

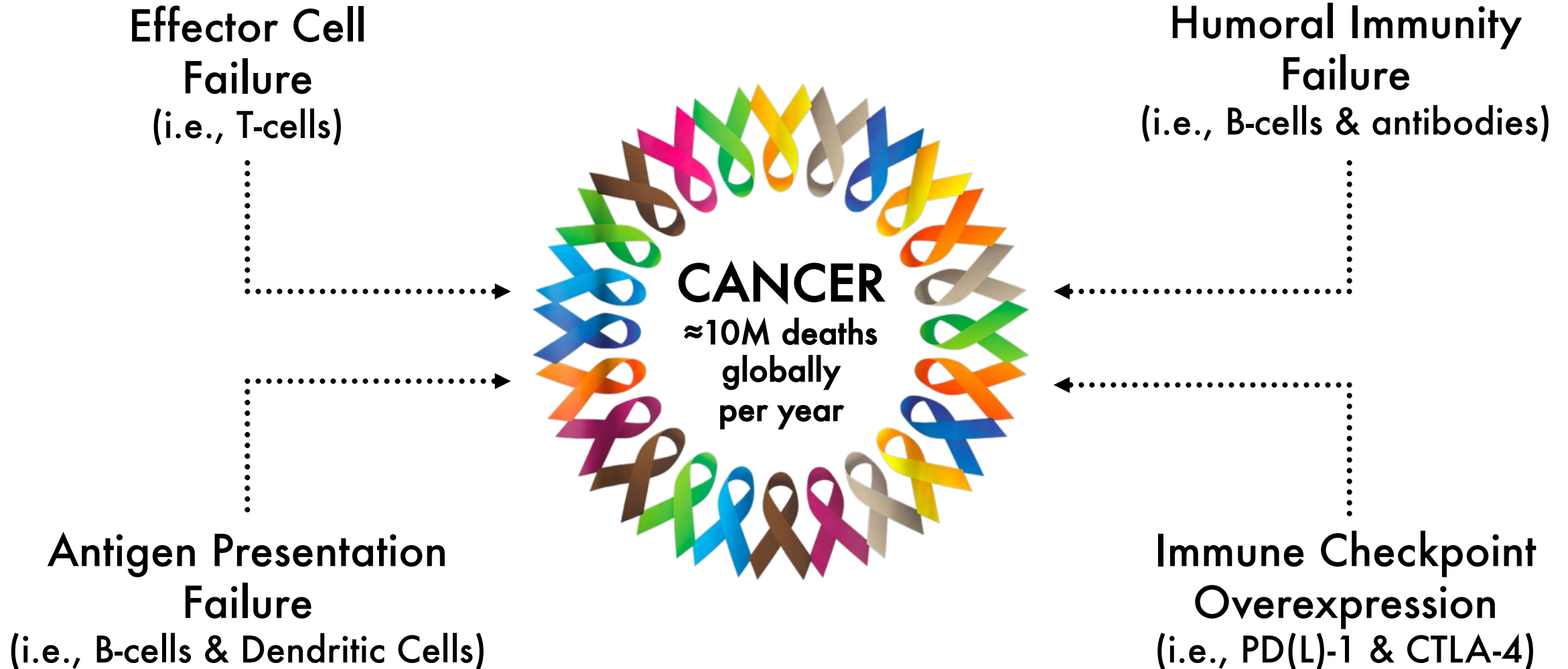
BESPOKE
BIOTHERAPEUTICS

**B-cell Genome Engineering and
Synthetic Biology to Cure Cancer**

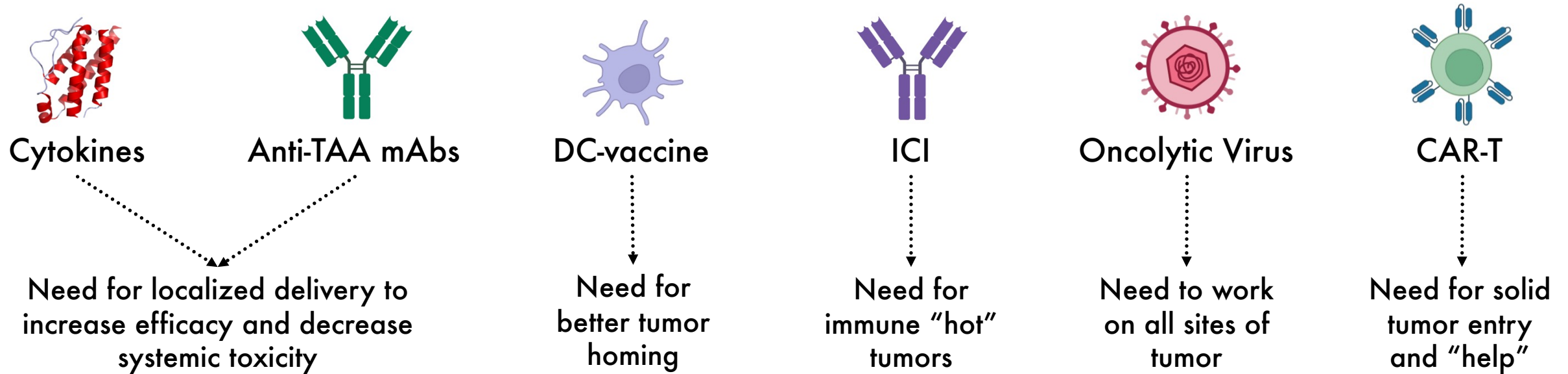
Introductory Slide Deck

February 1, 2023

Problem #1: Cancers Are Immune System Failures



Problem #2: Current I/O Drugs Have Major Limitations



We need a means of actuated, localized anticancer protein therapeutic delivery and tumor-associated antigen presentation to enhance on-tumor efficacy and eliminate systemic toxicity

Solution: Bespoke Engineered B-cell Therapeutics

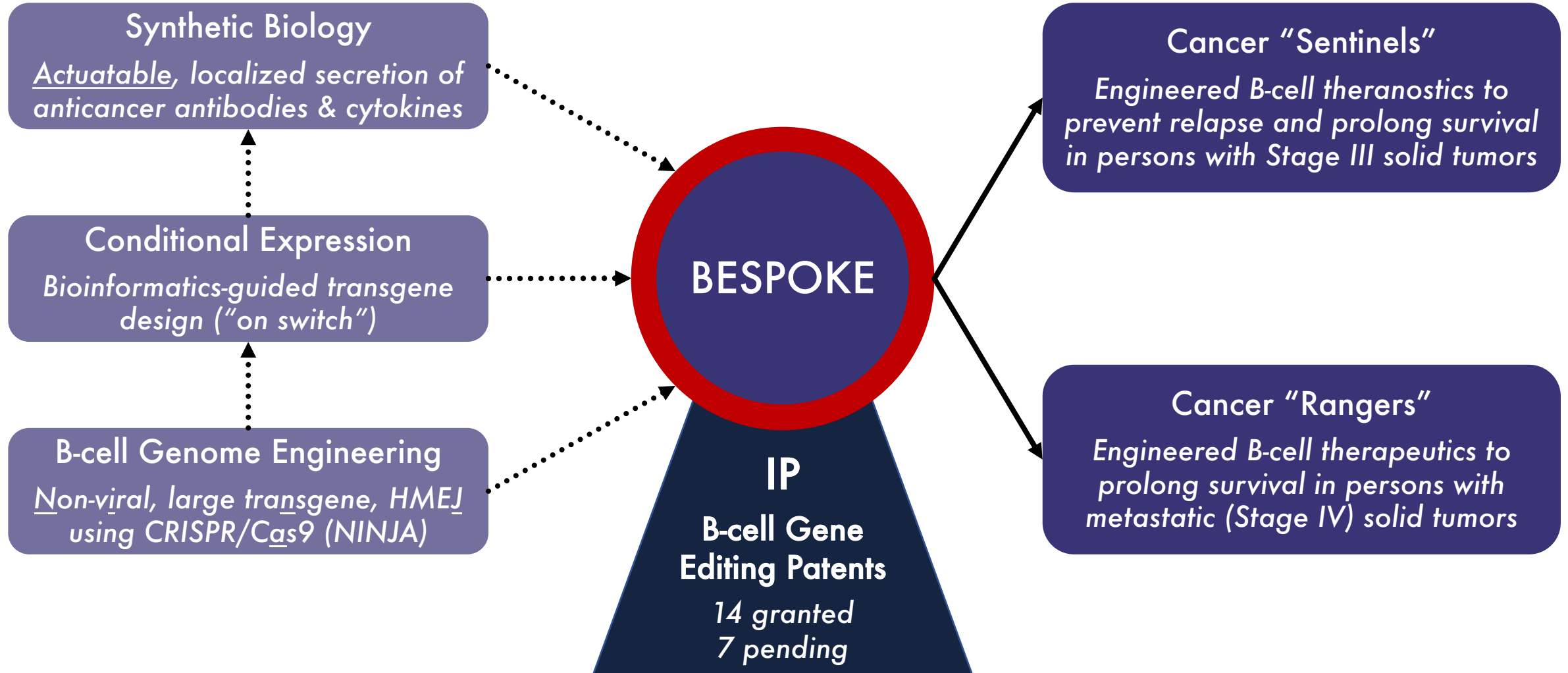
Bespoke's Mission

To reprogram human B-cells into intuitive “living drug” immunotherapies that traffic to solid tumors and tumor-draining lymph nodes where they locally express and secrete engineered anticancer protein therapeutics and present tumor antigen to T-cells

Bespoke Foundation, Innovations, and Platforms

TECHNOLOGIES

PLATFORMS



Deep Cell Therapy and B-cell Engineering Expertise



Steven R. Deitcher, MD

Founder, CEO, and Chairman

Serial biotechnology founder, oncologist, inventor, company builder, and C-suite executive
Cleveland Clinic • Talon • Medeor • Radimmune



Branden Moriarity, PhD

Scientific Co-Founder and CSO

B-cell genome engineering pioneer and serial entrepreneur
B-MoGen • Luminary • Catamaran



Kirk Trisler, PhD

Co-Founder and CTO

Cell, gene, and antibody therapy process development and manufacturing expert
GSK • Gritstone • Stanford • Harvard



Tullia C. Bruno, PhD

University of Pittsburgh

Tumor immunologist with expertise in B-cell spatial imaging and transcriptomics



Brad H. Nelson, PhD

University of British Columbia

B-cell bioinformatics, genomics, and anti-cancer immunotherapy expert

Scientific Advisors



Yuliya Pylayeva-Gupta, PhD

University of North Carolina

Regulatory B-cell, B-cells in pancreatic cancer, and tumor microenvironment expert



Justin Taylor, PhD

Fred Hutch Cancer Research Center

B-cell immunologist, B-cell engineering, and neutralizing antibody expert

Unequaled Foundational Intellectual Property

	B-cell Genome Engineering	Multi-specific CAR-T
Granted Patents	US 8,962,315	US 10,233,424
	US 9,175,072	US 10,597,442
	US 9,468,655	US 10,745,468
	US 9,512,213	US 11,180,729*
	US 9,637,540	DE 602012077140.2
	US 9,845,351	FR 2794858
	US 9,901,598	GB 2794858
Patent Applications	US 63/289,858 US 20210095010 HK 40006404A EP 3469069	EP 3768707 CN 109563482 CN 112105641
		US 9,499,855 US 9,587,237 US 9,662,354
		190091263

Contain composition of matter claims

*: Compositions and methods for engineered B-cell receptors, secreted antibodies, and secreted proteins (e.g., cytokines)

Non-viral HMEJ-mediated B-cell genome engineering (option from University of Minnesota)

CAR-T: chimeric antigen receptor T-cell

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Compelling Oncology Business Case

Large Oncology Market Opportunity

300K+ Stage III cancer diagnoses/year US

600K+ metastatic cancer cases/year US

Ex-US opportunities are even larger than the US opportunities

Markets Primed for B-cell Therapeutics

Systemic antibody-based cancer therapies generate > \$60B in annual sales¹

CAR-T, while relatively new and limited to blood cancers, has created > \$50B in combined company market value

Anticipated Premium Pricing

Annual per-patient single-drug costs can average or exceed \$450K for genetic, oncologic, & immunologic diseases^{2,4}

Blood cancer CAR-T priced at \$373-475K³
Hemophilia B gene therapy priced at \$3.5M

Extensive Growth Opportunities

Combined B-cell and CAR-T products

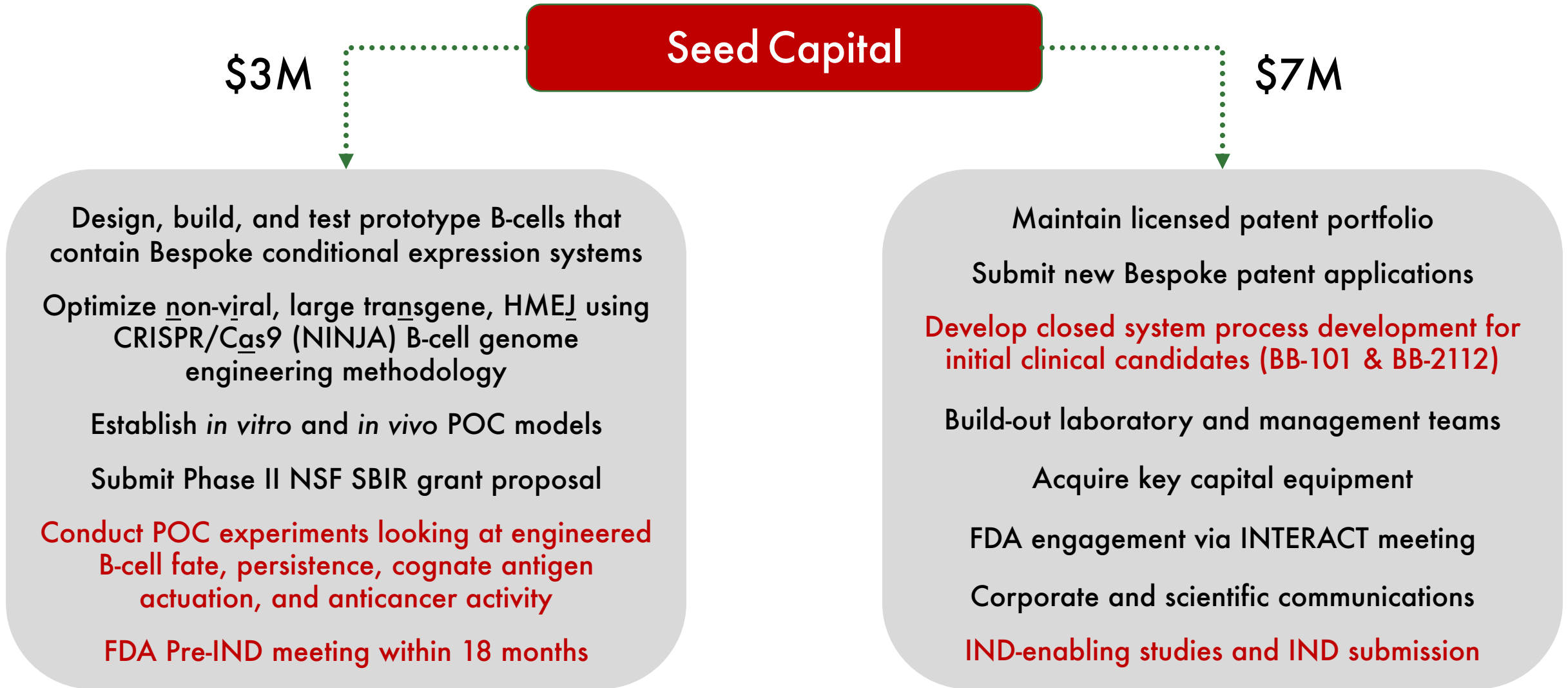
Combined B-cell and checkpoint inhibitors

Bioinformatics-driven personalized products

Non-cancer indications

Sources: ¹Fiercepharma.com/special-report/top-20-drugs-by-global-sales-2019. ²America's Health Insurance Plans. High Priced Drugs: Estimates of Annual Per-Patient Expenditures for 150 Specialty Medications. AHIP Issue Brief. April 2016. ³Hitchcock S. Does the cost outweigh the benefit for CAR T-cell therapy? Targeted Oncology 2019. ⁴Herper M. Alnylam prices first gene silencing drug at \$450,000 per patient but offers money-back guarantee. Forbes 2018.

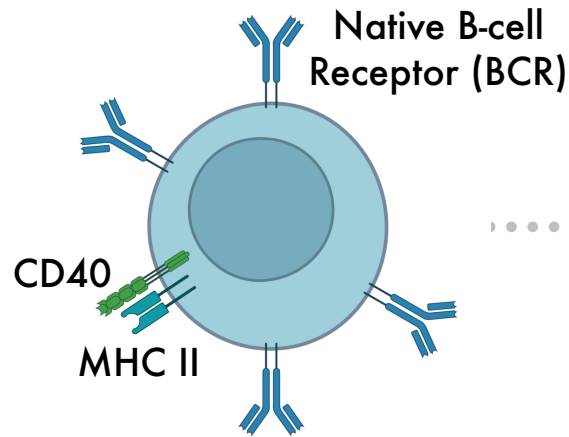
Seeking Exceptional Seed Round Lead and Investors



The Power of B-cells

Re-programming B-cells Unlocks Their Full Potential

NATIVE B-CELL



HETEROGENEOUS IMMUNE FUNCTION

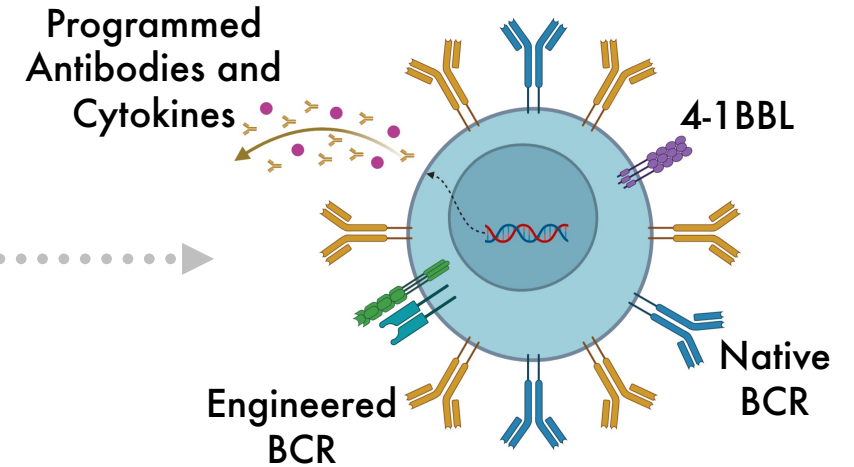
Each B-cell detects a different antigen

Each B-cell produces a different antibody

NINJA GENOME ENGINEERING

CONDITIONAL B-CELL EXPRESSION SYSTEM

ENGINEERED B-CELL



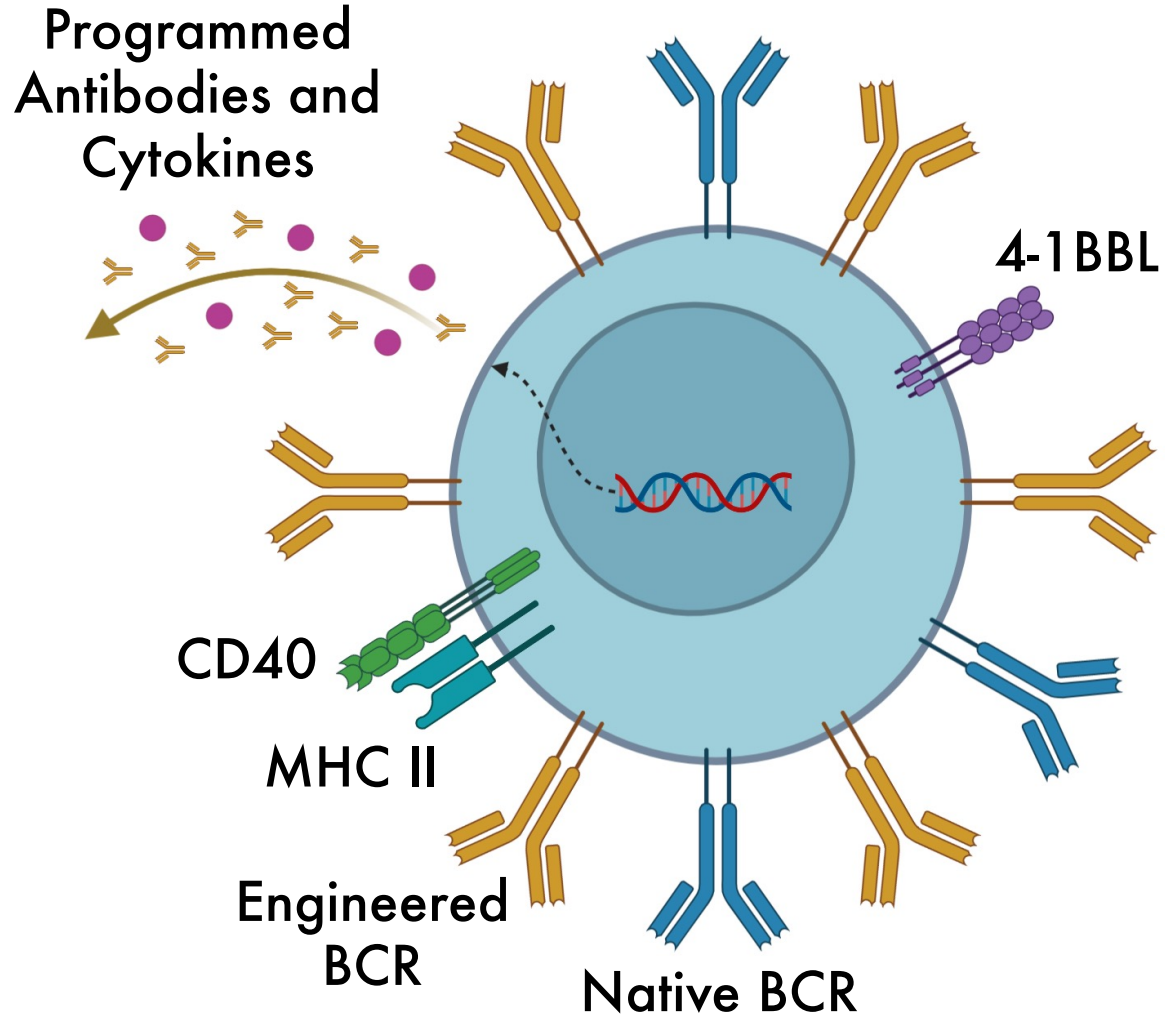
HOMOGENEOUS IMMUNE FUNCTION

Each B-cell detects the same tumor-associated antigen

Each B-cell produces the same antibodies and cytokines only after tumor antigen detection (i.e., actuation)

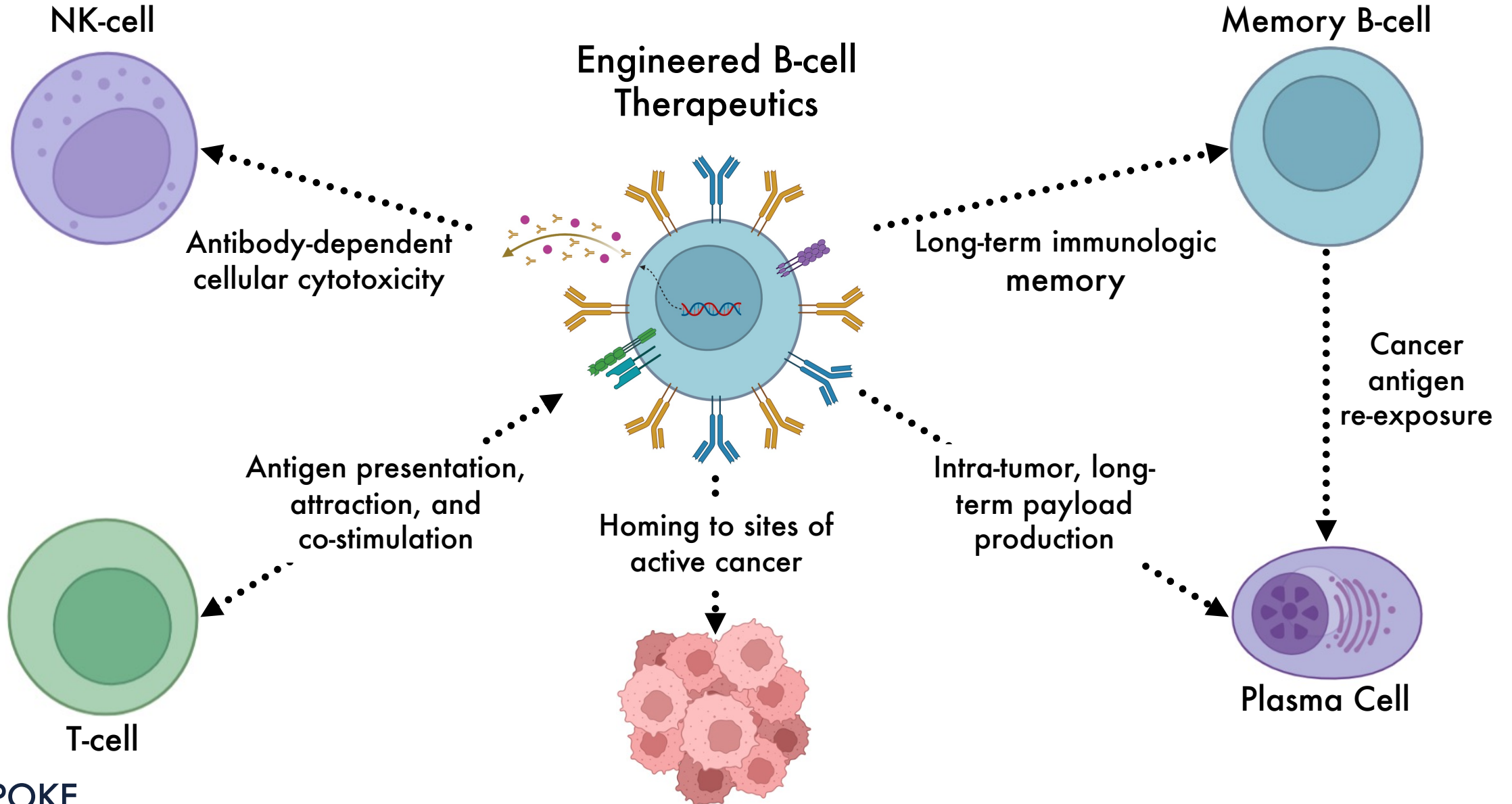
 : genome engineered

The Vast Abilities of Bespoke Engineered B-cells



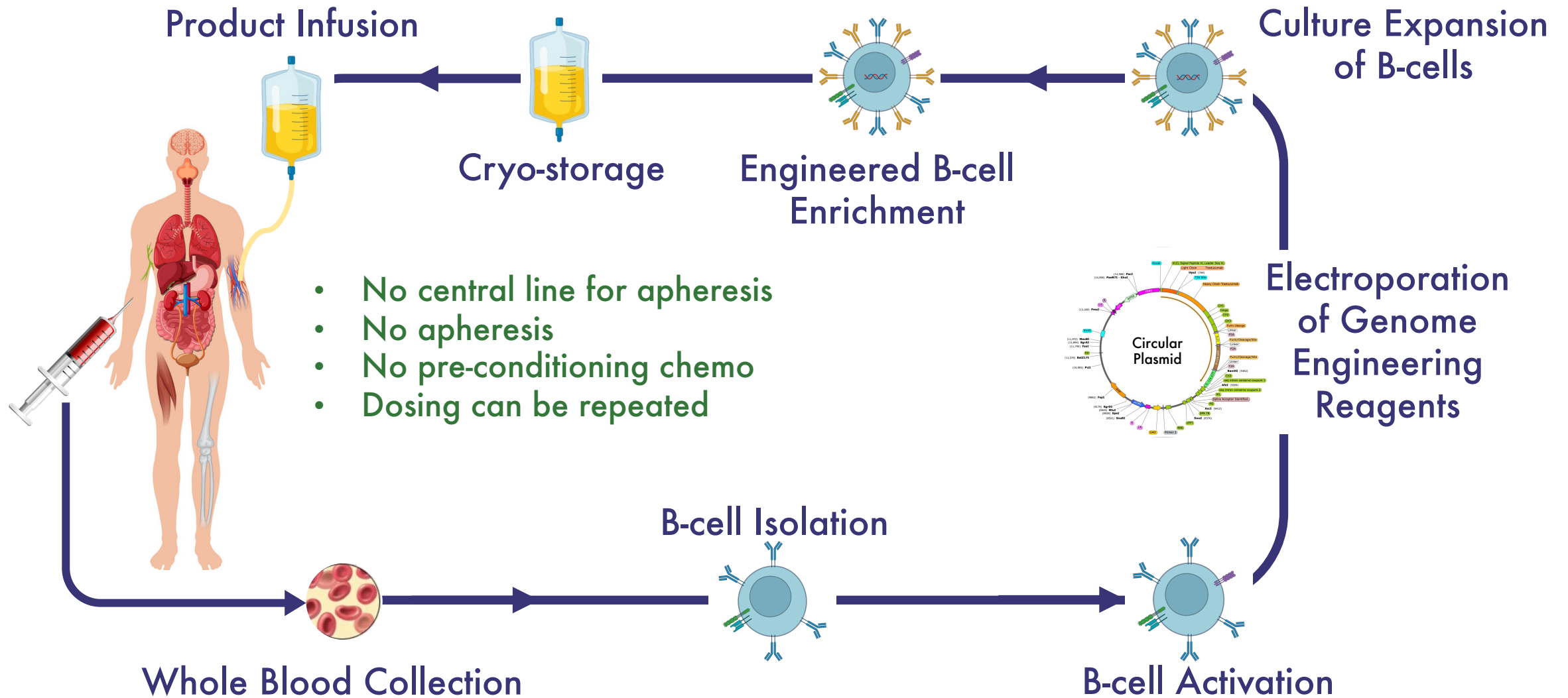
- Homing to tumors and tumor-draining lymph nodes to engage tumor cells and T-cells
- B-cell receptor (BCR) actuable (inducible) expression and secretion of engineered anticancer antibodies and cytokines
- Localized secretion of immunomodulatory anticancer antibodies and cytokines
- Attraction of cytotoxic T-cells and NK-cells
- Promotion of TLS Formation
- Enhancement of CAR-T-cell function
- Sensitize immunologically “cold & lukewarm” tumors to immune checkpoint inhibitors

Bespoke Engineered B-cells Play Pivotal Roles

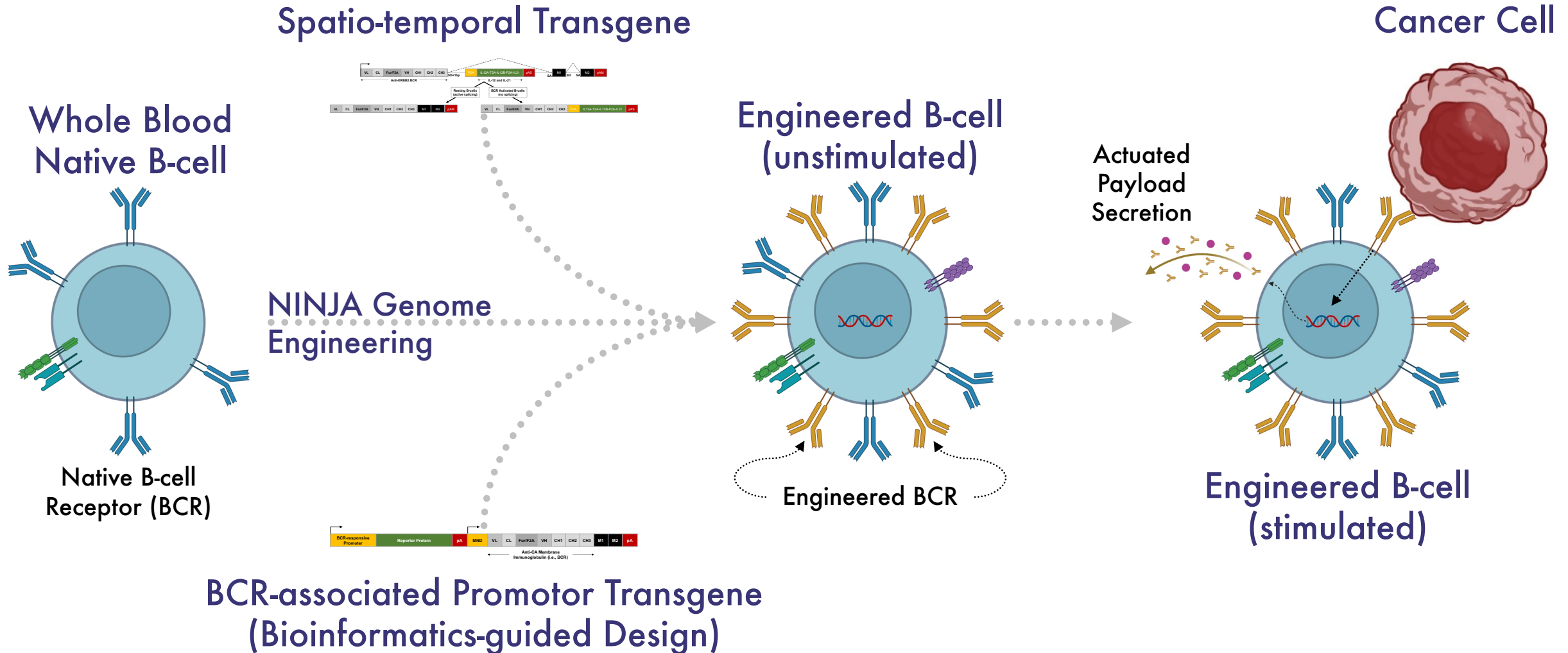


Innovation & Impact

Making B-cells into Precision "Living Drugs"



B-cell Conditional Expression Systems ("On Switches")



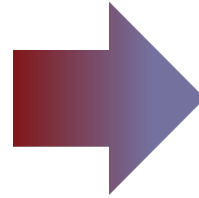
NINJA: non-viral, large transgene, HMEJ using CRISPR/Cas9 HMEJ: homology-mediated end-joining

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Preference for “On Switches” over “Kill Switches”

“Kill Switches” (“Suicide Genes”)

- Cause adoptive cell therapy apoptosis
- Apoptosis requires a second drug
- e.g., GCV $\xrightarrow{\text{HSV-TK}}$ GCV-TP (cytotoxic)
- Utilized in response to overt toxicity
- Delayed activation can be catastrophic



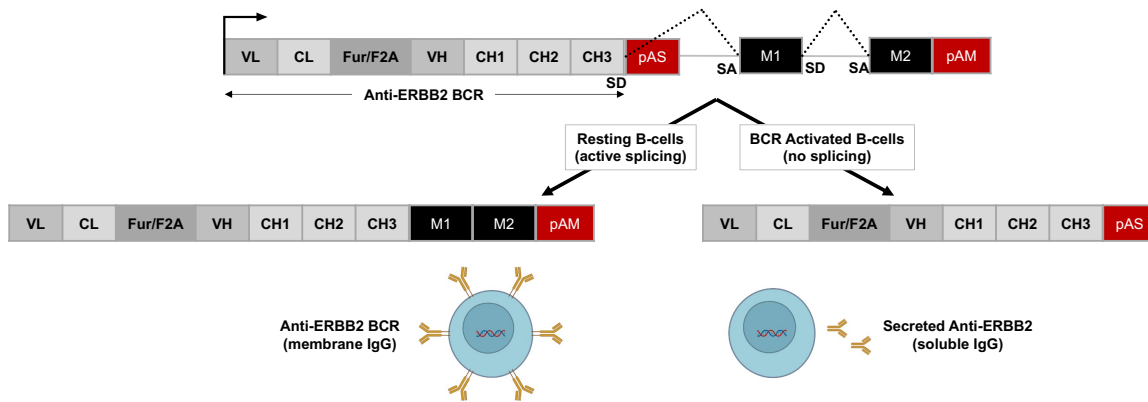
“On Switches” (Programmed B-cell Receptors [BCR])

- BCR activation triggers the “on” signal
- “On” triggers conditional expression
- Only activated B-cells deliver payload
- Tumor-concentrated payload delivery
- **Potential for zero off-tumor toxicity!**

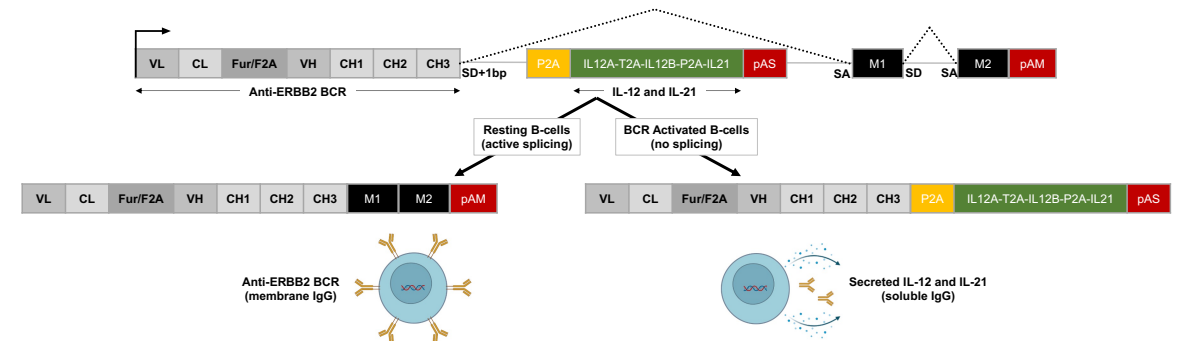
Our B-cell conditional expression system allows engineered BCR to act as “on switches” capable of actuating (i.e., inducing or triggering) anticancer antibody and/or cytokine production and secretion only near sites of detected cancer cells

B-cell Conditional Expression System ("On Switch")

BB-101



BB-2112



Our B-cell expression system emulates the physiologic spatio-temporal regulation of membrane-anchored immunoglobulin (i.e., BCRs on resting B-cells) and engineered secreted products (i.e., antibodies and/or interleukins from BCR activated B-cells)



NINJA Genome Engineering Platform

Non-Viral Engineering

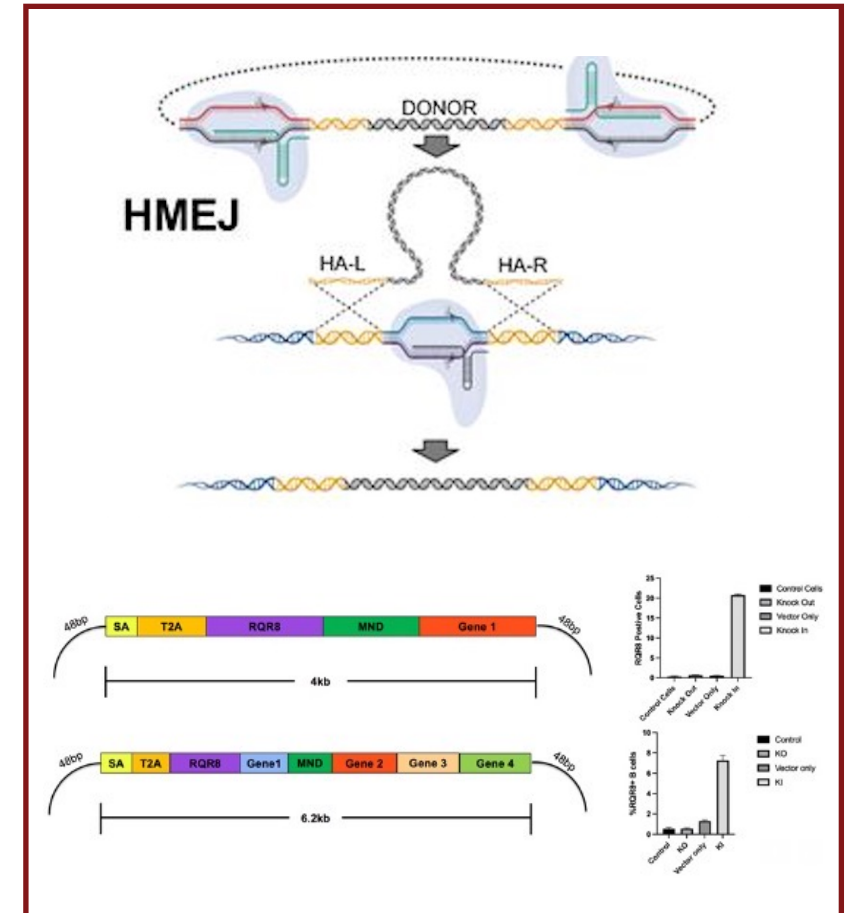
- Circular plasmid DNA allows for large transgenes
- Avoids costs and safety concerns of viral transduction

Large Transgenes (>5kb)

- Bespoke products will require large transgenes
- rAAV and gamma-retrovirus would be impossible to use

Homology-Mediated End Joining (HMEJ)

- HMEJ supports use of short homology arms (48bp vs 0.5-1kb)
- Short homology arms increase transgene size capacity
- HMEJ allows for giant transgene cargo size (>6kb to date)



Non-viral, large transgene, HMEJ using CRISPR/Cas9 and plasmid DNA allows for an engineered BCR, actuable secretion of programmed proteins

Opportunities that Need NINJA Genome Engineering

NINJA
Ability to introduce large cargo (>5kb) transgenes into B-cells

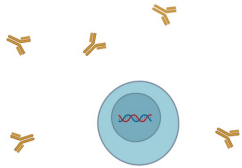
Indications Requiring a Single Large Transgene
(e.g., Factor VIII cDNA for Hemophilia A)

Indications Requiring Multiple Transgenes
(e.g., anti-HER2 antibody, IL-12, and IL-21 cDNAs for metastatic HER2+ cancers)

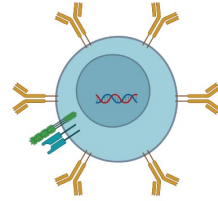
Platforms and Pipeline

Combining Engineered Functions into B-cell Platforms

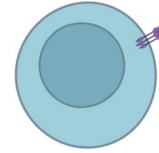
ANTIBODY ENGINEERING



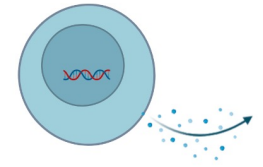
B-CELL RECEPTOR ENGINEERING



CD40L ACTIVATION ENGINEERING



CYTOKINE ENGINEERING



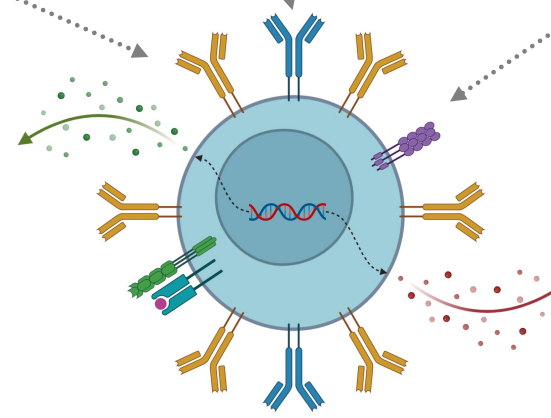
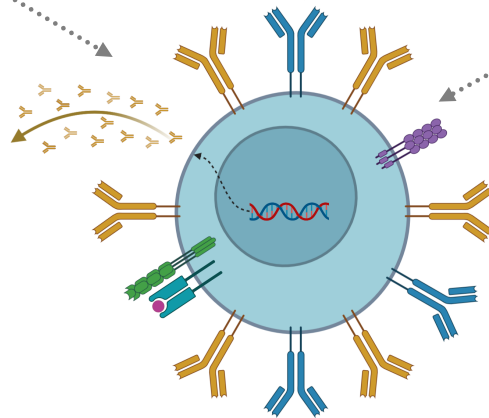
Program B-cells to secrete immunomodulatory and anticancer antibodies

Program B-cells to bind a tumor antigen and trigger payload secretion

Promote tumor homing, T-cell co-stimulation, and hostile TME resistance

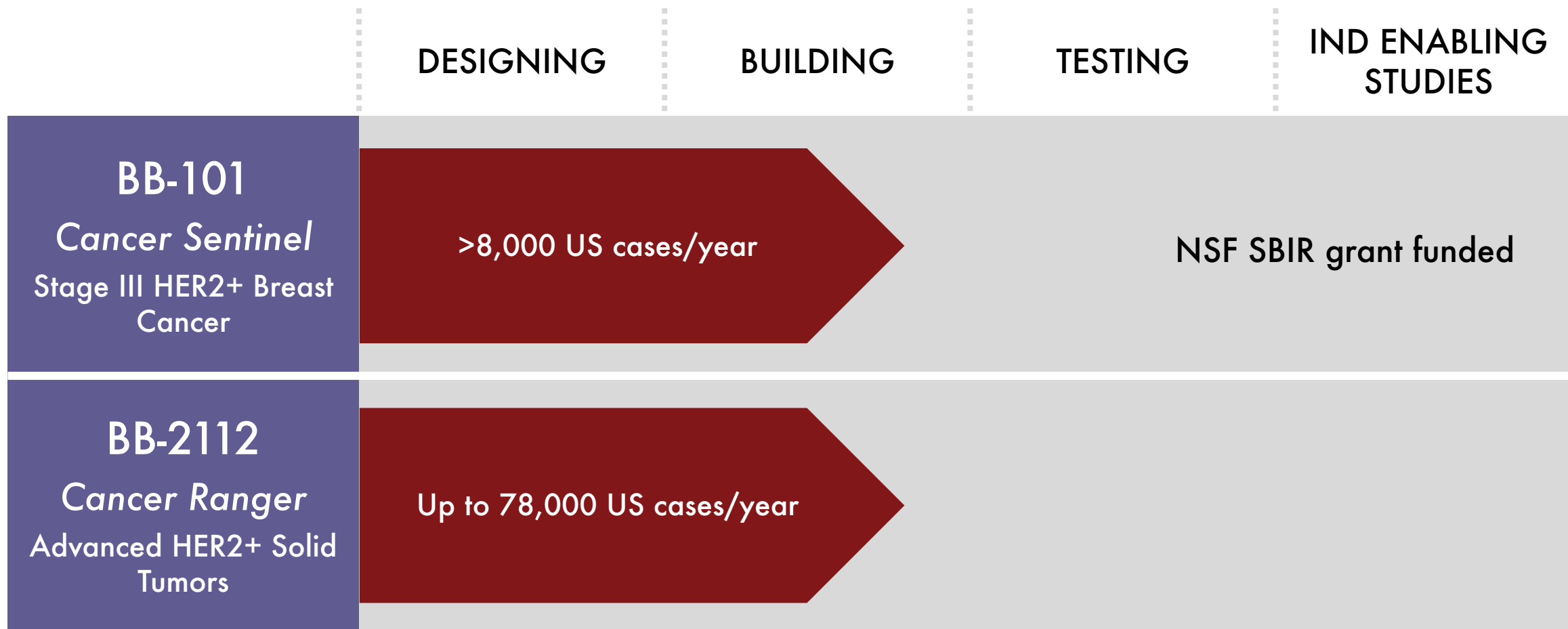
Program B-cells to secrete one or more cytokines that promote T-cell cytotoxicity

“Cancer Sentinels”
Platform for solid tumor recurrence detection and prevention



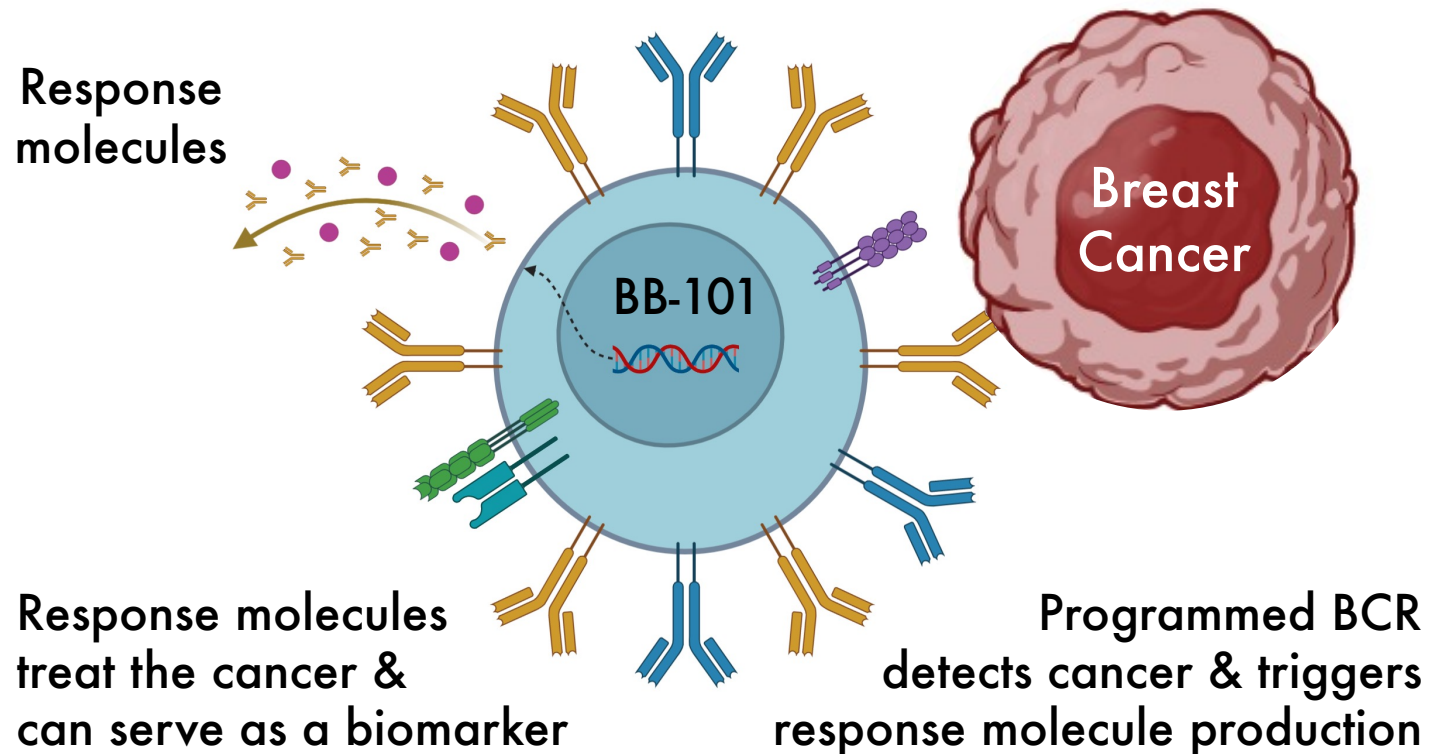
“Cancer Rangers”
Platform for metastatic solid tumor treatment

Platforms Support Expandable Pipelines

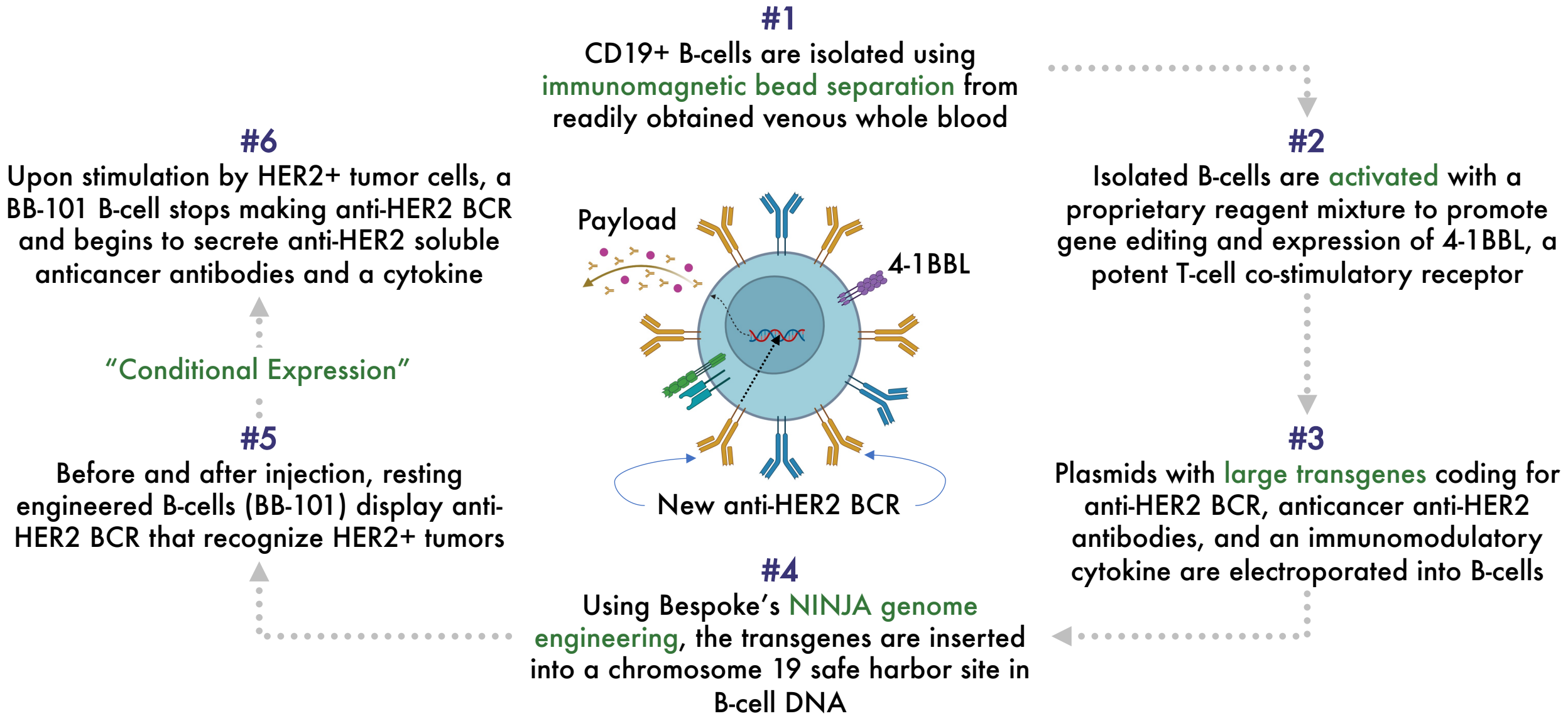


“Seek and Destroy” Replaces “Watch and Wait”

Cancer Sentinels will create a new Stage III solid tumor ($\approx 300,000$ new cases per year in the US) surveillance paradigm by detecting occult residual or relapsed Stage III cancer cells and responding by locally producing and secreting anticancer antibodies and/or cytokines



BB-101 Synthetic Biology

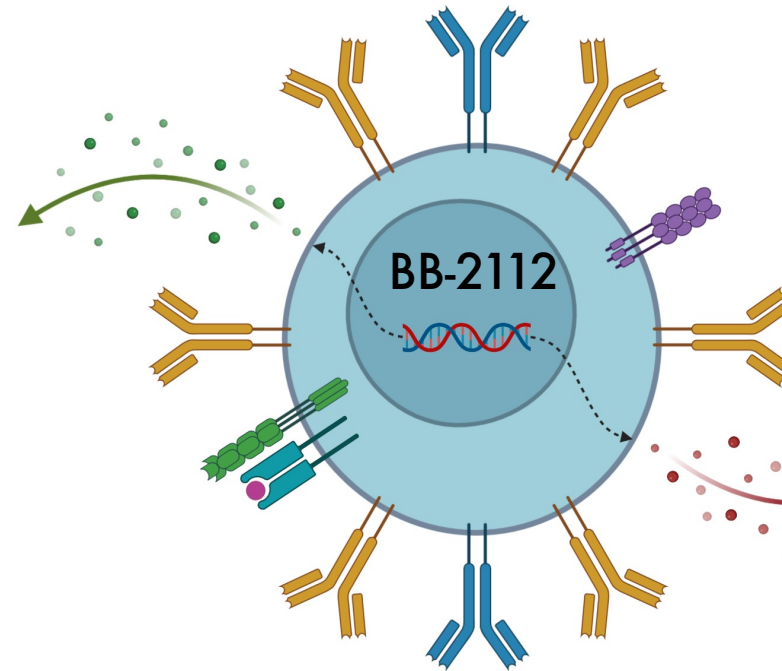


BB-2112: Tactical Weapon Against Metastatic Cancer

IL-21

- ↑ Lymphoid cell proliferation
- ↑ CD8+ T-cell cytotoxicity
- ↑ NK cell cytotoxicity
- ↑ B-cell differentiation
- ↑ Germinal center function

Spolski R and Leonard WJ. *Annu Rev Immunol* 2008; 26:57-79.



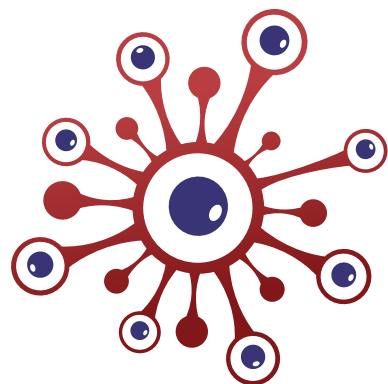
IL-12

- ↓ TAM/MDSC immunosuppression
- ↑ NK and CD8+ T-cell cytotoxicity
- ↑ CD8+ T-cell & ↓ Treg infiltration
- ↑ IFN- γ production by NK & T-cells
- ↑ Tumor cell MHC expression

Nguyen KG et al. *Front Immunol* 2020; 11:575597.

TARGET ONCOLOGY ROLES

- Single-agent treatment of metastatic solid tumors
- Combination with immune checkpoint inhibitors (turning “cold and lukewarm” tumors “hot”)
- Combination with CAR-T in order to limit exhaustion and enhance T-cell tumor penetration



BESPOKE

BIOTHERAPEUTICS

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