



*A platform company in cell,  
gene-editing & cytokine therapies*

# mRNA Engineered Cell & Genetic Medicines



January 2022

# Disclaimer



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# BTX is Led by a Strong, Experienced Management Team



**Howard Federoff**  
**MD, PhD**  
Chief Executive Officer and President



**Kevin D'Amour**  
**PhD**  
Chief Scientific Officer



**Roger Sidhu**  
**MD**  
Chief Medical Officer



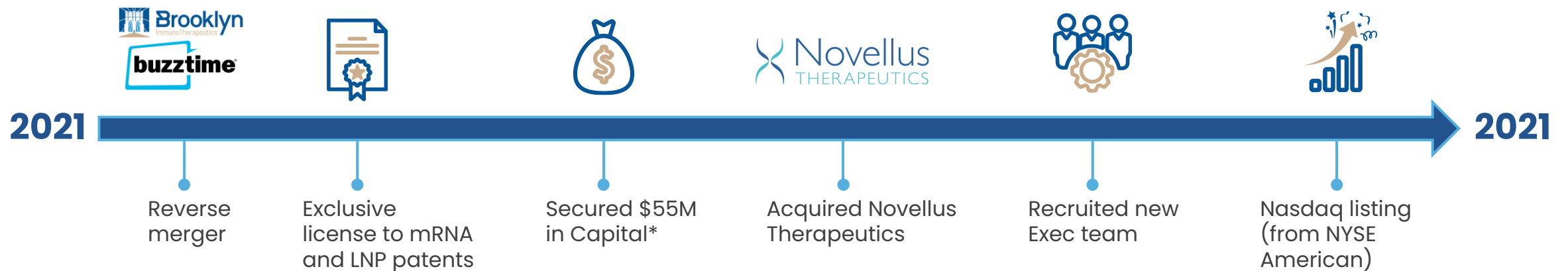
**Jay Sial**  
**MBA**  
Chief Administrative Officer



**Sandra Gurrola**  
**VP of Finance**



# BTX Transforms into Regenerative Medicine Company with Platform Technology



*\* Runway into 2023*

# Leveraging In-licensed Patent Portfolio to Advance Medicine



- BTX has an exclusive license from Factor Bioscience to a portfolio of granted patents around mRNA-based cell engineering that will provide a competitive advantage
- Major platform components:
  - mRNA Cell Reprogramming (25 patents, extensive cellular data)
  - mRNA Gene Editing (15 patents, extensive cellular data)
  - NoveSlice™ Gene-Editing Protein (15 patents, extensive cellular data)
  - ToRNAdo™ mRNA Delivery (4 patents, extensive cell and animal data)

*NoveSlice™ and ToRNAdo™ are trademarks of Factor Bioscience Limited.*

# BTX has a Broad Technology Landscape



**mRNA  
therapeutics**

**In Vivo  
gene editing**

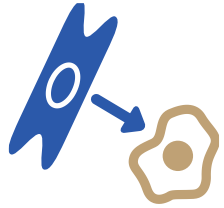
**Non-viral  
genetic  
medicines**

**iPSC-derived  
therapies**



*Footnote: doesn't represent ex vivo gene editing space*

# BTX's Licensed mRNA-Based and LNP Technologies

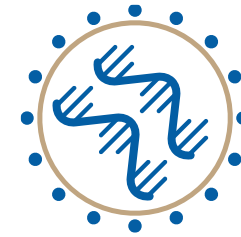


Cell reprogramming



Gene editing

*mRNA and LNP are tools  
to make engineered cell medicine*

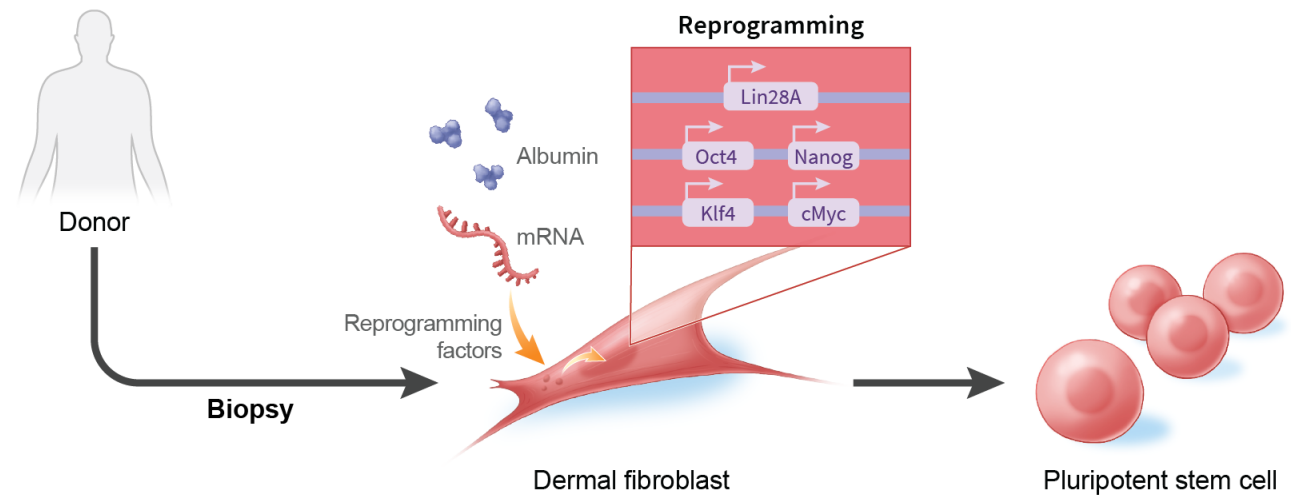


Nucleic acid delivery

*mRNA and LNP are the drug  
as in vivo gene-editing medicine*

# The Foundational mRNA Cell Reprogramming Platform

- Highest efficiency generation of iPSC:
  - 5 factors, rapid protein expression
  - Low toxicity, high percentage transfected
  - Custom reprogramming media
- Safe: no chance of genome integration
- Can combine reprogramming with gene editing to streamline autologous therapies in genetic disease
- Extensive in-licensed patent protection

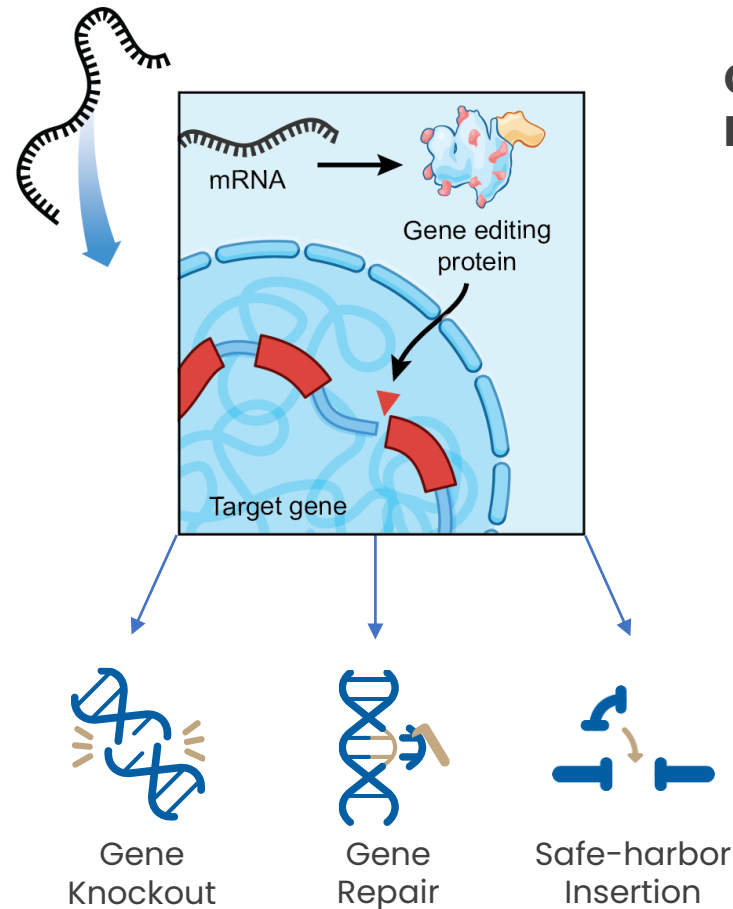




# Unique mRNA-Based Delivery of a Novel Gene Editing Platform

## Use of mRNA for Delivering Gene - Editing Proteins

- Rapid, high expression (efficiency)
- Transient expression (specificity)
- Amenable to non-viral delivery
- No risk of vector insertion
- Multiple in-licensed patents cover mRNA encoding CRISPR, TALEN, ZFN, etc



## Chromatin Context-Sensitive Gene Editing Endonuclease

- Novel nuclease (clear IP landscape)
- High specificity (36-40 base site)
- Blocked by histone modifications (specificity)
- Unlimited genomic sites (no PAM)

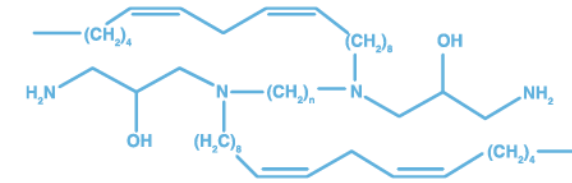
# Novel Lipid with Effective mRNA Delivery In Vitro and In Vivo

## Novel, single lipid component LNP

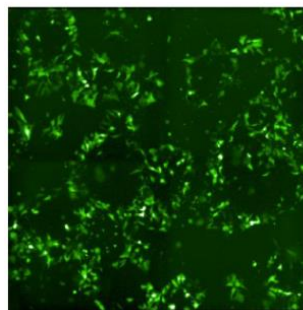
- Novel lipid, composition of matter IP
- Low toxicity enables repeated transfection
- Cargo delivery directly to cytosol without processing via endosomal pathway
- Efficient transfection in context of serum
- Transfection of many cell types demonstrated

U.S. Pat. No. 10,501,404

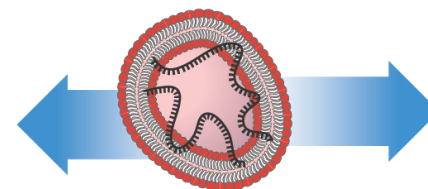
A compound of Formula (I)



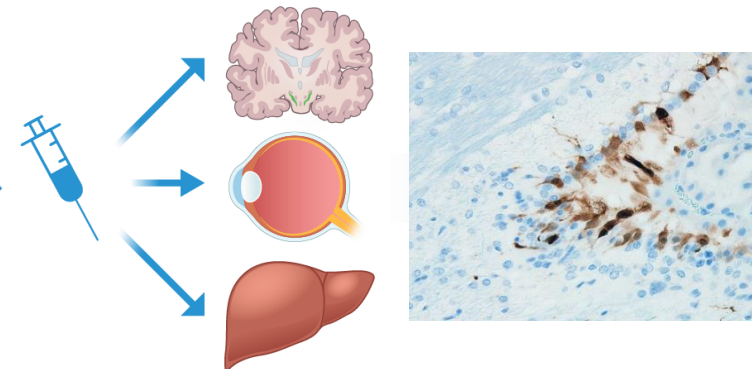
Wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15.



iPS cells



ToRNAdo™  
with mRNA



# Platform Technology Deployed in Four Regenerative Medicine Pillars

## Pillar I



### **Allogeneic Stem Cell Platform (iMSC)**

- ARDS
- Bone marrow transplant failure/poor function
- Solid tumors

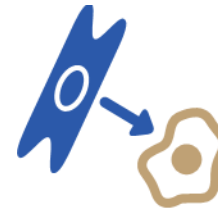
## Pillar II



### **Autologous, Gene Edited Platform**

- Hemoglobinopathies
- Opportunities in many genetic diseases

## Pillar III



### **Autologous iPSC Platform**

- Paroxysmal nocturnal hemoglobinuria
- Partnership opportunities

## Pillar IV



### **In Vivo Gene Editing Platform**

- Transthyretin amyloidosis
- Stargardt disease
- Non-syndromic hearing loss
- Opportunities in many genetic diseases

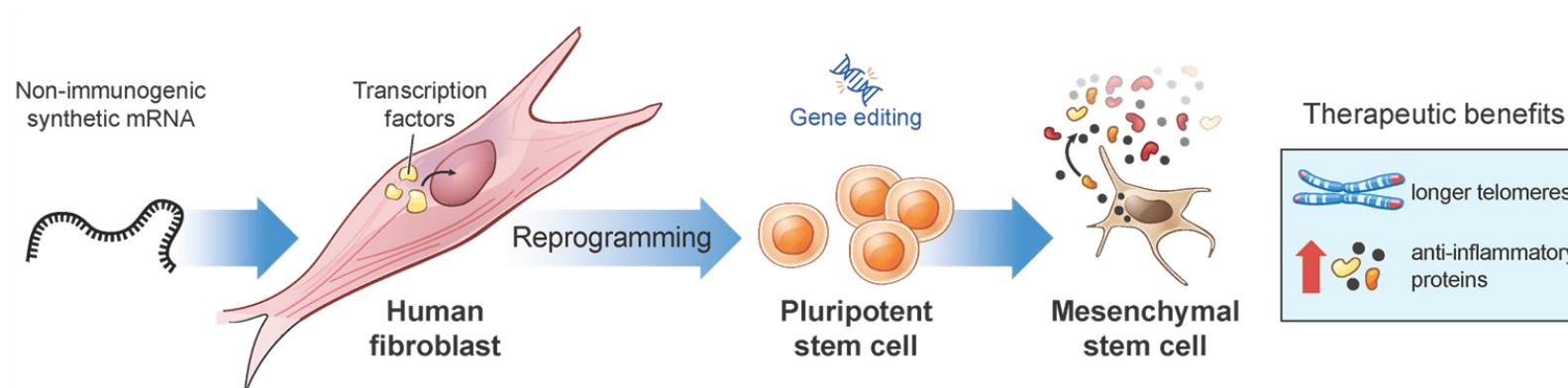
# Allogeneic iMSC Therapies

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# Allogeneic iMSC Product Platform

## iPSC-derived Mesenchymal Stem Cells (iMSC)

- Low risk of toxicity, proven across many clinical studies
- Low immunogenicity, no need for immunosuppressive drugs
- Leveraging decades of work with MSC process development and manufacturing
- A single Drug Product can be used across multiple and varied indications
- iPSC can be gene edited to program the iMSC with additional properties, expanding indications
- MSC therapies have had inconsistent clinical efficacy due to product heterogeneity



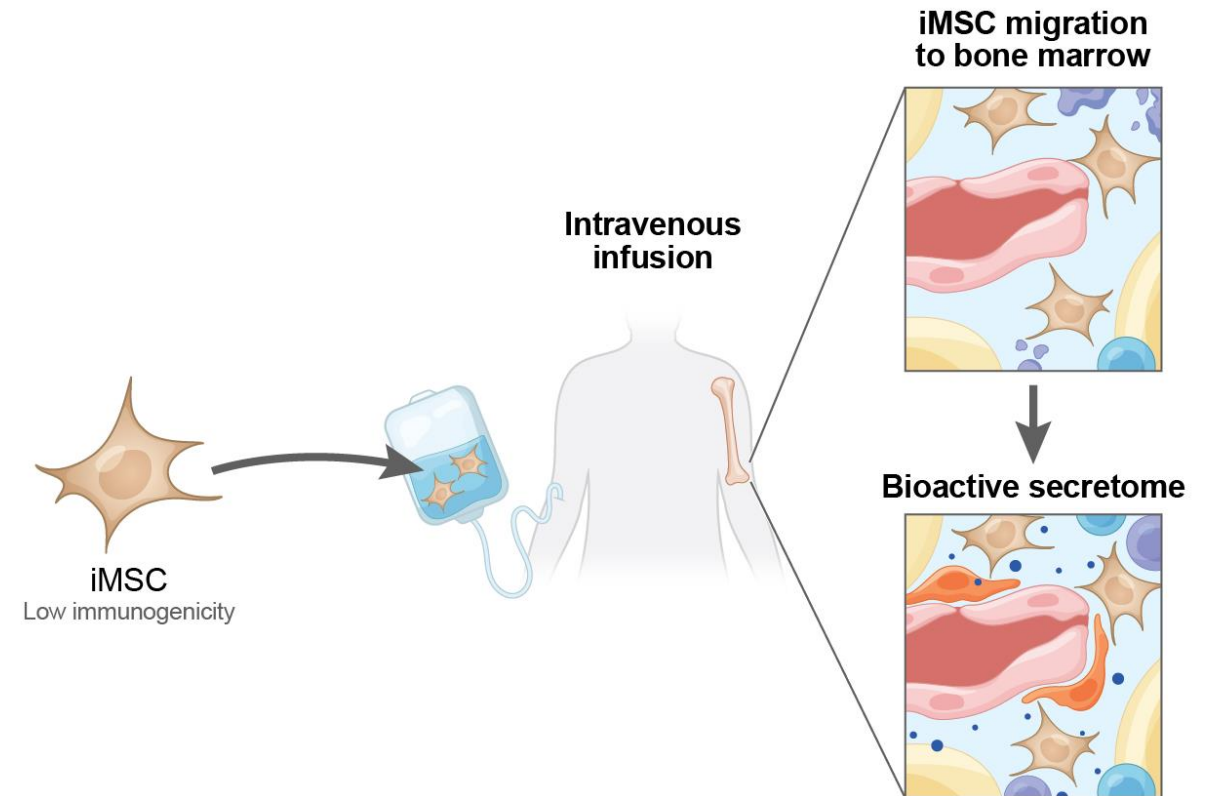
# Brooklyn's iMSC Address Issues with Tissue-derived MSC



Historical Issues with MSC field	Tissue-derived MSC	Brooklyn's iMSC
Donor to donor variability	✗	✓
Tissue source variability	✗	✓
Manufacturing variability	✗	✓
Limited or inconsistent characterization	✗	✓
Poor mechanistic understanding	✗	✓
Capacity to precisely genetically modify	✗	✓

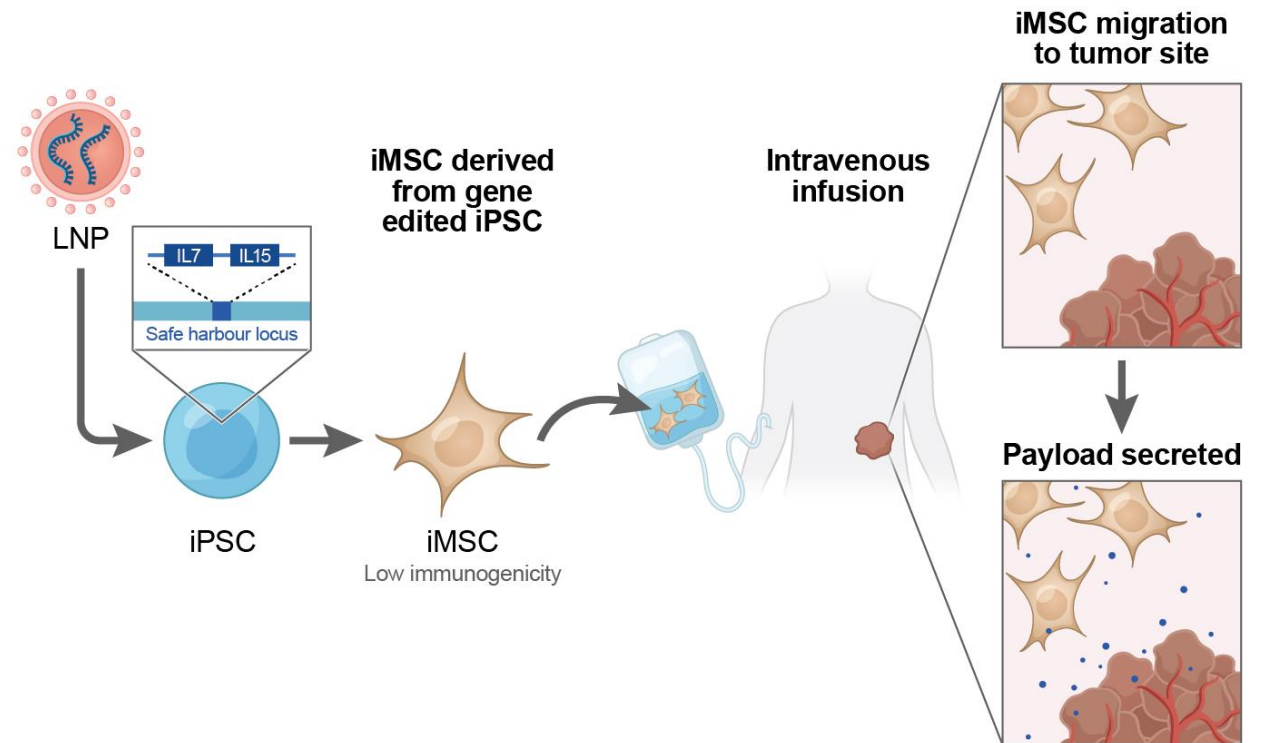
# iMSC Application in Graft Failure/Poor Graft Function

- MSCs modulate immunological responses, support hematopoiesis, and repair bone marrow stroma
- Clinical applications in hematopoietic stem cell transplant (HSCT)
  - Treating engraftment failure or poor graft function
  - Promoting HSC engraftment
- Working with world class KOLs in HSCT to focus on best clinical population(s) and trial design
- Anticipate FIH in 4Q-2023



# Developing a Family of Gene-edited iMSC Products To Address High Unmet Need Solid Tumors

- Gene-editing iPSC and thorough characterization; followed by differentiation to iMSC
- Multiple engineered iMSC products to deliver agents locally and avoid systemic toxicities
  - IL-7 & IL-15 drive expansion and engraftment
- Combination with CAR-T and checkpoint inhibitors



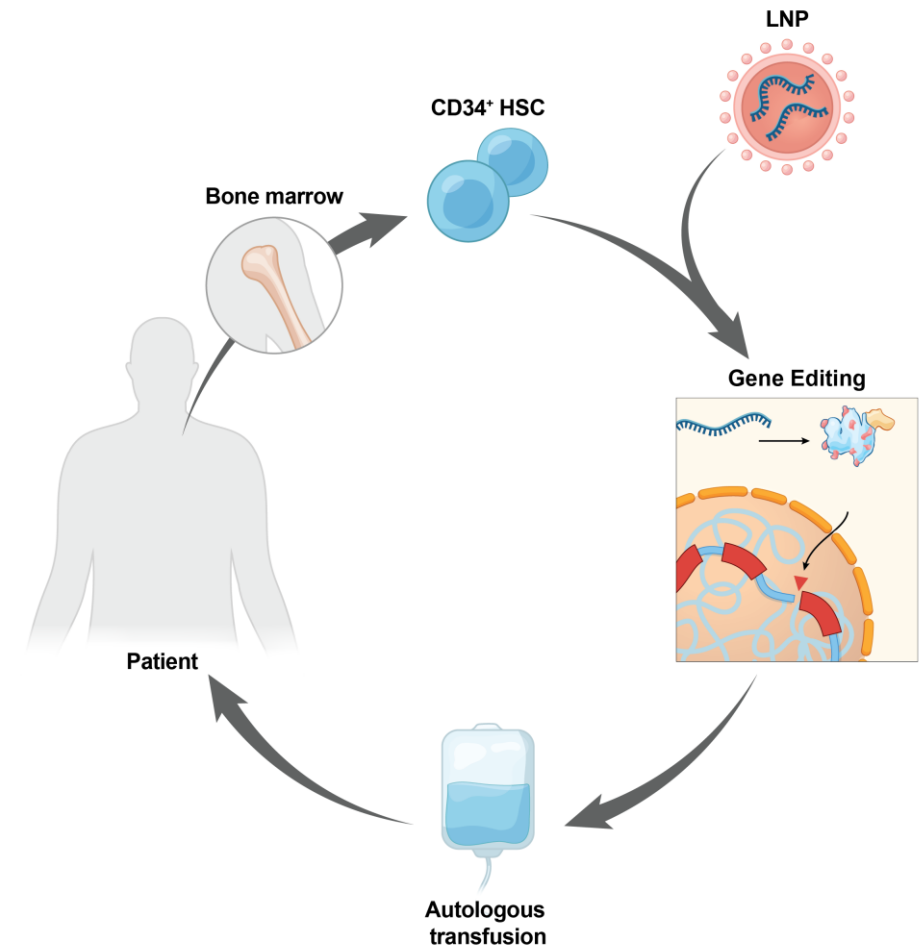


# Autologous Cell Therapies

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# Autologous Cell Therapy, Efficient mRNA Gene Editing

- Autologous HSC-based gene therapy for many addressable indications
  - Hemoglobinopathies
  - Primary immunodeficiencies
  - Congenital cytopenias
- Leverages 30 years of clinical experience and isolation techniques for CD34+ HSC; robust engraftment and safety
- mRNA-based gene editing is less complex than viral methods, safer than integrating viral vectors
- Future partnering possibilities



# Autologous iPSC Therapies

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# Autologous iPSC Cell Therapy Platform



## **Licensed technology is the safest, most efficient, and fastest method for iPSC derivation**

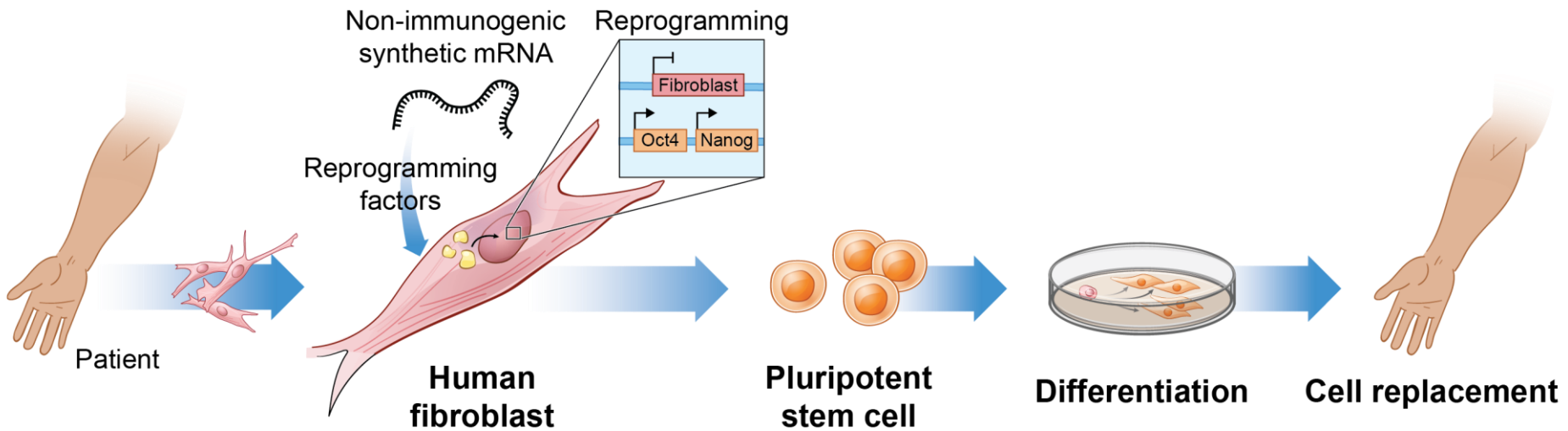
- Safe: Non-integrating method using synthetic mRNA to produce reprogramming factors
- Efficient: Uses LNP for repeated in vitro delivery with low toxicity
- Efficient: Can combine reprogramming and gene editing in single step derivation
- Fast: Reprogramming and iPSC colony formation within 2 weeks

## **The safety, reliability and speed enable autologous iPSC programs**

- Efficiency of reprogramming permits low quantity of cells from biopsy and simultaneous correction of gene defects
- Can quickly produce multiple iPSC clones per patient
- Absence of genome integration facilitates screening to identify and characterize a safe clone

# Autologous cells from iPSC

- Autologous iPSC / Gene-modified autologous iPSC for:
  - Paroxysmal nocturnal hemoglobinuria (*PIG1A*) – no gene editing required
  - Infectious disease (*CCR5*)
  - Monogenic diseases

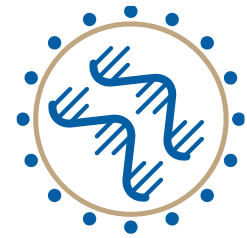


# In Vivo Gene Editing Therapies

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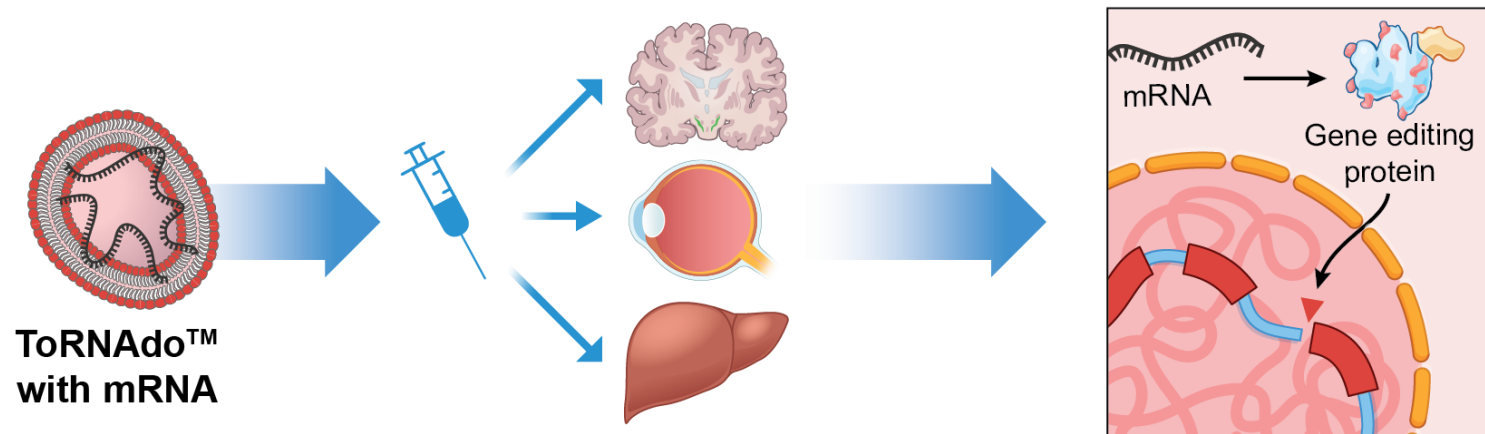
# Genetic Medicine Product Platform

- **Proprietary lipid nanoparticle** for nucleic acid delivery
  - Novel lipid with composition of matter IP
  - Properties can be tuned to target different cell types and tissues
  - Can deliver RNA or DNA; facilitates gene correction approaches
- 
- **Proprietary site-specific nuclease** delivered using mRNA
  - Can target any gene through design of protein binding domains
  - High specificity to target genomic site
  - Achieves high level but transient expression, enhancing safety



# Developing In Vivo Gene-editing Products Addressing Rare Disease Indications (Orphan Designation)

- Direct gene editing in the liver, brain or eye for monogenic disorders
- Ability to knock-out or correct the target gene
- Initial gene target is knock-out of *TTR* for Familial Transthyretin Amyloidosis (ATTR)

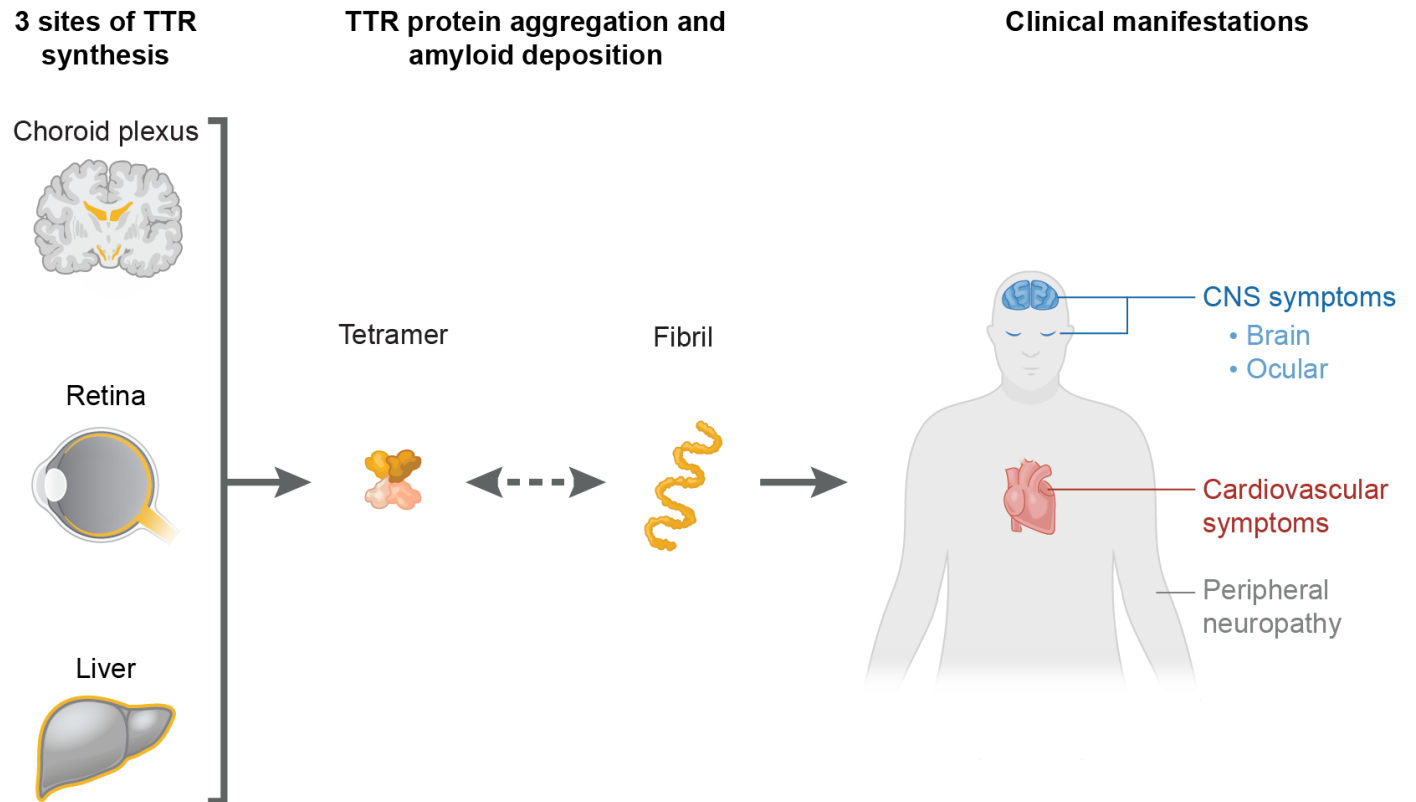


*ToRNAado™ is a trademark of Factor Bioscience Inc.*















# Amyloidosis Caused by Transthyretin (ATTR)

- Caused by misfolded transthyretin aggregating into toxic oligomeric forms
- Death 5-15 years after onset of symptoms is typical
- Non-Familial (200,000-500,000 worldwide)
  - Owing to tissue deposition of normal TTR amyloid
  - Common clinical feature is peripheral neuropathy
- Familial (~50,000 worldwide): BTX Focus
  - Autosomal dominant
  - Owing to mutations in *TTR* (>140)
  - Mutations increase amyloidogenic property



# BTX In Vivo Editing Addresses all ATTR Manifestations

	Polyneuropathy 	Cardiomyopathy 	Retinopathy 	Cognitive deficits 
Subtype	Observed across subtypes ( <u>except leptomeningeal</u> )	Observed across subtypes ( <u>except leptomeningeal</u> )	Chiefly leptomeningeal subtype	Restricted mutations + observed across subtypes
Epidemiology	Most common, hATTR and senile (WT) disease	25% of ATTR population over age 80	Rare restricted mutations; small other subsets	Rare restricted mutations; small other subsets
Approved/ R&D synthesis inhibitors siRNA, ASO, CRISPR	 IV/SC (hepatocytes)	 IV/SC (hepatocytes)		
<b>BTX: in vivo gene editing</b>	 IV (hepatocytes)	 IV (hepatocytes)	 <b>Subretinal injection</b> (Retinal Pigment Epithelium)	 <b>Intracisternal injection</b> (Choroid Plexus)

*BTX can treat all known ATTR regardless of mutation*

# BTX Cell Therapy and Gene-Editing Pipeline Summary

Indication	Gene targets	Delivery	Discovery	Preclinical	IND-enabling	Clinical	Comments
iMSC: iPSC-derived mesenchymal stem cells							
ARDS (all etiologies)	n/a	I.V. injection	<div></div>				NoveCite program
BMT/HSCT setting	n/a	I.V. injection	<div></div>				
TBD	n/a	I.V. or local	<div></div>				
Solid tumors	IL7, IL15	I.V	<div></div>				
Oncology	Undisclosed	I.V	<div></div>				
Autologous HSC, gene edited							
Undisclosed	Undisclosed	I.V.	<div></div>				
Autologous iPSC-derived cell therapy							
PNH	PIG1A	I.V.	<div></div>				
In vivo gene editing							
Transthyretin Amyloidosis	TTR	IV, CNS, retina	<div></div>				
Stargardt Disease	ABCA4	Retina	<div></div>				

# BTX Will Leverage Best In Class mRNA-based Technologies to Deliver Transformative Regenerative Medicines



- Exclusive license to foundational mRNA & gene editing IP



- Diversified product strategy for multiple clinical applications



- Experienced management team with deep expertise in C&GT



- Strong partnership for translational execution and future innovation



- In-licensed patent portfolio offers sub-licensing opportunities



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