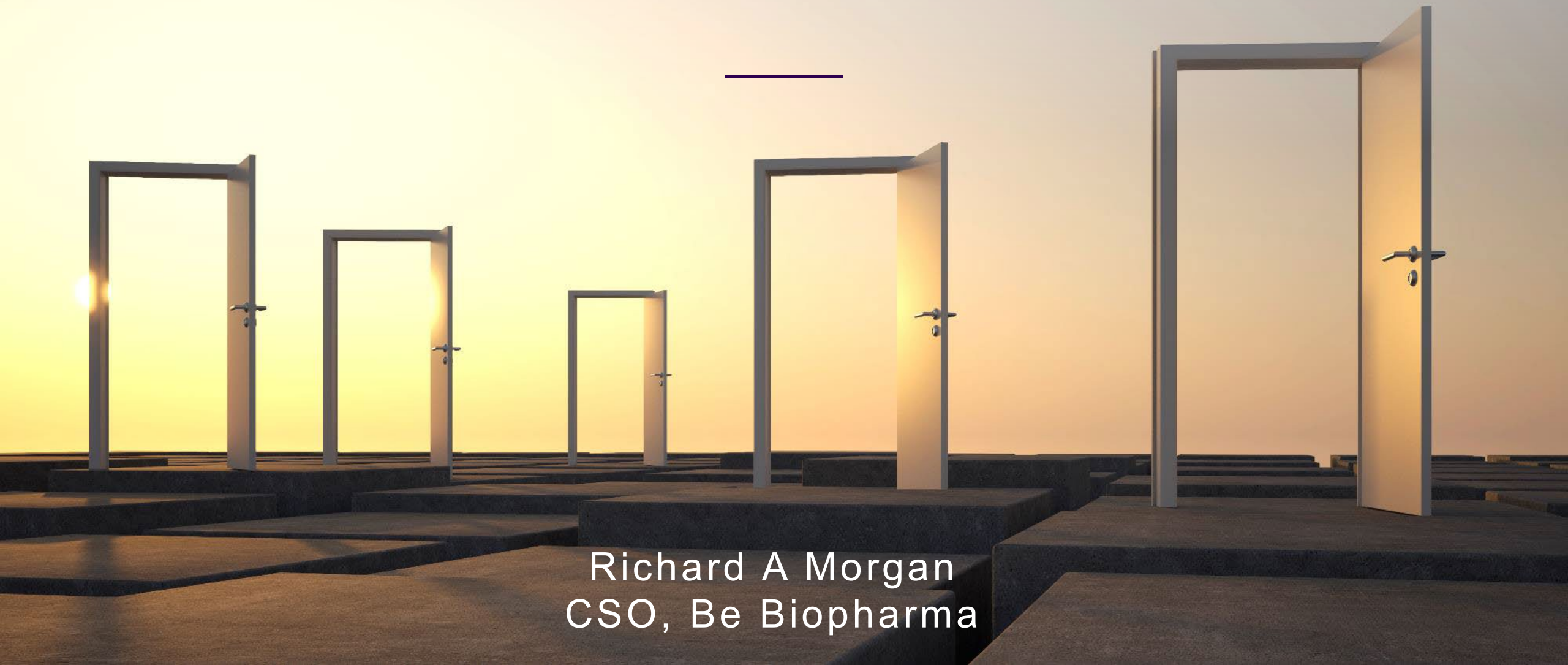
Engineered B Cells as a Novel Off-The-Shelf Therapy in Oncology

PEGS Boston Summit
May 5, 2022



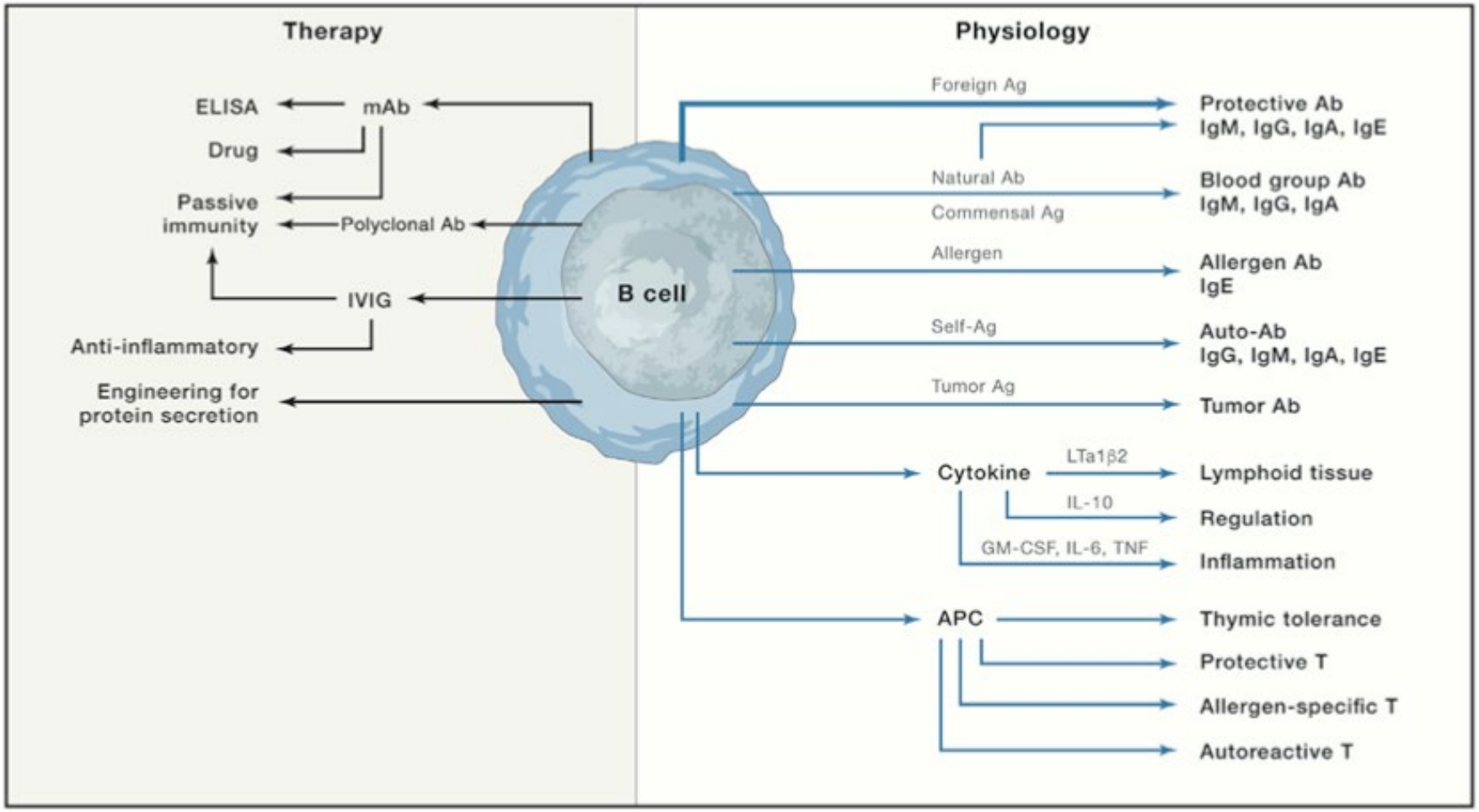
Richard A Morgan
CSO, Be Biopharma

Nature evolved a cell exquisitely designed to manufacture protein drugs to defend the body against pathogens & rogue cells

What if we could unleash that cell against our most serious diseases? Off-the-shelf. No pre-conditioning. Redosable.

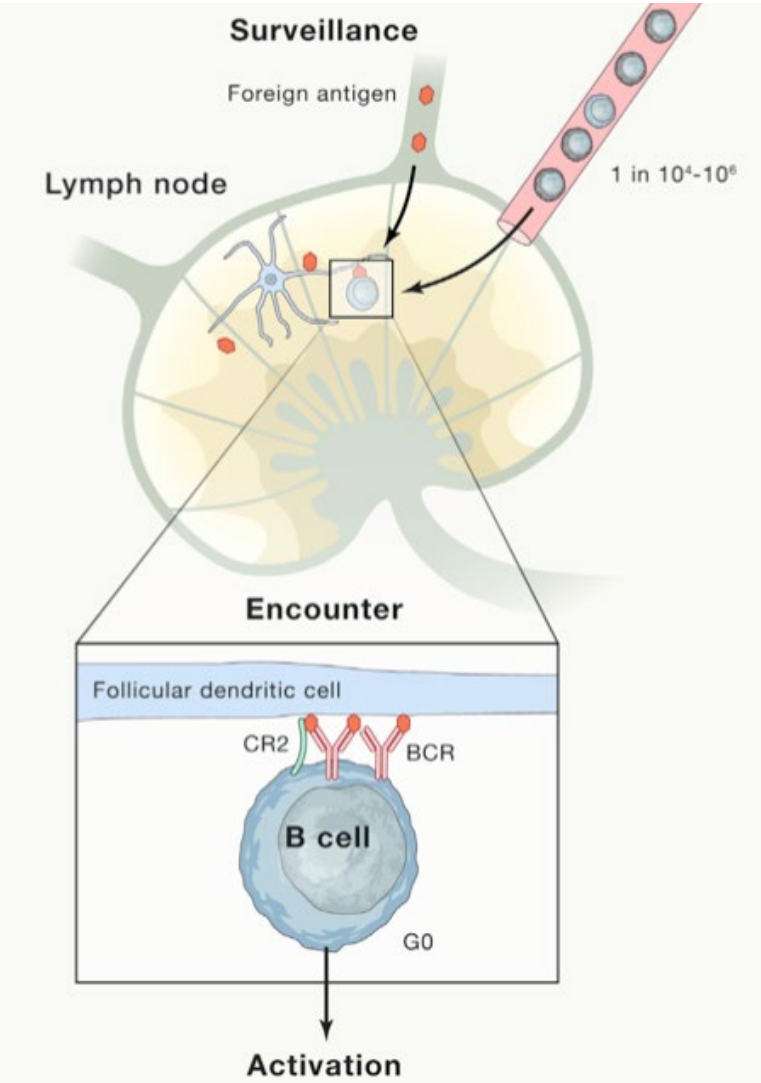
Be Bio. Pioneering Engineered B Cell Medicines. For Patients.

Introducing the B cell, Immunotherapy's silent partner

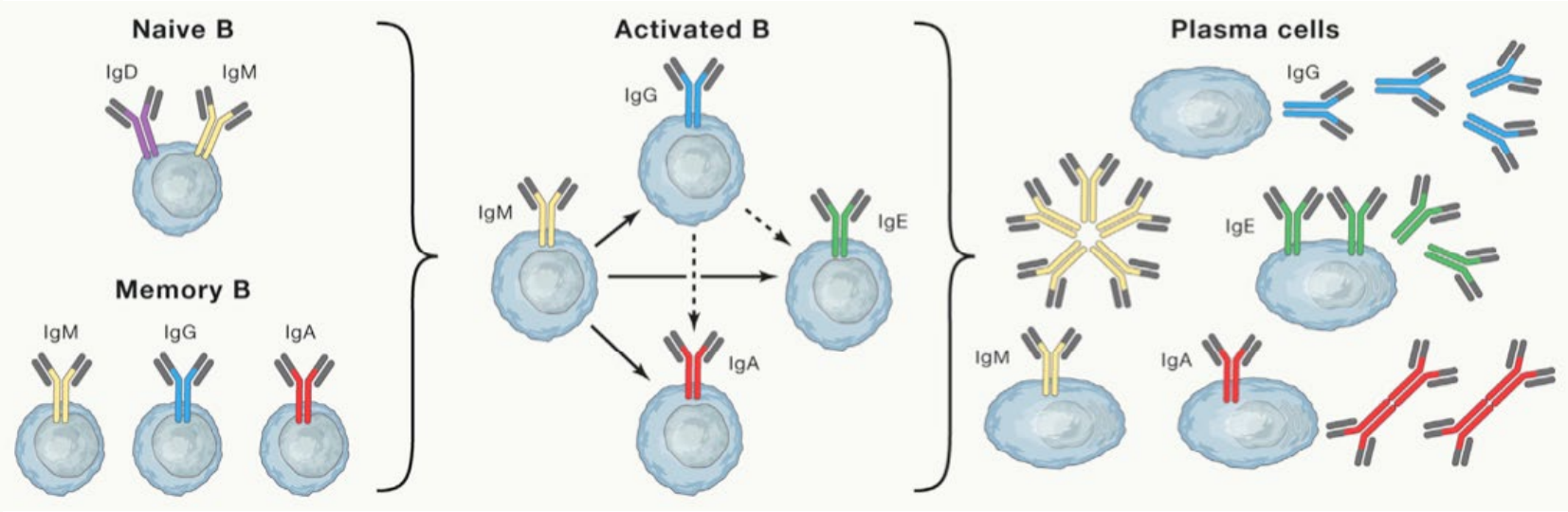


From, Jason G. Cyster, and Christopher D.C. Allen, B Cell Responses: Cell Interaction Dynamics and Decisions, https://doi.org/10.1016/j.cell.2019.03.016

B cells are matured in the LN germinal center and progress through multiple stages of differentiation that lead to long-live bone marrow resident plasma cells

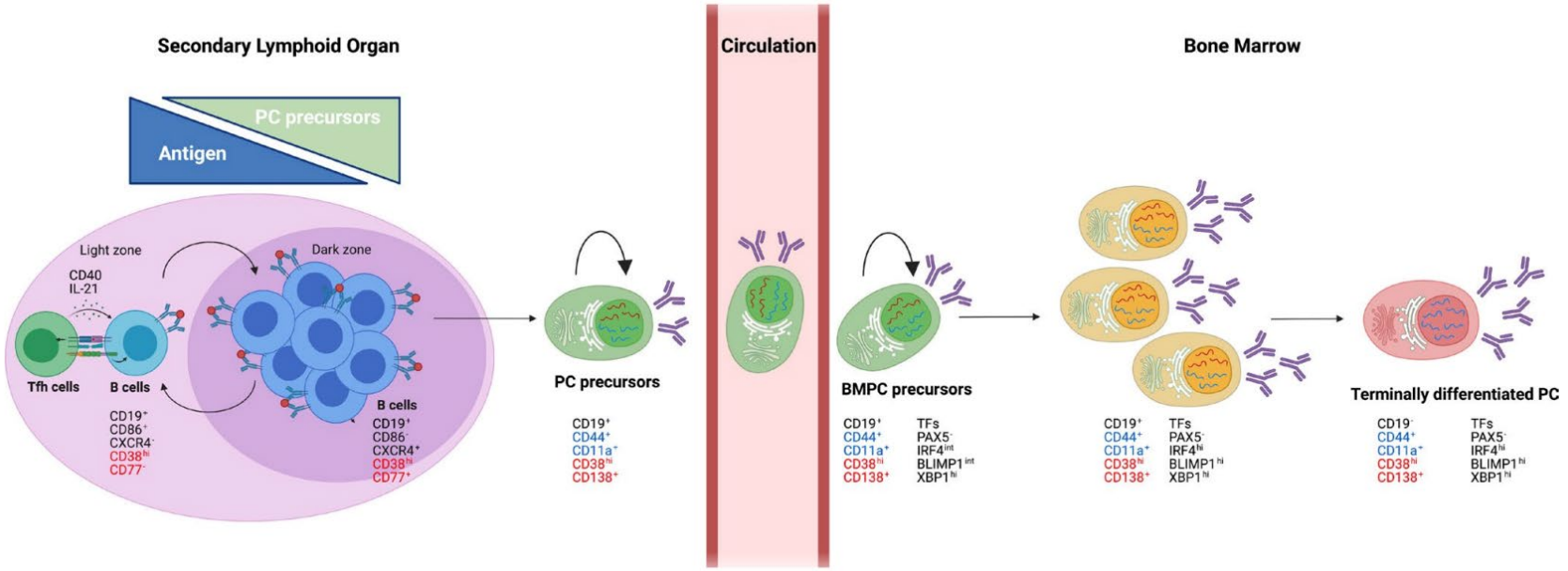


B cells produce a variety of antibody isotypes



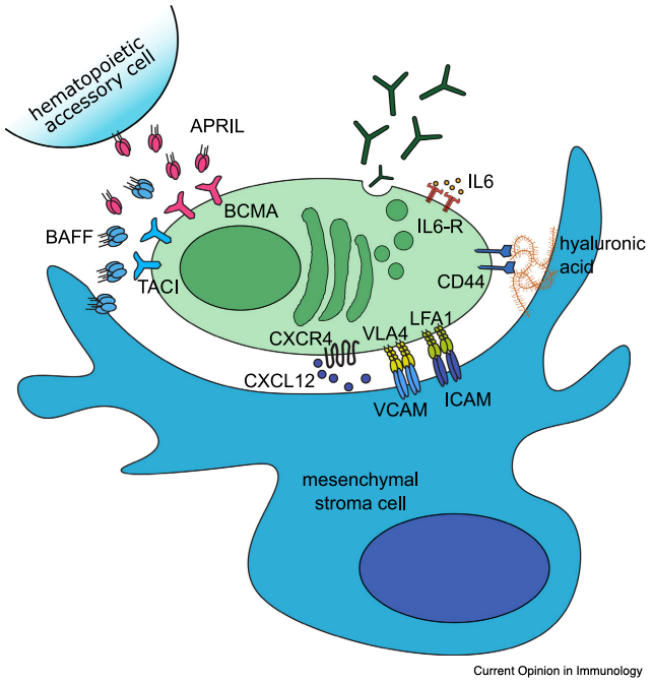
From, Jason G. Cyster, and Christopher D.C. Allen, B Cell Responses: Cell Interaction Dynamics and Decisions, https://doi.org/10.1016/j.cell.2019.03.016

Once generated in peripheral sites, PC migrate to the bone marrow where they take up residence and are supported by the BM niche



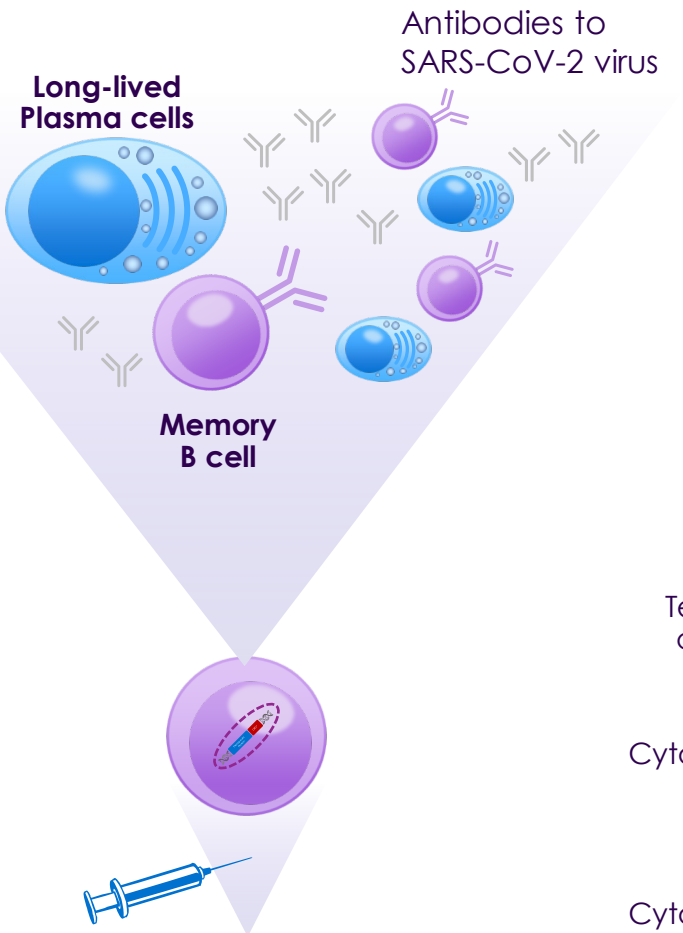
Adapted from, Immunological Reviews. 2021;303:62–71. DOI: 10.1111/imr.13010

BM niche



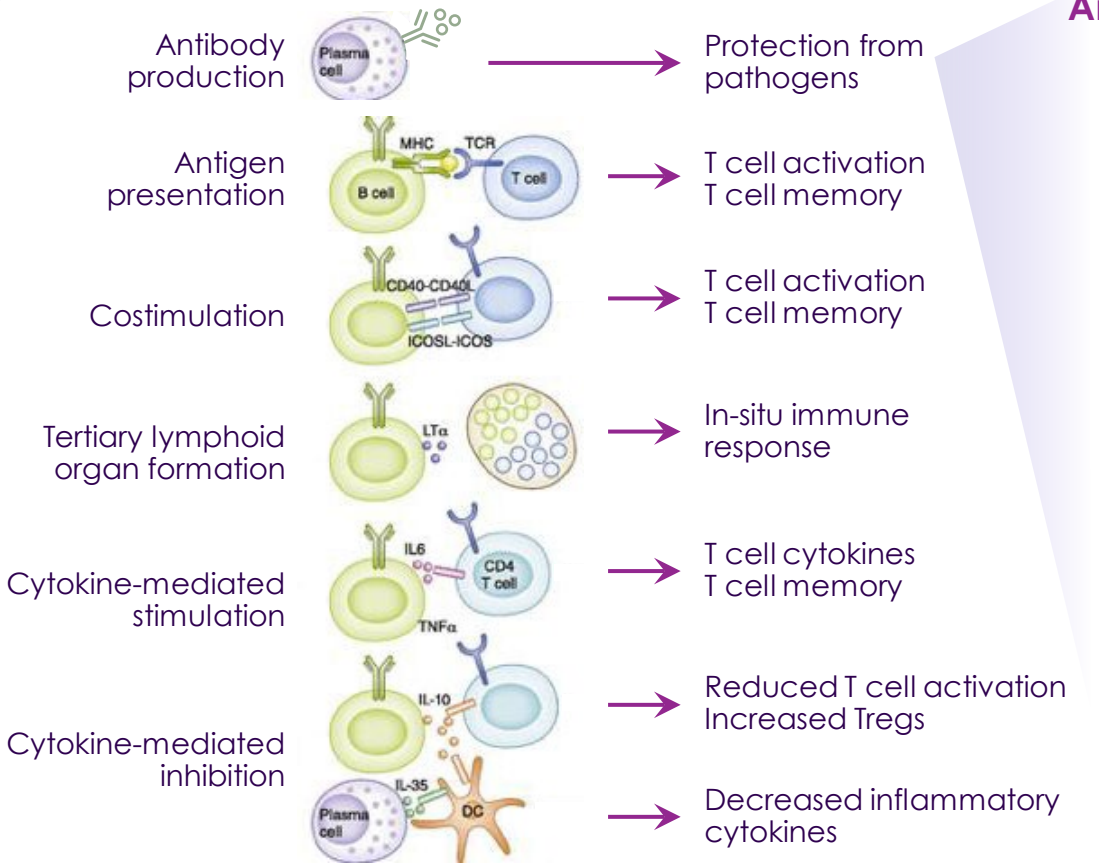
Adapted from, Current Opinion Immunol. July 2021. https://doi.org/10.1016/j.coi.2021.06.012

B Cells Are Nature's Medicines

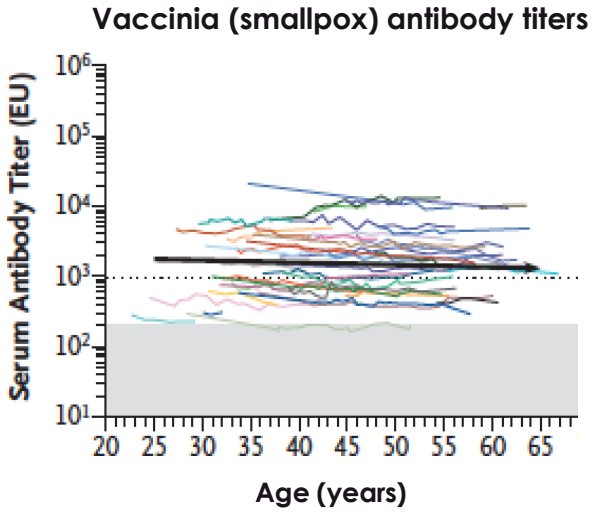


Example: COVID vaccine.
Protection from COVID-19 is mediated by B cells.

B Cells Have Broad Therapeutic Utility*



Long-lived Plasma Cells Can Survive Decades in People and Provide Durable Antibody Expression**



* https://doi.org/10.2215/CJN.09430915. ** doi:10.1016/j.it.2019.01.012

Be Bio's Engineered B Cell Medicines Leverage Inherent B Cell Properties To Unlock A New Class of Medicine With Exceptionally Broad Therapeutic Utility

What — Powerful, Durable, Therapeutic

Prolific Protein Producers
Continuous protein production, few cells needed for effective product

Durable Production
Long-lived plasma cells can produce proteins for decades

How — Without Traditional Cell Therapy Burden

Off-the-shelf
B Cells Are "Naturally Allogeneic," simple path to allogeneic product

No preconditioning
Plasma cells naturally engraft in the bone marrow without conditioning

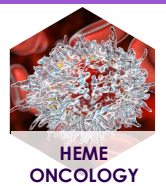
Precise & Repeatable Dosing
Multiple rounds of engraftment possible in large bone marrow niche

And more …
Low immunogenicity, expected outpatient administration

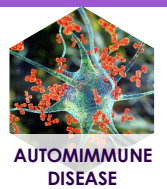
Why — Develop a new class of medicines with exceptional therapeutic breadth & profound patient impact


Rare Disease


SOLID TUMOR ONCOLOGY

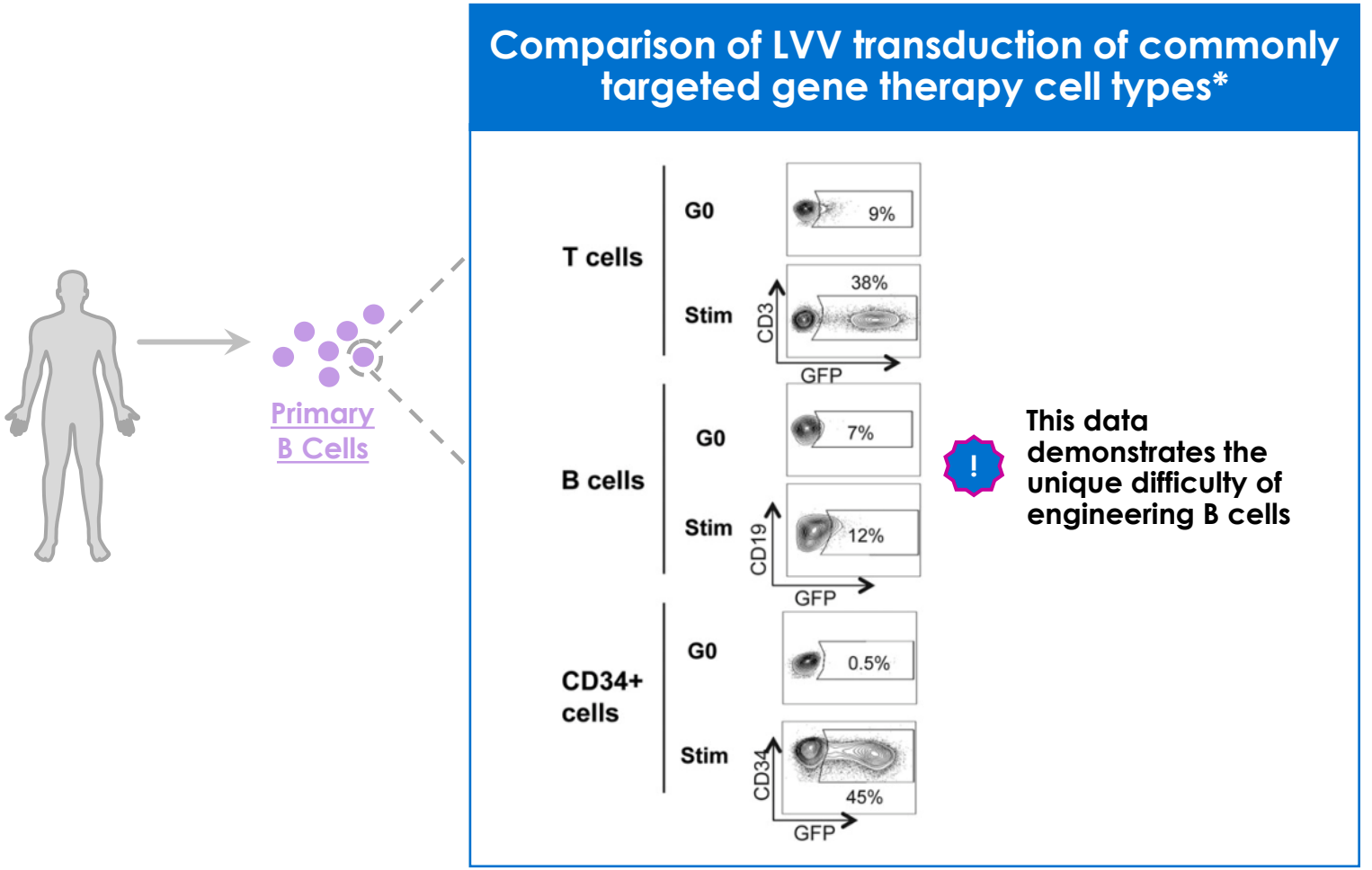

HEME ONCOLOGY


INFECTIOUS DISEASE


AUTOMIMMUNE DISEASE


CNS

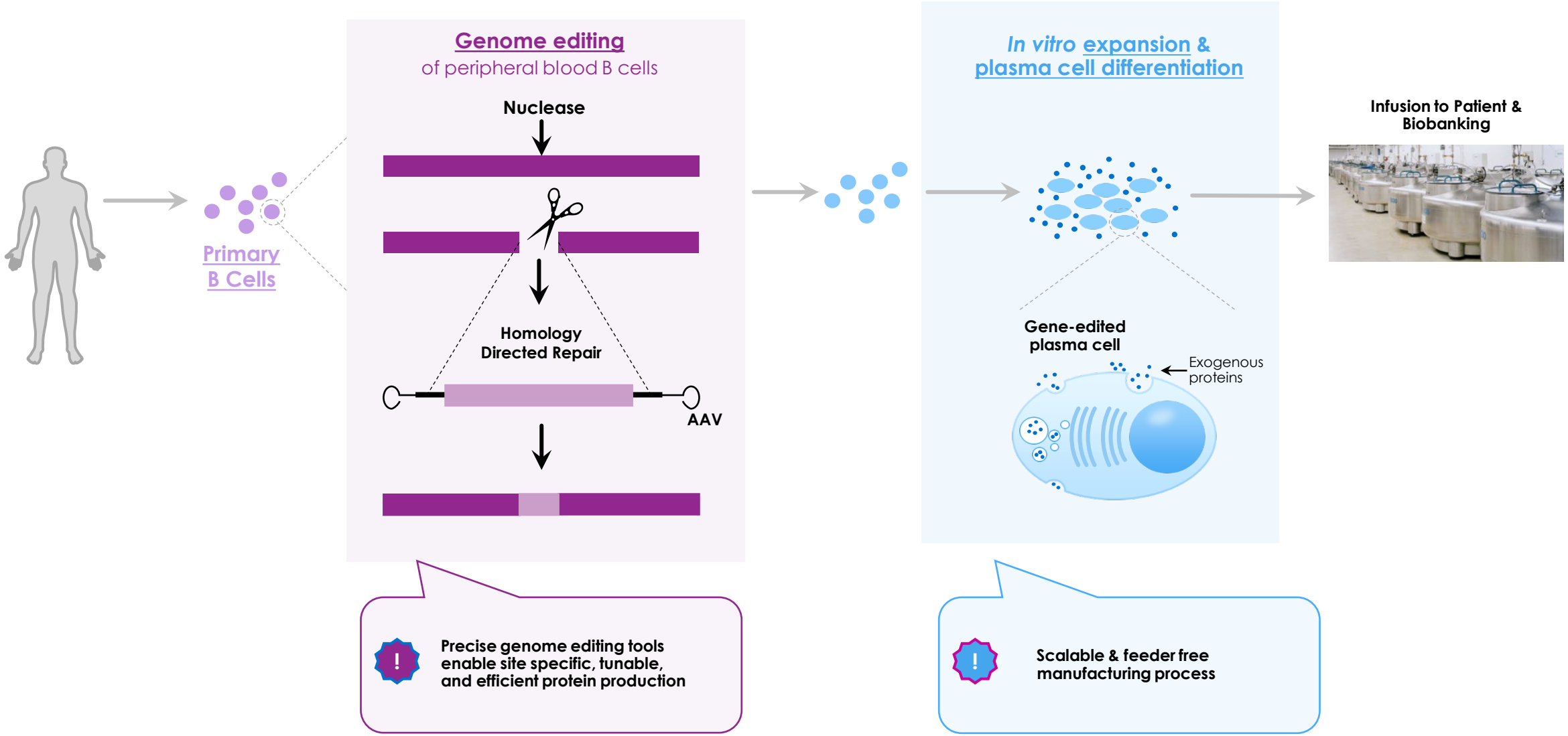
But… B Cells Have Been Notoriously Intractable to Engineering



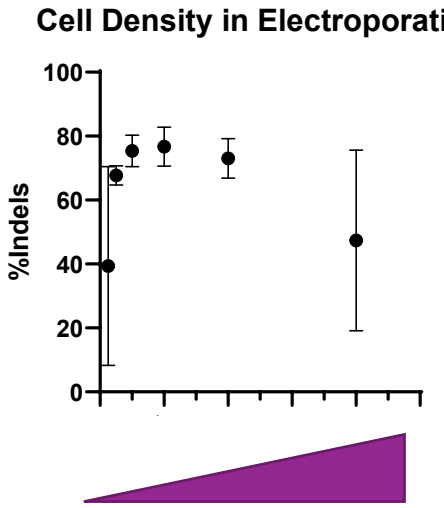
*From: Costa C., et al., BLOOD, 27 FEBRUARY 2014 x VOLUME 123, NUMBER 9

B Cells Have Been Notoriously Intractable for Engineered Medicines

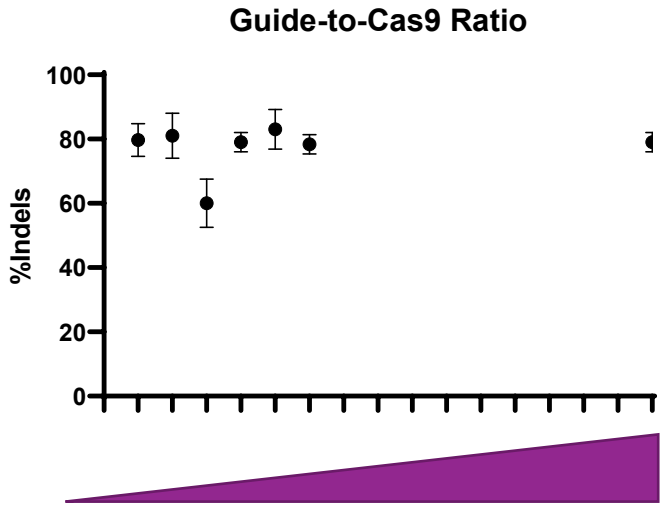
Be Bio's Platform Overcomes These Challenges



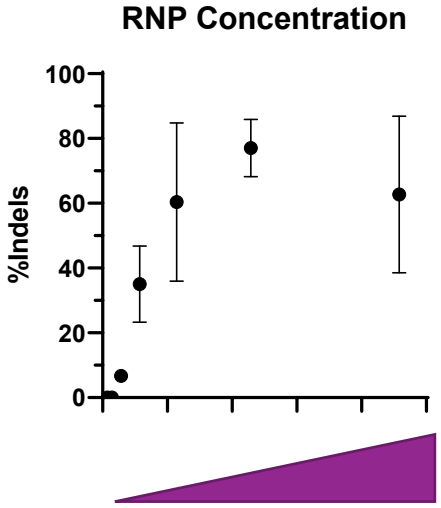
Be Bio optimization of B cell editing conditions



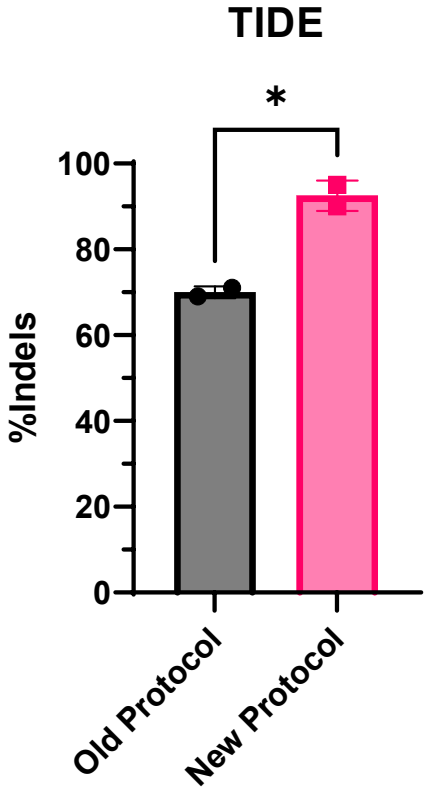
Density



Ratio

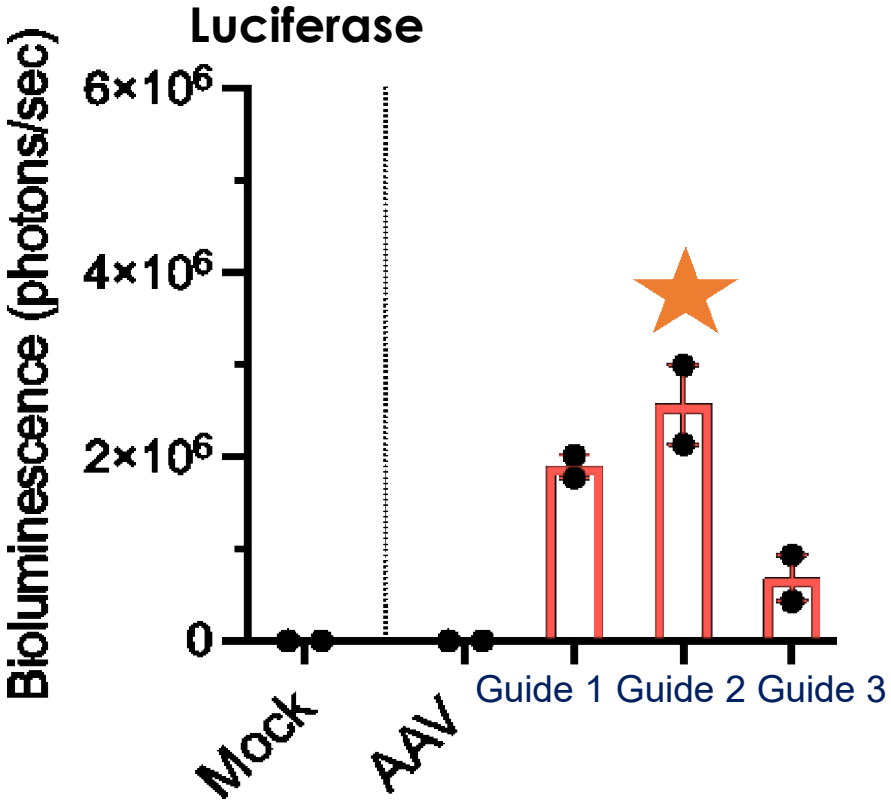


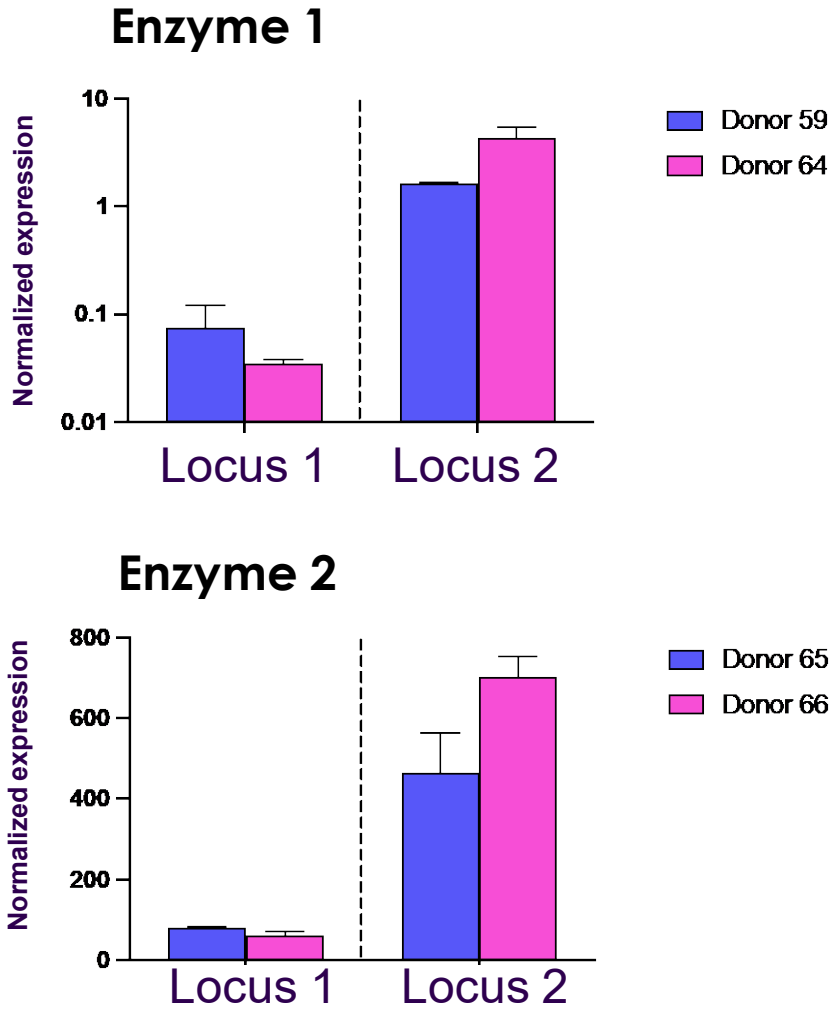
Concentration



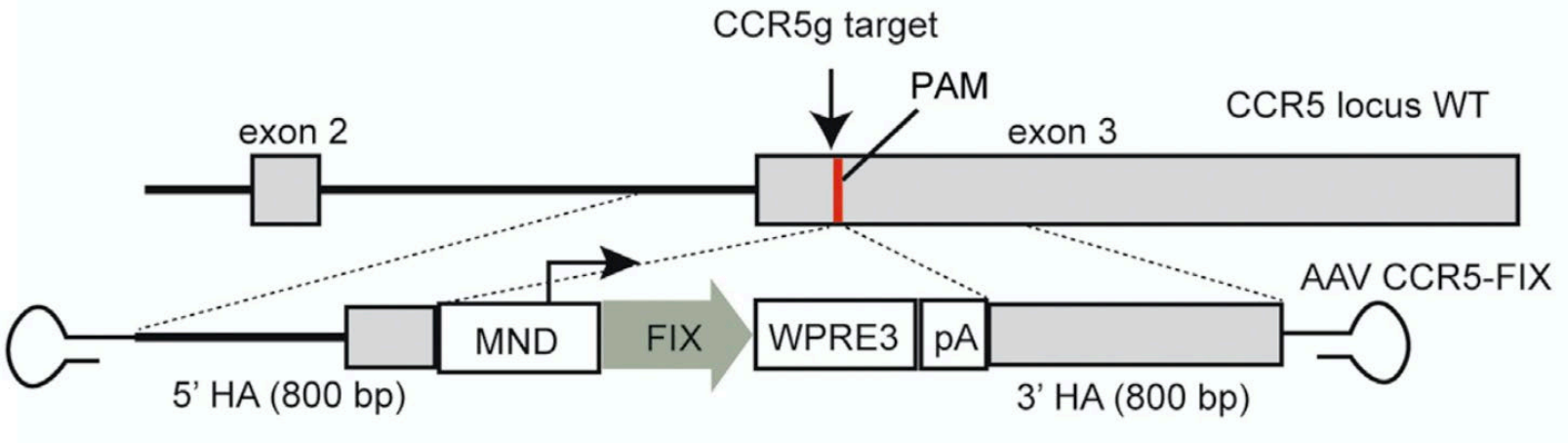
Optimization achieves >90% editing in human B cells

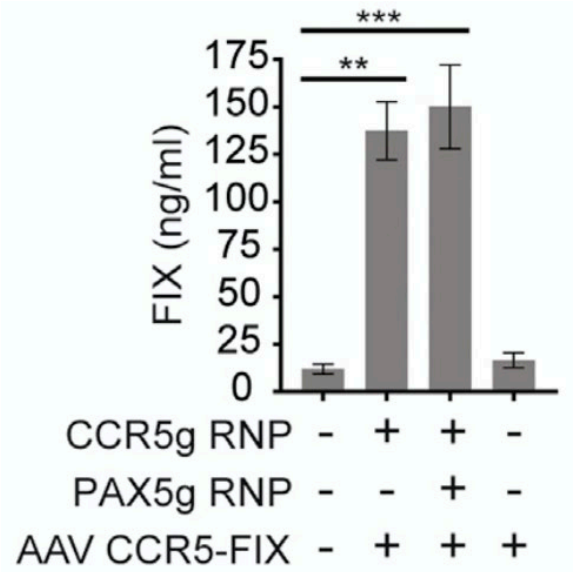
Be Bio engineering optimization: Guide screen to optimize gene editing/homology directed repair (HDR) in plasma cells

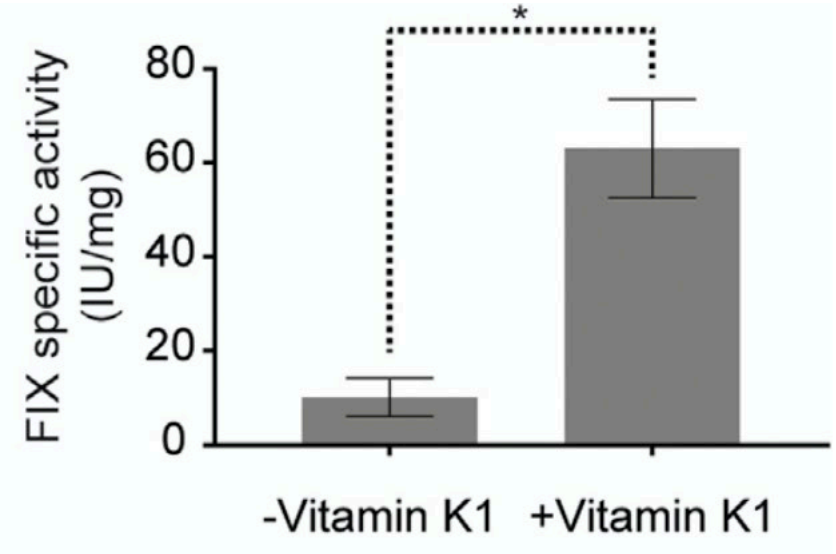




Putting it all together: Demonstration of biologically active factor IX by engineered plasma cells





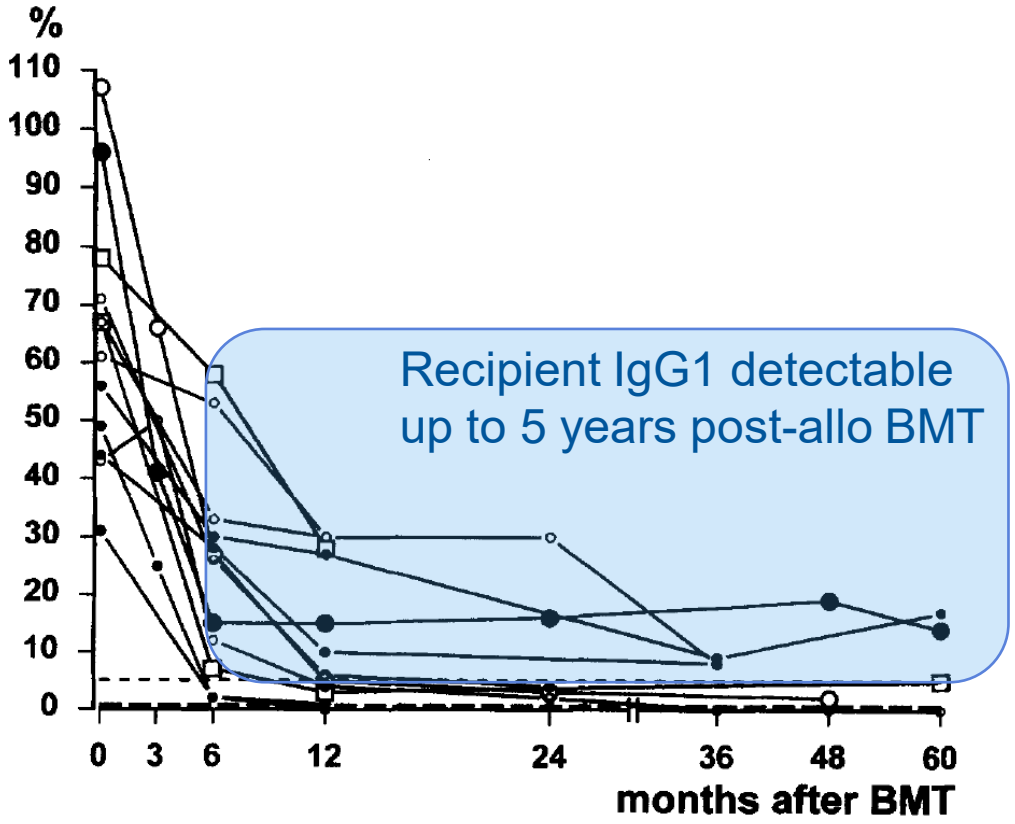


From : Hung KL., et al., https://doi.org/10.1016/j.ymthe.2017.11.012

Plasma cells can persistence in allogeneic bone marrow transplant recipients, “Naturally Allogeneic” and can be further engineered to resist T cells

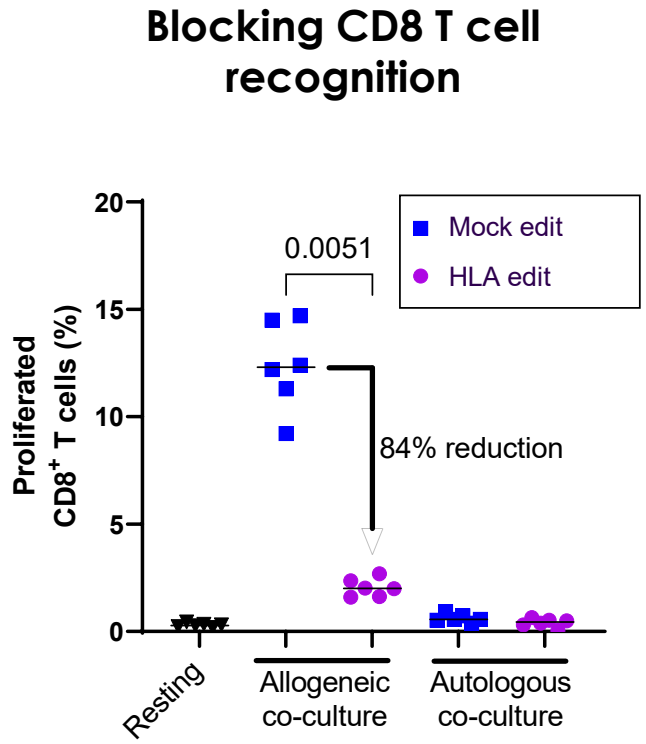
Persistence of recipient IgG allotype mismatched LLPCs following myeloablative bone marrow transplant (BMT)

Proportion of recipient allotype IgG1 to total IgG1

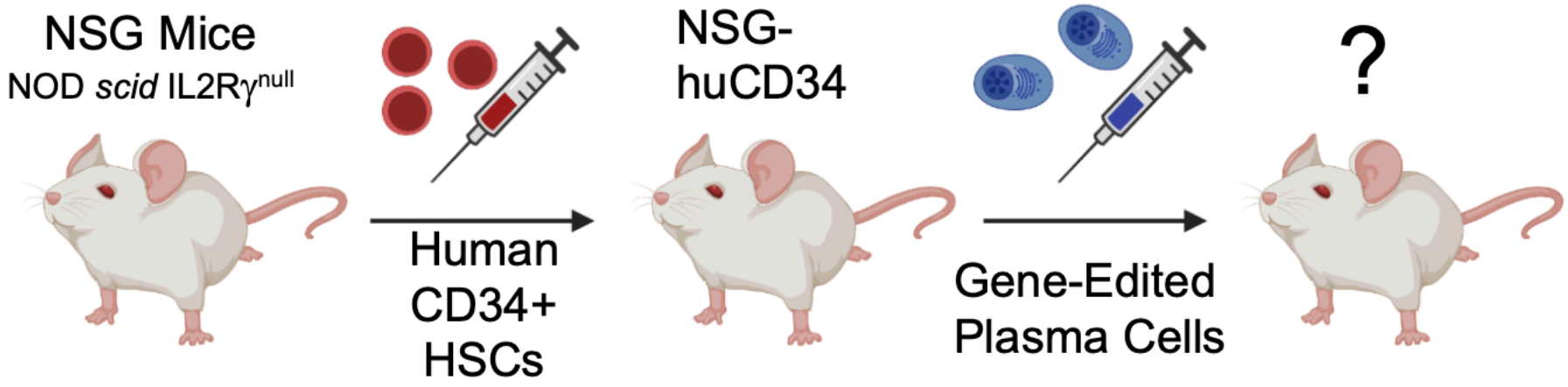


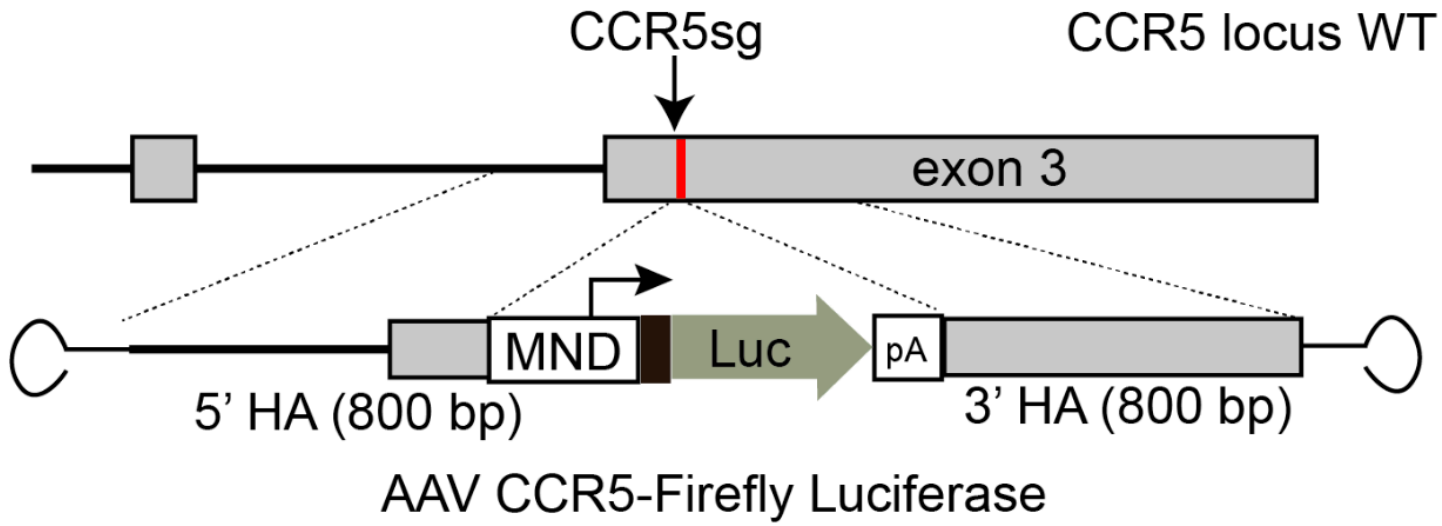
van Tol, M. J. et al. The origin of IgG production and homogeneous IgG components after allogeneic bone marrow transplantation. Blood 87, 818–826 (1996).

Gene editing can reduce CD8 T cell killing of allogeneic plasma cells



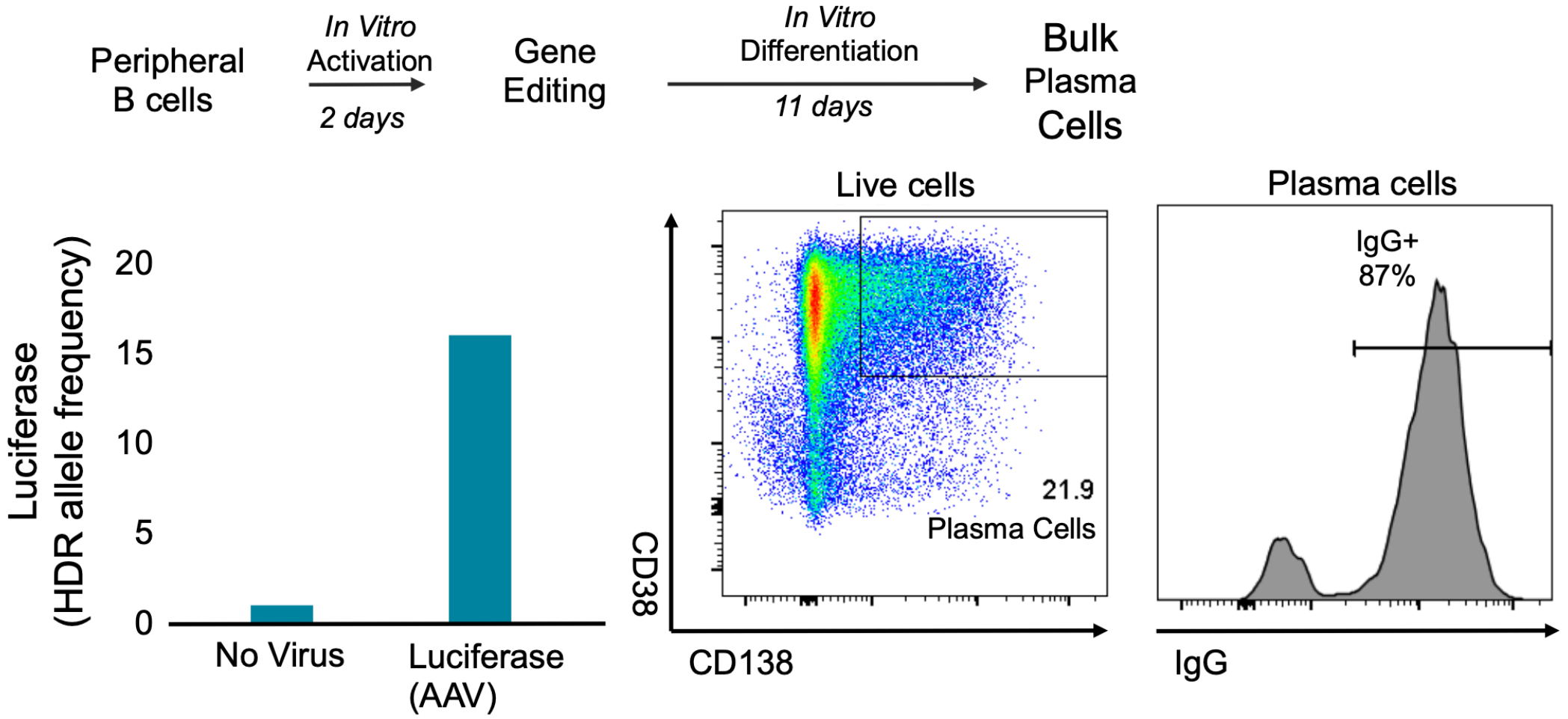
Demonstration of engineered plasma cell engraftment in human CD34+ HSC reconstituted mice – *Humanized Model System*



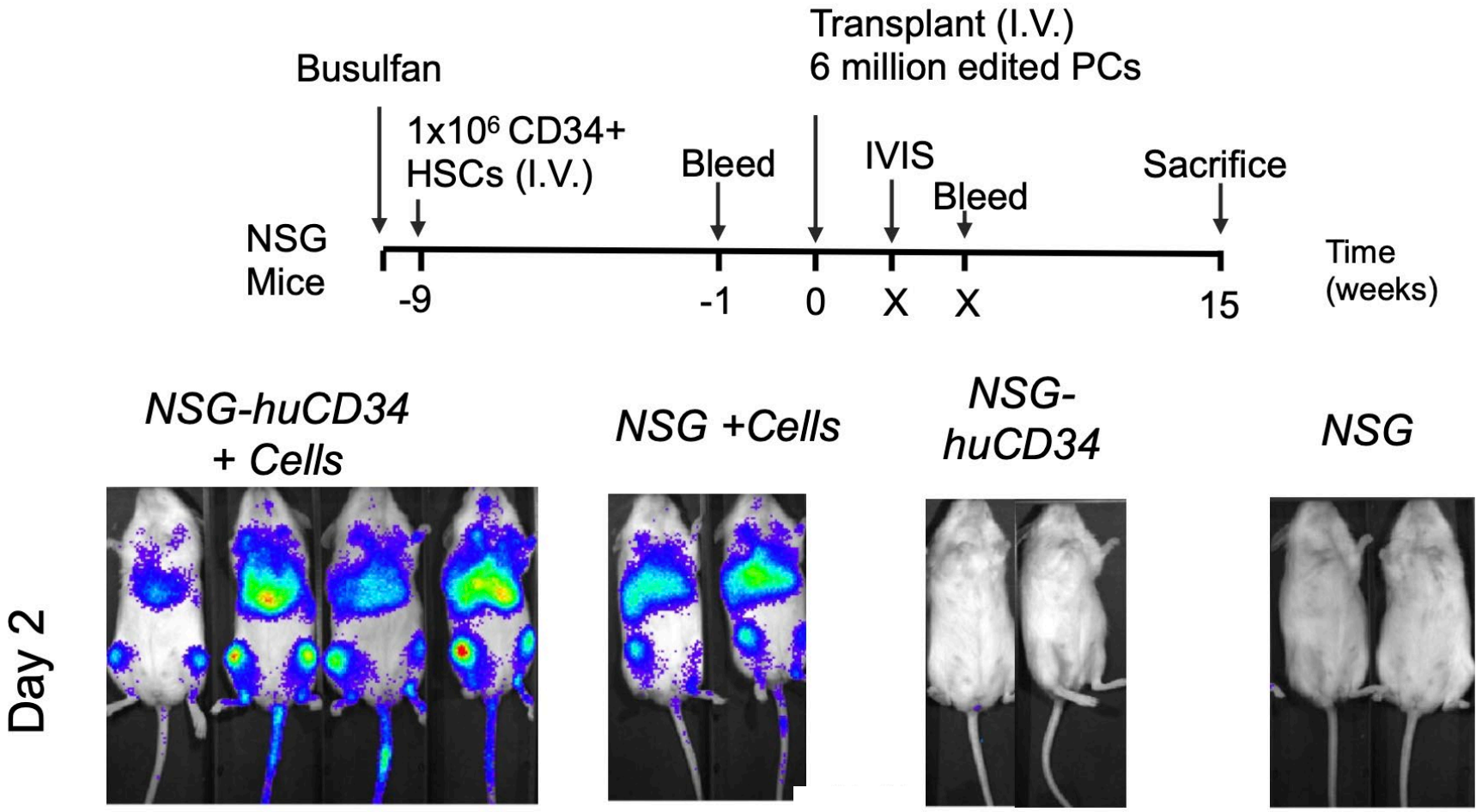


From: Hill, T., James, R. & Rawlings, D. J.
Keystone Symposia, Emerg. Cell Ther. Realiz. Vis. NextGen Cell Ther. EK15 (2021).

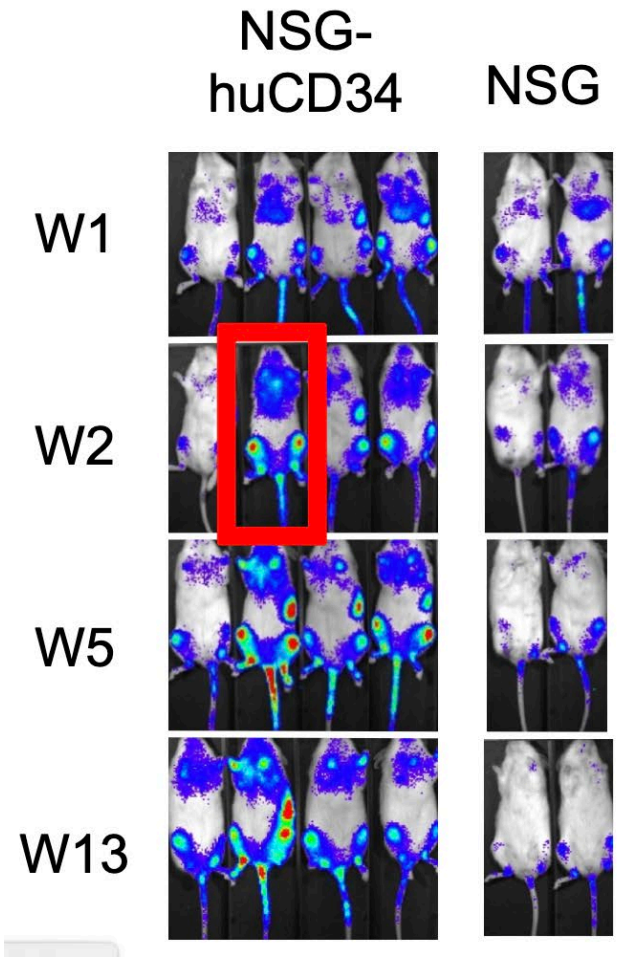
Demonstration of engineered plasma cell engraftment in human CD34+ HSC reconstituted mice – *Efficient ex vivo PC production*

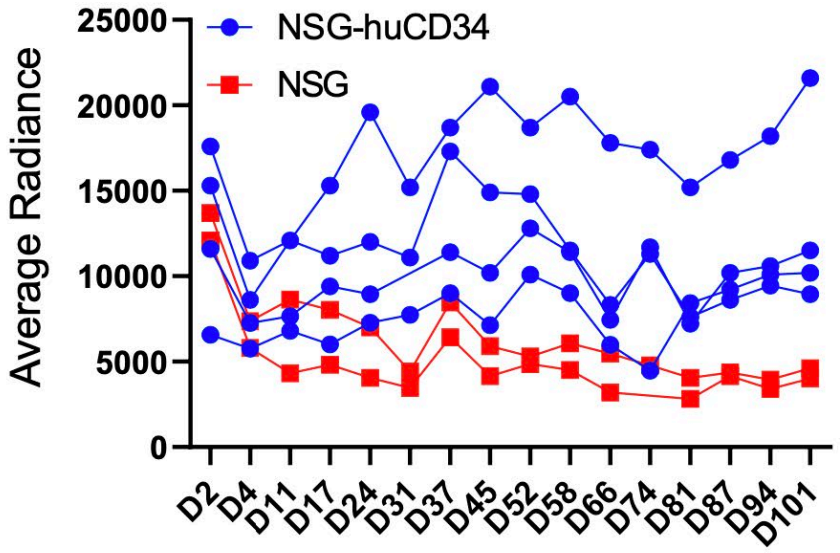


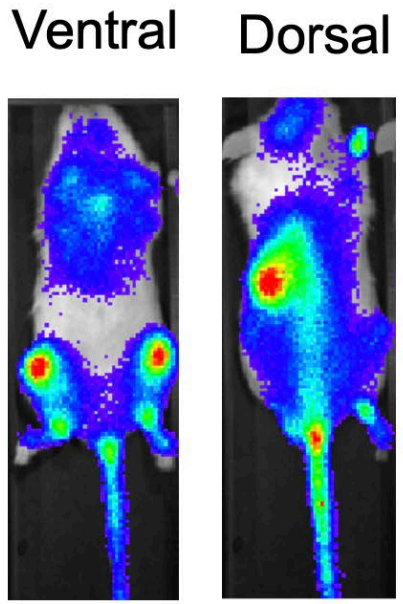
Demonstration of engineered plasma cell engraftment in human CD34+ HSC reconstituted mice – *Rapid engraftment w/o pre-conditioning*



Demonstration of engineered plasma cell engraftment in human CD34+ HSC reconstituted mice – *Human BM microenvironment facilitates PC engraftment out to > 100 days*







From: Hill, T., James, R. & Rawlings, D. J.
Keystone Symposia, Emerg. Cell Ther. Realiz. Vis. NextGen Cell Ther. EK15 (2021).

The growing link between positive clinical outcomes and tumor infiltrating B cells in Oncology

Article Nature | Vol 577 | 23 January 2020

B cells and tertiary lymphoid structures promote immunotherapy response

https://doi.org/10.1038/s41586-019-1922-8

NATURE REVIEWS | CANCER

Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities

https://doi.org/10.1038/s41568-022-00466-1

BRIEF COMMUNICATION
https://doi.org/10.1038/s43018-021-00232-6
nature cancer

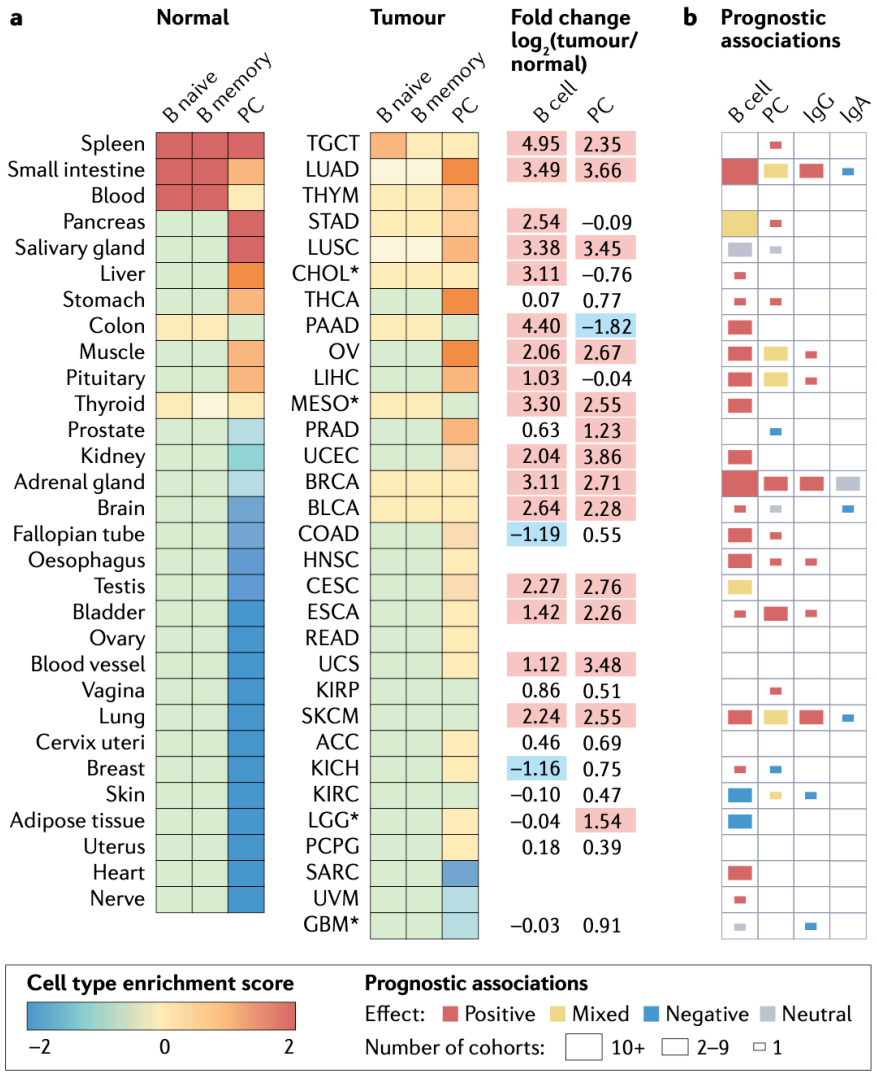
Mature tertiary lymphoid structures predict immune checkpoint inhibitor efficacy in solid tumors independently of PD-L1 expression

nature COMMUNICATIONS

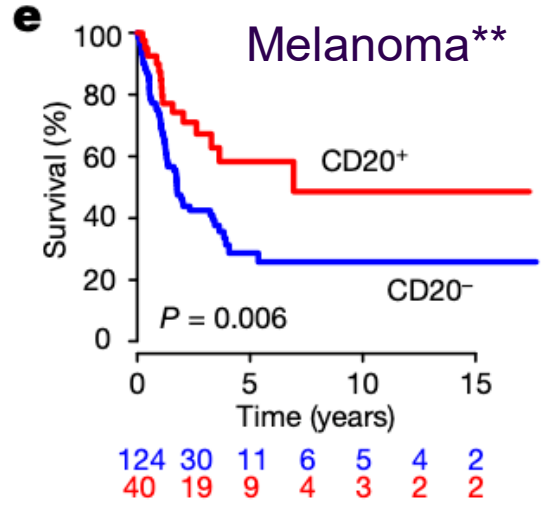
ARTICLE
https://doi.org/10.1038/s41467-021-23355-x OPEN

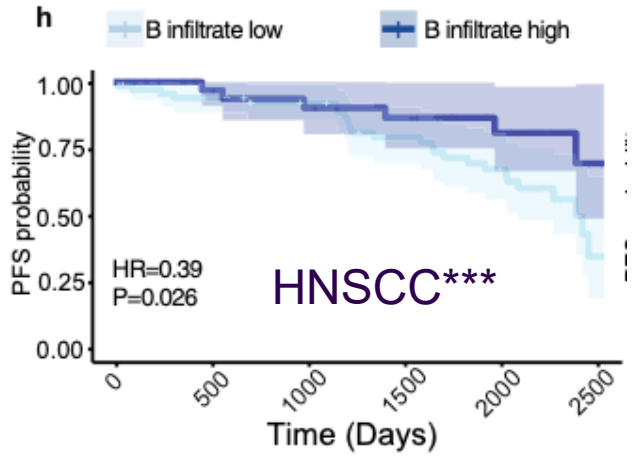
B cell signatures and tertiary lymphoid structures contribute to outcome in head and neck squamous cell carcinoma

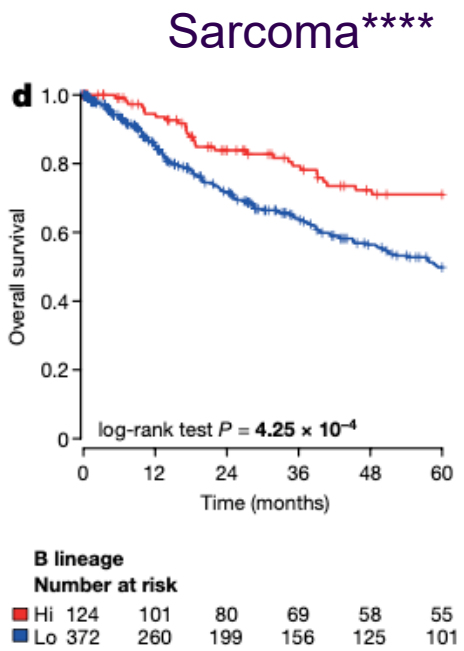
B Cells are associated with positive clinical outcomes across histology



From: Laumont CM., et a., https://doi.org/10.1038/s41568-022-00466-1



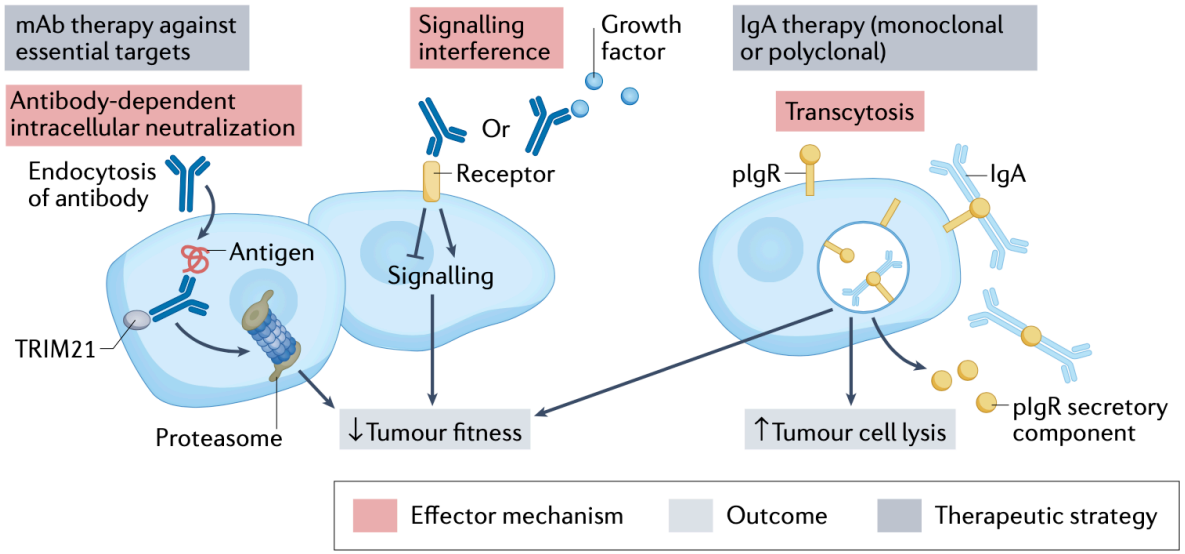




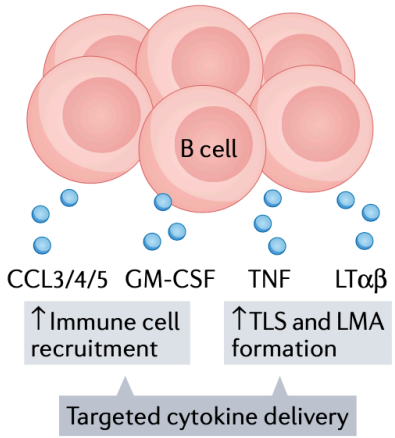
* https://doi.org/10.2215/CJN.09430915. **doi.org/10.1038/s41586-019-1914-8 ***doi.org/10.1038/s41467-021-23355-x , ****doi.org/10.1038/s41586-019-1906-8

B cell functions associated with cancer regression

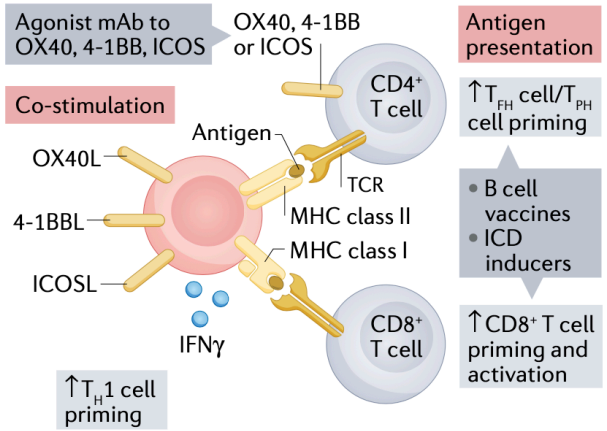
Direct antibody effects



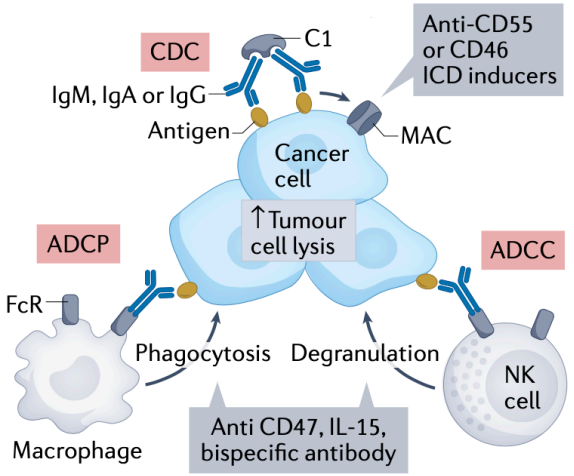
Immune cell recruitment and TLS formation



Prime, shape, and amplify T cell responses



Activation of innate immunity



From: Laumont CM., et a., https://doi.org/10.1038/s41568-022-00466-1

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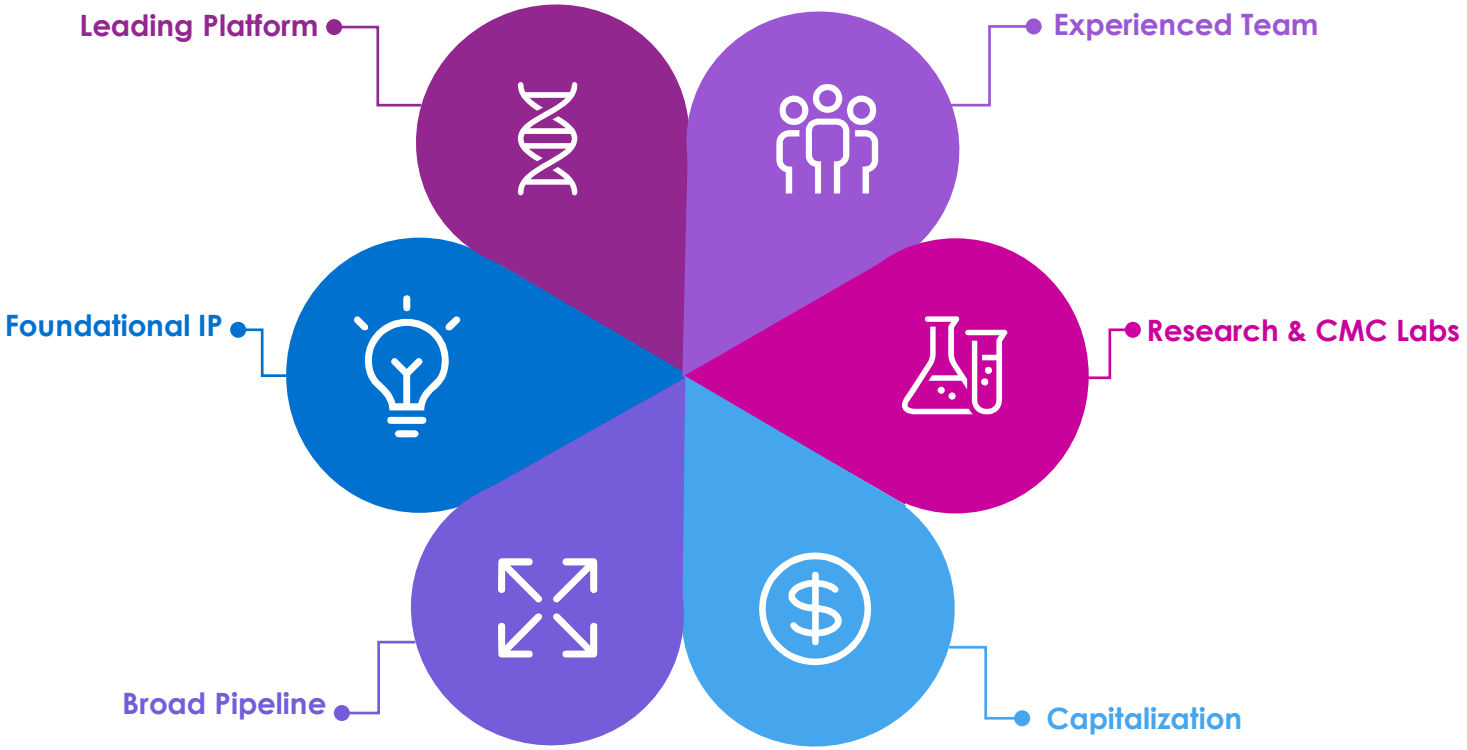
Summary

- B cells are an unexploited cell type for cell and gene therapy
- Be Biopharma technology combines gene editing/HDR with easily scalable cell manufacturing
- Plasma cells are naturally allogeneic and may be further modified to avoid immune rejection
- Animal models demonstrate rapid and long-term engraftment without pre-conditioning
- B cells ability to produce antibodies combined with mechanisms to stimulate the immune system make them an ideal anti-cancer cell therapy

Be Bio. Pioneering a New Class of Medicines for Profound Patient Impact



EXPERIENCED TEAM

- ✓ Cell therapy veterans + rapidly growing teams
- ✓ Expanded operational & executive team with 60+ FTEs

Joanne Smith-Farrell, PhD
Chief Executive Officer

Krishnan Viswanadhan, PharmD
President & Chief Operating Officer

Rick Morgan, PhD
Chief Scientific Officer

Lea Hachigian, PhD
VP, Strategy & Operations, Co-Founder

Brad Hartman
Chief People Officer

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