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# Cell Therapies that cure

October 2022 (TASE: KDST)

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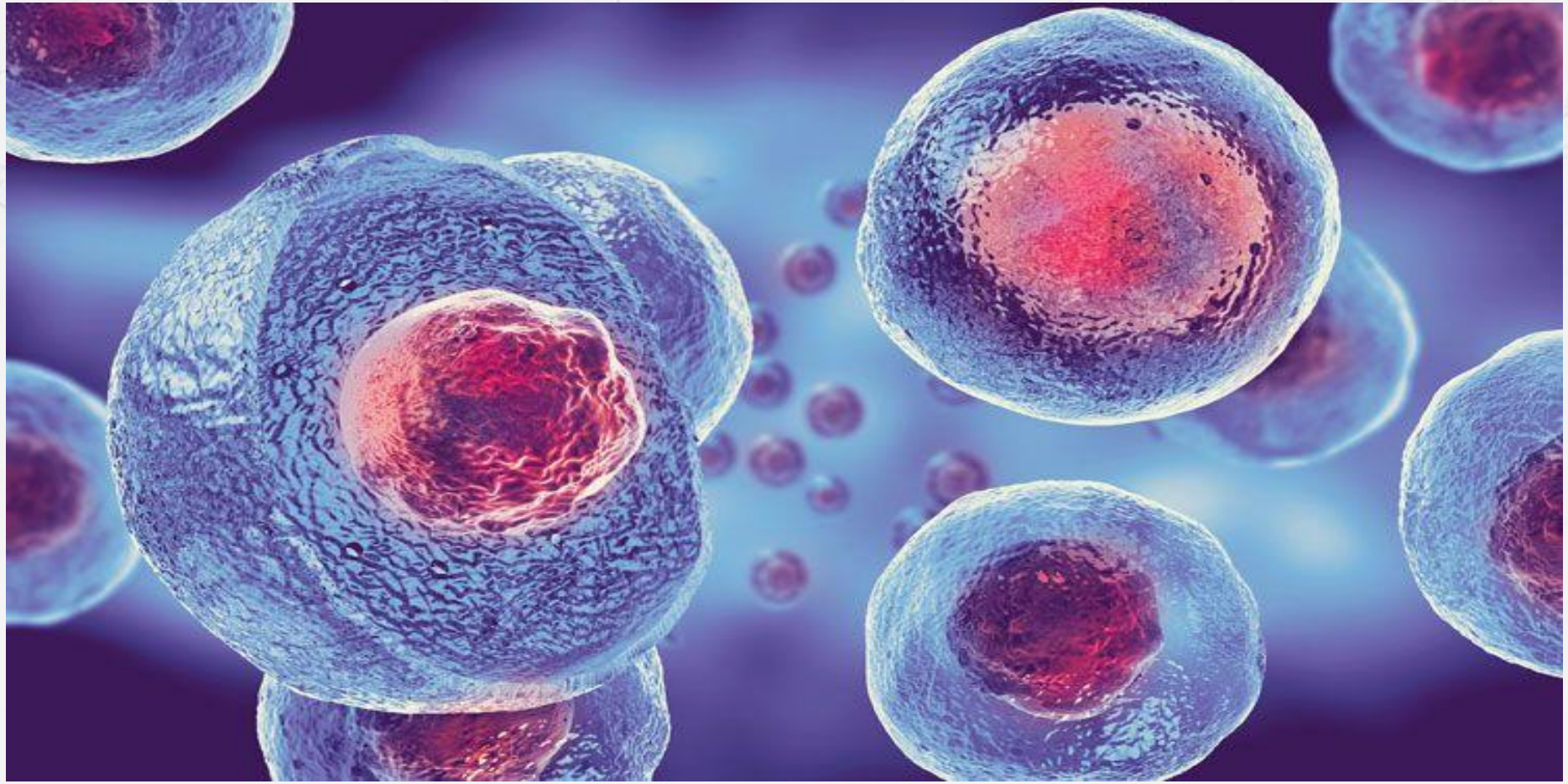
# **Kadimastem** – Stem Cell Derived Cell Therapy



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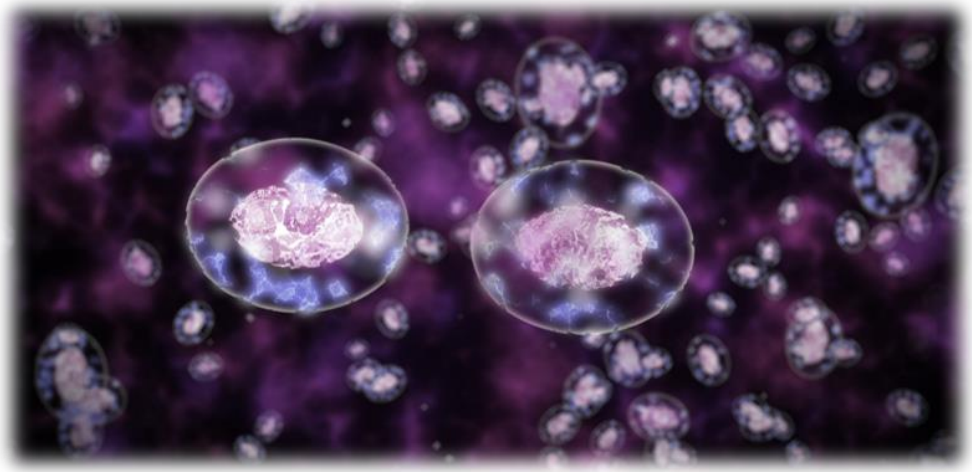
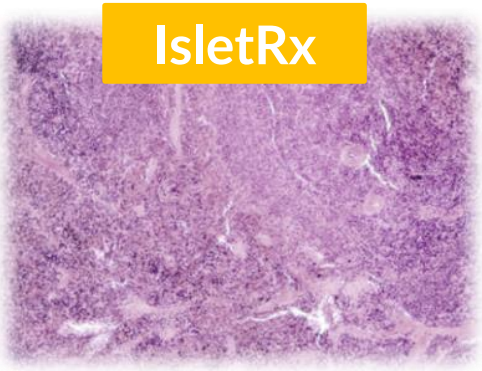
# Vision – Stem Cell Derived Cell Therapy

Replace, restore and repair the functionality of diseased and malfunctioning cells in various degenerative diseases by transplantation of our healthy and functional cells

**Developing proprietary cell lines optimized for the cure of Diabetes and to treat ALS**



GFAP/GLAST/DAPI




C-peptide/Glucagon/DAPI

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# Leadership

## Bringing extensive business, industry, and scientific experience

**Prof. Michel Revel**
Founder, Director & CSO

- Developed Merck's blockbuster drug REBIF® for multiple sclerosis ($1.7B USD in sales in 2016)
- Professor Emeritus of molecular genetics at the Weizmann Institute of Science
- More than 40 years of experience in development and global commercialization of advanced biotechnological products
- Awarded Laureate of Israel Prize for Medicine in 1999 and EMET Prize for Science in 2004

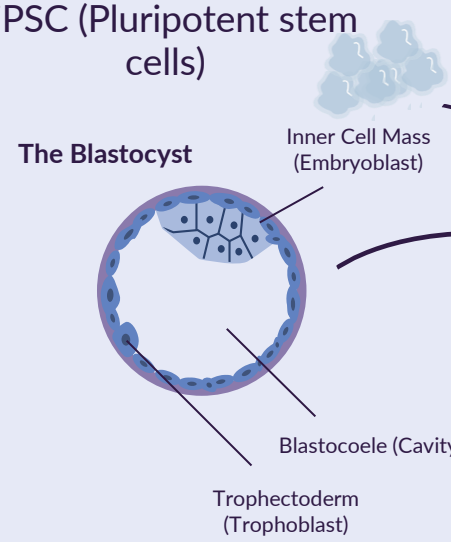
**Asaf Shiloni**
CEO

- More than 20 years of biotech executive experience and a deep knowledge of the cell therapy industry
- Mr. Shiloni served as Vice President Sales and Business development at PeproTech for 13 years, there he established collaborations and joint ventures with top US stem cell companies and leading research labs worldwide as well as led M&A processes.
- Company sold in 2021 for $1.85B.
- Prior to PeproTech, in 2007, Mr. Shiloni sold an Israeli biotech company CytoLab, that he co-founded and led for seven years
- Mr. Shiloni holds an MBA from Tel Aviv University

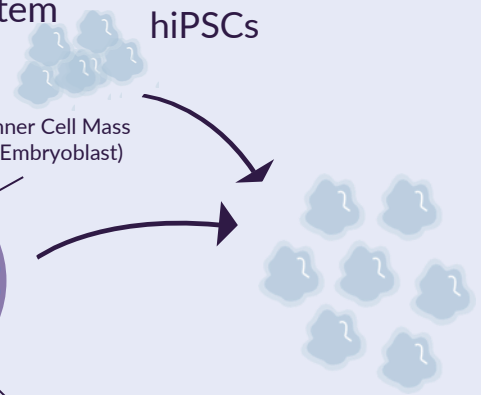
# Proprietary Innovative Platform

## Proprietary expansion and differentiation processes of cells intended for treatment of multiple diseases

**Starting material**
clinical grade human embryonic stem cells or hiPSC (Pluripotent stem cells)

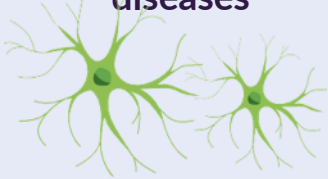


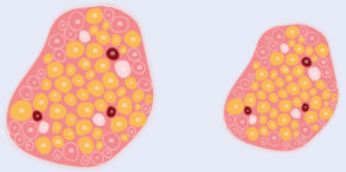

**Expansion**
Expand indefinitely

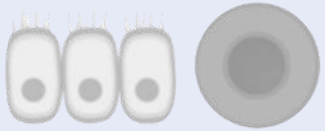



**Differentiation**
Committed progenitor cells

**Mature and functional target cells**
**treatment of a wide range of diseases**







| Cell product | Indication | |
|---|---|---|
| AstroRx® | ALS | Clinical Stage |
| | Additional neurological indication | |
| IsletRx | Insulin dependent diabetes | Pre-clinical Stage |

**Technology platform to allow for differentiation into different cell types**

# Product Platform Pipeline

CLINICAL

| | RESEARCH | PRE-CLINICAL | PHASE 1 | PHASE 2 | PHASE 3 | Market |
|---|---|---|---|---|---|---|

**AstroRx® cell Product**

**Neurology**

- ALS - demonstrated encouraging results in the clinical trial
- Multiple Sclerosis
- Other NDD indications
- Other NDD

NDD = Neurodegenerative Diseases

- ✓ Orphan drug designation (FDA)
- ✓ Completed Phase I/IIa (Israel)

Next:

- Q4 2022 - IND with the FDA for advanced clinical trial
- 2023 - Clinical Trial in the USA

**IsletRx Cell Product**

**Diabetes (Insulin dependent)**

- 1st Generation - Microencapsulation
- 2nd Generation - - Macroencapsulation

- ✓ Patented sorting and purification technology
- ✓ INTERACT with the FDA

Next:

- Macro encapsulation through collaborations.
- Implement New technologies.

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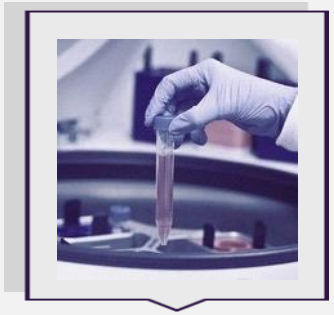
# History: Kadimastem's Way Forward

**2009**

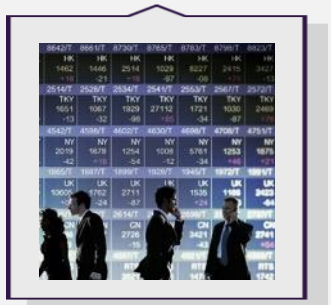
Company Founding

**2012**

Development of AstroRx from ESCs



**2013**



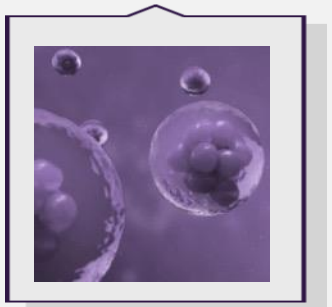
Public Company TASE

**2015**

Pre-IND meeting with FDA for Fresh AstroRx Product

Development of IsletRx from ESCs

**2017**



Developing Microencapsulation Technology for IsletRx

**2018**

Pre-Clinical success IsletRx

Develop Frozen AstroRx® product

Commencing phase 1-2a clinical trials for the ALS therapy program

**2021**

**INTERACT Meeting with FDA for IsletRx (Diabetes)**

**New Management New Directors taking Kadimastem forward**

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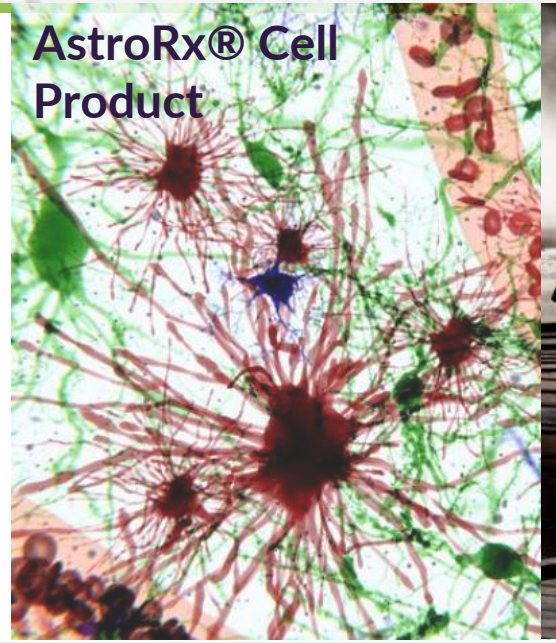
AstroRx ®

# Astrocytes- Cell Therapy Treatment for Neurodegenerative Diseases



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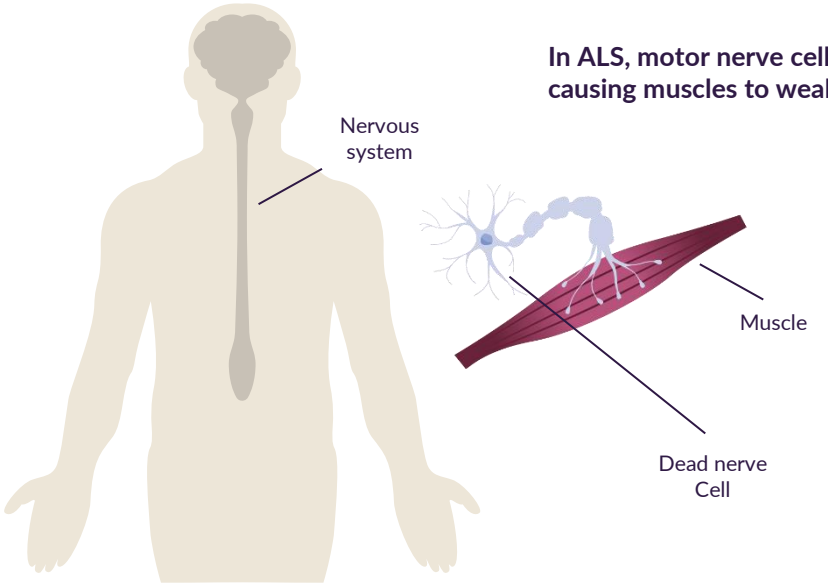
# ALS– Market and Facts

- Death of motor neurons
- Progressive loss of muscle control leads to eventual death
- 90-95% sporadic and 5-10% familial (C9orf72, hSOD1, TDP-43, FUS)
- Disease onset 45-65 years, survival from onset 2-5 years




- Current FDA approved treatments are Rilutek & Radicava with modest effect

- Around **500,000**[1] ALS patients estimated worldwide, **30,000** patients in the US[2]
- **ALS Annual drug sales:** (US, Canada, France, Germany, Italy, Spain, UK and Japan) [3, 4]

  2019: $282M
  - Estimate 2029: $1.04B
- **US ALS Healthcare costs:**
  - Up to $200K estimated annual medical expenses per patient[4]

1. https://www.massgeneral.org/neurology/als
2. https://www.als.net/als-resources/faq/
3. https://www.globaldata.com/store/report/amyotrophic-lateral-sclerosis-als-opportunity-analysis-and-forecasts-to-2029/
4. https://www.ajmc.com/view/als-managed-care-considerations-

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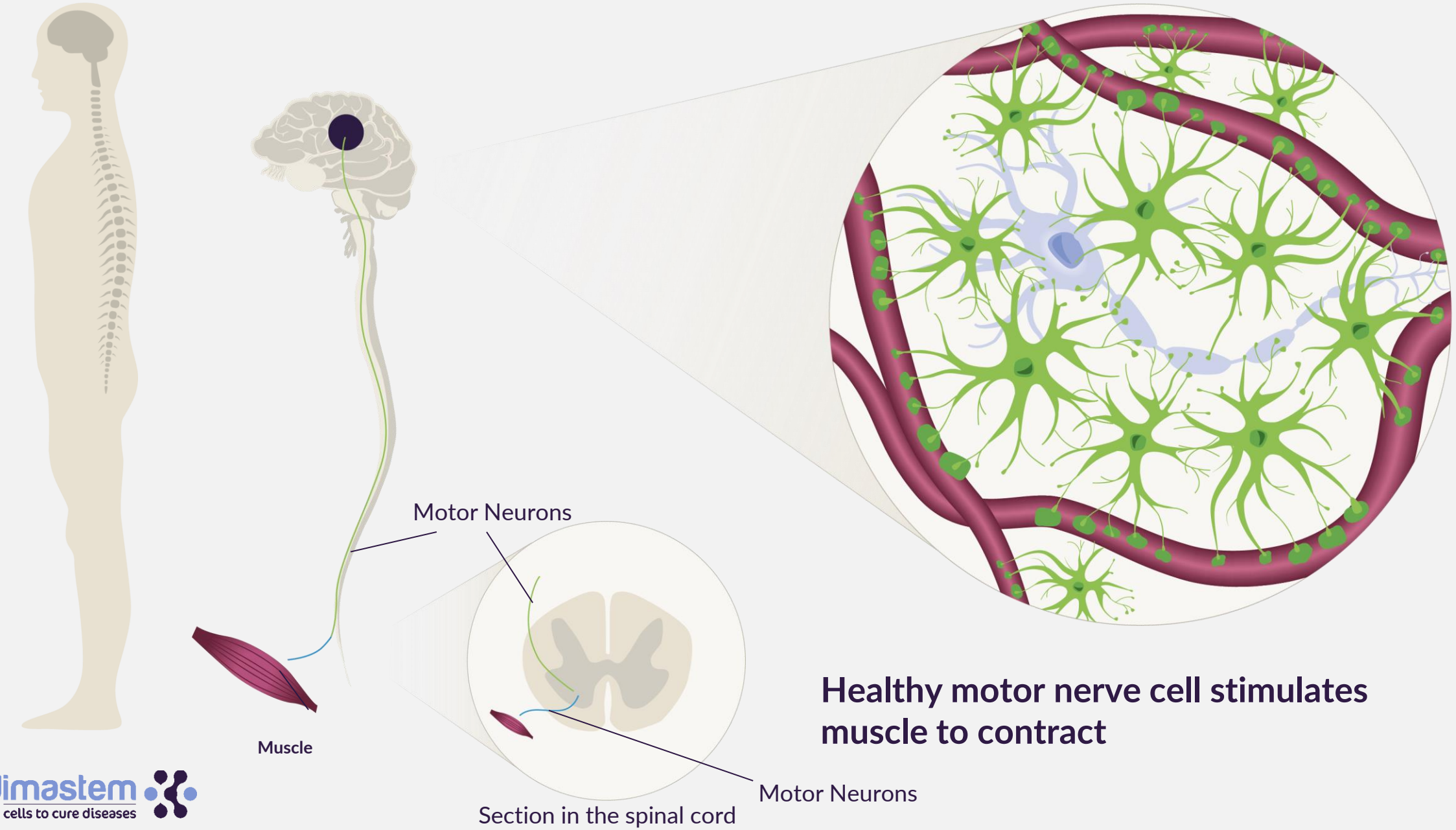
# The Central Nerves System




**Healthy motor nerve cell stimulates muscle to contract**

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# Why Use Astrocytes for ALS - AstroRx®

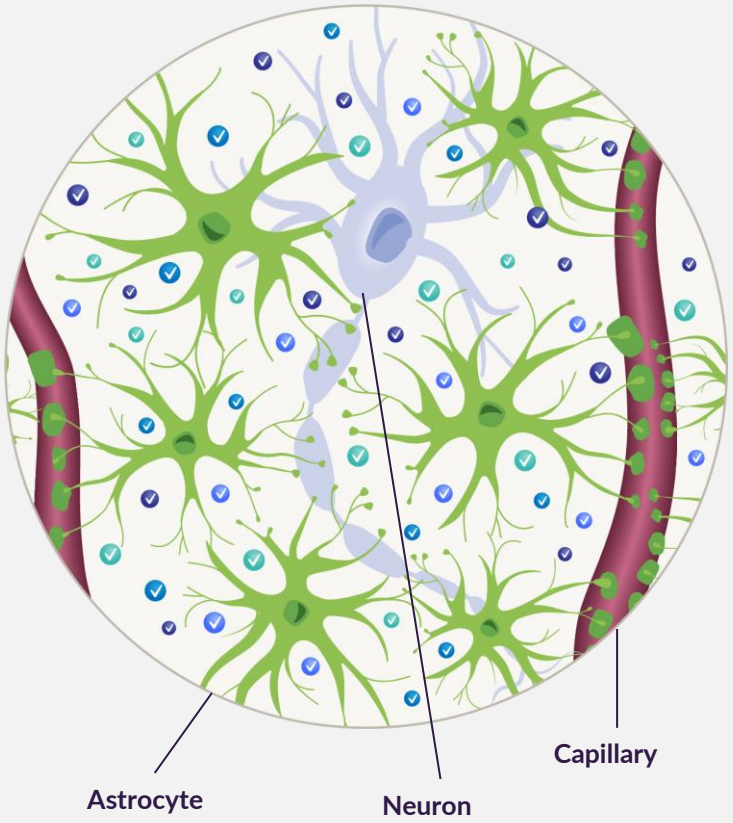
**AstroRx® contains functional healthy astrocytes to protect ALS-diseased motor neurons using multiple mechanisms of action**

| | Mechanism of Action | ALS Patients' Astrocytes | AstroRx® Healthy, Functional Astrocytes |
|---|---|---|---|
| **In ALS, the patient's own astrocytes fail to support motor neuron survival** | Secrete neurotrophic factors [1] | ✗ | ✓ |
| | Remove toxic factors (i.e. glutamate) [1] | ✗ | ✓ |
| | Regulate oxidative stress [1] | ✗ | ✓ |
| | Immune-modulation [2] | ✗ | ✓ |

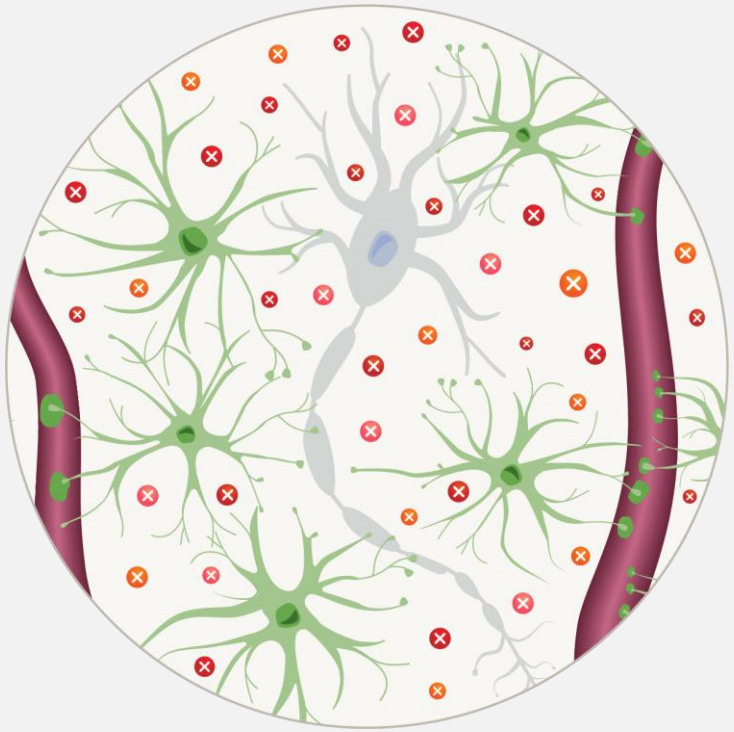

1. Izrael et al, 2020 Front Neurosci. 2020; 14: 824. doi: 10.3389/fnins.2020.00824
2. Izrael et al, 2021 Front Med (Lausanne) 2021; 8: 740071. doi: 10.3389/fmed.2021.740071

# Use Astrocytes for ALS - AstroRx®

Healthy CNS Environment

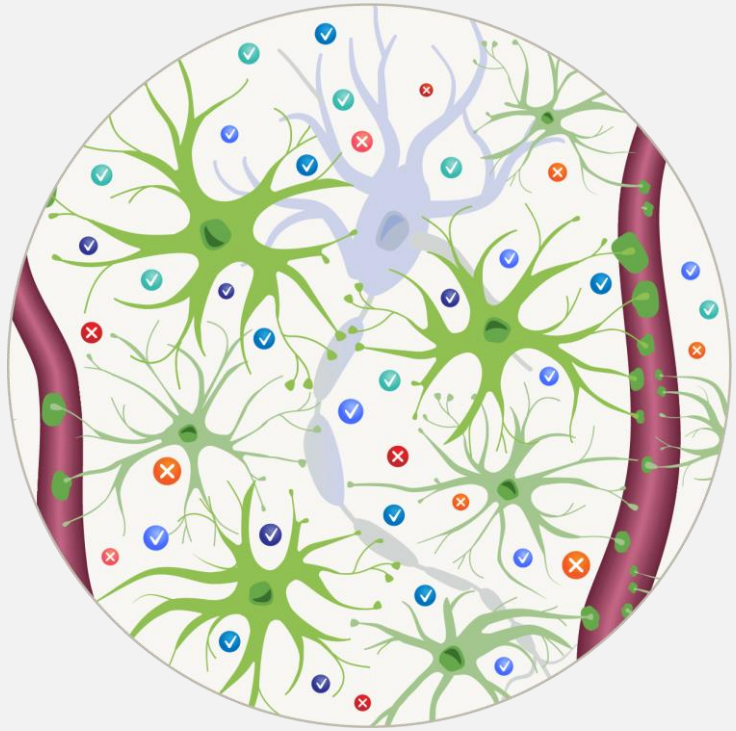



ALS Patients' CNS Environment



Astrocytes malfunction in ALS

Injecting AstroRx®
Healthy, Functional Astrocytes in the CNS



AstroRx® Support motor neurons by secreting neurotrophic factors and clearing toxic environment

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# Effect of AstroRx® on rat SOD1$^{G93A}$ ALS model In Pre-Clinical Trials

**Rat hSOD1 ALS Model:**

Study measurements

- Survival
- Grip strength
- Rotarod (ambulation)
- Muscle weight loss
- Paralysis (neurological score)

**AstroRx® cells were injected at day 50 and 70 of life**

Intrathecal injection of AstroRx®
(Lumbar puncture) between L5-L6
w/o immunosuppression

hSOD1G93A high copy number rat (ALS model)

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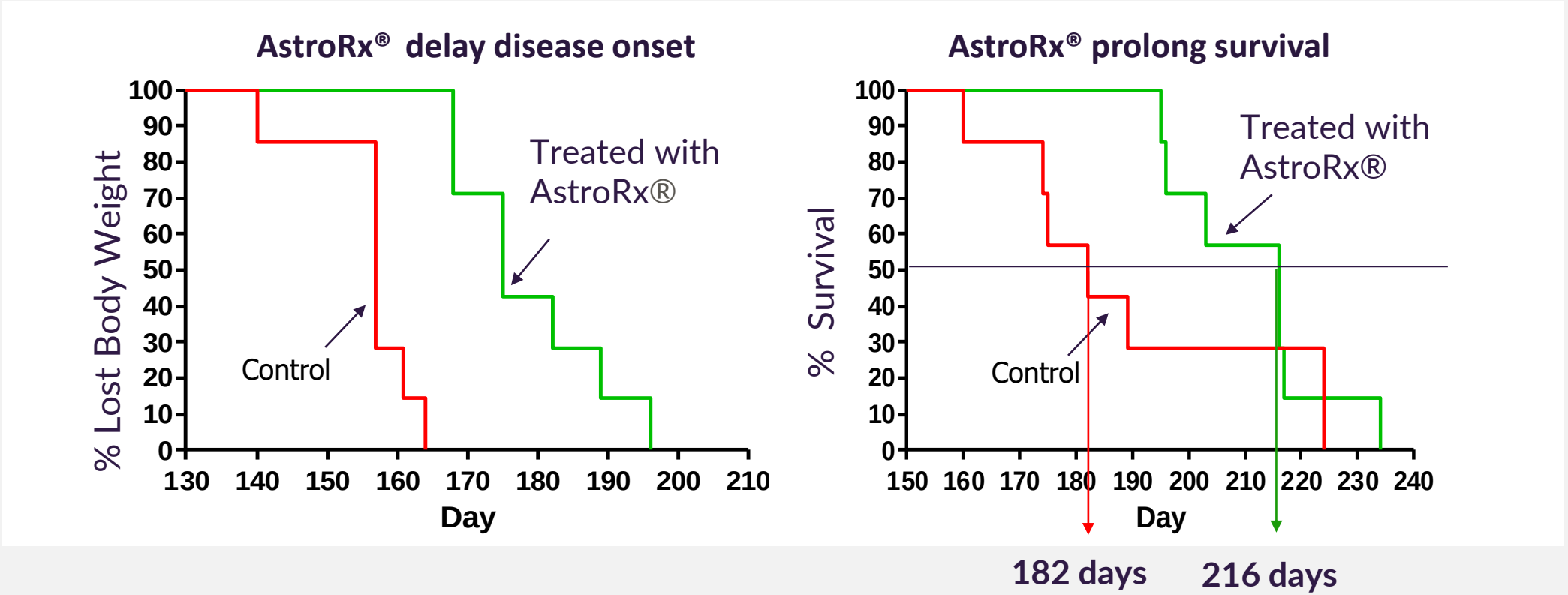
# AstroRx® Prolong Survival of hSOD1 Rats




- Significant delay in disease onset in AstroRx® treated rats (P=0.0001)
- Prolonged survival in AstroRx® treated rats

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# In Human Clinical Trials Using AstroRx®

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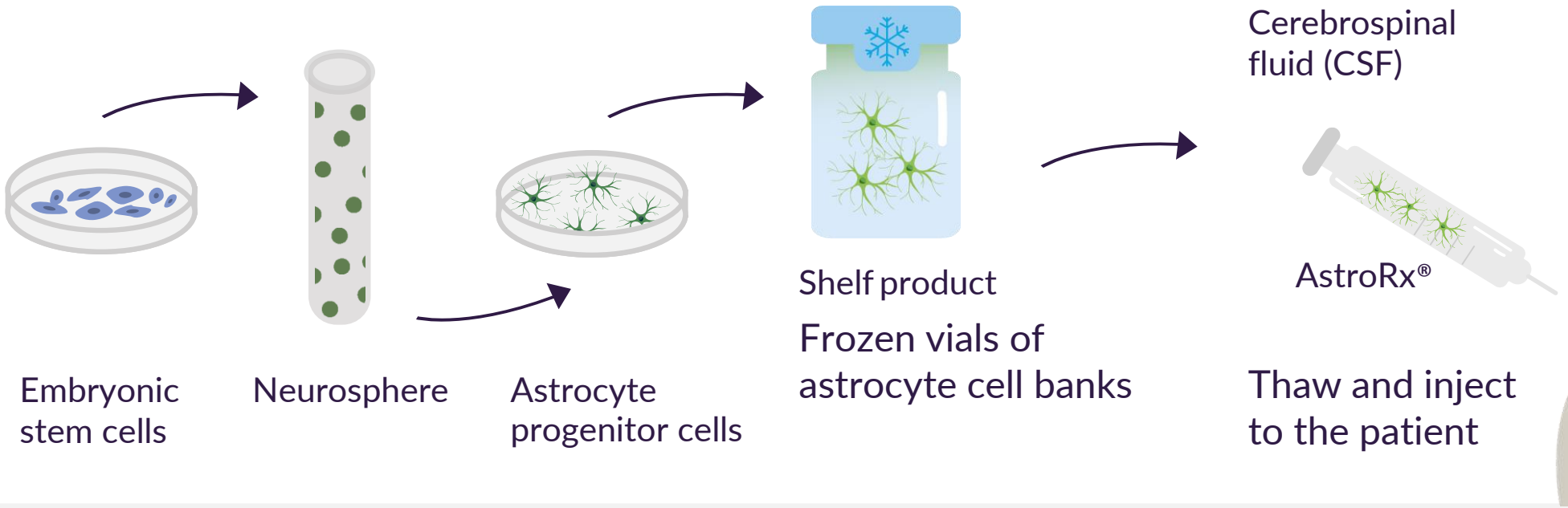
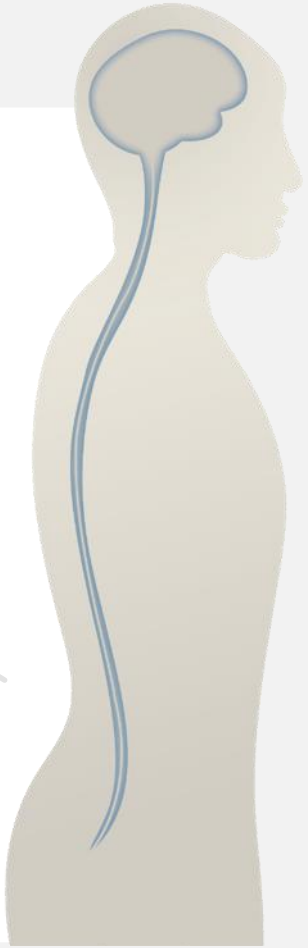
# Cell Therapy Using AstroRx® - The Process

**Production of human astrocytes from ES cells stored frozen for intrathecal injections**



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# AstroRx® Phase 1/2a Status

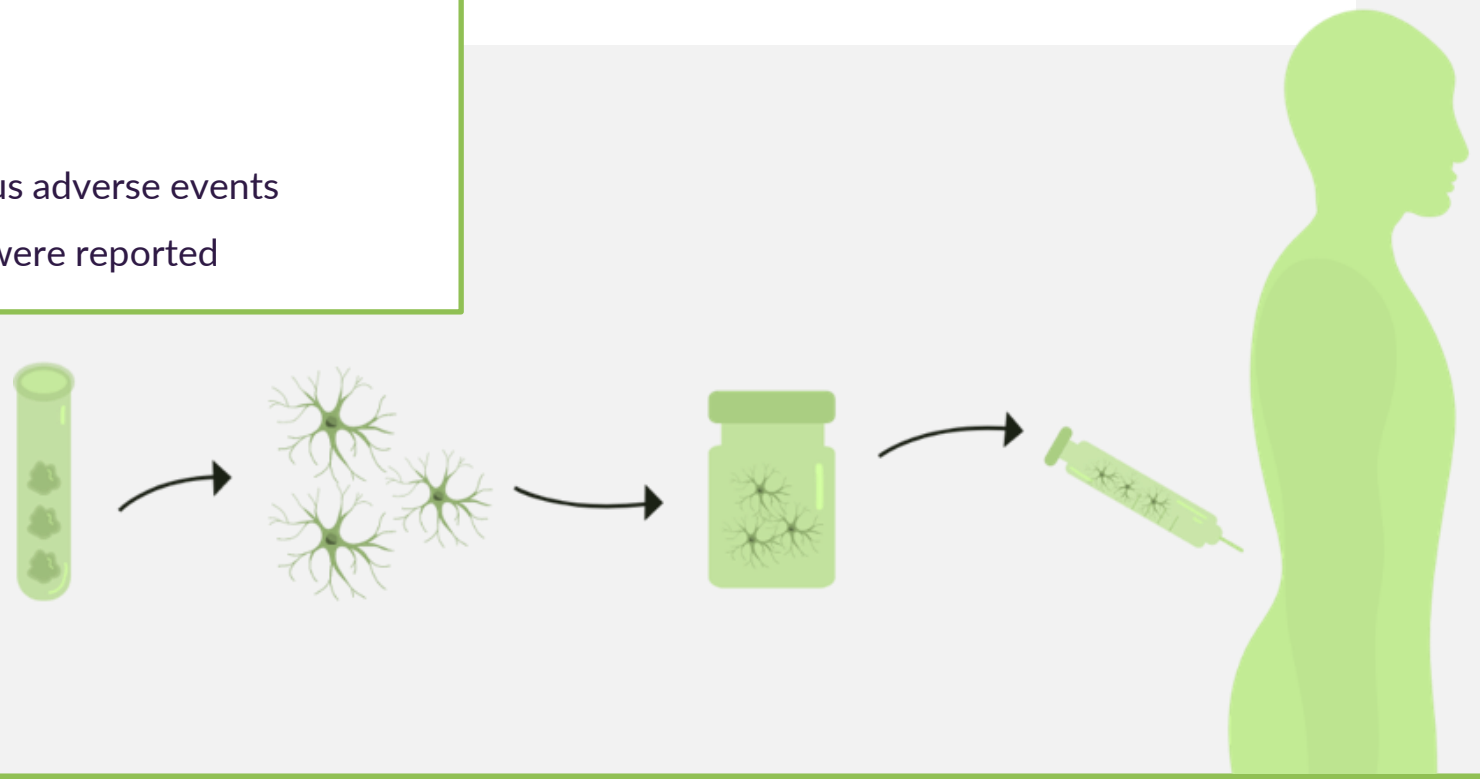
## Good Clinical Safety Profile

**Study Status:**

- 5 patients in Cohort A and 5 patients in Cohort B completed 12 Month follow up.
- Cohorts C&D were discontinued following Data Safety Monitoring Board (DSMB) recommendation due to COVID-19 pandemic

**Safety Results:**

- Good safety profile
- No treatment-related serious adverse events
- No dose-limiting toxicities were reported



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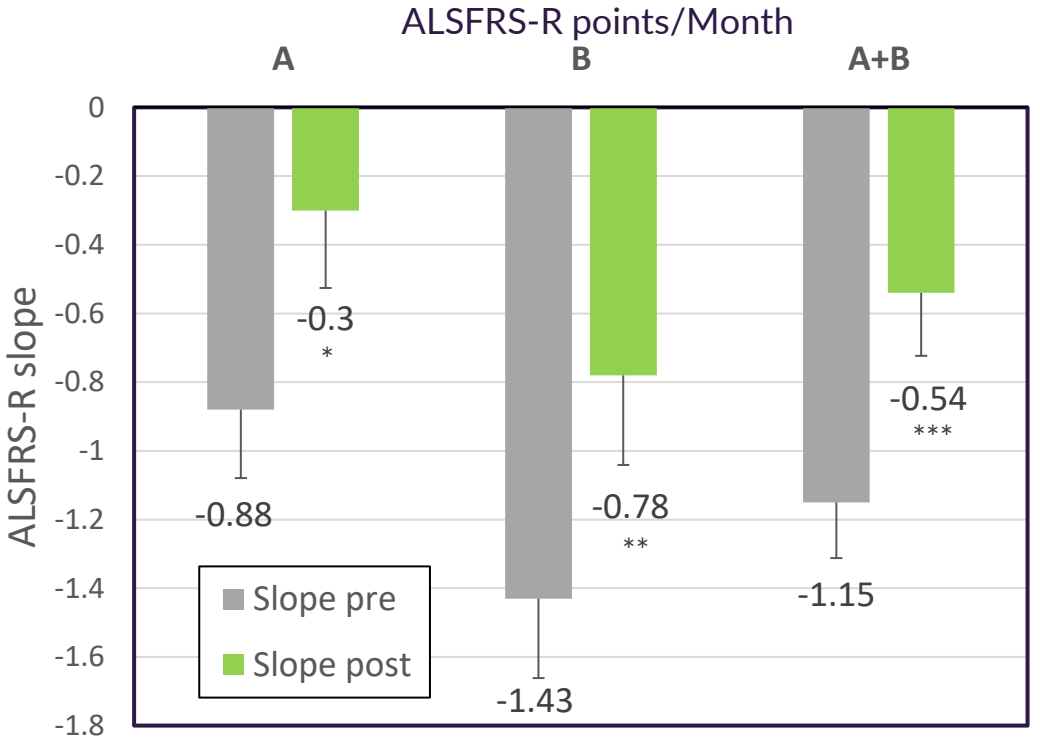
# AstroRx® 3-month Follow-up Results

## Demonstrated a Clinically Meaningful Decline in Disease Progression

**Clinical results are consistent between Cohorts A and B**

**ALSFRS-R slope difference between 3 months pre- and post-treatment in Cohorts A and B**




* p=0.0396, **p=0.0023, *** p=0.0004 (MMRM analysis)

ALSFRS-R is a Clinically Accepted Measure of Disease State

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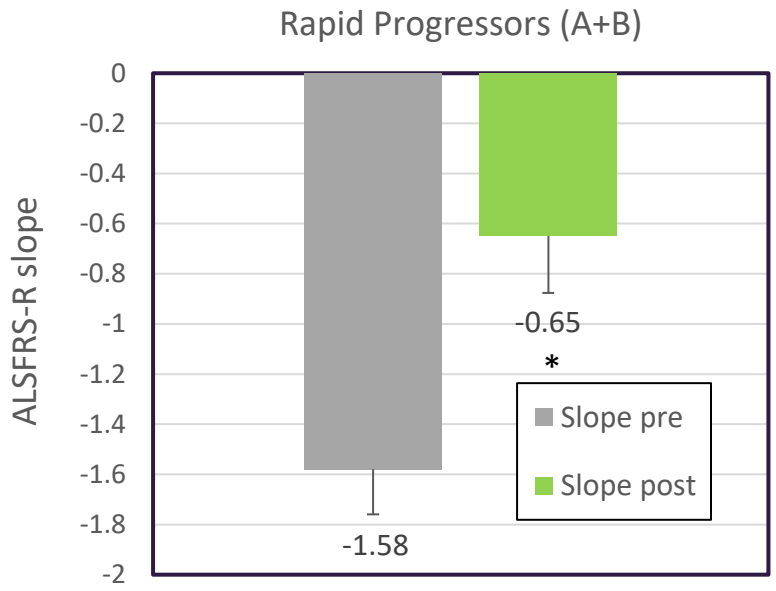
# AstroRx® Efficacy Among ALS Rapid Progressors (3-month Follow-up)

**80% of rapidly progressing patients responded to treatment of AstroRx®**

## ALSFRS-R Slope Analysis




* p=0.0003 (MMRM analysis)

- Rapid progressors are defined as patients who deteriorate at least 1.1 points of ALSFRS-R per month in the run-in period
- Analysis of rapid progressors is particularly important since the inclusion of this sub-population of patients in clinical trials in ALS increases the likelihood of demonstrating a drug effect
- Responders are defined as showing improvement of at least 25% in the ALSFRS-R rate of decline between pre- and post-treatment periods

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# AstroRx® study: 1-year Follow-up Results

**The results support our plan for a further clinical trial with repeated intrathecal administrations of AstroRx®, in order to prolong the clinical effect seen by a single dose**

- Safe and well tolerated in both treatment doses over 12-months
- No treatment-related serious adverse events (SAEs) nor dose-limiting toxicities were reported

## AstroRx® Continued Safety Results

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# AstroRx® Clinical and Regulatory Plan

- An IND supporting the approval of the next set of clinical trials expected in Q4 2022.
- Clinical Trial in the USA in 2023.
- A clinical development strategy to support the product intended use.
- A RMAT* designation application is planned, to enable expedited development, reviews and to accelerate approval.

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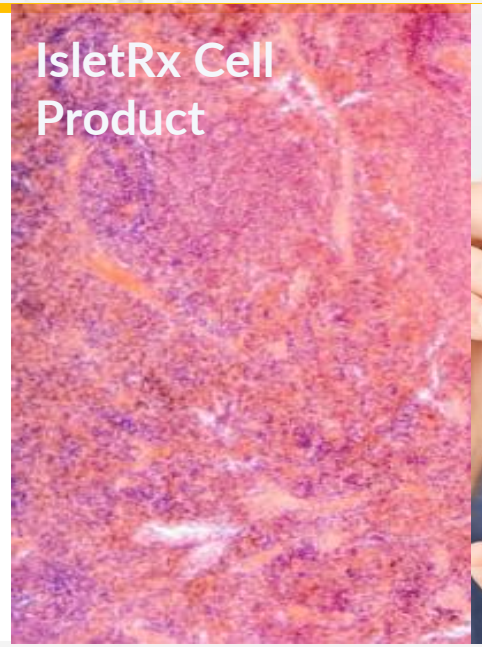
*RMAT - Regenerative Medicine Advanced Therapy

IsletRx

# Functional Islet Cells - Potential Cure for Insulin Dependent Diabetes



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# Insulin Dependent Diabetes - Market and Facts

**~190 Million People** worldwide suffer from Insulin-Dependent Diabetes*

Highly demanding disease management. Insulin injection treatment does not prevent long term complications**

~50 million* people suffer from Type-1 Diabetes worldwide. More than 1.1 million are children and adolescents (<20 years) (US > 200,000)**

High health expenditure Type 1 Diabetes associated healthcare expenditures in the US = 16B$ annually (adjusted)*** **and ~90 B$ globally**

* IDF diabetes atlas 2021 (https://diabetesatlas.org/)
** https://www.jdrf.org/t1d-resources/about/facts/
***Tao et al 2010, PLoS One. 2010; 5(7): e11501. doi: 10.1371/journal.pone.0011501
**** IDF diabetes atlas 2021 (https://diabetesatlas.org/). T1D stands for 9-10% 0f all diabetes cases

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# Unmet Need in Insulin Dependent Diabetes

## Insulin Therapy and glucose management are not a cure

Even with strict insulin treatment regimens, patients experience:

- Frequent episodes of severe, undetected hypoglycemia;
- Severe glycemic lability
- Progressive diabetic complications:
  - Neuropathies
  - Heart Disease
  - Retinopathy
  - Kidney failure
  - Stroke

## Islet Transplantation

**Restoring patient's ability to naturally produce insulin**

- Healthy and functional islet cells can produce and secrete insulin in a regulated manner
- Cadaveric donor islet cell therapy is a safe and clinically validated treatment for Insulin-Dependent Diabetes*
- Patients treated achieved Insulin independence for ~2 years following treatment**
- Main challenges remaining: ***a severe shortage of donor islet cells and immune suppression that is unhealthy and not always prevent immune rejection***

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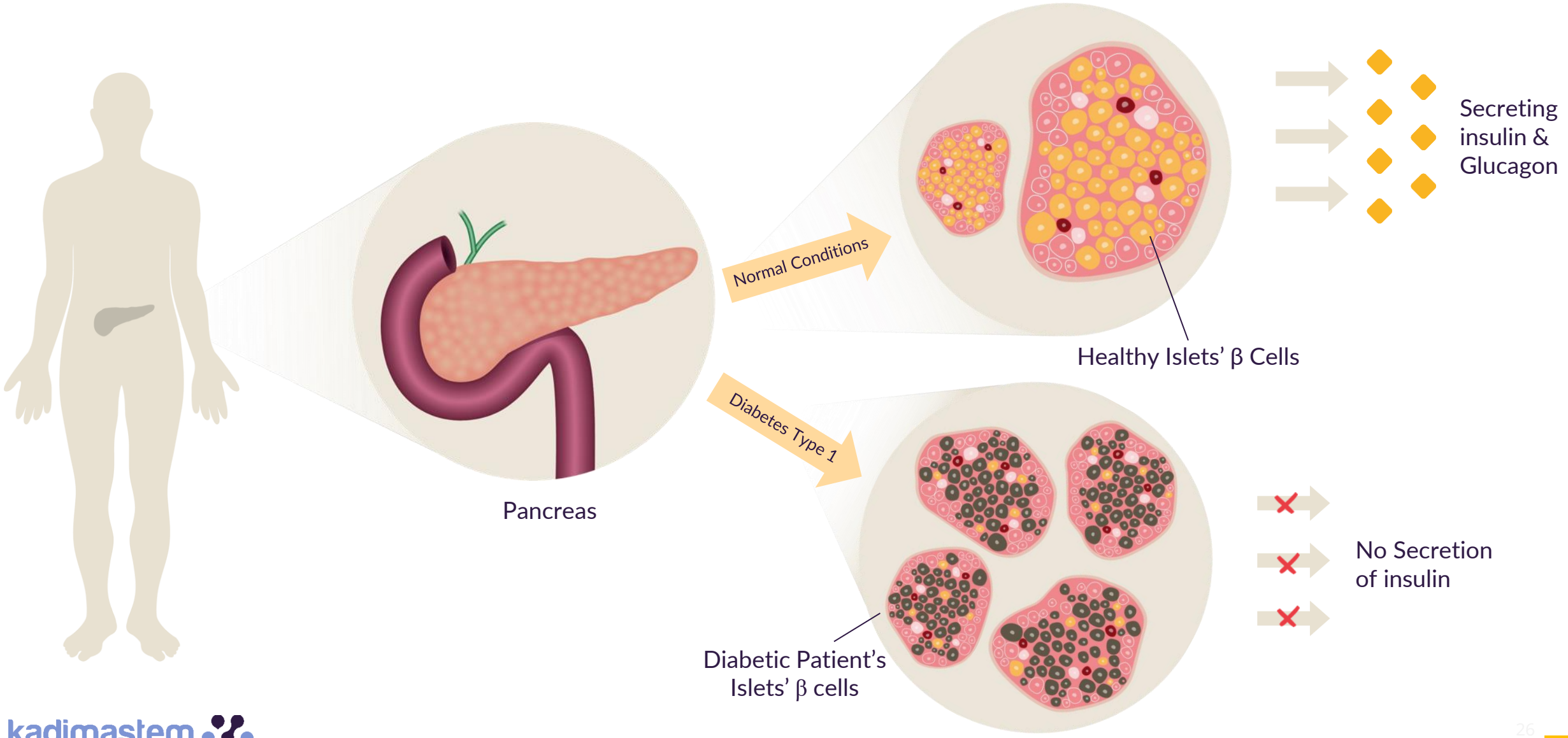
* Shapiro et al 2000
** Bernhard J. Hering 2016
*** https://doi.org/10.1016/B978-0-12-809880-6.00056-4

# What Happens in Diabetes Type 1

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# Cure for Insulin Dependent Diabetes using IsletRx

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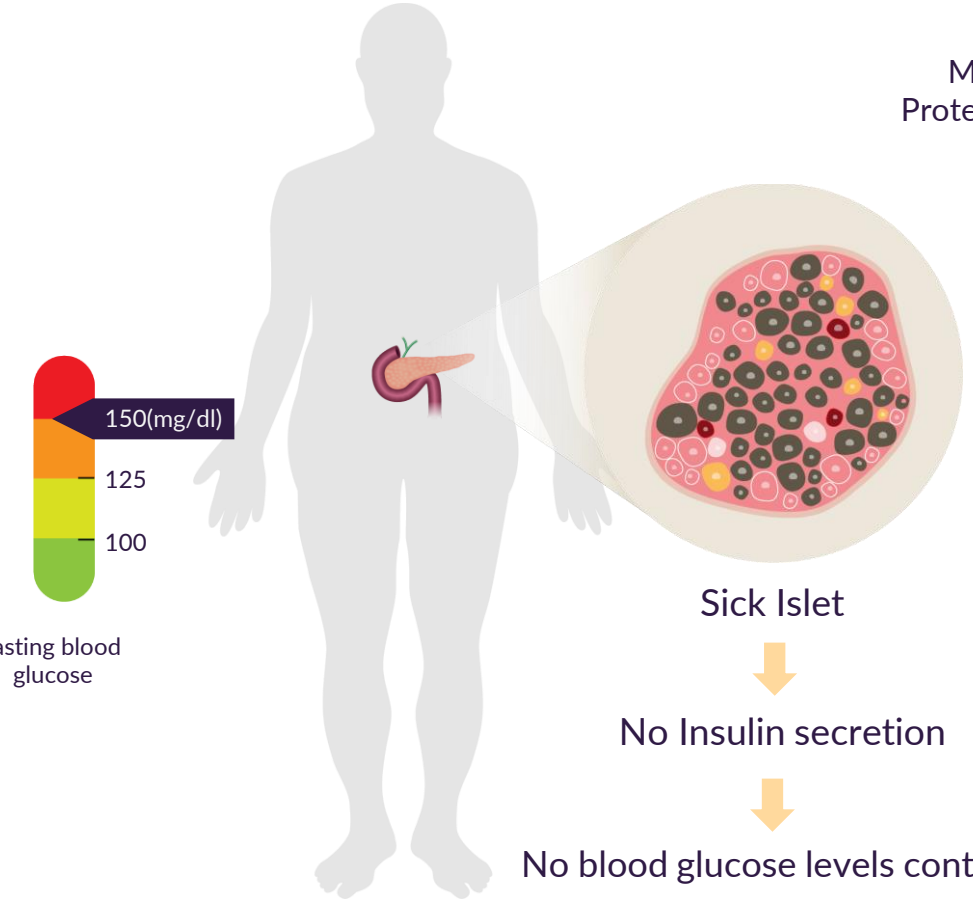
# Our Treatment = Cure

## Problem




Fasting blood glucose

Sick Islet

↓

No Insulin secretion

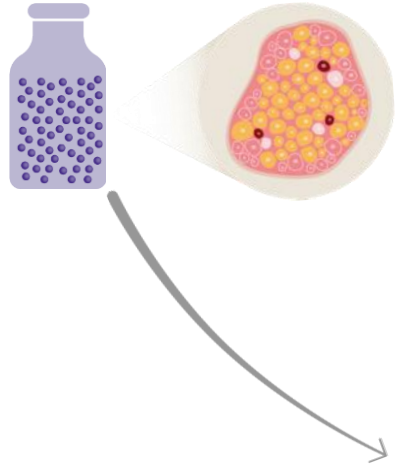
↓

No blood glucose levels control=Diabetes

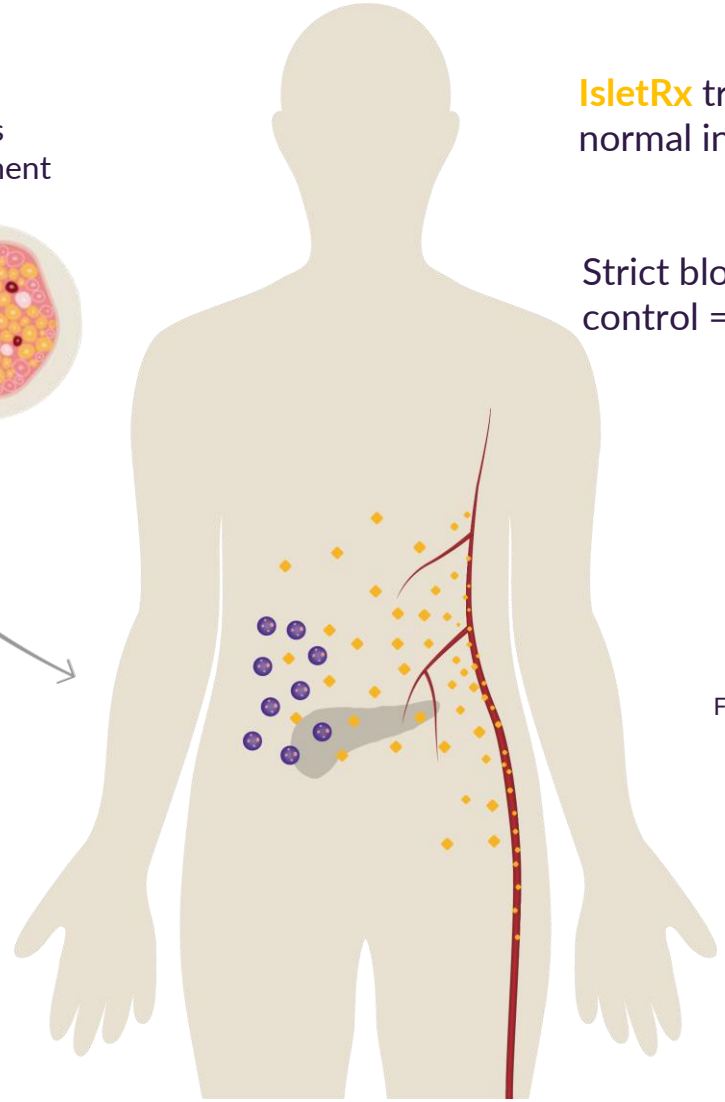
## Our Treatment

IsletRx

Microencapsulated Healthy Islet Cells
Protection From Rejection – in development



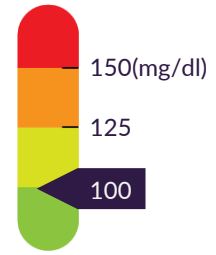
## Cure



IsletRx treatment results in normal insulin secretion

↓

Strict blood glucose levels control = cure for diabetes




Fasting blood glucose

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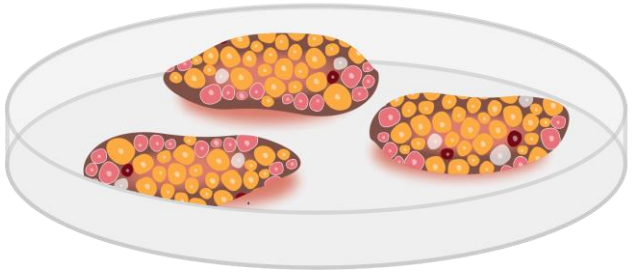
# IsletRx - Our Solution

## Functional pancreatic islets from ES cells that produce and secrete insulin and glucagon

- Overcome donor tissue availability shortage
- Replace malfunctioning patient islet cells
- Maintain continuous balanced glucose levels



- Show long term functionality, protected from host immune response, **without immune suppression drugs -** in development

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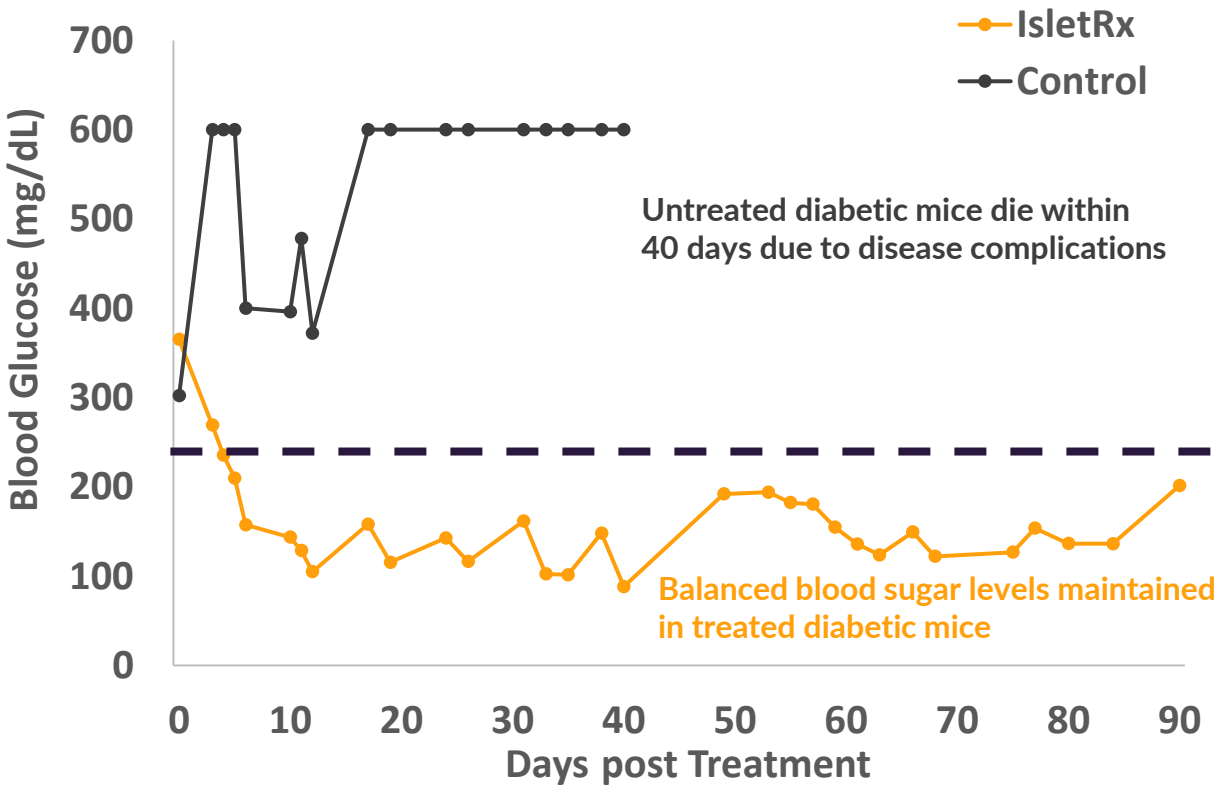
# IsletRx - Preclinical Demonstration of Efficacy

**IsletRx treated diabetic mice (STZ) demonstrated balanced and normal blood glucose levels**

- Long-term therapeutic effect was achieved in an **immunocompetent animal model** (C57BL/6 mice)
- IsletRx cells well protected from host immune system

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Molakandov et al 2021, Frontiers in Endocrinology

# IsletRx - Production, Selection and Encapsulation

## Large Scale Production:

Scalable 3D bioreactor production

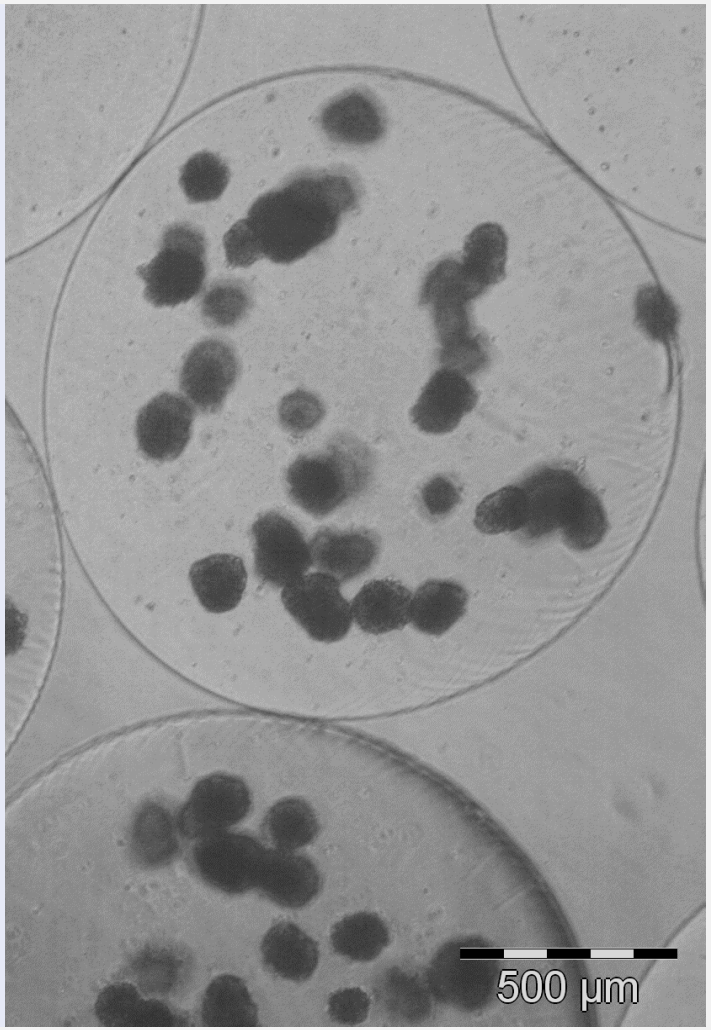
## Selection & Enrichment:

Proprietary technology (IP) enables islet cell enrichment and selection, achieving well characterized cell identity

- Novel CD26-/CD49a+ signature cell surface markers are used to identify and select highly functional insulin producing cells, thereby increasing the probability of clinical efficacy

## Unique Microencapsulation Technology:

***Demonstrate positive results in protecting IsletRx cells from host immune system response***, overcoming a major challenge in allogeneic cell therapy




Microencapsulated ILCs - IsletRx

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# IsletRx Potential Advantages vs. Available Treatments

| | IsletRx<br>Allogeneic Islet Transplantation | Insulin Injections | Insulin Pumps |
|---|---|---|---|
| **Periodic Treatments, Long-term Effect** | ✓ | ✗ Daily injection | ✗ Ongoing |
| **Balanced Glucose Levels** | ✓ | ✓✗ Manual monitoring and balancing of glucose levels | ✓✗ Delay in real-time glucose measurement and insulin infusion |
| **Personal Comfort** | ✓ | ✗ Daily routine interference- injections and laborious monitoring | ✗ External device necessitating maintenance |
| **Compliance** | ✓ | ✗ Requires high-level treatment management | ✗ External device necessitating maintenance |
| **Prevention of Long-term Complications** | ✓ | ✗ | ✗ |

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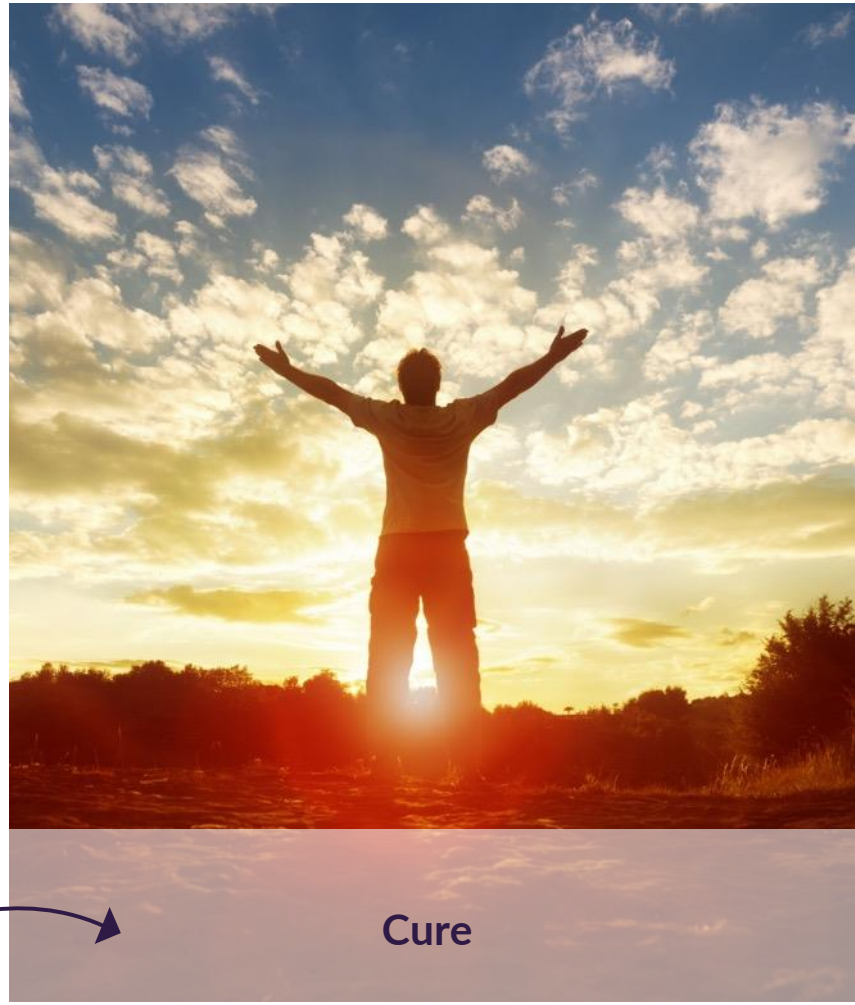
# Our Treatment = Cure

Problem

Our Treatment



Cure

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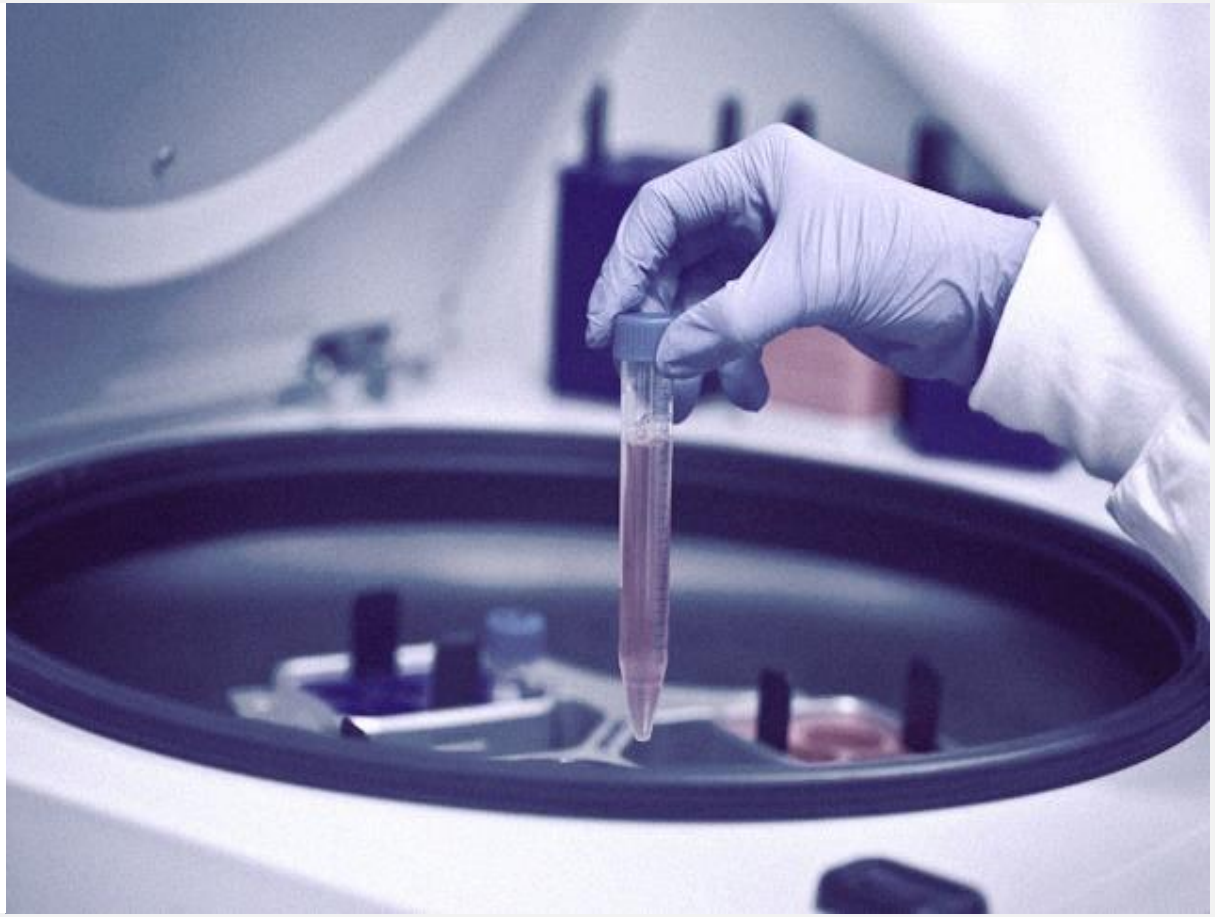
# IsletRx Next Steps

- Pre-IND meetings with FDA
- Implementation of 2nd generation micro and macro encapsulation products through collaborations.
- Upscaling and GMP production



*Initial Targeted Engagement for Regulatory Advice on CBER producTs - preliminary consultation for regulatory advice with FDA before the pre-IND consultation

# Leadership

**Asaf Shiloni**
CEO

**Michal Izrael, PhD**
VP R&D

**Prof. Michel Revel**
Founder, Director & CSO

**Arik Hasson, PhD**
EVP of Business Development

**Ronen Twito CPA**
Chairman of the Board

**Kfir Molakandov, PhD**
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# *Thank You.*

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