Current Scenario of Clinical Trials of Cell, Gene and RNA Therapies

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Cell, gene, and RNA therapies have brought a quantum leap in the treatment of diseases such as cancer, genetic disorders, and autoimmune conditions by replacing dysfunctional molecules with correct molecules at the molecular level. Clinical trials for such therapies need regulatory consultancy, drug development planning, site selection and data management that are usually taken care of by cell and gene-accredited contract research organizations (CROs). Cell and gene therapy trials are more prevalent in oncology, in particular blood cancers, viral infections, and solid tumors followed by infectious diseases, central nervous system (CNS) and cardiovascular diseases.

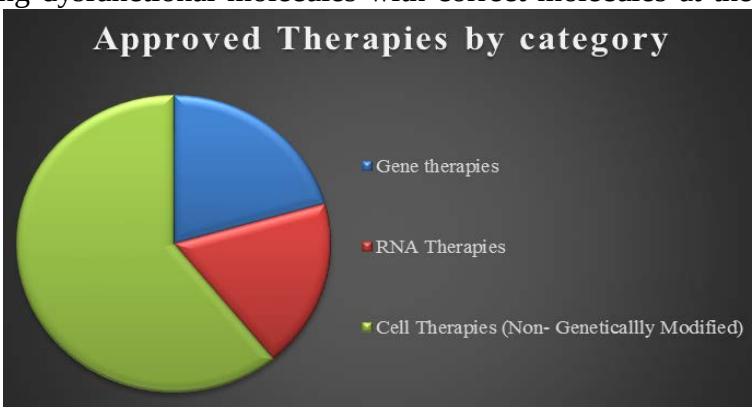

Figure 1: Categories of approved therapy (Source: Pharmaprojects | Informa, April 2022 (American Society of Gene + Cell Therapy))

Constant emergence of new gene therapies as well as refinement of the existing ones changes the global landscape of the cell and gene therapies clinical trials, where the US, China, and Europe are leading in respect of the number of trials conducted. As per Global Data, China showed 15% faster growth in cell and gene therapy clinical trials making the Asia-Pacific region contributes for one-third of the trial activities. As a result, the Asia Pacific region is witnessing 50% faster growth than the rest of the world (ROW). Asia Pacific region leads globally in terms of CAR-T cell gene therapy clinical trials for the time period 2015-2022 since China alone conducted ~60% of all CAR-T trials. Till April 2022, there are 19 approved gene therapies, 17 RNA-approved therapies while 56 non-genetically modified approved cell therapies (Figure 1). Details of the approved location of the clinical trials of gene therapies and RNA therapies drug product are provided in Table No.1 and Table No. 2 respectively, which presents a bird's-eye view of the landscape of the clinical trials of the approved gene and RNA therapies.

Table No. 1: Approved Gene Therapies till April'2022					
Location Approved	**Product Name**	**Generic Name**	**First Approval Year**	**Diseases**	**Innovator Company**
China	Gendicine	Recombinant p53 gene		Head and neck cancer	Shenzhen SiBonoGeneTech
	Oncorine	E1B/E3 deficient adenovirus	2005	Head and neck cancer; nasopharygeal cancer	Shanghai Sunway Biotech
	Relma-cel	Relmacabtagene autoleucel	2021	Diffuse large B-cell Lymphoma	JW Therapeutics
China, US, EU, UK, Japan, Canada	Yescarta	Axicabtagene ciloleucel	2017	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma	Kite Pharma (Gilead)
Japan	Collategene	Beperminogene perplasmid	2019	Critical limb ischemia	AnGes
Japan	Delytact	Teserpaturev	2021	Malignant Glioma	Daiichi Sankyo
Japan, US	Breyanzi	Lisocabtagene maraleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	Celgene (Bristol Myers Squibb)
Japan, US, Canada, EU, UK	Abecma	Idecabtagene vicleucel	2021	Multiple myeloma	Bluebird Bio
Japan, Australia, South Korea, Canada, US, EU, UK	Kymriah	Tisagenlecleucel-t	2017	Acute Lymphocytic Leukaemia; Diffuse large B-cell lymphoma	Novartis

Japan, Australia, South Korea, Canada, Brazil, Israel, Taiwan, US, EU, UK	Zolgensma	Onasemnogene abeparvovec	2019	Spinal Muscular Atrophy	Novartis
Australia, South Korea, Canada, US, EU, UK	Luxturna	Voretigene neparvovec	2017	Leber's congenital amaurosis, retinitis pigmentosa	Spark Therapeutics (Roche)
Philippines	Rexin-G	Mutant cyclin-G1 gene	2006	Solid tumors	Epeius Biotechnologies
Russian Federation, Ukraine	Neovasculgen	Vascular endothelial growth factor gene	2011	Peripheral vascular disease; limb ischemia	Human Stem Cells Institute
US, EU, UK, Australia	Imlygic	Talimogene laherparepvec	2015	Melanoma	Amgen
US, EU, UK	Tecartus	Brexucabtagene autoleucel	2020	Mantel cell lymphoma; acute lymphocytic leukaemaia	Kite Pharma (Gilead)
EU, UK	Strimvelis	Autologous CD34+ enriched cells	2016	Adenosine deaminase deficiency	Orchard Therapeutics
EU, UK	Zynteglo	Betibeglogene autotemcel	2019	Transfusion-dependent beta thalassemia	Bluebird Bio
EU, UK	Libmeldy	Atidarsagene autotemcel	2020	Metachromatic Leukodystrophy	Orchard Therapeutics
US	Carvykti	Ciltacabtagene autoleucel	2022	Multiple myeloma	Legend Biotech

Table 2: List of Approved RNA Therapies till April' 2022					
Location Approved	**Product Name**	**Generic Name**	**First Approval Year**	**Diseases**	**Innovator Company**
US	Exondys 51	Eteplirsen	2016	Duchenne Muscular Dystrophy,	Sarepta Therapeutics
US	Vyondys 53	Golodirsen	2019	Duchene Muscular Dystrophy	Sarepta Therapeutics
US	Amondys 45	Casimersen	2021	Duchenne Muscular Dystrophy	Sarepta Therapeutics
US	Nulibry	Fosdenopterin	2021	Molybdenum cofactor deficiency	Orphatec
US, Japan	Viltepso	Viltolarsen	2020	Duchenne Muscular Dystrophy	NS Pharma
US, Mexico, Argentina, South Korea	Kynamro	Mipomersen sodium	2013	Homozygous familial hypercholesterolemia	Ionis Pharmaceuticals
US, Brazil, EU, UK	Oxlumo	Lumasiran	2020	Hyperoxaluria	Alnylam
US, Canada, Brazil, EU, UK	Tegsedi	Inotersen	2018	Amyloidosis, transthyretin-related hereditary	Ionis Pharmaceuticals
US, Australia, Canada, Israel, EU, UK	Leqvio	Inclisiran	2020	Atherosclerosis; Heterozygous familial hypercholesterolemia, Hypercholesterolemia	Alnylam
US, Canada, Brazil, Israel, Japan, Switzerland, EU, UK	Givlaari	Givosiran	2020	Porphyria	Alnylam

US, Canada, Brazil, Switzerland, Israel, Taiwan, Turkey, Japan, EU, UK	Onpattro	Patisiran	2018	Amyloidosis, transthyretin-related hereditary	Alnylam
US, Denmark, Ireland, India, Japan, Mexico, Morocco, Indoesia, Australia, South Korea, UK	Lagevrio	Molnupiravir	2021	Infection, coronavirus, novel coronavirus	Ridgeback Biotherapeutics
US, Canada, Japan, Brazil, Switzerland, Australia, South Korea, China, Argentina, Colombia, Taiwan, Turkey, EU, UK	Spinraza	Nusinersen	2016	Spial Muscular Atrophy	Ionis Pharmaceuticals
US, Canada, Israel, Switzerland, Australia, South Korea, Singapore, Qatar, Vietnam, Philippines, Thailand, Japan, Brunei, Paraguay, Taiwan, Botswana, India, Indonesia, Saudi Arabia, Mexico, Nigeria, Colombia, EU, UK	Moderna Covid-19 vaccine	Covid-19 vaccine, Moderna	2020	Infection, coronavirus, novel coronavirus prophylaxis	Moderna Therapeutics
US, Bahrain, Israel, Canada, Rwanda, Serbia, UAE, Macao, Mexico, Kuwait, Singapore, Saudi Arabia, Chile, Switzerland, Colombia, Philippines, Australia, Hong Kong, Peru, South Korea, New Zealand, Japan, Brazil, Srilanka, Vietnam, South Africa, Thailand, Oman, Egypt, Malaysia, EU, UK	Comirnaty	Tozinameran	2020	Infection, coronavirus, novel coronavirus prophylaxis	BioNTech
Argentina	Ampligen	Rintatolimod	2016	Chronic fatigue syndrome	AIM ImmunoTech

In addition, there are 3579 gene, cell and RNA therapies are in the pipeline ranging from preclinical through pre-registration stages. Out of 3579 therapies, 1986 gene therapies that include genetically-modified cell therapies accounts for 55% whereas 816 non-genetically modified cell therapies accounts for 22% of gene, cell and RNA therapies as shown in Figure 2.

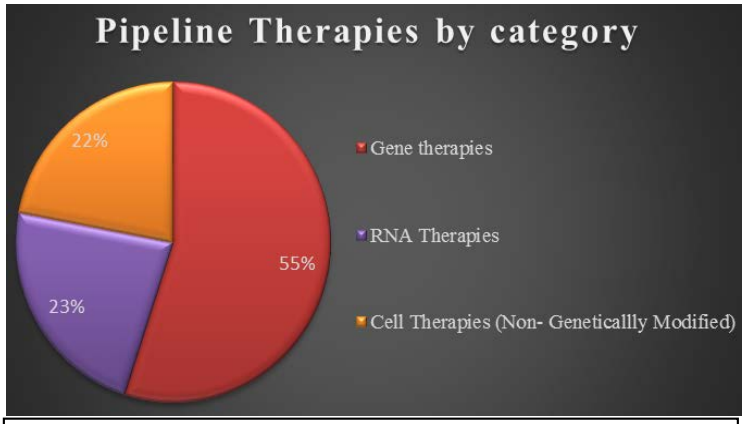

Figure 2: Categories of approved therapy (Source: Pharmaprojects | Informa, April 2022 (American Society of Gene + Cell Therapy))

Currently, RNA therapies that include RNAi, mRNA and antisense therapeutic products have clearly been dominated by preclinical development stage by 80%, 76% and 64% respectively as represented in Figure 3. RNA therapies are usually targeted for rare oncology diseases such as pancreatic, liver and ovarian cancer and in case of non-oncology rare diseases it's mainly targeted for Duchenne's muscular dystrophy, amyotrophic lateral sclerosis, and Huntington's disease.

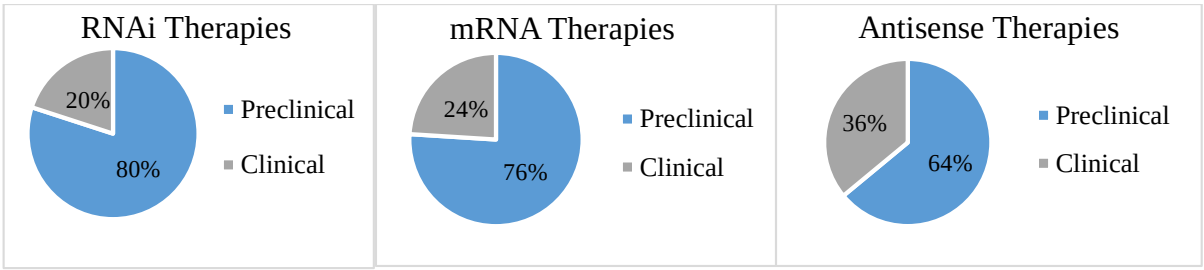

Figure 3: Preclinical v/s Clinical development percent of different RNA therapies (Source: Pharmaprojects | Informa, April 2022 (American Society of Gene + Cell Therapy))

Challenges and Demand associated with conducting Clinical trials for cell, gene, and RNA therapies:

Manufacturing and delivery methods of therapeutic products related to cell and gene therapy are different from routine pharmaceutical or biopharmaceutical products. Hence, clinical trials of cell, gene, and RNA therapies does not follow the traditional path of clinical trials that has been conducted for small molecules or proteins. Therefore, CROs having expertise in conducting these specialized type of complex clinical trials is the need of the hour to expedite the entire process by including virtual site monitoring, eConsent etc.

Though there are certain difficulties in the path of cell and gene therapy clinical trials development but it is needed to convert those stumbling blocks into the stepping stone because of the tremendously significant outcome of cell, gene or RNA therapies in treating several cancer or genetic disorders which were earlier incurable.

References:

1. Novotech the Asia Specific CRO website (https://novotech-cro.com/faq/cell-gene-therapy-clinical-trials-global-landscape)
2. Pharmaprojects | Informa, April 2022 (American Society of Gene + Cell Therapy)