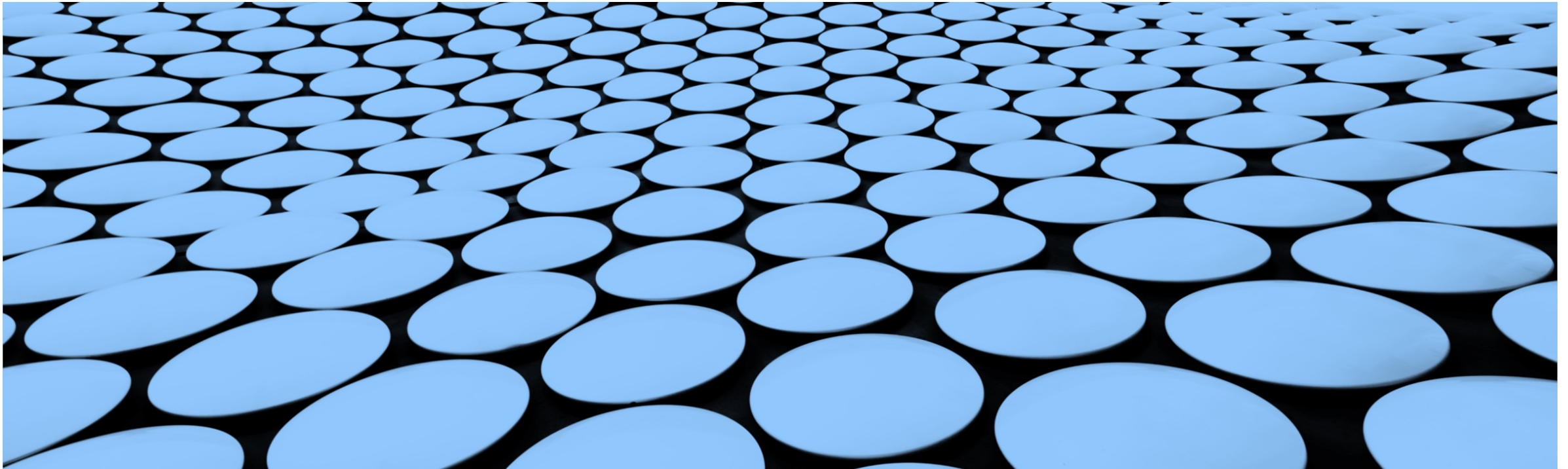


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# CLINICAL TRIAL ECOSYSTEM FOR IMMUNE TOLERIZATION

BRIAN WEINSHENKER MD,  
UNIVERSITY OF VIRGINIA



# Ultimate Goal: Curative Therapy

***ULTIMATELY A CURATIVE STRATEGY WILL REQUIRE DURABLE OR PERMANENT INTERFERENCE WITH MECHANISMS THAT LEAD TO AUTOREACTIVE ANTIGEN PRESENTATION AND PROPAGATION OF IMMUNE MISRECOGNITION TO HUMAN PROTEINS SUCH AS AQP4, MOG OR OTHER DISEASE-SPECIFIC AUTOANTIGEN***

# Basic Premise of Immune Tolerization



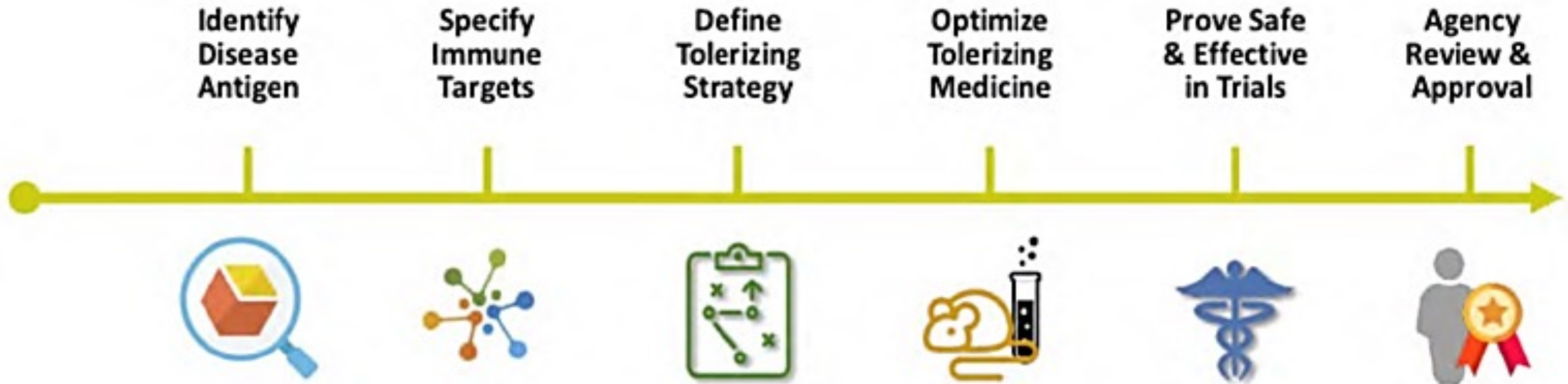
## Ideal Features of Tolerizing Therapies:

- **More Specific**
  - Antigen-targeted
  - Critical immune effectors
- **Boosts Tolerance**
  - Enhances regulation
  - Central or peripheral
- **Long-Term Efficacy**
  - Extended dosing intervals
  - Potential permanent cure
- **Improved Safety**
  - Less immunosuppressive
  - Spares host defenses
- **Better Tolerability**
  - Fewer off-target effects
  - Autologous / Inert

# NMO: Ideal Model for Immune Tolerization

- ✓ Auto-Ag AQP4 & critical epitope targets are known
- ✓ Pathogenic mechanisms and pathways established
- ✓ Specific clinical phenotypes & relapse adjudication
- ✓ Robust & increasing prevalence in US & worldwide
- ✓ Orphan disease status and fast-track opportunities
- ✓ 4 approved drugs: relapses occur; key AEs & costs
- ✓ GJCF assets: CIRCLES, genotypes, patient synergies

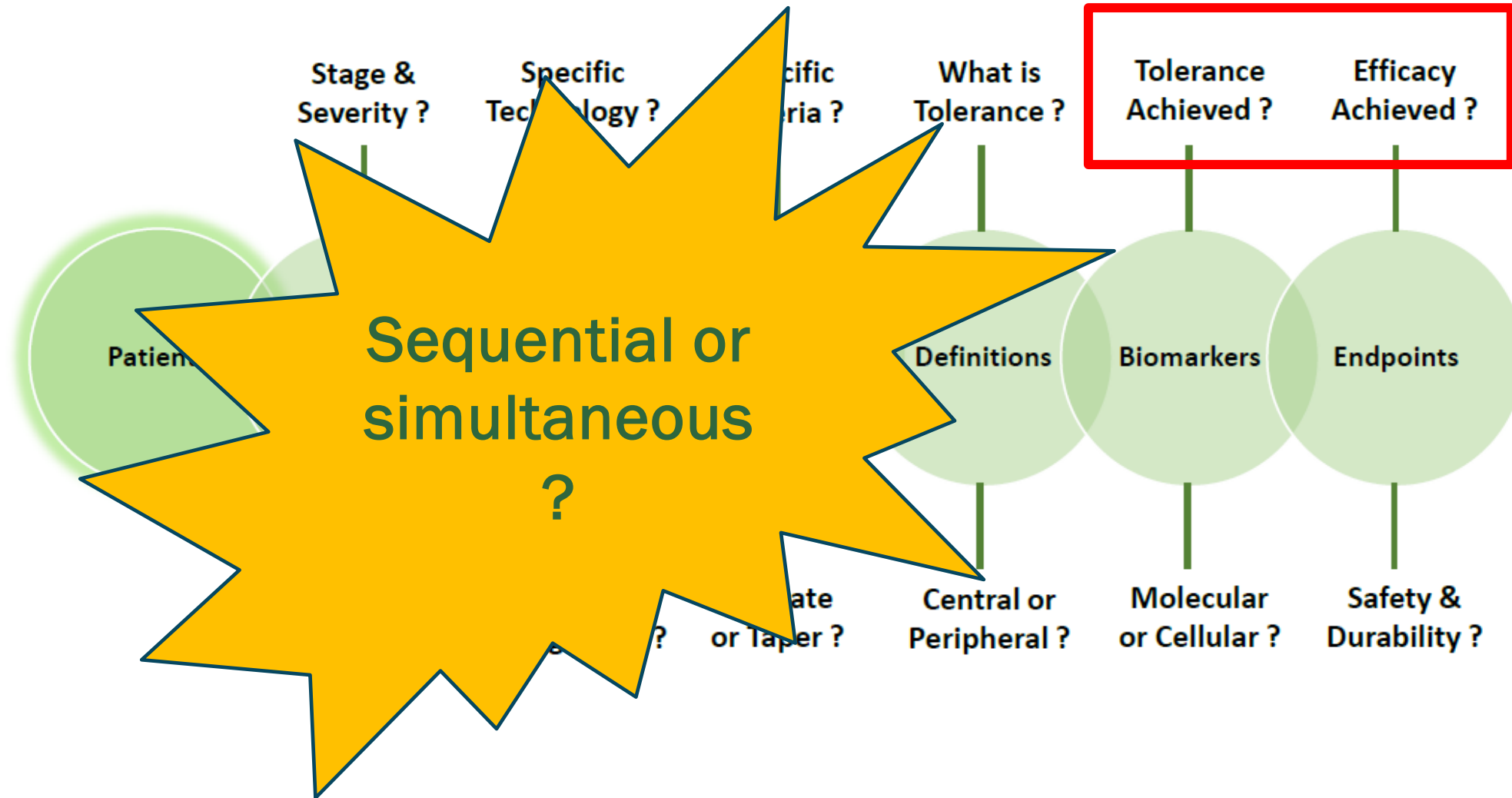
# — Roadmap to Immune Tolerization Cures —



**Source:** GJCF-ITN-NIH Tolerization Summit [2016] Access: [www.guthyjacksonfoundation.org](http://www.guthyjacksonfoundation.org)  
Modified from **Immune Tolerance Network** [2022] Access: [www.immunetolerance.org](http://www.immunetolerance.org)

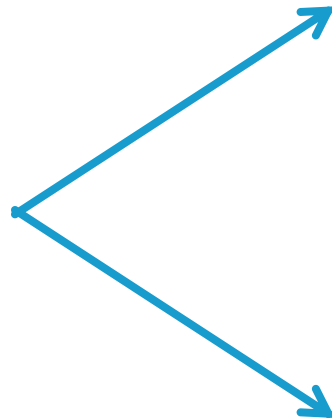


# Key Concepts in Tolerization Trial Design

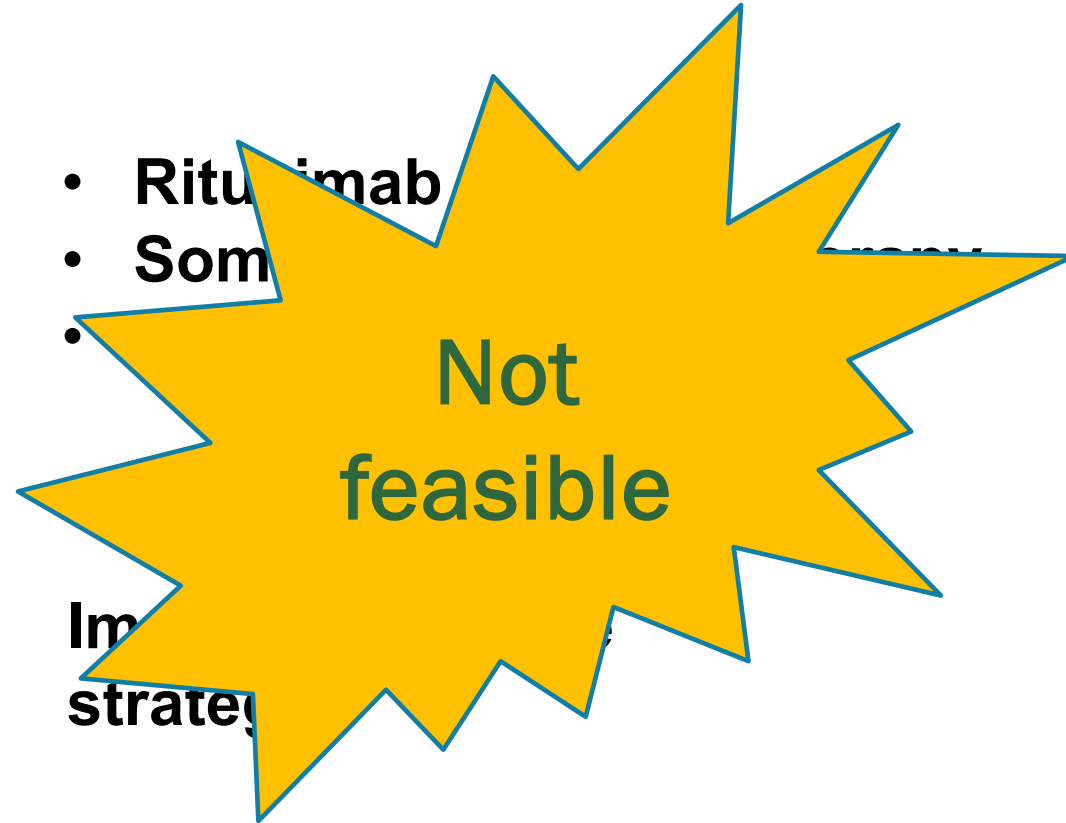


# Potential Investigative Strategy

## INVESTIGATIVE STRATEGIES



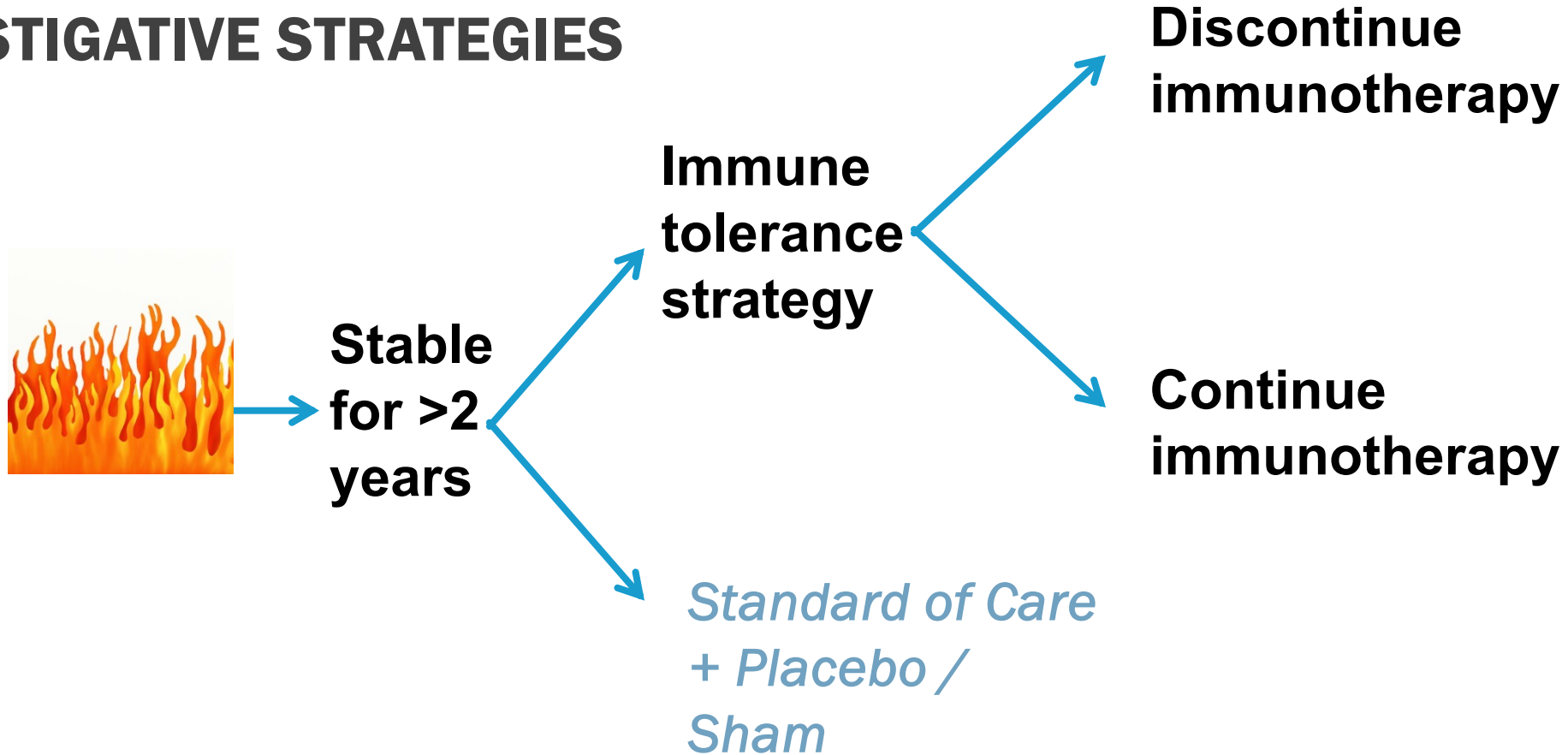
- Rituximab
- Some
- 



Im  
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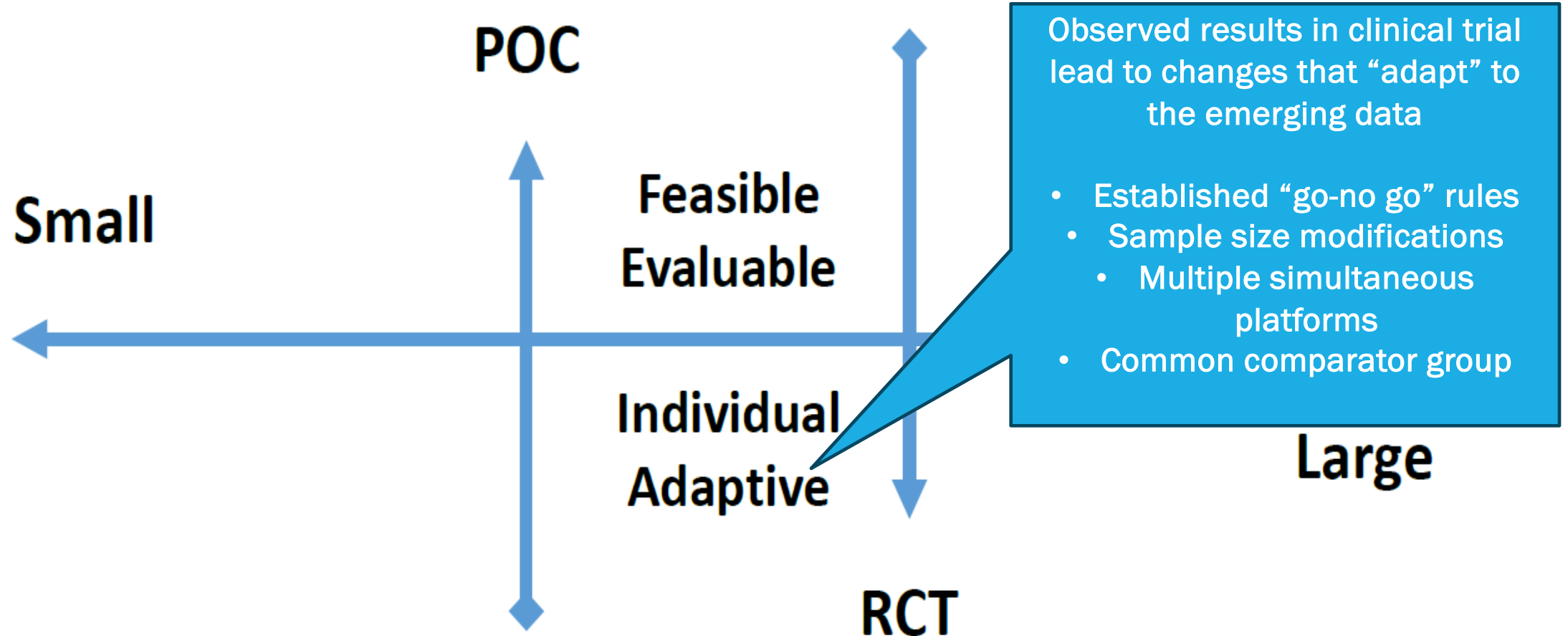
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## INVESTIGATIVE STRATEGIES

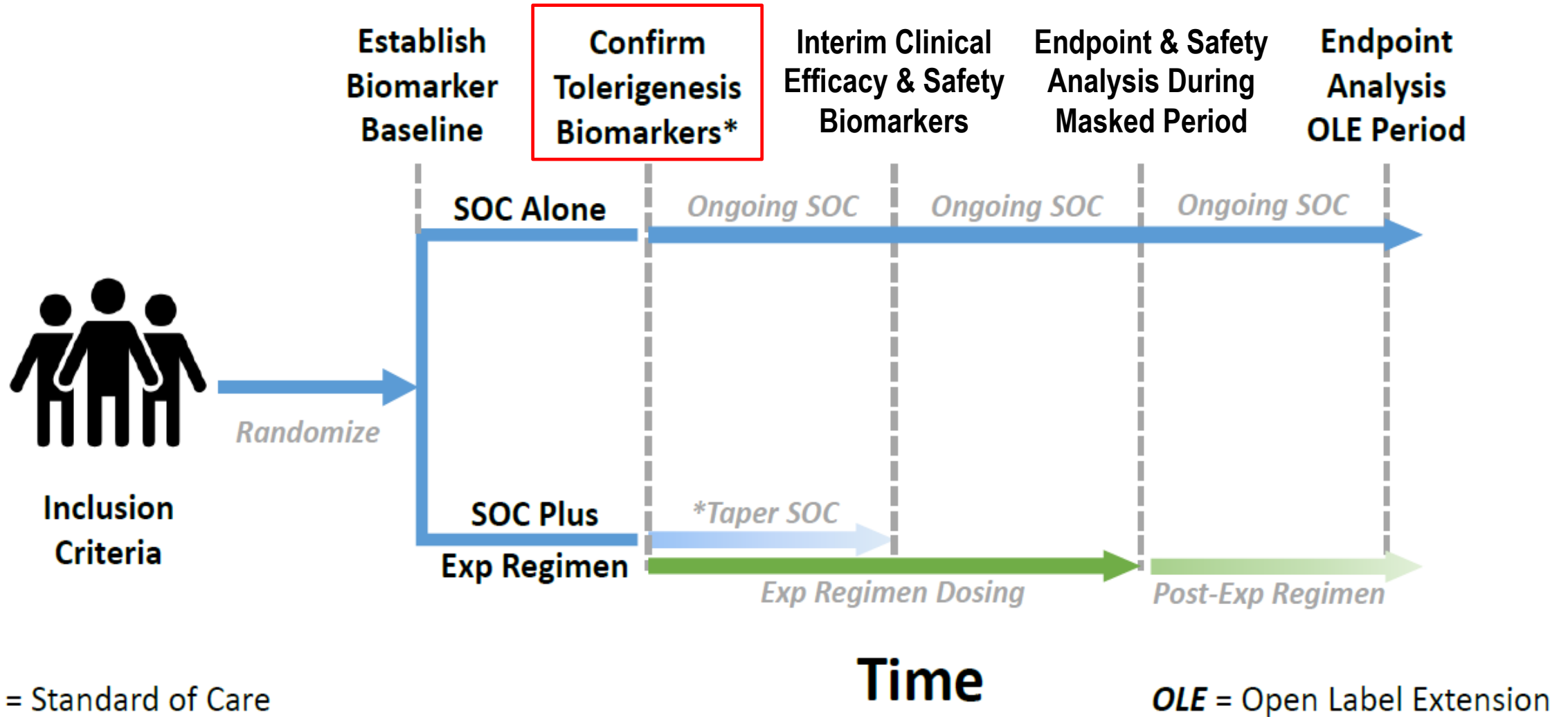




# Tolerization Clinical Trial Options



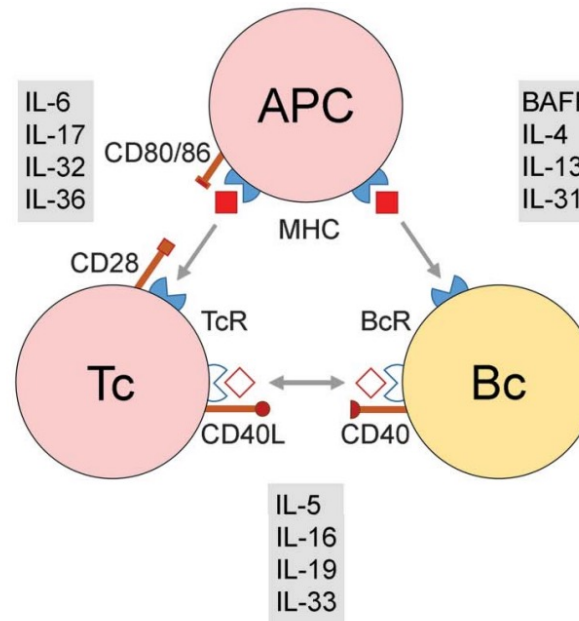
# Clinical Trial Consensus Working Model



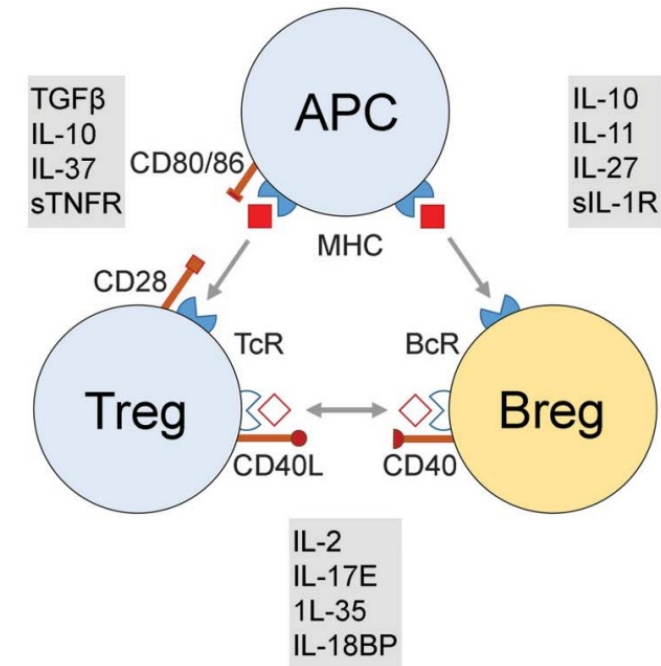
# Biomarkers of Immune Tolerization

- Antigen reactivity
- B cell activation
  - AQP4-IgG/MOG-IgG titers
  - Class switching in cervical lymph nodes
- Cell subsets
  - T vs B cell
  - Effector vs suppressor
- Autoreactive cells
- Cytokine signatures:
  - IFN alpha
  - Th2/Th1
    - Confounding by cytokine release (e.g. CAR-T therapy)

## Autoreactive



## Tolerigenic

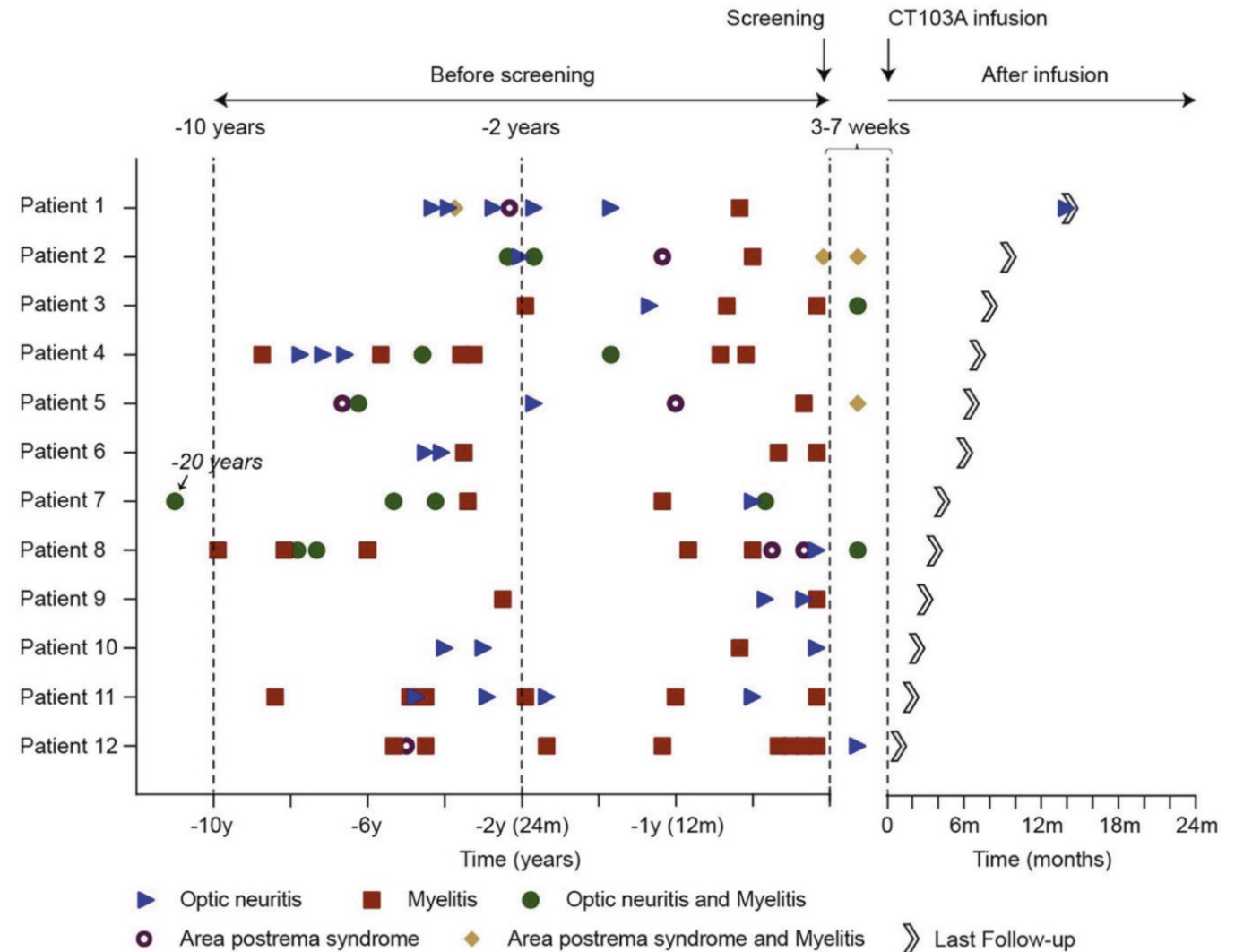


# Equecabtagene Autoleucel in AQP4-IgG+ NMO

- BCMA aka TNFRSF17 aka BAFF Ligand
- fhCT103A Autologous Anti-BMCA CAR-T
- 12 Patients – Median Age 49.5; 83% F
- History: ARR  $\geq 2$  and Tx-Refractory Dz
- All Patients Experienced Grade 3 AEs
- Pan-Cytopenia and/or CRS; No ICANS
- UTI, CMV Common ID Issues; No PML
- No Patient Needed Tocilizumab (CRS)

## RESULTS

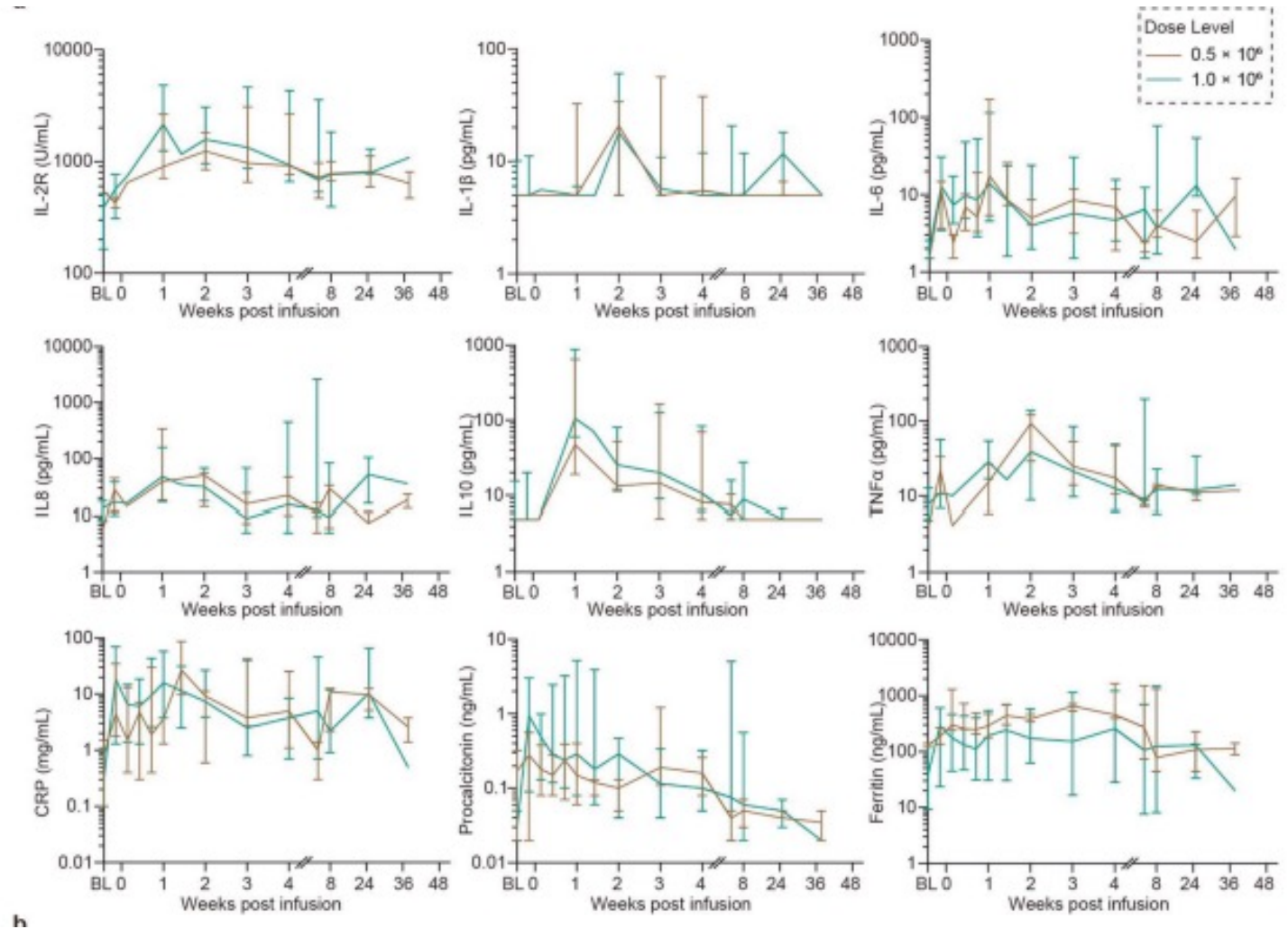
- No Relapse in 11/12 Pts Up to 14 Mo
- Anti-AQP4+ Titer: 1:1400 down to 1:5
- Median EDSS: Pre = 7.0 vs. Post = 4.5
- IASO Biotherapeutics files BLA (China)



# ■ Equecabtagene Autoleucel in AQP4-IgG+ NMO ■

## BIOMARKERS

- Antigen reactivity
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Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory...  
Qin et al.

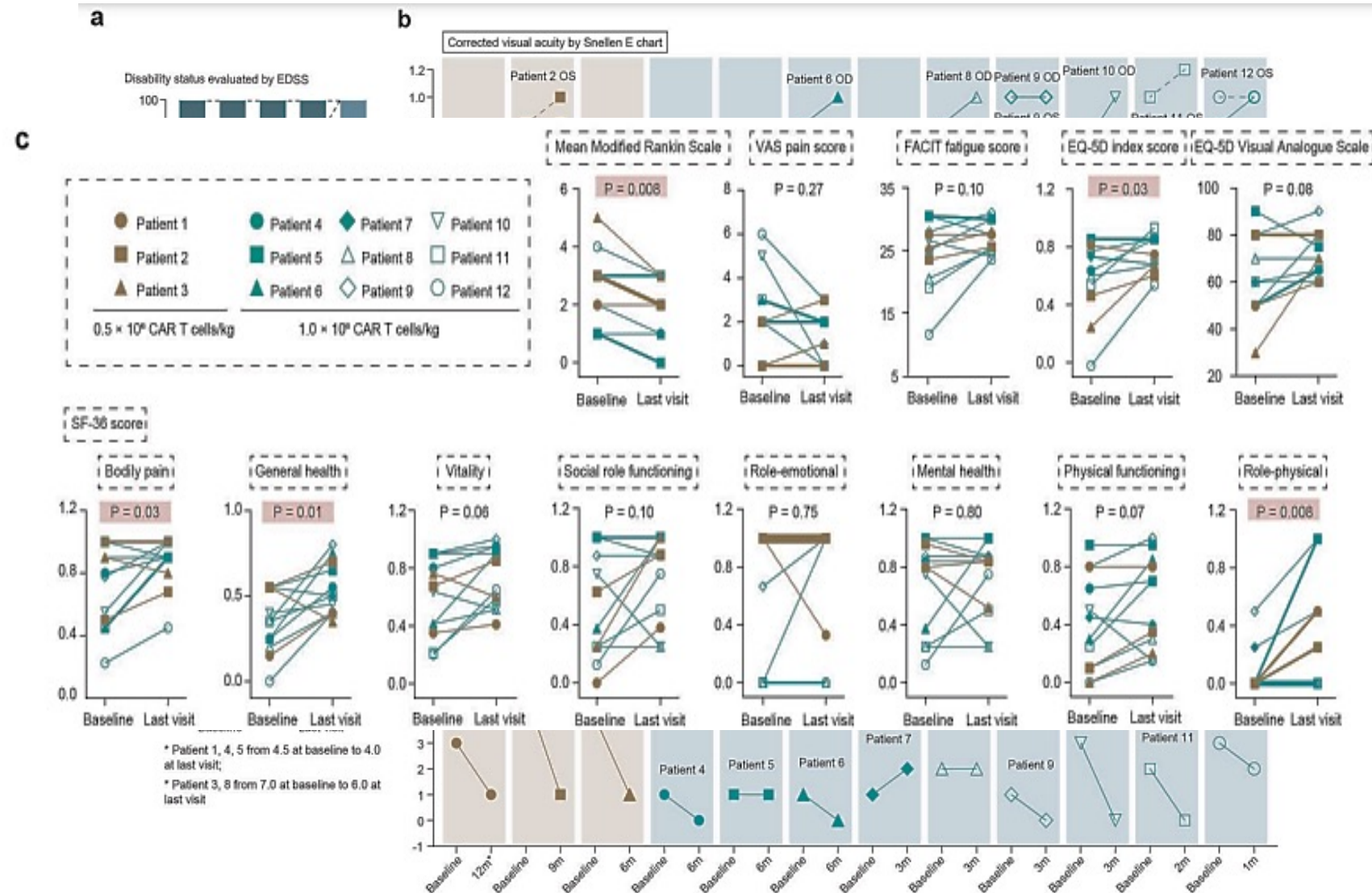
*Signal Transduction and Targeted Therapy* (2023)8:5  
<https://doi.org/10.1038/s41392-022-01278-3>



(continued)

## CLINICAL EFFICACY

- Relapses
- MRI activity
- GFAP and markers of cellular injury
- Disability
- Fatigue
- Pain



Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory...

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# Summary & Prospectus

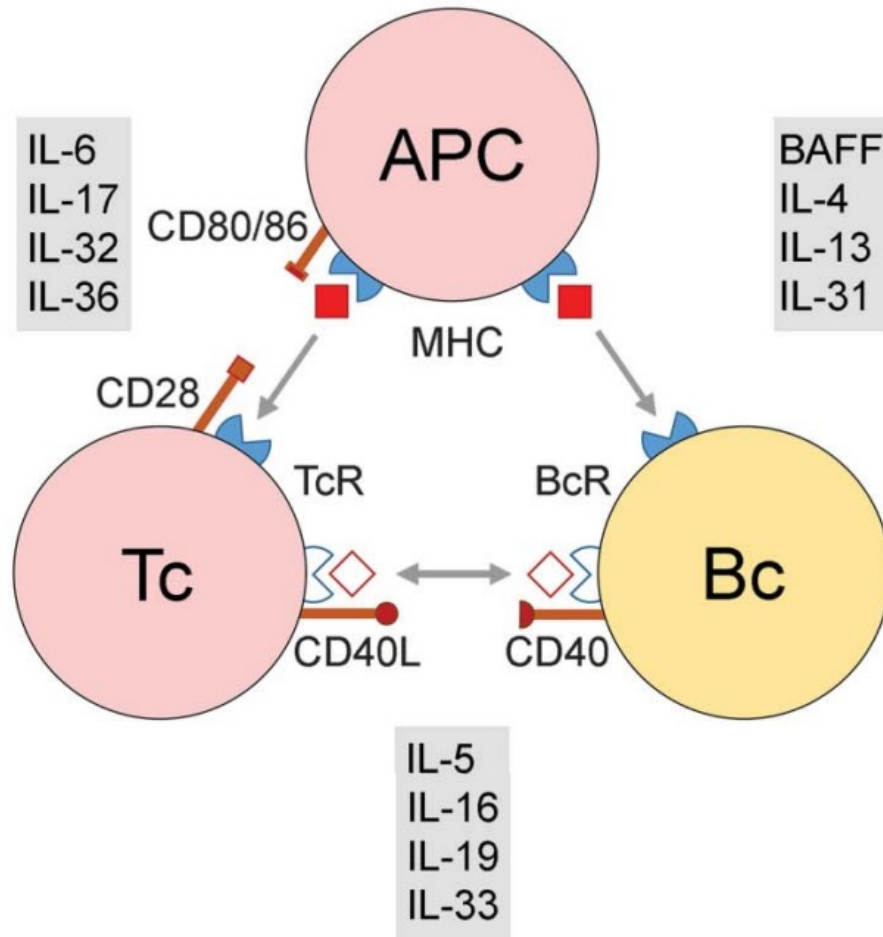
## Key Trial Design Questions & Challenges

- Which patients: *Stable or Failing Treatment ?*
- Disease stage: *Early Onset or Later in Course ?*
- Technology platforms: *Priorities & Comparators ?*
- Tolerigenesis biomarkers: *Known or Needed ?*
- Safety signals: *Relapse and Key Adverse Events ?*
- Efficacy signals: *Remission & Reduced Disability ?*
- Treatment history: *Current and Past Heterogeneity ?*
- Concomitant therapy: *Reduced informativeness; mitigate risks ?*
- Comparator group: *Modified Placebo Control (SoC) ?*
- Endpoints: *Credible Non-relapse Metrics of Efficacy ?*
- Trial network: *Multi-Platform and Adaptive Designs ?*
- Durable efficacy: *Boosting vs. Permanently Curative ?*

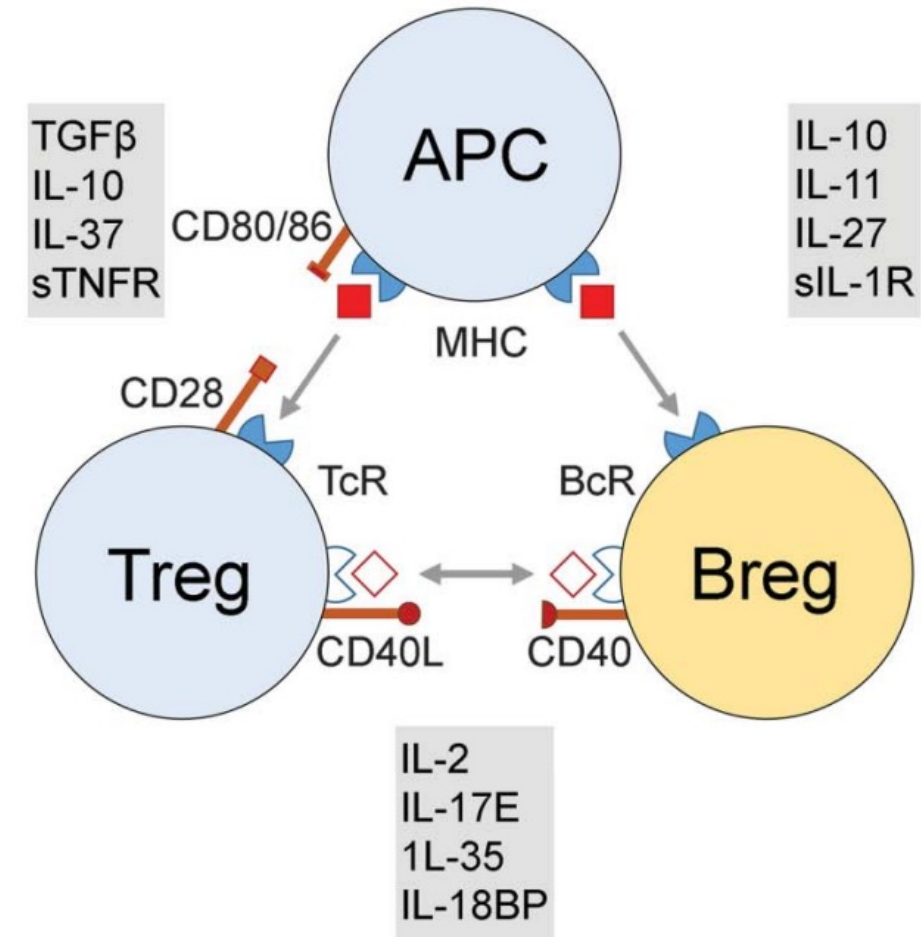


# Biomarkers of Immune Tolerization

## Autoreactive



## Tolerigenic



(continued)

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