



# Next-Generation Therapeutic Modalities

Biophysical Oncology & Advanced  
Immune Tolerance Modulation

A Technical Briefing on Targeted Osmotic Lysis (TOL) and Antigen-Specific Tolerance Platforms

# Two Pillars of Therapeutic Innovation



## Biophysical Oncology

The Physical Kill-Switch

- **Focus:** Utilizing **ionic gradients** to selectively destroy refractory solid tumors.
- **Key Asset:** **Targeted Osmotic Lysis** (TOL) by Oleander Technologies.
- **Core Mechanism:** Simultaneous stimulation of **Voltage-Gated Sodium Channels** (VGSCs) and blockade of sodium pumps (Na<sup>+</sup>, K<sup>+</sup>-ATPase).



## Advanced Immune Tolerance

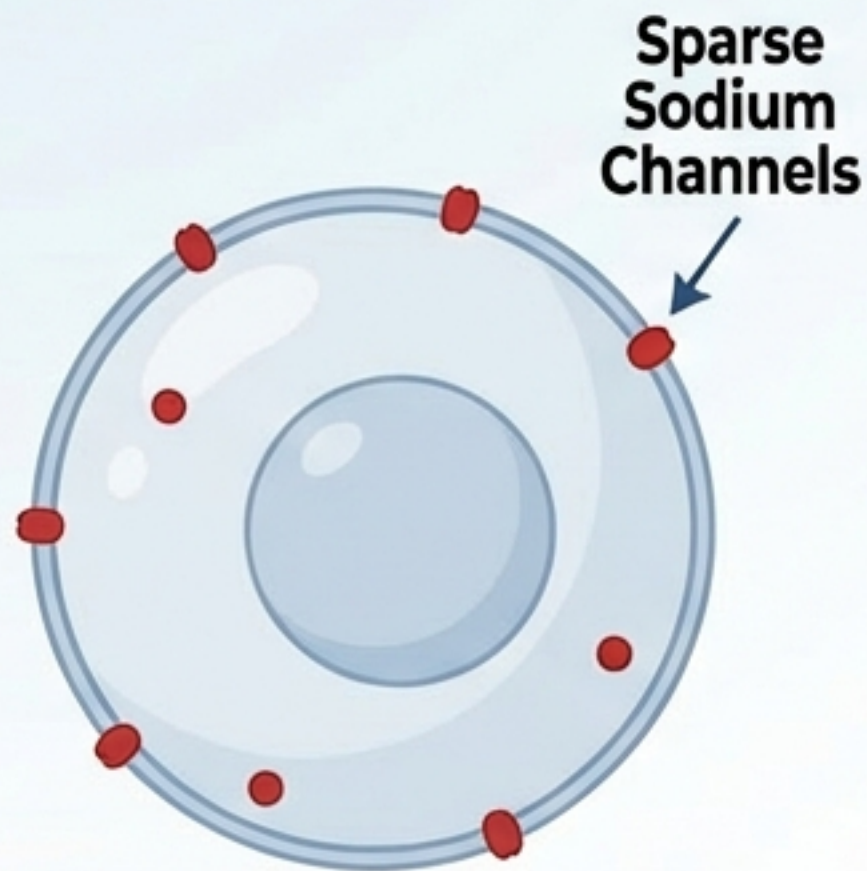
The Biological Peace Treaty

- **Focus:** Reprogramming the immune system to accept biologics and auto-antigens.
- **Key Assets:** **ImmTOR™** (Selecta/Sobi), **CNP-104** (COUR), and **MIC-Lx** (TolerogenixX).
- Nanoparticle and cell-based induction of regulatory T-cells (Tregs) to prevent Anti-Drug Antibodies (ADAs).

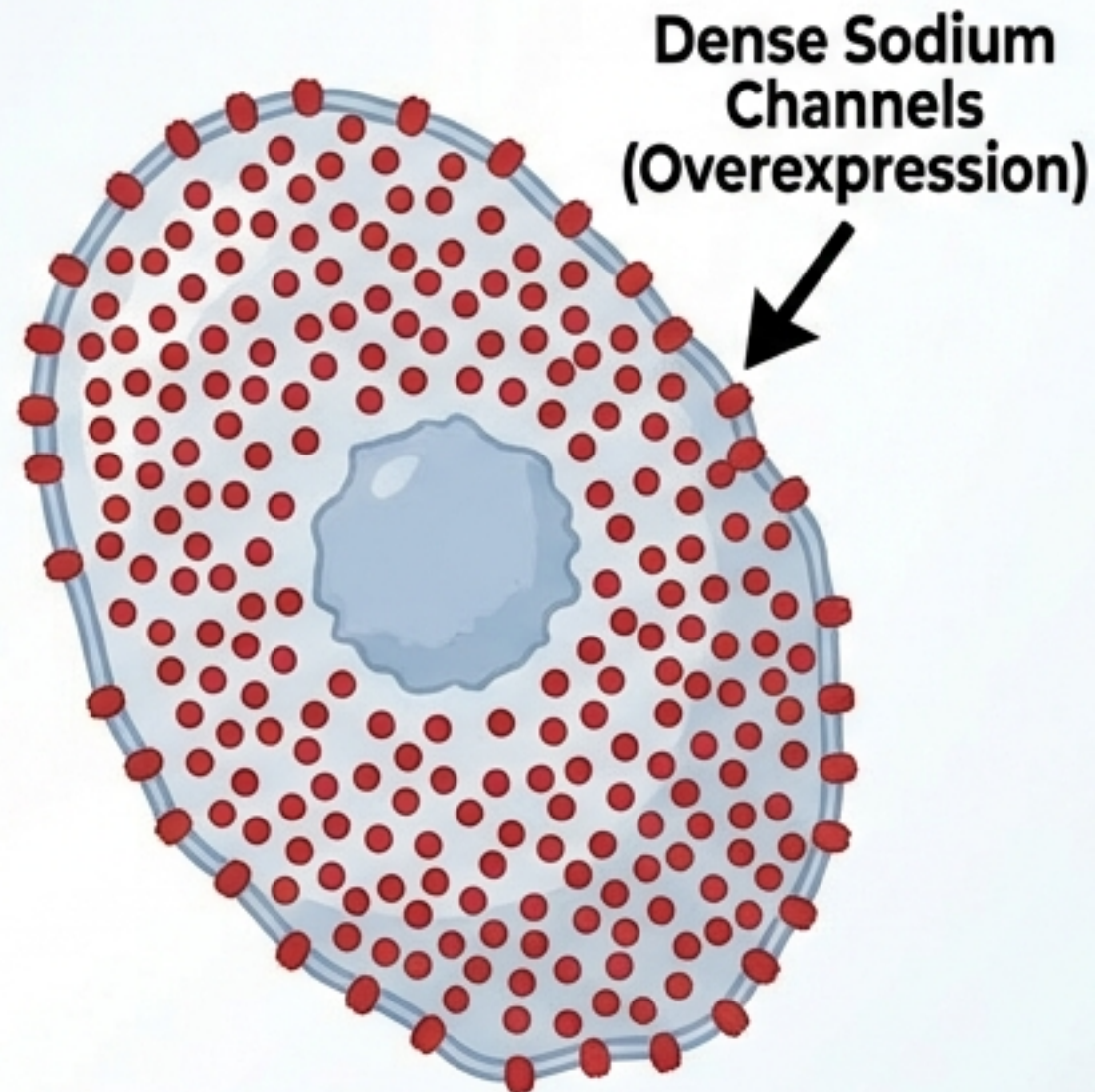
# The Physiological Vulnerability: VGSC Overexpression

Metastatic carcinoma cells possess a unique biophysical signature distinct from healthy tissue.

## Normal Epithelial Cell Low Channel Density (1x)



## Metastatic Breast Cancer Cell (MDA-MB-231) High Channel Density (10-50x)

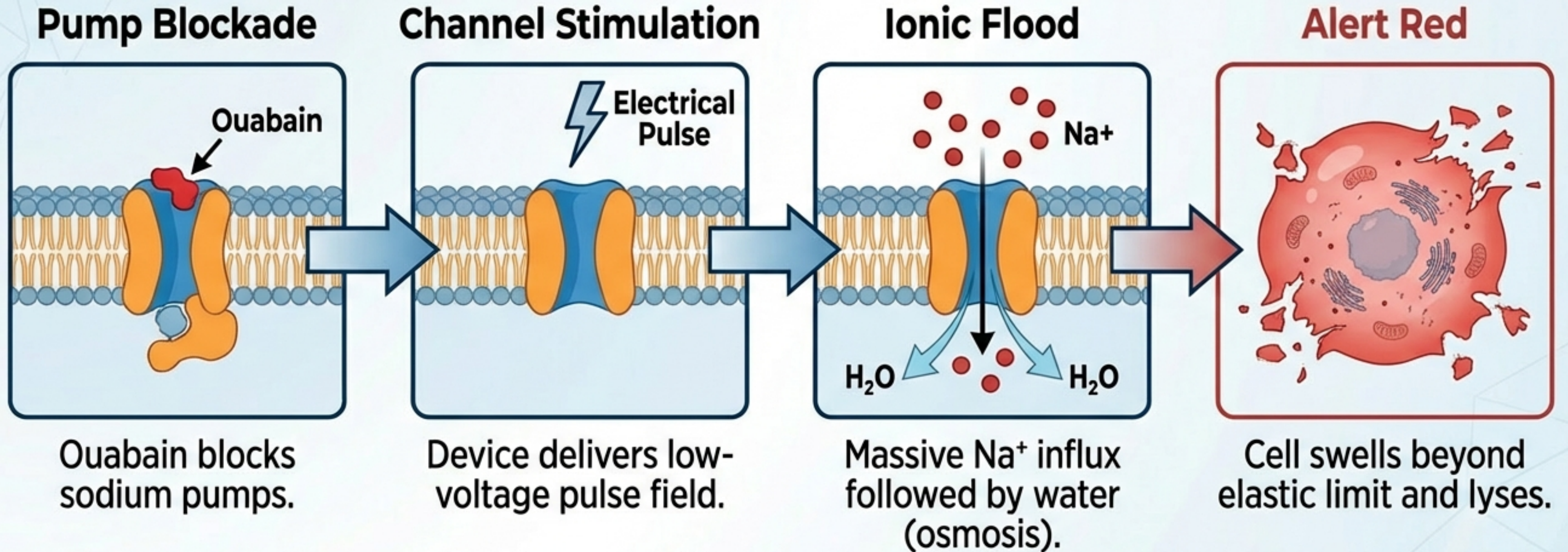


- **10–50x Overexpression:** Late-stage cancer cells possess significantly more sodium channels than normal cells.
- **Invasiveness Correlation:** High VGSC expression correlates directly with metastatic potential.

*“The overexpression of sodium channels in the metastatic cells... suggests that many of them will also respond to this treatment.”*

**— Oleander Technologies**

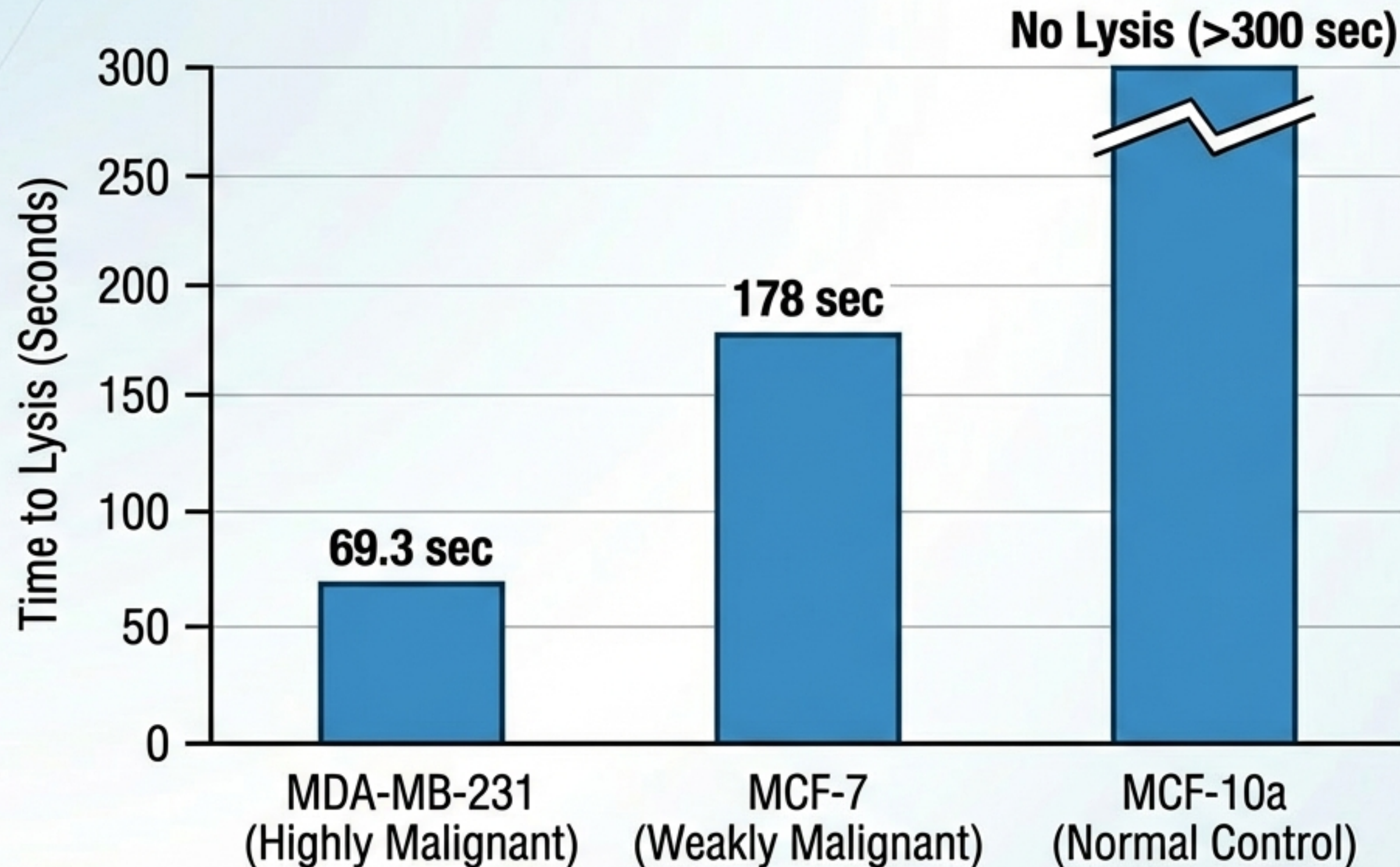
# Mechanism of Action: Targeted Osmotic Lysis (TOL)



**Differentiation:** Unlike irreversible electroporation (IRE) which ablates all tissue via high voltage, TOL is selective to cells with high channel density.

# Pre-Clinical Efficacy: Rapid and Selective Necrosis

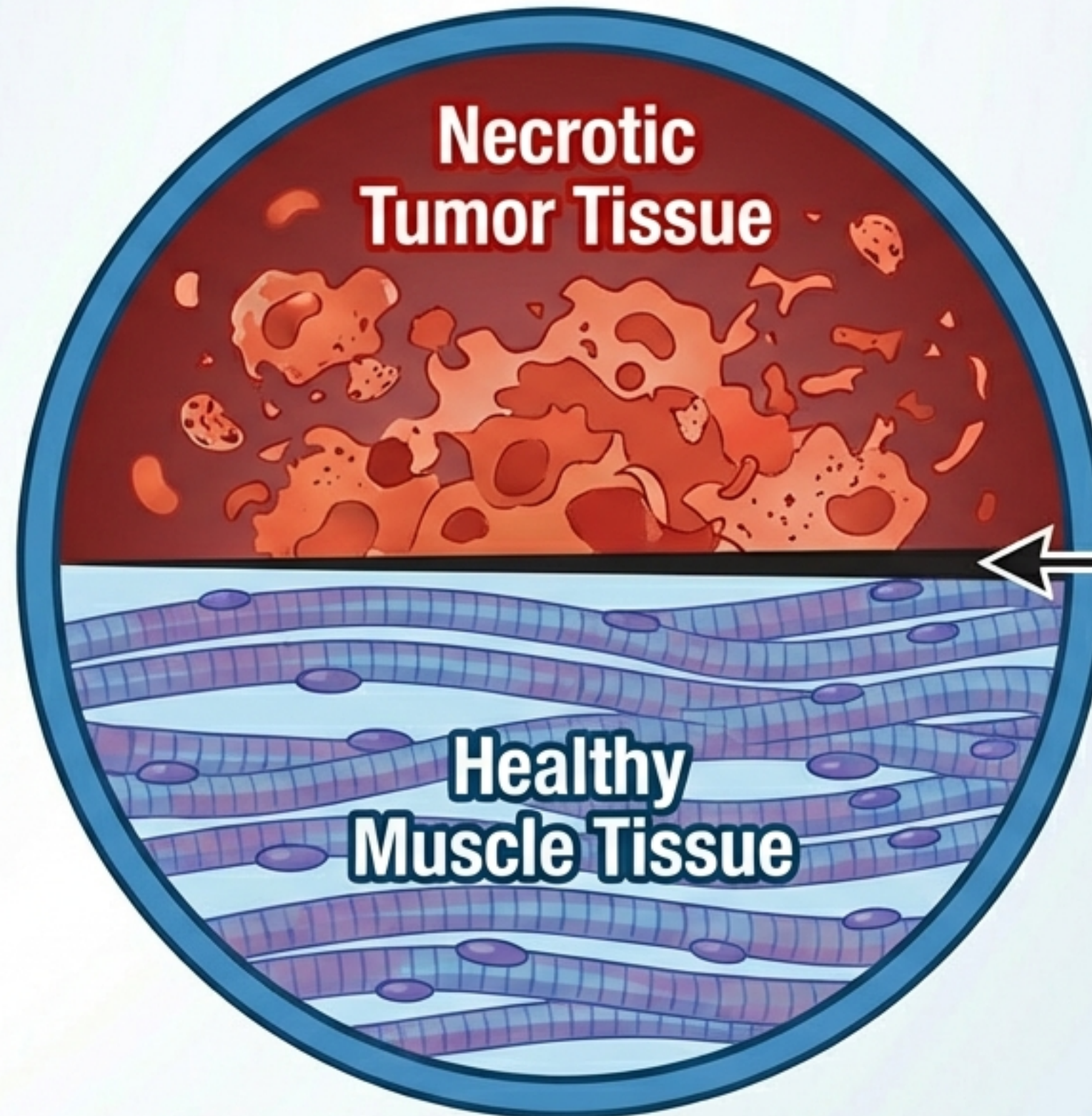
Data Source: Oncotarget, 2018



- **Key Finding:** Lysis speed correlates with sodium channel density.
- **Insight:** “TOL works most effectively on advanced cancers... Earlier stage cancer cells are more like normal cells.”

# In Vivo Safety and Tumor Reduction

- **Study Context:** MDA-MB-231 xenografts in Nu/J mice.
- **Efficacy:** TOL treatment resulted in 60–80% tumor necrosis.
- **Tumor Growth:** Significantly slower tumor growth over 3-week survival period vs controls.



**Safety Profile:** Adjacent muscle tissue remained uninjured despite proximity to lysis event.

# Oleander Technologies: Path to Commercialization



## Regulatory Strategy

- **Classification:** Combination Product.
- **Components:** Generic Drug (Ouabain) + Novel Stimulation Device.
- **Advantage:** Potential for shorter/less complicated FDA pathway compared to de novo drug discovery.



## Intellectual Property

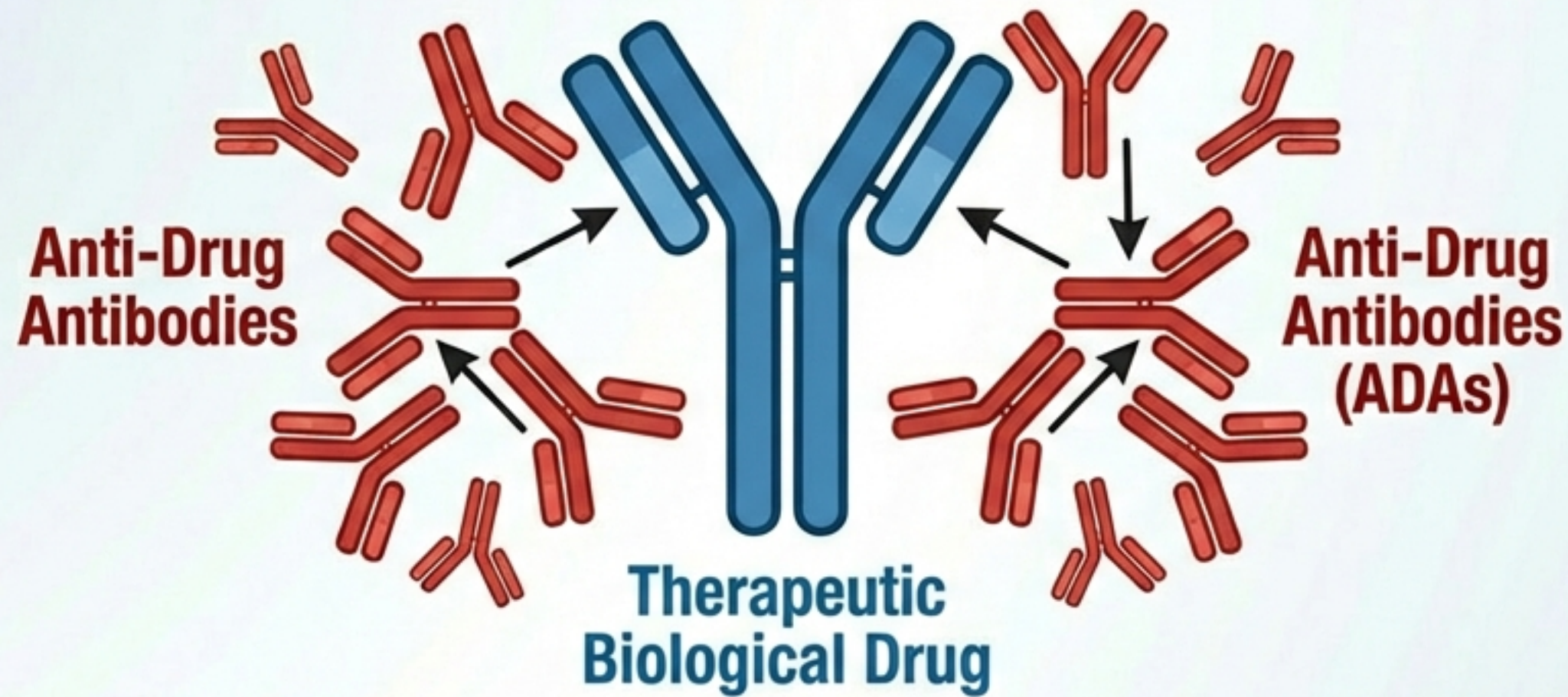
- **US Patents:** 8,921,320 (TOL of Cancer Cells) & 11,554,292 (Pulsed Magnetic Field Gradients).
- **Global Reach:** Patents approved in EU, Japan, Australia, and Canada.



## Leadership

- **Inventors:** Dr. Dennis Paul and Dr. Harry Gould (LSU Health Sciences Center).

# The Immunology Challenge: Anti-Drug Antibodies (ADAs)

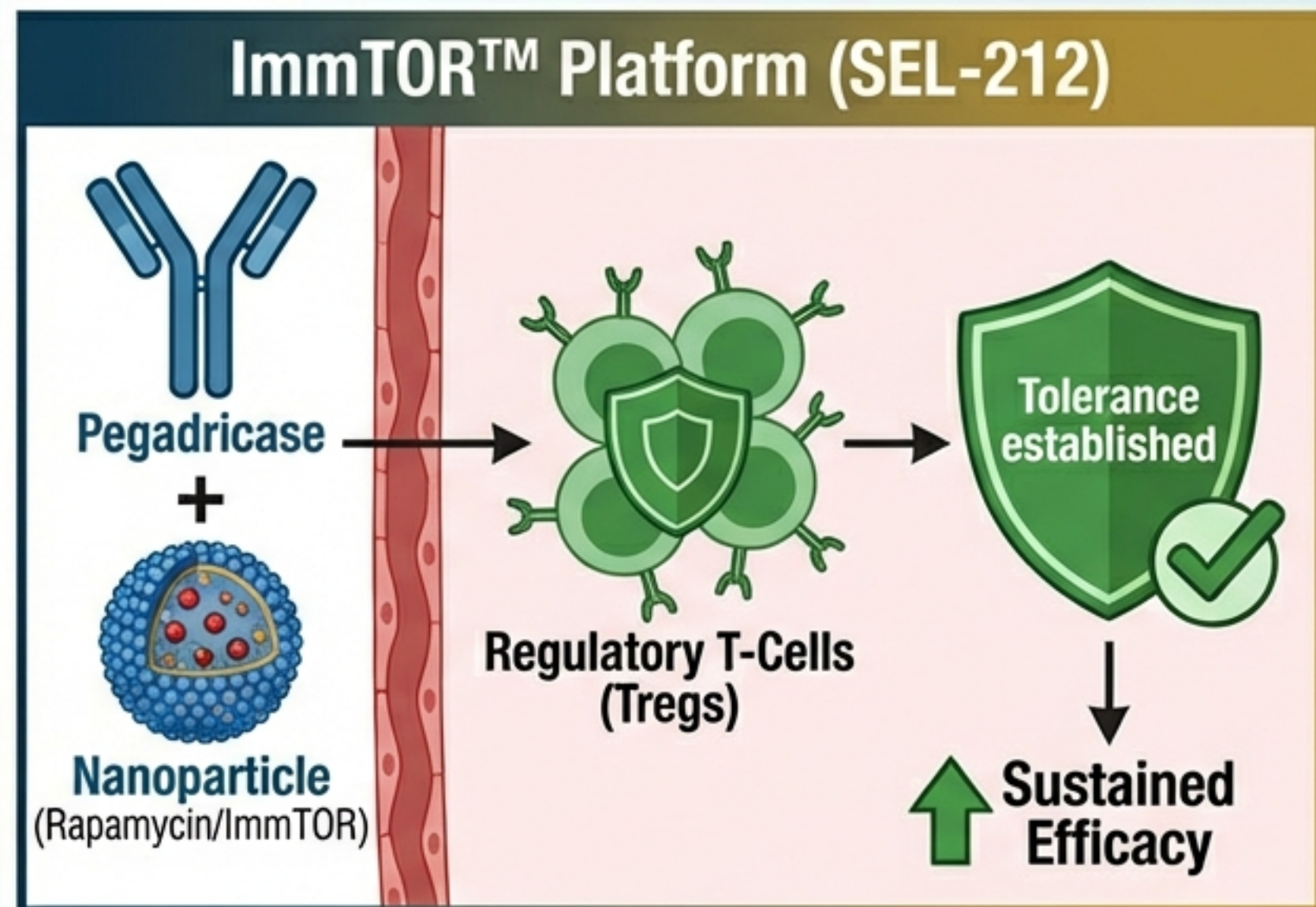
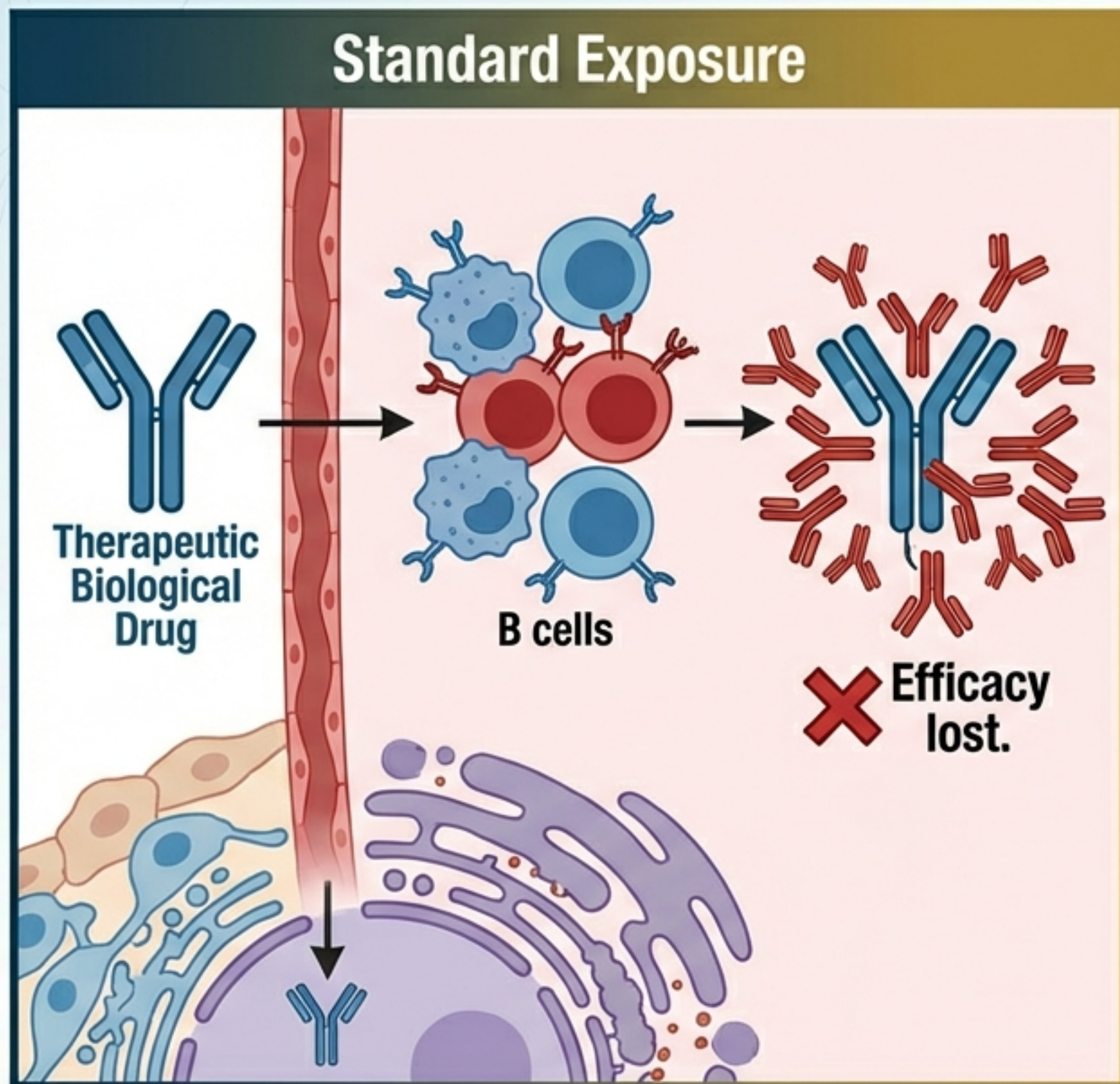


**Problem:** Biologic therapies often fail because the immune system recognizes them as foreign threats.

## Case Study Box: Refractory Gout

- Standard of Care (Pegloticase) fails in >50% of patients due to ADA formation.
- Current mitigation requires co-administration with Methotrexate (broad immunosuppression), introducing toxicity risks.

# SEL-212: Nanoparticle-Induced Tolerance



- **Technology:** Rapamycin-containing nanoparticles (ImmTOR™).
- **Result:** Prevents formation of ADAs without broad immunosuppression.
- **Dosing:** Once-monthly infusion (vs. bi-weekly for standard of care).

# The COMPARE Trial: SEL-212 vs. Pegloticase

## Head-to-Head Phase 2 Data in Refractory Gout

	Endpoint/Category	SEL-212	Pegloticase
1.	Primary Endpoint (Serum Urate <6 mg/dL)	<b>53%</b> (Months 3 & 6)	<b>46%</b> (Months 3 & 6)
2.	Statistical Superiority (Month 3)	<b>79.2%</b> Response <i>P</i> =0.02 (Statistically Significant)	<b>43.7%</b> Response
3.	Safety & Convenience	<ul style="list-style-type: none"><li>• Monthly dosing</li><li>• Reduced steroid burden</li></ul>	<ul style="list-style-type: none"><li>• Bi-weekly dosing</li><li>• Requires Methotrexate co-admin.</li></ul>

# Commercial Outlook: A 'Drug to Watch'

Source: Clarivate Drugs to Watch 2025 Report

**\$1.7  
Billion**

Expected Sales in  
G7 Markets by 2030

**95%**

Probability of Success  
(US Market)

**Premium  
Pricing**

Positioned to command  
~10% premium over  
KRYSTEXXA due to  
monthly dosing advantage.

# Platform Expansion: Autoimmune Disease

Applying nanoparticle tolerance beyond Gout

## Primary Biliary Cholangitis (PBC)

- **Asset:** CNP-104 (COUR)
- **Target:** PDC-E2 antigen encapsulated in nanoparticles.
- **Data:** Phase 2a showed reduction in pathogenic Th17 cells and liver stiffness stability.



## Celiac Disease

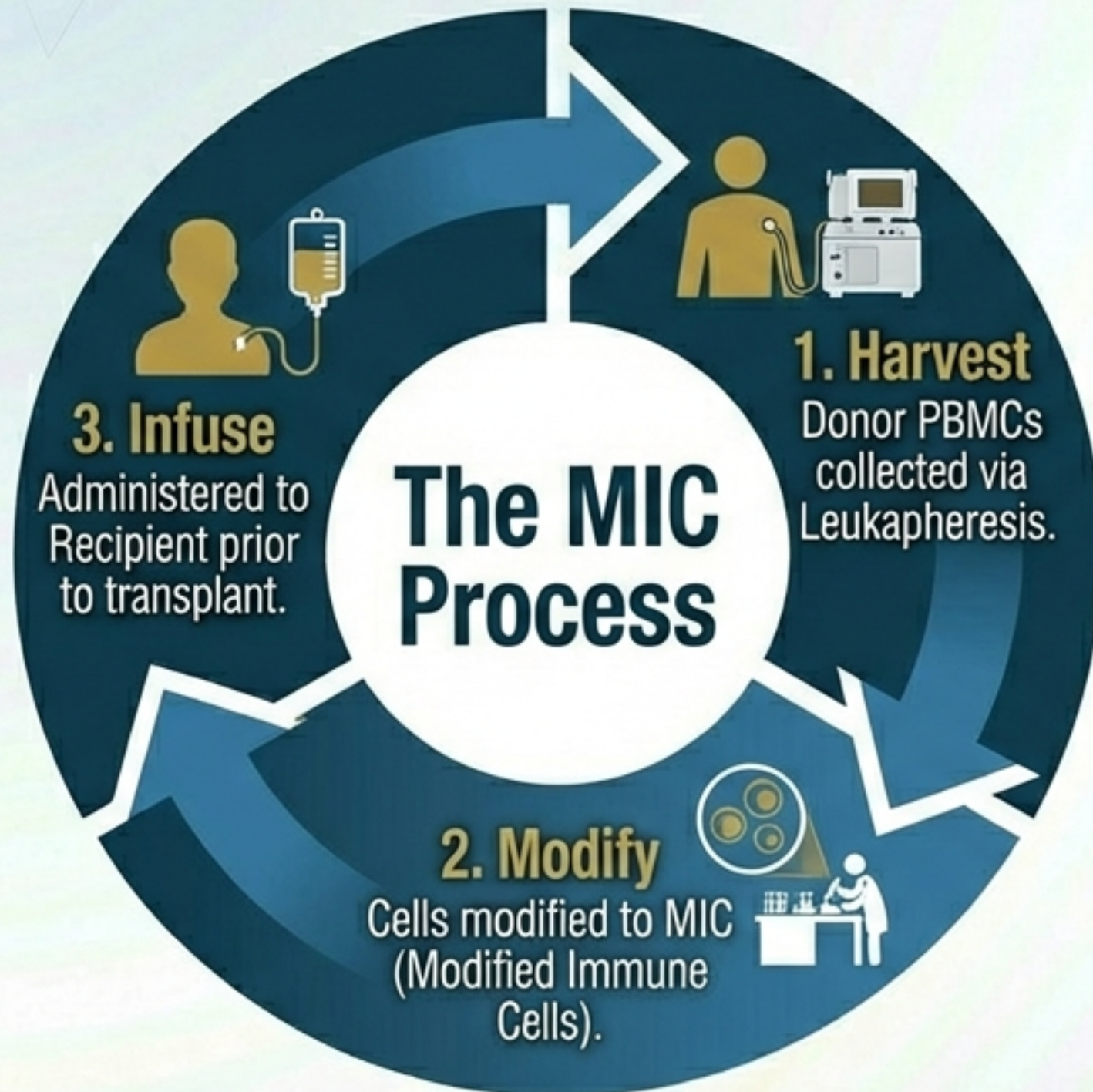
- **Asset:** TAK-101 (Takeda)
- **Target:** Gliadin-encapsulating nanoparticles.
- **Concept:** Inducing gluten tolerance to move from symptom management (diet) to disease modification.

# Cellular Therapy: MIC-Lx for Transplant Tolerance







Company: TolerogenixX

## 5-Year Clinical Follow-Up (Phase I)

- **100%** of treated patients showed stable graft function.
- **No Donor-Specific Antibodies (DSA)** or acute rejections.
- **Significant reduction** in immunosuppressive drugs required.



# The Future of Care: Mechanistic Precision

Biophysical Oncology (TOL)	Immune Tolerance (ImmTOR/MIC)
 <b>Current State:</b> Toxic Systemic Therapy	 <b>Current State:</b> Broad Immunosuppression
 <b>Future State:</b> <b>Biophysical Selectivity</b>	 <b>Future State:</b> <b>Antigen-Specific Tolerance</b>
 <b>Mechanism:</b> Targeting ion channel overexpression (VGSCs) for physical lysis.	 <b>Mechanism:</b> Targeting T-cell response for biological acceptance.

A paradigm shift from blunt force medicine to precision reprogramming of cellular biology.