Joan Adamo, PhD
Hani Awad, PhD
Ben Miller, PhD
George Truskey, PhD

Breaking into ISTAND: Training a disease-agnostic tissue chip platform to speak FDA

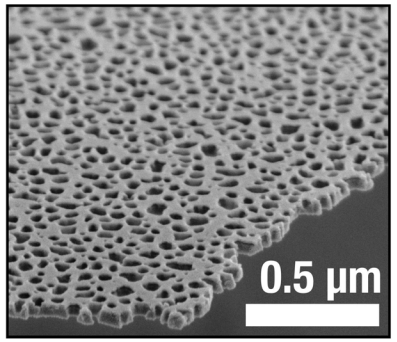
James L. McGrath, PhD

Translational Center for Barrier Microphysiological System

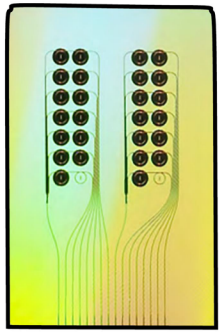
U2CAG088071

TRACE-BMPS: ONE PLATFORM, MANY MODELS

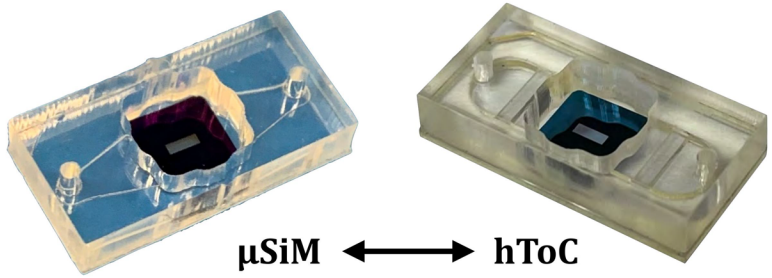
The Platform



Ultrathin nanomembranes



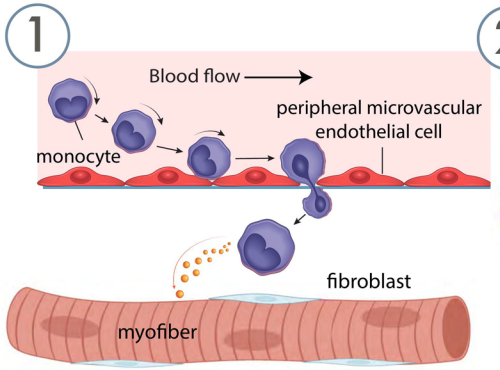
Photonic Sensors



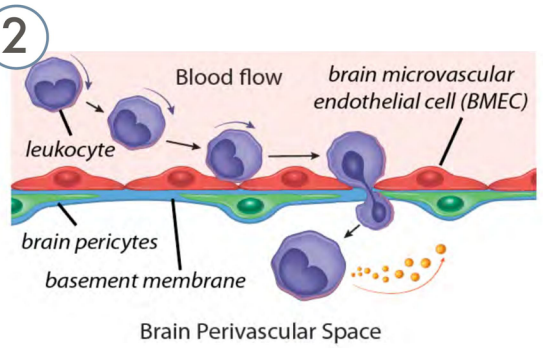
µSiM ⟷ hToC

Modular components for rapid customization

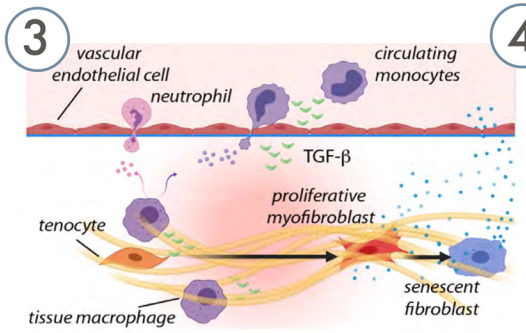
Core Models



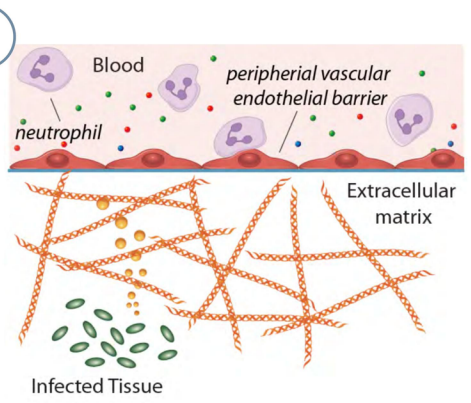
Muscle-Immune Interface



Neuroinflammatory injury



Synovial barrier remodeling



Immune Cell Trafficking

5 Blood-retinal barrier

The Engine

- **Resource sharing**
- **Chips used by 21 labs**
- **35 projects**
- **5,000+ chips per year**
- **Quality system development**
- **50+ SOPs**
- **Reproducibility 'dashboard'**

The Network

Duke University · RIT · BARDA · ALINE · AIM Photonics · SiMPore · SiObex · phlotonics · abbvie · B+L Bausch + Lomb · Pfizer · Ap·Glyx · Critical Path Institute 20 Years

Interpreting ISTAND

FDA's LOI rejections are brief and cryptic. Interpreting these for lessons and pivots is challenging.

LOI #1 2024 — µSiM-CA

Osteomyelitis (bone infection)

COU: Identify drugs that effectively block S. aureus invasion of the osteocyte canalicular network

FDA SAID

"Does not fall under the FDA framework. A tool for optimization at a company.

TRANSLATION

Your tool may be useful, but not to us. A chip focused on establishing efficacy for a unknown drug class does not address a regulatory need.

OUR RESPONSE

Abandoned this LOI. Commit to finding regulatory anchors.

NOT REVIEWABLE

LOI #2 2025 — µSiM-hMoC

Juvenile dermatomyositis (rare disease)

COU: Assess starting dose (MRSD) of IFNß-based therapeutics for JDM in Phase 1/2 trials

FDA SAID

"Primary drugs in this space are immunomodulatory"

TRANSLATION

Efficacy for rare disease appears to acceptable. But the tool targets the wrong drug class.

OUR RESPONSE

Focus on efficacy of immune modulators (corticosteroids, immune suppressors). Resubmission in progress.

NOT REVIEWABLE

LOI #3 2026 — µSiM-CRS-ICANS

CRS/ICANS from immunotherapy

COU: Nonclinical safety evaluation of CD3-engaging bsAbs for FIH dose selection

FDA SAID

Submitted Feb 20, 2026. Awaiting FDA response.

TRANSLATION

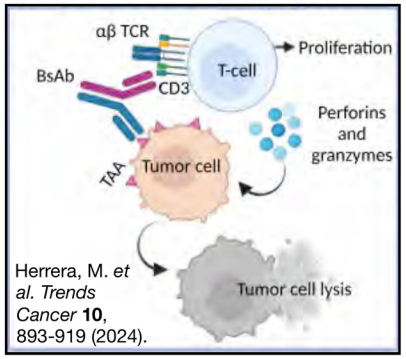
WHAT CHANGED

Built from FDA Immunotoxicity Guidance. Safety-focused COU. Scoped to the dominant emerging drug class for hematologic cancers (bsAbs).

UNDER REVIEW

T-CELL ENGAGING (TCE) IMMUNOTHERAPIES FOR HEMATOLOGIC CANCERS TRIGGER CYTOKINE STORMS AND NEUROTOXICITY

Bispecific antibody (BsAbs) as T Cell Engagers (TCE)



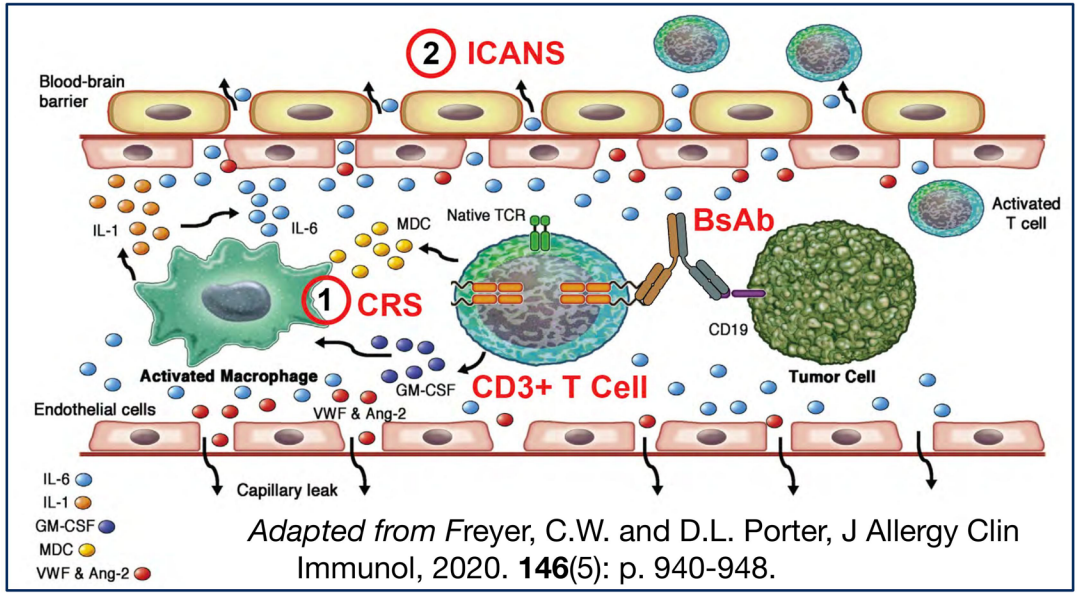
Herrera, M. *et al. Trends Cancer* **10**, 893-919 (2024).

BLINCYTO (blinatumomab) for injection
35 mcg single-dose vial

epkinly epcoritamab-bysp
SUBCUTANEOUS INJECTION 4mg 48mg

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO and treat with corticosteroids as recommended. (2.4, 5.1)**
- **Neurological toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS), which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.4, 5.2)**



Adapted from Freyer, C.W. and D.L. Porter, J Allergy Clin Immunol, 2020. **146**(5): p. 940-948.

Significant Drug Development Effort

- > 100 are TCEs for blood cancers
- All 7 FDA approved BsAbs are TCEs for B-cell cancers (lymphomas and myelomas)

CRS = Cytokine Release Syndrome

- Any-grade CRS occurs in ~60% of patients
- Can progress to multi-organ failure and death

ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome

- Downstream of CRS in ~20% of cases
- Can be lethal or lead to long term cognitive or neurological deficits.

REGULATORY ANCHORS

FDA U.S. FOOD & DRUG ADMINISTRATION

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FDA NEWS RELEASE

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

More Press Announcements **For Immediate Release:** April 10, 2025

Content current as

disease susceptibility and progression.[5] Moreover, some safety risks may go undetected in animals – a notable example is the mAb TGN1412, which caused a life-threatening cytokine release syndrome in human volunteers despite appearing safe in preclinical monkey studies. That tragedy highlighted the limitations of animal models for certain immune-activating mAbs and spurred efforts to develop *in vitro* assays to better predict human-specific responses (7).

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

SUMMARY

Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and [illegible] tension. Within 12 to 16 hours after infusion, they became critically ill, with pul[illegible] infiltrates and lung injury, renal failure, and disseminated intravascular coag[illegible] Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti–interleukin-2 receptor antagonist antibody. Prolonged cardiovascular shock and acute respiratory distress syndrome developed in two patients, who required intensive organ support for 8 and 16 days. Despite evidence of the multiple cytokine-release syndrome, all six [illegible] over the 30 days [illegible] sponse syndrome [illegible] lying disease.

CRS

Table 3. Common Features after Infusion of TGN1412.

Neurologic	Delirium Partial amnesia Paresthesia or localized numbness Difficulty concentrating (late) Headaches (early and late)
Autonomic, gastrointestinal, or both	Bowel urgency or diarrhea Nausea or vomiting
Musculoskeletal	Myalgia in lower back (early) and calves (late)

ICANS

FDA guidance on CRS / ICANS concerns for T Cell ‘redirectors’

- Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals: Guidance for Industry. June 2023.
- FDA. Bispecific Antibody Development Programs: Guidance for Industry. May 2021.
- FDA. Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products: Guidance for Industry. January 2024.

Drug Development Need

Current preclinical tools cannot predict or model the two most dangerous complications of CD3-engaging immunotherapies.

CRS MODEL GAP

Cytokine Release Syndrome

Current preclinical tools miss key elements of human CRS

WHAT'S MISSING

- **Innate immune cells** — neutrophils, monocytes, platelets are key CRS amplifiers, absent from PBMC assays
- **Plasma components** — fibrinogen and complement are drivers of downstream toxicity in severe CRS
- **Vascular barrier** — capillary leak and endothelial activation are CRS hallmarks, invisible without a vessel wall
- **Blood-brain barrier** — cytokine transport to the CNS cannot be assessed
- **NHP models** — CRS in macaques is poorly predictive of human response

Models capture T cell activation but miss key elements of the CRS profile

INCOMPLETE MODELS

ICANS GAP

Immune Effector Cell-Associated Neurotoxicity

No preclinical model exists — in vivo or in vitro

THE PROBLEM

- **20–60% neurotoxicity** in patients receiving CD3-engaging therapies, entirely unpredicted by preclinical testing
- **Can be lethal** or cause long-term cognitive and neurological deficits
- **Mild CRS → severe ICANS** — CRS grade does not predict neurotoxicity severity
- **Macaques develop CRS but not ICANS** — the standard in vivo safety model cannot detect neurotoxicity

No tool exists to predict ICANS risk before first-in-human dosing

NO MODEL EXISTS

› **A whole-blood, vascularized MPS with a blood-brain barrier addresses both gaps in a single platform**

CONTEXT OF USE

The µSiM-CRS-ICANS drug development tool will be used to evaluate the safety of T-cell engaging monoclonal antibodies used as immunotherapies. The tool will provide donor-specific risk assessments for both cytokine release (CRS) and downstream ICANS, and will inform dose justification for Investigational New Drug (IND) applications prior to first-in-human trials.

Lessons Applied

What we learned from two FDA rejections and how we built the CRS-ICANS LOI differently.

Pick a drug class the FDA is already watching

600+ bispecific antibodies in clinical trials globally. **7 approved in 3 years**, all carrying CRS/ICANS boxed warnings. FDA doesn't need convincing this is a problem.

LOI #1 targeted an unknown drug class
LOI #2 targeted a low priority drug class

Align with active regulatory priorities

Three independent anchors: **FDA phasing out animal testing** for mAbs (Apr 2025), **Immunotoxicity Guidance** calling for in vitro cytokine release testing, and **Bispecific Ab Guidance** establishing the safety evaluation framework.

COU sits at the intersection of all three

Frame a safety question, not efficacy

COU: Nonclinical safety evaluation of CD3-engaging bsAbs for first-in-human dose selection. **ISTAND qualifies drug development tools**. Safety-focused COUs align with the program's core purpose.

LOI #1 proposed an efficacy tool, outside the framework

Fill a gap no existing tool can fill

PBMCs miss CRS amplifiers (neutrophils, complement, endothelium). **Macaques don't develop ICANS**. No preclinical model for neurotoxicity prediction exists. The platform doesn't compete; it fills a void.

Whole blood + vascular barrier + BBB = both gaps addressed

› Result: an LOI built on regulatory logic, not just scientific capability

Drug Development Use

Replacing sequential preclinical steps with integrated, human-relevant safety evaluation

Current paradigm limitations

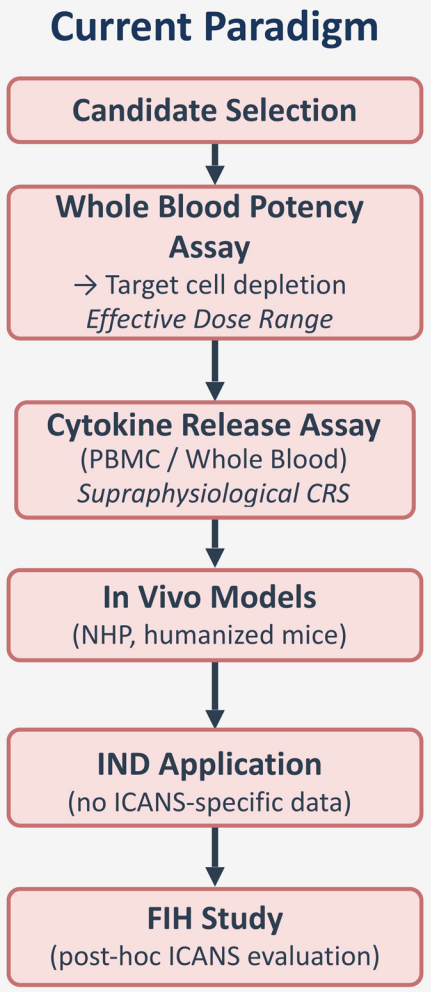
- PBMC assays produce **supraphysiologic CRS**, missing neutrophils, endothelium, platelets, and plasma factors
- NHP models have limited **predictivity** for human CRS (TGN1412 disaster)
- **No preclinical model predicts ICANS;** neurotoxicity evaluated only post hoc in FIH studies

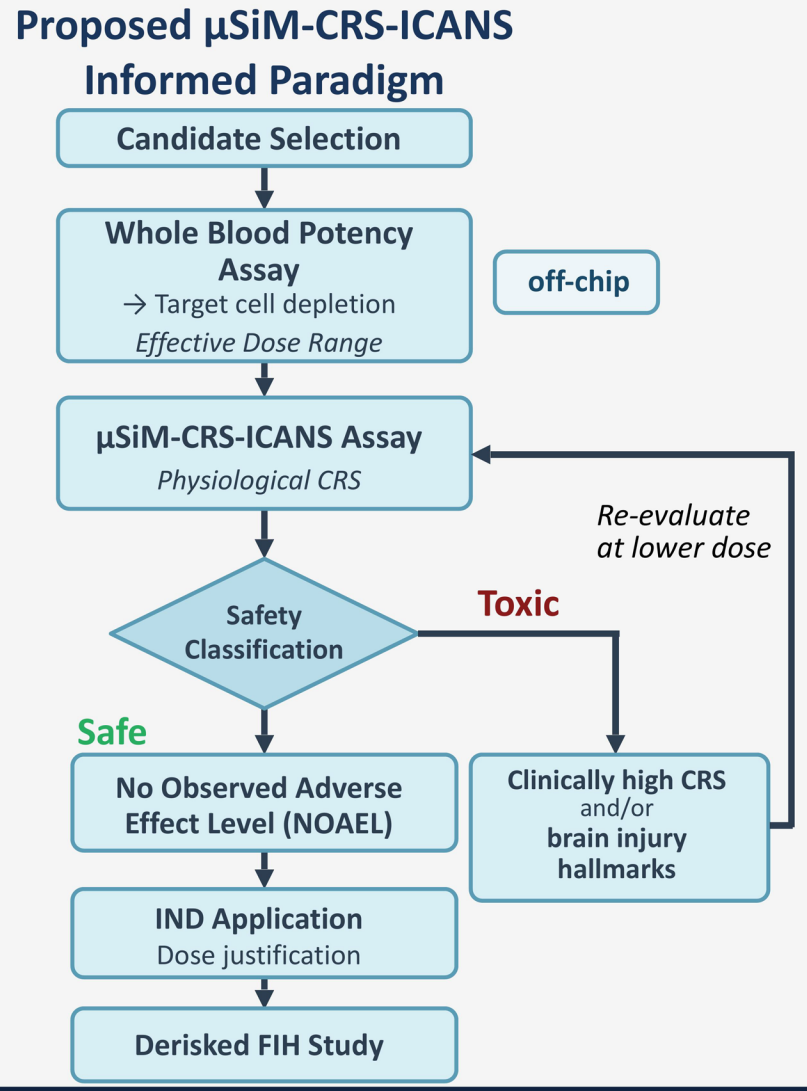
µSiM-CRS-ICANS: two integrated readouts

- **Physiological cytokine profile** from whole blood with endothelial contributions to IL-6 and IL-1β
- **Brain injury hallmarks:** BBB permeability, fibrinogen transit, immune cell recruitment as ICANS risk surrogates

Decision logic

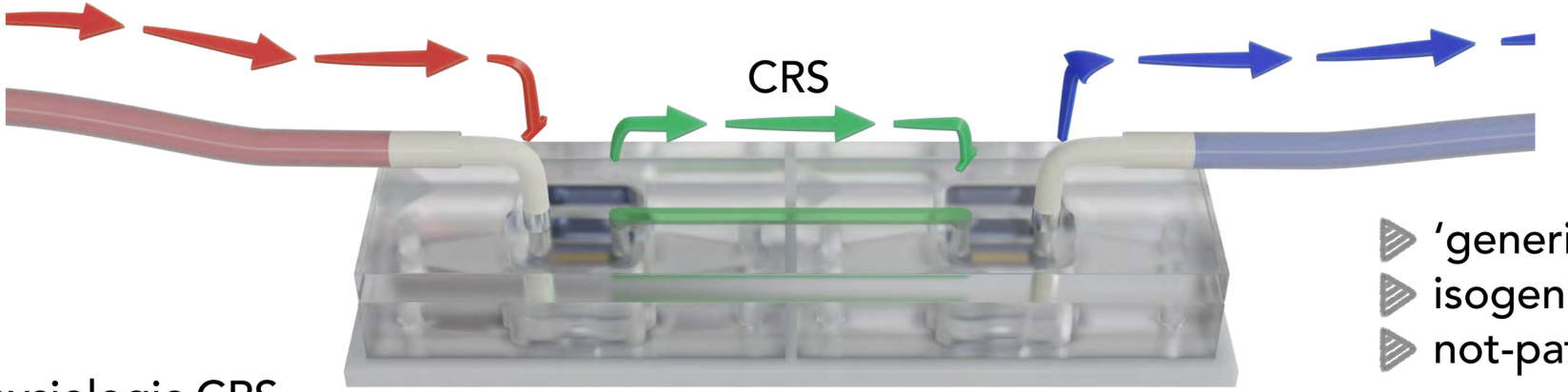
- Doses classified as **Safe** (NOAEL for dose justification) or **Toxic** (re-evaluate at lower dose), relative to reference compounds with known clinical profiles





› **Regulatory outcome: IND submission with integrated CRS + ICANS safety data for de-risked FIH dosing**

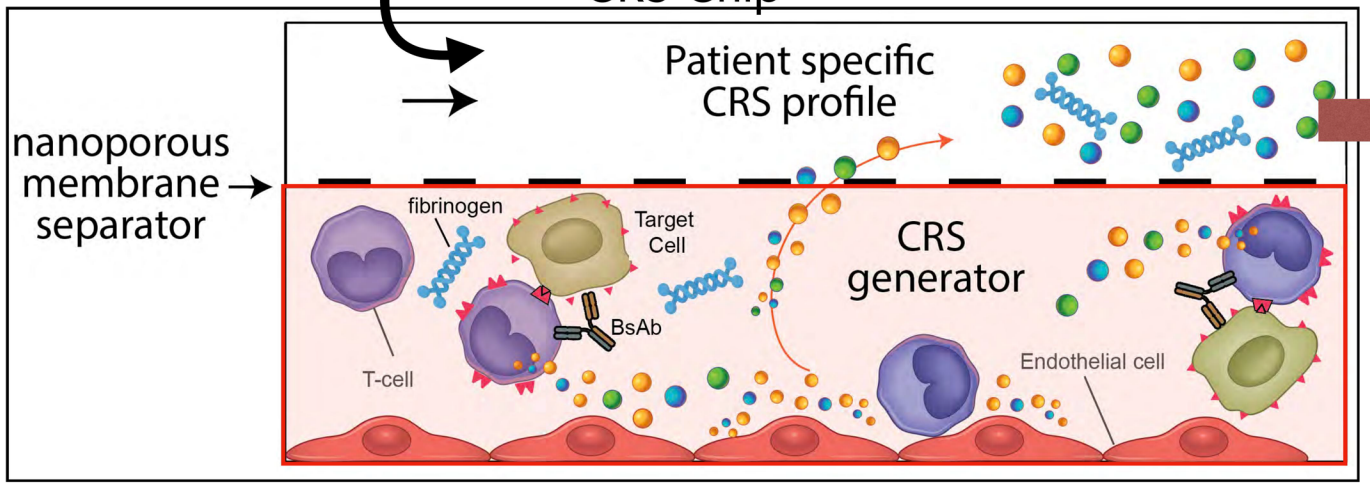
TECHNICAL DESCRIPTION



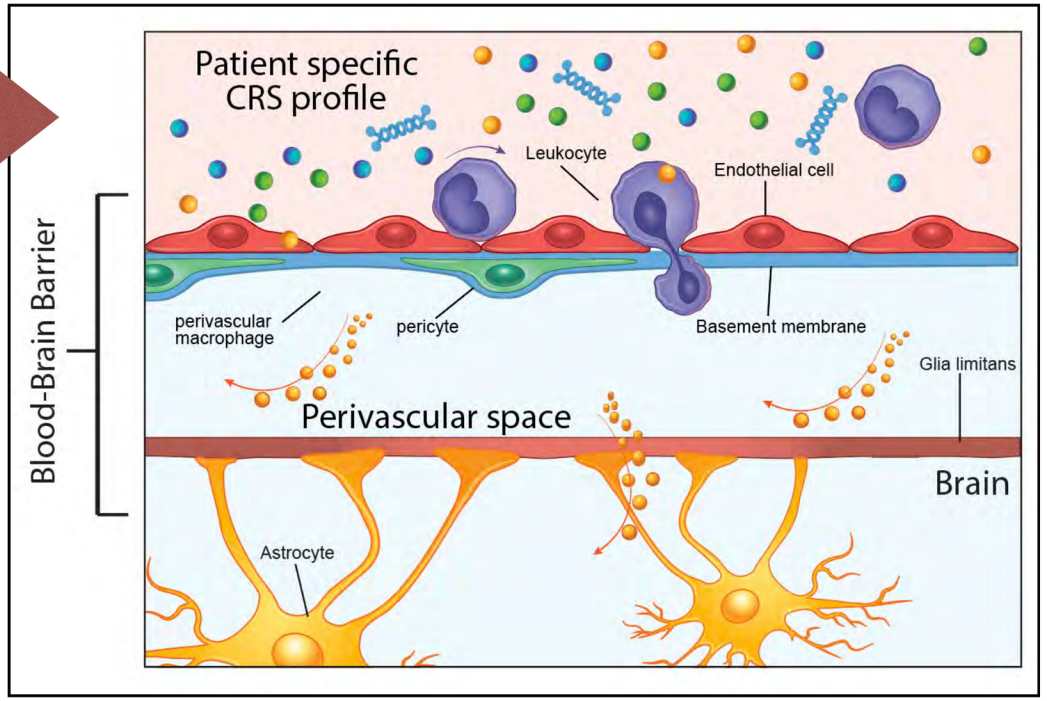
- 'generic' BBB
- isogenic cells from iPSCs
- not-patient specific

dilution to physiologic CRS

CRS Chip



ICANS Chip

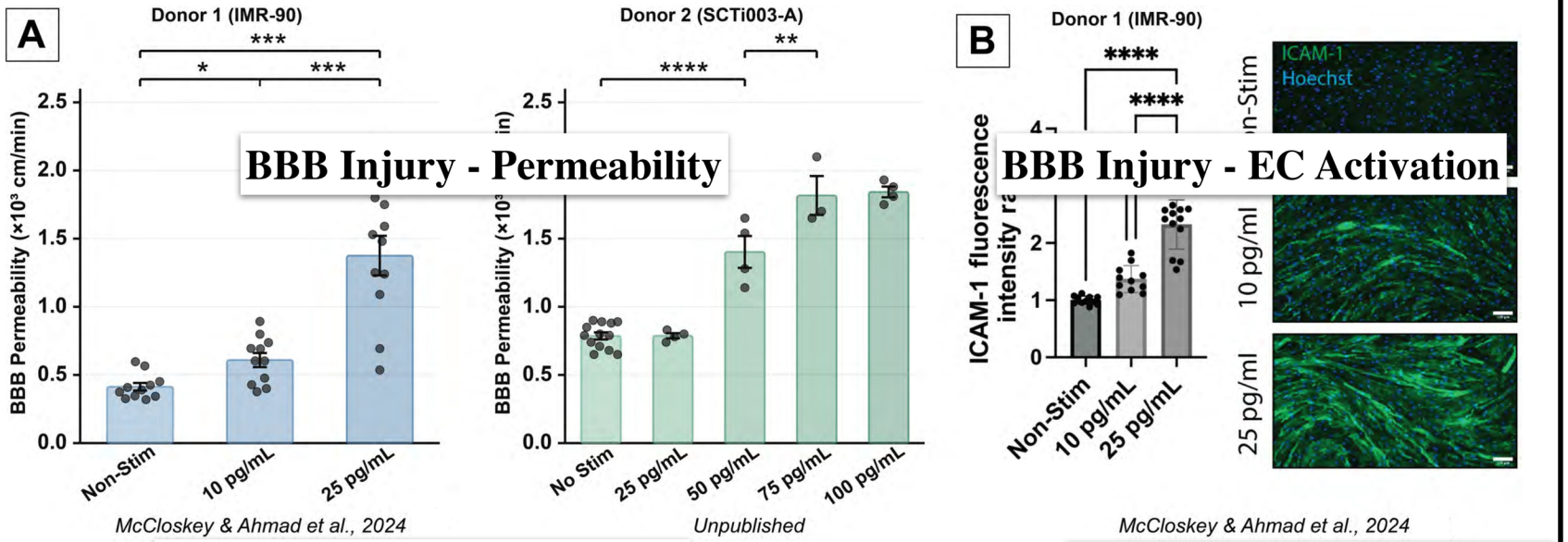


Metrics

1. *Patient specific CRS plasma* (select cytokines)*
2. *Brain injury (BBB permeability**, Fibrinogen leakage*, immune cell trafficking)*

Methods: *integrated sensors; ** imaging

SUPPORTING DATA



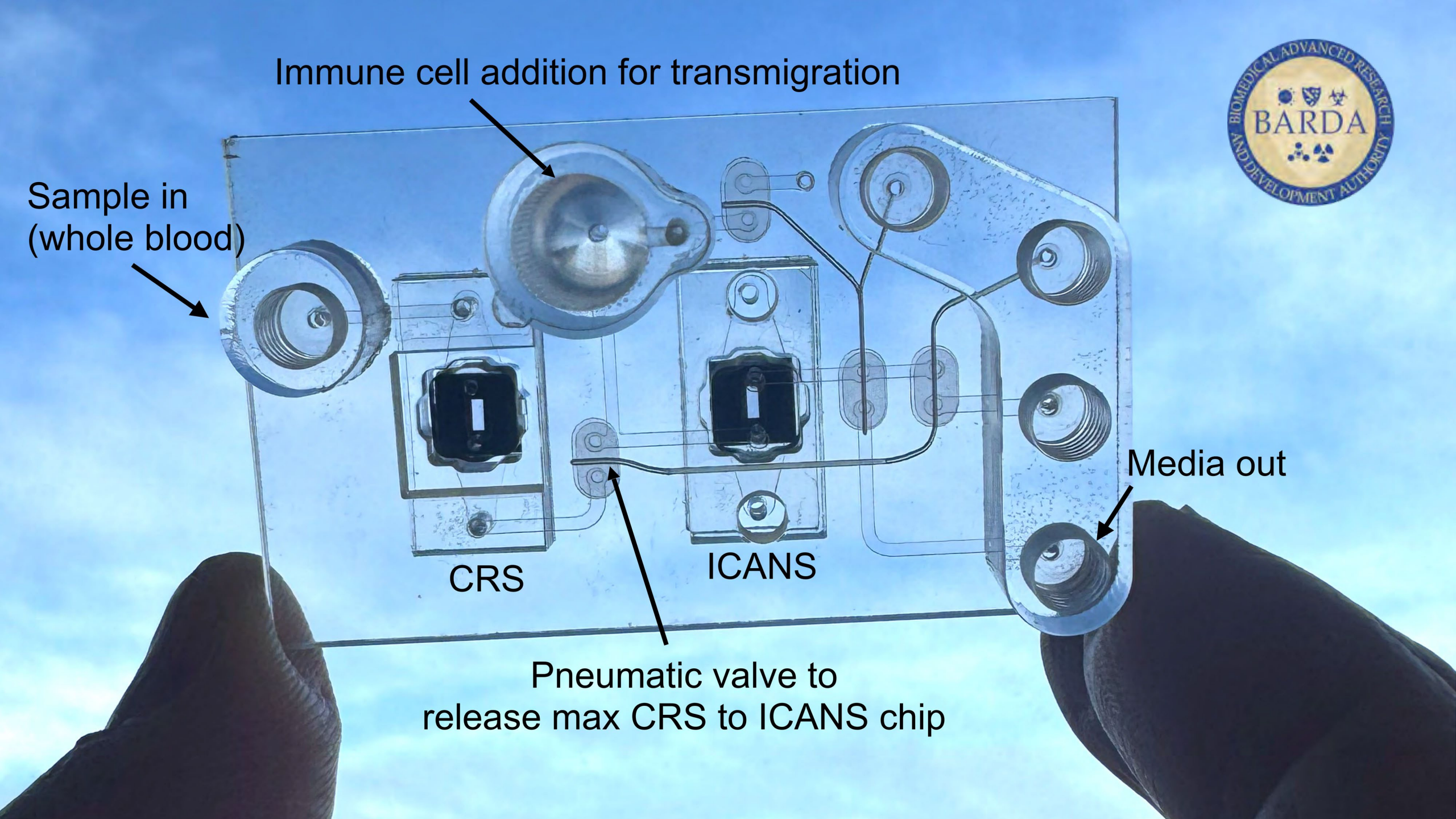
Supporting Literature

- **15 publications from McGrath and Miller labs**

  Barrier models, μSiM platform, integrated biosensing, and BBB injury readouts (eg. McCloskey et al. 2024, McCloskey & Ahmad et al. 2024, Cognetti et al. 2023, Chen et al. 2025)

- **Well-established in vitro CRS literature**

  Adapting well-established whole blood cytokine release assays (Leclercq-Cohen et al. 2023, Leclercq et al. 2022, Liebers et al. 2018, Jorda et al. 2024) to the CRS chip format.


Immune cell addition for transmigration
Sample in
(whole blood)
Media out
CRS
ICANS
Pneumatic valve to
release max CRS to ICANS chip
BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY
BARDA

SELECTING REFERENCES AND CONTROLS

Reference Compounds

Drug / Class	Target(s)	Indication(s)	CRS (incidence/notes + primary source)	ICANS / neurotoxicity (incidence/notes +	Status	CRS Risk	ICANS Risk	Procured as reference for	RUO Vendor (Catalog #)
Blinatumomab (BiTE)	CD3 × CD19	R/R B-ALL (adult/peds), others	CRS reported in phase 3 adult R/R B-ALL trial; safety profile consistent with T-cell–redirecting toxicities. (New England Journal	Neurologic toxicity (incl. ICANS) highlighted in prescribing info/label; serious or life-threatening	FDA-approved (Amgen)	High	High	High	ThermoFisher (Catalog # MA5-41729)
Teclistamab (IgG-like, Fc-silenced)	CD3 × BCMA	R/R multiple myeloma	MajesTEC-1 (NEJM): CRS in ~72% (mostly grade 1–2); durable responses.)	ICANS generally infrequent/low-grade; detailed management and low severe ICANS burden	FDA-approved (Janssen)	Moderate–High	Low–Moderate		
Epcoritamab (IgG-like, SC)	CD3 × CD20	R/R B-cell NHL (incl. LBCL)	EPCORE NHL-1 (JCO): manageable safety; CRS common and largely low-grade with SC step-up. (ASC Publications)	ICANS events observed at low frequency in EPCORE cohorts; overall manageable in dose-	FDA-approved (Genmab/ AbbVie)	Moderate	Low		
Glofitamab (2:1 CD20:CD3 format)	CD3 × CD20	R/R LBCL	NEJM pivotal: any-grade CRS frequent; obinutuzumab pre-treatment used to mitigate. (New England Journal of Medicine)	Neurotoxicity/ICANS reported but less frequent than CRS; captured in phase 1/2 studies of	FDA-approved (Genentech)	High	Moderate		
Mosunetuzumab (IgG-like)	CD3 × CD20	R/R follicular lymphoma; R/R DLBCL (studies)	Monotherapy studies show **lower rates of severe CRS**; suitable for outpatient administration in many settings. (PubMed)	ICANS uncommon/ typically low-grade in monotherapy series and reviews of FL/DLBCL	FDA-approved (Genentech)	Moderate	Low	Low	IchorBio (ICH5026); BiCell Scientific (BCBI13)
Talquetamab (IgG-like, Fc-silenced)	CD3 × GPRC5D	R/R multiple myeloma	MonumenTAL-1 (NEJM phase 1): CRS ≈70–75% (mostly grade 1–2) with step-up dosing.	ICANS ~10–11% in phase 2 updates; mostly low grade.	FDA-approved (Janssen)	Moderate–High	Low–Moderate	Moderate	IchorBio (ICH5207)
Elranatamab (IgG-like, SC)	CD3 × BCMA	R/R multiple myeloma	MagnetisMM-3/-1: CRS frequent but largely low-grade with two-step priming.	ICANS infrequent; few discontinuations for CRS/ ICANS in MagnetisMM trials.	FDA-approved (Pfizer)	Moderate–High	Low–Moderate		

+ Controls

Drug / Antibody	Target(s)	Indication / Context	ICANS/CRS Association	Status
OKT3 (Muromonab-CD3)	CD3	Historical T cell activator (transplant rejection)	Severe CRS and ICANS-like encephalopathy; multiple neurotoxicity case reports	Withdrawn
TGN1412 (Anti-CD28 mAb)	CD28	First-in-human trial (2006)	Life-threatening CRS with neurotoxicity in all 6 volunteers	Development halted

Neg Controls

Isotype-matched non-binding antibody

Path Forward

µSiM-CRS-ICANS Platform for ISTAND Qualification

No validated preclinical tool currently exists for integrated assessment of CRS and ICANS risk prior to first-in-human trials with CD3-engaging bispecific antibodies. The µSiM-CRS-ICANS platform is positioned to fill this gap, with regulatory anchors in FDA guidance, supporting data across all three integrated readouts, and an active qualification pathway through ISTAND.

Current Status

- ✓ **ISTAND Letter of Intent submitted**: February 2026 (DDT-IST-000065)
- ✓ **Development:** Reference compound panel procured. Validation studies initiated.
- ✓ **C-Path regulatory facilitation**: Critical Path Institute (Graham Marsh)
- ✓ **Industrial partnership**: Pfizer (TCE development team providing quarterly guidance)