



Eterna Therapeutics: Redefining Possibilities with Transformative Cellular and Gene Therapy

April 2024

Safe Harbor Statement

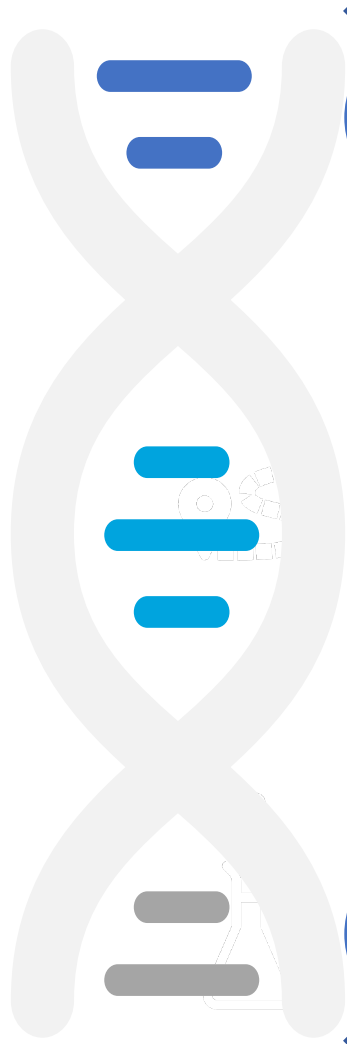
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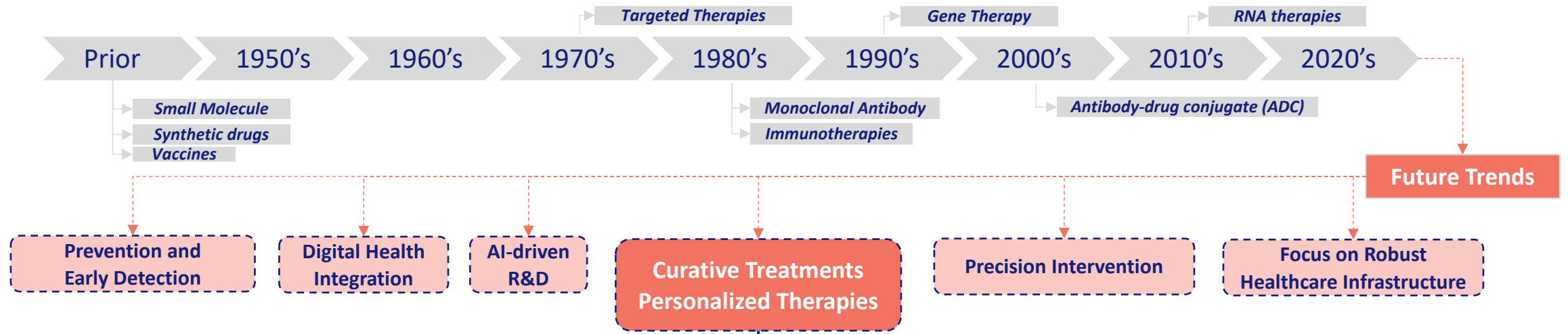


-  Introduction & Company Overview
-  Eterna's Science
-  Selected Preclinical Data
-  Eterna's Strategy
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Introduction & Company Overview

The Future of Biopharma: Gene and Cellular Therapy



Curative therapies, such as Gene and Cellular therapies (GCT) **have the potential to alleviate the underlying cause of genetic diseases and acquired diseases**¹

With increasing groundbreaking approvals, **there is significant traction for GCT going into 2024 and beyond**²

GCT provides the exciting opportunity of **curative single treatment for devastating diseases, eradicating the need for chronic medication**³

Scope across various disease areas:

- Cancer
- Genetic disorders
- Disorders affecting the hematopoietic system
- Infectious diseases
- Metabolic diseases etc.

Global CGT **market size** is expected to hit around **USD 42.56 billion by 2030**, growing at a CAGR of 39.42 % during the forecast period 2022 to 2030⁴

A Study ([Quinn et al., 2019](#)) projected that about **350,000 patients will have been treated with 30 to 60 GCT products by 2030**

¹Gene & Cell Therapy FAQs | ASGCT; ²2024's Market Outlook For Cell & Gene Therapies; ³Marrone et al., 2022;

⁴Cell and Gene Therapy Market Size, Growth, Trends, Forecast Report 2022-2030

Eterna Therapeutics: Preclinical-Stage Publicly Traded Biopharmaceutical Company



Vision

We aspire to become a gene and cell therapeutics company through multiple approved products that meaningfully improve the lives of patients with difficult-to-treat diseases



Mission

Leveraging the company's robust intellectual property portfolio to co-develop or out-license our technology platforms and provide transformational new medicines to patients



Science

Portfolio of over **100 patents** covering key mRNA cell engineering technologies, including technologies for **mRNA cell reprogramming**, **mRNA gene editing**, and **mRNA delivery system**, which we collectively refer to as our **“mRNA technology platform”**

Eterna Therapeutics: Pipeline of Gene & Cellular Therapy Candidate



Therapeutic Area	Indication	Therapeutic Candidate	Preclinical*	Phase 1	Phase 2	Phase 3
Rare Disease	Sickle Cell Disease	UltraSlice™ Based mRNA Candidates				
Autoimmune Disease	Multiple Sclerosis	iPSC-Derived iMSCs				
Oncology	Platinum-Resistant, TP53-Mutant Ovarian Cancer	IL7/IL15-Secreting iMSCs				
	Triple-Negative Breast Cancer	IL7/IL15-Secreting iMSCs				

*The objective of the studies is to evaluate the efficacy (e.g. antitumor effect in case of cancer etc.) and in the case of sickle cell disease, compare the efficacy with Casgevy™
iPSC: Induced Pluripotent Stem Cell
iMSCs: Induced Mesenchymal Stem Cells

Our Target Indications have a Considerable Market Size and Medical Unmet Needs



Sickle Cell Disease (SCD)

- Sickle Cell Disease affects approximately **100,000 people** in the US¹
- GCT is considered a curative therapy for SCD, but **safety issues related to unintended genetic modifications (off-target effect)** are still concerning for this indication²

Multiple Sclerosis (MS)

- Nearly **one million people** are living with MS in the US³
- Evidence shows **continued deterioration in function despite treatment with disease-modifying therapies (DMT)**. There is an **ongoing need for new effective and safe treatments** for patients with progressive MS—particularly those with nonactive disease⁴

Platinum-Resistant Ovarian Cancer (PROC)

- **Estimated** incidence of platinum-resistant, TP53-mutant ovarian cancer in the US is **14,626**
- Effective therapies in heavily pretreated platinum-resistant ovarian cancer (PROC) are an **ongoing challenge**⁵. **The response rate to anti-PD1/PD-L1 monotherapy is low, not exceeding 8%**⁶, and **checkpoint inhibitors have had limited success in improving outcomes for patients with PROC**⁷

Triple-Negative Breast Cancer (TNBC)

- **Estimated** incidence of TNBC in the US is **44,669**
- Despite several quite impressive advances, the **treatment of metastatic TNBC is still heavily dependent on chemotherapy, or chemotherapy-based approaches and a good targeted therapy is still lacking**⁸

¹CDC. *Data & Statistics on Sickle Cell Disease* | CDC; ²Tang et al., 2024; ³MS Prevalence. *National Multiple Sclerosis Society*; ⁴Watson et al., 2023; ⁵Eskander et al., 2023; ⁶Saux et al., 2021; ⁷Richardson et al., 2023; ⁸Breast Cancer Breakthroughs Episode 4: Unmet Needs in TNBC



Eterna's Science

Eterna's Science: mRNA Technology Platform



mRNA

Cell Reprogramming Technology

- Eterna uses mRNA to express reprogramming proteins
- These proteins re-write a cell's gene expression program, **enabling a somatic cell, such as a skin cell, to transform into another type of cell, such as a neuron or a stem cell [e.g., induced pluripotent stem cells (iPSCs) or Induced mesenchymal stem cells (iMSCs) - cell types that can differentiate into many desired cell types]**

mRNA

Gene Editing Technology

Eterna's proprietary mRNA gene editing technology consists of:

- mRNA encoding gene-editing proteins
- Novel mRNA structures and designs
- A novel gene editing endonuclease (**UltraSlice™**) optimized for mRNA expression

mRNA

Gene Delivery Technology

- Eterna formulates mRNA using lipid nanoparticle (LNP) technology
- Eterna has a proprietary library of ionizable lipids
- Eterna's proprietary LNP based delivery system (**ToRNA^{do}™**) surrounds and protects the mRNA cargo, enabling efficient delivery into human cells

These three technologies can be used in tandem

Eterna's mRNA Technology Platform: Key Differentiator



Limitations of Conventional Technologies

Eterna's Technology: Key Differentiator

Cell Reprogramming

Conventional cell-reprogramming technologies (e.g., using **Sendai virus or episomal vectors**):

- Can result in **low-efficiency reprogramming**
- Can produce cells with **abnormal growth characteristics**
- Can **leave traces of the vector** in reprogrammed cells

Our proprietary cell reprogramming technology is designed for:

- **Rapid**
- **High-efficiency**
- **Footprint-Free** cell reprogramming

Gene Editing

Conventional gene editing technologies (e.g. **plasmids or viruses mediated**) result in **nucleic acid fragment insertion at random locations** in the genome and cause:

- **Low-efficiency editing**
- **Unwanted mutagenesis**

Note: CRISPR-based gene editing may cause off-target modifications and require PAM near the target site and guide RNAs

Our proprietary gene editing technology is designed for:

- **mRNA-mediated optimized transgene expression**
- **Sustained transgene expression over multiple passages and even after long term cryopreservation**
- **Generation of immuno-nonreactive or “stealth” cells with inactivated or altered expression of one or more components of the human leukocyte antigen (“HLA”) complex**

Gene Delivery

Conventional delivery systems (e.g. **LNP**) often suffer from **endosomal entrapment and toxicity**

Adeno-associated virus (AAV) mediated gene delivery may cause **immunogenic protein impurities** and AAV is **unable to deliver larger genes**

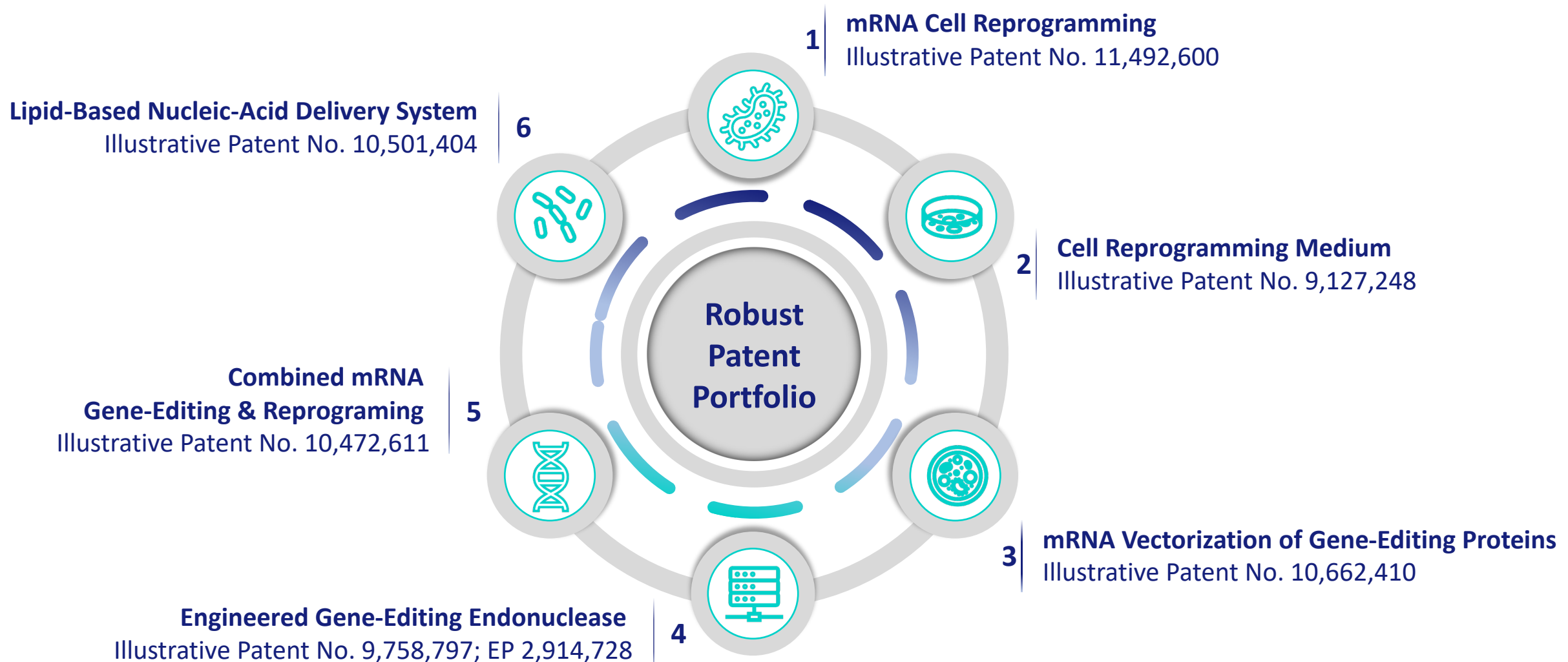
Our proprietary mRNA delivery technology is potentially capable of:

- Delivering nucleic acids to cells **both ex vivo and in vivo**
- Inserting exogenous sequences into **genomic safe-harbor loci**
- Delivering nucleic acids to the **brain, eye, skin, and lung in vivo**

Eterna Therapeutics IP Portfolio: Key Granted Patents



Each technology is supported by a significant intellectual property estate (54 US and 51 Ex-US granted patents) designed to both support and foster candidate development



Eterna's Science: mRNA Cell Reprogramming

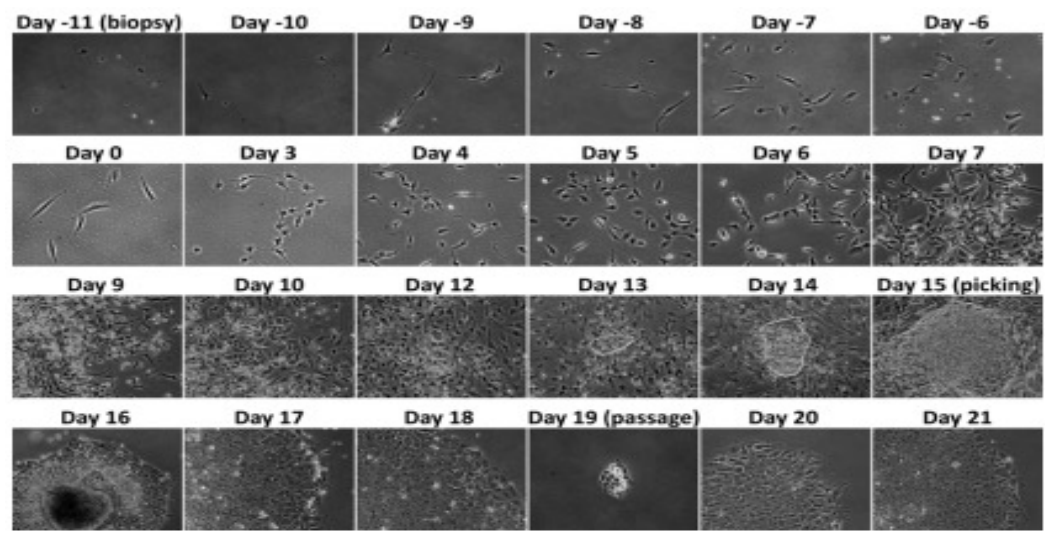
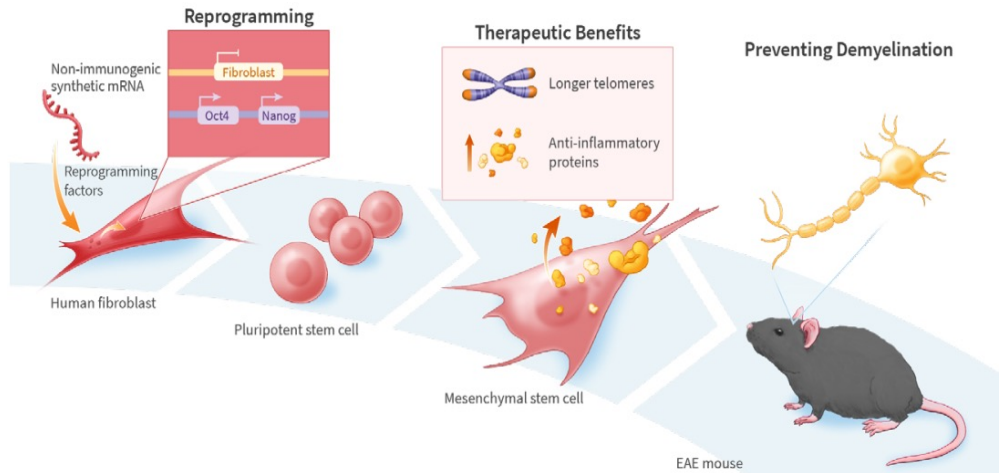


Figure: mRNA Cell Reprogramming from biopsy to pluripotent stem cell line.

Overview:

- ❖ A technology for reprogramming cells that uses mRNA to express reprogramming factors¹
- ❖ Protected by nine U.S. patents, as well as patents in Australia, China, Europe, Japan, Mexico, and Russia
- ❖ Certain granted patents include claims that are not limited by disease indication, cell type, reprogramming factor(s), mRNA sequence or chemistry, or method of transfection

Example Applications:

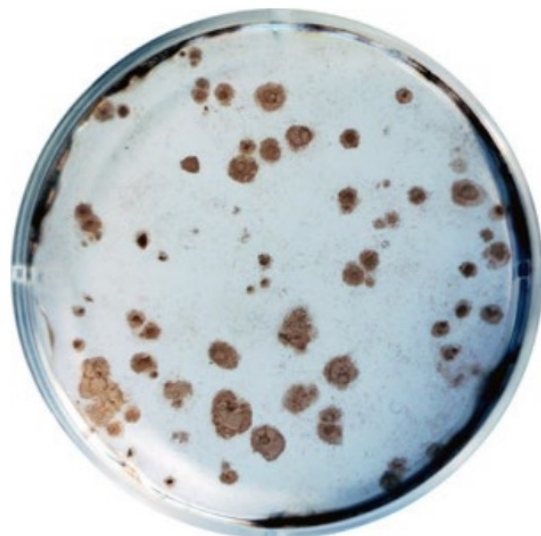
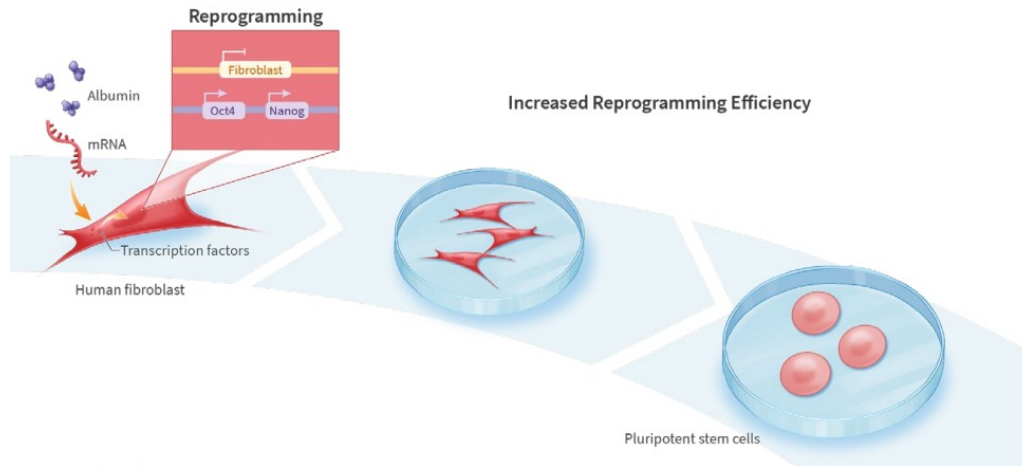
Ultra-high efficiency reprogramming (e.g., reprogram single cells)	Reprogram cells quickly, and using a simple protocol (e.g., 4-6 transfections, pick colonies in 8-12 days)	Combine with Eterna's Chromatin Context Sensitive Gene-Editing Endonuclease and/or Eterna's Combined mRNA Gene Editing & Cell Reprogramming technology to generate models of genetic disease, gene-corrected patient-specific cell therapies, and allogeneic (i.e., immunononreactive or "stealth") cell therapies, including allogeneic pluripotent stem cell-derived CAR ² -T and CAR-NK ³ cell therapies for the treatment of cancer, and engineered mesenchymal stem cell (MSC) therapies for regenerative medicine, wound-healing, inflammatory and auto-immune diseases, and tumor targeting applications
Develop allogeneic or autologous cell therapies	Reprogram without feeders, conditioning, passaging, immunosuppressants, demethylating agents or other toxic small molecules, pre-mixing or aliquoting of RNA solutions	
Reprogram without using viruses or other potentially mutagenic vectors	Reprogram using a completely animal component-free process	

1. Harris, J., et al. Mol Ther, Vol 28 No 4S1, 2020; ²CAR: Chimeric Antigen Receptors; ³NK Cells: Natural Killer Cells

Overview:

- ❖ Conventional cell-culture media, including serum-free and animal component-free media, can result in very low-efficiency cell reprogramming.
- ❖ Our scientists developed a novel cell-culture medium that can exhibit dramatically higher efficiency cell reprogramming than conventional media, including when mRNA is used to express reprogramming factors¹.

Example Applications:



Ultra-high efficiency reprogramming (e.g., reprogram single cells)

Develop allogeneic or autologous cell therapies

Reprogram without using viruses or other potentially mutagenic vectors

Reprogram using a completely animal component-free process

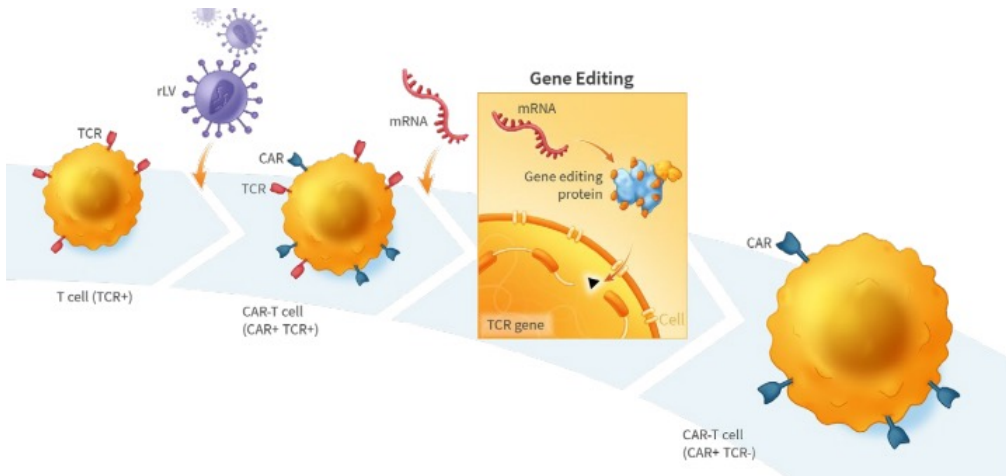
Reprogram cells quickly, and using a simple protocol (e.g., 4-6 transfections, pick colonies in 8-12 days)

Reprogram without feeders, conditioning, passaging, immunosuppressants, demethylating agents or other toxic small molecules, pre-mixing or aliquoting of RNA solutions

Combine with Eterna's Chromatin Context-Sensitive Gene-Editing Endonuclease and/or Factor's Combined mRNA Gene Editing & Cell Reprogramming technology to generate models of genetic disease, gene-corrected patient-specific cell therapies, and allogeneic (i.e., immunononreactive or "stealth") cell therapies, including allogeneic pluripotent stem cell-derived CAR-T and CAR-NK cell therapies for the treatment of cancer, and engineered MSC therapies for regenerative medicine, wound-healing, inflammatory and auto-immune diseases, and tumor-targeting applications

Figure: High-efficiency mRNA cell reprogramming of primary human fibroblasts (colonies stained for SSEA4).

¹Harris, J., et al. *Mol Ther*, Vol 29, No 4S1, 2021.



Overview:

- Gene-editing proteins can be used to inactivate, repair or insert sequences in living cells. Conventional approaches using plasmids or viruses to express gene-editing proteins can result in low-efficiency editing and unwanted mutagenesis when an exogenous nucleic acid fragment is inserted at random locations in the genome.
- Our scientists developed a technology that uses mRNA to express gene-editing proteins. This technology can exhibit dramatically higher efficiency gene editing, including in primary cells, than other approaches, without using viruses or DNA-based vectors that may cause unwanted mutagenesis.

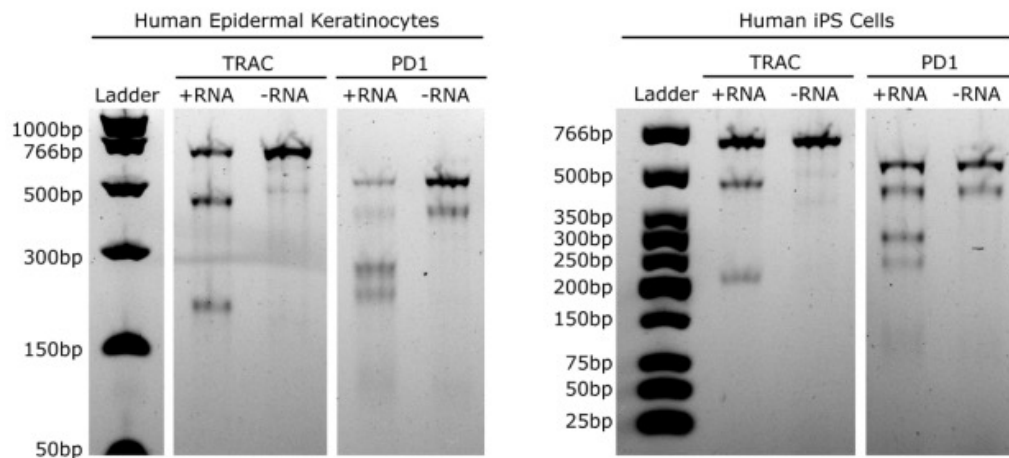


Figure: High-efficiency gene editing of TRAC and PD1 in human epidermal keratinocytes and human iPS cells¹

Example Applications:

Ultra-high efficiency editing of T cells, fibroblasts, keratinocytes, and pluripotent stem cells

Gene repair using a DNA-repair template

Gene-editing therapies (ex vivo and in vivo)

Donor sequence insertion into a target genomic locus (e.g., TRAC, AAVS1 safe harbor, etc.)

Autologous and allogeneic engineered cell therapies (e.g., CAR-T, CAR-NK, stem cell-derived therapies, etc.)

Virus-free and DNA-free gene editing

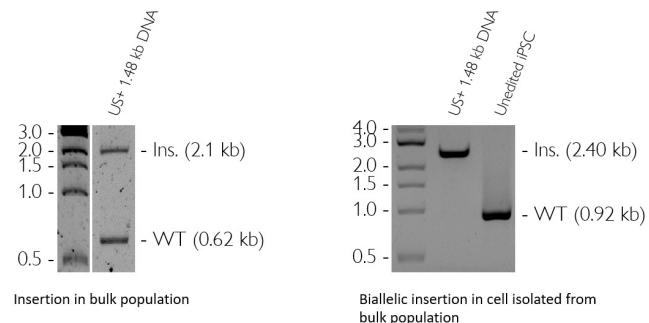
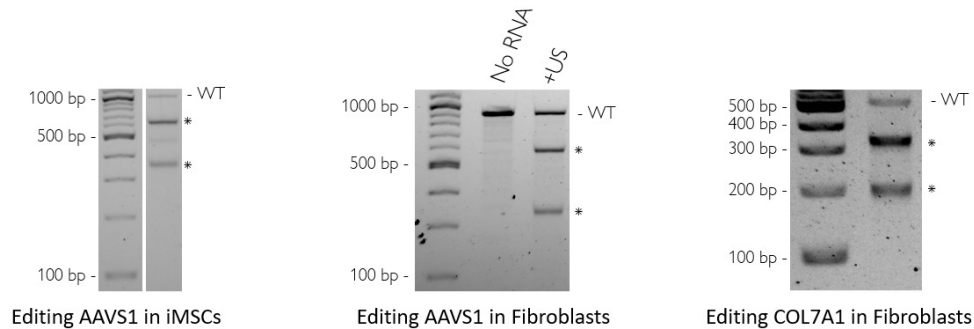
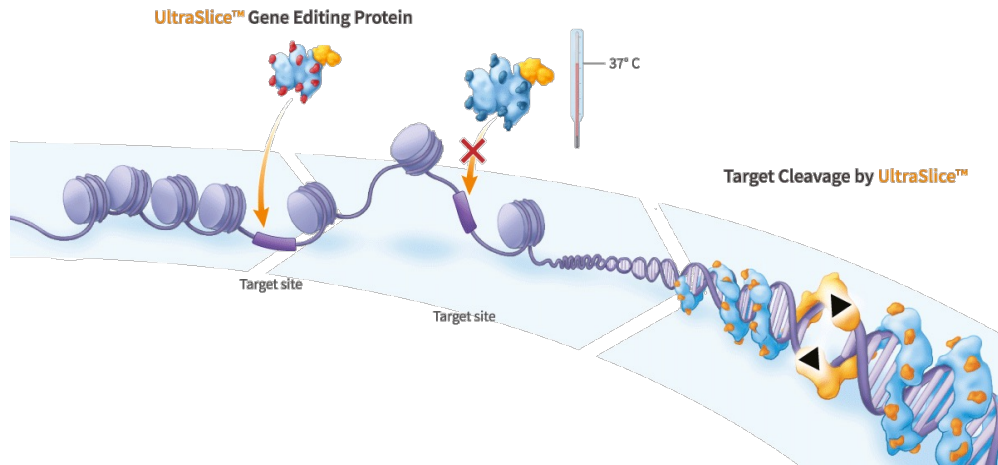
Overview:

- ❖ A novel high-specificity gene-editing endonuclease that exhibits high-efficiency on-target cutting at sub-physiological temperatures¹
- ❖ This technology can be used to target cutting activity to specific organs and tissues, allowing higher doses, minimizing systemic effects, and enabling enhanced safety for therapeutic applications
- ❖ The Temperature-Tunable Gene-Editing Endonuclease is protected by a pending U.S. patent (with additional patents pending in other countries)

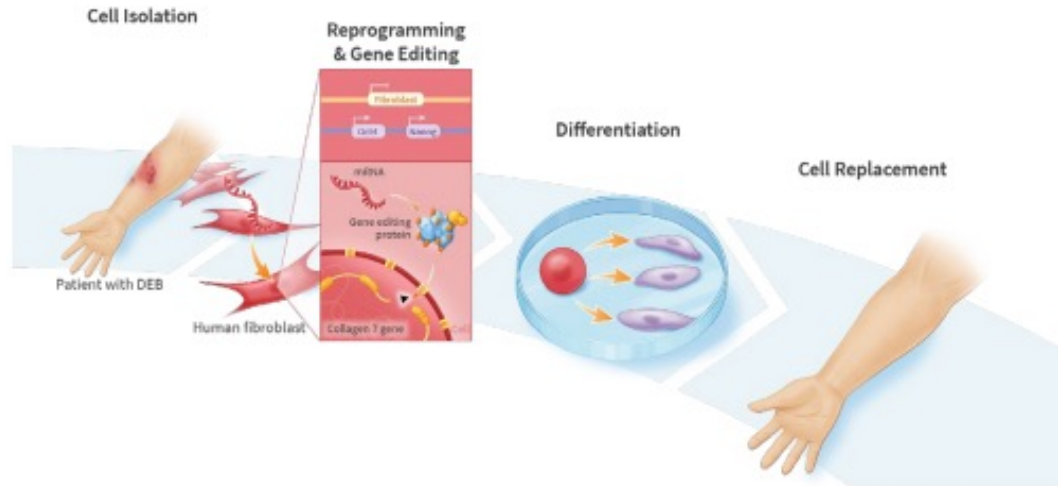
Example Applications:

Virus-free and DNA-free gene editing	Autologous and allogeneic engineered cell therapies (e.g., CAR-T, CAR-NK, stem cell-derived therapies, etc.)
Gene repair using a DNA-repair template	Combine with Eterna's mRNA Cell Reprogramming technology to generate models of genetic disease, gene-corrected patient-specific cell therapies, and allogeneic (i.e., immuno-nonreactive or "stealth") cell therapies, including allogeneic pluripotent stem cell-derived CAR-T and CAR-NK cell therapies for the treatment of cancer, and engineered MSC therapies for regenerative medicine, wound-healing, inflammatory and auto-immune diseases, and tumor-targeting applications.
Donor sequence insertion into a target genomic locus (e.g., TRAC, AAVS1 safe harbor, etc.)	
Gene-editing therapies (<i>ex vivo</i> and <i>in vivo</i>)	

¹ Osayame, Y., et al. *Mol Ther*, Vol 29 No 4S1, 2021.



Eterna's Science: Combined mRNA Gene-Editing & Cell Reprogramming



Overview:

- ❖ Combining gene editing with cell reprogramming results in the generation of gene-corrected personalized cell therapies, models of genetic disease, engineered cell therapies, including allogeneic (i.e., immuno-nonreactive or “stealth”) cell therapies, including CAR-T, CAR-NK, and engineered MSC therapies for regenerative medicine, wound-healing, inflammatory and auto-immune diseases, and tumor-targeting applications.
- ❖ Our scientists developed a technology that uses mRNA to express both gene editing proteins and reprogramming factors.
- ❖ Combined mRNA Gene Editing & Cell Reprogramming is protected by U.S. Patent Number 10,472,611 (with additional patents pending in the U.S. and in other countries). Of note, the granted patent includes claims that are not limited by disease indication, cell type, reprogramming factor(s), mRNA sequence or chemistry, transfection method, target sequence, or type of gene-editing protein.

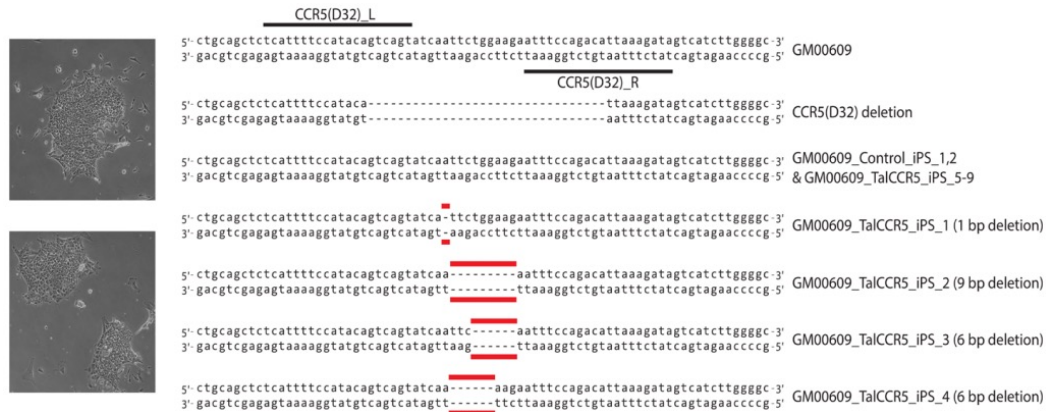


Figure: Combined mRNA Gene Editing & Cell Reprogramming to create clonal pluripotent stem cell lines containing defined deletions in the CCR5 gene.

Example Applications:

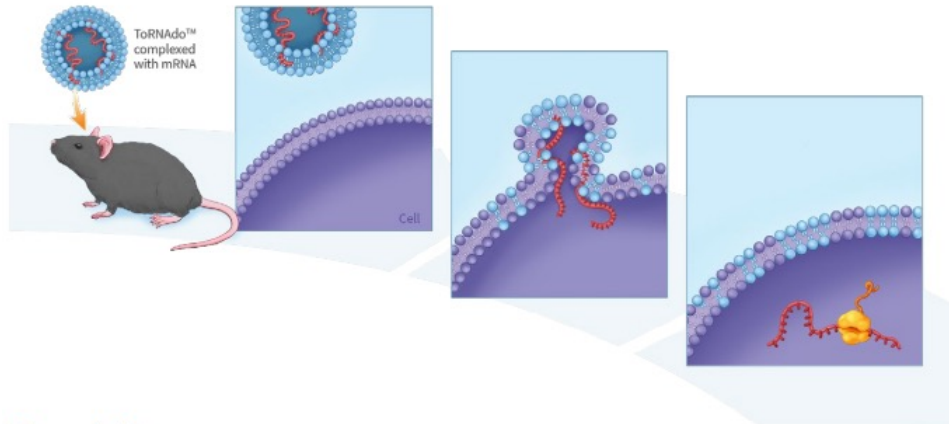
Generate gene-corrected personalized cell therapies

Take advantage of the clonality of mRNA Cell-Reprogramming to generate defined clonal populations of gene-edited cells

Simplify manufacturing of engineered cell therapies by eliminating serial gene-editing and cell-reprogramming steps

Generate allogeneic pluripotent stem cell-derived CAR-T and CAR-NK cell therapies for the treatment of cancer, and engineered mesenchymal MSC therapies for regenerative medicine, wound-healing, inflammatory and auto-immune diseases, and tumor-targeting application

Eterna's Science: Nucleic-Acid Delivery System* (ToRNAdo™)



Overview:

- ❖ Delivery systems can be used to **enhance the uptake of nucleic acids by cells**
- ❖ **Conventional delivery systems often suffer from endosomal entrapment and toxicity**, which can limit their therapeutic use
- ❖ Our scientists developed a novel chemical substance that we believe is **effective at delivering nucleic acids**, including mRNA, to cells both *ex vivo* and *in vivo*

Example Applications:

Use fusogenic lipid/nucleic-acid particles made with ToRNAdo™ to avoid endocytosis pathways that require “endosomal escape”

Achieve ultra-high-efficiency transfection in up to 100% serum

Deliver nucleic acids, including mRNA, *in vivo* – proven delivery to brain, eye, skin, and lung¹

Protect cargo from nuclease attack

Combine with Eterna's mRNA Cell Reprogramming technology to generate footprint-free pluripotent stem cells

Generate non-toxic formulated nucleic-acid products (ToRNAdo™ is made using omega-6 unsaturated tails derived from sunflower seed oil)

Delivery of mRNA, siRNA, and plasmid efficiently to a variety of cell types

Combine with Eterna's Chromatin Context-Sensitive Gene-Editing Endonuclease for high-specificity *in vivo* gene editing

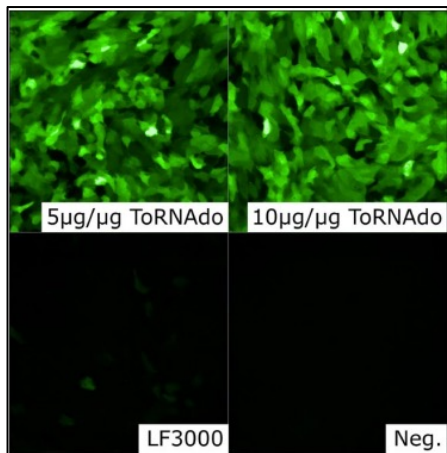


Figure: ToRNAdo™ delivery of GFP mRNA to human epidermal keratinocytes *in vitro*.

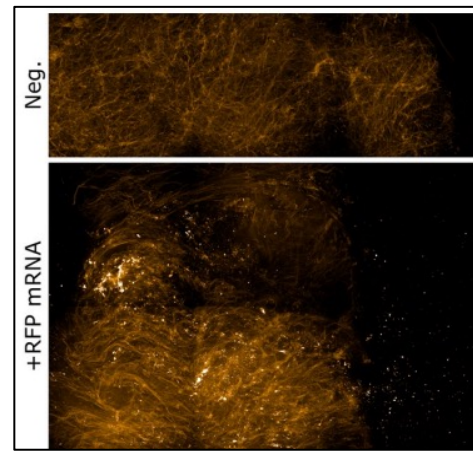


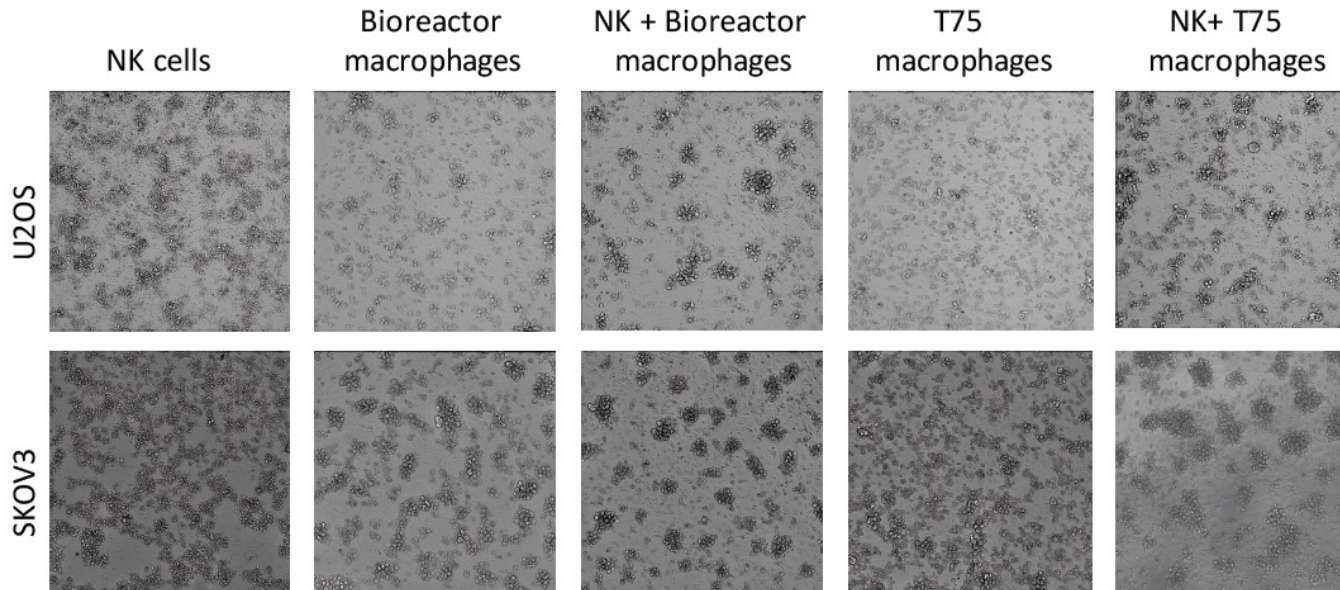
Figure: ToRNAdo™ delivery of RFP mRNA to human skin *in vivo*.

¹Kostas, F., et al. *Mol Ther*, Vol 28 No 4S1, 2020



Selected Preclinical Data

In Vitro Efficacy of Eterna's Proprietary iPSCs Derived NK Cells and Macrophages Against Ovarian Adenocarcinoma and Osteosarcoma Cells

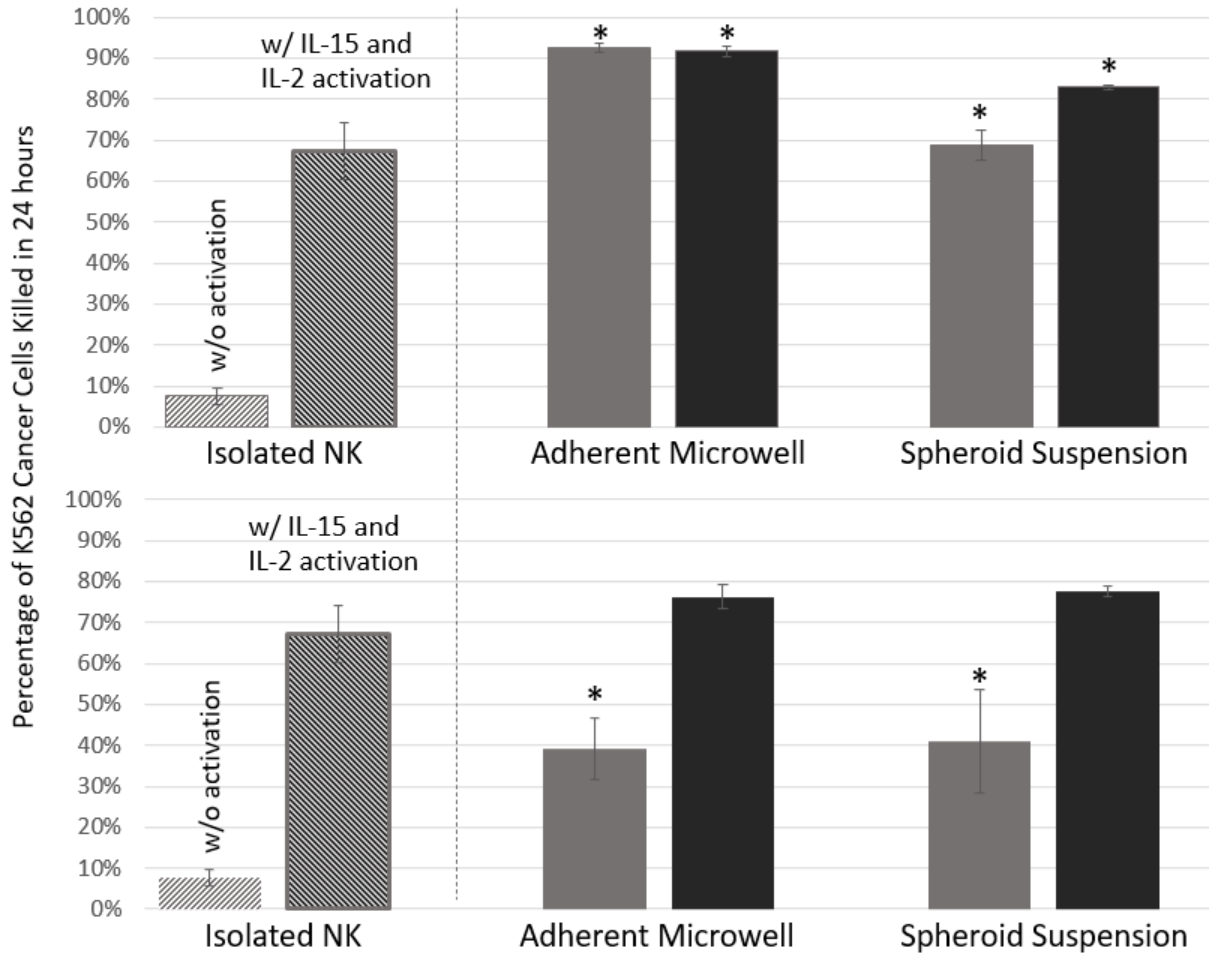


- ❖ After 24 hours, **there was increased cell clustering when the two cell types were combined**
- ❖ NK cells were thawed and seeded directly into the assay. Cells were harvested fresh from the T75 (D83) and bioreactor (D68)
- ❖ **When the two cell populations were combined, there was increased cell clustering in both U2OS and SKOV3 cells***

- ❖ iPSC derived NK Cells and macrophages were seeded with **Osteosarcoma (U2OS) and ovarian adenocarcinoma cell line (SKOV3) cells at a 5:1 E:T ratio**

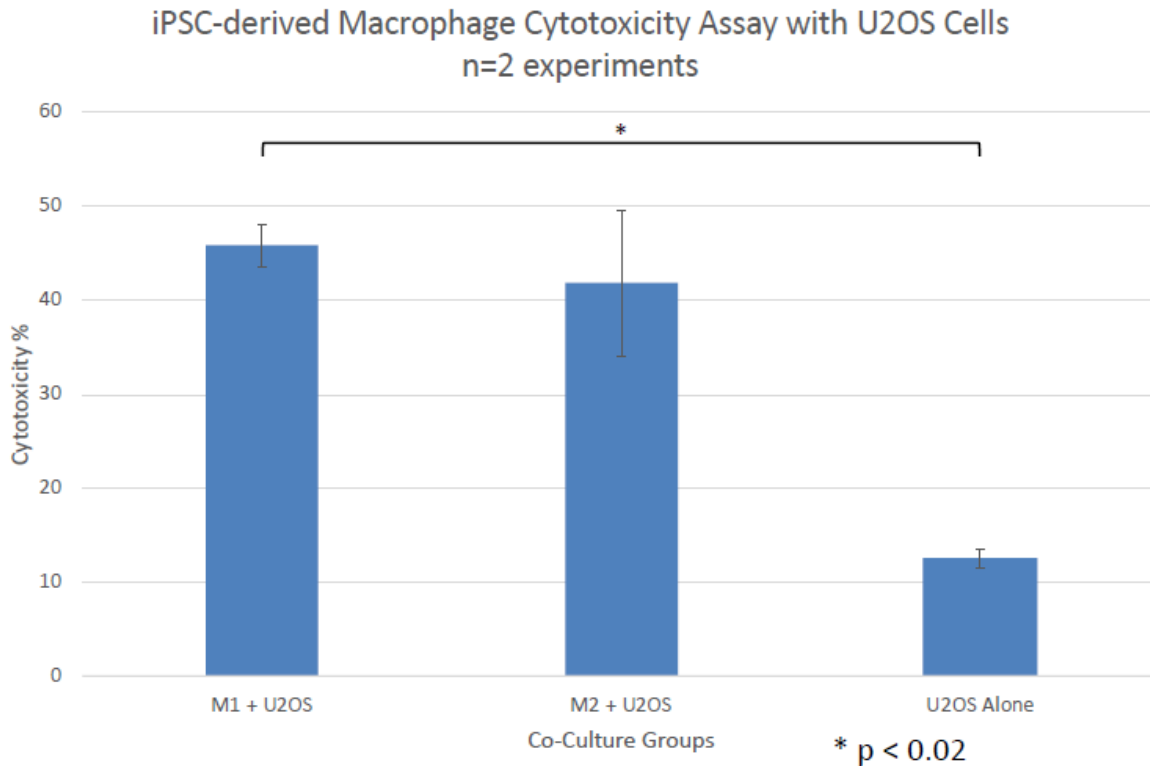
*Presented at 26th Annual Meeting of the American Society of Gene & Cell Therapy ([Blatchford et al., 2023](#))

In Vitro Efficacy of Eterna's Proprietary B2M Knockout Lymphocytes Against Chronic Myeloid Leukemia Cells



- ❖ Cytotoxic Lymphocytes, including NK and T cells can be used as allogeneic cell therapies for the treatment of cancer. However, these cells face challenges of limited expansion potential and in vivo persistence due to host immune rejection
- ❖ Major Histocompatibility Complex (MHC) class I molecules play a crucial role in immune rejection and beta-2 microglobulin (B2M) in association with MHC class I molecules is crucial for their stability and proper function
- ❖ Eterna developed iPSC-derived B2M knockdown (KO) lymphocytes with its proprietary technology
- ❖ B2M KO cytotoxic lymphocytes showed cytotoxicity against Chronic Myeloid Leukemia cell lines (K562) in the presence of cytokines (IL-2 and IL-15) while wild-type (WT) cytotoxic lymphocytes showed un-controlled cytotoxicity*

In Vitro Efficacy of Eterna's Proprietary iPSC-Derived Macrophages Against Osteosarcoma Cells

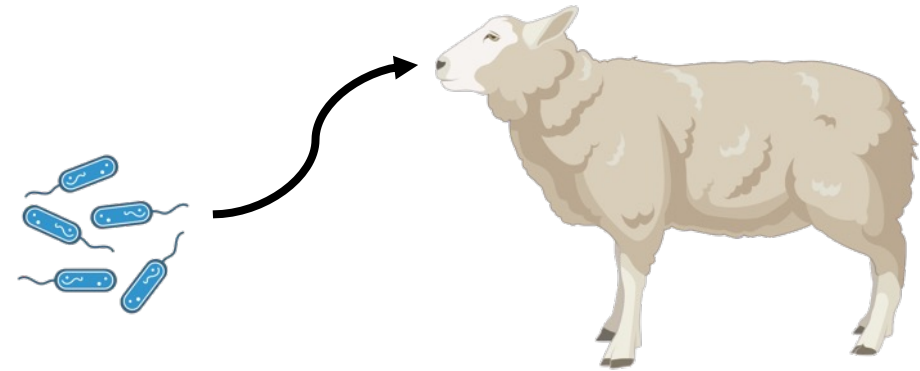


- ❖ iPSCs-derived monocytes were differentiated into macrophages by Eterna's proprietary technology
- ❖ **iPSC-derived macrophages exhibited cytotoxic activity against osteosarcoma cells (U2OS) with 45% cell killing in vitro after 24 hours of incubation** (when cocultured at 5:1 E:T ratio)

In Vivo Efficacy of Eterna's Proprietary Induced-Mesenchymal Stem Cells (iMSCs) in Sepsis-Induced ARDS: Study Rationale & Design*

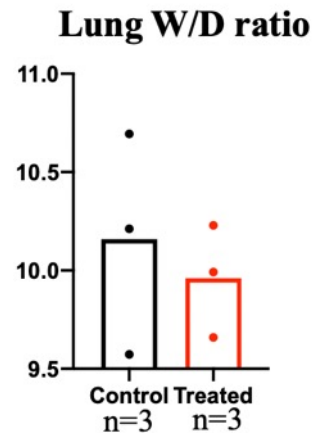
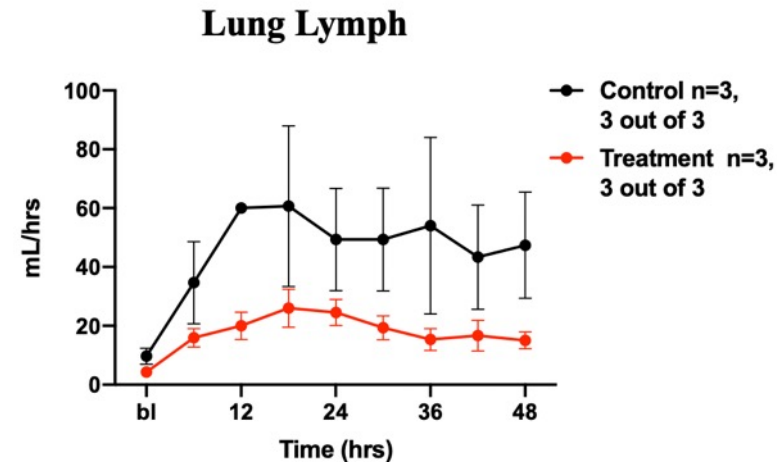
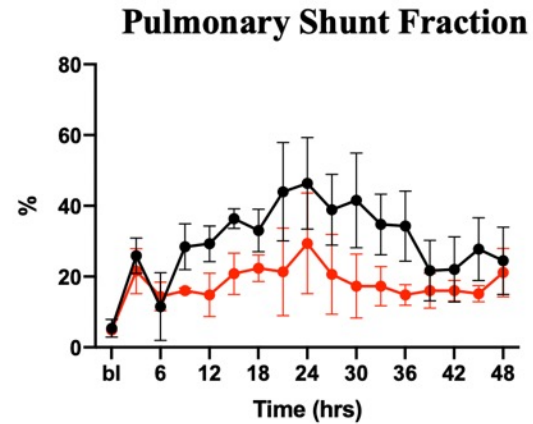
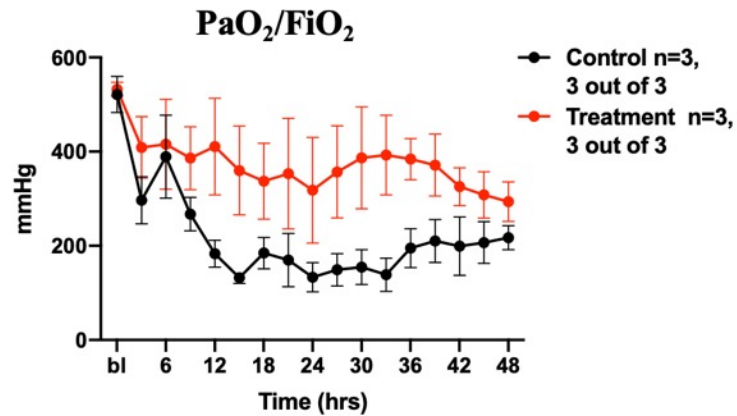


- ❖ Mesenchymal stem cells (MSCs)- target a large number of dysregulated inflammatory cytokines and provide tissue repair and pathogen-clearing capabilities via multimodal mechanisms of action
- ❖ So, a **growing body of evidence supports mesenchymal stem cells (MSCs)-based therapy as a potential treatment for sepsis-induced acute respiratory distress syndrome (ARDS)**
- ❖ A sheep model for pneumonia/sepsis was developed by the instillation of *Pseudomonas aeruginosa* into the lungs



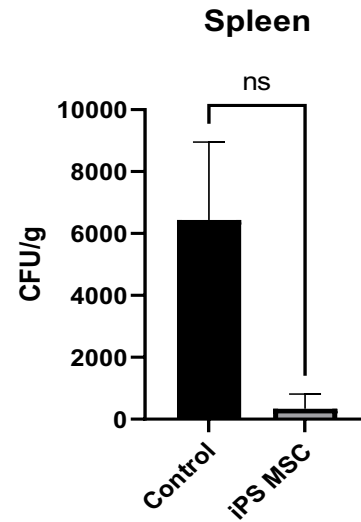
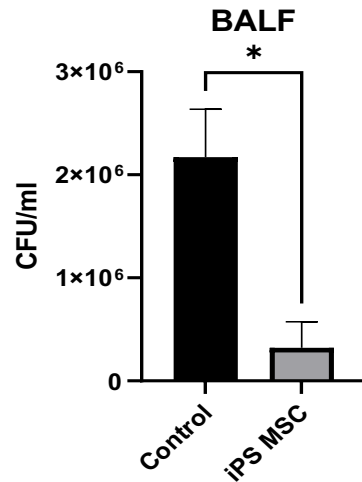
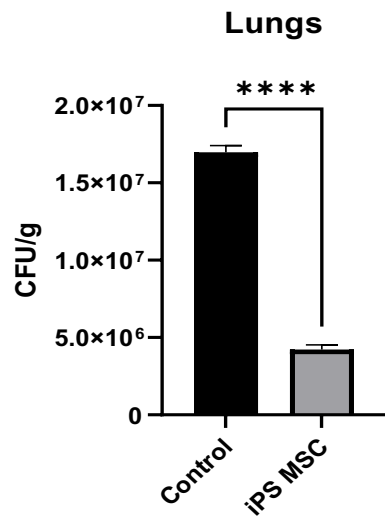
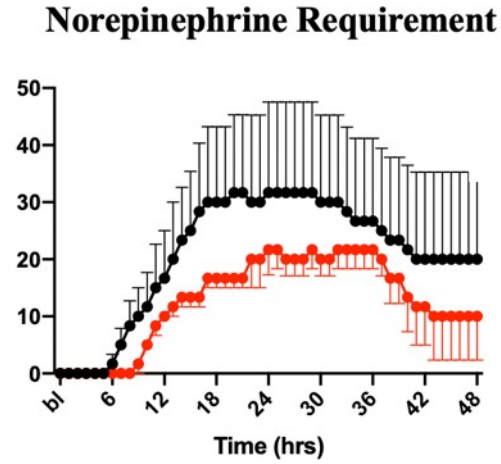
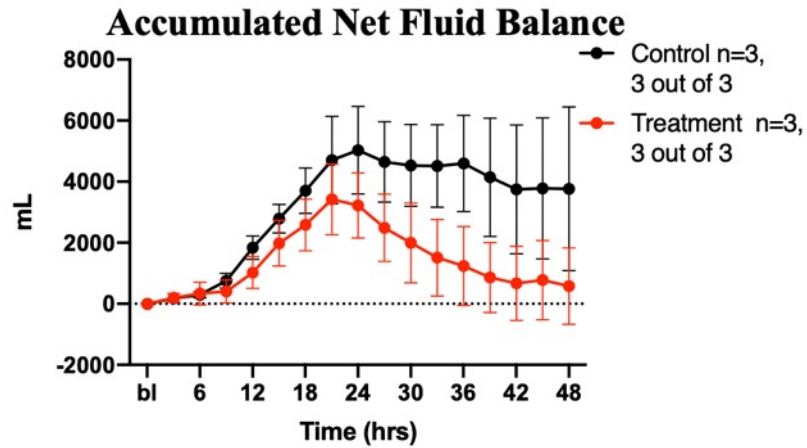
- ❖ **iPSCs generated from adult human fibroblasts were differentiated into Induced-Mesenchymal Stem Cells (i-MSCs) by Eterna's proprietary cell reprogramming technology**
- ❖ **Two groups of sheep (n=3 in each) were randomized either to intravenous allogenic iMSCs treatment at 1 and 24hrs after the injury or intravenous vehicle treatment**

In Vivo Efficacy of Eterna's Proprietary Induced-Mesenchymal Stem Cells (iMSCs) in Sepsis-Induced ARDS: Study Result* (1/2)



- ❖ Native iMSCs reduced pulmonary shunt and improved oxygenation, thus preventing onset of ARDS
- ❖ Native iMSCs markedly reduced pulmonary edema assessed by measuring lung lymph flow and lung wet-to-dry weight ratio. These data indicate that the native iMSCs reduced pulmonary microvascular hyperpermeability to water

In Vivo Efficacy of Eterna's Proprietary Induced-Mesenchymal Stem Cells (iMSCs) in Sepsis-Induced ARDS: Study Result (2/2)



- ❖ Native iMSCs markedly **reduced excess fluid requirement**, supporting that iMSCs are safe to use in this model
- ❖ Native iMSCs **reduced vasopressor (norepinephrine) requirement**
- ❖ Native iMSCs significantly **reduced the bacterial burden in the ovine lungs, bronchoalveolar lavage fluid, and spleen**

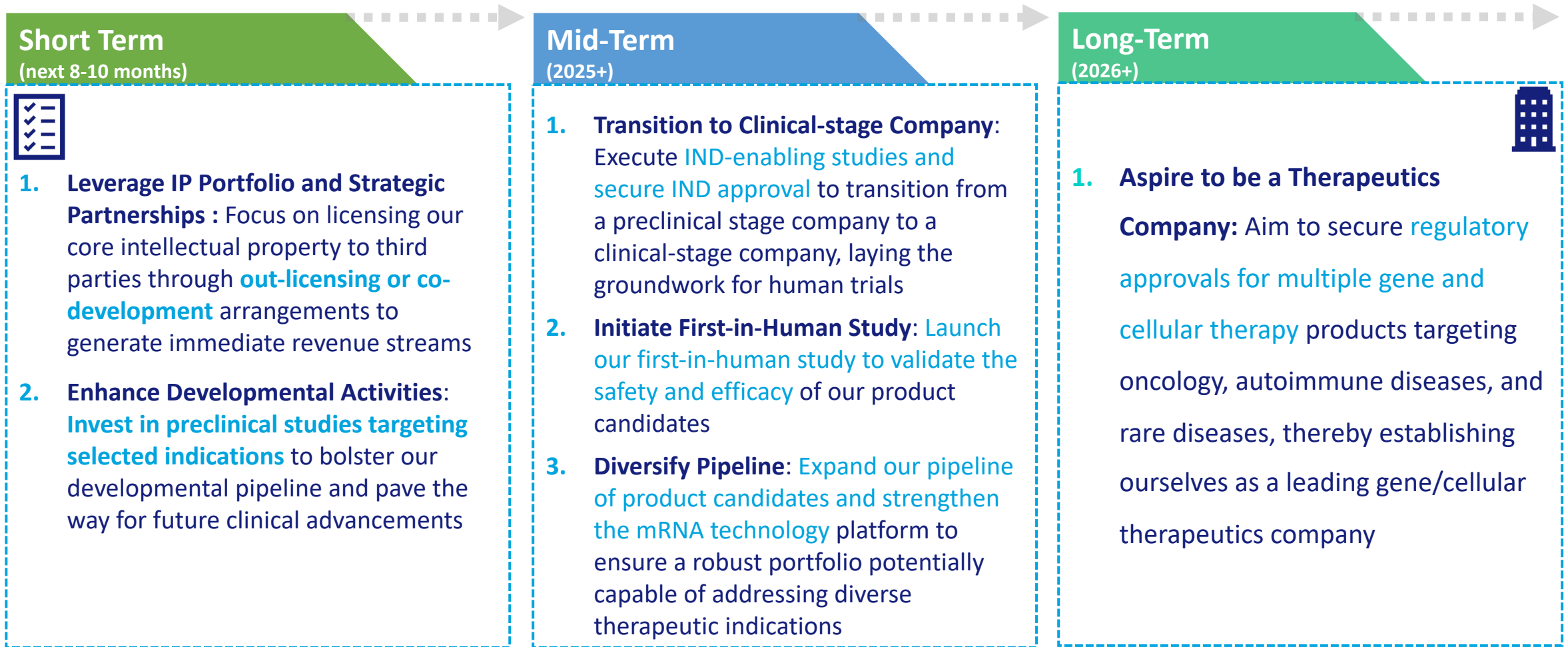


Eterna's Strategy

Our Strategy



We believe that our proprietary technology platform can be used to develop novel pharmaceutical products to treat a broad range of diseases and address unmet medical needs





Key Takeaway

Key Takeaway: In-licensing Opportunity of Eterna's Technology with Strong IP & Scientific Rationale



Our Science



- ❖ Novel **non-viral vectors-based** approach to mRNA cell reprogramming and gene therapy designed for **rapid, high-efficiency, footprint-free** cell reprogramming and gene therapy
- ❖ Exhibited **sustained expression of transgene** over multiple passages and even after long-term cryopreservation
- ❖ **Immuno-nonreactive or “stealth” cells** with the potential to be used as **allogeneic “off the shelf” therapy**
- ❖ Potentially capable of delivering nucleic acids to cells **both ex vivo and in vivo**
- ❖ Potentially capable of inserting exogenous sequences into genomic **safe-harbor loci**
- ❖ Can deliver mRNA to the **brain, eye, skin, and lung in vivo**
- ❖ **Strong preclinical evidence supporting therapies for multiple indications**

Strong IP



Portfolio of over **100 patents** covering key mRNA cell engineering technologies and protected until **2032 and beyond** across the **U.S., Canada, Brazil, Mexico, EU, Russia, Australia, and major markets of Asia**

Management



Management with **extensive experience in the discovery and development of gene /cellular therapy products**



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