Cabaletta Bio®

Single-cell profiling of PBMC subsets following rese-cel (Resecabtagene Autoleucel) treatment across the RESET-Myositis®, RESET-SSc™, and RESET-SLE trials™ Phase 1 / 2 Cohorts

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Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements.

Various risks, uncertainties and assumptions could cause actual results to differ materially from those anticipated or implied in our forward-looking statements. Such risks and uncertainties include, but are not limited to, risks related to the success, cost, and timing of our development activities and clinical trials, risks related to our ability to demonstrate sufficient evidence of safety, efficacy and tolerability in our clinical trials, the risk that the results observed with the similarly-designed construct, including, but not limited to, dosing regimen, are not indicative of the results we seek to achieve with rese-cel, the risk that signs of biologic activity or persistence may not inform long-term results, risks related to clinical trial site activation or enrollment rates that are lower than expected, risks that modifications to trial design or approach may not have the intended benefits and that the trial design may need to be further modified; our ability to protect and maintain our intellectual property position, risks related to our relationships with third parties, uncertainties related to regulatory agencies' evaluation of regulatory filings and other information related to our product candidates, our ability to retain and recognize the intended incentives conferred by any regulatory designations, risks related to regulatory filings and potential clearance, the risk that any one or more of our product candidates will not be successfully developed and commercialized, the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies, risks related to volatile market and economic conditions and our ability to fund operations and continue as a going concern. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, you are cautioned not to place undue reliance on these forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ materially from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent annual report on Form 10-K and quarterly report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our other filings with the Securities and Exchange Commission. Certain information contained in this Presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this Presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. The Company is the owner of various trademarks, trade names and service marks. Certain other trademarks, trade names and service marks appearing in this Presentation are the property of third parties. Solely for convenience, the trademarks and trade names in this Presentation are referred to without the ® and TM symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

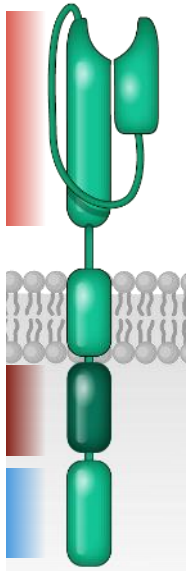
Rese-cel: CD19-CAR T designed for autoimmunity

Rese-cel binder with similar in vitro & in vivo activity to construct used in academic studies in autoimmunity[1,3]

Fully human anti-CD19 binder

4-1BB costimulatory domain

CD3-ζ signaling domain



Rese-cel[4]

Rese-cel product design & clinical / translational data

4-1BB costimulatory domain with fully human binder

- Binder with similar affinity & biologic activity to academic FMC63 binder while binding to the same epitopes[1,2]

Same weight-based dose as in academic studies

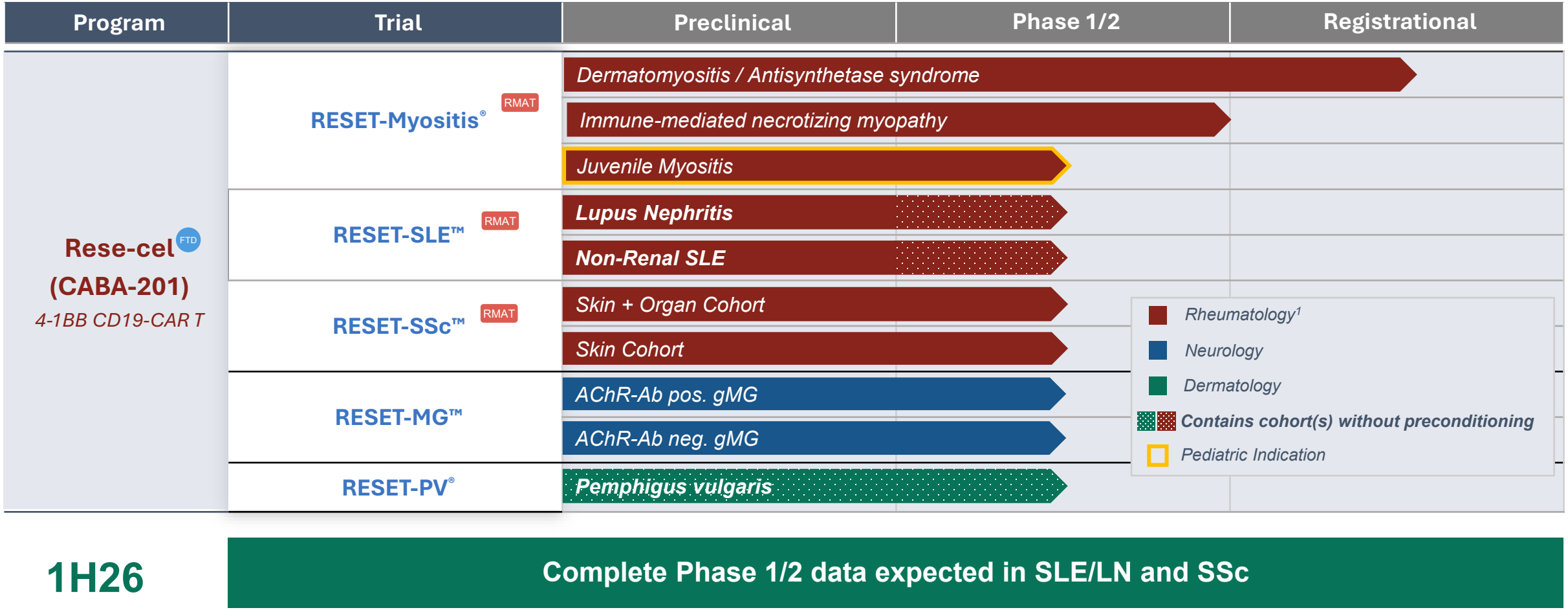
- Potential to provide immune reset based on clinical and translational data[5]

Patients treated with rese-cel have shown compelling clinical responses with safety data that supports outpatient use for autoimmune patients[6]

1. Peng BJ, et al. Mol Ther Methods Clin Dev. 2024;32(2):101267.
2. Dai, Zhenyu, et al. "Development and functional characterization of novel fully human anti-CD19 chimeric antigen receptors for T-cell therapy." Journal of Cellular Physiology 236.8 (2021): 5832-5847.
3. Müller, Fabian, et al. "CD19 CAR T-Cell Therapy in Autoimmune Disease—A Case Series with Follow-up." New England Journal of Medicine 390.8 (2024): 687-700.
4. Maschan, Michael, et al. “Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients.” Nature Communications 12, 7200 (2021). Transmembrane domain in rese-cel is CD8α vs. TNFRSF19 (Troy) utilized in the academic construct. The two transmembrane domains have not been shown to have a significant difference in function or IFN-γ production in preclinical studies. The CD8α transmembrane domain is employed in tisagenlecleucel.
5. Volkov, Jenell, et al. “Case study of CD19 CAR T therapy in a subject with immune-mediate necrotizing myopathy treated in the RESET-Myositis phase I/II trial.” Molecular Therapy 32.11 (2024): 3821-3828.
6. Abstract 1733: Safety and Efficacy of CABA-201, a Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Patients with Immune-Mediated Necrotizing Myopathy and Systemic Lupus Erythematosus from the RESET-Myositis™ and RESET-SLE™ Clinical Trials. ACR 2024.

Innovative clinical strategy to support accelerated regulatory path

SLE registrational design in hand; SSc pivotal design anticipated 1H26 and MG anticipated mid-2026



1H26 — **Complete Phase 1/2 data expected in SLE/LN and SSc**

RESET™ – **RE**storing **SE**lf-**T**olerance; Ab – Antibody; AChR – Acetylcholine receptor; gMG – Generalized myasthenia gravis; PV – Pemphigus vulgaris; SLE – Systemic lupus erythematosus; SSc – Systemic sclerosis

1. Myositis patients can also be treated by neurologists or dermatologists; lupus nephritis patients can also be treated by nephrologists.

● FDA Fast Track Designation received in dermatomyositis, SLE and lupus nephritis, systemic sclerosis, generalized myasthenia gravis and multiple sclerosis.

■ FDA Regenerative Medicine Advanced Therapy (RMAT) received in myositis, SLE, LN and systemic sclerosis.

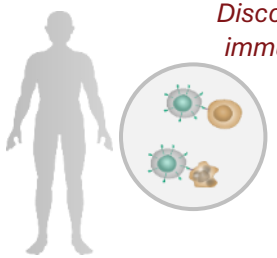
RESET™ clinical trials have consistent design principles[1]

Many of the RESET trials share common elements of preconditioning, dose, and study design

Screening

Day -5 to Day -3

Leukapheresis and rese-cel production



Discontinuation of all immunomodulatory agents

T cells isolated from patient's own PBMCs (autologous CAR T)

Preconditioning

FLU 25 mg/m² x 3 days
CY 1000 mg/m² x 1 day
(if required)

Day 1

Single infusion of rese-cel

Weight-based dosing
1×10⁶ cells/kg

Day 29

Primary endpoint: Incidence and severity of AEs

Study follow-up through Year 3†

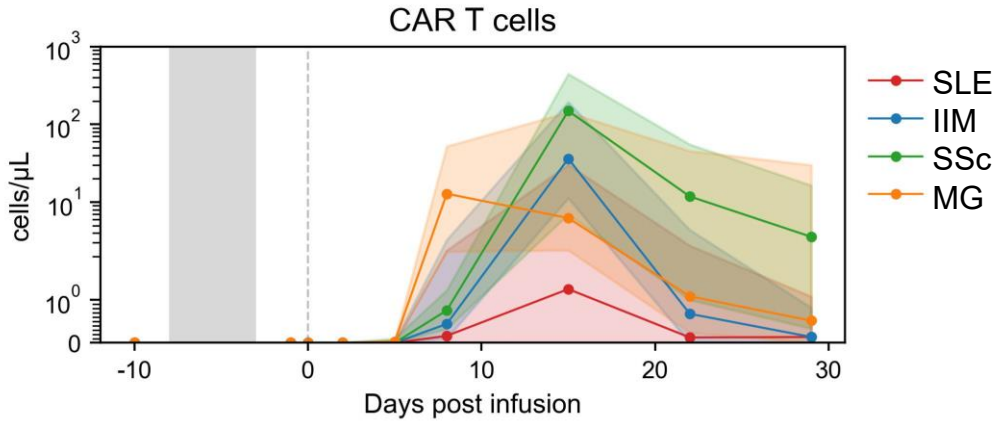
Additional Endpoints

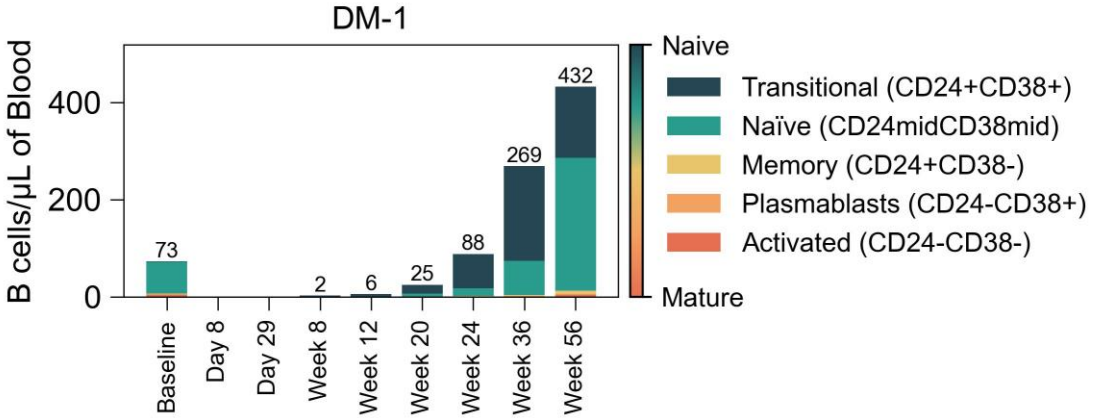
- Clinical efficacy measuring:
  - Drug-free responses
  - Validated endpoints
- PK/PD analysis:
  - Rese-cel expansion
  - B cell depletion
  - Peak BAFF levels
  - B cell repopulation
- Adverse events & safety
- Biomarker analysis, including autoantibody levels

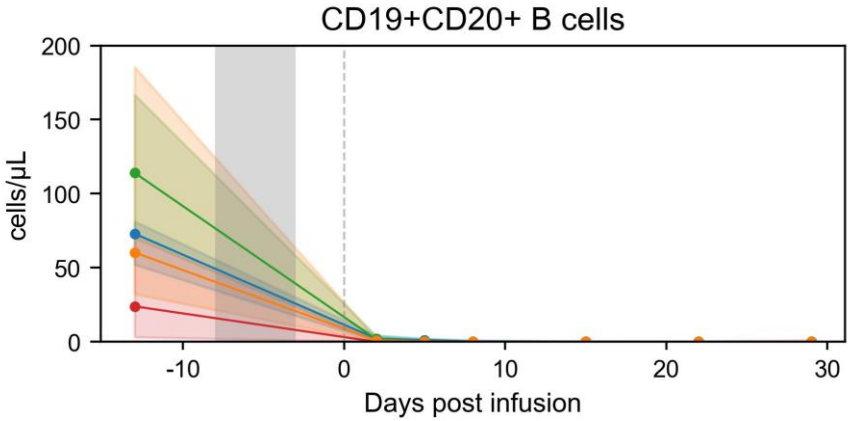
†Follow up period encompasses at least 15 years in total, ed to regulatory guidance for CAR T cell therapies.
AE, adverse event; CABA, Cabaletta Approach to B cell Ablation; FLU, fludarabine; CY, cyclophosphamide; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamics; PK, pharmacokinetics; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
Cabaletta Bio: Data on file; 1. Peng BJ, et al. Mol Ther Methods Clin Dev. 2024;32(2):101267.

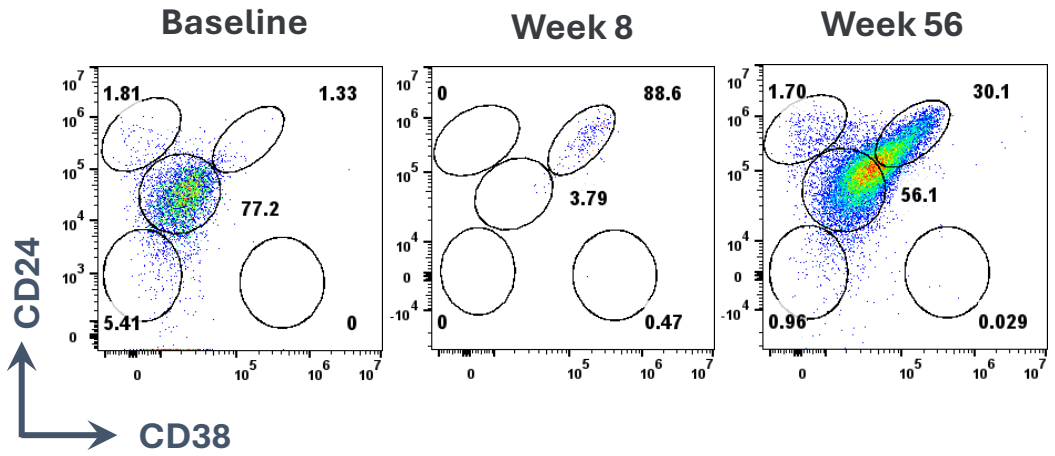
Rese-cel expansion & B cell kinetics across SLE, IIM, SSc, and MG*

Peak rese-cel expansion occurred within ~2 weeks post-infusion, accompanied by peripheral B cell depletion that lasted 8 to 12 weeks



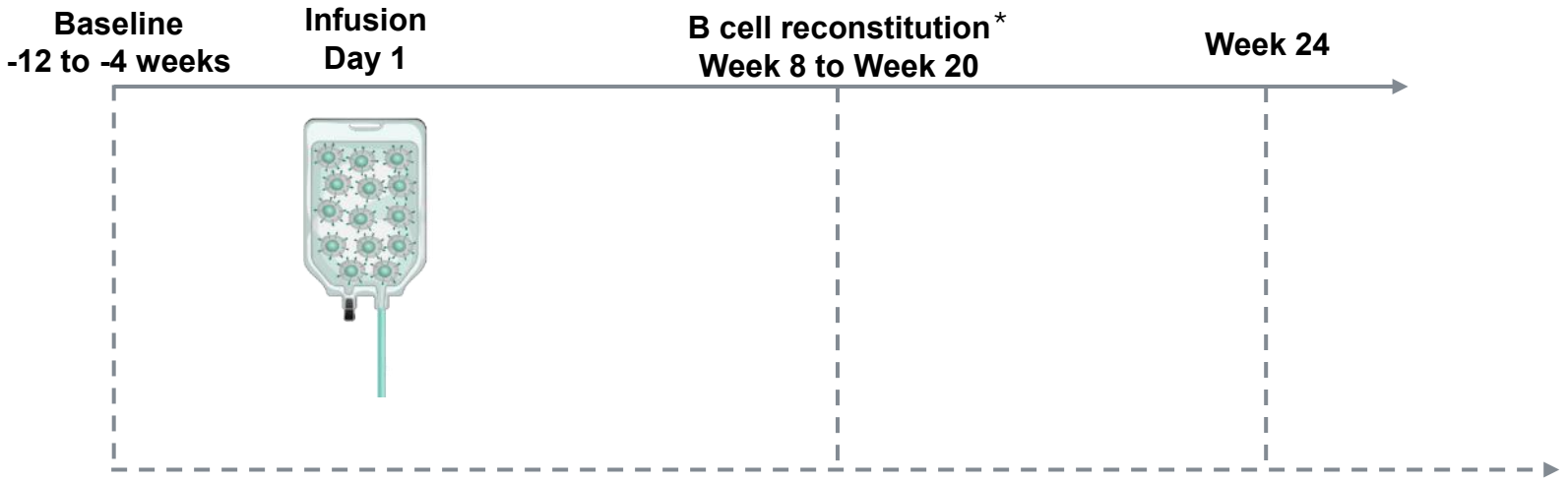






*All data is as of 30 Oct, 2025, except DM-3 which includes Week 24 data as of 08 Oct 2025.
**LN-1 had prolonged rese-cel detection due to TCR activation that corresponded to longer time to B cell repopulation. LN-4: follow up ongoing
† DM-3 rese-cel PK at Week 20 was artifactually elevated due to low circulating lymphocyte counts.
‡ Reduced rese-cel expansion observed in AChR-pos-1 may be attributed to patient's continued use of azathioprine, a prohibited medication, until day of infusion (Day 1).
ASyS, antisynthetase syndrome; CAR, chimeric antigen receptor; DM, dermatomyositis; IMNM, immune-mediated necrotizing myopathy; LN, lupus nephritis; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus, SSc, systemic sclerosis, TCR, T cell receptor.
Cabaletta Bio; Data on file

Sampling and methods



mRNA
Surface proteins (175)
BCR
TCR

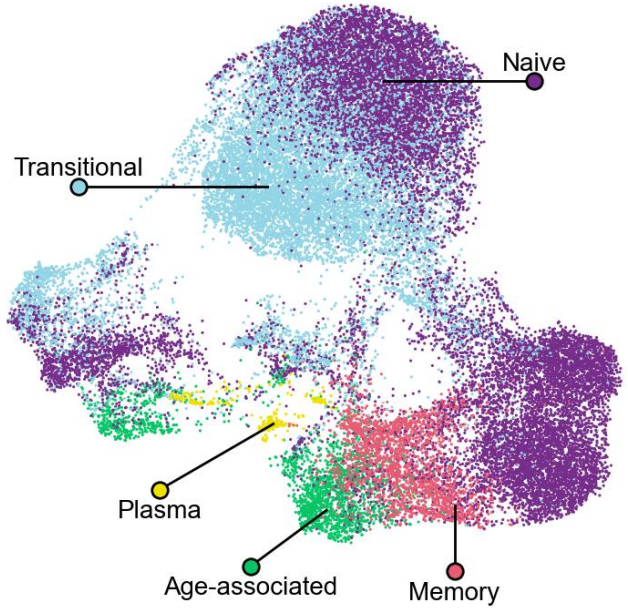
Subjects in analysis:

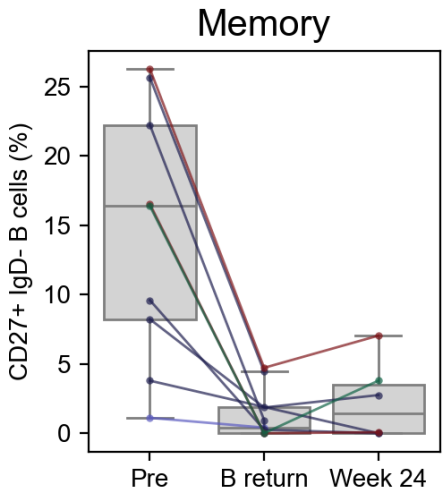
- **RESET-SLE™**
  - 2 Systemic Lupus Erythematosus (SLE)
- **RESET-SSc™**
  - 1 Systemic Sclerosis (SSc)
- **RESET-Myositis®**
  - 5 Dermatomyositis (DM)
  - 1 Antisynthetase syndrome (ASyS)

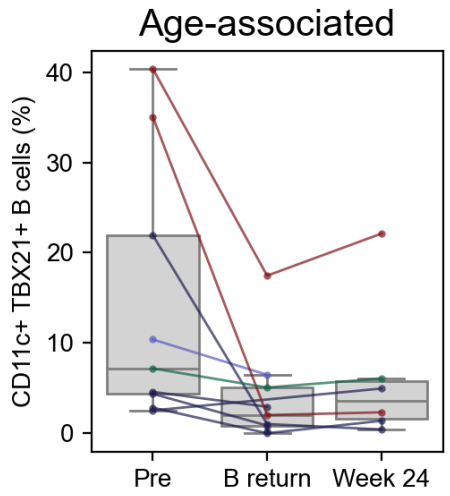
*Defined as first time point port reconstitution where B cells reach above 2.5% of lymphocytes..

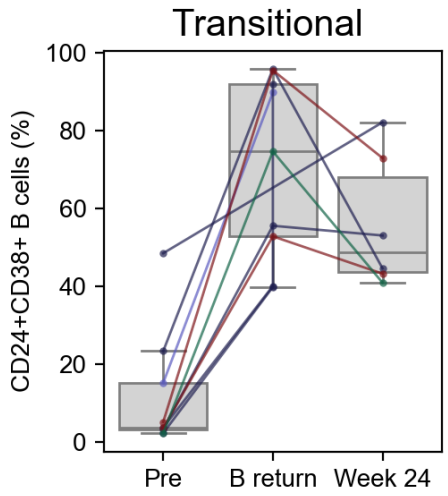
Age associated and memory B cells disappear after B cell depletion

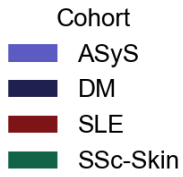
Transitional B cells, which are recent bone marrow emigrants, are majority of B cells at re-population

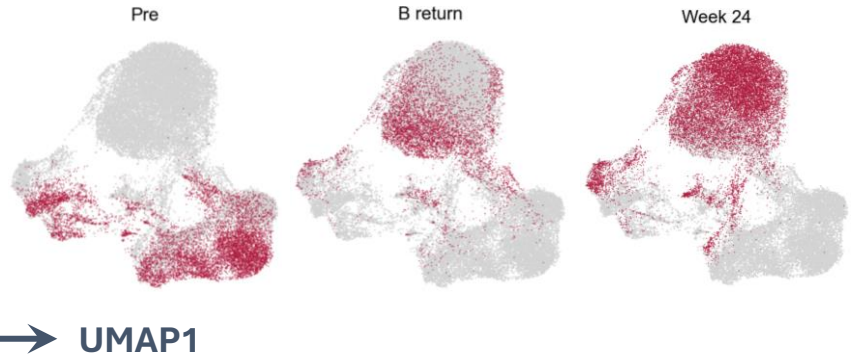








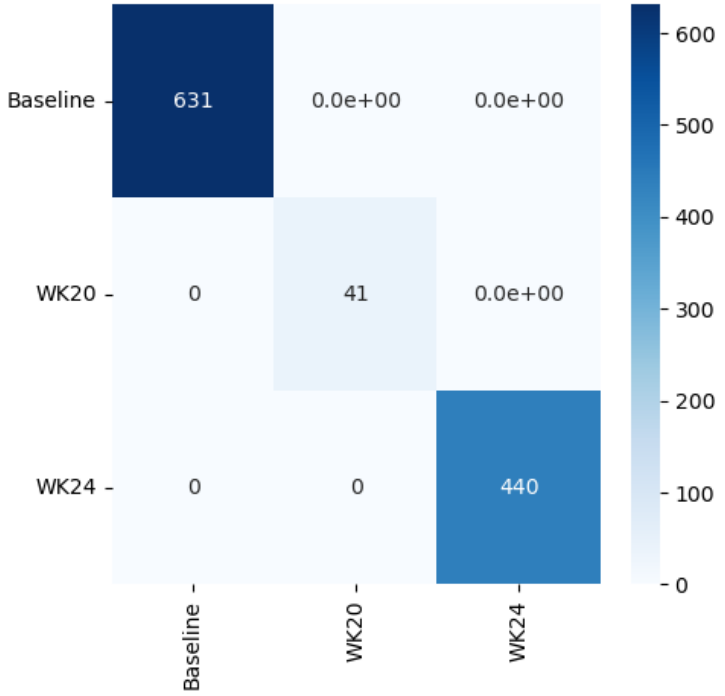




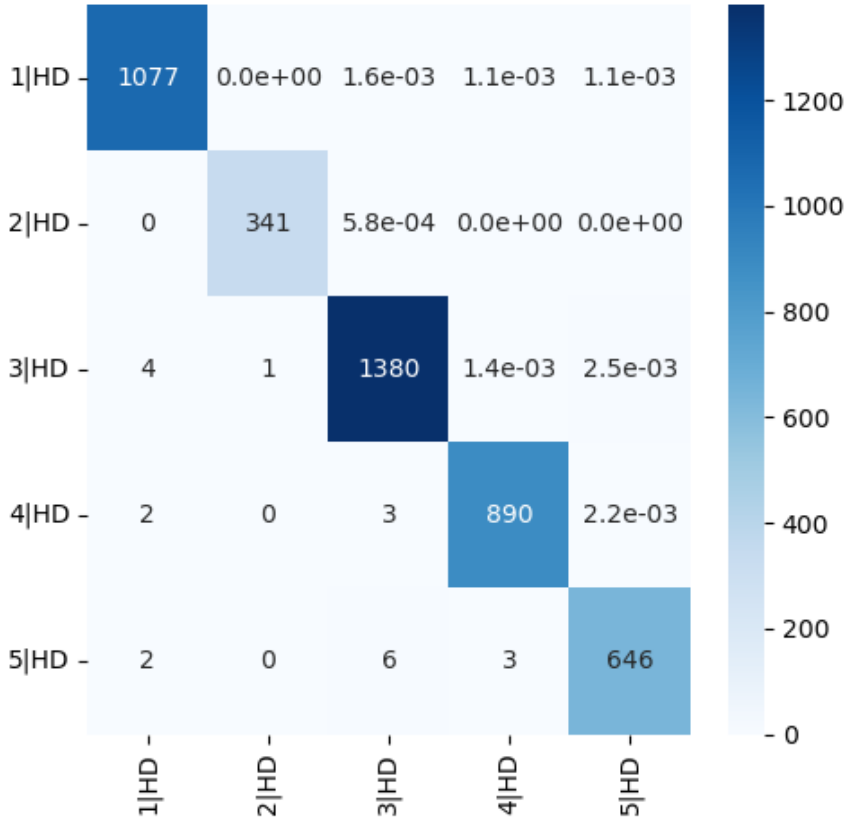
Clone overlap between samples is highly dependent on sequencing depth

BCR clone diversity makes it difficult to interpret absence of clone overlaps as a replacement of the B cell repertoire

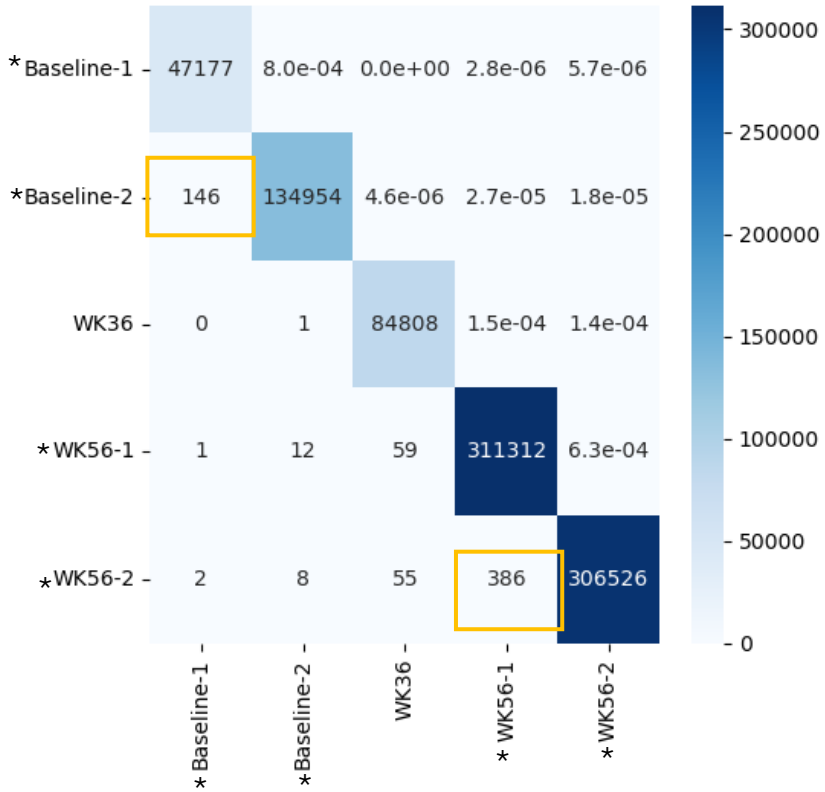
DM-1 single-cell RNAseq

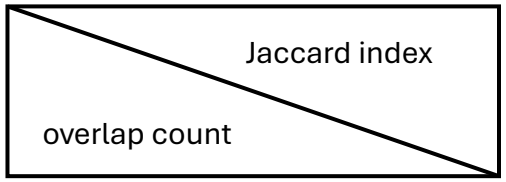


Healthy donor single-cell



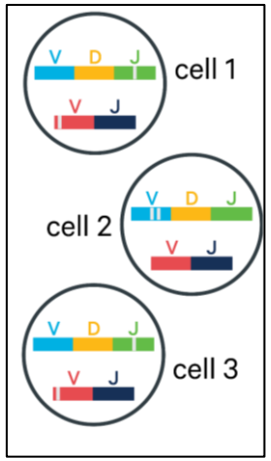
DM-1 bulk DNAseq





*Aliquots from same sample..

Somatic Hypermutation



Assign V,J gene to all contigs based on reference alignment

↓

For each V gene create the donor specific germline allele.

Germline variant assessment for J genes is currently not performed as it does not greatly enhance clonotype specificity.

↓

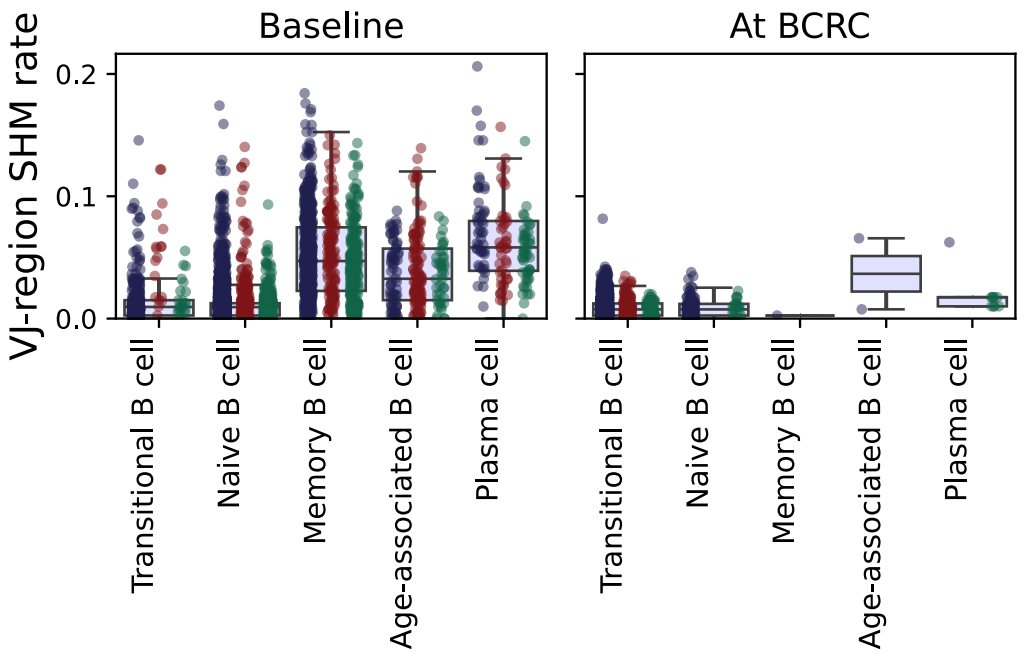
For each cell annotate the SHM (substitutions or indels relative to donor germline)

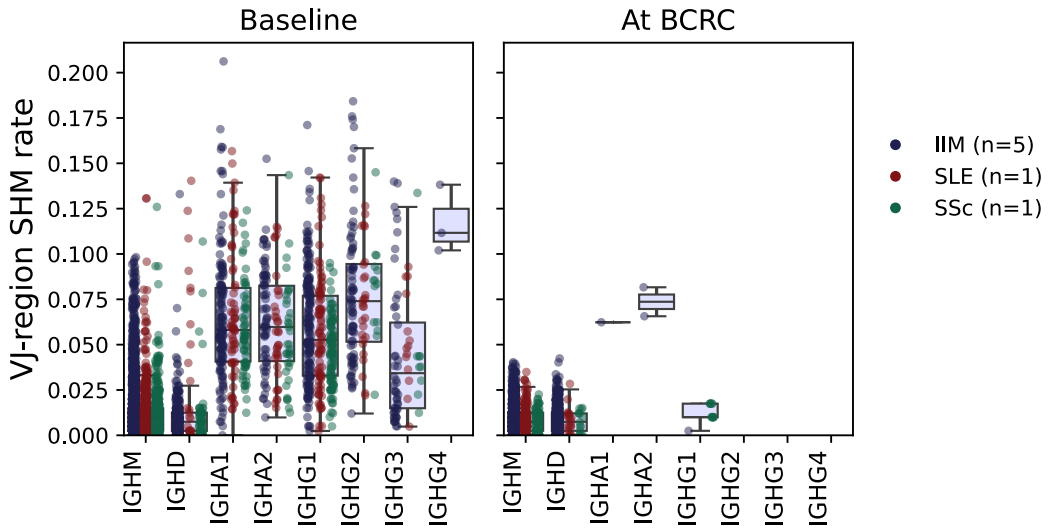
↓

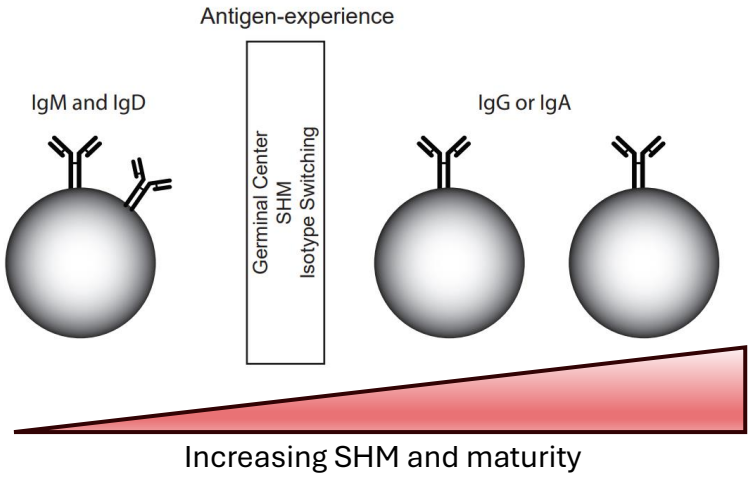
$$\frac{\#V \text{ gene mutations} + \#J \text{ gene mutations}}{V \text{ gene length} + J \text{ gene length}}$$

Re-emergent B cells have decreased somatic hypermutation signature

BCR profile reflects new transitional naïve B cell population

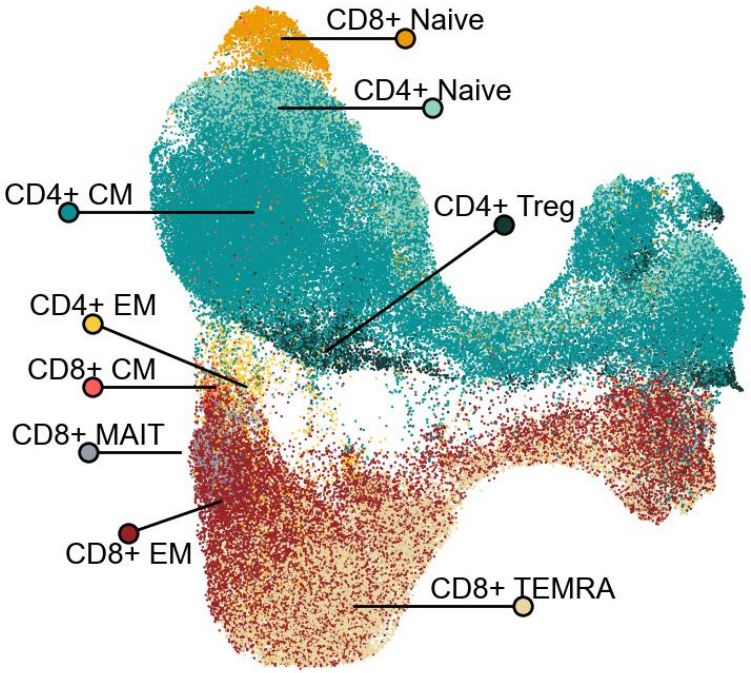


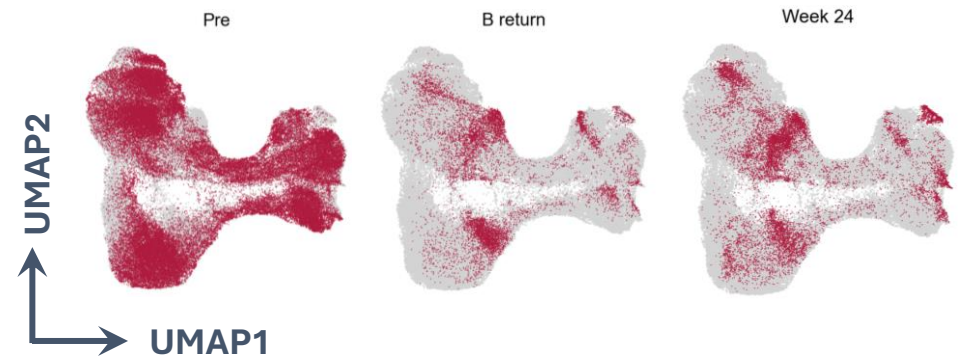


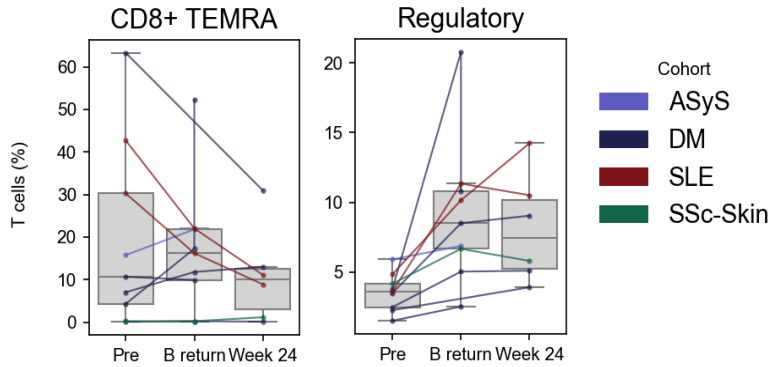


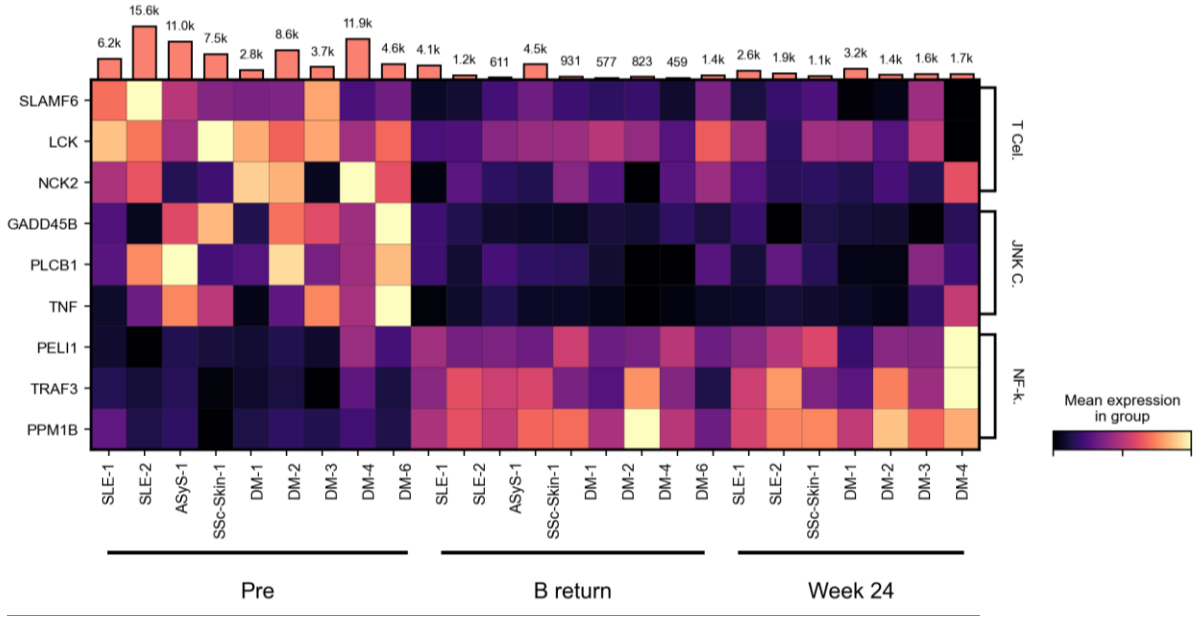
T cell activation decreases post rese-cel infusion

Decreased CD8⁺ EMRA population and increased Treg population in periphery following infusion

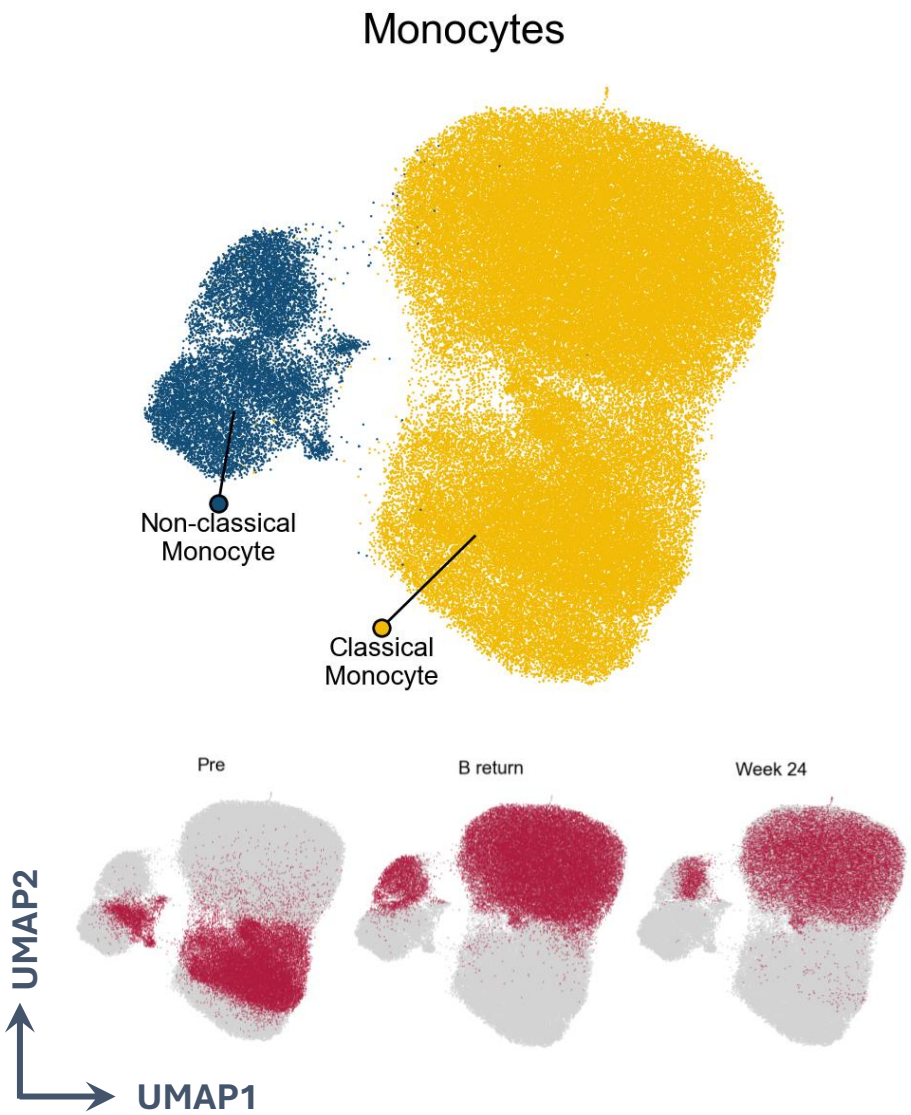


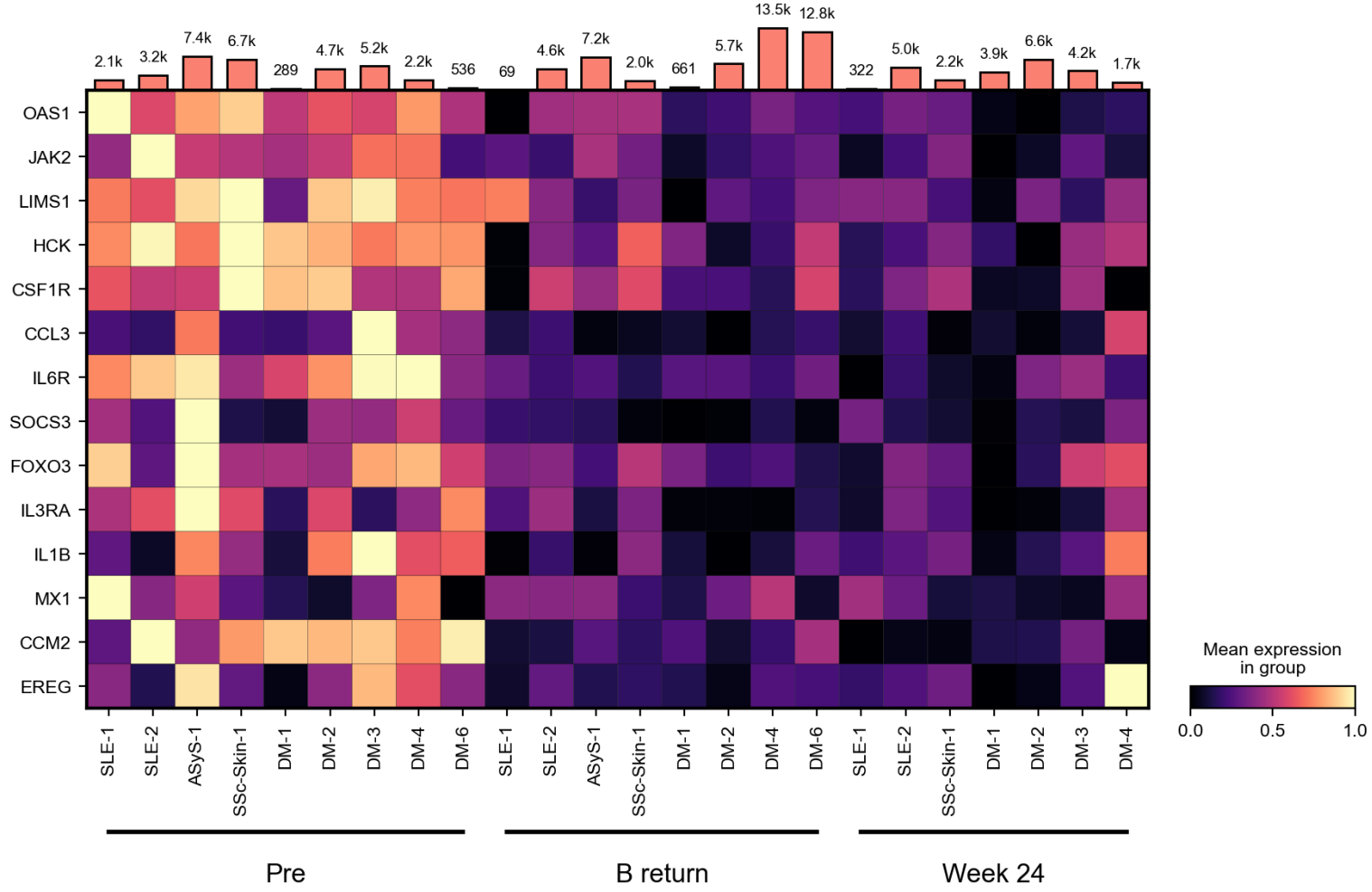






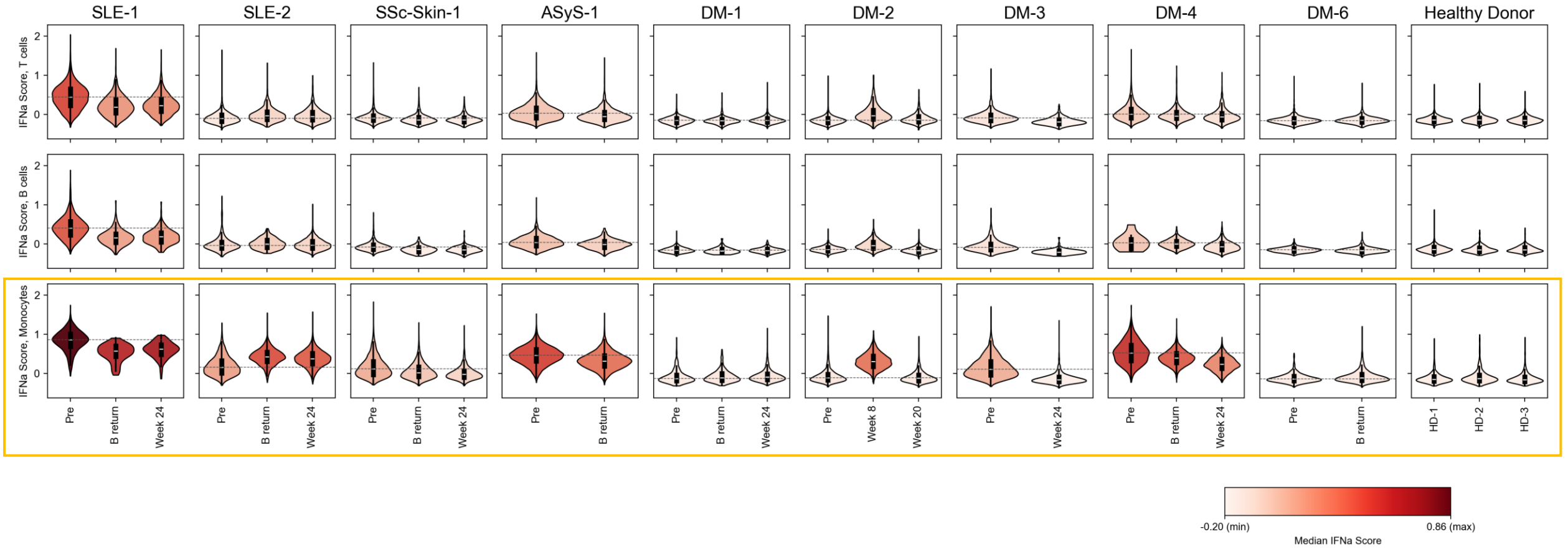
Monocyte activation decreases post rese-cel infusion





Type-I Interferon Gene Signature Decreases Post Treatment in most Patients

Type-I Interferon Gene Signature is more strongly expressed in Monocytes



Type-I IFN Score Genes: IFI27, RSAD2, IFI44, IFI44L, IFI6, USP18, LY6E, OAS1, SIGLEC1, ISG15, IFIT1, OAS3, HERC5, MX1, LAMP3, EPSTI1, IFIT3, OAS2, RTP4, PLSCR1, SPATS2L

Type-I IFN Score correlates with disease in SLE (Yao et al. 2010)

Conclusions

- The diversity of BCR repertoires makes it difficult to interpret the absence of clone overlaps as a replacement of the B cell repertoire
- Single-cel sequencing provides key evidence in understanding how B cell depletion reprograms the immune system:
  - B cells, including more somatically hypermutated, age-associated and memory subsets, are depleted within 2 weeks post rese-cel treatment
  - Reconstituting B cells are transitional naive in phenotype and less somatically hypermutated
  - T cells post treatment are marked by a reduction in TCR and cytokine-mediated activation
  - Monocytes post treatment are marked by a reduction in cytokine-mediated activation
- These results suggest that B cell depletion following rese-cel treatment has a suppressive effect on other immune compartments which may lead to an attenuation of disease associated immune hyperactivity

Acknowledgements

Patients and caregivers involved in the RESET™ clinical program

Site investigators and staff involved with these patients from the RESET™ clinical program

Cabaletta Bio team

- Biostatistics
- Clinical Development
- Clinical Operations
- Computational Biology
- Manufacturing
- Medical Affairs
- Translational Medicine
- Quality Assurance