Sequential immunotherapy for functional cures in autoimmunity

Robert Plenge, MD, PhD

EVP, Chief Research Officer, Head of Research

Three key Research principles to improve R&D productivity

Causal human biology

Application of human data (e.g., genetics, longitudinal profiling of patient samples) for rigorous target validation in drug discovery

Matching modality to mechanism

Invention of high-quality therapeutics that match a modality to a molecular mechanism of action

Path to clinical proof-of-concept

Targeted patient selection (e.g., biomarkers) and clear translational endpoints for improved clinical success

Our ambition is to increase the number of INDs with transformational potential and increased probability of success across all stages of clinical development

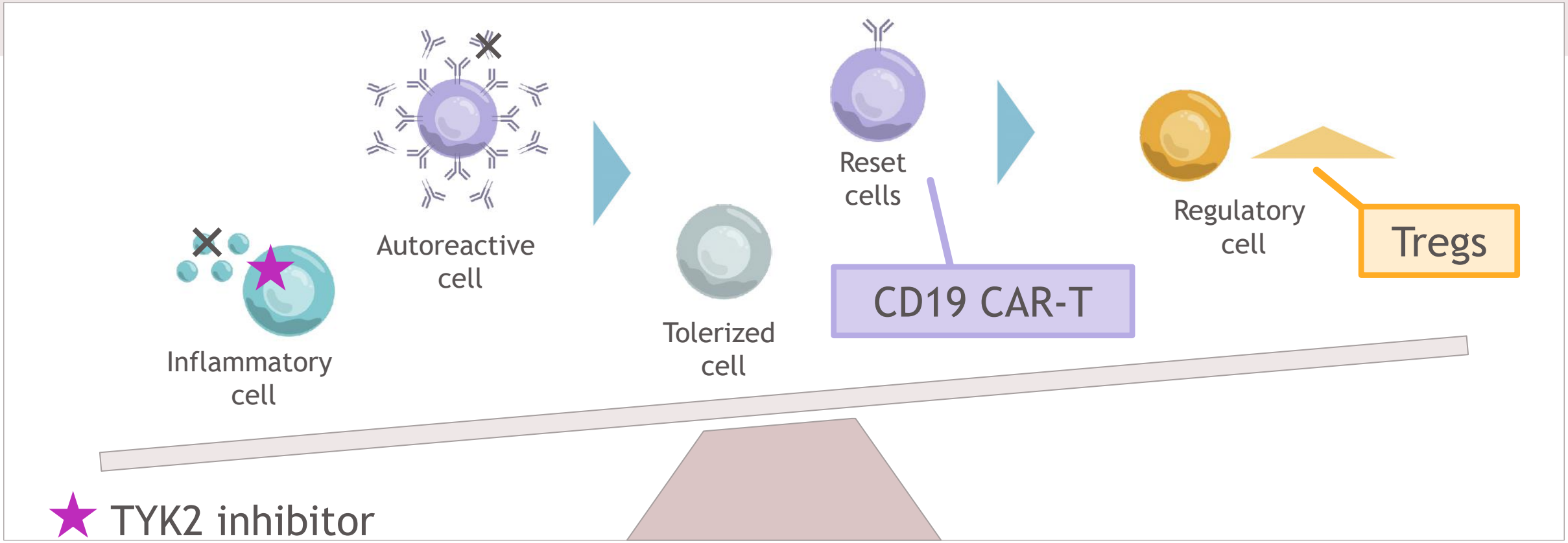

WE WORK FOR
Monique
Living with lupus and awaiting new treatment options - U.S.

Sequential Immunotherapy strategy in SLE

01
Suppress inflammation

02
Reset the immune system

03
Promote homeostasis and tissue repair



Francisco Ramirez-Valle, et al Nature Reviews Drug Discovery 2024 *in press*

Focus on two programs: TYK2 inhibition and CD19 CAR-T

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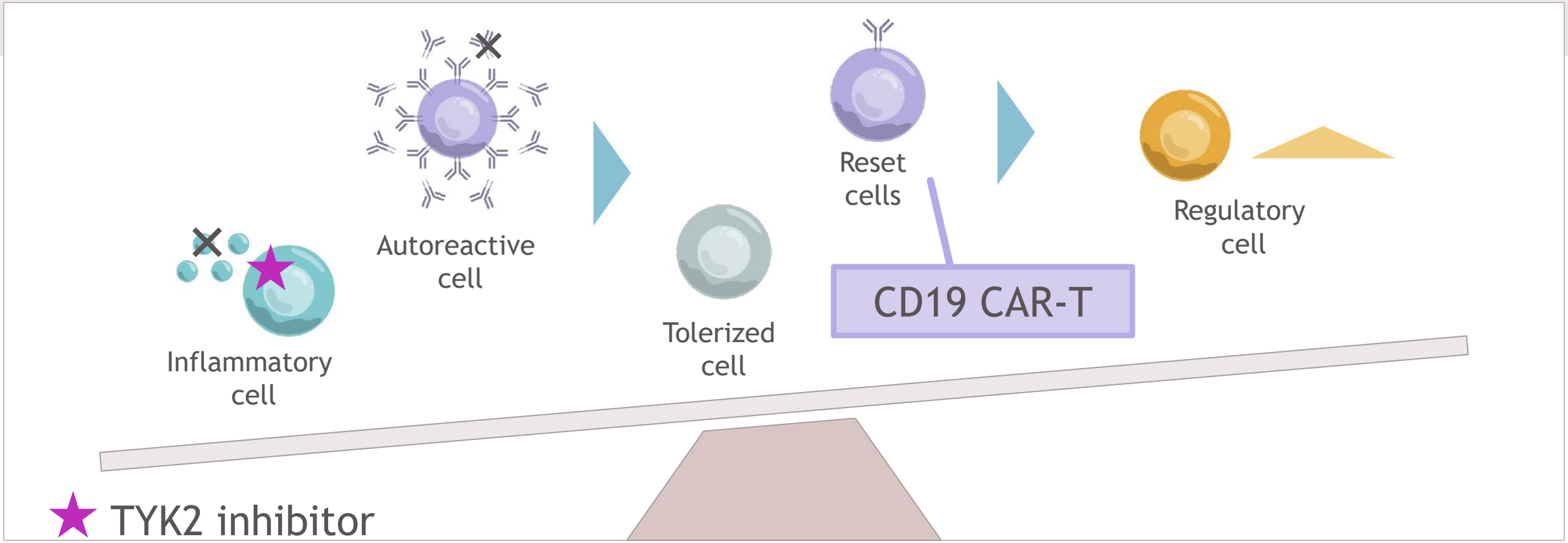

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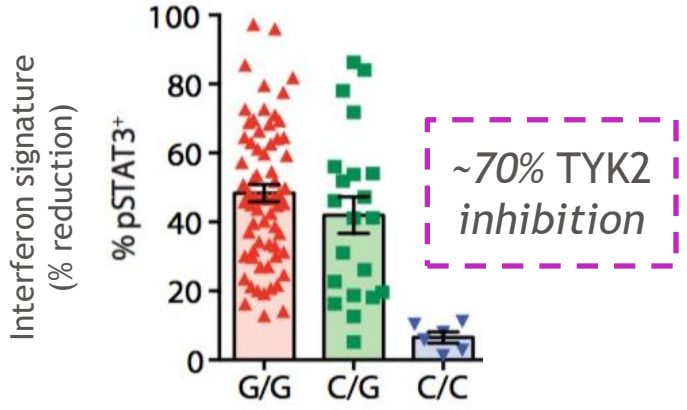
Research framework is effective: *TYK2* genetics and *TYK2* inhibition in systemic lupus erythematosus (SLE)

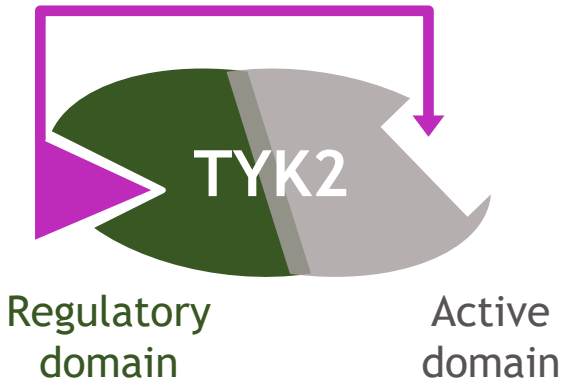
Causal human biology

Human genetics (*P1104A*): implicates TYK2 in multiple immunologic diseases



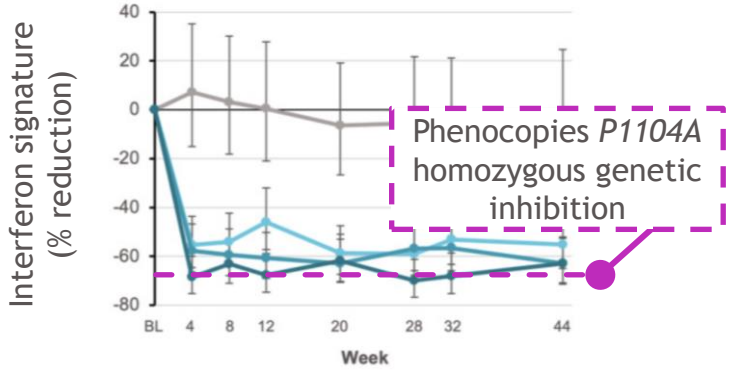
Matching modality to mechanism

Allosteric inhibitor: A highly selective small-molecule drug



Path to clinical proof-of-concept

Initially psoriasis: now systemic lupus erythematosus (SLE)



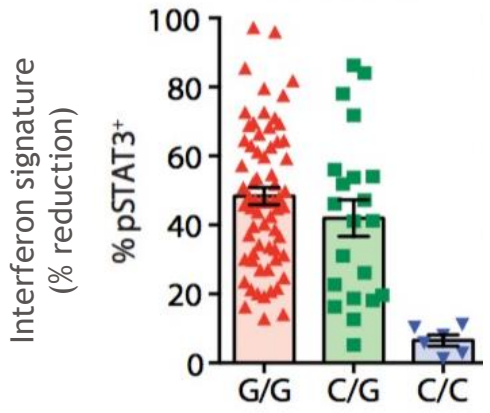
We now <u>consistently</u> apply this Research framework to all our programs to deliver transformational medicines with an increased probability of success in development

Sci Transl Med 2016 Nov; 8(363): 363ra149
PLoS One 2015 April; 10(4): e0122271
Arthritis Rheumatol. 2023 Feb; 75(2): 242-252.
Clin Transl Sci. 2023 Jan; 16(1): 151-164

Deep mutational scanning (DMS) to understand genotype-phenotype correlations of TYK2

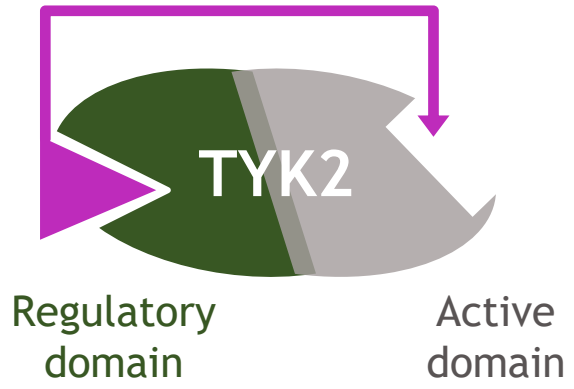
Causal human biology

Can we recapitulate the findings of P1104A with DMS?



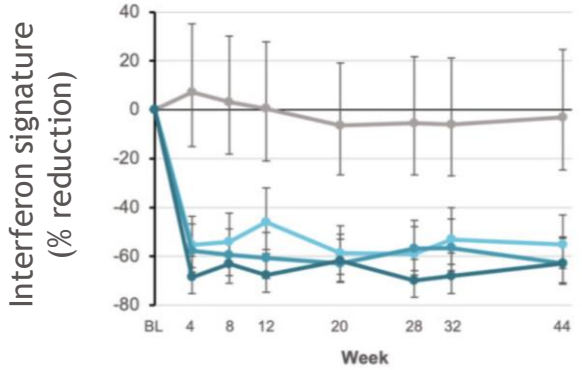
Matching modality to mechanism

Can we uncover the active site and regulatory sites with DMS?



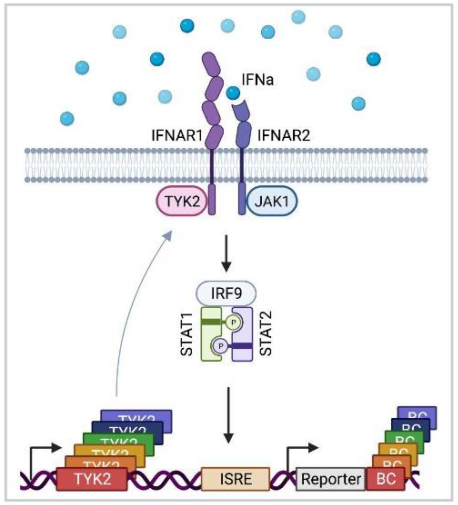
Path to clinical proof-of-concept

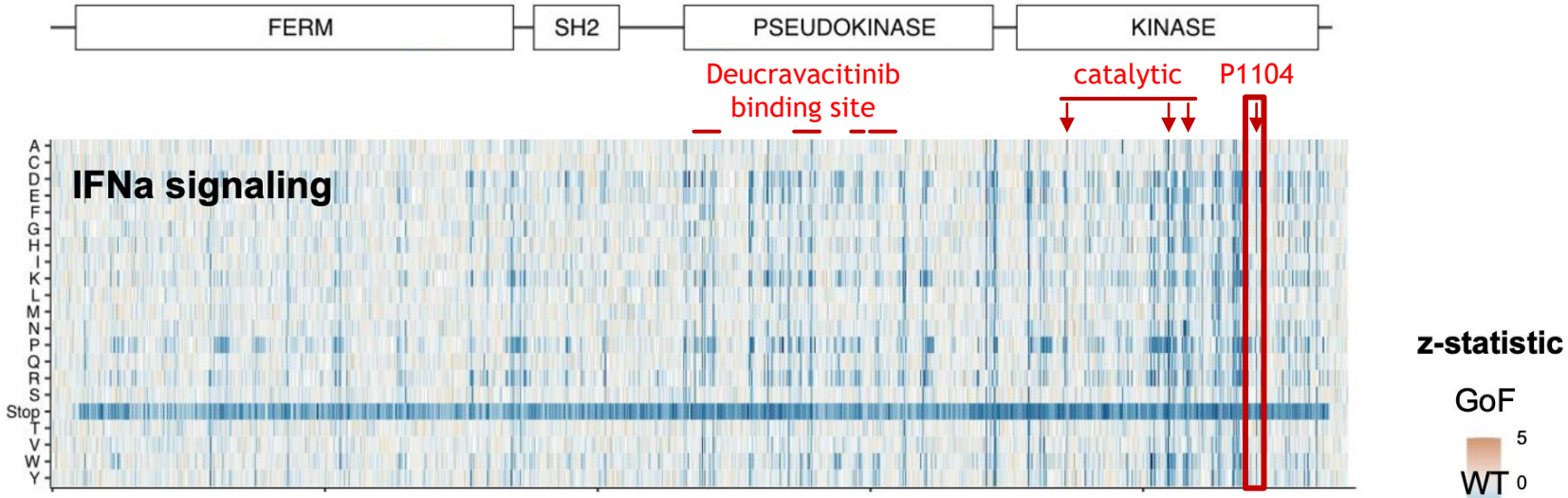
Can DMS improve rare variant genetic association studies for new indications?



And if yes to all three, can DMS be applied to other high-value genetic targets to improve productivity of R&D?

Estimating the effects of >20,000 TYK2 variants from two deep mutational scans (DMS) with Octant





For more: Diane Dickel from Octant presenting poster

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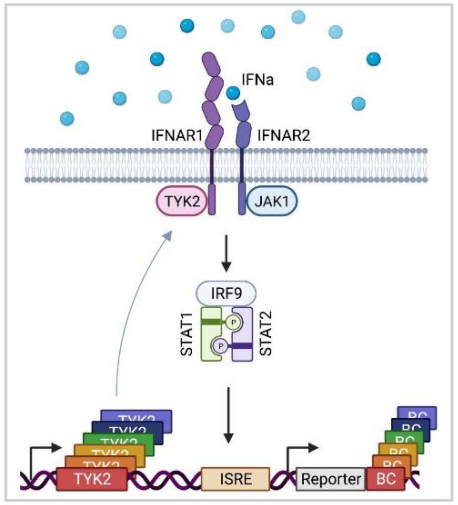

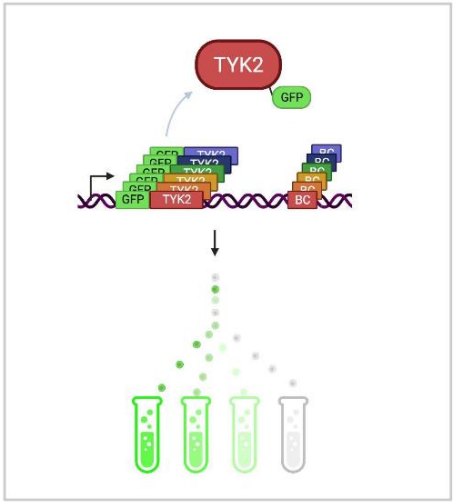

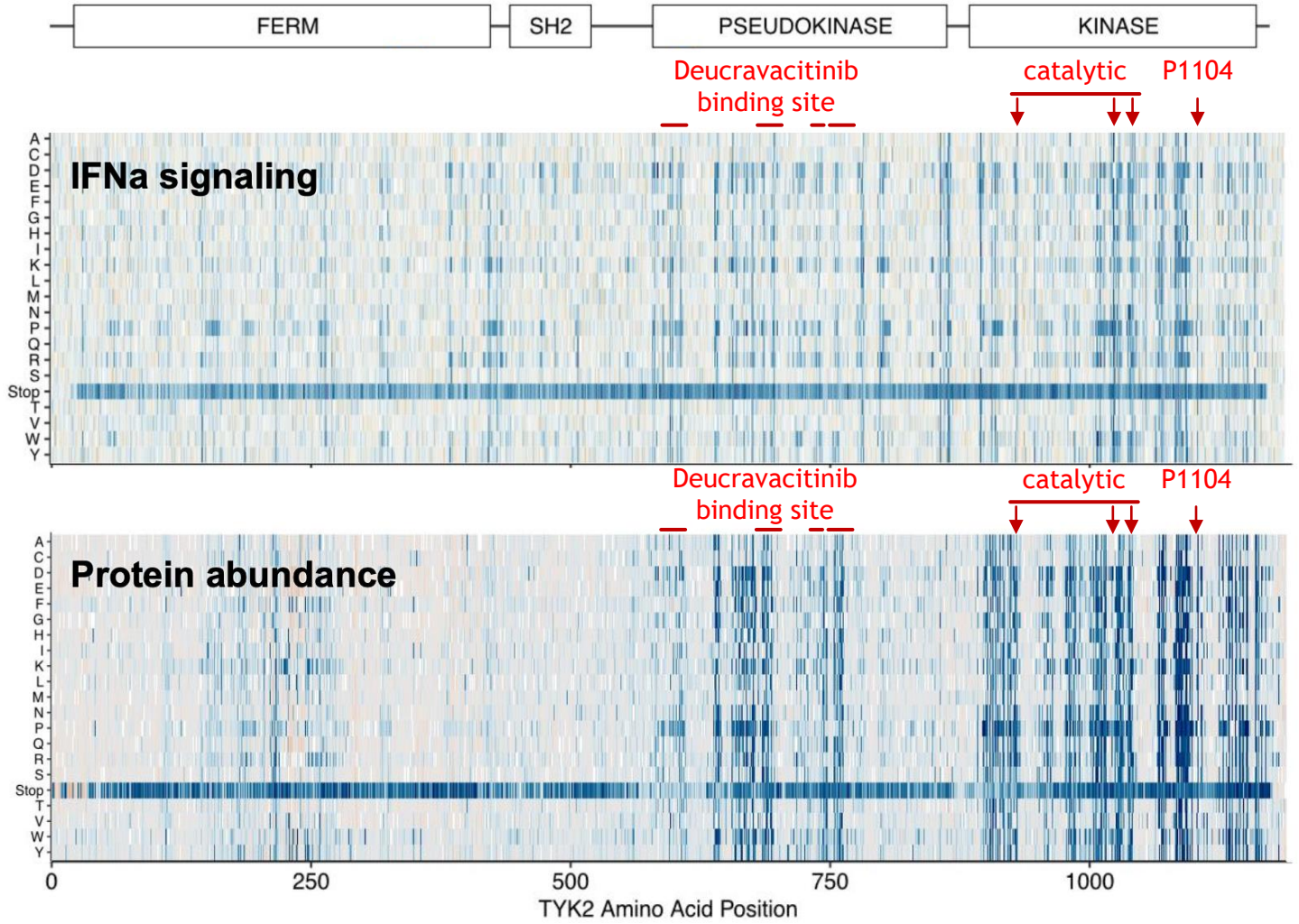

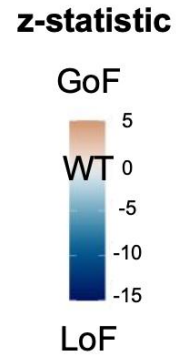

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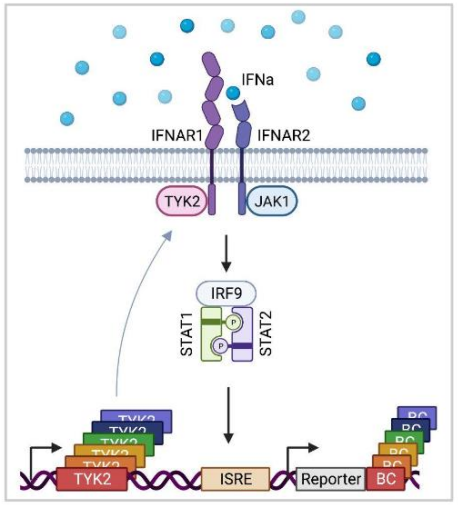
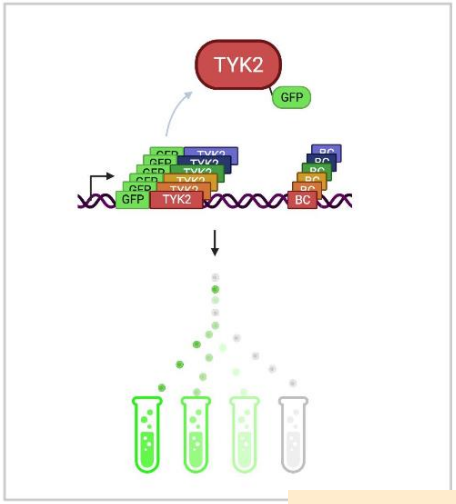
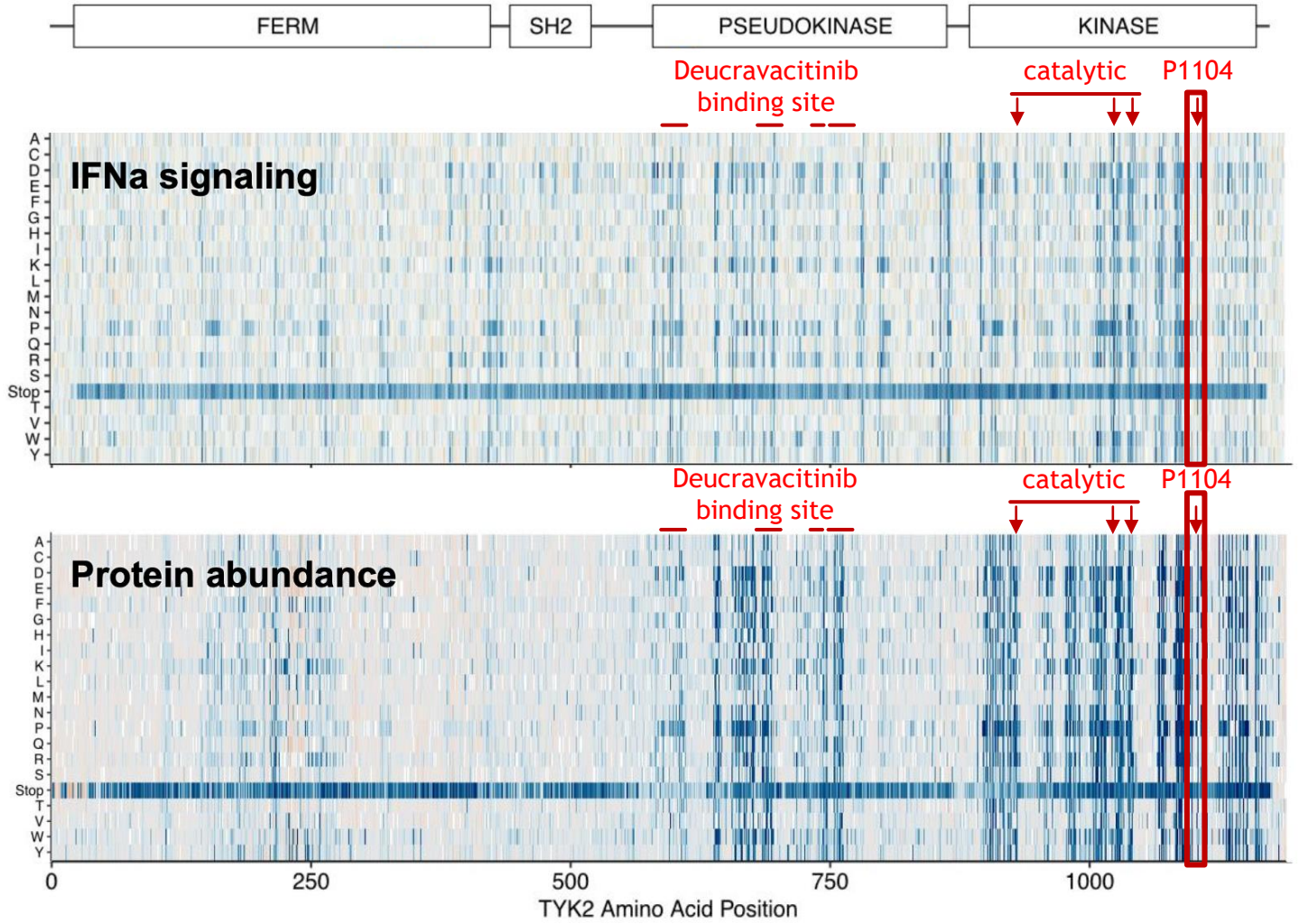


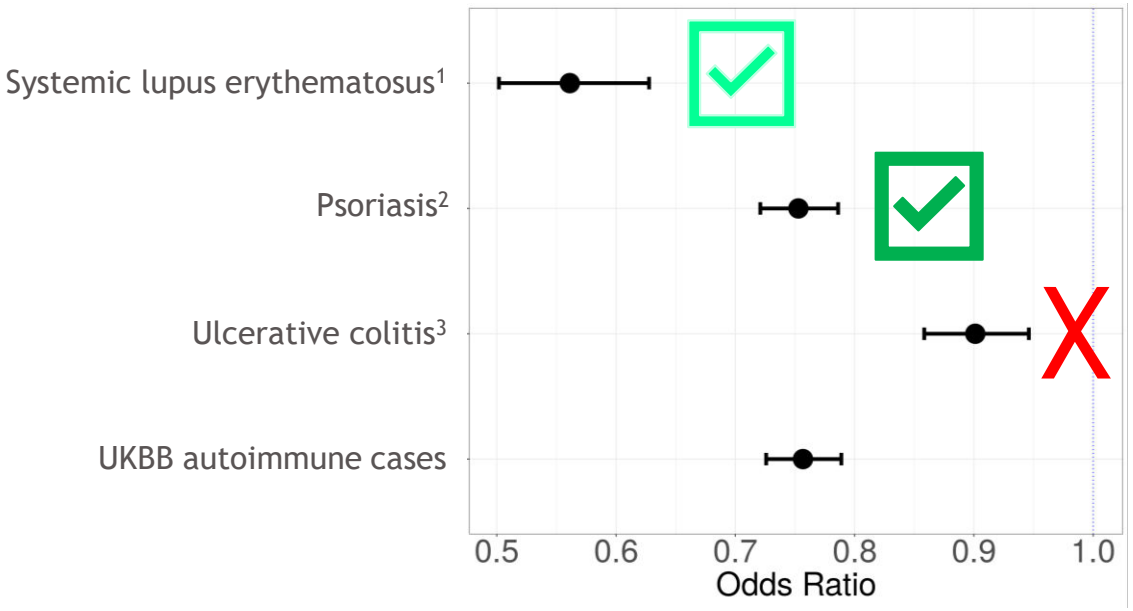




~**26** barcoded lines / codon x **49** codons X **1187** aa x **13** conditions = ~**20M** data points
(one of the largest DMS experiments ever performed in human cells)

Estimated effect of carrying rare variants based on DMS (DMS-score) associates with autoimmune disease endpoint

P1104A is associated with autoimmune diseases



Positive phase 2 clinical trial

Approved medicine

Negative phase 2 clinical trial

31,726 autoimmune disease cases in UK Biobank, including: Psoriasis (11,070), Rheumatoid arthritis (10,652), Ulcerative colitis (5,474), Crohn's disease (2,777), Multiple sclerosis (2,097), Ankylosing spondylitis (1,623), Systemic lupus erythematosus (743), Primary biliary cholangitis (414)

1) Systemic lupus erythematosus from meta-analysis of FinnGen, UKBB, Estonia Biobank, and public GWAS (PMID: 28714469)
2) Psoriasis from meta-analysis of FinnGen, UKBB, Estonia Biobank, and public GWAS (PMID: 23143594)
3) Ulcerative colitis from meta-analysis of FinnGen, UKBB, Estonia Biobank, and public GWAS (PMID: 26192919)

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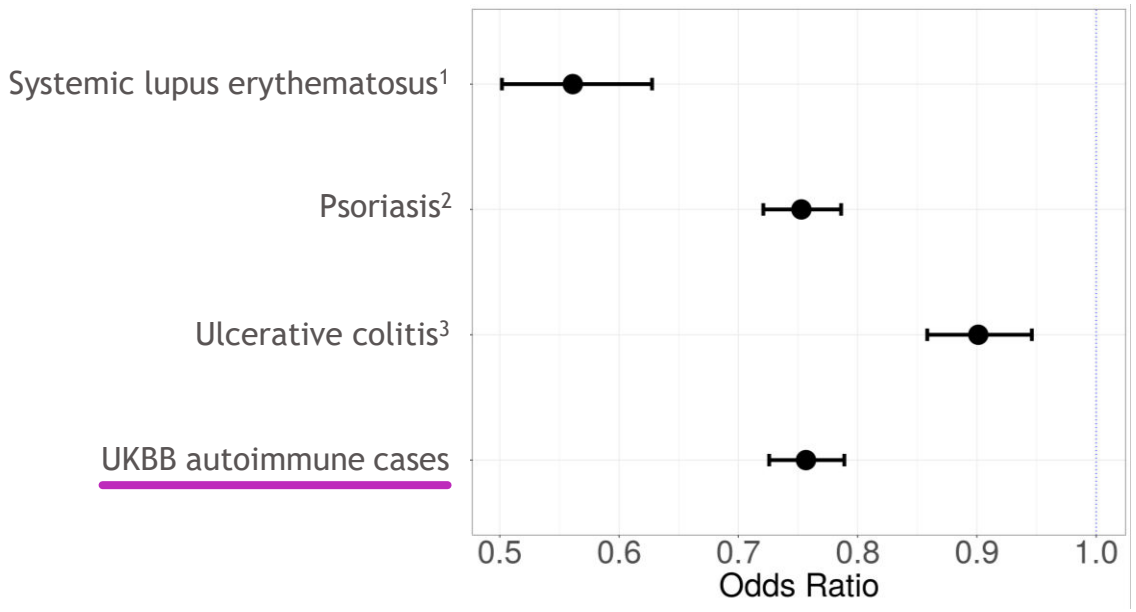

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Can we use DMS-score to weight loss-of-function genetic burden tests to improve power for rare variant association tests?

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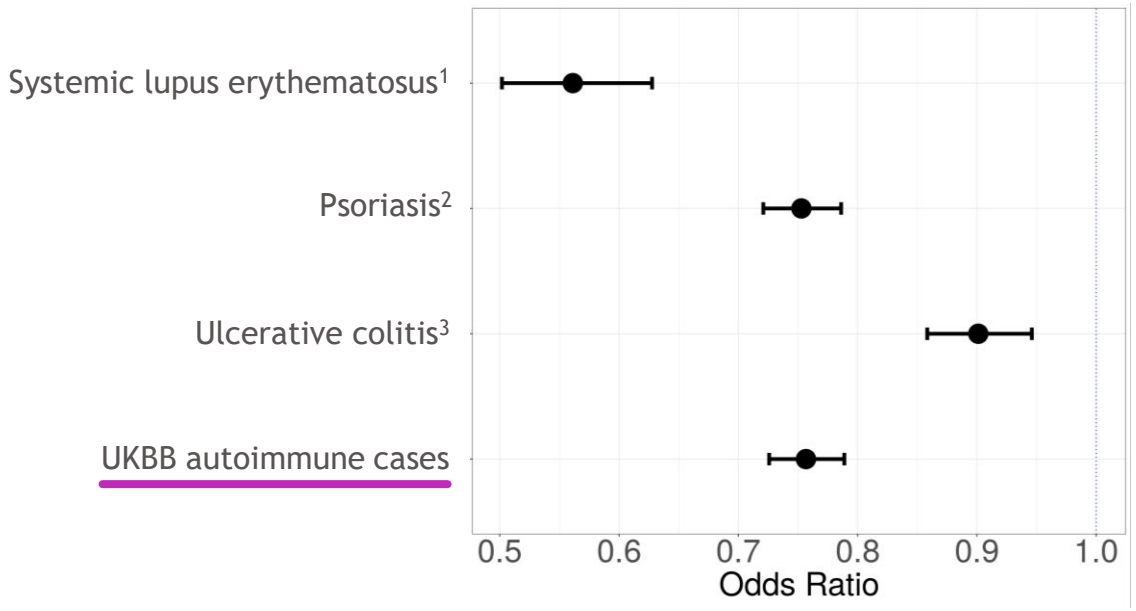

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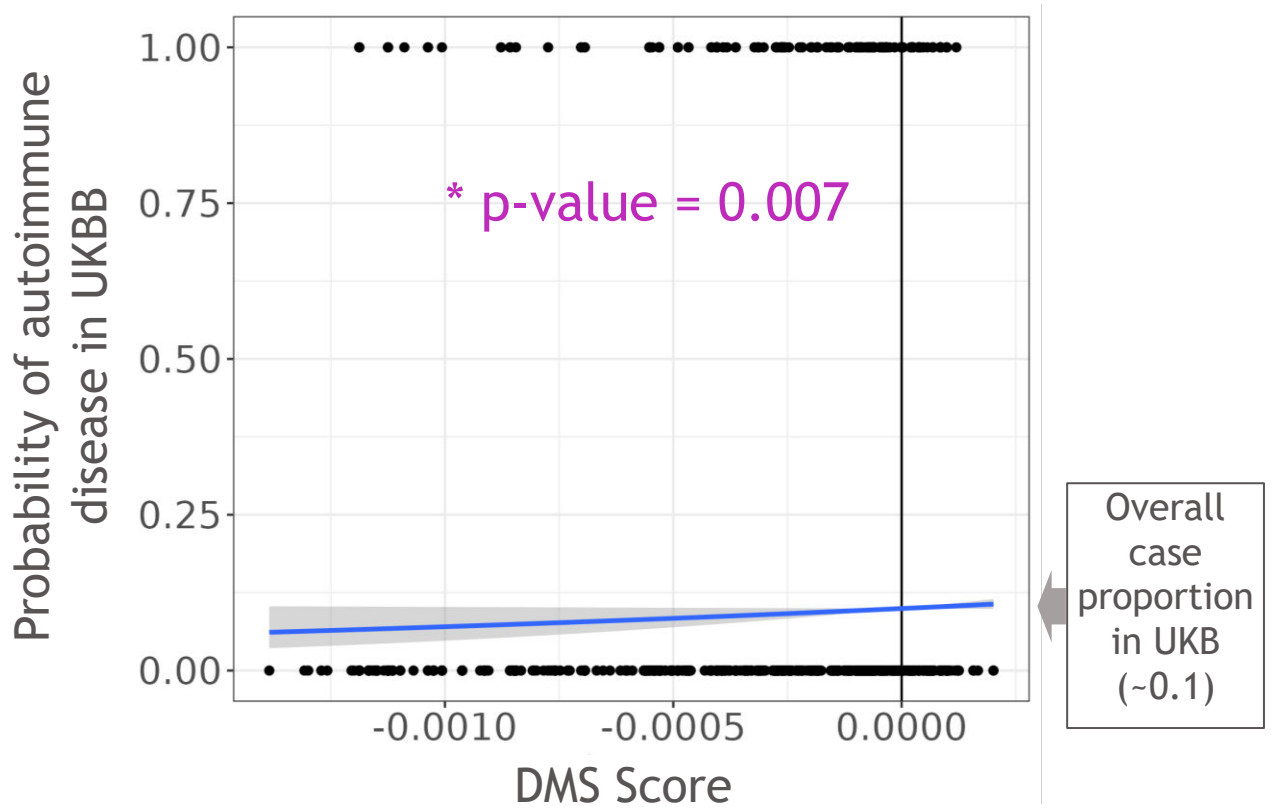
DMS-informed rare variant burden test independently associated with autoimmune disease (MAF<10^{-4})



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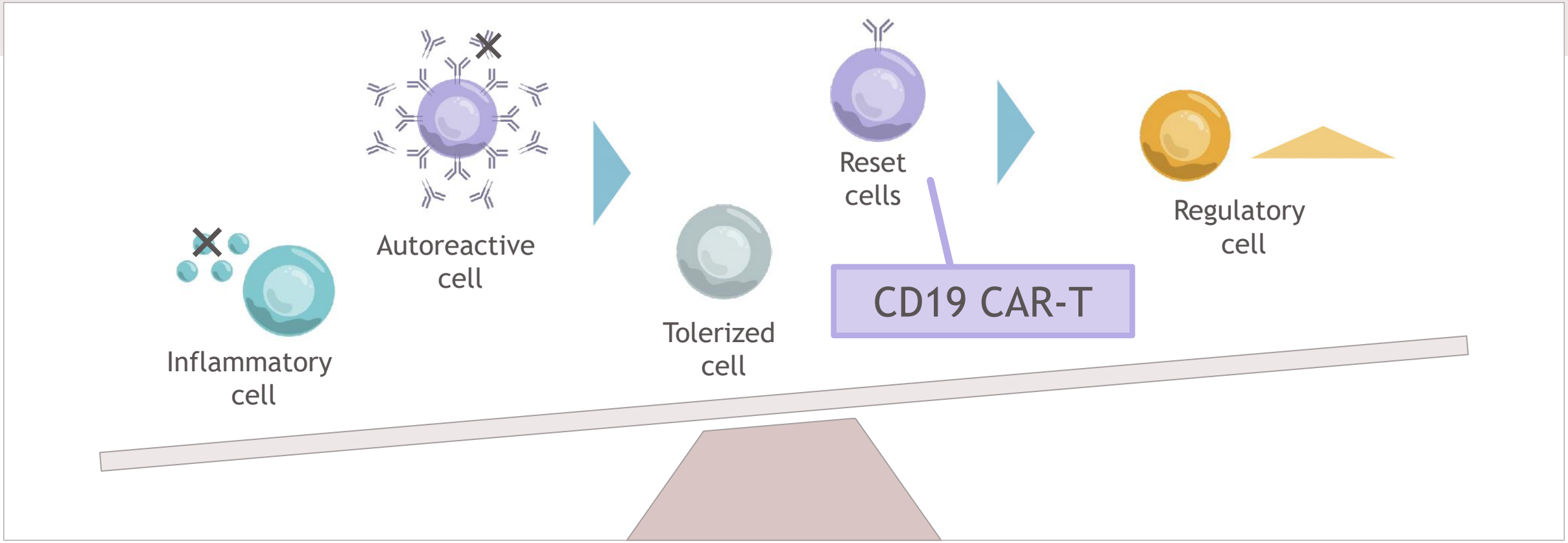
CD19 CAR-T to “reset” the immune system in SLE

01
Suppress inflammation

02
Reset the immune system

03
Promote homeostasis and tissue repair



Francisco Ramirez-Valle, et al Nature Reviews Drug Discovery 2024 *in press*

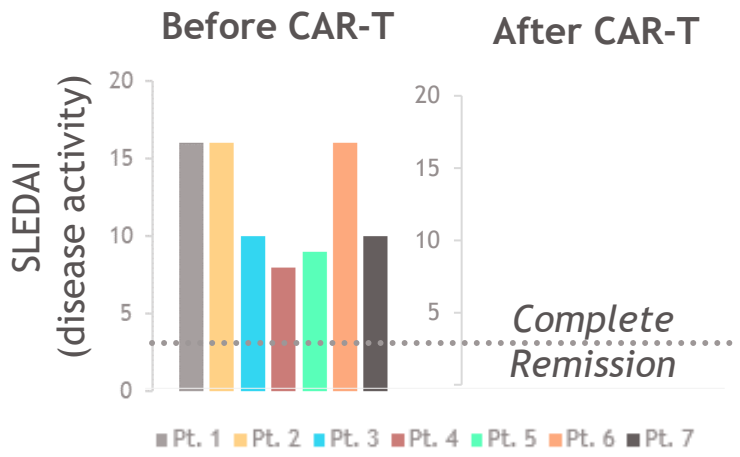
CD19 CAR-T to reset the immune system in multiple immunology indications (e.g., SLE)

Transformational potential

Sequential immunotherapy offers the potential for a functional cure in autoimmunity: 1: Control inflammation; **2**: Reset immune memory; **3**: Promote homeostasis and repair

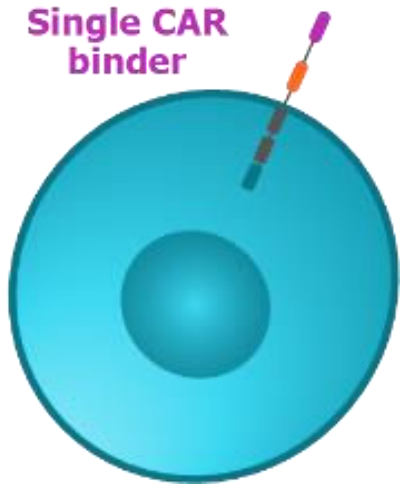
Causal human biology

Academic study of CD19 CAR-T demonstrates B cell memory reset and functional cure in SLE.



Adapted from Taubmann, J., et al EULAR (2023): 93-94

Matching modality to mechanism



Chimeric antigen receptor (CAR): CD19 and intracellular domains same as BMS' FDA-approved cell therapy

Manufacturing: autologous, single train with shortened turn-around time, lower failure rates

Path to clinical proof-of-concept

- Expand on findings from academic study in SLE
- Monitor biomarker predictors of cell therapy safety and efficacy
- Demonstrate evidence of resetting immune memory

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2024 VOL. 390 NO. 8

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.

BACKGROUND

Treatment for autoimmune diseases such as systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, and systemic sclerosis often involves long-term immune suppression. Resetting aberrant autoimmunity in these diseases through deep depletion of B cells is a potential strategy for achieving sustained drug-free remission.

METHODS

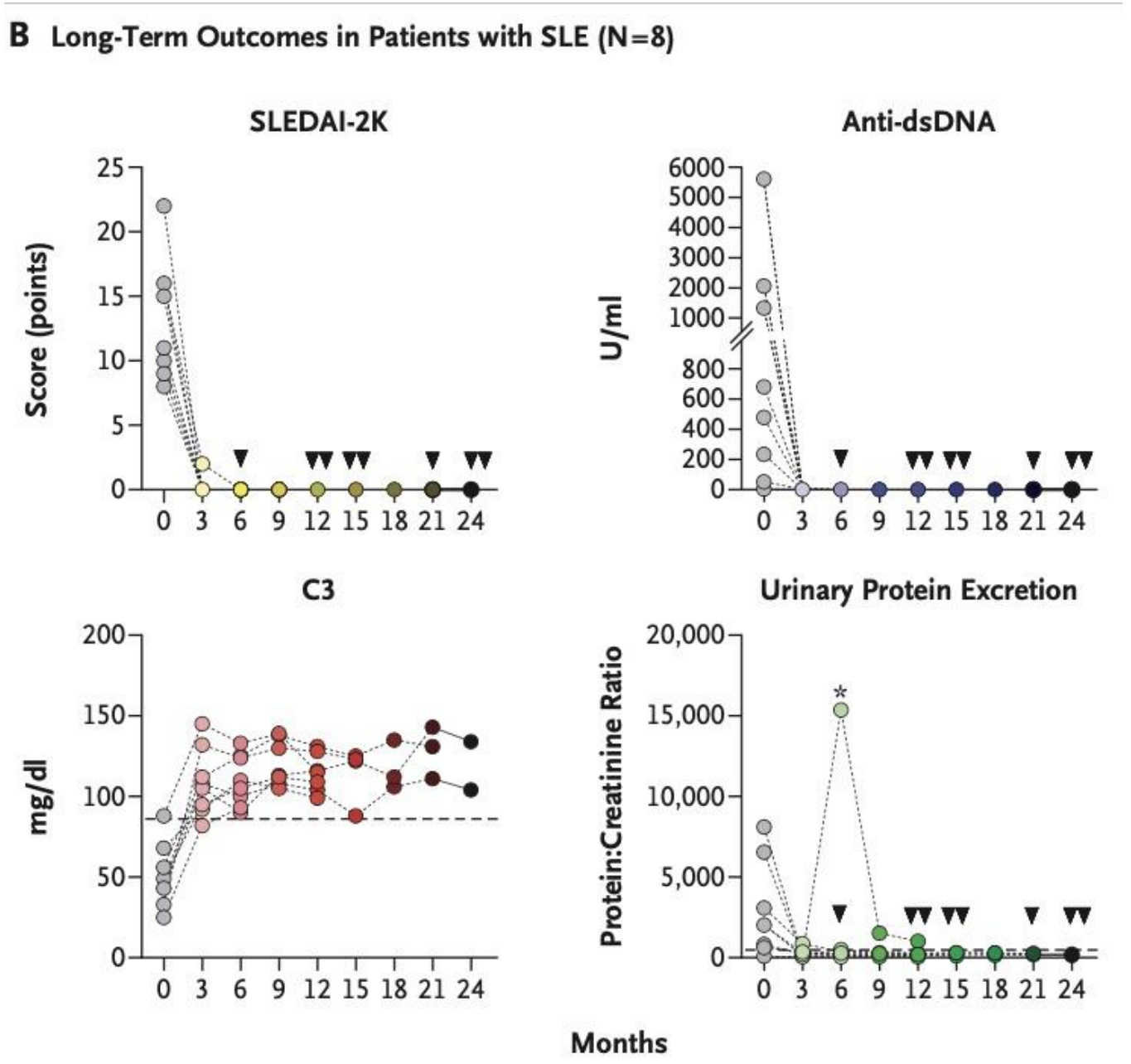
We evaluated 15 patients with severe SLE (8 patients), idiopathic inflammatory myositis (3 patients), or systemic sclerosis (4 patients) who received a single infusion of CD19 chimeric antigen receptor (CAR) T cells after preconditioning with fludarabine and cyclophosphamide. Efficacy up to 2 years after CAR T-cell infusion was assessed by means of Definition of Remission in SLE (DORIS) remission criteria, American College of Rheumatology–European League against Rheumatism (ACR–EULAR) major clinical response, and the score on the European Scleroderma Trials and Research Group (EUSTAR) activity index (with higher scores indicating greater disease activity), among others. Safety variables, including cytokine release syndrome and infections, were recorded.

RESULTS

The median follow-up was 15 months (range, 4 to 29). The mean (±SD) duration of B-cell aplasia was 112±47 days. All the patients with SLE had DORIS remission, all the patients with idiopathic inflammatory myositis had an ACR–EULAR major clinical response, and all the patients with systemic sclerosis had a decrease in the score on the EUSTAR activity index. Immunosuppressive therapy was completely stopped in all the patients. Grade 1 cytokine release syndrome occurred in 10 patients. One patient each had grade 2 cytokine release syndrome, grade 1 immune effector cell–associated neurotoxicity syndrome, and pneumonia that resulted in hospitalization.

CONCLUSIONS

In this case series, CD19 CAR T-cell transfer appeared to be feasible, safe, and efficacious in three different autoimmune diseases, providing rationale for further controlled clinical trials. (Funded by Deutsche Forschungsgemeinschaft and others.)



Conclusions

- Key to R&D productivity is increase probability of success (PoS) in clinical development
- A framework anchored on causal human biology, matching modality to mechanism, and path to clinical proof-of-concept will increase PoS in clinical development
- Example of sequential immunotherapy in SLE, with focus on TYK2 inhibition (Step 1) and CD19 CAR-T depletion of B cells (Step 2)
- Example of deep mutational scanning (DMS) to guide drug R&D for future programs