Resetting the immune system for autoimmune and inflammatory diseases

Development of a first-in-class antibody to deplete chronically stimulated T cells for autoimmune disease

Carrie Lucas, PhD
Associate Professor, Immunobiology
Associate Director, Human and Translational Immunology Program
Yale School of Medicine

Expertise and novel insights of the team

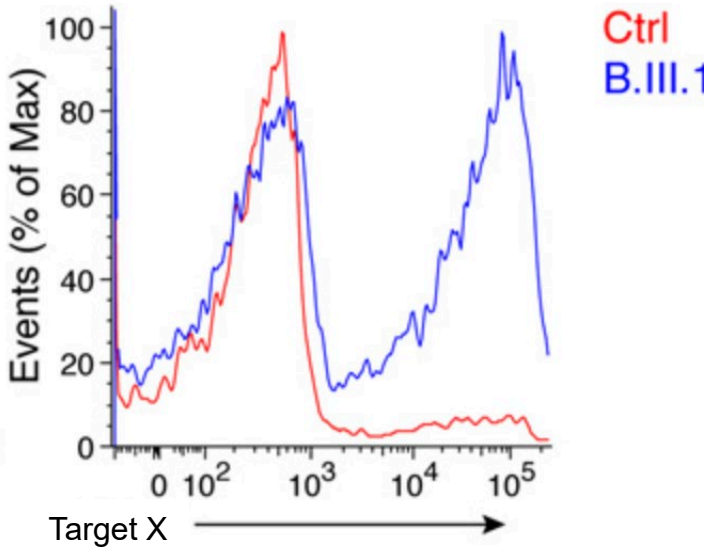
Carrie Lucas, PhD

Rare diseases, common insights

- We are a team of multidisciplinary scientists and clinicians with a track record of discovery in immunodeficiency & autoinflammatory diseases.
  - Discoveries of monogenic drivers of rare immune diseases
  - Elucidates validated human targets

There is strong untapped potential to advance from rare human disease to novel drugs with novel MOAs in patients with more common diseases.

Target X marks disease-associated T cells



Genetic hyperactivation of T cell responses underscores utility of Target X in identifying pathogenic T cells.

Unique to human (not on mouse) T cells.

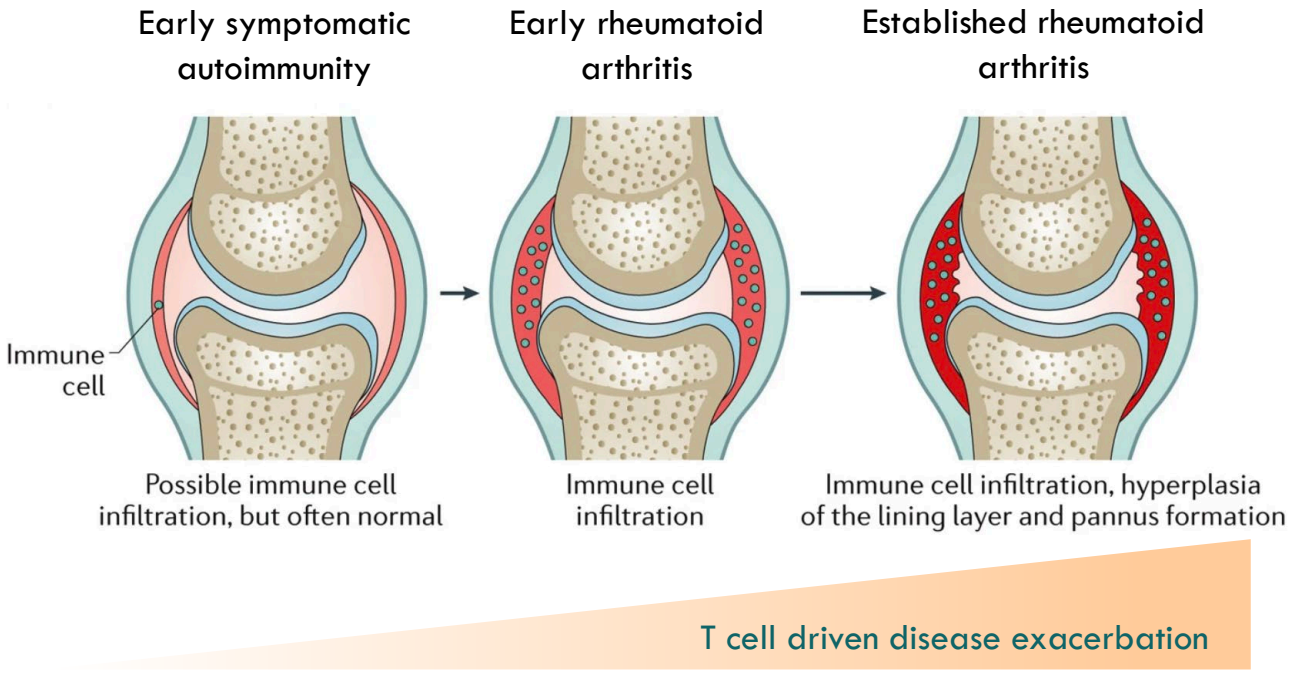
Despite available therapies, patients with refractory rheumatoid arthritis still suffer from decreased quality of life

Standard of care & unmet needs in rheumatoid arthritis

- Immunosuppressants and **disease modifying drugs** are standard of care in early and established disease and are **used chronically**

There is a need to identify drugs with novel MOAs addressing underlying disease etiology for patients with refractory RA

Overview of disease biology across stages of RA



Opportunity in advanced T cell-driven autoimmune diseases, starting with refractory RA

8% of RA patients do not respond to 2 lines of biological or targeted disease modifying drugs

Addressable patient populations		
	1.5M Total - US	**120K** Refractory - US
	350M Total - Global	**28M** Refractory - Global

MOA broadly applicable to **T cell-driven** autoimmunity and "inflamm-aging"

- Ankylosing spondylitis
- Systemic sclerosis
- Neuromyelitis Optica
- Type 1 Diabetes
- Multiple sclerosis

A small piece of a large market, with opportunity to target early RA where immune infiltrates are present

Clear clinical & regulatory pathway

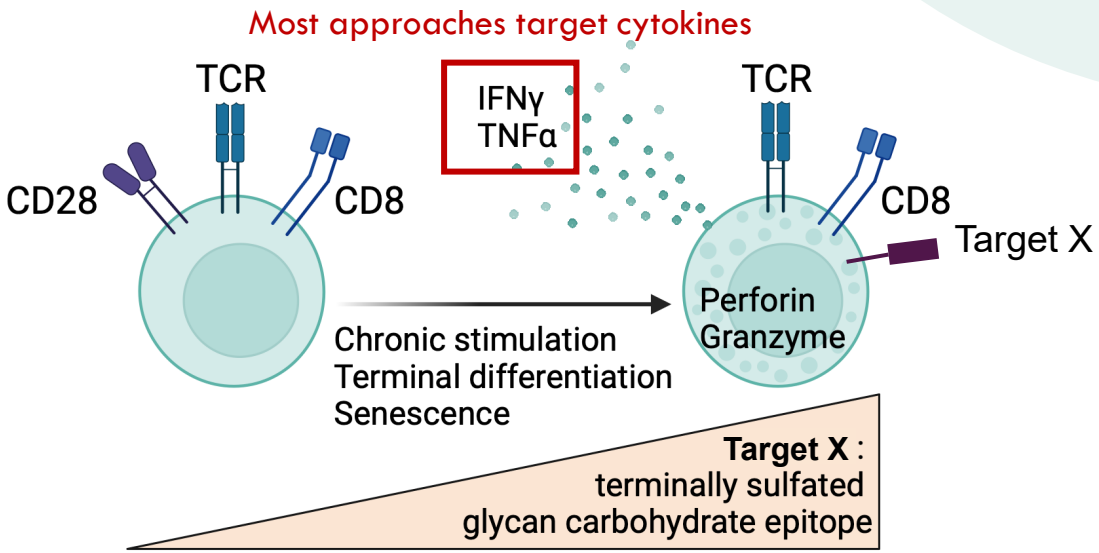
We propose a novel target on pathologic T cells that are chronically stimulated in autoimmune conditions

Target X+ T cells exacerbate inflammatory disease

- Rheumatoid arthritis is driven by autoreactive T cells against citrullinated autoantigens – potential sexual dimorphism
- Chronic autoantigen stimulation drives acquisition of a Target X+ profile

An immune reset is needed to revitalize healthy T cells

Addressable patient population: Refractory RA, failing 2L of disease modifying drugs including biologics

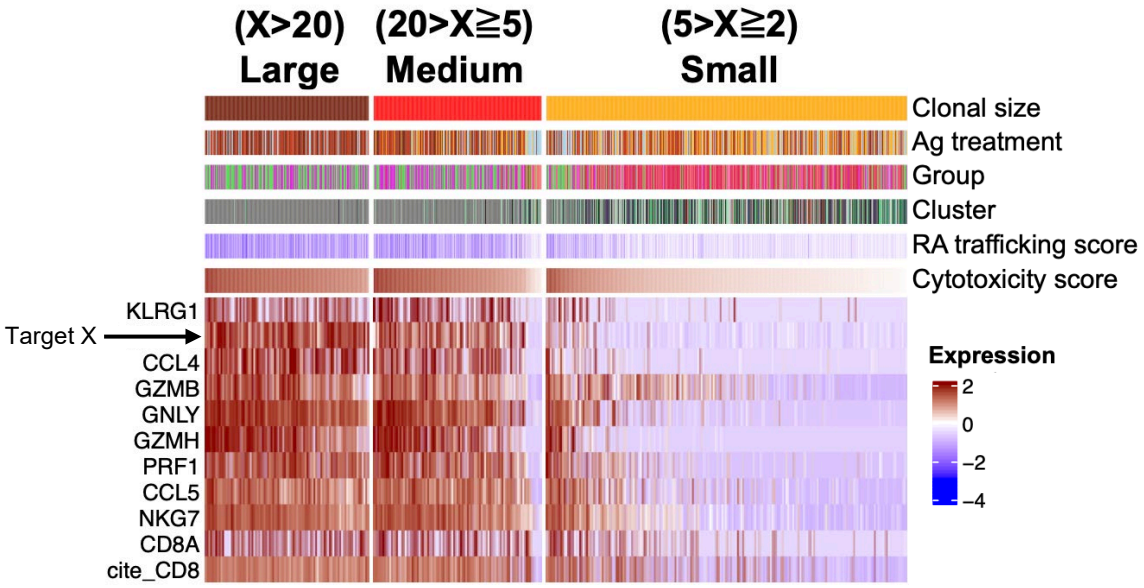


Target X is a **sugar epitope** expressed on human T cells, and has not been therapeutically targeted before

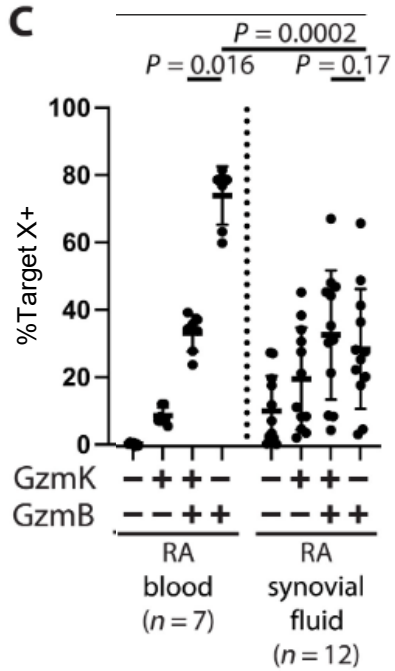
Target validation: Target X is highly expressed in pathogenic T cells in rheumatoid arthritis patients

Highly expressed marker of expanded autoreactive T cells, correlates with cytotoxicity in RA

Target X expression in expanded, pathogenic CD8+ T cells



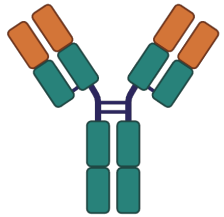
Target X correlation with cytotoxic phenotype in RA T cells



Blavatnik Milestones and 2-year Development Plan

Current Foundation

- Target identified through study of human disease.
- Prototype antibody binding specificity validated.
- Prototype chimeric antibody cloned.

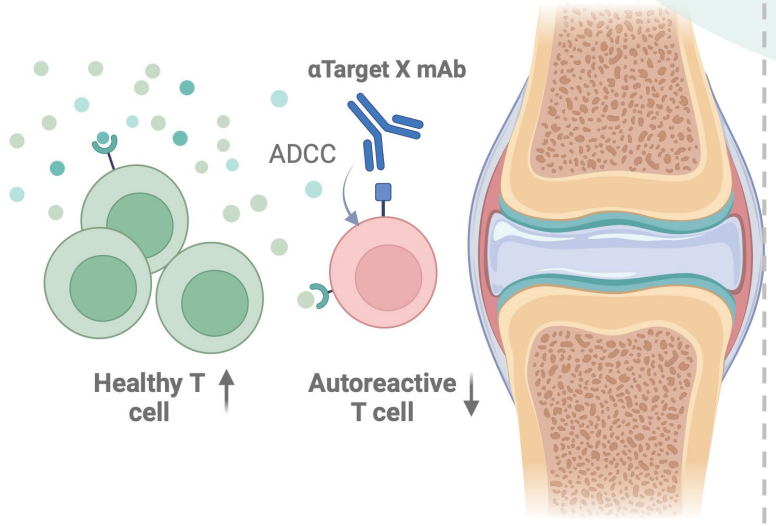


Q3,2025

Milestone 1 ($90K)
Antibody synthesis and *in vitro* ADCC of human Target X+ T cells and additional target validation work

Milestone 2 ($90K)
Generation of a panel of new, highly specific antibodies using phage or yeast display

Q3,2026



Milestone 3 ($120K)
Model characterization + preliminary *in vivo* testing of antibody in humanized mouse models of RA

Q3,2027

Asset characteristics:

Chimeric antibody incorporating:
- Variable regions from a mouse IgM Ab
- Nonfucosylated IgG1 Fc

Likely favorable half life ~21 days, capable of depletion via NK-mediated ADCC

IP Status:

IP will incorporate methods of targeting the new moiety, along with CDRs of newly generated antibodies.
Will be filed with Yale during course of Blavatnik funding.

Competitive Landscape: A differentiated approach in a crowded space with limited new MOAs for refractory RA

There are many approved and pipeline therapies that tackle a small "piece" of RA disease pathogenesis.

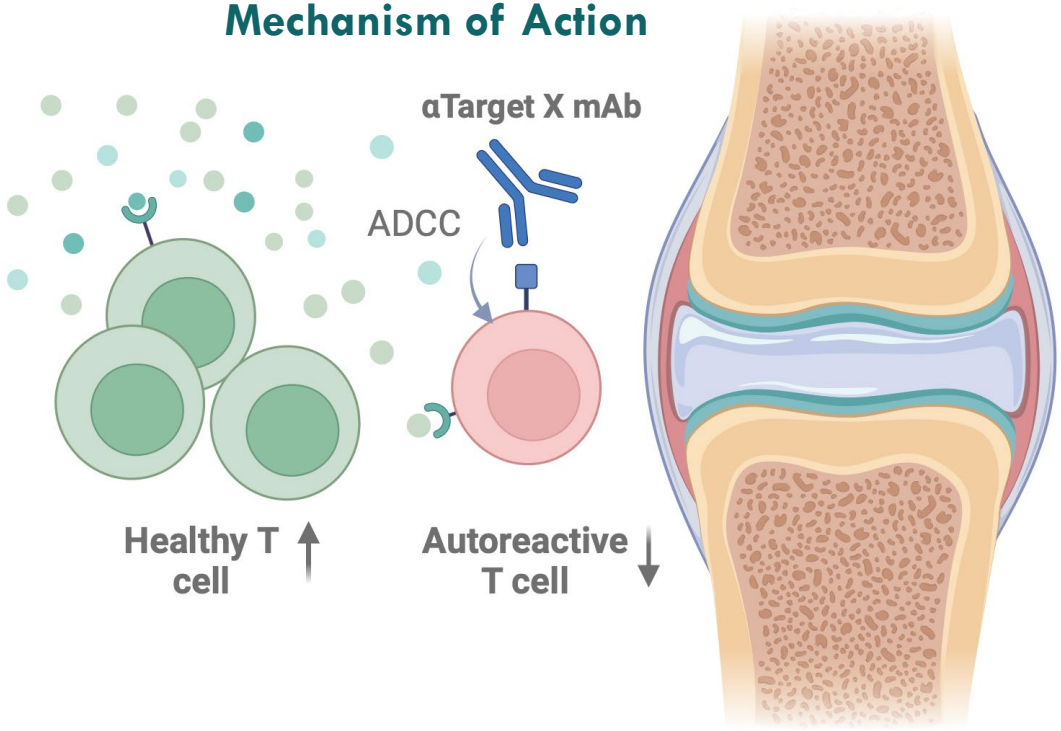
None provide an opportunity for T cell reset.

Approach	Companies	Drugs	ROA	Competitive differentiation
Cytokine therapies (TNF blockers, IL-6) bDMARD (1st or 2nd line)	Pfizer, Abbvie, Biogen, Amgen, others.	Adalimumab, infliximab, etanercept	Subq	Crowded with biosimilars across a few targets
JAK/STAT, kinase inhibitors tsDMARD (1st or 2nd line)	Eli Lilly, Pfizer	Tofacitinib	Oral	Unfavorable tox profile
Inhibition of T or B cell activation / autoantibodies (2nd or 3rd line)	Bristol Myers Squibb, Merck, Amgen	Abatacept, BTKi, rituximab, anti-CD40, FcRn	IV	Generalized mechanisms, not specific to RA disease biology

We have generated humanized anti-Target X antibodies capable of target cell depletion

Our approach targets chronically activated T cells for depletion, ***providing an immune reset that is likely to allow longer redosing windows.***

Mechanism of Action

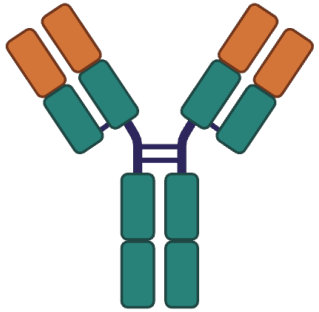


Asset characteristics:

Chimeric antibody incorporating:

- Variable regions from a mouse IgM Ab
- Nonfucosylated IgG1 Fc

Likely favorable half life ~21 days, capable of depletion via NK-mediated ADCC



IP Status:

IP will incorporate methods of targeting the new moiety, along with CDRs of newly generated antibodies.

Will be filed with Yale during course of Blavatnik funding.