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Regenerative Medicine Landscape Overview

Teaser Q1 2022

www.aginganalytics.com

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'Regenerative Medicine Q1 2022' gives a comprehensive overview of the global Regenerative Medicine market for controlling Human Longevity and the repairing, replacement, and regeneration of tissues and organs affected by injury, disease, or the natural ageing process.

All the technologies described in the analytical case study are already in use, available, and ready for further research.

This report includes a detailed **quantitative analysis** of the market trends over the **last few decades** to identify the prevailing opportunities. The global market is segmented and analysed according to **product type**, **material, application, and region**. Market estimations are based on a comprehensive analysis of the key developments in the industry. An in-depth analysis based on **geography** helps to understand the regional market to assist in strategic business planning. The

The **comparison of different approaches** is based on their **clinical efficacy** and the **cost** and **complexity** of organ regeneration.

Against this background, a separate chapter provides an overview of several interesting scientific and technological **convergences between ageing and organ healing** as well as how the **specific therapeutic approaches are used to protect and preserve the health and functionality of human body** intersect with Practical Healthy Human Longevity. As an overall product, this analytical case study offers a one-stop expert evaluation of a novel and dynamic industry with high growth potential.

Approach of the Report

Database

>490 Companies	>590 Investors	>50 R&D Centres

The database was formed by:

- **identifying the companies** that conduct or have conducted clinical or preclinical research; and
- **distinguishing the investors** that contributed money to these companies.

Applied Research and Analytics Methods

Descriptive Analysis	Mixed Data Research	Data Triangulation
Comparative Analysis	Qualitative Data Collection	Data Filtering

Data Sources

Media Overview (Articles, Press Releases)	Industry-Specialised Databases	Patent Analysis	Publicly Available Sources (Websites)	Industry Reports and Reviews

Relying on various research methods and analytics techniques, the analytical report provides a comprehensive overview of the Preclinical and Clinical Trials Industry. This approach has certain limitations, especially when using publicly available data sources and conducting secondary research. Aging Analytics Agency is not responsible for the quality of the secondary data presented herein; however, we do our best to eliminate the said risks by using different analytics techniques and cross-checking data. Please note that we did not deliberately exclude certain companies from our analysis. Nor were they excluded due to the data-filtering method used or difficulties encountered. The main reason for their non-inclusion was incomplete or missing information in the available sources.

Executive Summary

Regenerative medicine is multidisciplinary science that aims to regenerate or replace human cells, tissues or organs, to restore or establish normal function. Number of research in regenerative medicine is currently increasing. In this report we analyse the potential applications of different approaches such as small and large molecules, gene and cell therapy, tissue engineering and some medical devices in regenerative medicine. These include enabling novel therapy approaches and augmentation of endogenous cells for tissue regeneration, facilitating the generation of target cells, improving the interactions between cells and biomatrixes for tissue engineering, and enhancing endogenous stem cell function for tissue regeneration. We also analyse the potential challenges for small molecule drugs in regenerative medicine.

Numerous studies and clinical trials led experts to believe that regeneration is the important for treatment of the human systemic health worsening and premature aging.

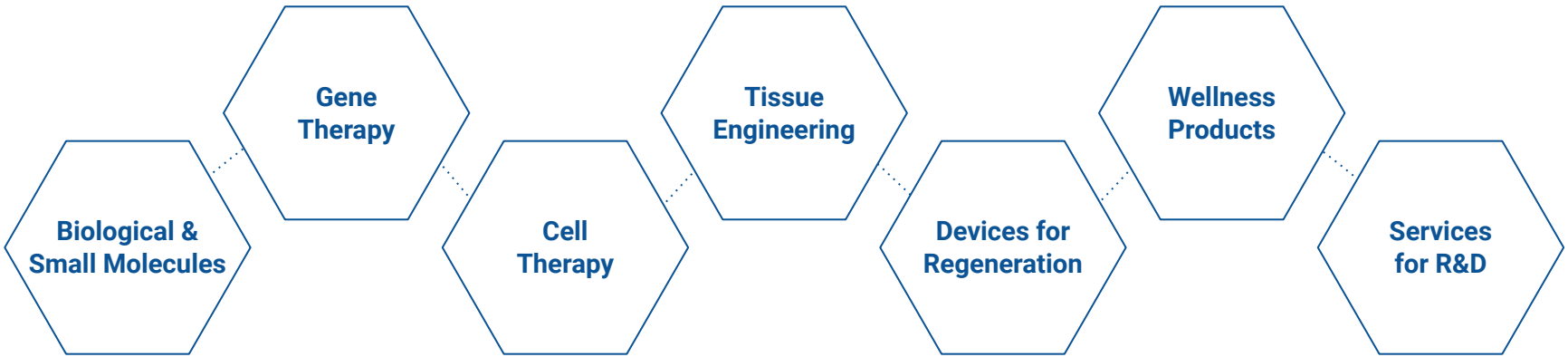
Main Features of the Analytical Case Study

- Robust Market Players Database
- Overview of Clinical Trials for Regeneration on all Phases
- In-depth Review of Notable Regeneration Trials for Aging
- Comparison of Clinical Trial Results
- Analysis of Service for R&D in Regenerative Medicine
- Trends on the Market of Regenerative Medicine

Regenerative Medicine Framework

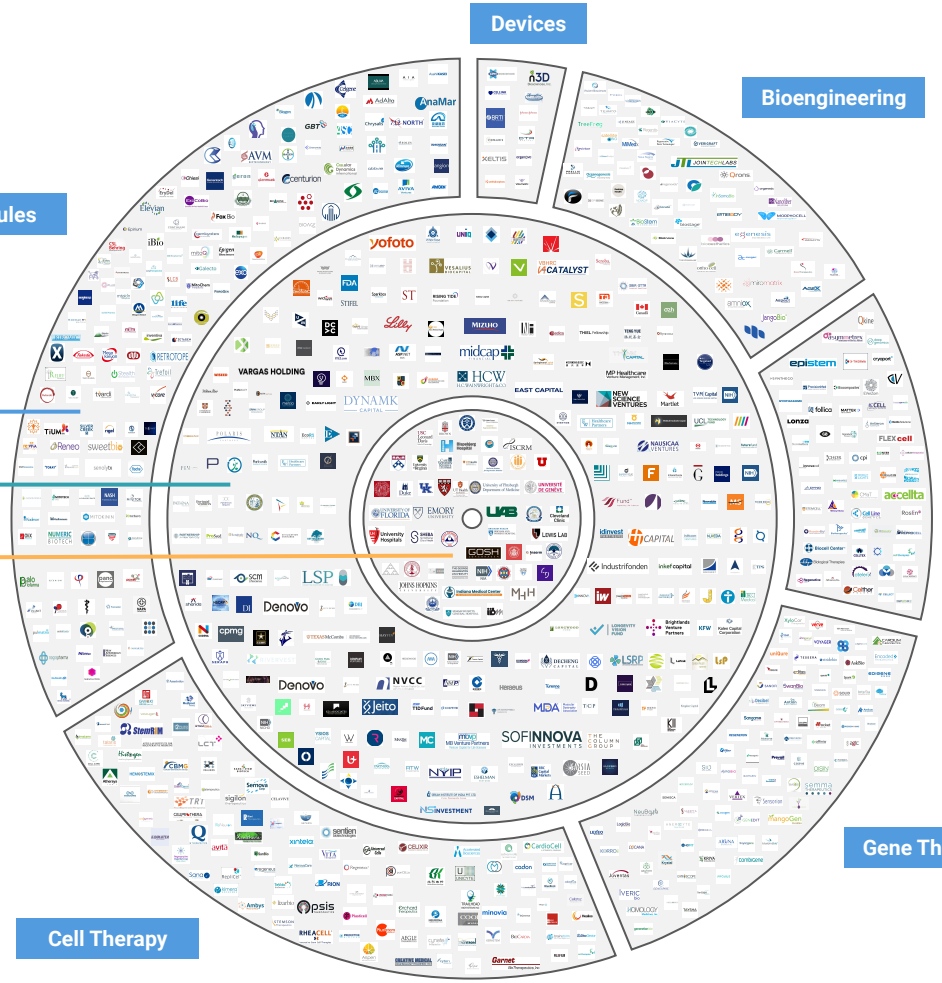
Before creating the database, we picked the **most significant fields of preclinical and clinical studies in Regenerative Medicine**. The categorisation of companies in the report is based on the main approaches that are applied to tissue and organ regeneration and is **supported by the latest scientific evidence.** We have analysed and compared the results on clinical efficacy for the advanced approaches. Based on this data, companies have been ranked and the most perspective technologies have selected. In this way, the framework not only offers a **comprehensive view of the market** but also **sustains relevance in advance to the development** of technologies and R&D approaches.

By Research Field



Regenerative Medicine Landscape Overview

Companies – >490
Investors – >590
R&D Centres – >50



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Regenerative Medicine Clinical Trials by Phase and Technology Types

Under Section 3033 of the 21st Century Cures Act, the **Regenerative Medicine Advanced Therapy** ("RMAT") Designation programme aim signed by the FDA in March 2017, a drug is eligible for RMAT designation if:

- the drug is a Regenerative Medicine therapy;
- the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; or
- preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.

A drug constitutes a "Regenerative Medicine therapy" if it is a **cell therapy**, **therapeutic tissue**, **engineering product**, **human cell** and **tissue product**, or any combination product using such therapies or products.

In accordance with some scientific concepts, **small and large molecules** that stimulate tissue regeneration and cell proliferation in injured sites in the patient`s organism are considered part of this category of regenerative therapies.

Clinical Trials - Q1 2022

~250
Clinical trials underway worldwide, end of Q1 2022

Ph-1: 48
Ph-1/2: 74
Ph-2: 65
Ph-3/4: 45

Number of Clinical Trials Utilizing Specific Technologies for Regeneration:

Small and Large Molecules *

Total: 87
Ph-1: 28
Ph-1/2: 4
Ph-2: 37
Ph-3/4: 18

Gene Therapy

Total: 38
Ph-1: 10
Ph-2: 22
Ph-3: 6

Cell Therapy

Total: 88
Ph-1/2: 70
Ph-3/4: 18

Tissue Engineering

Total: 19
Ph-1: 10
Ph-2: 6
Ph-3: 3

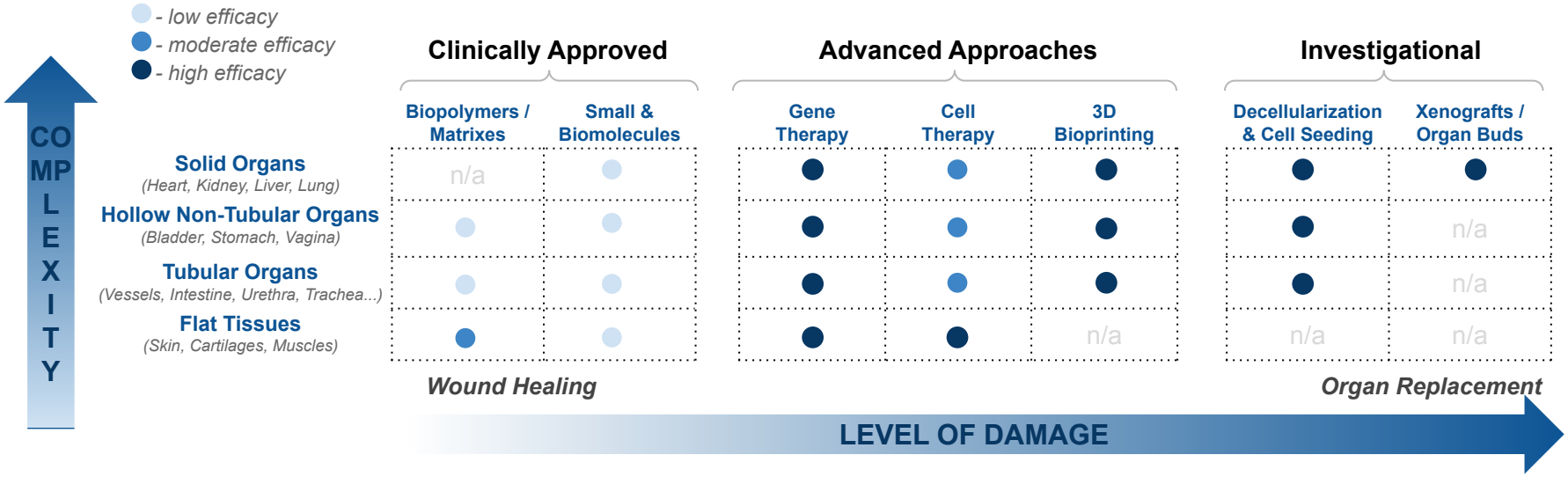
Medical Devices

Total: 25
(in clinical testing)

Note: *Anti-cancer programmes and immuno therapy are not included in analysis.*
** Stimulation host stem cells*

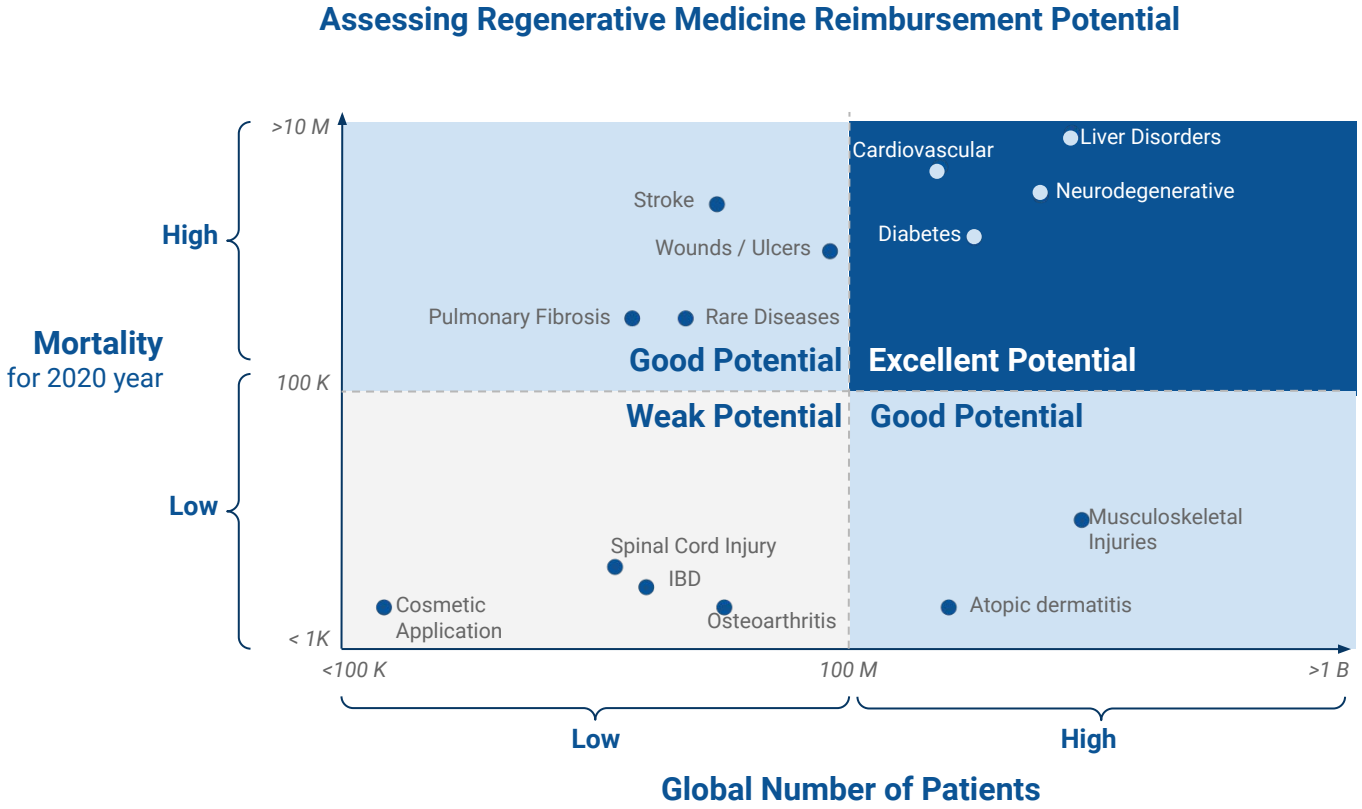
Source: Aging Analytics Agency analysis

Efficacy of Different Approaches



Depending on the **age of the patient,** some regenerative medicine strategies can utilize and **accelerate the body's own natural healing process**. These strategies are aimed at changing the tissue environment by the introduction of exogenous material and biological factors with the sole aim of accelerating and improving the body's healing process. Most **Biopolymers** and **Small & Biomolecules** are clinically approved but they are effective only for **regeneration of tissues on early stages**. **RMAT strategies** to be successful, the material used, mostly **combinations of scaffolds**, **growth factors**, and **stem cells**, must be able to **replace the damaged tissue** and be able to function as the original tissue or be able to stimulate regeneration of the original tissue. Cells used in regenerative medicine and tissue engineering can **come from the same patient** (autologous) or from **another individual** (allogeneic). In addition, **xenogenic cells** such as those from animals can also be adopted in regenerative medicine strategies. Cells that have been used so far include **stem cells**, **fibroblasts**, **chondrocytes**, and **keratinocytes**. Though allogeneic cells might **elicit an immune reaction**, this can be alleviated by prescribing immunosuppressants to patients.

Areas of Disease Expected as Possible Indications for Regenerative Medicine



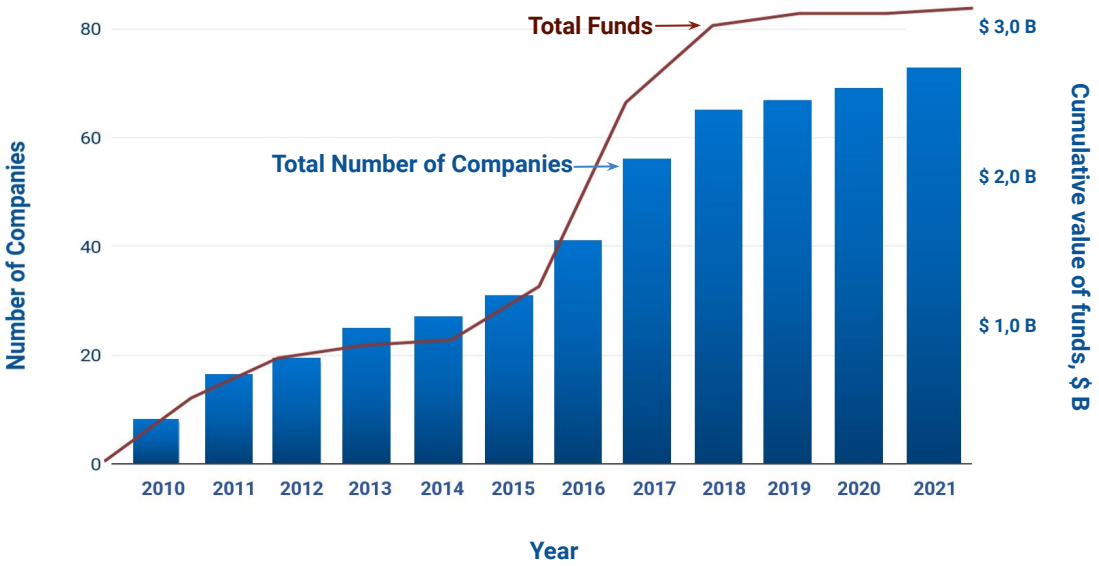
The **RMAT designation** offers a few important **benefits** to drug sponsors:

- increased and **earlier interactions with drug control agencies** to expedite development and review of the therapy;
- RMAT products may be eligible for **priority review** and **accelerated approval** by drug control agencies;
- once approved, sponsors of RMAT-designated products can satisfy **post-approval requirements** through the submission of real-world clinical evidence.

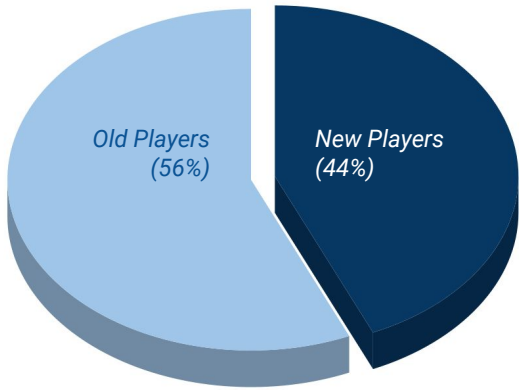
In most countries RMAT can be included to the reimbursement drug list with **100% compensation of cost**.

Growth of the Small and Large Molecule Industry

Cumulative Number of Companies and Total Value of their Funds, 2010-2021



Proportion of New Players on the Market, Q1 2022

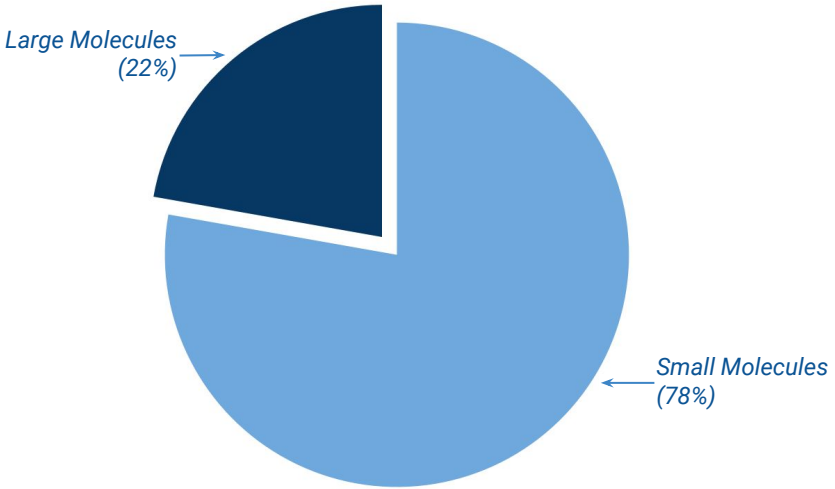


Though the most advanced therapies currently dominate headlines, small and large molecules remain of great significance for the industry – and patients. The share of **new players** on the market is **44%**. The small and large molecule **drug discovery market** for Regenerative Medicine is valued at approximately **USD 136.98 million** in Q1 2022, and it is **expected to reach to 35,261 million** by 2026, registering a **compound annual growth rate** (CAGR) of nearly **8.05%** during the forecast period, 2022-2026.

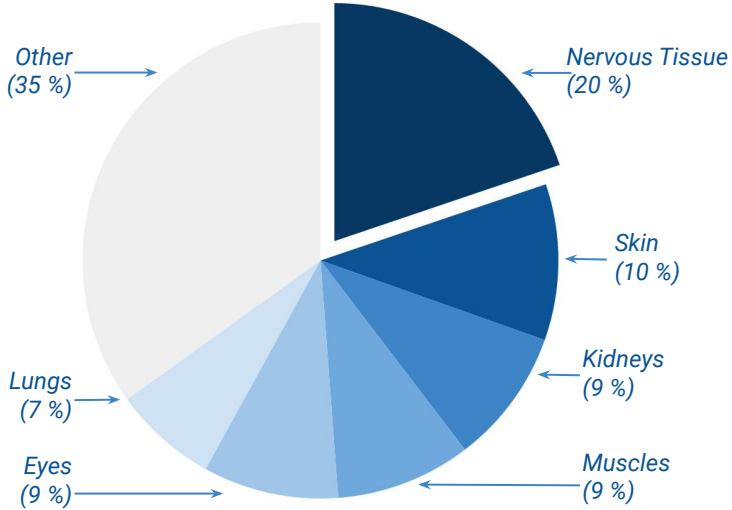
Source: Aging Analytics Agency analysis

Large Molecules vs Small Molecules in Regenerative Medicine

Different Approaches in Regenerative Medicine



Different Systems of Organs Targeted in Regenerative Medicine



Conventional regulation of regenerative pathways is possible with **large molecules** (proteins, peptides, natural products, etc.) and **small, chemical molecules**. They facilitate the **proliferation of target cells for tissue regeneration**. So far, **small molecules are used in 78% of the research programmes**, comparing to 22% using large biomolecules. The majority of programmes are directed for targeting specific organs. Regeneration of **Nervous Tissue contributes 20%** of the total number of regenerative programmes, while treatment of disorders of the Skin, Kidney Muscle, Eyes, and Lungs are each present in 7-10% of all research programmes. The regeneration of other organ systems such as Bone, Liver, Pancreas, Ears, etc. are also investigated in the report.

Source: Aging Analytics Agency analysis

List of Companies vs Pathways

Mitochondrial Pathways

DHODH OPA1 OMA1 PINK1 NAD+

mtCOXI,II DJ-1 APJ FXN SOD MTP

IGFR1 LRRK2 FRX ACC GLP1R etc...

Proliferation & Development

HGF c-MET Rho/ROCK GDF11

ESR1 PARP-δ PDGF Wnt3

Growth factors FGF-1 OGFR

Inflammation

Cytokines Growth factors

KOR PEG1 PGI2 PGES

HTRA1 CHF/CFI

Apoptosis and Senescence

FOX4/p53 Bcl-xl HSP70 Klotho

Telomerase HSP90 HIF1 mTOR

Proteases Bcl-2 HSP27 SIRT1,3

Angiogenesis & Extracellular Matrix

Tie2 CDH1 DCLK1

PKal VEGF Tumstatin

GTx Keratin Protein kinase

Metabolic Pathways

IGFR1 APJ SGLT2 CFTR GLA

GLP1/GIP Phospholipids SIRT1

mTOR Phosphotransferase AMPK

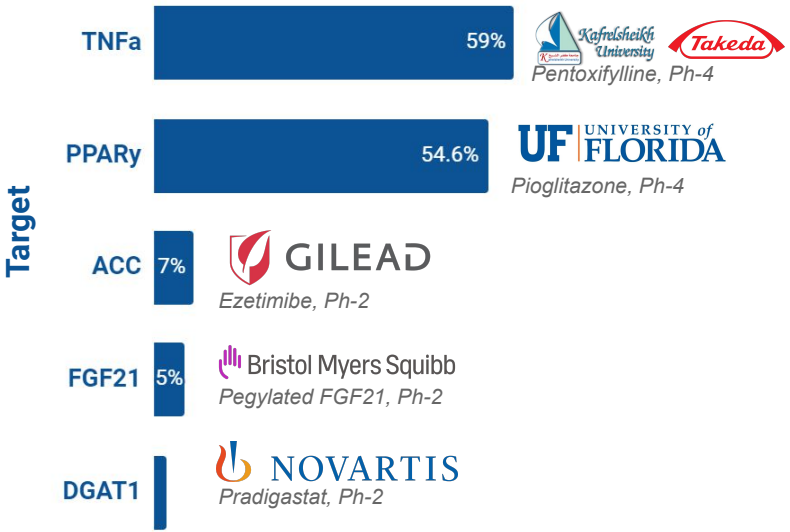
Note: Programs for anti-cancer and autoimmune disorders not included.

Source: Aginganalytics.com

Example of Clinical Efficacy for Selected Programmes

Liver Regeneration, %

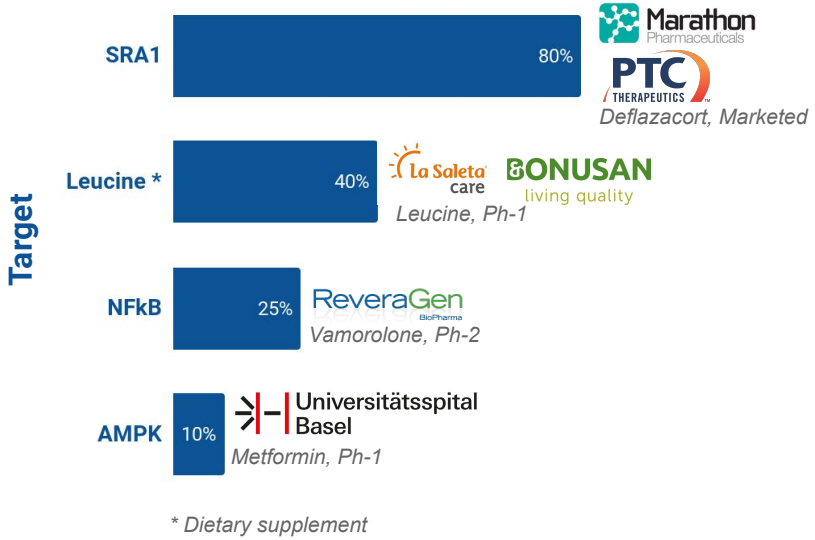
(NASH patients vs Placebo)



Note: liver regeneration = histologically confirmed reduction of fat in liver

Muscle Regeneration, %

(DMD patients vs Placebo)



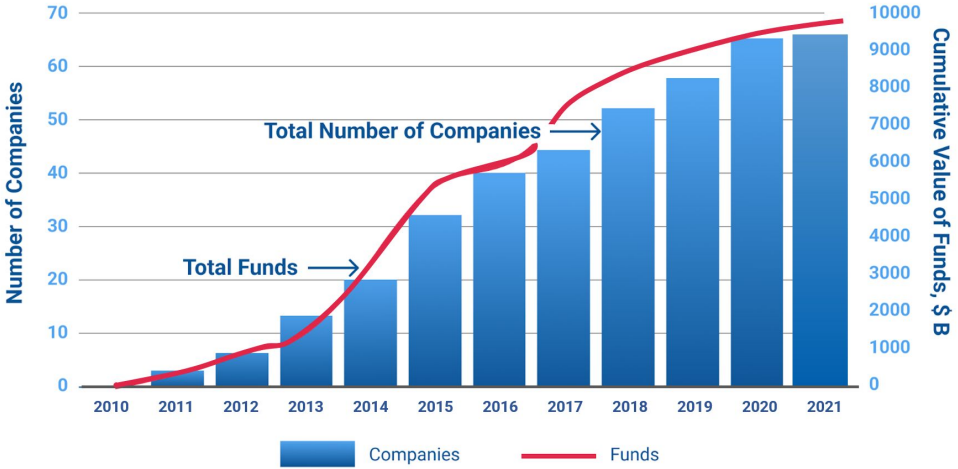
* *Dietary supplement*

Note: muscle regeneration = improvement of muscle function confirmed with walking test

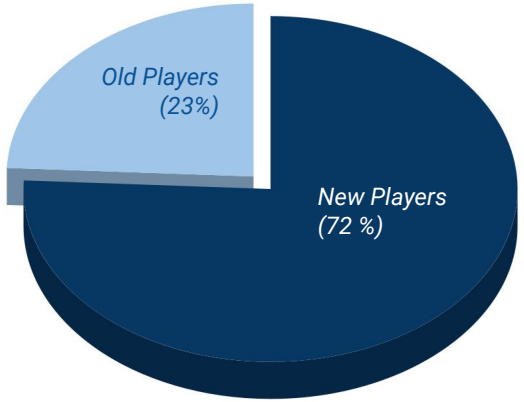
Source: Aging Analytics Agency analysis

Growth of Gene Therapy Market

Cumulative Number of Companies and Total Value of their Funds, 2010-2021



Share of New Players on the Market, Q1 2022

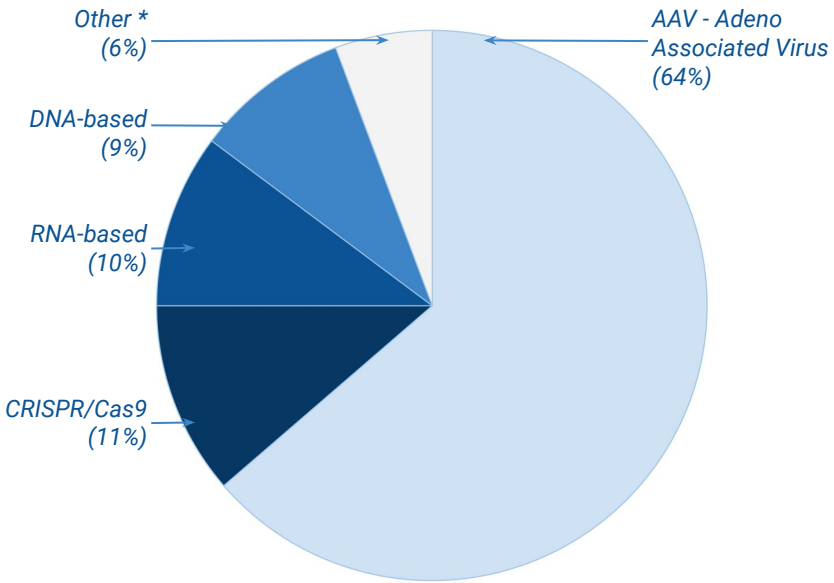


The Gene Therapy market has grown significantly over the last ten years. The share of new companies from the 2010-2020 period is 72%. The Gene Therapy **market** for Regenerative Medicine is valued at approximately **USD 9,314 million** as of Q1 2022, and it is **expected to increase two-fold** by 2026 at a **CAGR of ~28.5%**. Growth in this period resulted from an increase in investments in gene therapies, growth in research and development, a rise in public-private partnerships, strong economic growth in emerging markets, increased healthcare expenditure, and a rise in pharmaceutical R&D expenditure. **Currently, the market is restrained** by inadequate reimbursements, challenges due to regulatory changes, low healthcare access, and a limited number of treatment centres.

Source: Aging Analytics Agency analysis

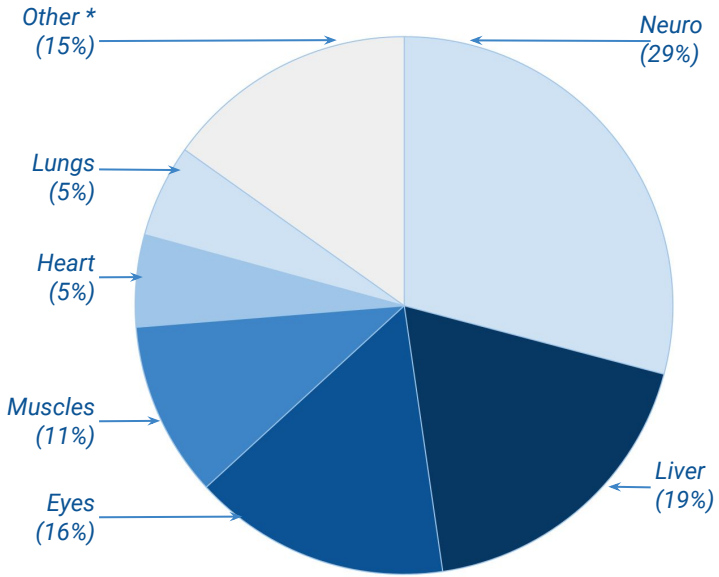
In vivo Gene Therapy & Gene Editing for Regenerative Medicine

Gene Approaches in Regenerative Medicine



** Other: Herpes virus, Baculovirus, Lentivirus, Adenovirus, Antisense Nucleotides*

Regeneration of Organs with Gene Therapy



** Other: Ears, Vessels, Soft Tissues, Cartilages*

Adeno-associated vectors (AAV), lentivirus, and **retrovirus** have been successfully implemented accounting for **19 FDA approved** gene therapy products. AAV gene delivery accounts for 64% of programmes in Regenerative Medicine. This novel gene delivery system effectively treats neurological, liver, eye, and muscle disorders. In vivo gene therapy drugs are directly injected into their target tissue or organ.

Source: Aging Analytics Agency analysis

List of Gene Therapy Companies and Delivered Genes

Metabolic Pathways

CFTR SGSH NAGLU ARSA
GAA I-1c FKRP GLA GBA1 MFN2
GALC G6PAse OTC *(+30 more)*

Treatment products

4DMT, AskBio, affinia THERAPEUTICS, Abeona THERAPEUTICS, POSEIDA THERAPEUTICS, FREELINE THERAPEUTICS, PassageBio, CRISPR THERAPEUTICS, ultragenyx, arbor, spirovant, SANOFI, Spark THERAPEUTICS, Beam THERAPEUTICS

20+ Companies

Cellular Architecture

MYO7A RPGR CHM AGA FIG4 CNGB3
OTOF AQP1 CLRN1 GJB2 RHO RPE65
CEP290 R2E3 UPF1 USH1G

Treatment products

agtc, GenSight BIOLOGICS, AKOUOS, ATSENA Therapeutics, editas MEDICINE, MEIRAGTx, SwanBio THERAPEUTICS, ocugen, IVERIC BIO, Sensorion The Inner Ear Diseases Company, Decibel THERAPEUTICS

Developmental Pathways

GDNF PDGF HTT SMN1 MECP2
ATOH1 USH2A HGF RORa
BEST1 TNNI4 CX43 PKP2 FXN

Treatment products

AskBio, mangoGen PHARMA, coave, Voyager THERAPEUTICS, LOCANA, avalis, LEXEO therapeutics, ocugen, IVERIC BIO, HELIXMITH, editas MEDICINE, Decibel THERAPEUTICS

Angiogenesis

VEGF
KLKB1
FGF4

Treatment products

ADVERUM, CARDIUM THERAPEUTICS, REGENXBIO, AKOUOS, Oxford Biomedica, XyloCor Therapeutics, HUMAN STEM CELLS INSTITUTE, Intellia THERAPEUTICS, Pfizer

Other Pathways

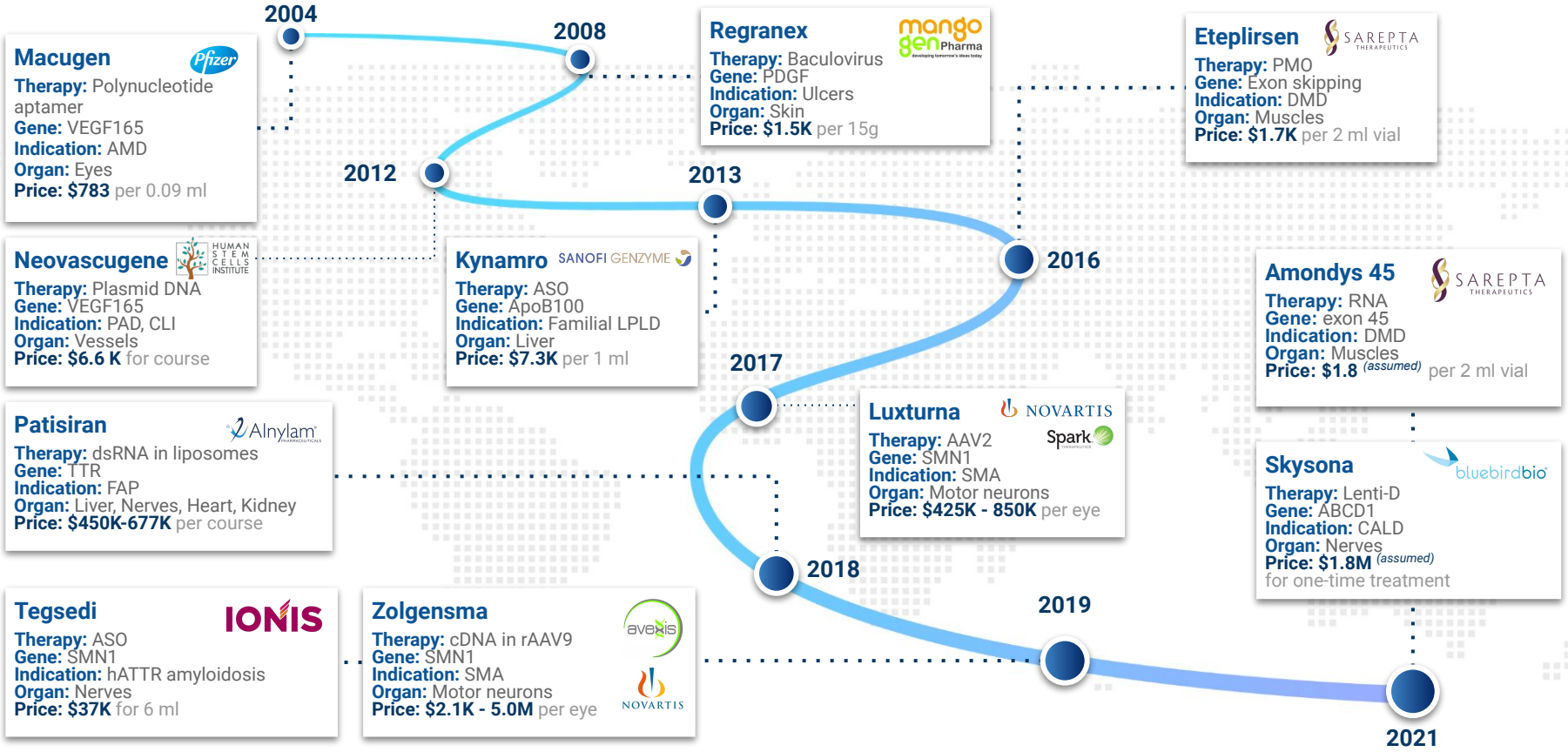
COL7A1 GTx CCR5 TGM1 ND1/4
NXNL1 SCN1A CFH CFI HTRA1
SOD Lamina 332 p16 FOXO3

Treatment products

Antion BIOSCIENCES, SPARING VISION, ARUNABIO, HOLOSTEM THERAPEUTICS, Voyager THERAPEUTICS, gemini, GenSight BIOLOGICS, Encoded THERAPEUTICS, OISÍN BIOTECHNOLOGIES, GYROSCOPE VISION FOR LIFE, innoskel, SENISCA, Krystal

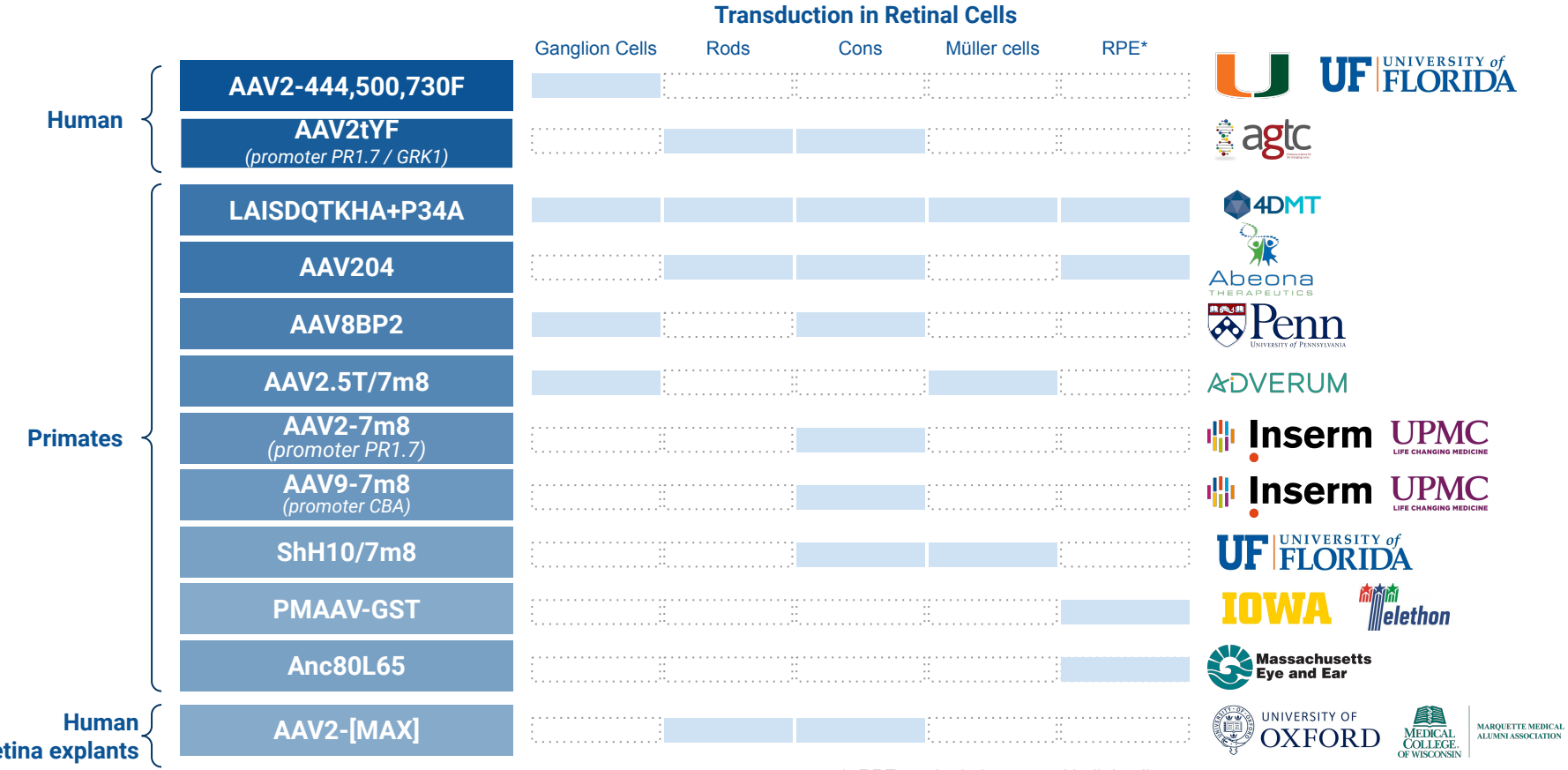
Source: Aginganalytics.com

Approved Gene Therapy Products for Regenerative Medicine (non-Cancer)



Source: Aging Analytics Agency analysis

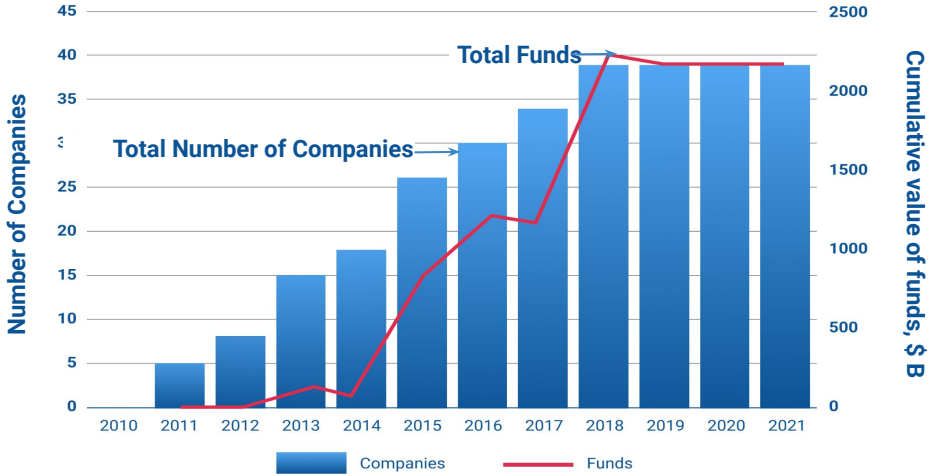
Efficacy: Transduction of New AAV Capsids in Retinal Cells



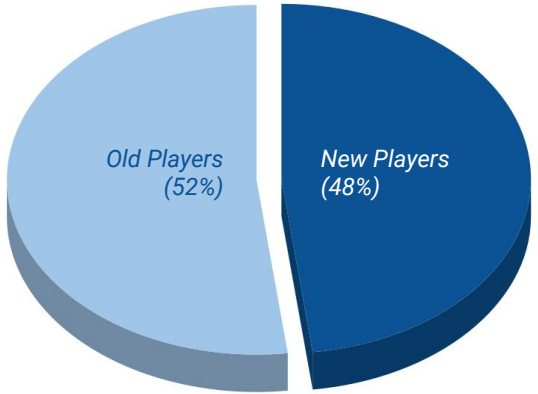
* RPE - retinal pigment epithelial cells

Growth of Cell Therapy Market

Cumulative Number of Companies and Total Value of their Funds, 2010-2021



Share of New Players on the Market, Q1 2022

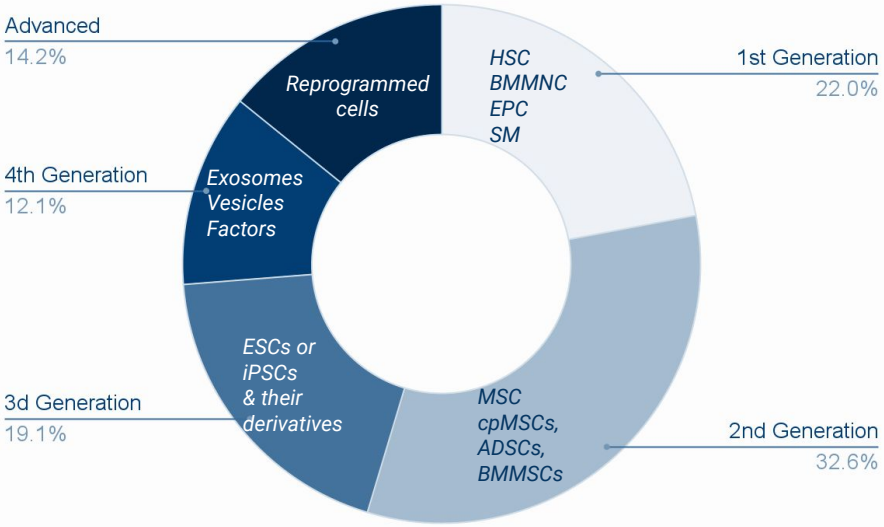


The Cell Therapy market for Regenerative Medicine has shown an uneven pattern of growth during the last ten years. Only in 2015 and 2018 was significant growth noticed in the number of new companies. In the last two years, the **market shows stagnation**. This is the result not only of the worldwide effects of the COVID-19 pandemic but also of the high health risks associated with cell therapy.
The share of new and old players is approximately 50:50. The Cell Therapy **market** is valued at approximately **USD 2,193 million** as for Q1 2022. The CAGR for the total market (including cell therapy for oncology such as CAR-T and other forms) is about 14.5%. For the Regenerative Medicine market, this rate is only half of that, and **no significant market growth is expected over the next five years.** Just like the Gene Therapy market, the Cell Therapy **market is currently held back** by inadequate reimbursements, challenges due to regulatory changes, low healthcare access, and a limited number of treatment centres.

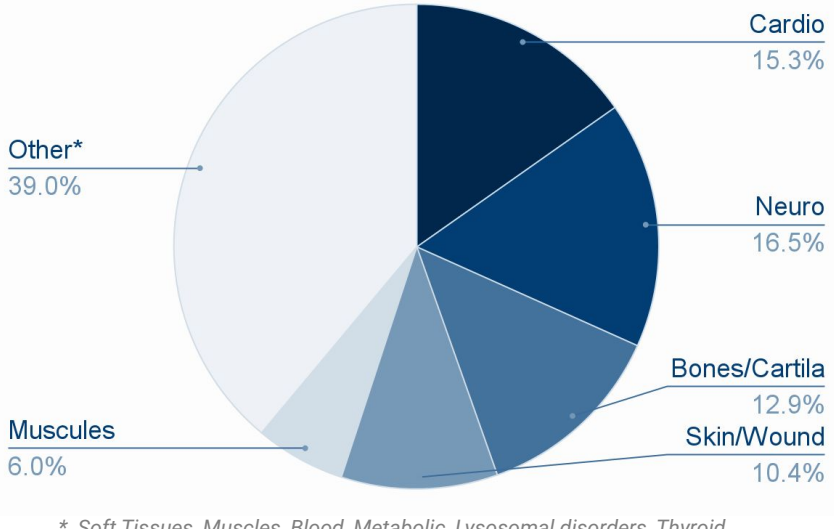
Source: Aging Analytics Agency analysis

Cell Therapy in Regenerative Medicine

Cell therapy Generations in Regenerative Medicine



Regeneration of Organs with Cell therapy



** Soft Tissues, Muscles, Blood, Metabolic, Lysosomal disorders, Thyroid gland, Thymus, Pancreas, Reproductive system, Intestine, Hair loss, Aging*

The most popular current type of the Cell Therapy belongs to the **2nd Generation** and is based on **multipotent adult tissue derived stem/progenitor cells** with **low immunogenicity**. Next generations are created to provide possibilities to obtain **any specialised cell type** (**3rd Generation**), **cell-free therapy** (**4th Generation**), and to **edit cell properties** in accordance with clinical demand (**Advanced**). Cell Therapy replaces a variety of injured organs, most of programs target nerve tissue (16.5%), heart and vascular system (15.3%), bones and cartilages (12.9%), and skin (10.4%).

List of Companies vs Cell therapy Generation

1st Generation

Oligopotent somatic stem cells / Tissue-specific cell types

Replacement of injured cells, pure populations of therapeutic cells

Heterogeneous outcomes

Treatment products

14+ Companies

2nd Generation

Multipotent stem cells with paracrine activity: MSCs, BMSCs, ADSCs

Replacement /Host cells mobilization / Angiogenesis / Immunomodulation/ Immune-privileged

Limited set of possible cell types Limited expansion potential

Treatment products

15+ Companies

3d Generation

Pluripotent stem cells (ESCs, iPSCs) / Induced progenitor cells

Ability to differentiate to any specialized cell types

Immunogenicity

Treatment products

12+ Companies

4th Generation

Cell free (acellular) therapy: conditioned media, exosomes, extracellular vesicles

Secretome (enzymes, growth factors, cytokines, RNAs, microRNAs) Low or null immunogenicity

Low potential for cell replacement

Treatment products

9+ Companies

Advanced

Reprogramming, cell engineering, gene editing (HLA engineering etc)

Any desired cell type, Immune privileged

Unclear safety

Treatment products

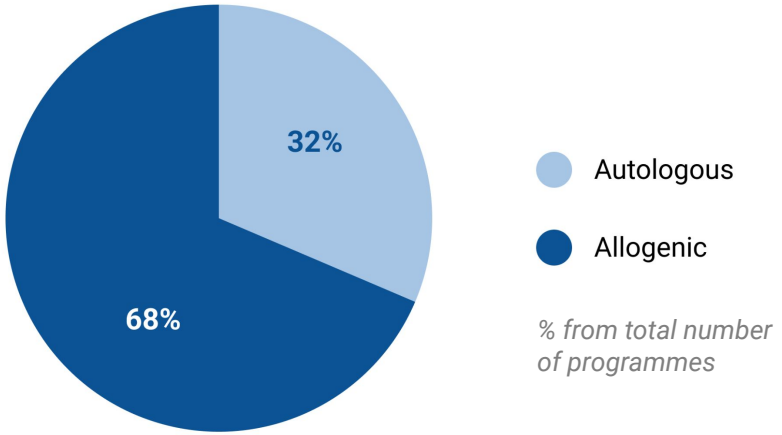
7+ Companies

Somatic stem cells/Tissue-specific cells and **multipotent stem/progenitor cells** are widely developed currently. **Pluripotent ESCs/iPSCs platforms** with ability to get any cell type follow them. **Exosomes** are attractive due to the simplicity of manufacture, low immunogenicity. **Advanced cell therapy** with **cell reprogramming/editing technologies** is novel approach which is potentially possible to solve all bottlenecks of current cell therapy approaches.

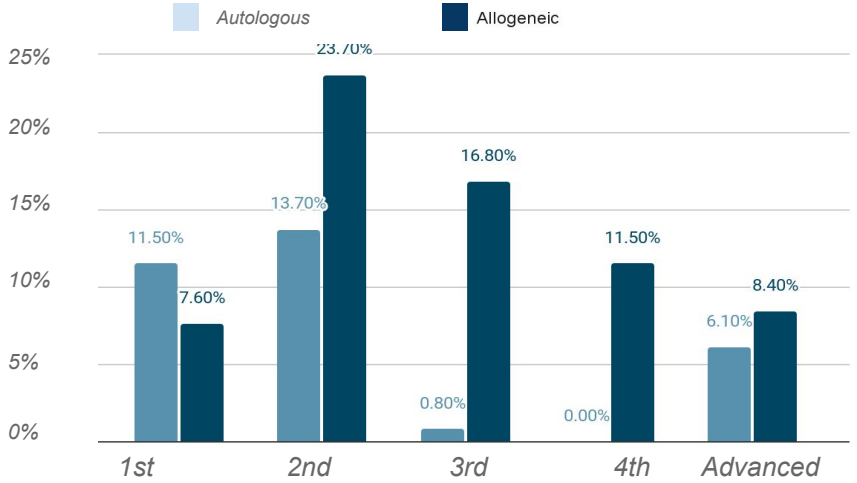
Source: Aginganalytics.com

Different Approaches of Personalised Cell Therapy Products

Proportion of Cell Therapy Generations Approaches on the Market



Different Approaches vs Cell Therapy Generations



Autologous cells are cells isolated from the patient's tissue sample. Autologous cell therapy is a **patient-oriented approach** with the benefits of **high safety**, **null immunogenicity**, and **no need of immunosuppressant therapy**. However, production of autologous cells often requires a lengthy procedure for each patient, and this is why it is **not appropriate for ready-to-use product creation**. It is also **difficult to standardise** autologous cell manufacturing. Moreover, the cells isolated from a patient's own tissues may already be **injured** or possess **reduced regenerative potential**.

Allogeneic therapy uses **standardised cells** from **healthy donors** which are expanded and cryopreserved as **ready-to-use off-the-shelf products** to treat urgent states. A **bottleneck** of allogeneic therapy is **immunogenicity**; it is solved in different ways in subsequent generations of cell therapies. That is why allogeneic cell therapy has become the leading approach.

Source: Aging Analytics Agency analysis

Geography of Approved Cell Therapy Medical Products (non-Cancer)

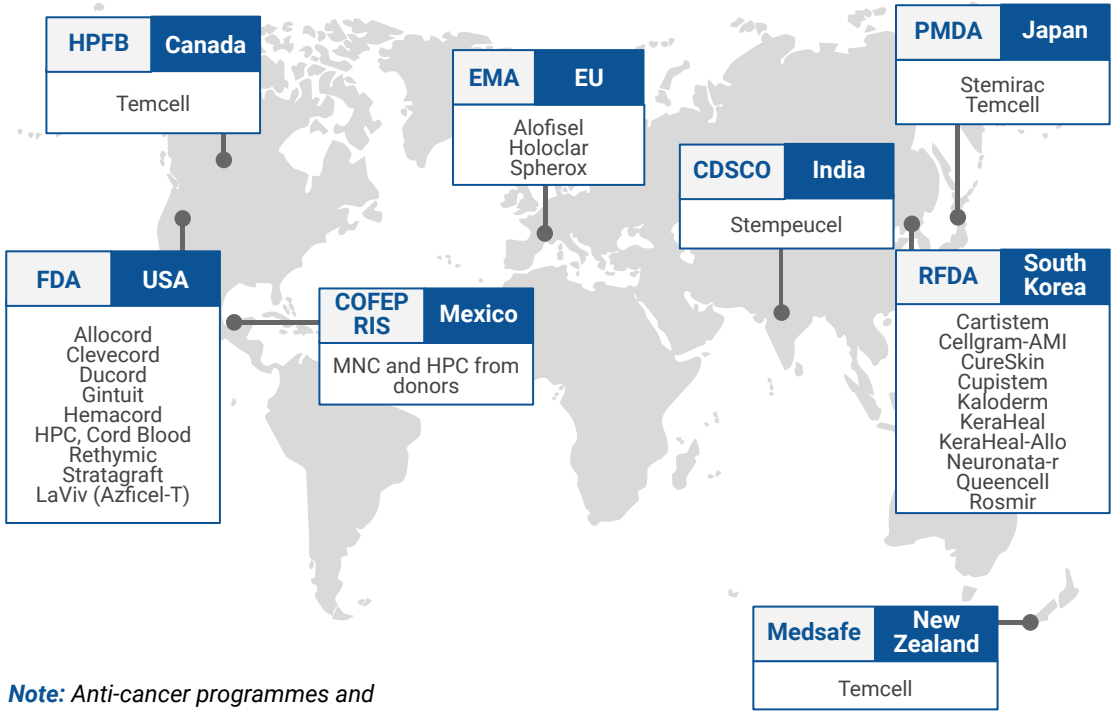
The current boom in cell-based therapy research started more than ten years ago. Until this time some advanced therapies were launched on the world market. The leaders are the **USA** and **South Korea**. These countries were the first to create the regulatory procedures for registering cell therapy medical products and to allow their use in clinical practice.

Medical products approved for use **in the USA** include **hematologic** products (Allocord, Clevecord, Ducord, Hemacord etc.), **skin treatment and wound healing** (Gintuit, Stratagraft, LaViv) and **thymus regeneration** (Rethymic).

In **South Korea**, advanced cell therapy is oriented towards the treatment of **cartilages** (Cartistem, Cupistem), **myocardial infarction** (Cellgram-AMI), **skin and wound healing** (CureSkin, Queencell, Rosmir, Kaloderm, KeraHeal, KeraHeal-Allo), and **neurological disorders** (Neuronata-r).

One such product is **Temcell** (also known at Prochymal), an allogeneic MSC indicated for **acute radiation injury**, **COPD***, **Crohn's disease**, **GvHD****, **Type I diabetes** and **myocardial infarction**. Fully approved by Japan in October 2015 and conditionally approved in Canada and New Zealand.

** COPD - chronic obstructive pulmonary disease;*
*** GvHD - graft-versus-host disease*

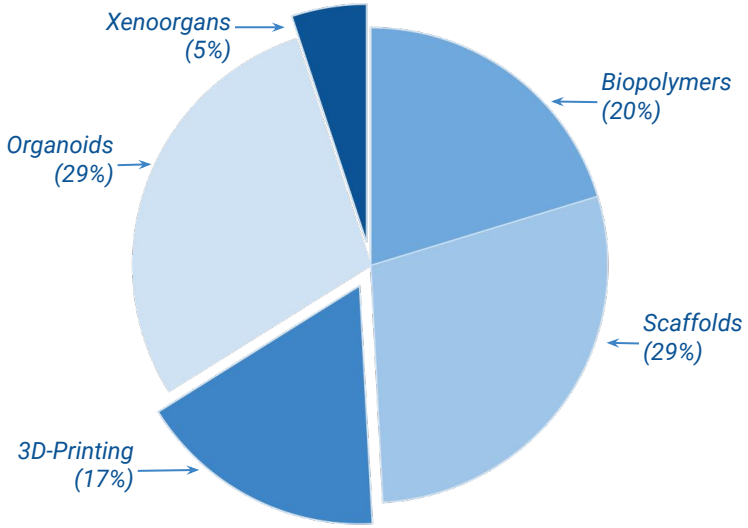


Note: *Anti-cancer programmes and Immunotherapy are not included*

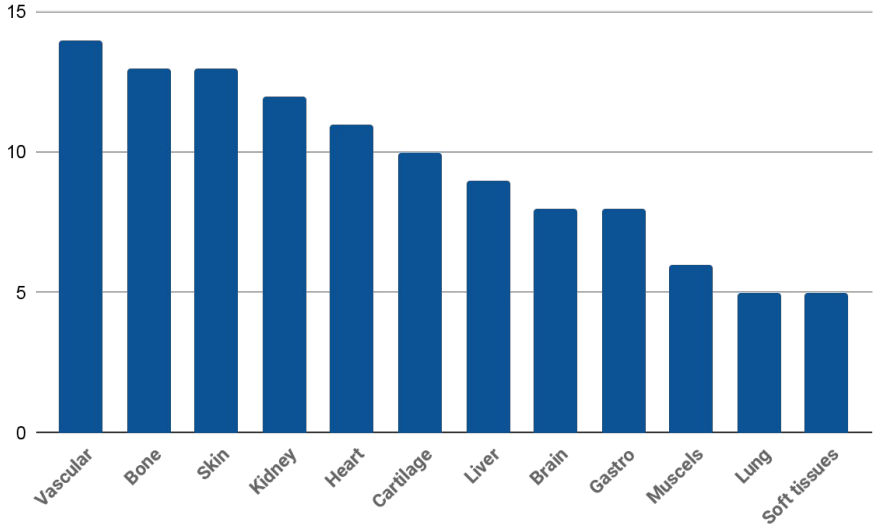
Source: Aging Analytics Agency analysis

Tissue & Organ Engineering in Regenerative Medicine

Distribution of Companies by Approach



Distribution of Programmes by Target Organ/Tissue



The most popular approaches for tissue and organ bioengineering are **organoids** and **scaffolds**, with **57.6%** of all companies that specialise in bioengineering implementing one of these approaches. These approaches are followed by **biopolymers** (**20.3%** of all companies) and **3D-bioprinting** (**16.9%**).

The majority of programmes target **vascular tissues** (**14 programmes**), closely followed by **bones** and **skin** (**13 programmes** each). The dominance of these tissues in the programmes can be explained by the relative simplicity of the tissues structures.

Source: Aging Analytics Agency analysis

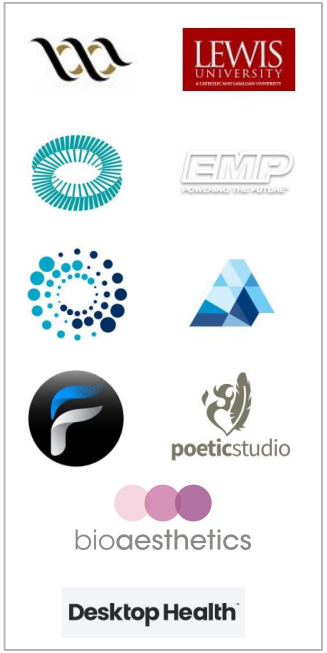
List of Companies

Organoids

Scaffolds

Biopolymers

3D-bioprinting



Chimera

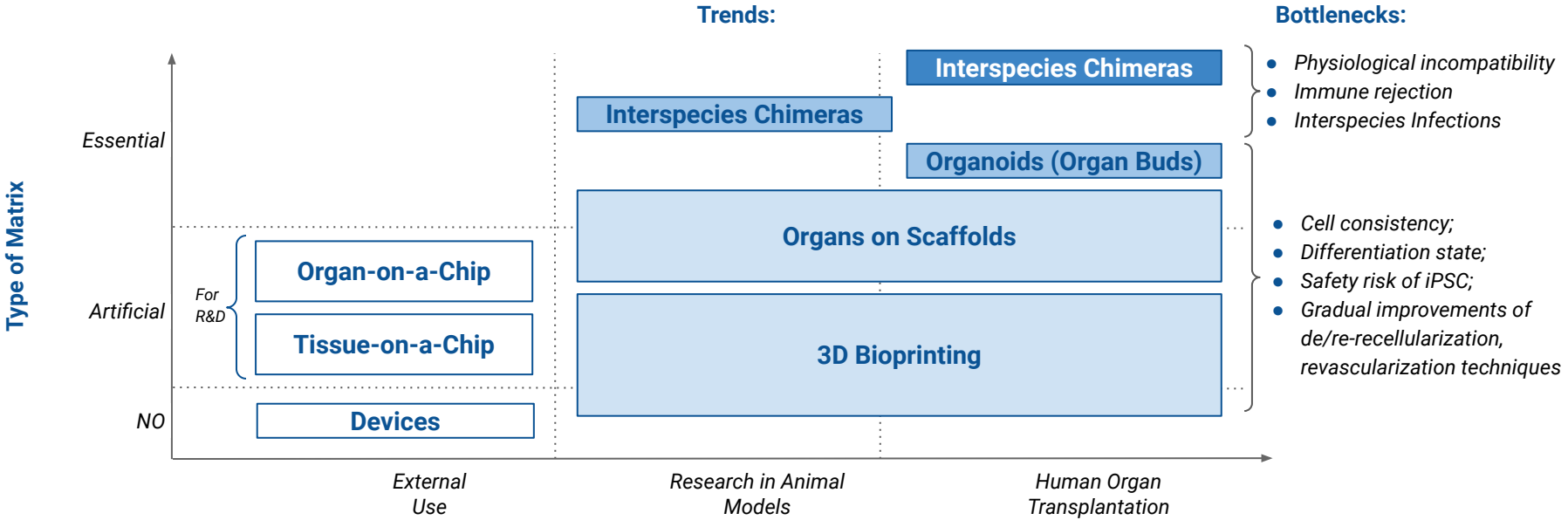
Xenoorgans

Nanobiotechnology

Note: Scaffolds and organoids are the most popular technology in the market. The reason for this may be the relative simplicity of these techniques. Biopolymers and 3D-bioprinting follow them.

Source: Aginganalytics.com

Biomanufacturing: Trends and Bottlenecks of Organ Engineering



There is reason to hope that **organ engineering** will become a commercial reality within the next decade. However, there are still several major barriers to commercialisation that need to be systematically addressed. **Engineering whole-organ** constructs with homogenous cell density and adequate cell populations **is a significant technical barrier.** To address this, stem-cell research must be developed to improve cell invasion and adhesion of organ constructs. Though the **organs on scaffolds and cell bioprinting** approaches have demonstrated the ability to **incorporate multiple cell types** into engineered organ constructs, this is often for the purpose of replicating just a single part of an organ's function, rather than replicating the entirety of the organ's functions. Regulatory pathways are an additional challenge for the utilisation of engineered whole organs as viable transplants and are principal among the non-technical barriers to commercial implementation.

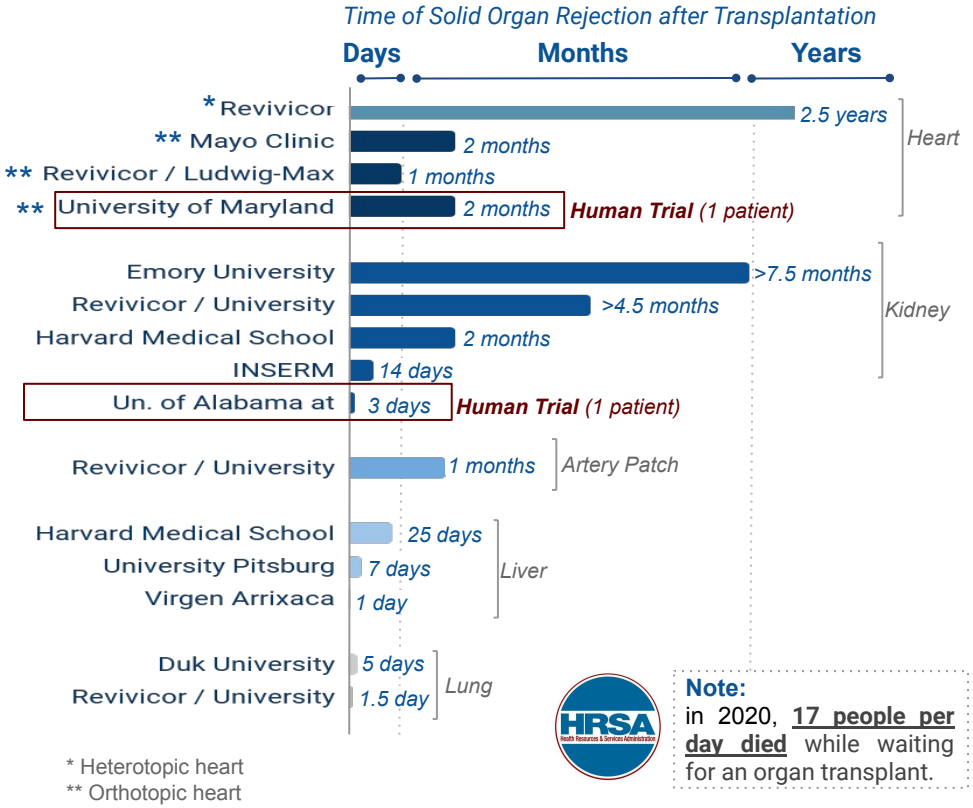
Source: Aging Analytics Agency analysis

Stages of Development of Different Approaches

Note: Biopolymers are the most primitive technology, so most companies with this technology have already entered the market or are going through clinical studies. Many companies have succeeded with **scaffold technology**: most of such products have already entered the market or are in clinical trials. **3D-bioprinting** is a complex technology, and the majority of programmes that implement 3D-bioprinting are conducting pre-clinical trials or are in the early development stage.

Source: Aging Analytics Agency analysis

Preclinical Efficacy of Xenotransplantation from Pig to Primate



Note:
in 2020, **17 people per day died** while waiting for an organ transplant.

The increasing life expectancy of humans has led to **growing numbers of patients with chronic diseases and end-stage organ failure**. Transplantation is an effective approach for the treatment of end-stage organ failure; however, the **imbalance between organ supply and the demand** for human organs is a bottleneck for clinical transplantation. **Xenotransplantation** might be a promising alternative approach to bridge the gap between the supply and demand of organs, tissues, and cells; however, **immunological barriers** are limiting factors in clinical xenotransplantation.

Thanks to **genetically modified pigs** and **immunosuppressive therapy**, survival time results for xenografts have improved considerably in preclinical xenotransplantation models. Today, the **survival** of pig-to-nonhuman primate heterotopic heart and kidney xenotransplantation **reached >2.5 years and >7.5 months**, respectively. The leaders in this field of research are **Revivicor**, **Emory University** and **Harvard Medical School**. The availability of multiple-gene pigs (5 or 6 genetic modifications) and/or newer costimulation blockade agents significantly contributed to this success.

Now, **the field is getting ready for clinical trials** with an international consensus. Questions regarding the **regulatory challenges** and **ethical concerns** regarding clinical xenotransplantation are being asked worldwide. In 2003, the **US FDA published** comprehensive **guidelines for xenotransplantation**. In January 2022, surgeons at the **University of Alabama at Birmingham** reported that they had for the first time successfully **transplanted kidneys** from a genetically modified pig into the abdomen of a **57-year-old brain-dead man**. The kidneys functioned and produced urine for **three days**.

At the same time a **genetically modified pig heart** was transplanted into **57-year-old David Bennett** at the **University of Maryland Medical Centre in Baltimore**. After surgery the patient has **lived 2 months**

Source: Aging Analytics Agency analysis

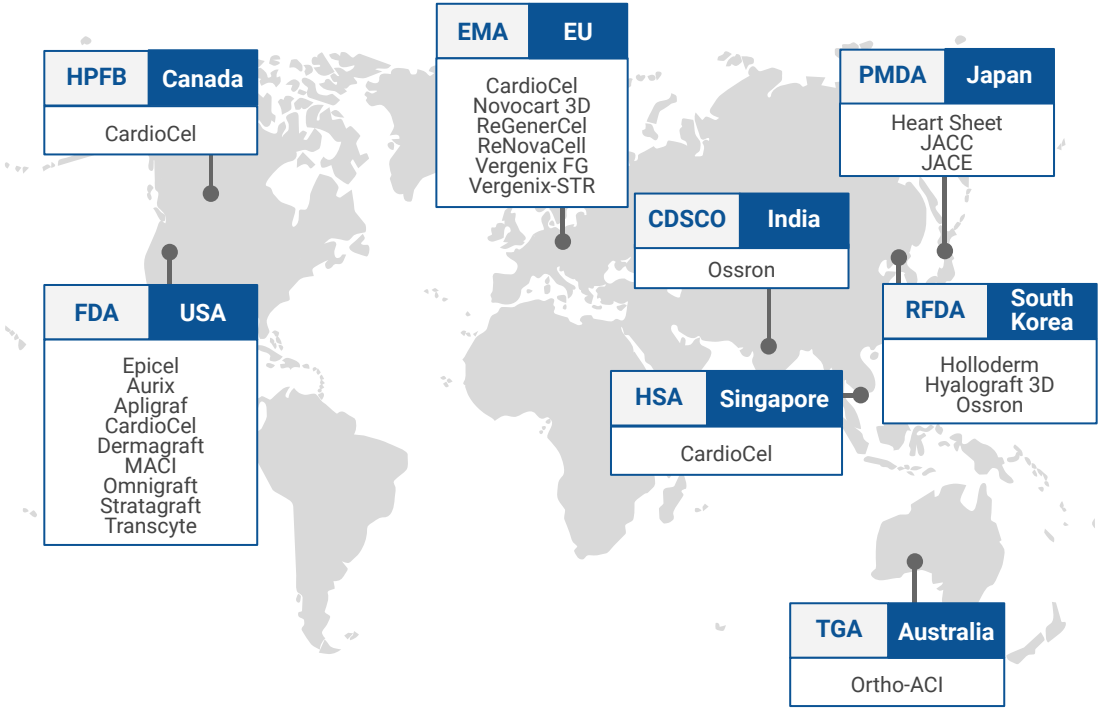
Distribution of Tissue-Engineered Products Approval by Region

The first tissue-engineered product used in clinical practice is **Epicel (Vericel)**, a permanent skin replacement product grown from a patient's own skin cells. Epicel has been used in **the USA** and other countries **since 1988**; it was approved in the USA **in 2007** as a **Humanitarian Use Device (HUD)** under a Humanitarian Device Exemption (HDE). Now almost all tissue-engineered medical products approved in different countries are used for **treatment skin or cartilages**.

But a few products really deserve more attention, including **CardioCel (CadMedus) –** a **cardiovascular scaffold** which facilitates endogenous stem cells and other cells to regenerate and repair damaged tissue for the treatment of **cardiovascular abnormalities**. This product was marketed in the **USA** from **2014**; marketed in **Europe** under CE Mark as of **2013**; received medical device license in **Canada** in **2014**; approved in **Singapore** in **2015**.

Heart Sheet (Terumo BCT) – an autologous skeletal myoblast preparation approved in **Japan in 2015** for the treatment of patients with **serious heart failure**.

Ossron – an autologous bone cell implantation for the treatment of **bone defects** in patients caused by degeneration, drugs, intense physical stress, diet, genetics, obesity, smoking, alcohol or disease. Approved in **South Korea in 2009**, approved in **India in 2017**.



Note: *Anti-cancer programmes and Immunotherapy are not included*

Source: Aging Analytics Agency analysis

List of Companies by the Device Type

Cell Delivery System	Wound Care	Cosmetology	Surgical Repair
Immunoprotection	Hygienic Wound State	Body/Face Bio-stimulation	Synthetic & Natural Materials
Targeted delivery	Wound bed preparation	Collagen & Elastin Synthesis	Tissue restoration
Increased efficacy of Cell therapy	Optimal Healing	Hair Growth	Artificial Grafts

Different **Devices for Regenerative Medicine** are developed currently on the market. **Cell Delivery systems** are provided to improve Cell Therapy outcomes, to ensure cell or therapeutic factors effect in target injured site. **Wound Care Devices** are applied for advanced treatment both of Surgical and Chronic Wounds. **Surgical Repair Devices** are used to provide matrix for cell migration, to connect and fix damaged tissues. Devices For **Cosmetology** provide solutions to support health state of skin, muscle, hair and are attractive due to possibility of use the devices at home.

Source: Aginganalytics.com

Application of Devices for Cell Delivery

Device Features for Delivery of Regenerative Medicine

	Device Type	Cell Type	Targeted delivery	Cell immobilization *in target site*	Implanted Cell Retrieval	Low Immunogenicity	Cell Factors Release	Application
External devices	**Spraying System**	Keratinocytes MSCs	✓	✓	*No*	*No*	✓	*Wound treatment*
External devices	**Magnetic Patch**	Corneal Endothelial Cells	✓	✓	*No*	*No*	✓	*Corneal edema, Glaucoma, Macular Degeneration*
External devices	**Cell Factors Delivery**	MSCs	*No*	*No*	✓	✓	✓	*Kidney injury, Myocardial Infarction, Diabetes type I, GVHD **
Implantation devices	**Islets Delivery**	Pancreatic cells	*No*	*No*	✓	✓	✓	*Diabetes*

** GVHD - graft-versus-host disease*

Benefits of Devices for Wound Care

Device Features for Delivery of Regenerative Medicine

	Device type	Debridement	Antimicrobial Action	Moist Environment	Angiogenesis Promotion	Tissue Granulation	Exudate Management	Application	
Wound Therapy	Negative Pressure	No	✓	No	✓	✓	✓	Chronic Wounds	Smith+Nephew
	Bioelectric Therapy	No	✓	No	✓	✓	No	Wounds	VOMARIS
	Skin Adhesive Applicator	No	✓	No	No	No	No	Surgical Wounds	Johnson & Johnson MEDICAL DEVICES COMPANIES
Wound Dressings	Collagen Sheet	✓	✓	✓	✓	✓	✓	Chronic Wounds Ulcers	Organogenesis Empowering Healing
	Hydrocolloids Foams / Films	✓	✓	✓	✓	✓	✓	Chronic Wounds Ulcers	CPN BIOSCIENCES; B|BRAUN SHARING EXPERTISE

Benefits of Devices for Surgical Repair

	Device type	Tissue Replacement	Function Restore	Scaffold *(patient's cell migration)*	Integration with host tissue	Bio-absorbable	Tissue Regeneration	Application	
Orthopedic *Devices*	**Calcium Composites**	✓	✓	✓	✓	✓	✓	*Bone fractures Ligaments reconstruction*	Biocomposites
	Osteoconductive Matrix	✓	*Time consuming*	✓	✓	✓	✓	*Surgical & Sport medicines*	Organogenesis
	Integrated Knee	✓	✓	*No*	✓	*No*	*No*	*Joint reconstruction*	Johnson & Johnson
Cardio-vascular *Devices*	**Artificial Heart Valves / Vessel Grafts**	✓	✓	✓	✓	✓	✓	*CVD CKD*	XELTIS
Nerve *Devices*	**Nerve Graft / Connector / Protector**	✓	✓	✓	✓	✓	✓	*Peripheral nerve function restore*	axogen

CVD - cardiovascular disease, CKD - chronic kidney disease

Source: Aginganalytics.com

Market and Tech Trends

Q3 2021

Regenerative Medicine for Aging: SWOT Analysis

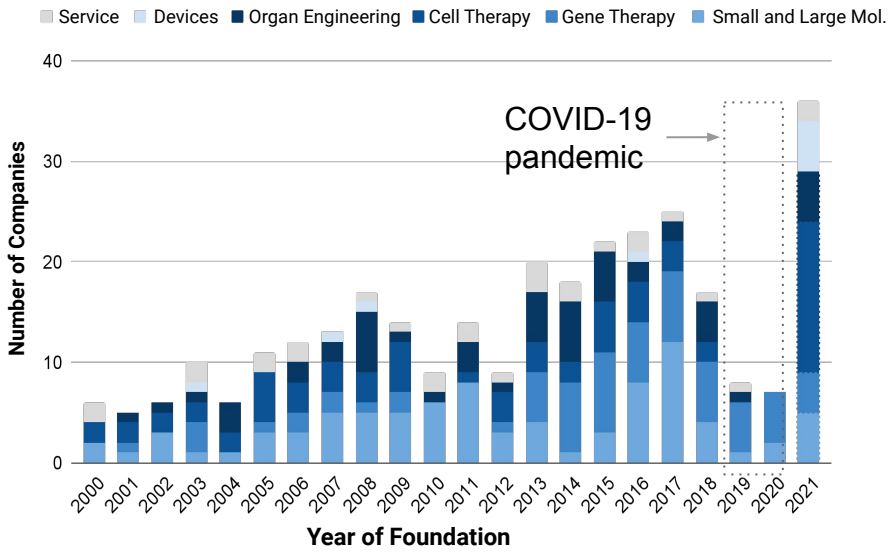
	Strengths	Weaknesses	Opportunities	Threats
Small Molecules	●Variability of compounds for regulation of different pathways ●Cheap cost of developing new drug candidates	●Possible adverse effects ●Low efficacy on the latest stages of disease	●Stimulation of self-healing processes ●Development drugs with lower adverse effects ●Repeated use of therapy as needed	●Low clinical efficacy ●High competition in the market
Gene Therapy	●High clinical and economical value ●Single or acute administration ●Targeting underlying biology ●Dramatic magnitude of effect	●Repeat administration may not be feasible ●Irreversible procedure ●Potential inability to switch to alternative therapies	●Potential for surge adoption at approval ●Raising awareness of current use and research efforts ●Current research offers better understanding of certain disease	●Higher one-time price ●Long-term clinically uncertainty of approval ●Technical uncertainty ●Need for specialized centers of excellence ●Negative image created by religious and activist groups
Cell Therapy	●High efficacy in multiple clinical trials ●The application of multidisciplinary approach have lead to better overall performance	●Controversy has slowed the pace of Stem Cell Science ●Impact on the quality of life ●Limited funds		
Tissue Engineering	●Full replacement unfunctional organ/tissue	●Need for surgery ●GVHD implication ●Limited funds	●Modest functional improvements have been witnessed with variable outcomes	

Market Trends

The graph to the right illustrates the growth of the number of companies on the market. For the last decade the growth of the number of projects working on Regenerative Medicine for longevity has been **stimulated by the synergy of 4 key factors**:

Key Market Trends	Determinant
Activation of self-regeneration	Small and Large Molecules
Tissue functionality repair	Gene Therapy
Tissue regeneration	Cell Therapy
Whole organ replacement	Tissue/Organ Engineering

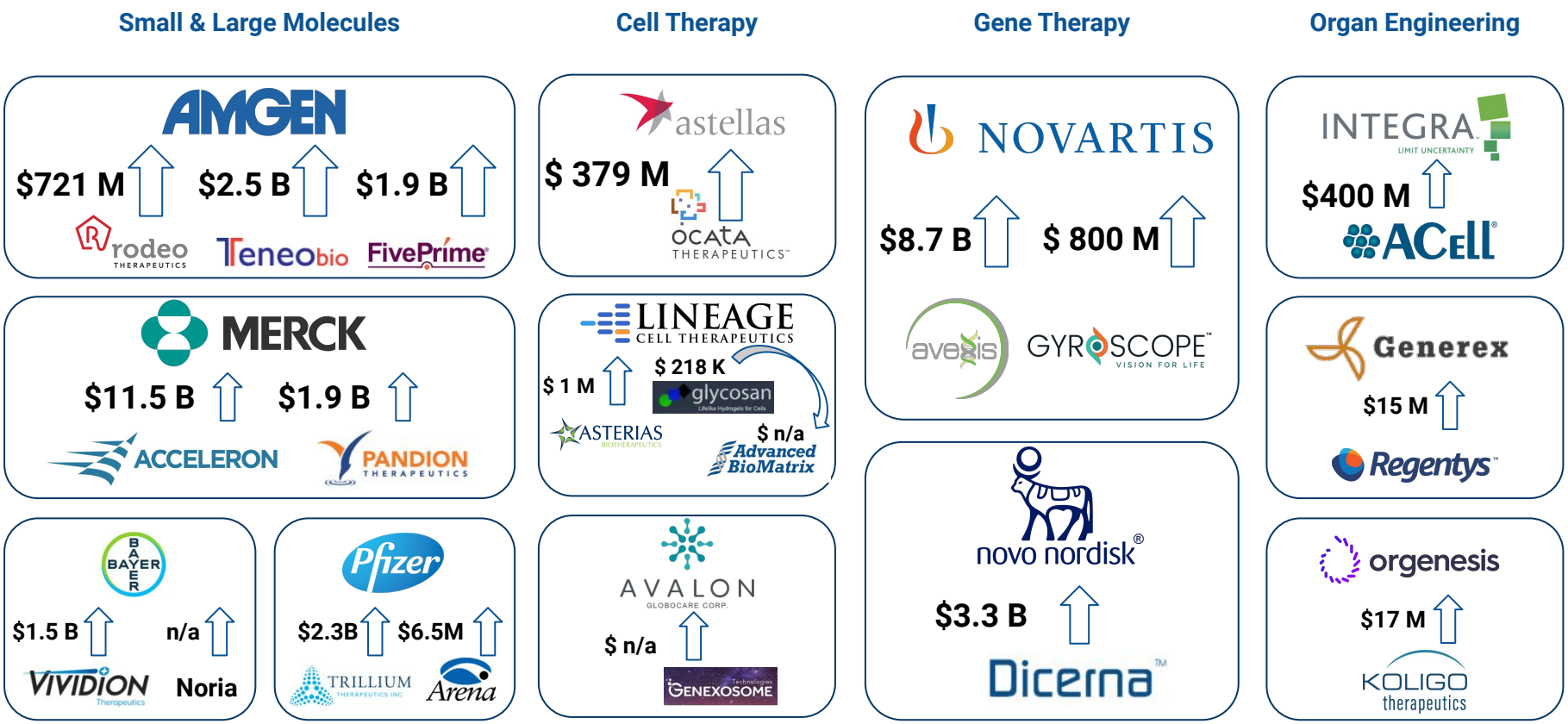
New Companies: Regenerative Medicine for Longevity



Note: More than 250 BioTech companies and start-ups are carrying out work that may lead to a form of rejuvenation, or are focused on interventions that target the mechanisms of ageing. Nearly all of these companies are no more than a few years old, in preclinical development or in early trials, and Big Pharma has yet to become earnestly involved in the Longevity Industry.

Source: Aging Analytics Agency analysis

The Most Important Acquisitions on the Market



Source: Aging Analytics Agency analysis

Conclusions

Key Takeaways

Though the most advanced therapies currently dominate the headlines, **Small and Large Molecules for Longevity** remain of great significance for the industry – and for patients. The small and large molecule **drug discovery market** for Regenerative Medicine was valued at approximately **USD 17,630 million** in Q1 2022 and is **expected to reach 35,261 million** by 2026, registering a **compound annual growth rate** (CAGR) of nearly **8.05%** during the forecast period, 2022-2026.

The **Gene Therapy for Longevity** market has grown significantly over the last ten years. The proportion of new (created in 2021-2022) and old companies is 72% and 28%, respectively. The Gene Therapy **market** for Regenerative Medicine is valued at approximately **USD 9,314 million** in Q1 2022, and it is **expected to increase two-fold** by 2026 at a **CAGR of ~28.5%**.

There has been no significant growth in the **Cell Therapy for Longevity** market. The **market has shown stagnation** in the last two years. The share of new and old players is approximately 50:50. The Cell Therapy **market** was valued at approximately **USD 2,193 million** in Q1 2022. The CAGR for total market (including cell therapy for oncology, including CAR-T and other forms) is about 14.5%.

The most popular approaches for **Tissue and Organ Engineering** are **organoids** and **scaffolds**. Some **57.6%** of all companies that specialise in bioengineering implement one of these approaches. The next two most widely implemented approaches are **biopolymers** (implemented by **20.3%** of companies) and **3D-bioprinting** (**16.9%**).

More than **250 BioTech companies and start-ups** are carrying out work that may lead to a form of rejuvenation, or are focused on interventions that target the mechanisms of ageing. Nearly all of these companies are at most a **few years old**, in preclinical development or in early trials, and Big Pharma has yet to become earnestly involved in the Longevity Industry.

Glossary of Key Terms

Key Terms: Types of Therapy

- **Antisense therapy** – Antisense compounds under development as potential therapeutics. These may be synthetic oligonucleotides, or antisense RNA may be expressed from a vector as a form of gene therapy. They may prevent the expression of a specific protein in vivo by binding to and inhibiting the action of mRNA, since they have a specific oligonucleotide sequence which is complementary to the DNA or RNA sequence which codes for the protein.

- **Cellular therapy, stem cell** – Regenerative therapy that promotes the repair response of injured tissue using stem cells (cells from which all other specialised cells would originate).

- **Gene therapy** – Therapies containing an active ingredient synthesised following vector-mediated introduction of a genetic sequence into target cells in- or ex-vivo. Used to replace defective or missing genes (as in cystic fibrosis) as well as to introduce broadly acting genetic sequences for the treatment of multifactorial diseases (e.g. cancer). Direct administration of oligonucleotides without the use of vectors is covered separately in the antisense therapy class; the RNA interference class; and the oligonucleotide, non-antisense, non-RNAi class. Platform technologies for gene delivery are covered separately in the gene delivery vector class.

- **Oligonucleotide, non-antisense, non-RNAi** – Synthetic therapeutic oligonucleotides which operate by a mechanism other than antisense or RNA interference (RNAi). This includes ribozymes, aptamers, decoys, CpGs, and mismatched and immunostimulant oligonucleotides. Sequences delivered using vectors (gene therapy) are covered separately in “gene therapy.” Antisense and RNAi oligonucleotides are covered separately in “antisense therapy" and "RNA interference,“ respectively.

- **Transduction** – the process by which a virus transfers genetic material from one cell to another.

Development status definitions

Pipeline – Drugs that are in active development.

Preclinical – Not yet tested in humans.

Phase I – Early trials, usually in volunteers, safety, pharmacokinetic (PK), pharmacodynamic (PD).

Phase II – First efficacy trials in small numbers of patients.

Phase III – Large-scale trials for registrational data.

Pre-registration – Filing for the approval of regulatory authorities.

Approved – Approval from relevant regulatory authorities for human use.

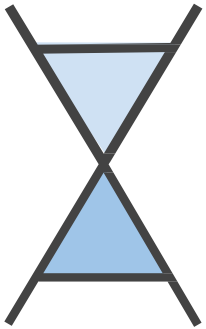
Alliances – Co-marketing, co-promotion, disease management, joint venture, manufacturing or supply, marketing licensing, product or technology swap, product purchase, R&D and marketing-licensing, reverse licensing, trial collaborations.

Acquisitions – buy-out, divestiture, spin-out, full acquisition, partial acquisition, reverse acquisition.

Longevity Investment: Big Data Analytics Dashboard

Source: Longevity Investment Big Data Analytics Dashboard

About Aging Analytics Agency



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Aging Analytics Agency is primarily interested in strategic collaboration with international corporations, organisations, and governments in Longevity-related projects and initiatives.

Aging Analytics Agency is open to cooperation with strategic clients via a variety of approaches, including:

- Conducting customised case studies, research and analytics for internal (organisational) use, tailored to the precise needs of specific clients.
- Producing open-access analytical reports.
- Offering customised analysis using specialised interactive industry and technology databases and IT-Platforms.

In certain specific cases, if it meets our interests, Aging Analytics Agency is open to co-sponsoring research and analytics for the production of internal and open-access industry reports, as well as special case studies for a variety of governmental, international, and corporate clients. Their topics of interest may include Longevity, the Longevity Financial Industry, Longevity Policy and Governance, and the development and execution of fully-integrated National Healthy Longevity Development Plans tailored to the specific needs of national governments and economies.

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