical need remains in immune disorders

- **Big Market**: Immune-inflammatory disorders are responsible for substantial morbidity and mortality, and affect at least 4% of the global population.
- **Current B cell therapies have limitations** in their efficacy and side-effects; and certain patient populations remain underserved.
- **Immune disorders mediated by activated T cells need to be addressed**.
  - These include systemic lupus erythematosis, psoriasis, rheumatoid arthritis, inflammatory myositis and type 1 diabetes, among others.

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CD52 is a natural immune checkpoint
Evidence

Clinical Evidence

- CD52hi T cells act as suppressor T cells in healthy humans, and are distinct from natural regulatory T cells
- Humans **with type 1 diabetes** had a lower frequency and diminished function of CD52hiCD4+ T cells responsive to the autoantigen GAD65
- Depletion of CD52hi cells (CD52-depleting Campath antibody therapy for certain forms of leukemia) is associated with **de novo onset of autoimmune disorders**

Preclinical Evidence

- In diabetes-prone mice of the non-obese diabetic (NOD) strain, transfer of lymphocyte populations depleted of CD52hi cells resulted in a substantially accelerated onset of **diabetes**.
- **Responses to LPS** are enhanced in CD52 knockout mice

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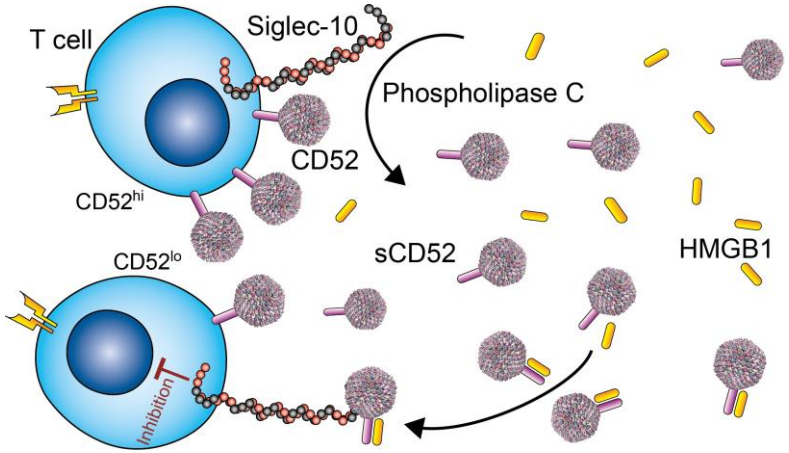
CD52 is a natural immune checkpoint Mechanism

- Activated T cells release soluble CD52, a glycopeptide
- Soluble CD52 captures and inactivates HMGB1
- CD52/HMGB1 binds to *suppressor* Siglec-10 receptor
- Siglec-10 is expressed on activated T cells
- Soluble CD52 also suppresses innate immune cells by inhibiting signaling though NF-kB



Soluble CD52 acts on activated T cells and other immune cells by mimicking a natural physiological mechanism of immune homeostasis, thus likely to have fewer side-effects than depletion of B cells or other broad immune suppression

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The team and expertise

- The team: Len Harrison and Esther Bandala-Sanchez, and collaborators with expertise in glycan chemistry and mass spec analysis.
- Unique expertise in CD52 structure-function and biology, production-purification.
- Availability of animal models of inflammatory-immune disease.
- CD52-related assays/resources/expertise to advance development towards clinical trials and/or other development milestones.
- History of conducting multiple Phase 2 clinical trials.

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CD52-Fc exerts a dual mechanism of action targeted to activated T cells and HMGB1

- CD52-Fc data on human cell systems *in vitro*

  1. CD52-Fc inhibits T-cell activation by suppressing TCR signaling to inhibit T cell proliferation and cytokine secretion

  – CD52-Fc induces antigen-specific anergy in T cells

  – CD52-Fc binds to Siglec-10 on T cells via its glycan moiety

  2. CD52-Fc bound to HMGB1 **suppresses HMGB1 pro-inflammatory activity**

  – The soluble inflammatory mediator HMGB1 is required for CD52-Fc binding to Siglec-10 and immune suppressive activity

- CD52-Fc supportive POC data in mouse models
  – Sepsis, multiple sclerosis, type 1 diabetes, induced arthritis (KBxN model)
  – Plans to test CD52-Fc in arthritis and psoriasis models in near future

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Intellectual Property

- Fully owned patent families in all major markets
  - Granted claims to novel soluble CD52-based therapy
  - Method of treatment for immune disorders, inflammatory diseases
  - Normal expiry 2032 to 2033
- Currently protecting further IP related to novel insights on structure – function relationship
  - Native CD52 is a mixture of several glycosylated forms of glycopeptide
  - Receptor ligation and bioactivity is related to specific glycosylation forms

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What we are looking for

- An industry partner with:
  - expertise in glycosylated protein engineering
  - commercial interest in immune-inflammatory disorders
- To co-develop this novel immune checkpoint inhibitor, design a pathway to clinical trials and select a target indication
- Next de-risking milestones
  - technical development to ensure production of target glycoforms
  - exploration of chemical synthesis
  - generation of preclinical data in target indications

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Selected Publications

- Bandala-Sanchez E, Zhang Y, Reinwald S, Dromey JA, Lee B-H, Qian J, Böhmer RM, Harrison LC (2013). T cell regulation mediated by interaction of soluble CD52 with the inhibitory receptor Siglec-10. *Nat Immunol* 14:741-748.
- Rashidi M, Bandala-Sanchez E, Lawlor KE, Zhang Y, Neale AM, Vijayaraj S, O'Donoghue R, Adams TE, Wentworth JM, Vince JE, Harrison LC (2018). CD52 inhibits Toll-like Receptor activation of NF-kB and triggers apoptosis to suppress inflammation. *Cell Death Diff* 25:392-405.
- Bandala-Sanchez E, Bediaga NG, Goddard-Borger ED, Ngui K, Naselli G, Stone NL, Neale AL, Pearce LA, Wardak A, Czabotar P, Haselhorst T, Maggioni A, Hartley-Tassell LA, Adams TE, Harrison LC (2018). CD52 glycan binds the pro-inflammatory B box of HMGB1 to engage the Siglec-10 receptor and suppress T-cell function. *Proc Natl Acad Sci (USA)* 115(30):7783-7788.
- Shathili AM, Bandala-Sanchez E, John A, Goddard-Borger ED, Thaysen-Andersen M, Everest-Dass A, Adams TE, Harrison LC, Packer NH (2019). Specific sialoforms required for the immunosuppressive activity of human soluble CD52. *Front Immunol* (in press).

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