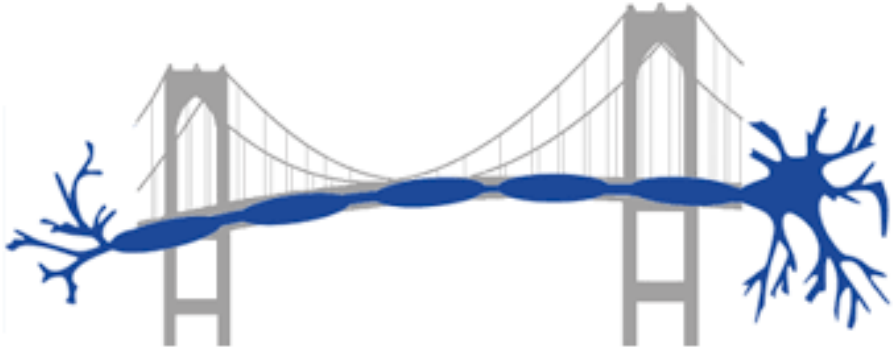
Standards for the Development of

Cell Therapy Technology Infrastructures



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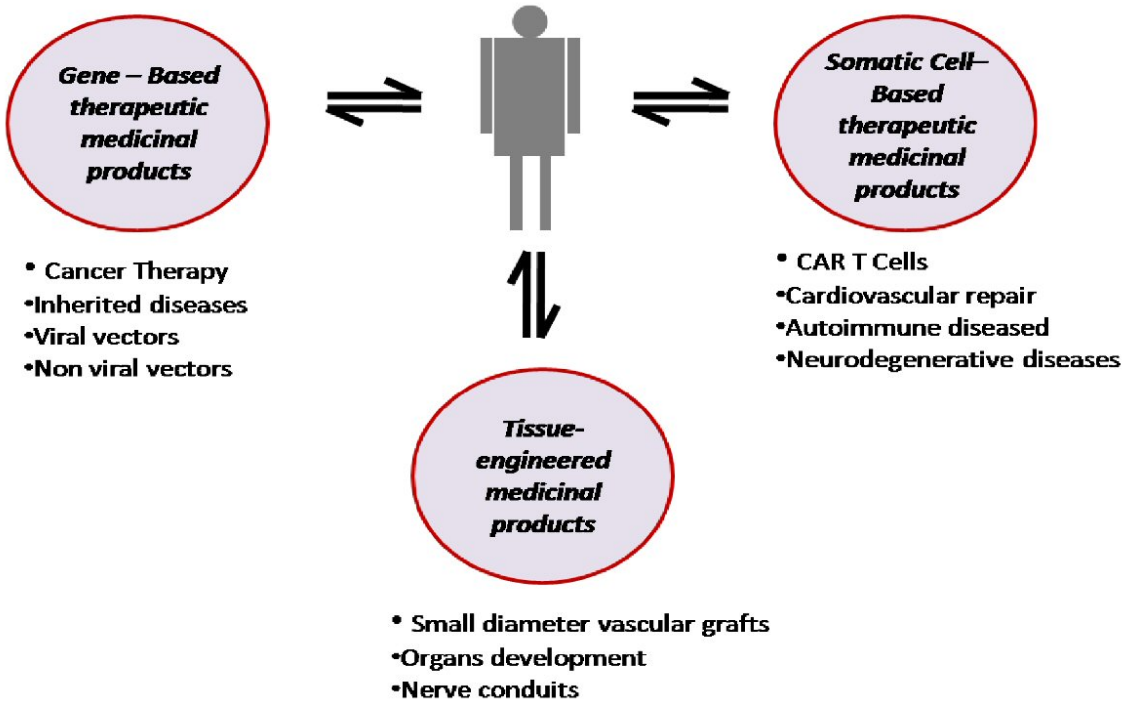
Stem Cell and Regenerative Medicine Research Center
Iran University of Medical Sciences

US Food and Drug Administration, in January 2019 stated that:

”… by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on assessment of the current pipeline and the clinical success rates of these products.”

Advanced Therapeutic Medicinal Products



Advanced therapy medicinal products (ATMP) are pharmaceutical products based on genes, modified cells or engineered tissues, intended for treating or curing disease in humans.

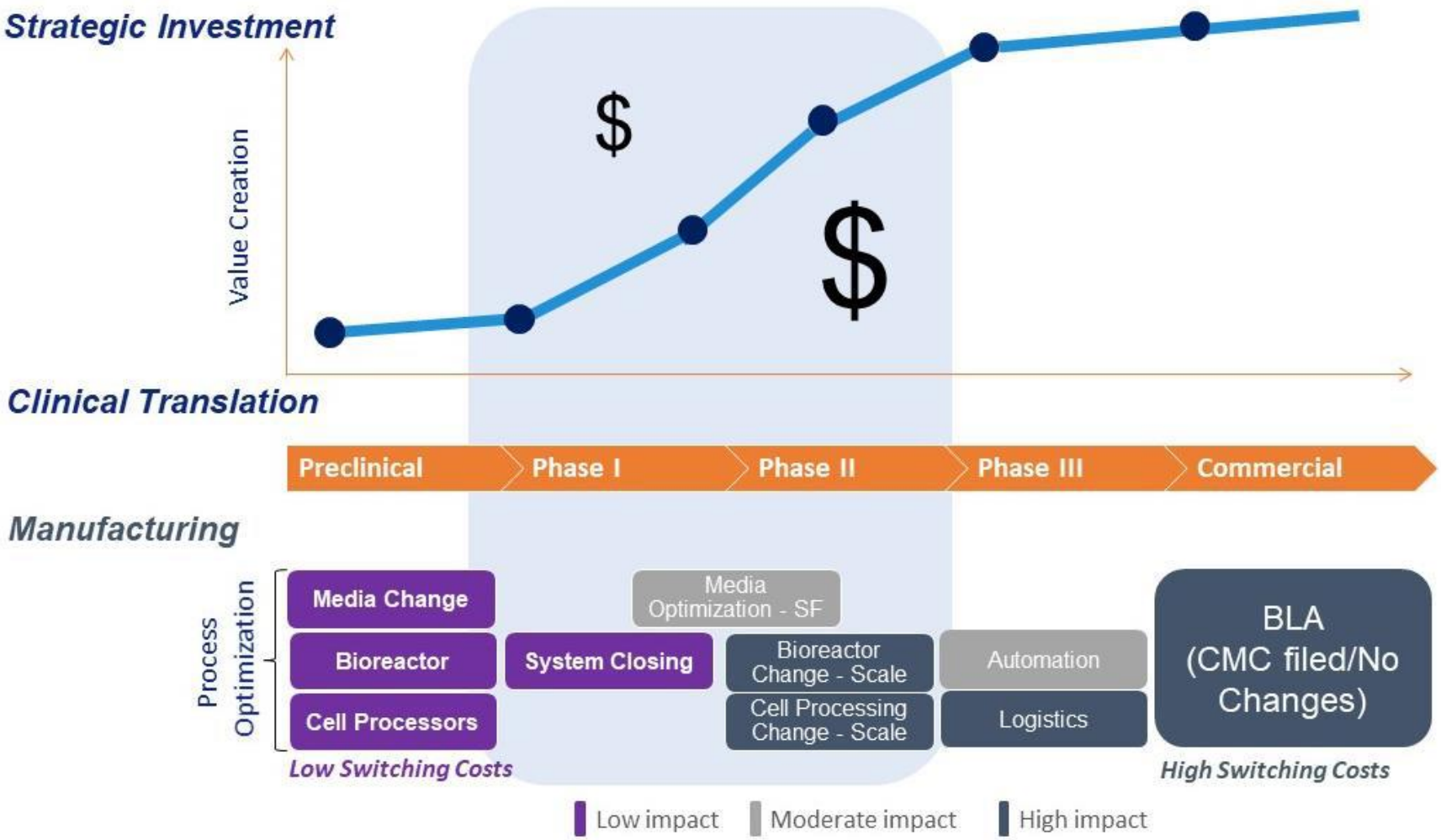
One major gap in the Iranian ATMP innovation system is the lack of accessible and efficient infrastructure for supporting the ATMP-developing SMEs in the critical step of translating their projects to clinical phase.

ATMPs differ from traditional molecule-based drugs in many respects, such as technological complexity, mode of action, ways of administering and not the least potential clinical efficacy and patient benefits.

Whereas the innovation processes, infrastructures and ecosystems around traditional medicines are well established, the novel features of ATMPs lead to new challenges when it comes to their development, manufacturing and implementation in health care.

	Cell therapies	Traditional biomanufacturing
Time to market	Extensive competition + accelerated programs for product candidates	High competition + conservative programs for product approvals
Development	Changes and development at fast speed incl. GMP regulations	Moderate changes and development at lower speed incl. less GMP changes
Complexity	HIGH – many process steps and variables	MEDIUM – fewer process steps and variables
Scale	SMALL (LAB) scale + Therapy targeted for smaller patient populations	LARGE scale + products targeted for larger patient populations
Tech availability	Non-GMP, rapid evolvement, advanced	GMP availability + tailormade for industry + finetuning of available platforms
Automation	Limited possibilities at early stages of manufacturing	Range of possibilities + proven technologies

The scope of the proposed commercialization infrastructure marked in blue.



ATTRACT focuses on support for investors including technology discovery and assessment of interesting technologies.

LAUNCH, launches new companies and perform Ideation and IP development for established companies.

ADVANCE is examining preclinical data, regulatory strategy and development.

BRIDGE is the modular process development facility closely linked with the clinical grade GMP-manufacturing facility DELIVER

SCALE is focused on company growth and consider issues such as manufacturing change requirements and facilitating further investments.

Start-up phase costs

Design, construction and commissioning of laboratory and clean-room space, with special requirements on the ventilation system including both negative and positive air pressure spaces. This is expected to involve extensive use of external consultants.

Equipment for process development and bioanalytical laboratory, clean rooms for GMP-production and a QC-laboratory. The types of necessary equipment include, for example, controlled air flow cabinets, different types of bioreactors for cell culture, bioanalytical instrumentation, freezers, microscopes, sterilization equipment, and equipment for fill and finish.

Setting up and obtaining a certified Quality System, qualification of personnel, validation of instrumentation and methods, and acquiring necessary permits and accreditations.

Operative costs

- Personnel costs
- Maintenance costs; service contracts for maintenance of instrumentation and ventilation systems, maintaining permits and accreditations
- Consumables in process development, GMP-production, and collaborative research projects
- Rent for laboratory, cleanroom, office and storage space

- Other costs (IT-infrastructure, travel, indirect costs…), estimated at 25% salary costs)

The investors in the Life Science sector have so far not entered the ATMP field, most likely due to high perceived risks or uncertainty.

There are very few CDMOs and CMOs with capacity and competence in ATMPs active in Iran.

The existing infrastructures for development and GMP manufacturing of ATMPs exist mainly in academic and hospital settings and are not primarily organized for, and do not have the capacity or incentive to meet the needs of industry regarding process development and production.

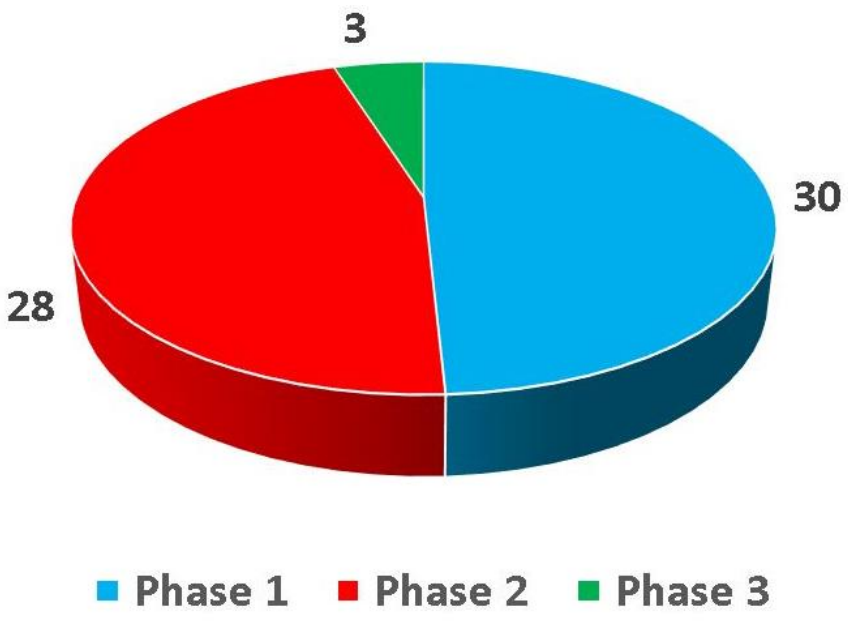
The lack of capital and critical supporting infrastructure has led to:

-A limited number of SMEs have built the capacity in-house at great cost and effort.

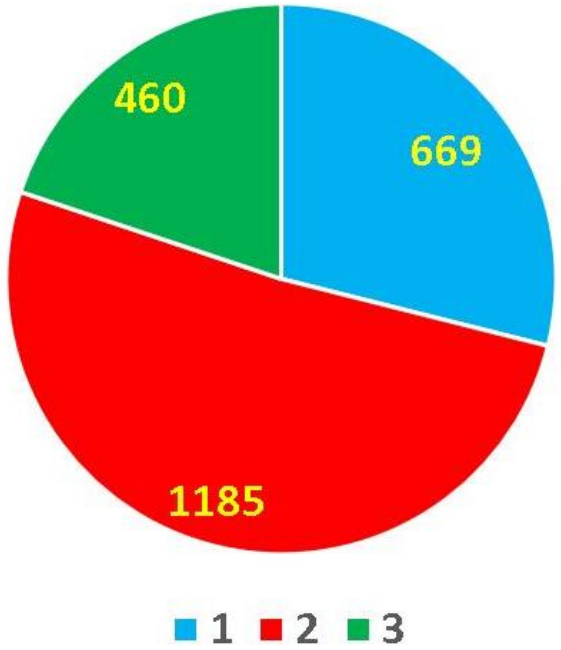
-The majority of the SMEs are outsourcing development and manufacturing.

Stroke Cell Therapy Clinical Trials

Number of patients involved in Stroke Cell Therapy Clinical Trials



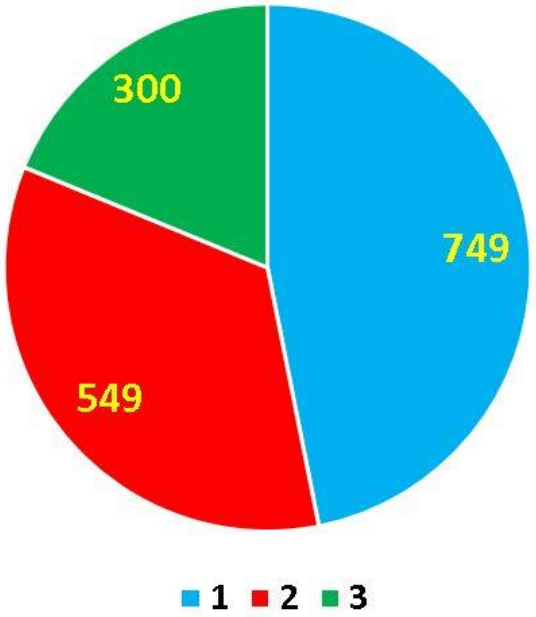
Number of Stroke Cell Therapy Clinical Trials in different Phases



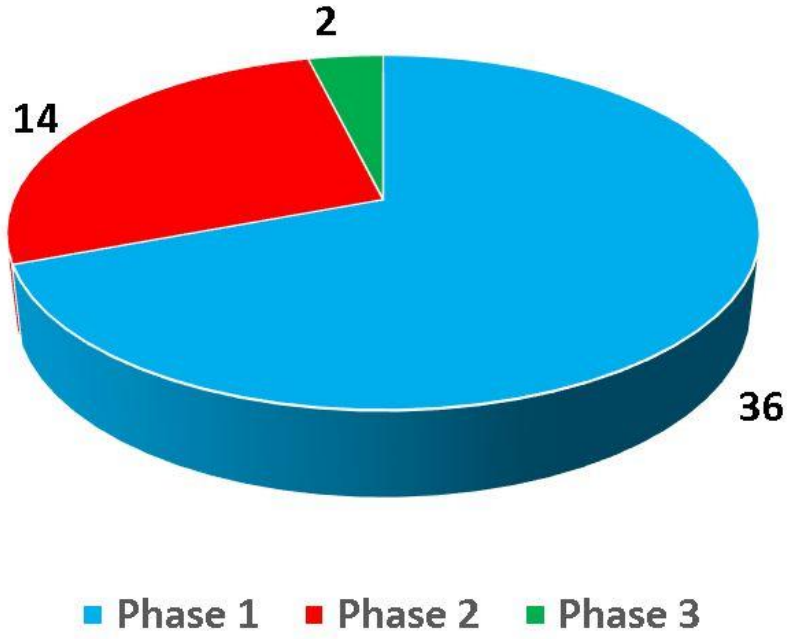
Clinicaltrials.gov

SCI Cell Therapy Clinical Trials

Number of patients involved in SCI Cell Therapy Clinical Trials



Number of SCI Cell Therapy Clinical Trials in different Phases



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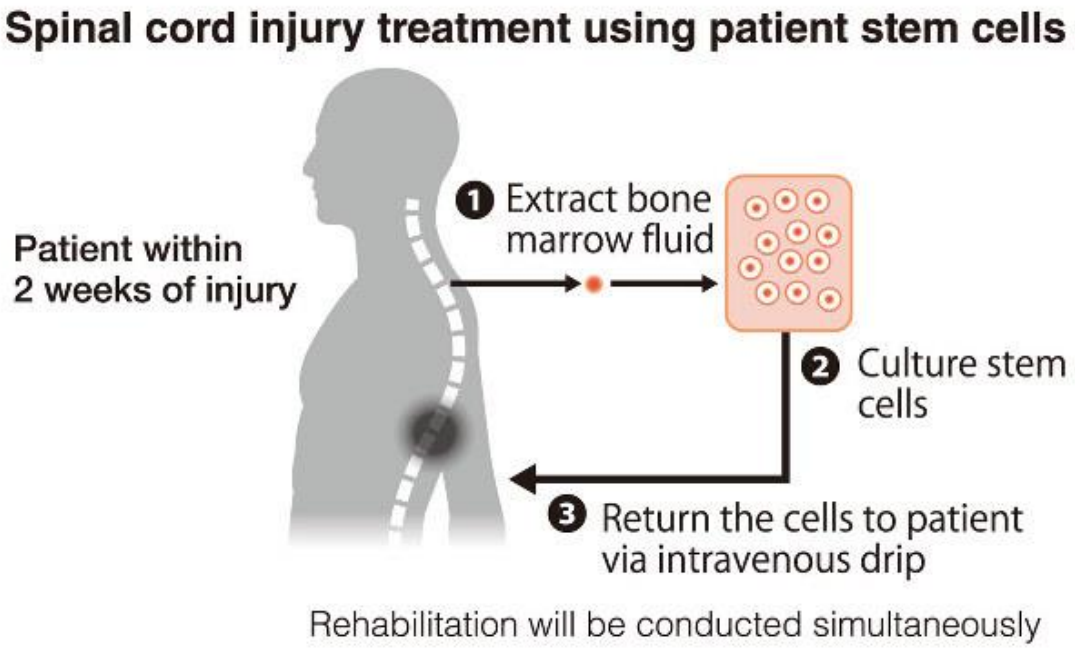
Spinal Cord Injury

Stemirac

NIPRO CORP

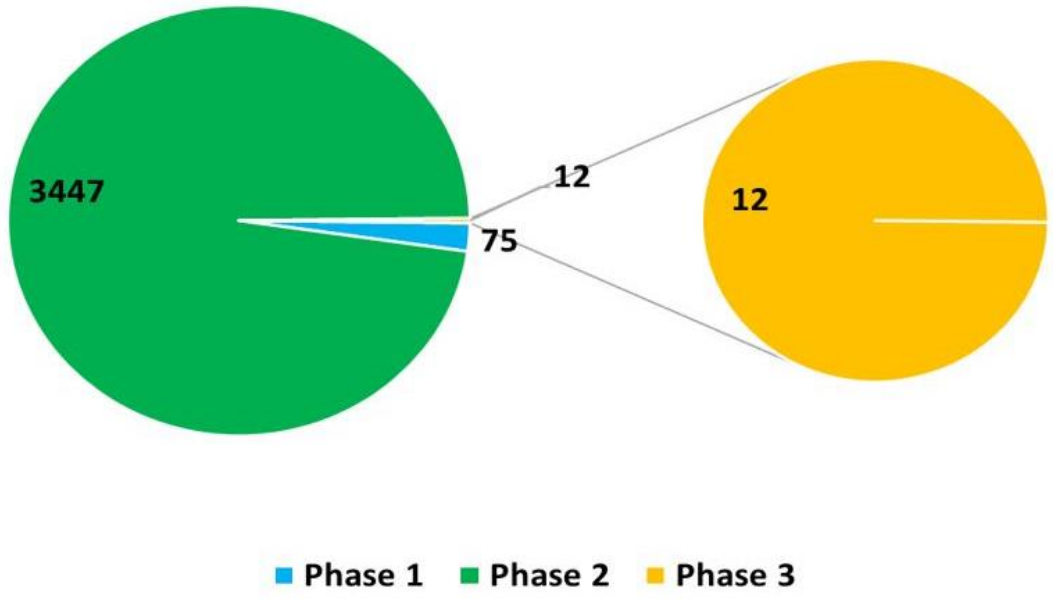
A mesenchymal stem cell therapy approved in Japan in December 2018 for the treatment of spinal cord injury.



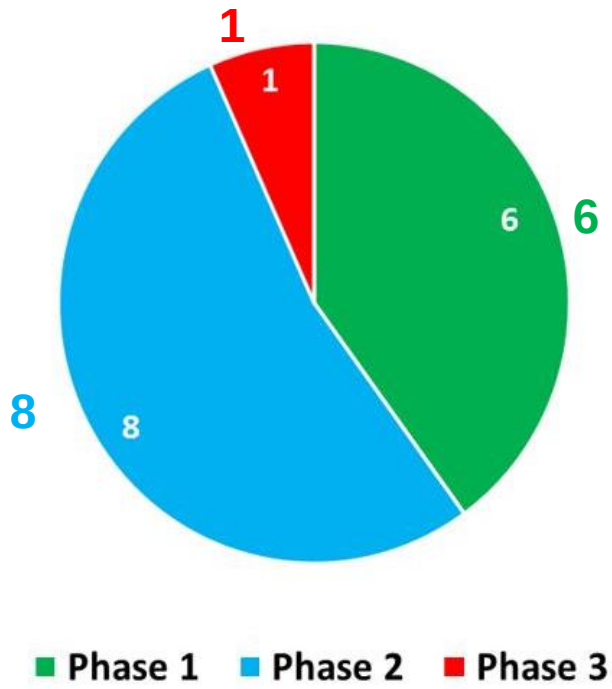
Japan has approved a stem-cell treatment for spinal-cord injuries. The event marks the first such therapy for this kind of injury to receive government approval for sale to patients.

Parkinson Disease Cell Therapy Clinical Trials

Number of patients involved in Parkinson's disease Cell Therapy Clinical Trials



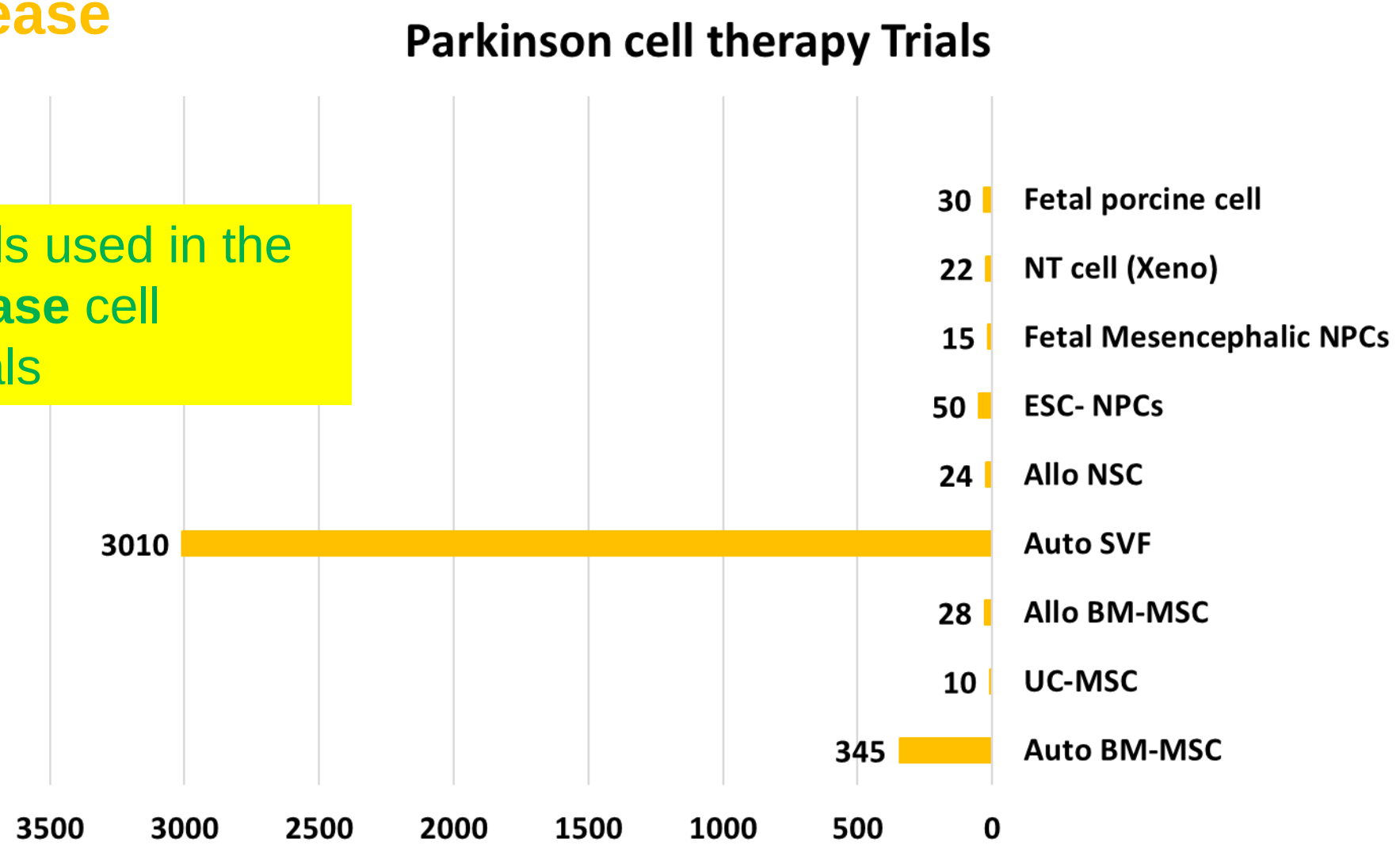
Number of Parkinson's disease Cell Therapy Clinical Trials in different Phases



Clinicaltrials.gov

Parkinson Disease

The Source of Cells used in the **Parkinson's disease** cell therapy clinical trials



Clinicaltrials.gov

Parkinson Disease

FDA Places DA01 Bayer's Advanced Parkinson's stem cell therapy, on Fast Track

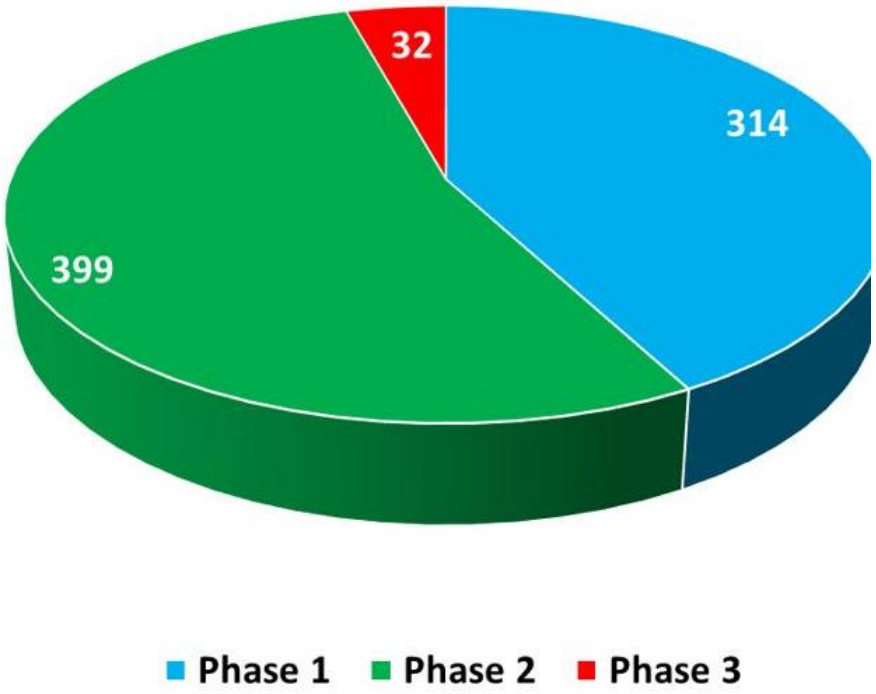
July 20, 2021

Bayer subsidiary BlueRock Therapeutics has been granted a fast-track review by the FDA for ***DA01***, its stem cell-based therapy for Parkinson's disease which is currently in early-stage clinical testing.

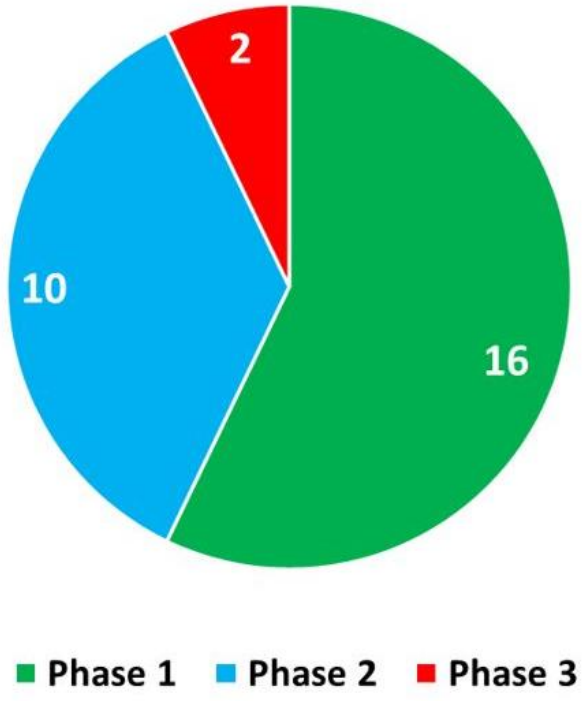
The therapy involves implantation of **dopamine-producing cells** under general anesthesia into a part of the brain called the putamen, which is particularly affected by neuron loss in Parkinson

Amyotrophic Lateral Sclerosis

Number of patients involved in ALS Cell Therapy Clinical Trials



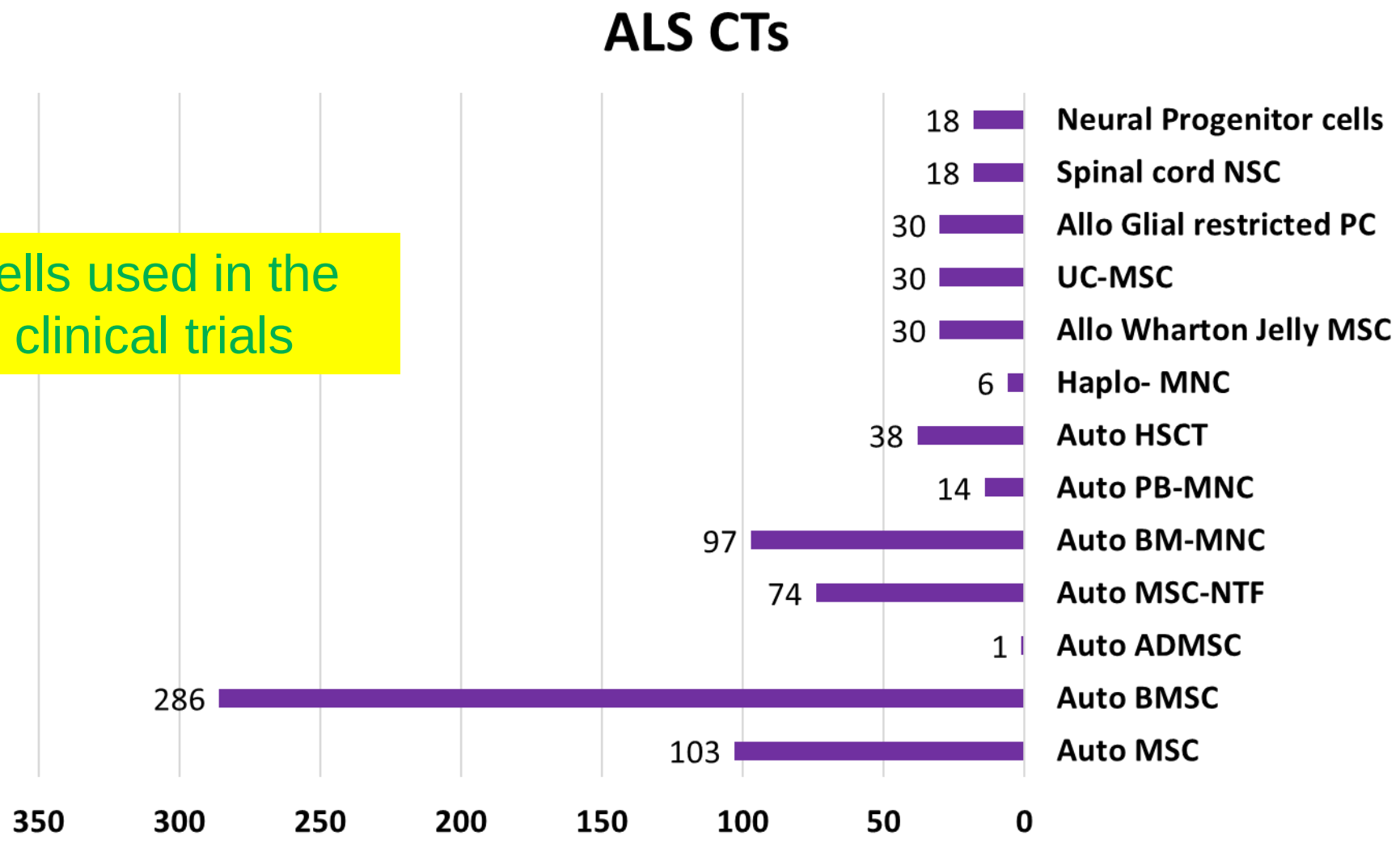
Number of ALS Cell Therapy Clinical Trials in different Phases



Clinicaltrials.gov

ALS

The Source of Cells used in the **ALS** cell therapy clinical trials



Clinicaltrials.gov

ALS

CORESTEM

CORESTEM is a biotechnology company specializing in the research and development of personalized stem cell therapies for neurological and autoimmune diseases. Its lead product is **NeuroNata-R** (lenzumestrocel), the world's first stem cell-based therapy for amyotrophic lateral sclerosis (ALS).

NeuroNata-R is an **autologous bone marrow-derived mesenchymal stem cells (MSCs)**. Treatment mixing with cerebro-spinal fluid collected from the patient and administering the final product by intrathecal injection.

The first NeuroNata-R injection typically takes place four weeks after the first bone marrow extraction, followed by a second injection four weeks later.

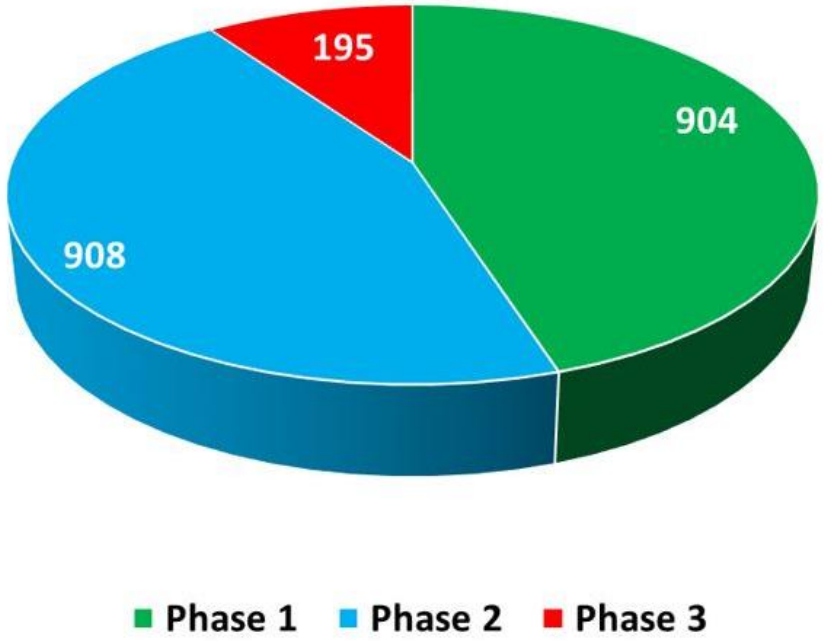
ALS

BrainStorm Cell Therapeutics developed a cell type trademarked as **“NurOwn™”** for the treatment of ALS. The cells can differentiate into specialized neuron-supporting cells capable of stably secreting neurotrophic factors (MSCNTFs).

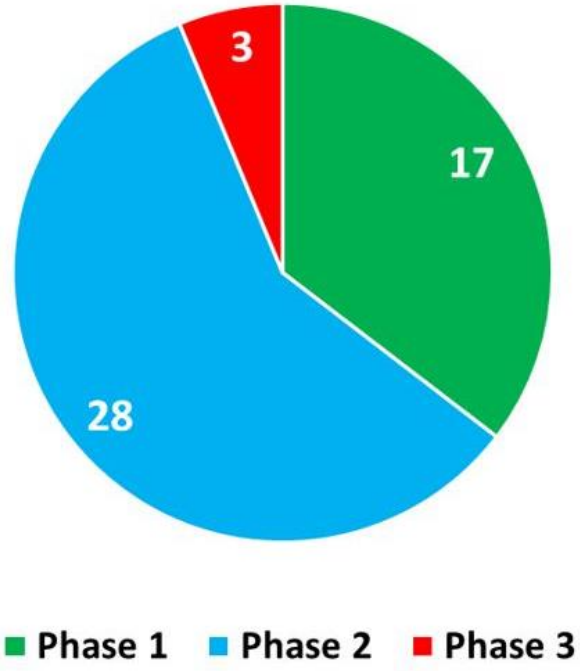
Currently, a phase III clinical trial using **NurOwn** cells began to evaluate the safety and efficacy of the cells (ClinicalTrials.gov Identifier: NCT02017912).

Multiple Sclerosis

Number of patients involved in MS Cell Therapy Clinical Trials



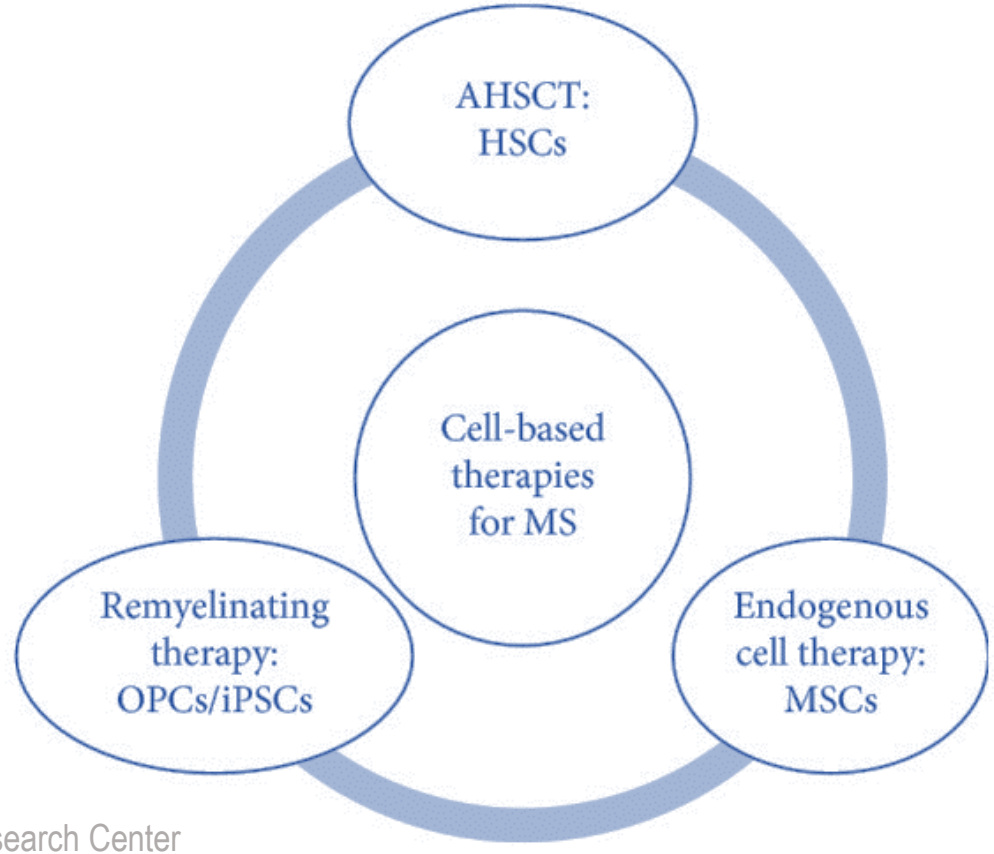
Number of MS Cell Therapy Clinical Trials in different Phases



Clinicaltrials.gov

Multiple Sclerosis

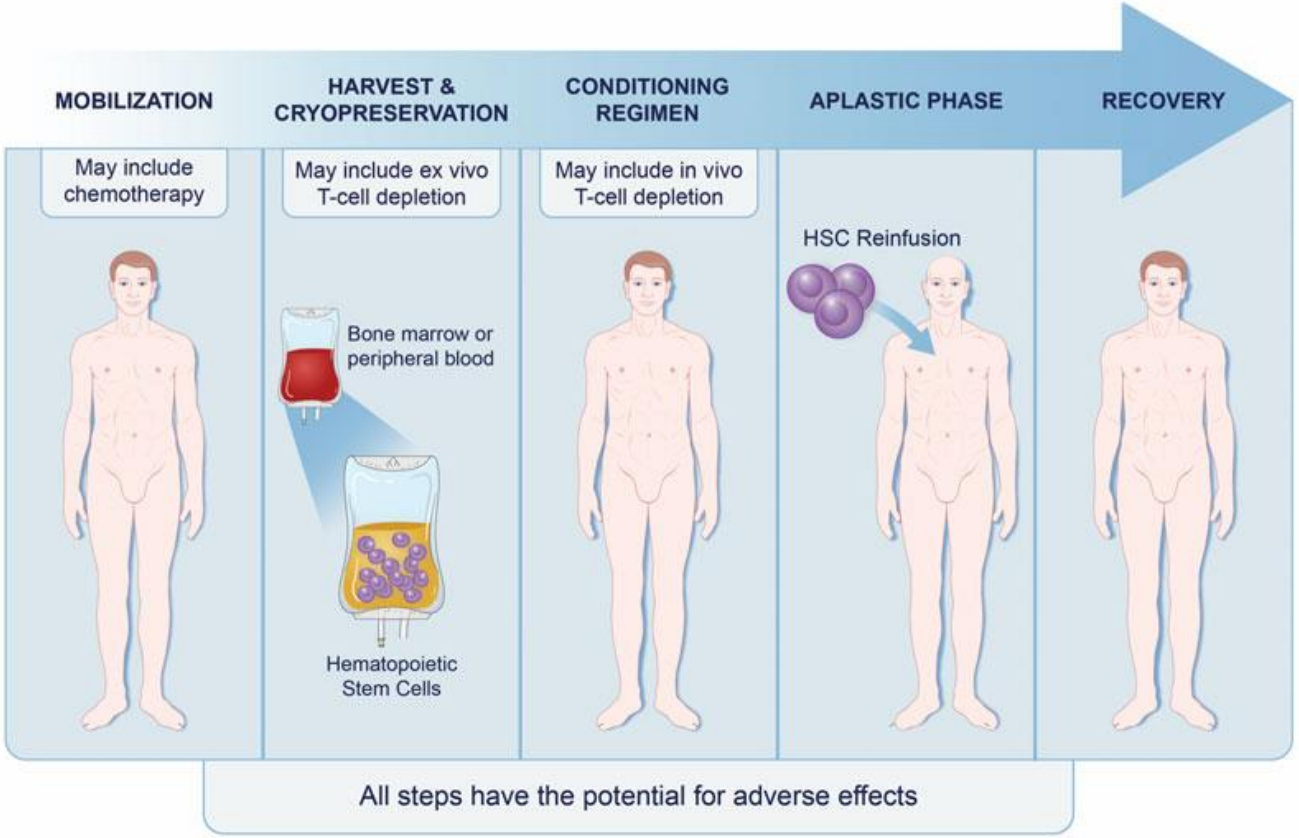
A schematic representation of cell-based therapies in multiple sclerosis. **AHSCT**: autologous hematopoietic stem cell transplantation; **MSCs**: mesenchymal stem cells; **OPCs**: oligodendrocyte progenitor cells; **iPSCs**: induced pluripotent stem cells.



Stem Cell Res Ther. 2016; 7: 12

MS & Hematopoietic Stem Cell Transplantation

Autologous hematopoietic stem cell transplantation (aHSCT) is able to induce durable disease remission in people with multiple sclerosis.



HSCT has proven to **be very effective for people with highly active MS**. It can reduce relapses and stabilize or even improve disability for some.

Stem Cell Res Ther. 2016; 7: 12

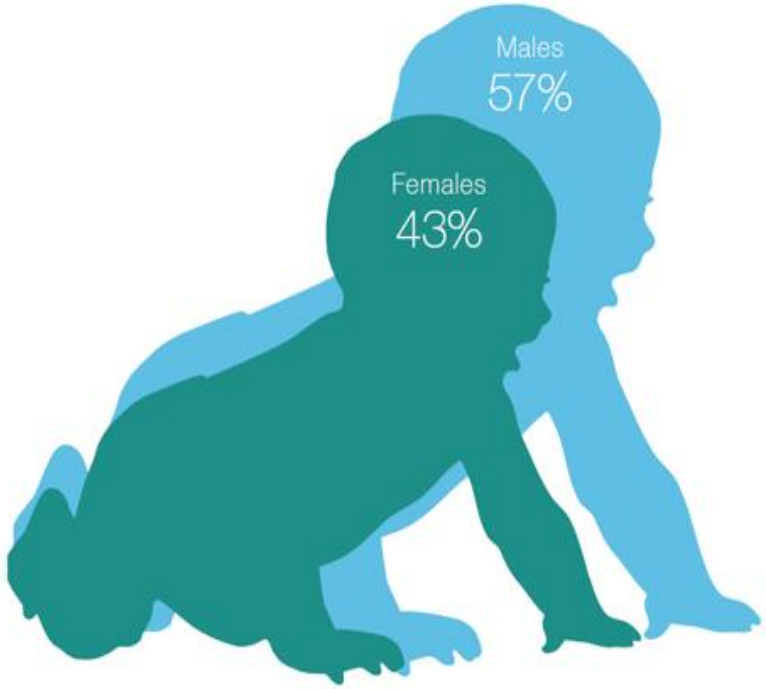
Clinical Trial of Companies in Neurological Disorders

Product	Company	Disease	Phase
NurOwn	BrainStorm Cell Therapeutics	Amyotrophic lateral sclerosis	III
NurOwn	BrainStorm Cell Therapeutics	Multiple Sclerosis	II
Engensis	Helixmith	Amyotrophic Lateral Sclerosis	II
HYNR-CS inj	Corestem	ALS	I/II
Q-Cells	Q Therapeutics	ALS	I/II
RAPA-501 Autologous T cells	Rapa Therapeutics	ALS	I/II
Neuro-Cells	Neuroplast	Spinal Chord Injuries	I/II/III
Umbilical Cord Blood Mononuclear Cell	StemCyte	Spinal Chord Injuries	II
itMSCs	Stemedica Cell Technologies	Alzheimer's Disease	I
Lomecel-B	Longeveron	Alzheimer's Disease	I

https://markets.businessinsider.com

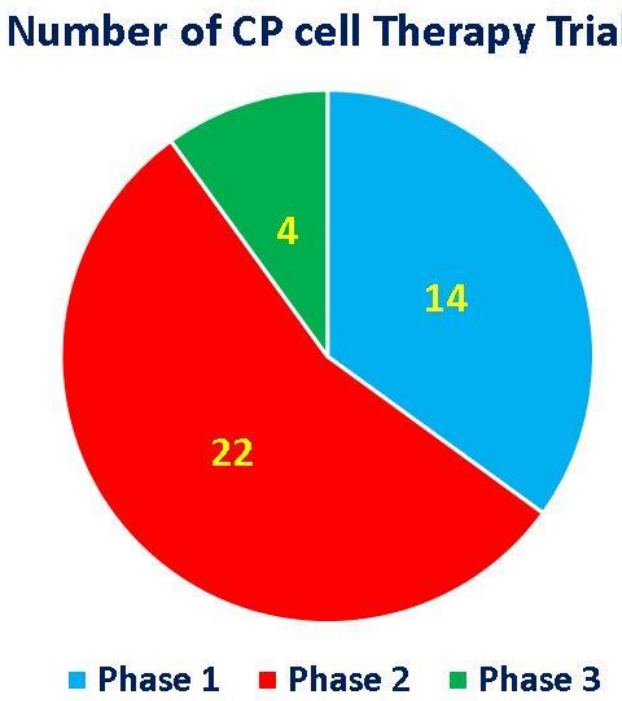
Cerebral Palsy

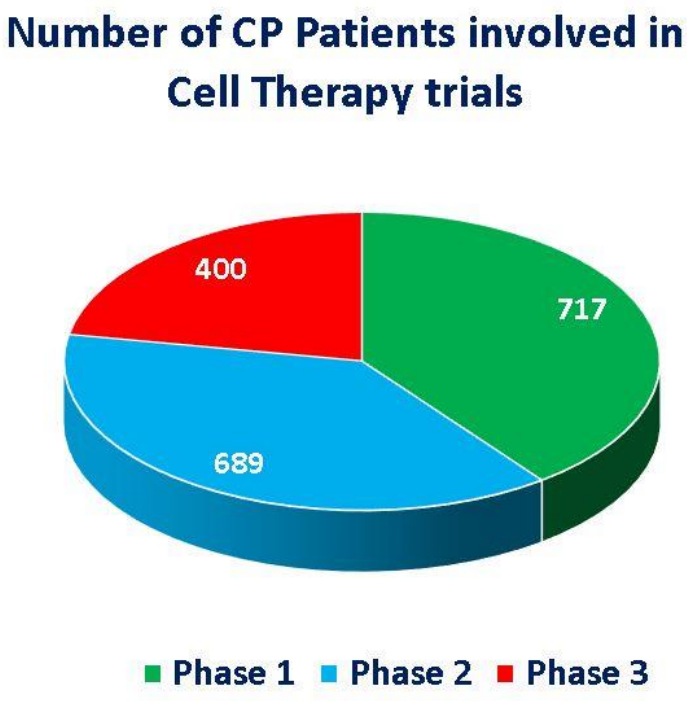
The prevalence of cerebral palsy has increased among the children with low birth-weight, jaundice, respiratory distress and intrauterine infection and so on.



Although there are many kinds of functional therapy programs especially the rehabilitation treatment for cerebral palsy, their effects are limited.

Cerebral Palsy





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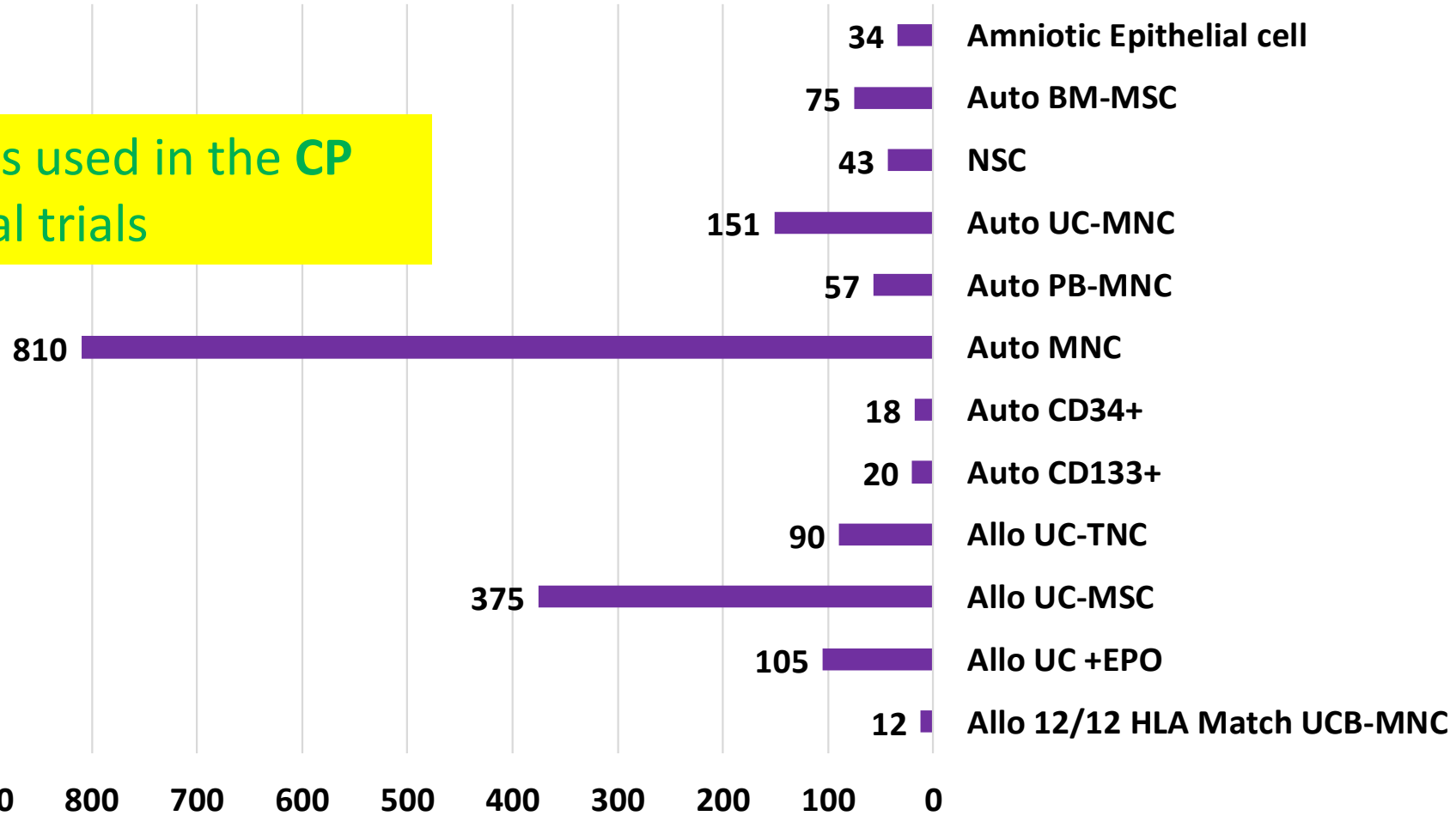
Cerebral Palsy

The Source of Cells used in the **CP** cell therapy clinical trials



Clinicaltrials.gov

The Iranian guideline outputs

The final guideline of the "Establishment and Operation of Cell Therapy and Regenerative Medicine Departments in Public, Public-Nongovernmental, and Private hospitals" was announced by the Curative Affairs Deputy of MOHME on 19 Nov 2018 to the all Universities of Medical Sciences and Iranian Medical Council.

The main topics which have been discussed in the guideline are as follows:

Conditions of establishment and operation of the department
Activity time of the department
The Validity of legal licenses
Duties of Technical Officers
Personnel Terms
Quality controls
Data management
Building Criteria
Equipment regulations
Health and safety standards

Key characteristics of the process development facility and GMP manufacturing facility

Process development facility key characteristic

- Employees
- Bioanalytics
- Manufacturing technology development
- Process development
- ------ m^2 modular laboratory
- Strategic partnership with manufacturing technology companies

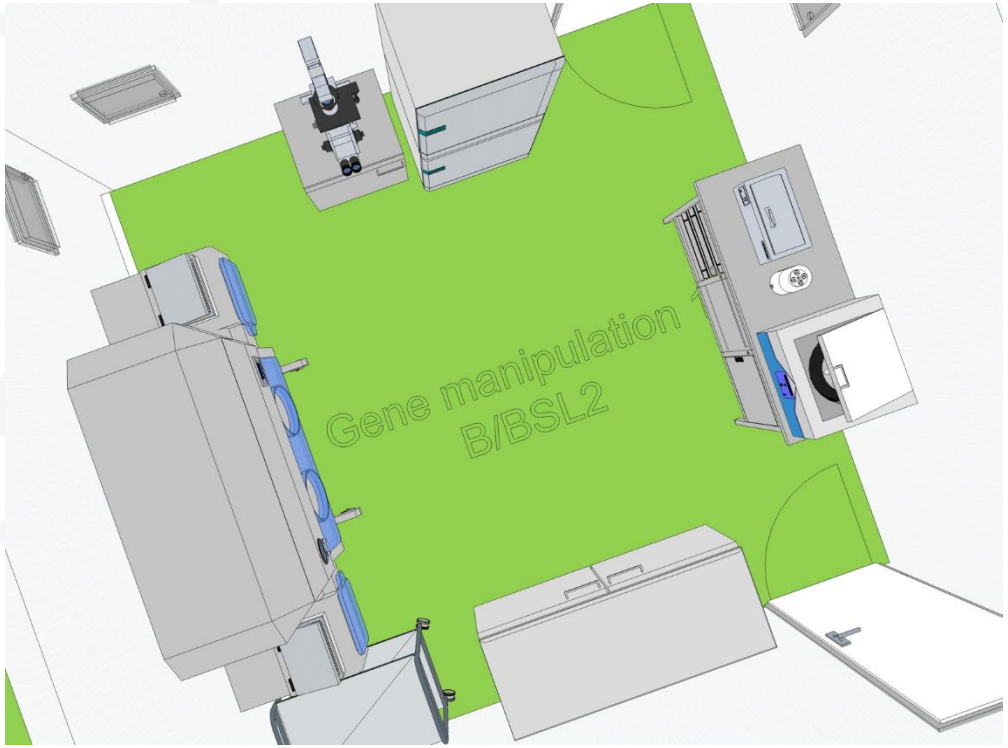
Equipment needed to start a cell processing lab		
Required equipment:		
Biosafety cabinet (or equivalent)	Refrigerator	Balance (Scale)
Water bath	Centrifuge (with carriers to hold 600 mL blood bags)	Freezer (⩽ −70 °C)
Plasma extractor	Tubing sealer	Tubing stripper
Cryo-transporter (−80 °C) or liquid nitrogen dry shipper	Micropipettes (100 µL and 1000 µL)	Reference thermometer
Pipette aid	Hemostats	
Desired equipment:		
Sterile connecting device	Controlled rate freezer	LN_2 storage freezer
Label printer	CO_2 incubator	Hemocytometer
Microscope	Personal computer	
Shared equipment:		
Flow cytometer	Automated instrument for cell processing	Microbiology lab for bacterial and fungal culture
Hematology analyzer		

Abbreviation: LN_2 = liquid nitrogen.

Key characteristics of the process development facility and GMP manufacturing facility

Cell and vector production facility key characteristics/figures

- Employees
- Class B cell processing cleanrooms
- Viral vector production suites
- QC/QA laboratory
- Phase I/II clinical scale
- --------- m^2 space



Stem cell banks

Stem cell banks aim to ensure the quality, availability, and ethical provenance of tissues, cells, or embryos used for research and eventual therapies.

Existing regulatory frameworks ensure proper methods for donation, procurement, processing, and preservation of cells and tissues but are often based on standard pharmaceutical paradigms.


Cell therapy development
INFRASTRUCTURE
DISCOVERY
TRANSLATIONAL
CLINICAL
EDUCATION
Bridging the Gap
Turning ideas into therapies
Life-saving therapies for patients