MEETING OF THE MINDS

WESTIN HARBOUR CASTLE, TORONTO

SATURDAY, November 15, 2025

Canada Future Directions in IBD

Co-Chairs: **Remo Panaccione**, MD FRCPC and **A. Hillary Steinhart**, MD MSc FRCPC

crohn's colitis canada | crohn colite canada

UNIVERSITY OF ALBERTA

UNIVERSITY OF CALGARY MEDICINE

McGill UNIVERSITY

McMaster University

UNIVERSITY OF TORONTO FACULTY OF MEDICINE

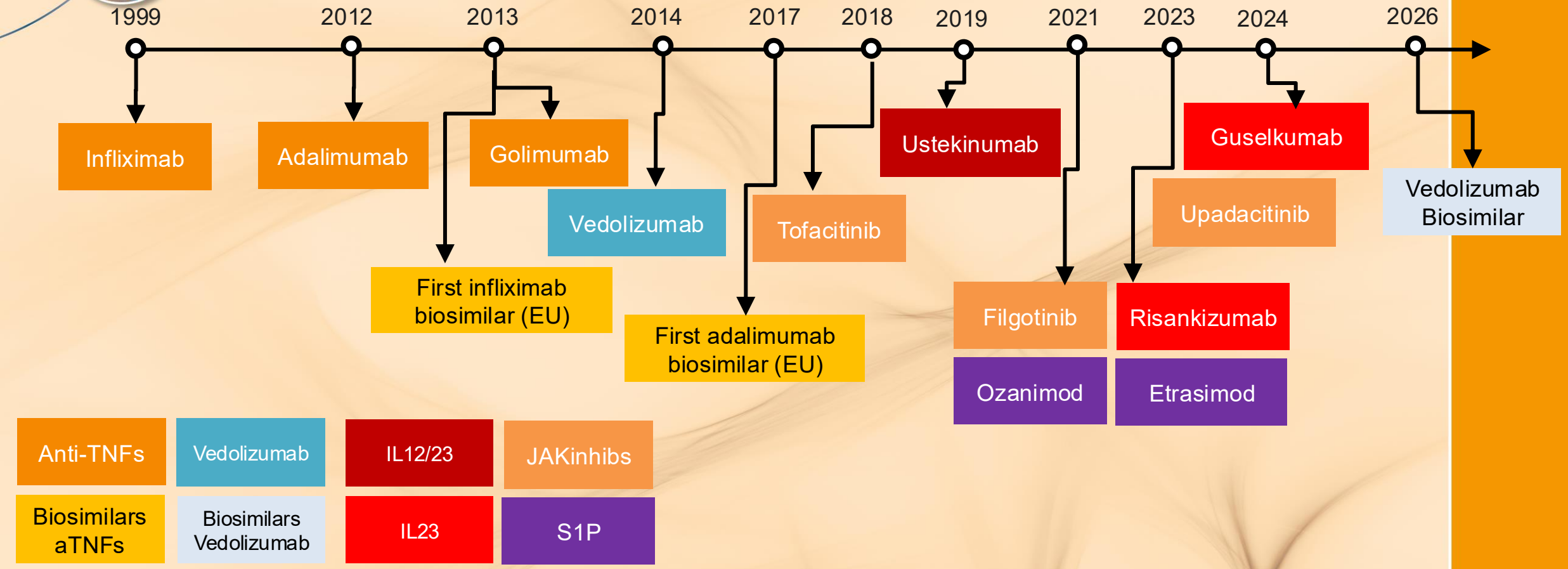
Workshop 3.1
Cell-Based Therapies in IBD: Past, Present and Future

Ted Steiner & Ryan Ungaro

Objectives

- Summarize the current evidence supporting the use of cell-based therapies in IBD
- Evaluate the potential risks, benefits and clinical scenarios where cell-based therapy may be considered

Rapid Advances in Treatment Options for Patients…



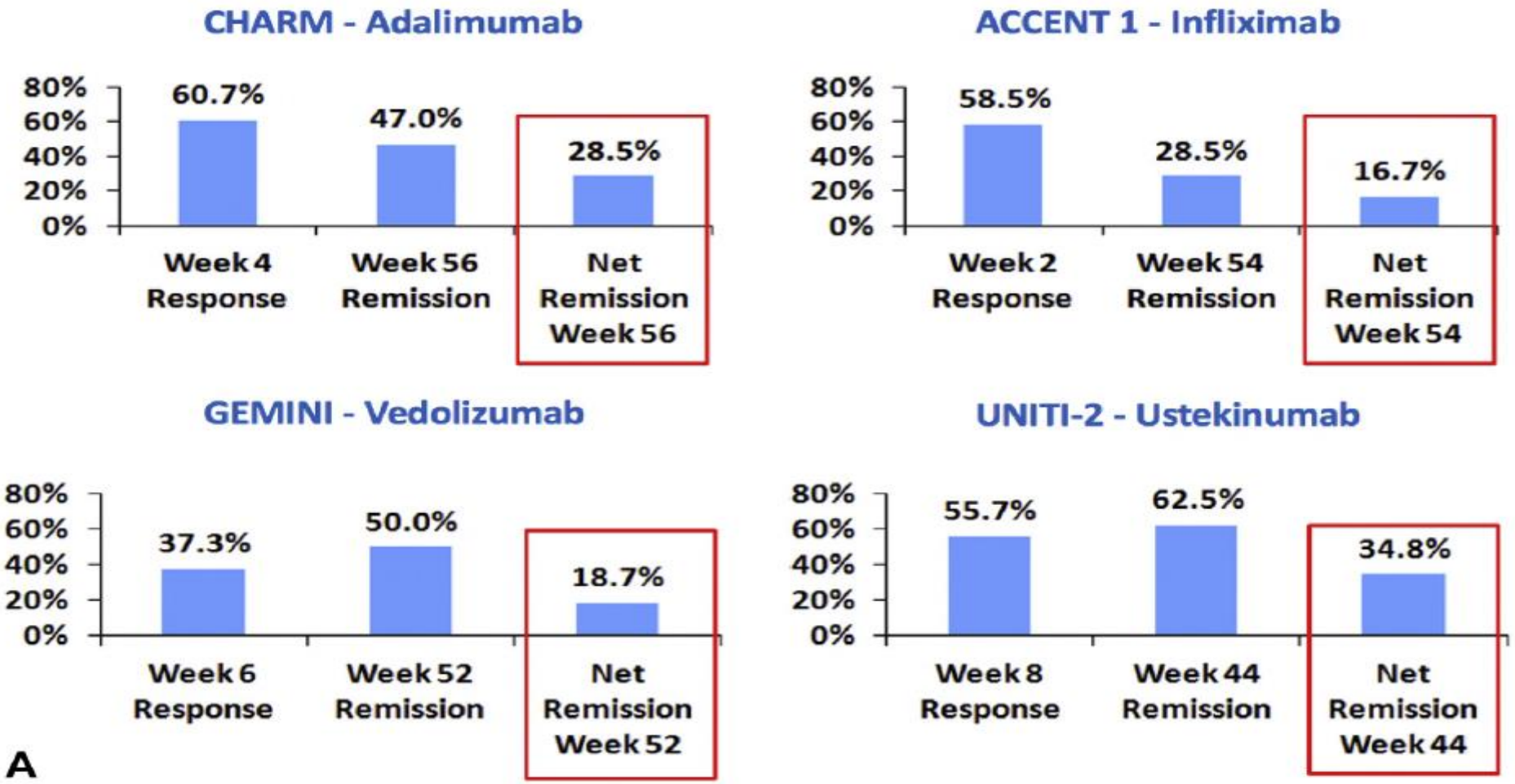
Canada Future Directions in IBD

Alsoud et al. Lancet Gastroenterology and Hepatology. 2021.

But we still have a problem…

We are plateauing !

"Net" remission rates in anti-TNF Naïve CD Population



Canada Future Directions in IBD

Kayal M, Ungaro R et al. Clin Gastroenterol Hepatol 2022

What are the potential types of cell-based therapy in IBD?

- Stem Cell Therapy
  - Hematopoietic
  - Mesenchymal
- Treg / Tr1 Based Therapy
- Chimeric Antigen Receptor T Cell Therapy (CAR-T)
  - Cytotoxic or regulatory

What are the potential types of cell-based therapy in IBD?

- **Stem Cell Therapy**
  - **Hematopoietic**
  - Mesenchymal
- Treg / Tr1 Based Therapy
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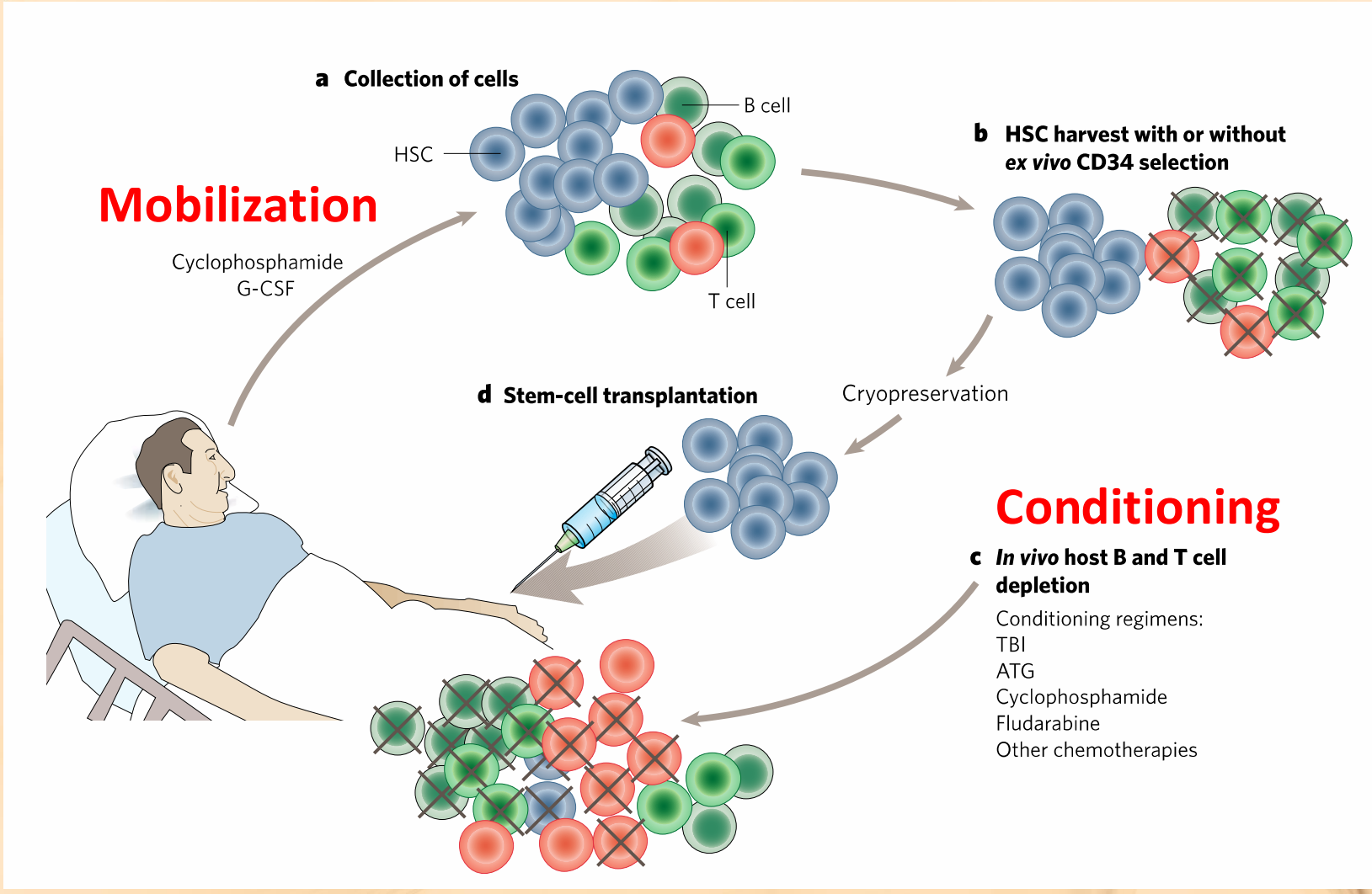
Autologous Hematopoietic Stem Cell Transplant



Nature 2005

ASTIC Trial

Original Investigation

Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease

A Randomized Clinical Trial

Christopher J. Hawkey, FMedSci; Matthieu Allez, PhD; Miranda M. Clark, BSc(Hons); Myriam Labopin, MD; James O. Lindsay, PhD; Elena Ricart, PhD; Gerhard Rogler, PhD; Montserrat Rovira, MD; Jack Satsangi, DPhil; Silvio Danese, PhD; Nigel Russell, MD; John Gribben, MD; Peter Johnson, MD; Jerome Larghero, MD; Catherine Thieblemont, PhD; Sandro Ardizzone, MD; Daan Dierickx, PhD; Adalberto Ibatici, MD; Timothy Littlewood, MD; Francesco Onida, MD; Urs Schanz, MD; Severine Vermeire, PhD; Jean-Frederic Colombel, MD; Jean-Paul Jouet, MD; Elizabeth Clark, MSc; Riccardo Saccardi, MD; Alan Tyndall, FRACP; Simon Travis, DPhil; Dominique Farge, PhD

JAMA December 15, 2015 Volume 314, Number 23 **2525**

45 treatment-refractory (previous therapy with at least three immunosuppressive or biological agents and corticosteroids) CD patients receiving immediate autologous HSCT (n= 23) or stem cell mobilization followed by conventional care (n= 22)

Hawkey C JAMA et al 2015
Lindsay J et al Lancet Gastro Hep 2017

ASTIC Trial

Original Investigation

Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease

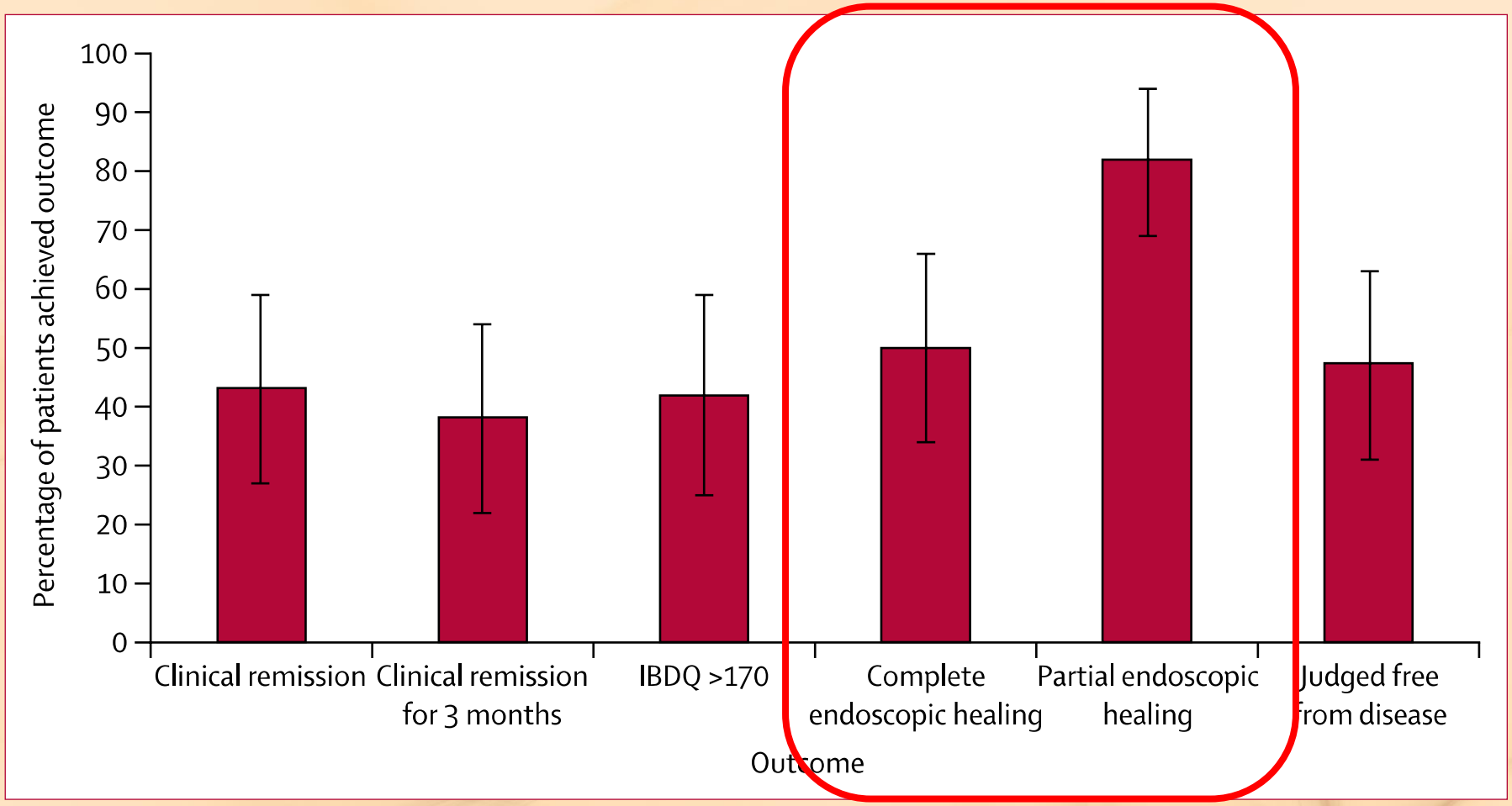
A Randomized Clinical Trial

	No. (%)			
	HSCT (n = 23)	Control (n = 22)	Difference Median, % (95% CI)[a]	*P* Value (Adjusted for Center)
Primary Outcome[b]				
Sustained disease remission[c]	2 (8.7)	1 (4.5)	4.2 (−14.2 to 22.6)	.60
Components of primary outcome				
No active treatment last 3 mo	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	.01
CDAI <150 last 3 mo	8 (34.8)	2 (9.1)	25.7 (1.08 to 47.1)[a]	.052
Free of active disease on imaging	8 (34.8)	2 (9.1)	25.7 (1.08 to 47.1)[a]	.054

Primary Outcome: Sustained disease remission at 1 year, a composite primary end point comprising clinical remission (Crohn Disease Activity Index (CDAI) <150 [range, 0-600]), no use of corticosteroids or immunosuppressive or biologic drugs for at least the last 3 months, and no endoscopic or radiological evidence of active (erosive) disease anywhere in the gastrointestinal (GI) tract.

Hawkey C JAMA et al 2015
Lindsay J et al Lancet Gastro Hep 2017

ASTIC Trial: Outcomes



Hawkey C JAMA et al 2015
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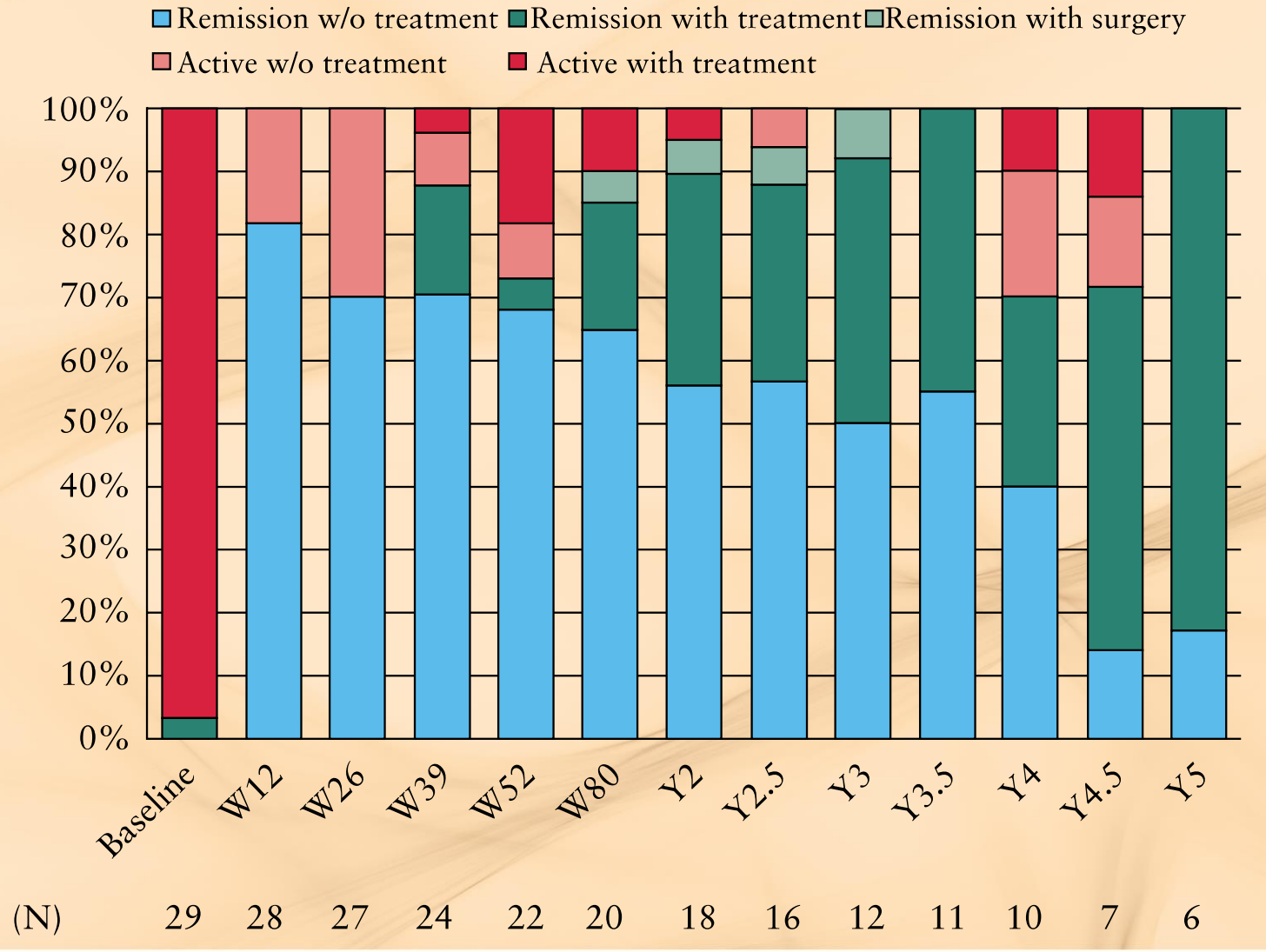
ASTIC: Outcomes



Restore response to therapy

Hawkey C JAMA et al 2015
Lindsay J et al Lancet Gastro Hep 2017

ASTIC: Safety

- Adverse events (cyclophosphamide/ATG)
  - 32 events in 14 patients during follow up
    - Infectious complications (12 events)
      - Viral, perianal
    - Disease flare (7 events)
    - Smoking + perianal disease risk factors
- Death (1/45 patients)
  - Sinusoidal obstructive syndrome
    - Likely related to cyclophosphamide

These risks must be weighed relative to risk of doing nothing – 13% mortality at 5 years

Hawkey C JAMA et al 2015
Lindsay J et al Lancet Gastro Hep 2017
Crohn Colitis 360 2020 (2) 1-6
Clin Nutr ESPEN 2022 170-177

Lancet Gastroenterol Hepatol 2017 399-406

ASTIC-LITE: Safer Transplant?

Safety and efficacy of autologous haematopoietic stem-cell transplantation with low-dose cyclophosphamide mobilisation and reduced intensity conditioning versus standard of care in refractory Crohn's disease (ASTIClite): an open-label, multicentre, randomised controlled trial

James O Lindsay, Daniel Hind, Lizzie Swaby, Hannah Berntsson, Mike Bradburn, Uday Bannur C, Jennifer Byrne, Christopher Clarke, Lauren Desoysa, Ben Dickins, Shahida Din, Richard Emsley, Gemma A Foulds, John Gribben, Christopher Hawkey, Peter M Irving, Majid Kazmi, Ellen Lee, Amanda Loban, Alan Lobo, Yashwant Mahida, Gordon W Moran, Diana Papaioannou, Miles Parkes, Andrew Peniket, A Graham Pockley, Jack Satsangi, Sreedhar Subramanian, Simon Travis, Emily Turton, Ben Uttenthal, Sergio Rutella, John A Snowden

Conditioning regimen :
Reduced dose
Cyclophosphamide +
FLUDARIBINE

Lancet Gastroenterol Hepatol 2024 333-45

Lancet Gastroenterol Hepatol 2024 333-45

Lancet Gastroenterol Hepatol 2024 278

ASTIC-LITE: Significant Safety Signals

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9 SAE in 6 patients

- **3 renal failure – thrombotic microangiopathy**
- **2 deaths – pulmonary veno-occlusive disease, resp/renal failure**

Lancet Gastroenterol Hepatol 2024 333-45

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(1) These are known complications of fludarabine
(2) These events never observed with cyclophosphamide/ATG

9 SAE in 6 patients

- **3 renal failure – thrombotic microangiopathy**
- **2 deaths – pulmonary veno-occlusive disease, resp/renal failure**

MASCT-CD Trial – Mount Sinai NY Experience

Colonoscopy
- Samples

Mobilization
- Cyclophosphamide, G-CSF

Conditioning and Transplant
- Cyclophosphamide, ATG (Methylprednisolone)

Vedolizumab
- Samples
  - q3 mo
- Office visits monthly (safety)

Repeat Colonoscopy
- 6 months post transplant

Long-term Follow Up Study (3 years)

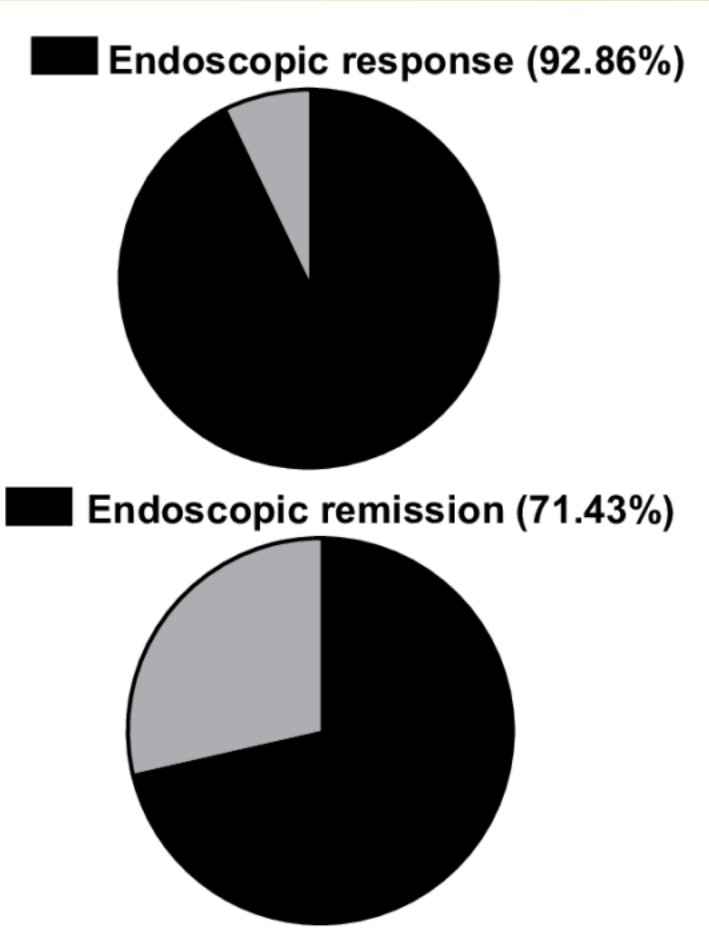
Louis Cohen MD

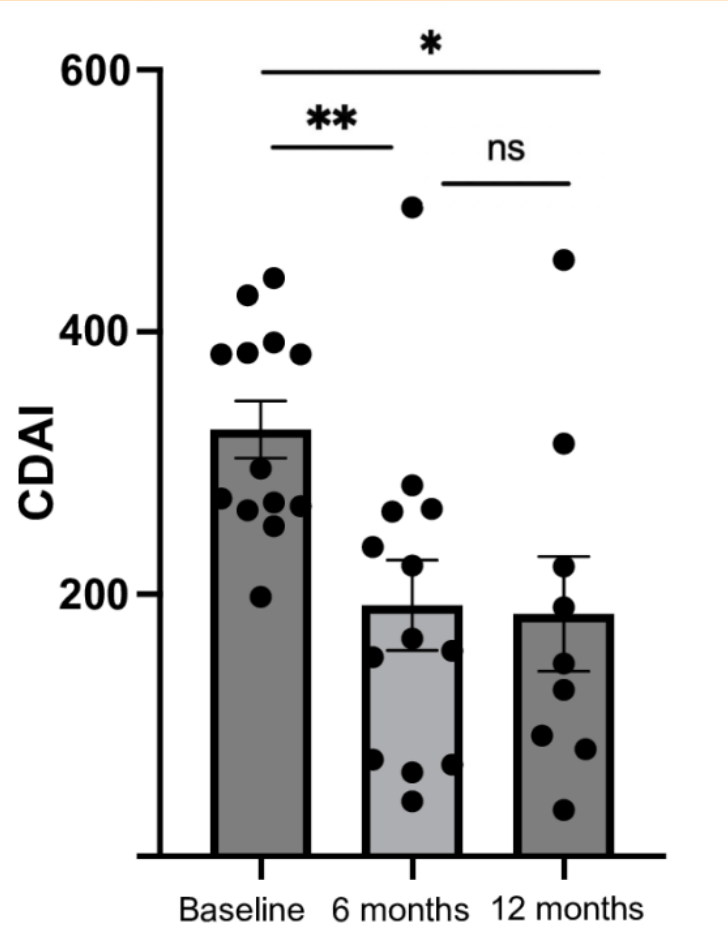
Canada Future Directions in IBD

Guisado et al Gut 2025

MASCT-CD Trial – Mount Sinai NY Experience

N=19





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Guisado et al Gut 2025

MASCT-CD Trial – Mount Sinai NY Experience

- 3 patient TPN dependent now eating and off TPN
- 1 patient with pulmonary crohns
  - Improvement in bronchoscopy and pathology
  - Improvement in PFT
- 2 patients on chronic narcotics now off narcotics

- 2/15 patients relapsed
  - 8 months – restarted Adalimumab with success
    - Antibodies to Infliximab
  - 3 years – restarted Adalimumab with success
- 2/15 patients poor response
  - 6 months – added Adalimumab with success

Serious Adverse Events – 9 events in 4 patients

1 patient (failed mobilization)

- Recurrent small bowel obstructions
  - GI hemorrhage
- Fungemia
- Worsening liver dysfunction
  - Hepatic encephalopathy

1 patient

- Fever leukocytosis post mobilization
  - G-CSF
- Pneumonia (treatment phase)
  - Known lung disease

1 patient

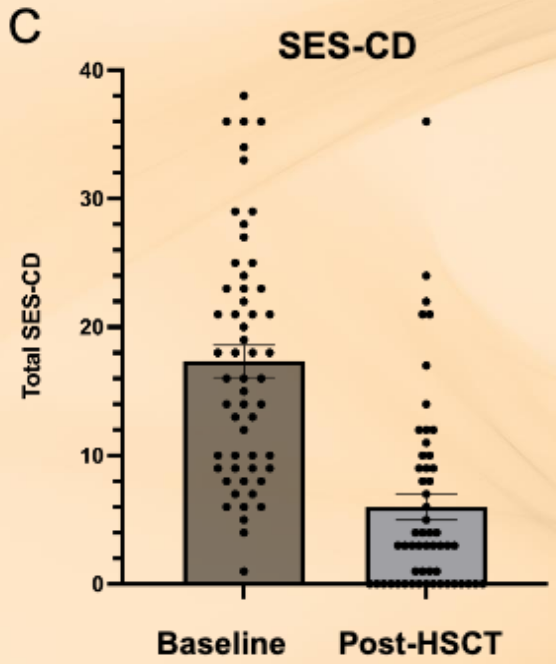
- Worsening perianal disease
  - During mobilization
  - **Diversion prior to transplant**
- Kidney stones
  - After diversion pre transplant

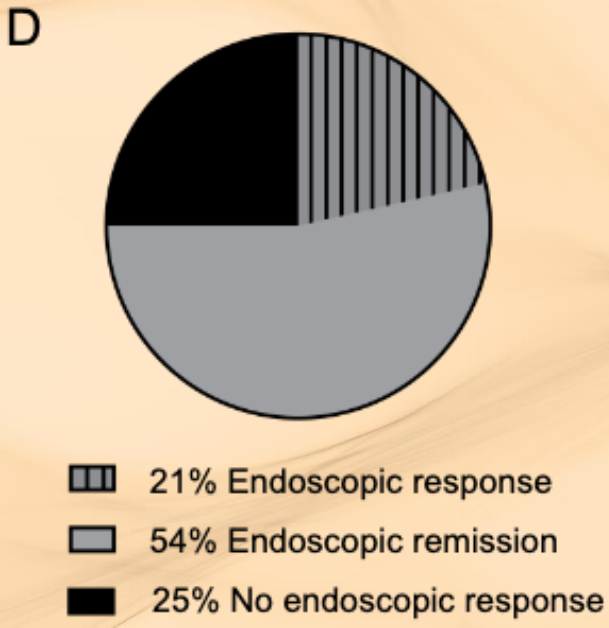
1 patient

- BK virus
  - Treated conservatively
- CMV virus
  - **Colitis – treated with ganciclovir**
- Shingles

Results from an International Stem Cell Transplant Consortium

- 68 patients with CD from NYC, Barcelona, and London
- **Conditioning regimen:** Cyclophosphamide, ATG





75% endoscopic response

Assessed at time of last follow up (median 2 yrs)

No renal failure, death, malignancy

Endoscopic response: ↓SES-CD by 50%
Endoscopic remission: SES-CD < 4, ulcer sub-score <1

Key Consideration for Stem Cell Transplant in IBD

- Available in few expert centers around the world
- Careful selection of patients
- Conditioning regimen has impact on safety
- Relapse can still happen but often can recycle prior therapies with success
- Long-term considerations? (secondary malignancies)

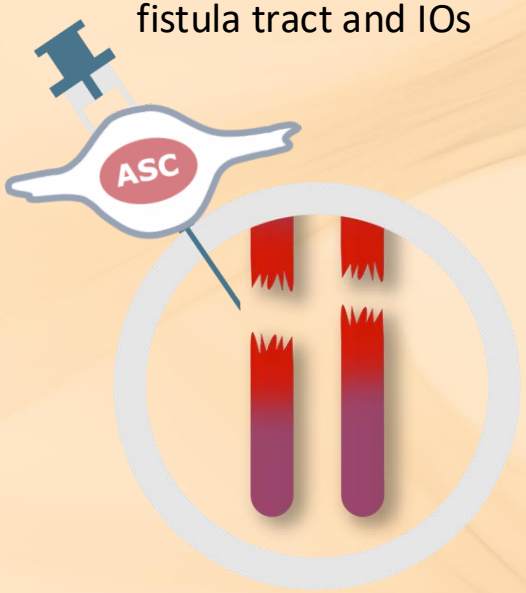
What are the potential types of cell-based therapy in IBD?

- **Stem Cell Therapy**
  - Hematopoietic
  - **Mesenchymal**
- Treg / Tr1 Based Therapy
- Chimeric Antigen Receptor T Cell Therapy (CAR-T)

Mesenchymal Stem Cell Therapy

Proposed mechanism of action of adipose derived stem cells in perianal fistula

Inject ASCs peri-luminal to the fistula tract and IOs

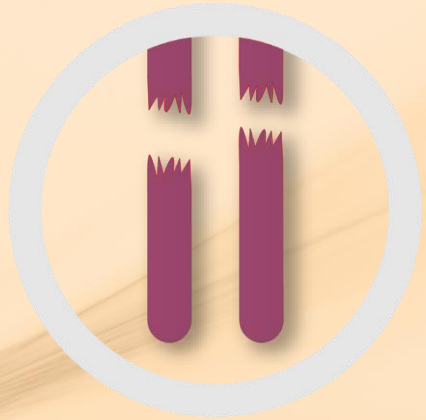


IFN gamma present at inflammation site activates ASC

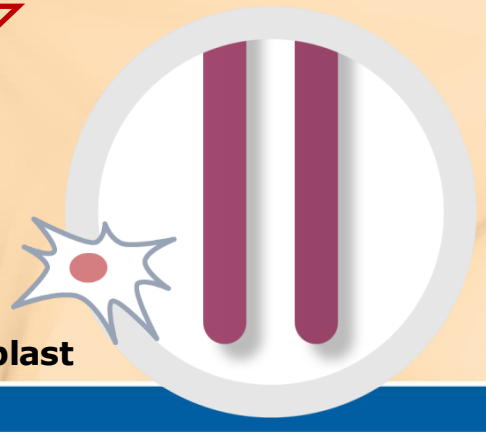
Cytotoxic cell proliferation

Secretion of anti-inflammatory cytokines

Inflammatory cell activation



Reduced inflammation



Fibroblast

The reduction of inflammation creates an environment that promotes healing through angiogenesis and chemoattraction

ASC, adipose-derived stem cells; IFN, interferon; IO, internal opening.

Singer NG and Caplan AI. *Annu Rev Pathol*. 2011;6:457–78.

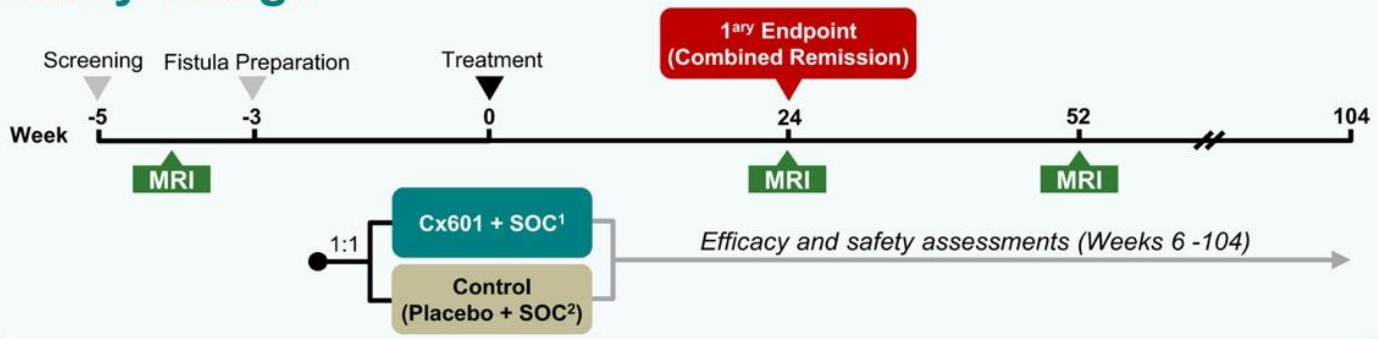
Mesenchymal Stem Cell Therapy

ADMIRE CD Study: Cx601 for Complex Perianal Fistulas in Crohn's disease

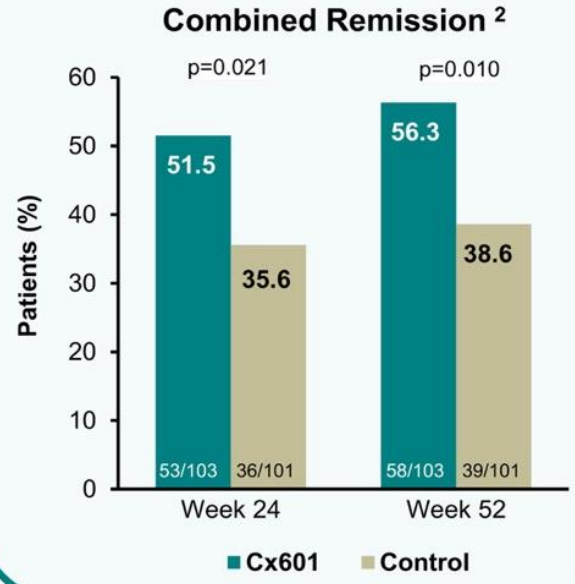
Treatment

Cx601 is a suspension of allogeneic expanded adipose-derived stem cells (eASC) injected locally, and has been shown to be efficacious and well tolerated in Crohn's disease patients with treatment-refractory complex perianal fistulas

Study design



Efficacy



1. Standard of care; 2. mITT population (modified intention to treat)

Gastroenterology

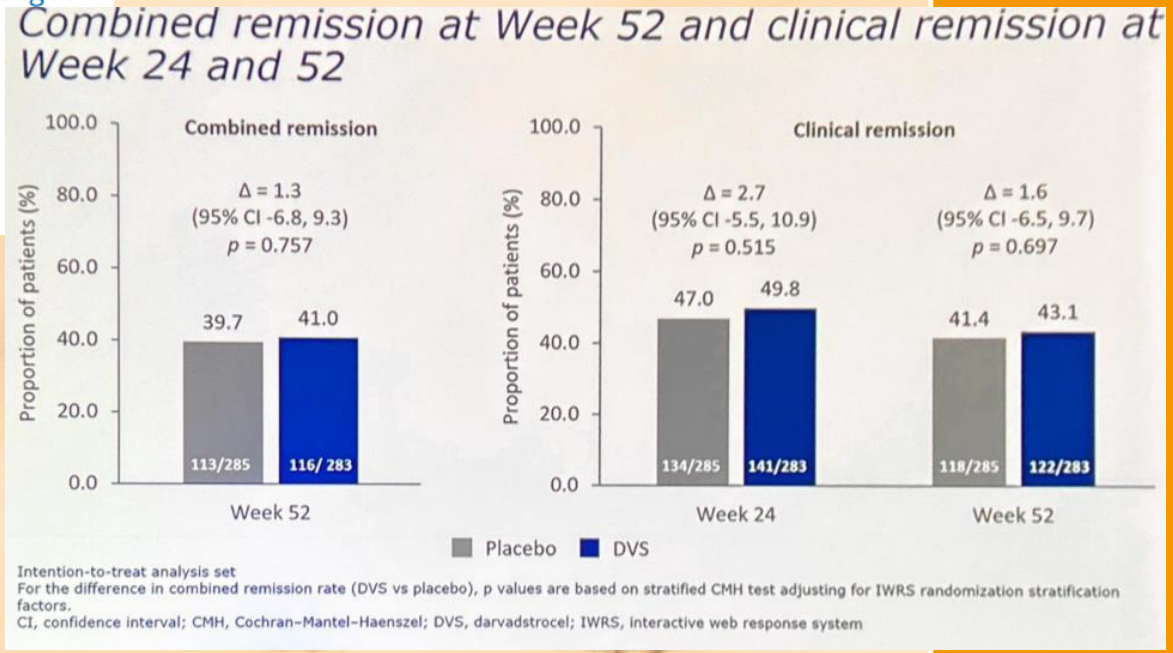
Panes et al. Gastroenterology 2018.

Stem cell product does not achieve greater fistula remission compared with placebo: ADMIRE-CD II study

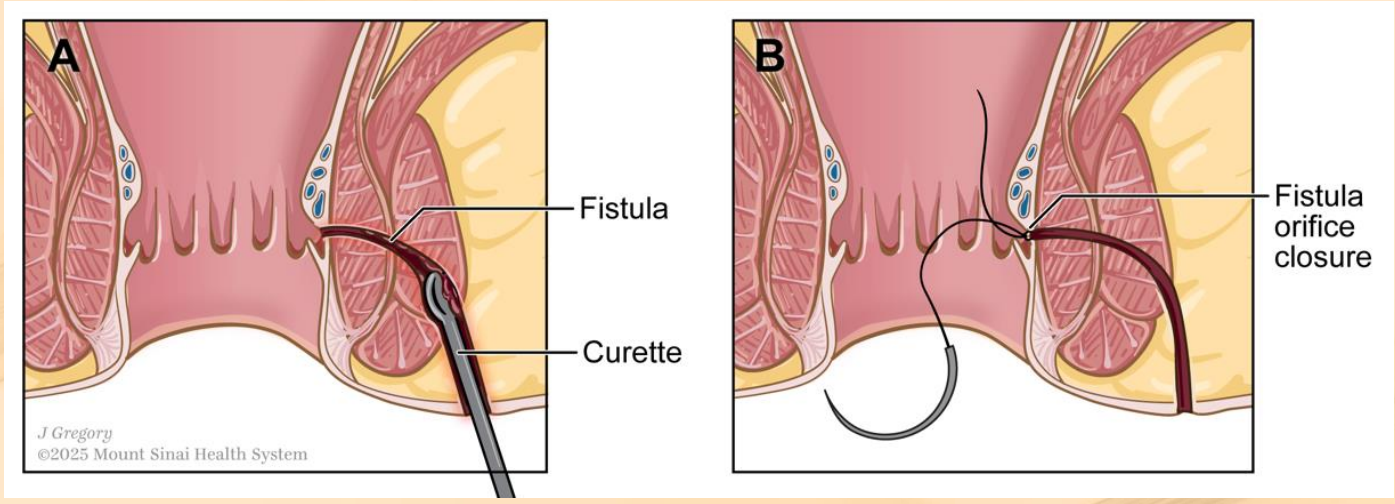
OP18 Efficacy and safety of darvadstrocel treatment in patients with complex perianal fistulas and Crohn's Disease: results from the global ADMIRE-CD II phase 3 study FREE

Z Serclova, D Garcia-Olmo, S T Chen, S Wexner, J Panés, C Wu, P Fleshner, B Zhang, J F Colombel, M Song ...
Show more

Journal of Crohn's and Colitis, Volume 18, Issue Supplement_1, January 2024, Pages i34–i35,
https://doi.org/10.1093/ecco-jcc/jjad212.0018
Published: 24 January 2024



ADMIRE “placebo” : Curettage and Closure

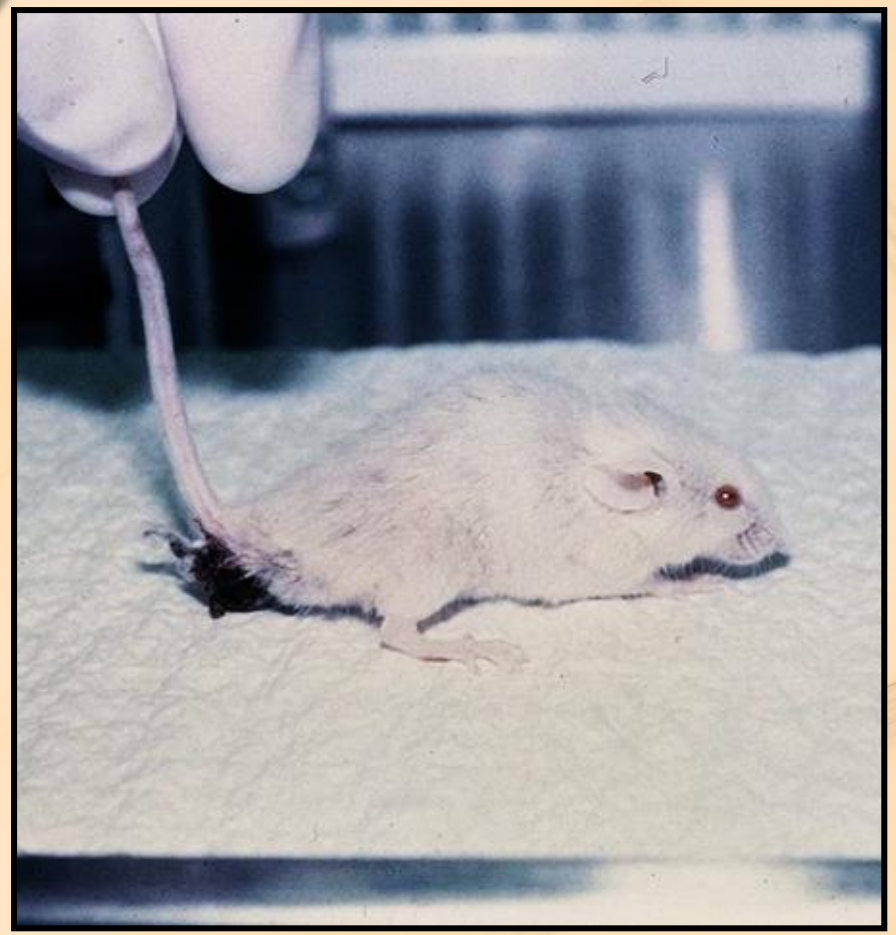


- Aka “scrape and close”
- Straightforward procedure
- No other data for efficacy in PFCD
- Can be applied to more fistulas than LIFT and FLAP

What are the potential types of cell-based therapy in IBD?

- Stem Cell Therapy
  - Hematopoietic
  - Mesenchymal
- **Treg / Tr1 Based Therapy**
- Chimeric Antigen Receptor T Cell Therapy (CAR-T)

Pre-clinical Evidence for Cell Tx in IBD: Tr1 cells play a key role in gut homeostasis: IL-10 production



IL-10 or IL-10R KO MICE:

- **Hypersensitive to LPS**
- **Exaggerated inflammatory reactions**
  e. g. DTH, contact hypersensitivity
- **Spontaneous IBD:**
  - Enteric microbiota and T cells required
  - IL-10 treatment (IL-10-/- mice) prevents but doesn't cure
  - Recapitulated in BALB/c mice by long-term high dose anti-IL-10R1

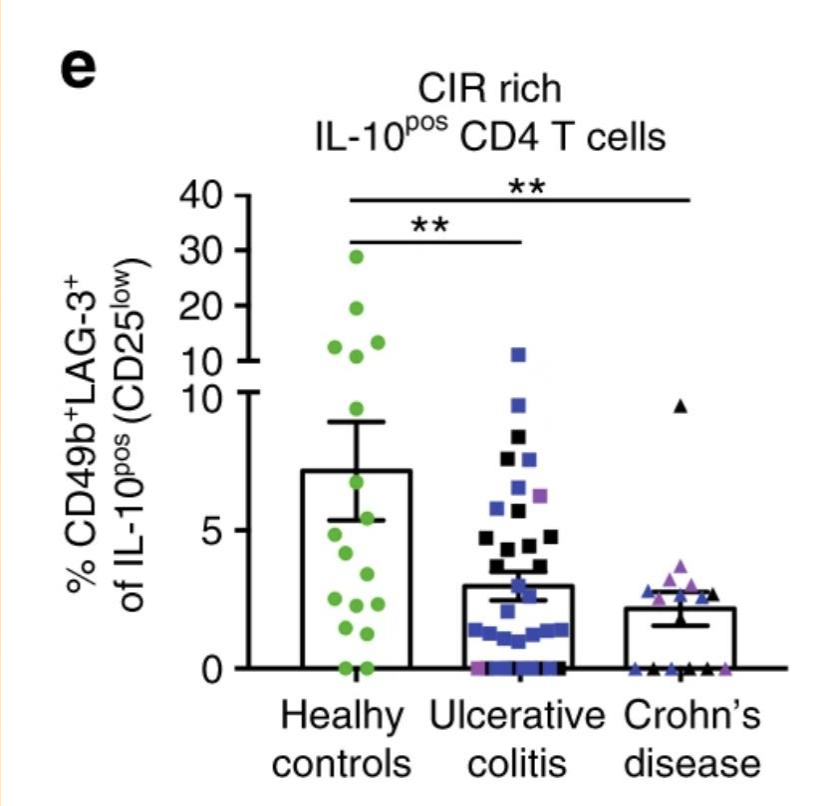
R. Kuhn et al. (1993) Cell 75, 263-74; S.D. Spencer et al. (1998) J. Exp. Med. 187, 571-8

Human IL-10 or IL10R Deficiency: a Model for Tr1 Cell Deficiency

- **Autosomal recessive (AR)**
- **Primary Immunodeficiency (disease onset 3 m-2 yrs)**
- **139 patients described**
- **Very early onset Inflammatory Bowel Disease, Inflammation, Autoimmunity:**
  - *Common IBD symptoms in first year of life*
  - *Intractable diarrhea*
  - ***Severe enterocolitis***
  - *Perianal disease (ulcer, abscesses)*
  - *Chronic folliculitis*
  - ***Arthritis***
  - *Recurrent respiratory infections*
  - *B-cell lymphoma*
  - *Abnormal Ig serum level*
- **Pharmacological therapies are not effective**
- **Allogeneic HSCT only cure: 40 patients transplanted**

Evidence for Cell Tx in IBD: Significantly Fewer Tr1 Cells in Patients With Crohn's Disease

Significantly reduced frequency of IL-10-producing CD25^{low} CIR rich CD4^{+} T cells (Tr1 cells) within IBD patients



Colon biopsies from IBD patients: UC active *n* = 22 (inflamed *n* = 20, blue dots; non-inflamed *n* = 17, black dots); UC Remission *n* = 2, violet dots; CD active *n* = 9 (inflamed *n* = 5, blue dots; non-inflamed *n* = 6, black dots); CD remission *n* = 5, violet dots and healthy controls (*n* = 18). Cells were stimulated with SEB overnight, One-way ANOVA (multiple comparisons) was used to calculate significance (**$p < 0.005$)

Brockmann, L. *et al.* Molecular and functional heterogeneity of IL-10-producing CD4^{+} T cells. *Nat Commun* **9,** 5457 (2018).

Autologous Tr1 Cells Clinical Proof of Concept: OVASAVE Experience

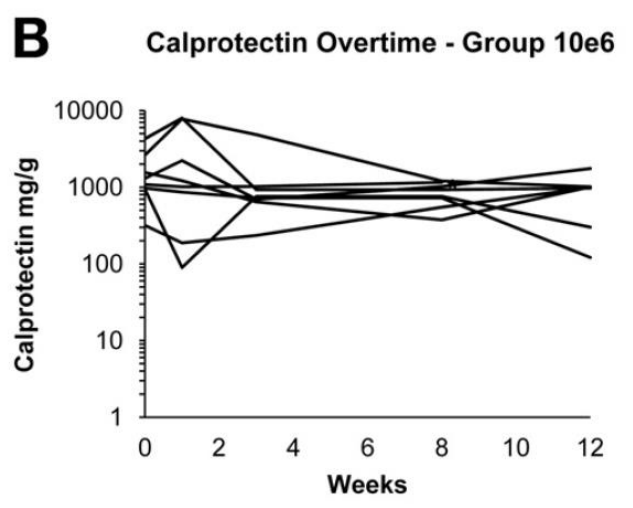
20 patients refractory to one or more biologics.

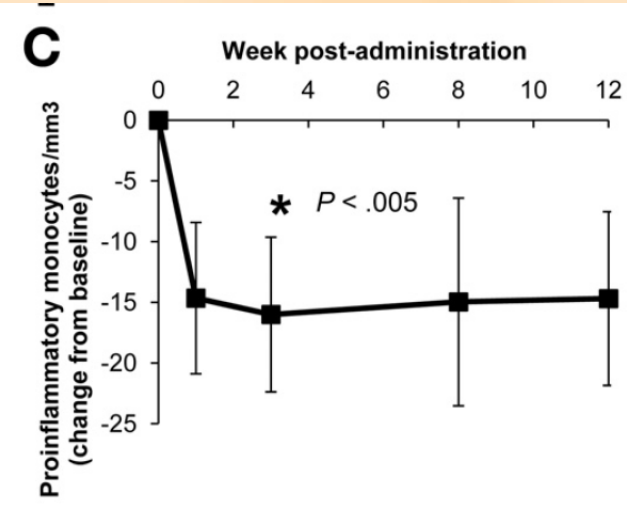
- Average of 13y of disease
- 381 Mean CDAI (moderate/severe borderline)
- 95% failed TNF, 50% failed 3 TNF, 30% failed >1 TNF + investigational agent, 30% prior surgery
- low-dose 20 mg/day corticosteroid administered

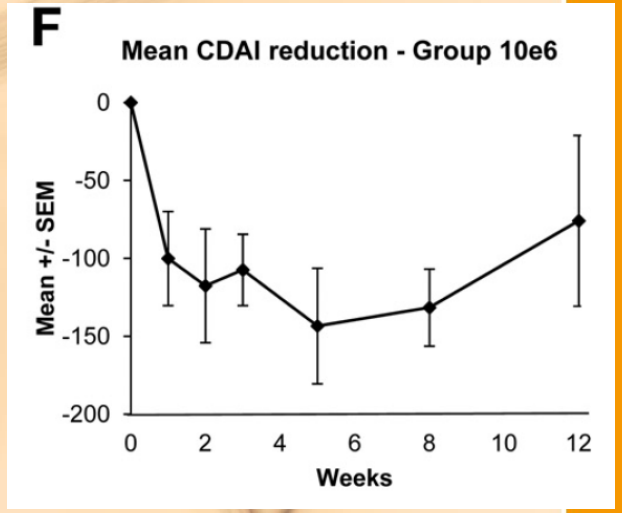
Multicenter Open-Label Study - Single IV Injection

- Ovalbumin -specific Tregs isolated from PBMCs
- 12 week endpoint
- Exhausted Tr1 clones, transient survival
- Autologous cells supernatant enriched in IL2, IL4 from Drosophila feeder cells having impurities

N = 8 low dose of 10^6 cells, OVASAVE demonstrated reduction in calprotectin, reduction in proinflammatory monocytes (CD14+/CD16+), and transient reduction in CDAI > 100 (6/8), good tolerability

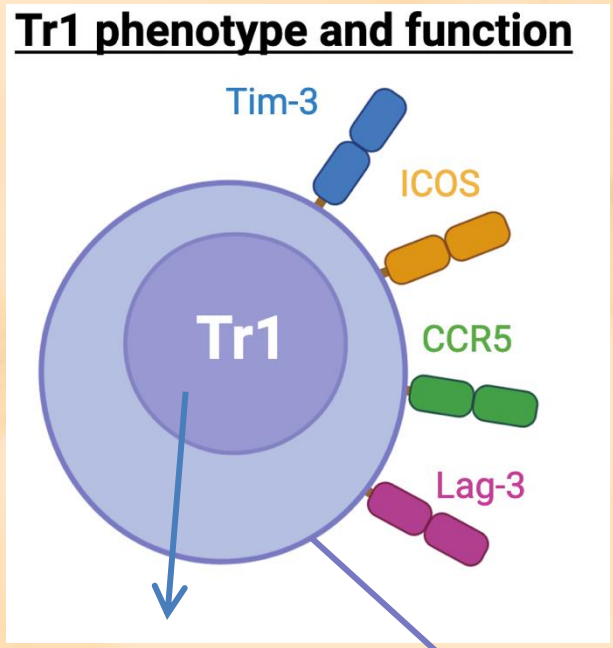


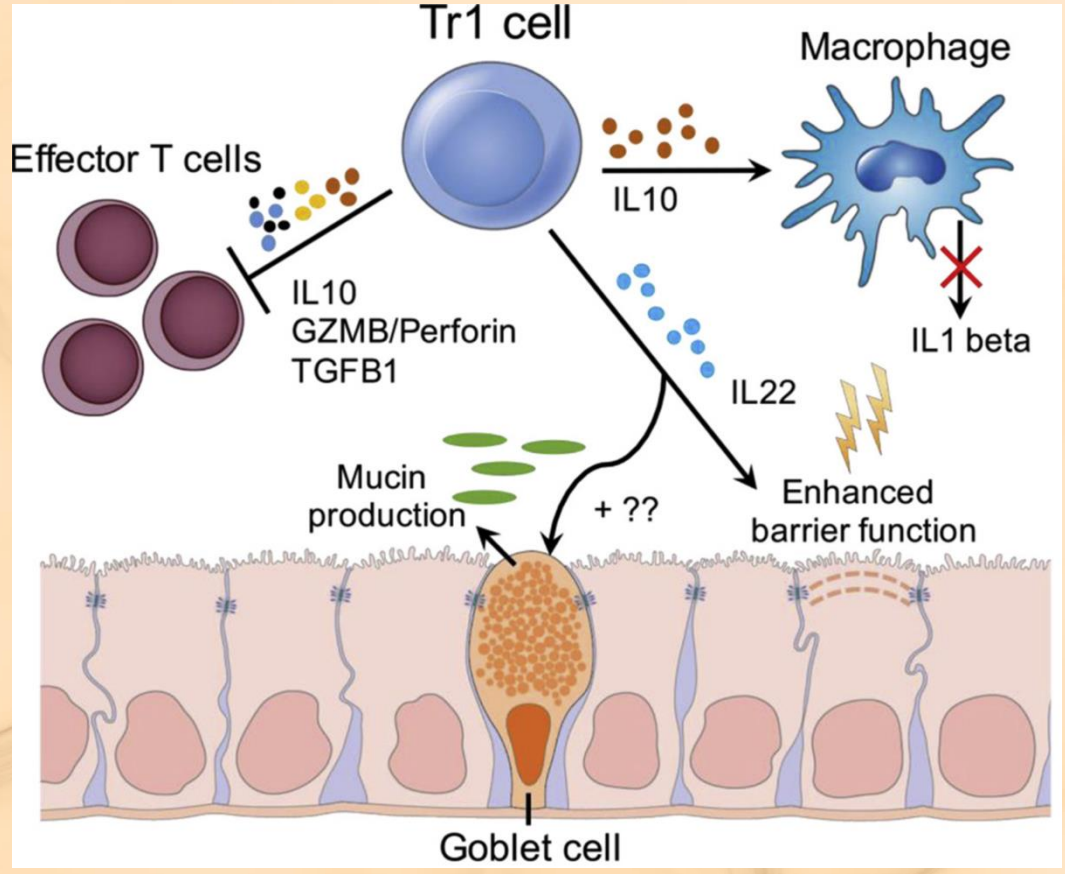




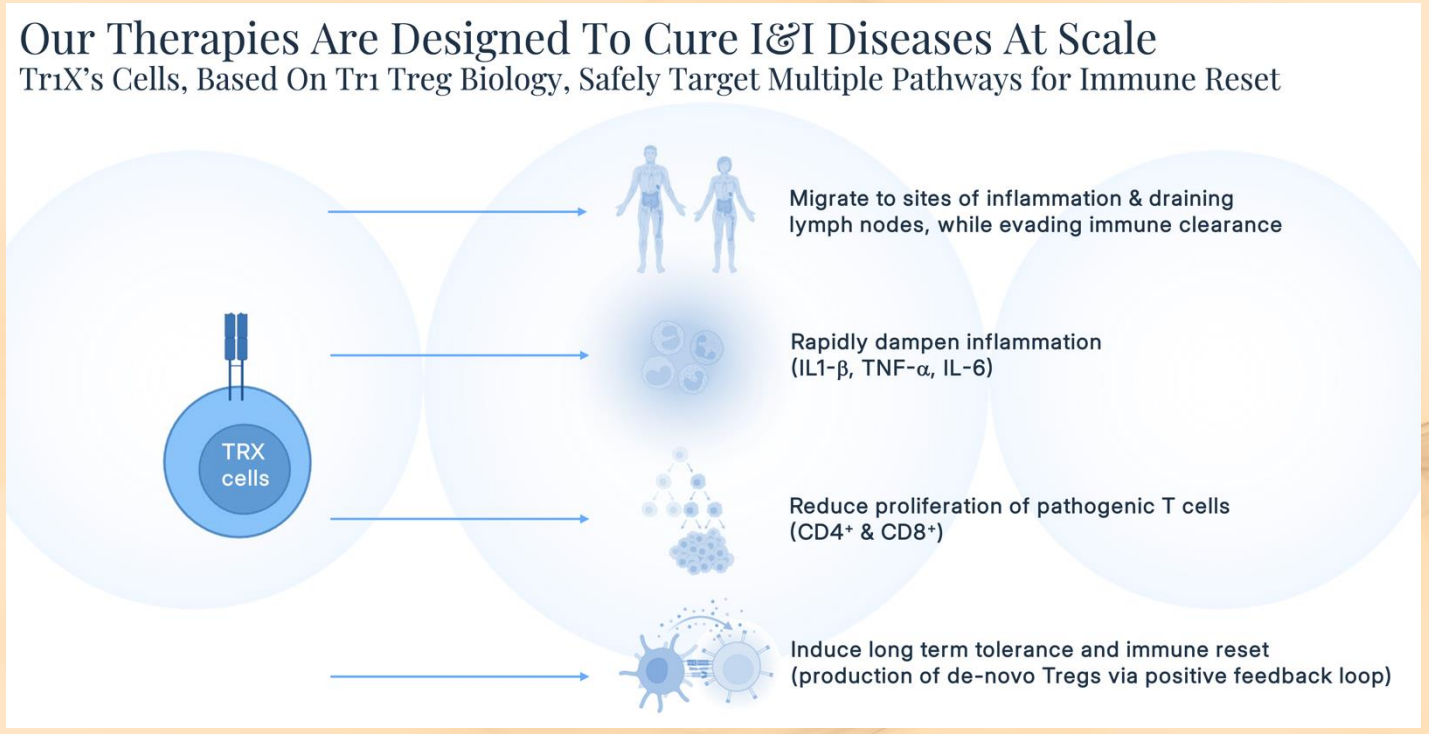
Desremeaux et al. Gastroenterology 2012.

Allogeneic Tr1 Cells for Refractory CD





From Tr1X (study sponsor)



- "off-the-shelf" engineered T cells pooled from healthy donors
- Demonstrated engraftment

TRX103-02- the RESTORE trial

RESTORE

Eligibility:
Patients who have failed two or more advanced therapies for the treatment of Crohn's, with ileal manifestation of disease, elevated CDAI Score 220-460 and SES-CD >6

Phase 1

- ✓ Cohort 1 – DL1 — N=3+3
- ✓ Cohort 2 – DL2 — N=3+3
- OR
- Cohort 3 – DL3 — N=3+3
- Cohort 2A – DL2 + lo LD — N=3+3
- Cohort 3A – DL3 + lo LD — N=3+3

Flexibility built in for additional cohort at higher dose or low levels of cyclophosphamide lymphodepletion [only if needed]

Phase 2

up to 15 pts

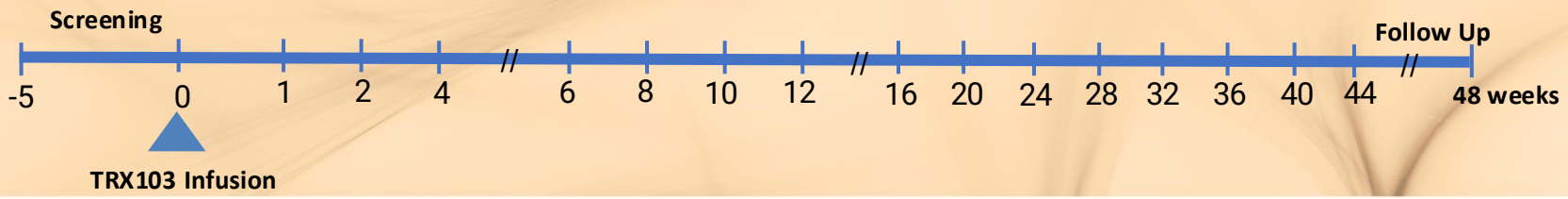
Assessments

SES-CD Endoscopic Response

Inflammation
- ✓ Fecal Calprotectin – stool
- ✓ CRP – blood
- ✓ Inflammatory biomarkers

PK/PD assessments
- ✓ $CD4^+CD271^+$, de novo Treg
- ✓ Cytokines, Transcriptomics
- ✓ Effector Immune Function

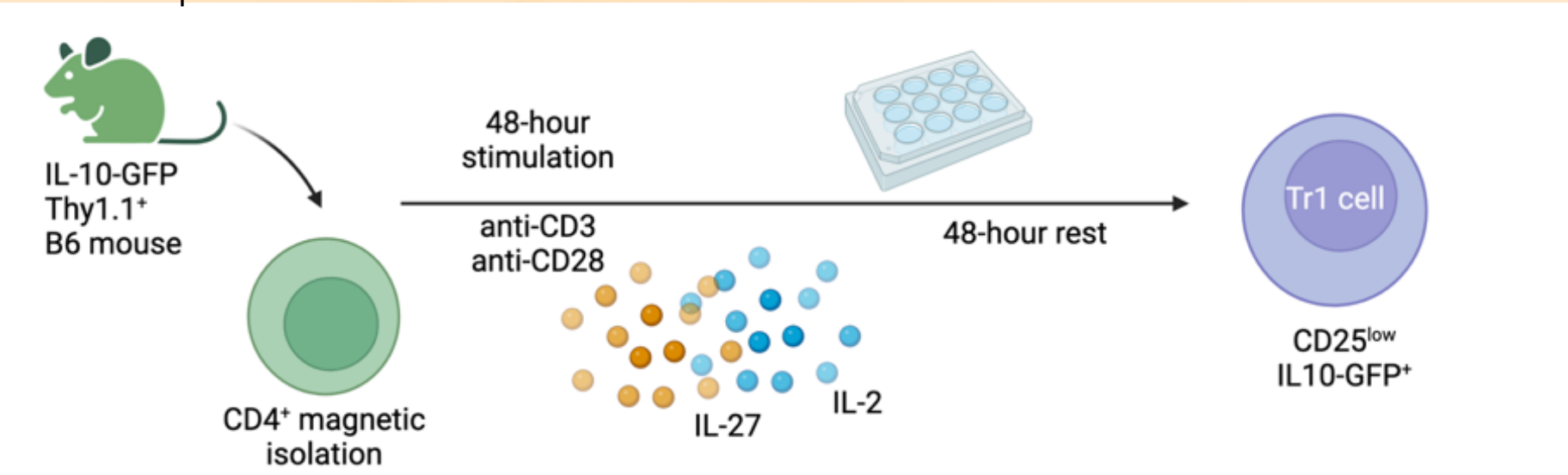
CDAI Scores and patient-reported outcomes collected on a weekly basis



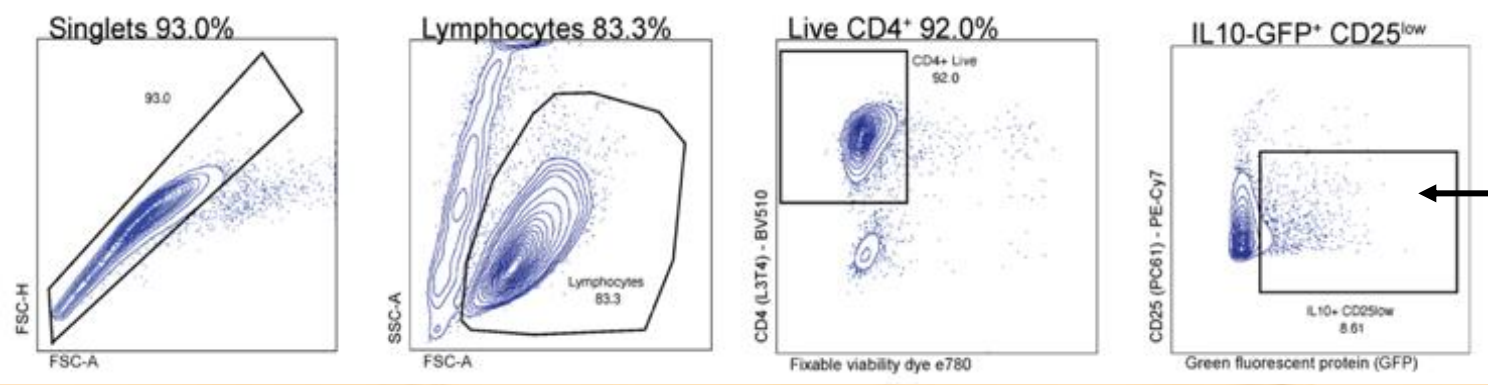
trXBIO

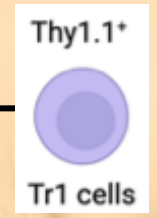
Canada Future Directions in IBD

Ex vivo expansion of Tr1 cells



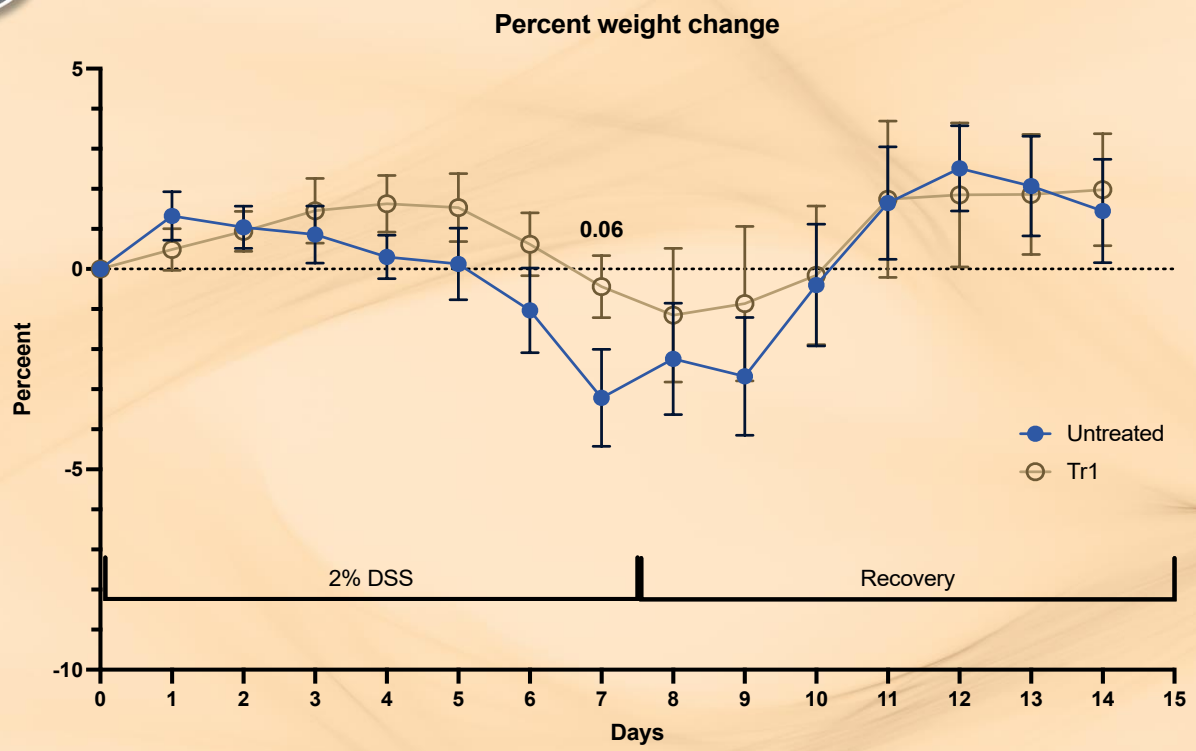
Thy1.1⁺ Tr1 isolation via FACS

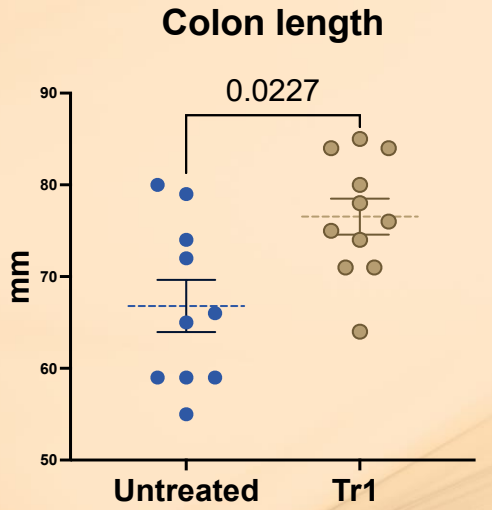


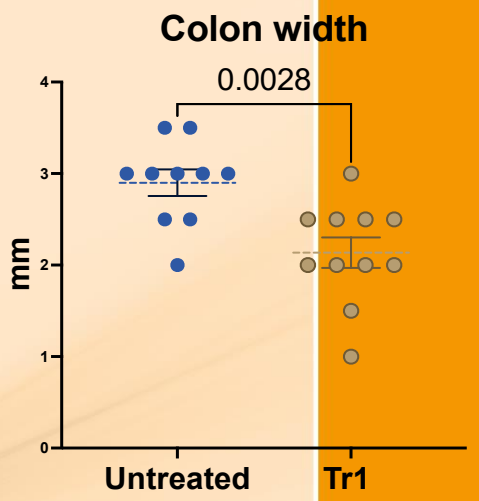


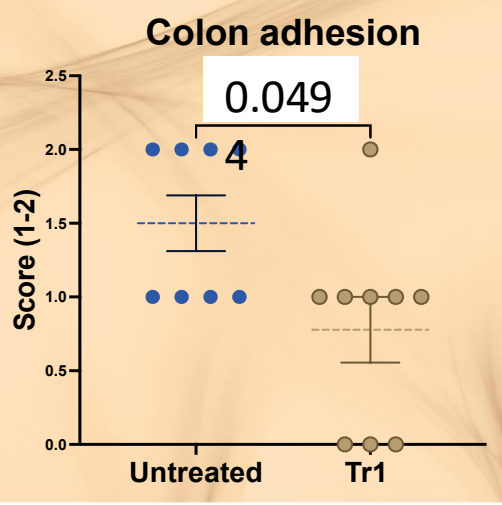
used for adoptive transfer

Tr1 adoptive transfer improves colon shortening in DSS-induced colitis mouse model





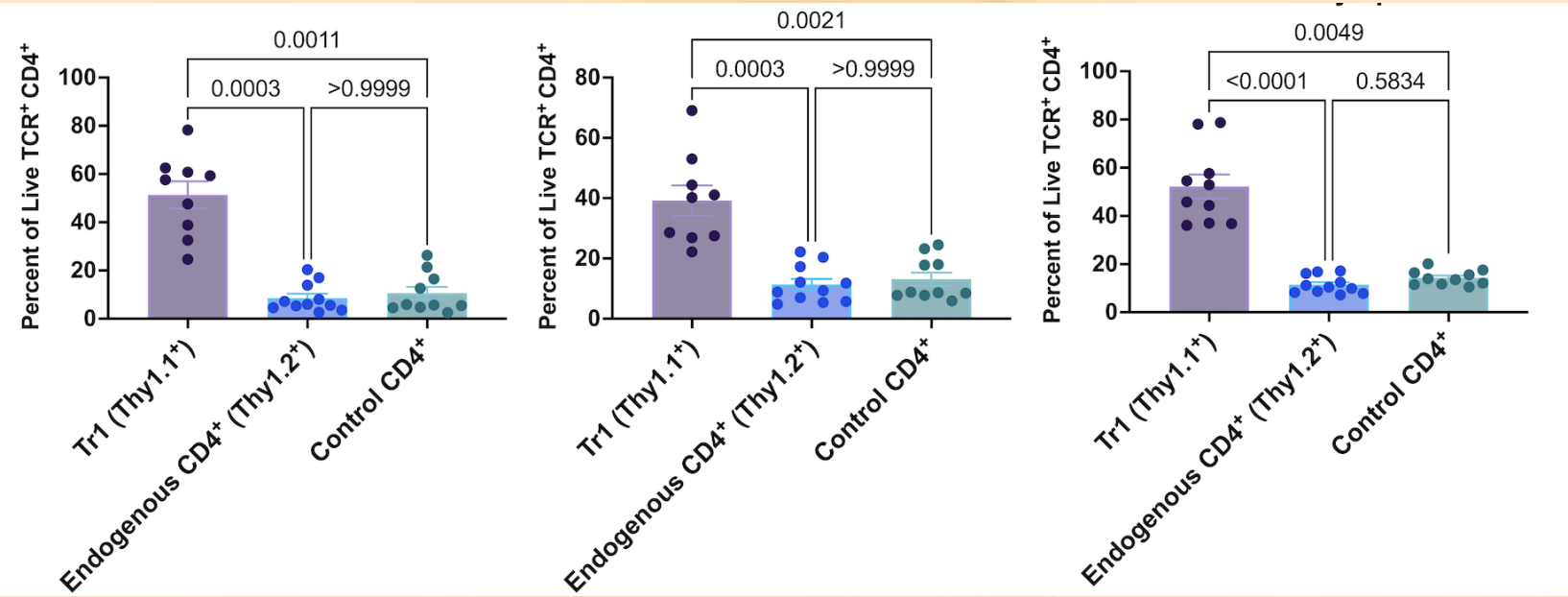


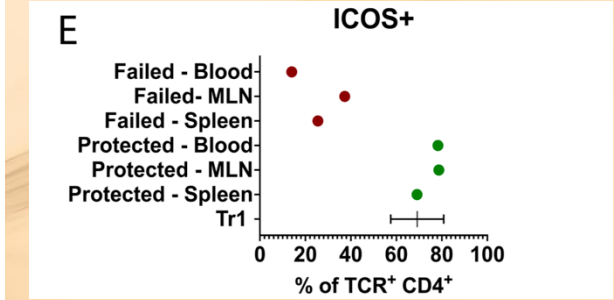


Untreated N = 10, Tr1 N = 11

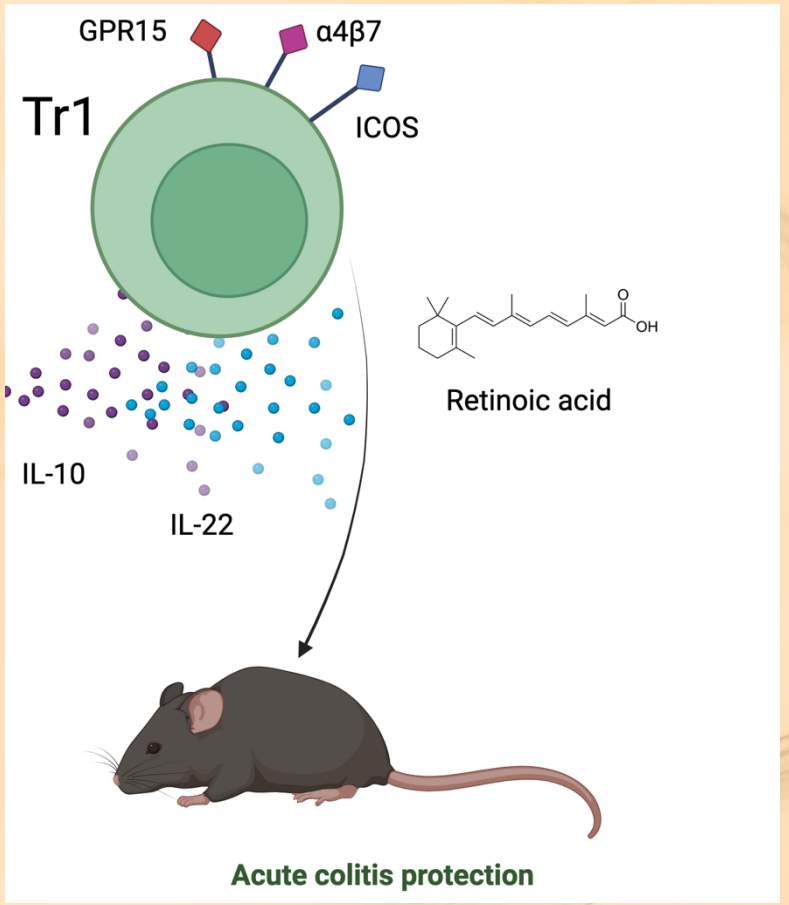
How do we identify the best Tr1 cells?

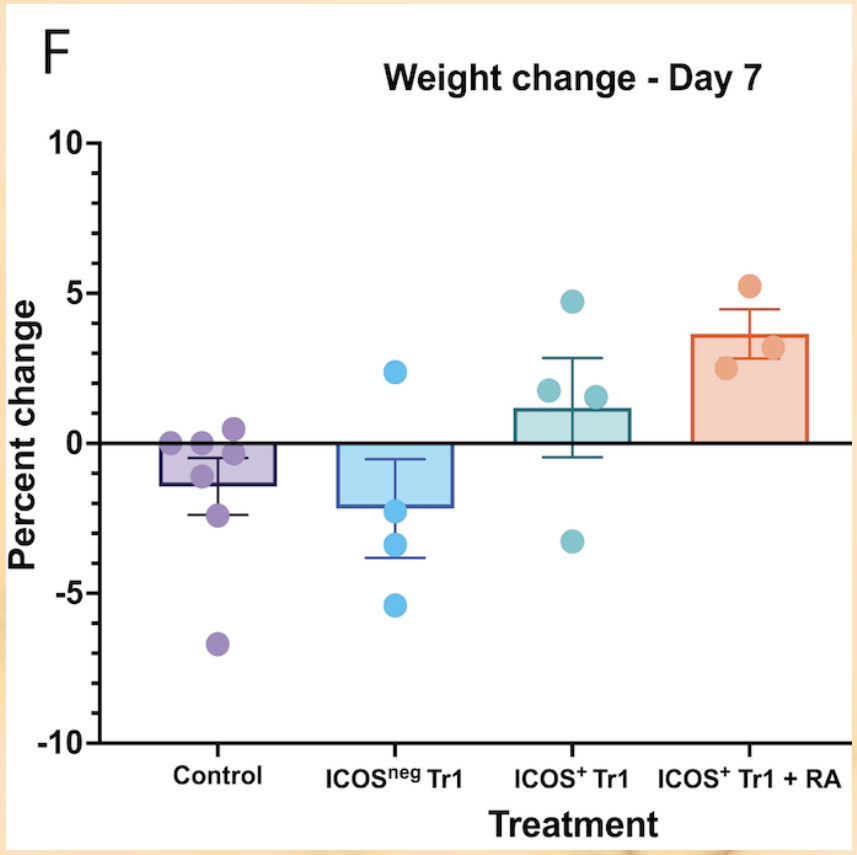
ICOS Expression





RA-conditioned Tr1 cells may improve protection



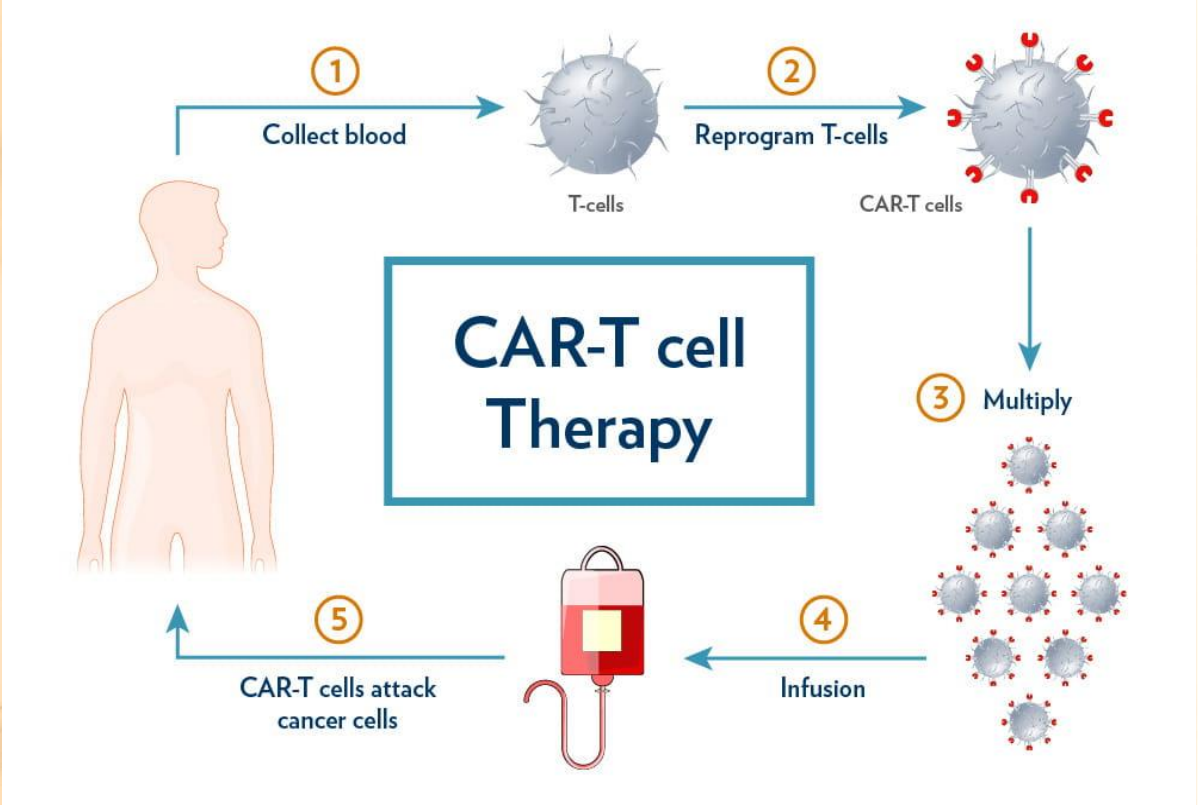


What are the potential types of cell-based therapy in IBD?

- Stem Cell Therapy
  - Hematopoietic
  - Mesenchymal
- Treg / Tr1 Based Therapy
- **Chimeric Antigen Receptor T Cell Therapy (CAR-T)**

CAR-T Therapy

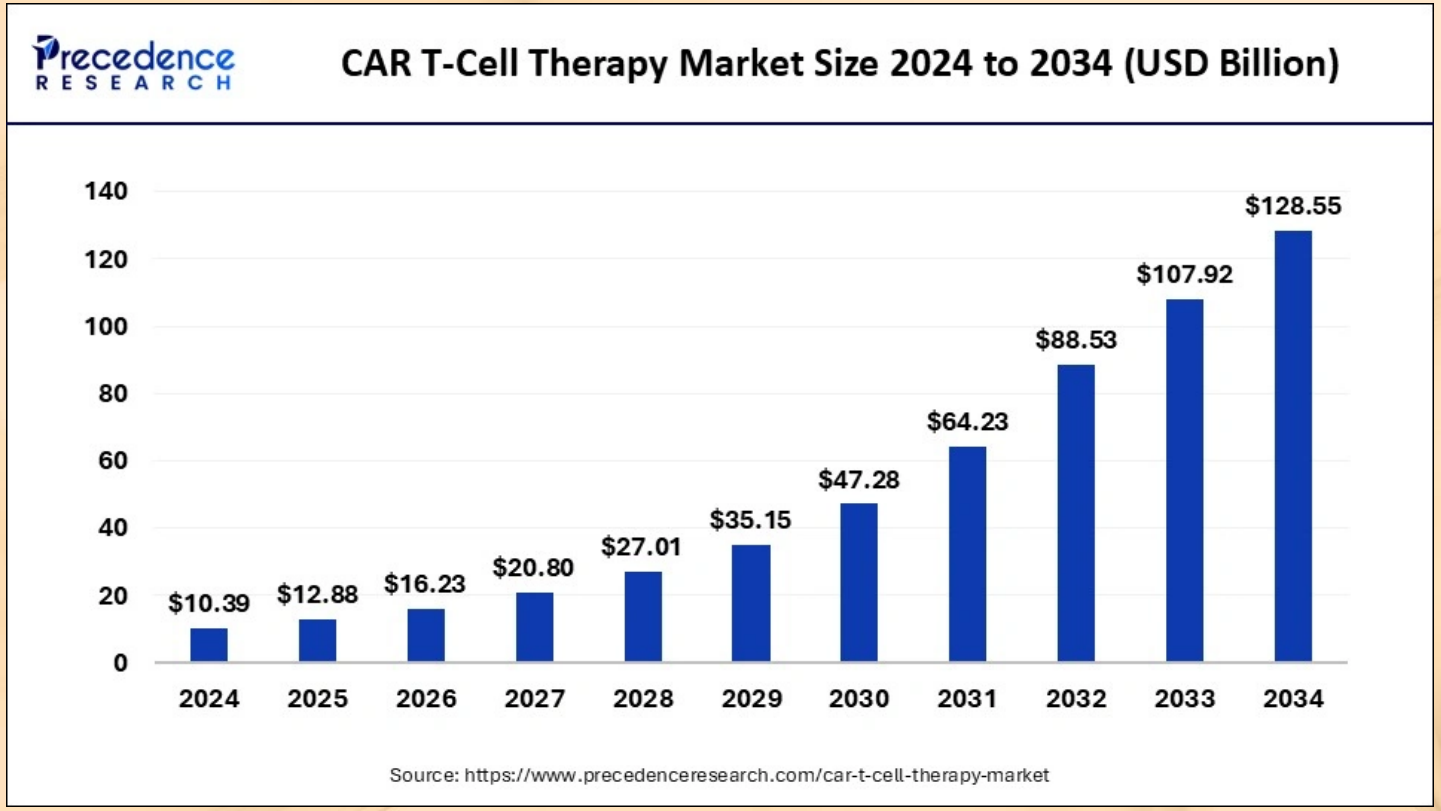
- Native T-cells genetically modified to target specific protein
- Based on single-chain antibody linked to TCR signaling domains
- Bypass normal antigen presentation pathways



B-cell targeted cytotoxic CAR-T cells

- Commercially approved in US in 2017: CD19-CAR
- Approved for refractory B-ALL and B-cell lymphomas
- Cost > $500k per patient
- Deplete endogenous and malignant clonal B cells

CAR-T therapy is expanding and poised to increase ten-fold by 2034



B cell dysfunction is being recognized in IBD

nature medicine

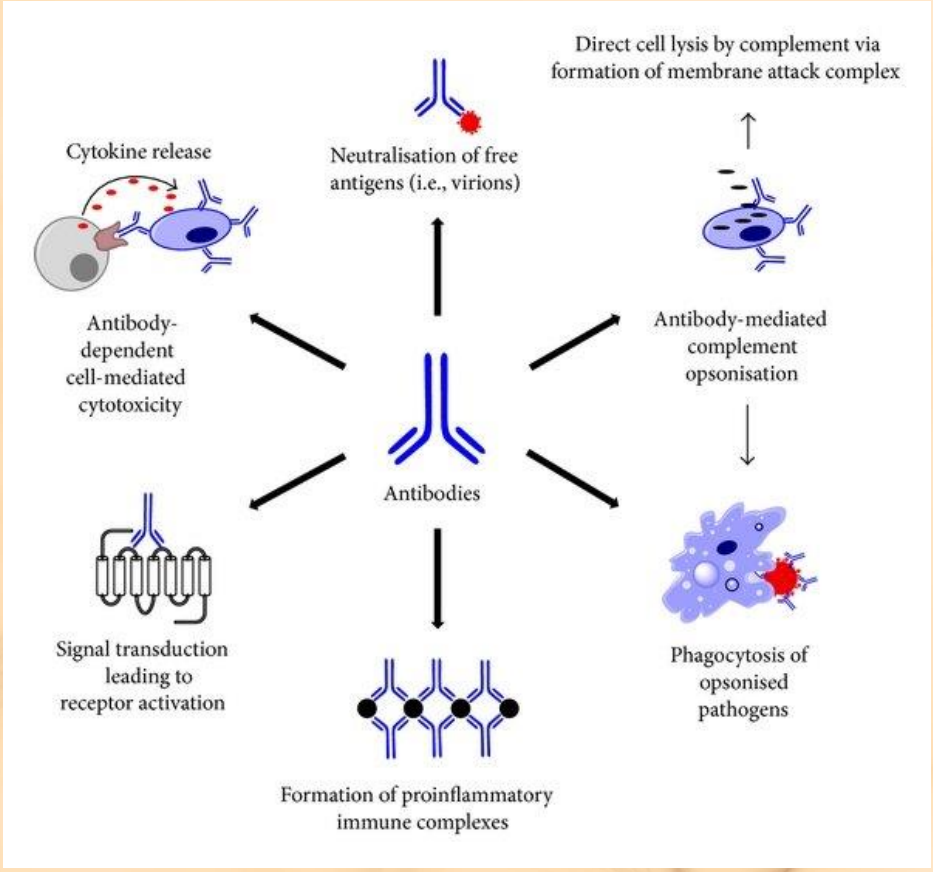
ARTICLES

https://doi.org/10.1038/s41591-022-01680-y

Check for updates

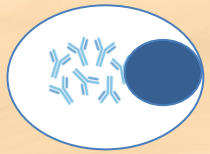
Ulcerative colitis is characterized by a plasmablast-skewed humoral response associated with disease activity

Emerging evidence of novel autoantibodies in patients with IBD



Uzzan et al, Nat Medicine 2022

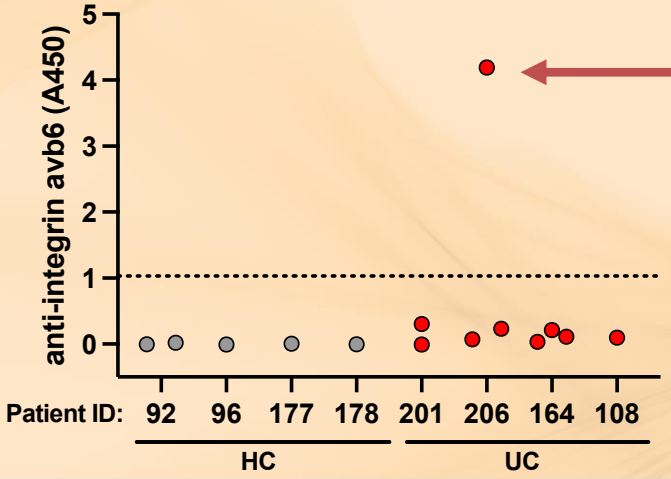
Can we detect autoreactive intestinal plasma cells in UC?

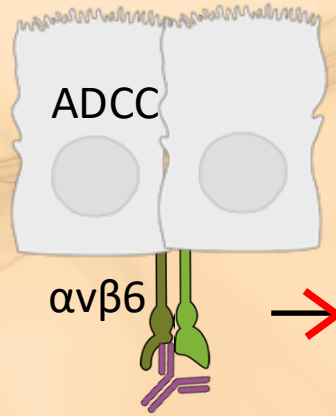


nested RT-PCR → Cloning

Antibody production and purification
UC clones
HC clones

Single cell sorted intestinal plasma cell from 4 HC and UC

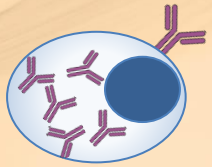




Barrier function

Intestinal inflammation

Active TGF-β



αβ6-specific plasma cells in UC

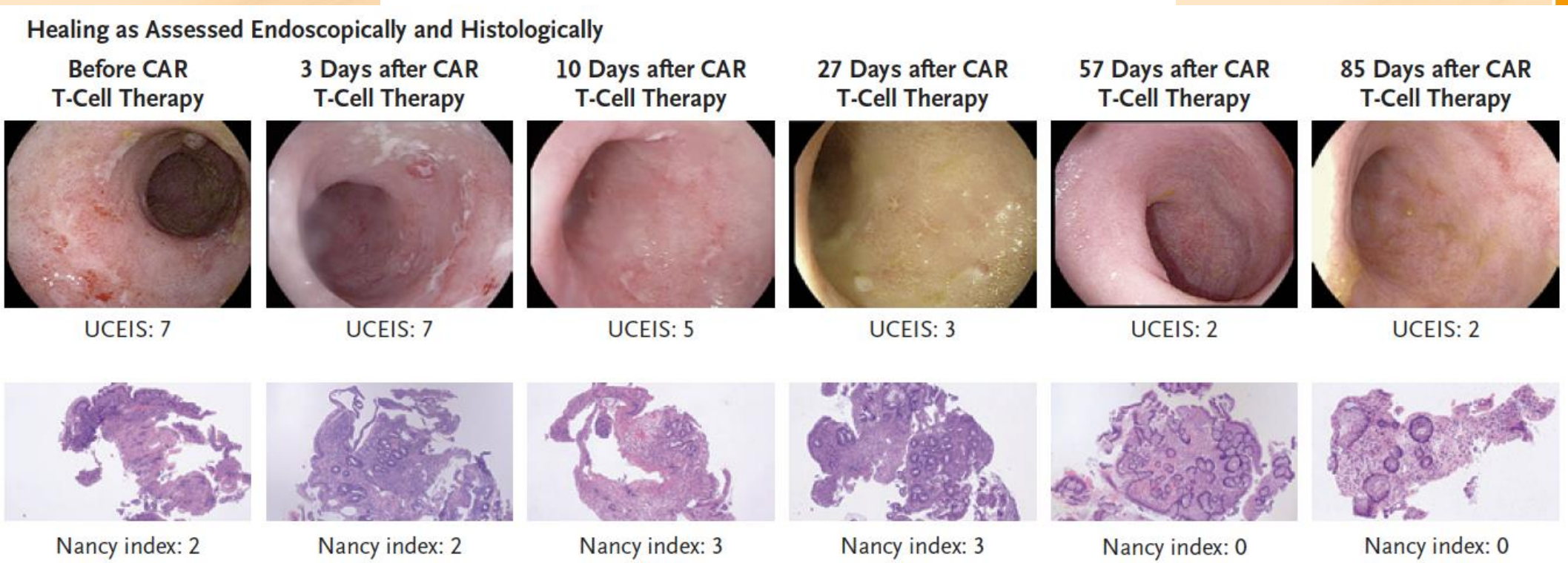
Uzzan et al. Nat. Med. 2022

Schied et al. J. Exp. Med. 2023

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

CD19 CAR T-Cell Therapy in Multidrug-Resistant Ulcerative Colitis



Muller F et al NEJM 2025

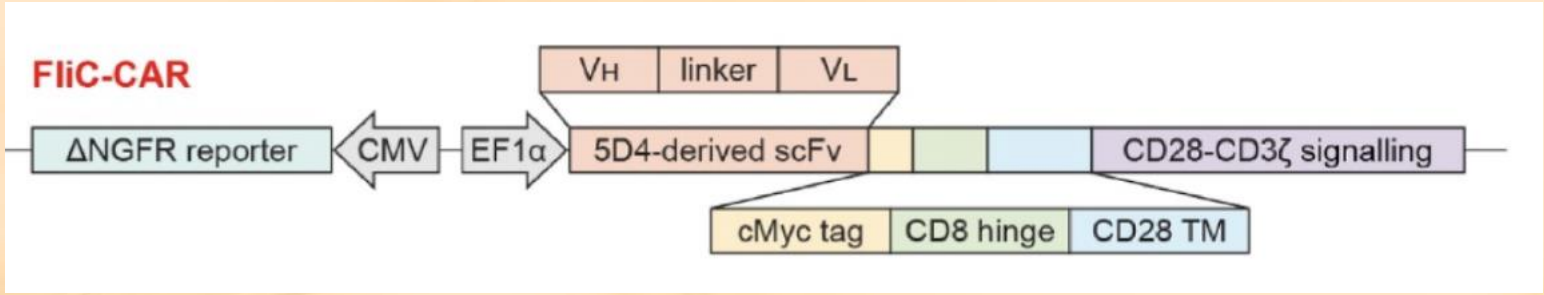
CAR-Tregs: Next frontier?

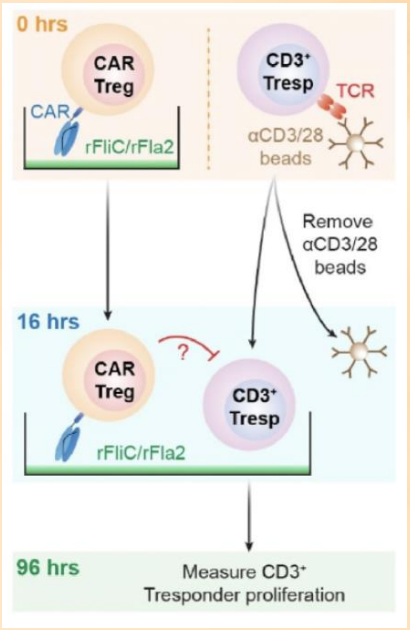
- Rather than cell depletion, goal is expansion of regulatory cells
- Treg suppression is more effective with Ag stimulation
- Targeting an Ag specific to the pathologic condition should theoretically improve activity and specificity
- Examples: HLA-A2 CAR for transplant rejection/GVHD

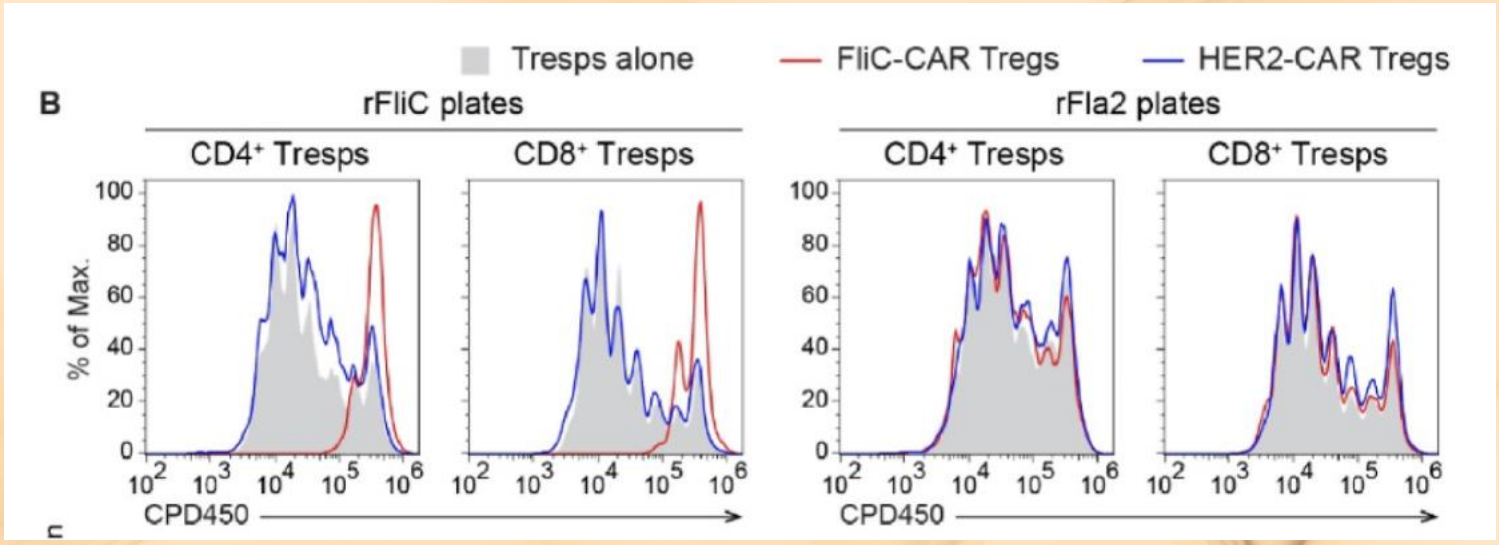
Ideal Ag for IBD?

- Should be found in the gut
- Could be human protein overexpressed in IBD, foreign protein (e.g. OVA), or microbial protein
- Should not be cancer-associated

FliC CAR-Tregs: Proof of principle







Boardman et al, J. Autoimmun. 2023

Future: Active Cell Therapy Trials in IBD

Program / Product	Cell type & source	Indication & delivery	Phase	Current status (per source)	Registry / Source (latest info)	Notes (latest)
TRX103 (Tr1X)	Allogeneic engineered **Tr1-Tregs**	**Crohn's disease (moderate–severe, refractory)**; IV infusion	Ph 1/2a (dose-esc/exp)	**Active** (US, multi-center)	**NCT06721962**	Novel tolerance-restoring approach (Tr1)
AVB-114 / STOMP-II (Avobis Bio)	**Autologous** MSCs **seeded on a matrix plug**	**Crohn's perianal fistula**; local surgical placement	Ph 2	**Active, not recruiting** (US)	**NCT04847739**	Biomaterial strategy for fistulas (tissue repair + immunomodulation).
TH-SC01 (UC-MSCs)	**Allogeneic umbilical-cord MSCs**	**Crohn's perianal fistula**; local injections	Ph 2/3 (regional)	**Active** (site-level registries)	**NCT04939337**	One of several UC-MSC programs pivoting into CPF post-darvadstrocel.
PF2020-CELL (UC-MSCs)	**Allogeneic umbilical-cord MSCs**	**Crohn's perianal fistula**; perilesional injection	Early phase	**Active** (site-level)	**NCT05039411**	Protocol specifies multi-site perilesional dosing spacing.
Remestemcel-L (BM-MSCs)	**Allogeneic bone-marrow MSCs**	**Ulcerative colitis**; **endoscopic** submucosal injection to inflamed segments	Ph Ib/IIa	**Active (academic)** — feasibility program with ongoing work	**NCT04543994**	Early signals of symptom/endoscopic improvement within weeks post-delivery.
CD19 CAR-T FAU Compassionate Use	Effector CD19 CAR-T cells + lymphodepletion	**Ulcerative colitis (refractory);** IV infusion	Single case study	**Active (academic) –** additional patients considered	n/a	Rapid and sustained B cell depletion resulted in endoscopic improvement
Autologous FOXP3 Nuremberg U.	Autologous enriched FOXP3 Tregs	**Ulcerative colitis (refractory);** IV infusion	Phase 1/2a	**Active (academic)** — feasibility program with ongoing work	n/a	Inflammatory biomarker improvements

Where May Cell Therapy Fit in Treatment of IBD?

- Multiple refractory patient
- Currently, HSCT only in select expert referral centers for most refractory patients
- Primarily in clinical trials or ”compassionate use” exceptions
- Need for further prospective trials
- Potential for earlier use and/or combination with other therapy?

Thank You!