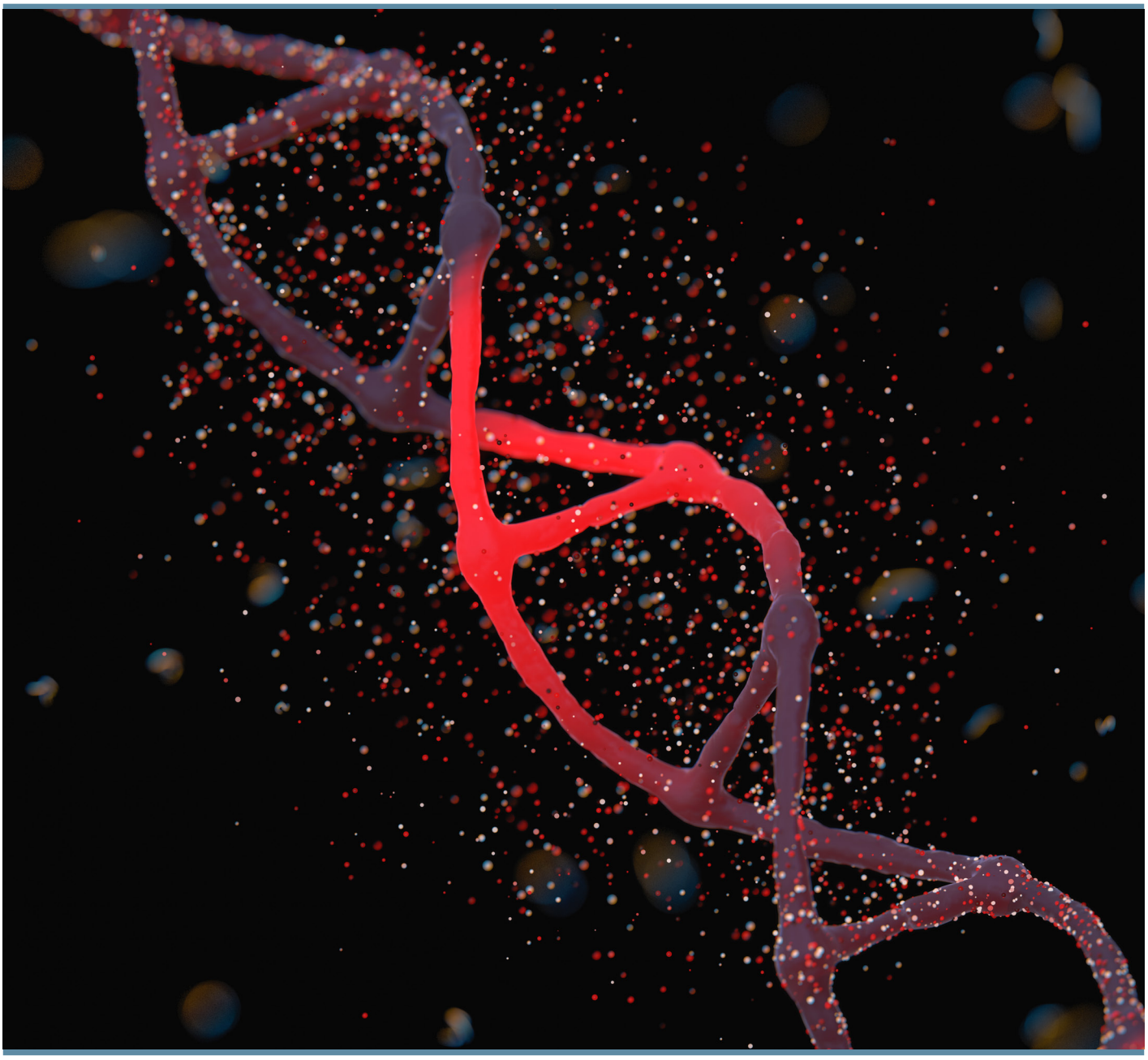
L.E.K.

Special Report

Regenerative Medicine Opportunities and Challenges in APAC



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Introduction

Regenerative medicine (RM) is defined as the branch of medicine intended to augment, repair, replace, or regenerate organs, tissues, cells, genes and metabolic processes in the body.

Following the successful sequencing of the human genome in the early 2000s, tremendous strides in biotechnology, systems biology, chemistry and bioinformatics have expanded our understanding of biological mechanisms of disease and equipped us with a diverse tool kit for new drug design and screening, which has enabled the advent of regenerative medicine.

Today, RM is challenging the current practice of medicine by treating the root causes of disease and disorders, making it an incredibly exciting space, but not without significant challenges and uncertainties that will need to be overcome to realize its full potential.

"My goals over the decade include developing new drugs to treat intractable diseases by using iPSC technology."
— Dr. Shinya Yamanaka, Nobel Prize in Physiology Medicine, 2012

For the purpose of this special report, we have segmented RM into three categories (Figure 1):

- The first major category, **gene therapies**, can be split into:
  - **DNA-based and RNA-based approaches** designed to introduce genetic material into cells to compensate for abnormal genes, either by silencing, via RNA interference or antisense oligonucleotides (ASOs), or by restoring functions such as protein synthesis; and
  - **Gene editing therapies** that remove or modify defective DNA either in vivo, typically administered through a viral vector, e.g., Spark Therapeutics' adeno-associated virus (AAV)-based therapy Luxturna, or ex vivo, which involves genetic manipulation of harvested cells before administering them back into the patient, e.g., Novartis' Kymriah and Gilead's Yescarta.
- The second category, **cellular therapies (CT)**, involves the transplantation of human cells to replace or repair damaged tissue or to fight cancer, and encompasses stem cell (SC) and adoptive cell therapies (ACT):
  - **Stem cells** include natural SCs from embryonic, hematopoietic, mesenchymal or somatic tissues, as well as induced pluripotent stem cells (iPSCs), which are somatic cells that have been reprogrammed to a pluripotent state, and subsequently differentiated into various somatic cells for therapeutic or disease modeling purposes.
  - **There are two approaches to ACT**: The first involves the isolation of the patient's immune cells and simply expanding their numbers (e.g., tumor-infiltrating lymphocytes (TILs)), whereas the other involves genetically engineering the immune cells (e.g., chimeric antigen receptor T cells (CAR-T)) to enhance their cancer-fighting ability.
- The final category encompasses **tissue engineering (TE)**, which seeks to restore, improve or replace damaged tissues and organs through the combination of SCs, biodegradable scaffolds and biologically active molecules.

Figure 1
Regenerative medicine modalities with example therapies, either launched or under clinical development

Category			Modality	Description	Example
Gene therapies	DNA-based therapies	Viral vector approach	Adeno-associated virus (AAV)	Deliver therapeutic DNA to the nucleus, where it remains episomal (separate) from the host genome.	Zolgensma
			Lentiviral vector (LVV)	Deliver RNA that is reverse transcribed into a DNA copy, which is then permanently incorporated into the genome of the host cell.	Zynteglo
		Nonviral approach	Nonviral plasmids (NVP)	Deliver therapeutic DNA to the nucleus, where it remains episomal, either using forced entry (e.g., electroporation) or delivery vehicles (e.g., LNP).	EYS606
	RNA-based therapies	RNA upregulation	Messenger RNA (mRNA)	Address loss-of-function diseases through a protein replacement approach.	AZD8601
		RNA interference	Short interfering RNA (siRNA)	Post-transcriptional gene silencing, binds to target mRNA with perfect complementarity, triggering its degradation.	Patisiran
			MicroRNA (miRNA)	Post-transcriptional gene silencing, binds to target mRNA with imperfect complementarity, triggering its silencing (suppression of transcription) or degradation. Tumor suppressor miRNA mimics restore miRNA suppressing function.	MC-30
		Oligo-nucleotides	Antisense oligonucleotide (ASO)	Selective, sequence-specific inhibition or alteration of gene expression via steric hindrance, splicing alterations, initiation of target degradation or other events.	Spinraza
			Other nucleotides	Decoy oligonucleotides stimulate gene expression by targeting transcriptional repressors. They can also be used as adjuvant to other drugs. Ribozymes downregulate gene expression via mRNA trans-cleavage.	Forigerimod
	Gene editing tools	CRISPR/Cas9	Single guide RNA (sgRNA)	Directs Cas9 to the target DNA site, resulting in site-specific DNA double-strand breaks that are subsequently repaired, resulting in precise gene correction or replacement.	CTX001
Cell therapies	Stem cell therapy	Pluripotent	Human embryonic stem cells (hESC)	Derived from the inner cell mass of human blastocytes, and involve the destruction of a human embryo.	ViaCyte
			Induced pluripotent stem cells (iPSC)	Produced by genetic reprogramming of differentiated adult somatic cells to lose tissue-specific features and gain pluripotency.	iPS cell therapy
		Multipotent	Mesenchymal stem cells (MSC)	Present in many adult tissues and give rise to cells from mesodermal, ectodermal and endodermal lineages. They are also suggested to exert therapeutic effect via paracrine secretions.	Remestemcel-L
			Hematopoietic stem cells (HSC)	Can be found in adult bone marrow, peripheral blood and umbilical cord blood, and give rise to all cells in the blood lineages through hematopoiesis.	Omidubicel
			Other multipotent stem cells	Present in small number in defined regions (brain, GI tract), such as neural and corneal epithelial stem cells.	EYE-01M
		Oligo-, unipotent	Progenitor cells	Immediate descendants of stem cells, are lineage-committed cells (e.g., chondrocytes, hematopoietic progenitor cells).	Ortho-ACI
	Adoptive cell therapy (ACT)		Chimeric antigen receptor T-cell (CAR-T)	T cells engineered ex vivo to express receptors that recognize cancer antigens expressed on the cell surface.	Kymriah
			T-cell receptor (TCR)	T cells engineered ex vivo to express receptors that recognize intracellular tumor-related antigens presented in the major histocompatibility complex on the cell surface.	Anti-KRAS G12V mTCR
			Adeno-associated virus (AAV)	Cells harvested from tumor sites and are expanded ex vivo using factors that increase specificity (IL-2).	MDA-TIL
Tissue engineering	Naked scaffold			Transplantable scaffolds made from biomaterials and biologically active molecules designed to recruit cells in vivo to restore function.	Omnigraft
	Pre-cultured in vitro			Transplantable tissues engineered using scaffolds, cells and biologically active molecules to restore, maintain or improve damaged tissues or whole organs.	Novocart 3D

Source: L.E.K. research and analysis

Global RM pipeline development trend expected to continue

As of 2020, ~2,300 RM pipelines are under clinical development. Cell therapies, comprising the most investigated branches of RM, have ~1,300 assets (Figure 2).

Stem cell research has experienced a resurgence in activity, particularly after the 2012 Nobel Prize was co-awarded to Sir John Gurdon and Dr. Shinya Yamanaka for **"the discovery that mature cells can be reprogrammed to become pluripotent."** Yamanaka's iPSCs are generated by genetic reprogramming of differentiated adult somatic cells (e.g., skin fibroblasts) to lose tissue-specific features and gain pluripotency before being differentiated into desired cell lineages (e.g., neural cells).

The advent of iPSCs was a turning point in SC research, as it has unburdened the field from the ethical issues around the use of the naturally pluripotent hESC, involving the destruction of a human embryo, and allowed unprecedented opportunities for disease modeling, drug screening and therapeutic applications. However, despite their high ethical ground, iPSCs pose inherent safety concerns due to higher risk of oncogenic aberrations, immunogenicity, batch variability and co-occurrence of heterogeneous populations of lineage subtypes. Consequently, in vivo clinical applications of iPSC-derived therapeutics have so far been limited to confined and immune privileged regions such as the eyes and central nervous system, while ex vivo applications (e.g., drug screening and disease modeling) are enjoying the full potential that iPSCs can offer.

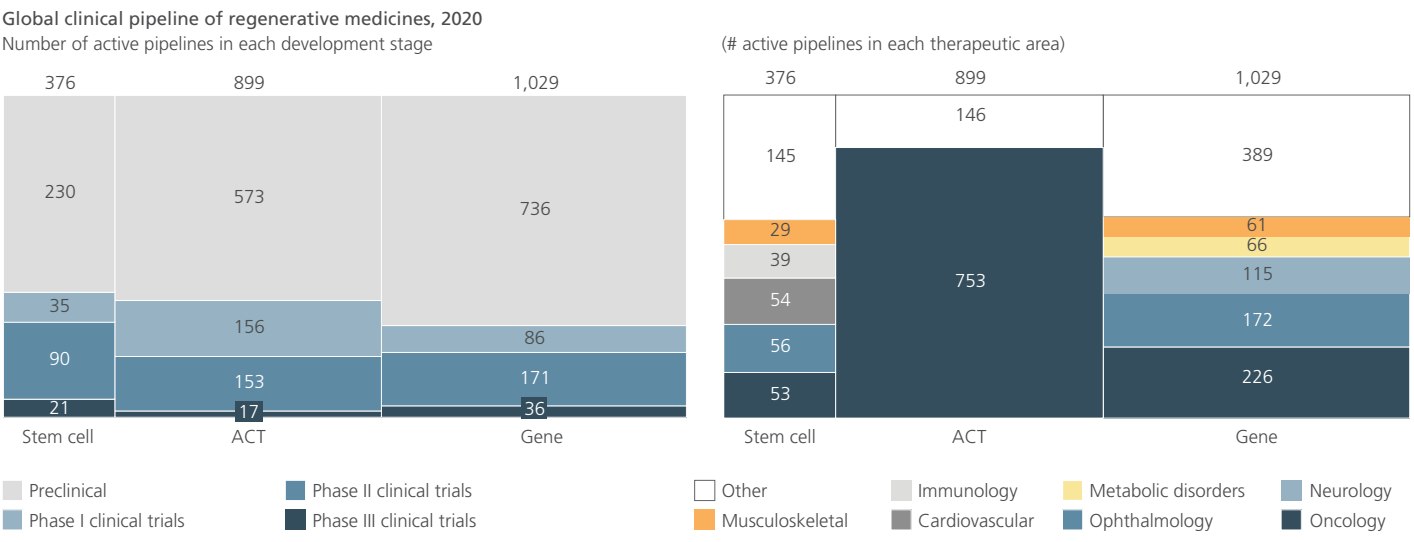
Dominating the pipeline are the multipotent MSC, which are the most widely studied stem cell type given that 1) they can be easily isolated in large quantities from different parts of the body with reduced morbidities and discomfort on the part of the donor, and 2) they have paracrine activity, which can address a wide range of conditions requiring immunomodulation (most commonly arthritis). However, MSC procurement in Japan is difficult under regulatory restrictions that limit donor sources to surgically removed and other "wasted" body parts (e.g., wisdom teeth and sixth fingers in polydactyly cases).

Except for HSCs, which are used to treat blood diseases, other adult stem cells (e.g., neural, epithelial stem cells) face limitations, as they are more difficult to collect from adults.

Regarding ACT modalities, early attempts involved isolating patient T cells and growing them ex vivo with IL-2, a potent T-cell growth factor, before reinfusing them into the patient. These seminal studies paved the way for the development of targeted CAR-T cells, which enable cells to recognize and destroy specific types of cancers, e.g., blood cell cancers. CAR-T's remarkable clinical outcomes have further boosted investments in novel CAR designs.

Today, a fourth generation of CAR-T is being investigated, with enhanced features such as cytokine overexpression, gene knock-out/knock-in, multiple antigens targeting, and precise control of CAR expression and signaling. Perhaps the most interesting feature of the fourth generation that is expected to drive future commercial potential is the ability to knock out human leucocyte antigen from healthy donor cells, allowing the development of off-the-shelf allogeneic CAR-T therapies for cancer. Other CAR-T variants such as chimeric antigen receptor-natural killer and chimeric antigen

Figure 2
Global clinical pipelines for regenerative medicines by phase and therapeutic area



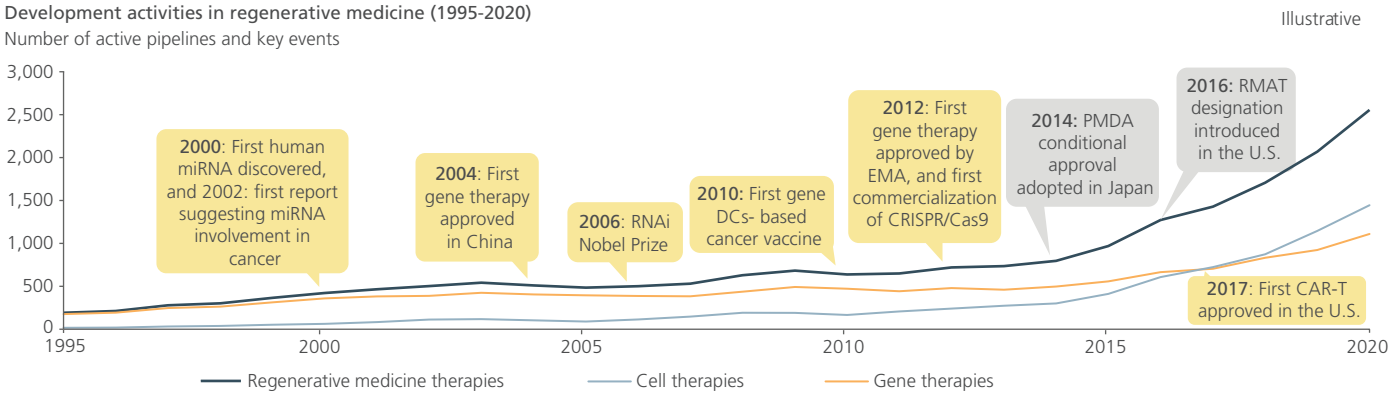
Source: Citeline; ClinicalTrials.gov; NCBI; company data; L.E.K. analysis

receptor macrophages are also poised to expand clinicians' RM oncology weaponry, particularly against solid tumors.

Over the past 25 years, a number of milestones have collectively led to transitioning an increasing number of RM therapies into the clinic to address critical unmet needs (Figure 3). These events can be clustered into five "enabling" categories:

- **Scientific innovations**: Significant advancements across various scientific fields have enabled regenerative medicines to become a medical specialty in their own right. RNA interference (RNAi) discovered in the late 1990s has greatly advanced the field of gene therapies by expanding our understanding of how to selectively switch off genes. Another highlight of the first few years of this century is the field of SC research, with the discovery of iPSCs. More importantly, such scientific breakthroughs are realized through the development of sophisticated technologies across a wide range of disciplines, including chemistry, systems biology, gene editing, cell culture techniques and bioinformatics, to cite a select few.
- **Clinical validation**: The novel nature of RM therapies leads to unique challenges related to the characterization and clinical translation of these types of products. Adverse events, such as the death of an American patient following a gene therapy experiment in 1999, have held the field back several years as U.S. regulators put some key experiments on hold. Hence, clinical validation of a new RM modality represents a tipping point for a wider adoption and commercial acceptance in key markets. For instance, Glybera's EU approval in 2012 fueled additional clinical development activities for gene therapies, and the oligonucleotides pipeline has been steadily growing following the successful launch of Spinraza in 2016 by Biogen.
- **Regulatory clarity**: The increasing enthusiasm around the potential of RM has led to a push to accelerate its clinical translation. However, ambiguous regulatory environments aimed at ensuring patient safety and safeguarding scientific development have historically hampered the translational process "from bench to bedside." As government agencies started to recognize the importance of RM, they allowed developers access to expedited approval pathways, such as the U.S. Food and Drug Administration's (FDA) regenerative medicine advanced therapy (RMAT) designation and the Pharmaceuticals and Medical Devices Agency's (PMDA) conditional approval pathways, encouraging the development of future RM pipelines.
- **Manufacturing advances**: Cell and gene products are challenging to manufacture. Improved processes are required to move RM therapies from lab-scale production to the factory floor. Incremental gains from suspension cultures and novel oligonucleotide synthesis methods, together with more significant technological innovations such as "good manufacturing practice (GMP)-in-a-box" systems (e.g., Miltenyi Biotec's CliniMACS Prodigy) for automated cell processing, have eased much of the manufacturing bottlenecks and enabled production of DNA and RNA at commercially viable scale. However, contract manufacturing organizations (CMOs) are much needed to accommodate the growing pipeline and address future capacity bottlenecks and relieve the industry's reliance on a limited pool of contractors.
- **Logistics**: Compared to molecular medicinal drugs, cell and gene therapies are relatively unstable and subject to logistical constraints to transport them to the point of care. The advent of supporting business models such as master cell

Figure 3
Global clinical development activities in regenerative medicine and key events (1995-2020)



Note: DC: Dendritic cells; EMA: European Medicines Agency
Source: Citeline

banking and storage and cryologistics have addressed some commercial barriers in the cell therapy space.

Clear advances within these five enabling categories have propelled biotechs to their position today, but while the U.S. and EU are the largest markets for RM therapies, with ~60 approved drugs as of 2020, the landscape is fragmented and immature.

Opportunities loom large in Asia, which is poised to join the ranks of other promising RM markets, driven by an aging population and growing prevalence of chronic diseases, as well as rapidly developing and favorable healthcare infrastructure and policies.

Opportunities exist for actors to capitalize on the prospects of growing key APAC markets

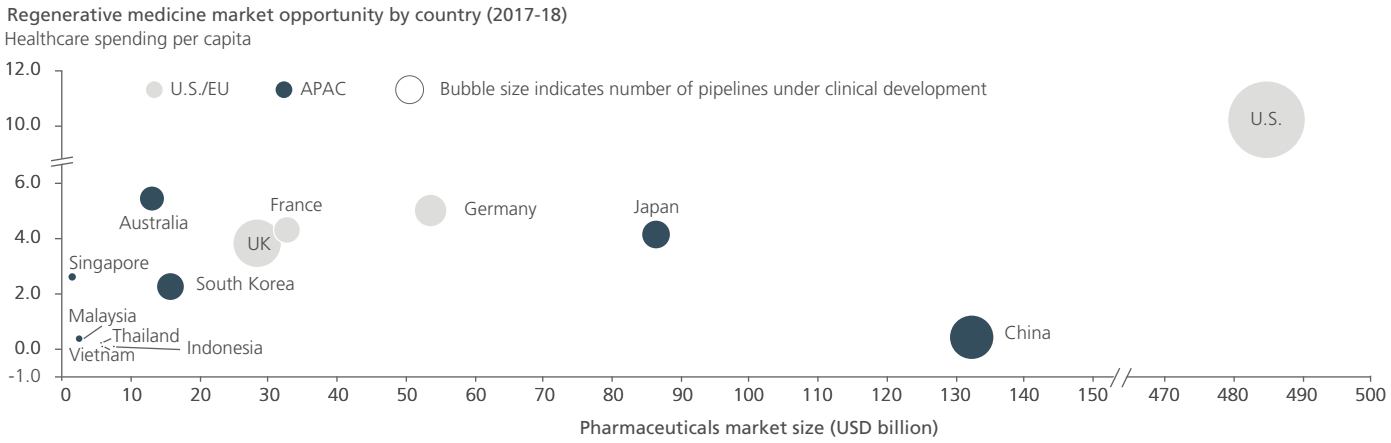
We believe China, Japan, South Korea and Australia are the most attractive destinations for RM players and their portfolios in the Asia-Pacific (APAC) region.

With potentially large addressable patient populations and rapidly developing RM ecosystems, each has relatively attractive healthcare spending dynamics that are on par with EU-5 markets, although spending is not as high as in the U.S. (Figure 4).

South Korea is a leader in the field of cell-based therapies, with significant development activity, particularly in the field of SC treatments. With the enactment of the Act on the Safety and Support of Advanced Regenerative Medical Treatment and Medicine in August 2020, South Korea's favorable market access can be expected to spur further development activities.

The case for China is more nuanced, as the large pharmaceutical market size is coupled with a lower per capita spending level. While this may make China appear unattractive to foreign actors, the case is very different for the four Tier 1 cities of Shanghai, Beijing, Guangzhou and Shenzhen, where rapidly increasing affluence has improved market access and healthcare infrastructure for innovative and expensive therapy modalities. Moreover, it is estimated that ~60 million people are suffering from genetic diseases across the nation,[1] suggesting China is attractive and should remain a priority market for international RM biotechs.

Figure 4
Pharmaceuticals market size and healthcare spending per capita for APAC, EU and US



Source: World Health Organization Global Health Expenditure database; Pharmaprojects; L.E.K. analysis

How can market participants win in the complex but exciting Asian RM landscape?

Launching RM therapies in Asia could prove very lucrative given available reimbursement and patient populations, but biotechs and other market participants (e.g., contract development and manufacturing companies (CDMOs), logistics companies and other supply chain vendors) will need to tailor and optimize their approaches carefully. We believe there are four areas that should be understood in greater detail:

- **The regulatory framework, market access and pricing** of the key APAC markets. Here we examine China and Japan. As those are the two largest markets, participants should balance their investments in light of the potential commercial payoffs.
- **Local clinical development activities** of each market. Companies should better understand how the APAC markets are set up to support their ability to win.
- **Supply chain considerations**, most importantly manufacturing and logistical infrastructure. Will companies be able to safely and securely manufacture and deliver their therapeutics to their desired patient populations?
- **Sales and marketing requirements**. It will be key for biotechs to target physician networks effectively and ensure that the case for their therapeutics is effectively communicated and products receive the traction they deserve.

Japan and China are looking to harmonize their regulatory frameworks with Western countries to facilitate the launch of RM therapies

Among the four major APAC markets, regulatory clarity is greatest in Japan and South Korea (Figure 5), which highlights their desire

Figure 5
Snapshot of the regulatory landscapes in Asia, EU and US

	United States	European Union	Japan	China	South Korea	Australia
Regulatory agencies	• FDA and CBER	• EMA, CAT, CHMP and NCA	• MHLW and PMDA	• NMPA	• MFDS	• TGA, AHPRA
Regulatory category	Biologics	RM	RM	Biologics	RM	Biologics
Approval pathway	• RMAT • Orphan/accelerated approval/fast-track/ breakthrough available (same as pharma)	• No ATMP-specific approval pathway, but still offers accelerated approval/conditional approval/etc. benefits (same as pharma)	• Conditional approval pathway for RM therapies that are heterogeneous • Sakigake and orphan are available	• Research track at hospitals and drug R&D track are available for SC products	• Expedited program for advanced therapy products that treat rare diseases and cancer	• The regulatory pathways allow for immediate leverage of investigational new drug (IND)/biologics license application (BLA)
Regulatory path certainty and challenges Time to approval Conditional approval Domestic procurement and manufacturing of cells	• Recent regulations/guidance establishing more certainty around the RM space (e.g., RMAT) • Likely longer than Japan; depends on qualifying for fast-track • Domestic procurement is not difficult • GMP requirements must be met from Phase II	• Uncertainty over qualification for fast-track programs prior to discussions with EMA • Likely the longest approval timeline; depends on qualifying for conditional approval and fast-track programs • Domestic procure-ment is not difficult; relative ease may differ by country • GMP requirements from the start of clinical development	• Uncertainty over qualification for fast-track programs prior to discussions with PMDA • Likely the shortest approval pathway (i.e., conditional approval after just one phase I/II trial in humans) • Difficulty in MSC procurement given limited allowed sources • GMP requirements from the start of clinical development	• Significant uncertainty from recent frequent changes in regulations • Foreign investment banned in human SC therapy • Several accelerated pathways could be leveraged • Domestic procurement is not difficult • GMP requirements from the start of clinical development	• Uncertainties from less evidence of efficacy and safety compared to standard approval pathway • Potential of immature development • Faster approval relies on use of surrogate endpoint in exploratory clinical study, with post-approval confirmatory clinical trial	• Accelerated approval of RM therapies determined on a case-by-case basis • ~40 cell manufacturing facilities across the country

Attractiveness High Medium

Note: CBER: Center for Biologics Evaluation and Research; CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; NCA: National Competent Authorities; MHLW: Ministry of Health, Labour and Welfare; PMDA: Pharmaceuticals and Medical Devices Agency; NMPA: National Medical Products Administration; MFDS: Ministry of Food and Drug Safety; TGA: Therapeutic Goods Administration; AHPRA: Australian Health Practitioner Regulation Agency; ATMP: Advanced Therapy Medicinal Product; IND: Investigational New Drug; BLA: Biologics License Application

Source: L.E.K. interviews, research and analysis

and commitment to supporting the RM industry. However, as markets for RM products are generally global due to their smaller addressable patient populations and significant research and development (R&D) and commercialization burdens, RM products should be considered from a global perspective.

RM regulatory environments, albeit favorable, can vary across the four markets in question, potentially hampering wider cross-country development and commercialization efforts. Asian regulators, particularly in Japan and China, are attuned to the potential economic and healthcare benefits of regenerative medicines, and are therefore striving to harmonize their frameworks with both the EU and the U.S. in an effort to pave the way for Western biotech RM portfolios.

Intentions may be clear from a regulatory standpoint, but what's next for market participants?

When launching new RM therapies, biotechs will need to work closely with regulators (e.g., PMDA for Japan), which will likely review them on a therapy-by-therapy basis. It is ideal for biotechs to have people close to these types of organizations.

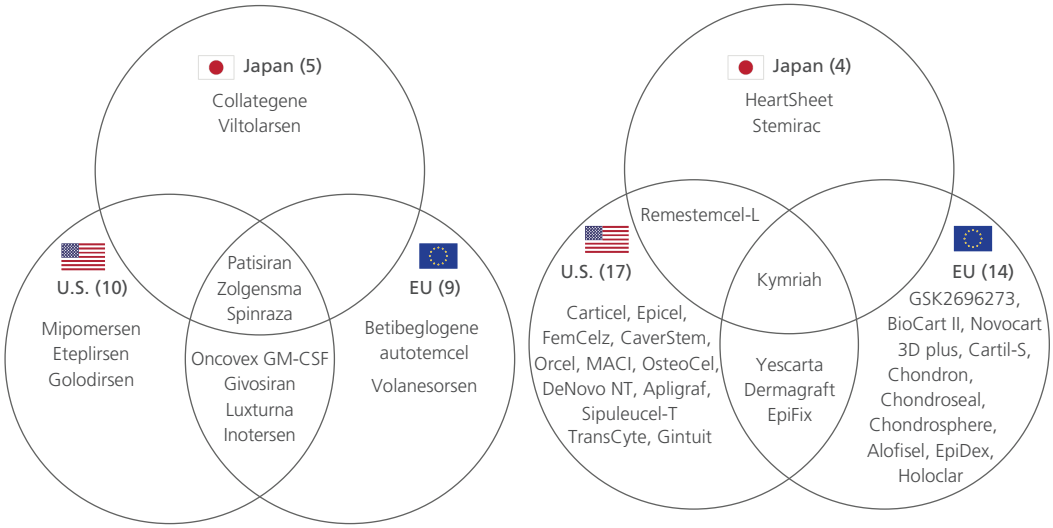
To date, fewer than 10 gene and cell therapies have been launched in Japan, whereas in Europe and the U.S. the figure is almost three times higher (Figure 6). As only four therapies have so far launched in all three markets (EU, the U.S. and Japan), the harmonization of regulatory frameworks is not yet having its intended effect, but we expect this to change in the near term and there are a few actions biotechs can take.

Prior to commencing clinical trials, biopharma companies and biotechs should consider consulting with the PMDA to understand the development process, local trials required and privileges potentially applicable. For example, orphan drug and Sakigake designations allow access to a priority review by the PMDA (about nine months for orphan drug designations and six for Sakigake versus a whole year for the standard approval process), priority clinical consultations from the PMDA and the National Institute of Biomedical Innovation (NIBIO), a potential for a 10%-20% premium and developmental grant from NIBIO (up to 50% of Japanese development costs), and tax deductions.

RM therapies with data confirming safety and directionally predicting efficacy may qualify for a "conditional and time-limited approval pathway" without confirmatory clinical trials, supported by the outcomes of post-marketing surveillance (PMS) required for continued commercialization (Figure 7). However, the conditional approval expires after seven years if the manufacturer fails to demonstrate full safety and efficacy.

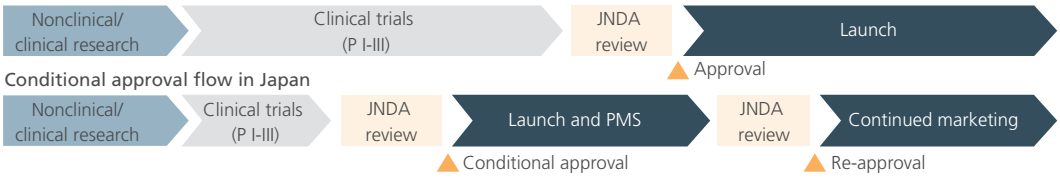
The conditional approval pathway, available for RM products since 2013, is aimed at bringing to market treatment options for severe diseases with a low prevalence, for which clinical trial recruitment may be difficult. However, while this pathway may naturally appeal

Figure 6
Approved RM. Left: Gene therapies; Right: Cell therapies (SC and ACT)



Source: Citeline

Figure 7
Regulatory approval flow of pharmaceuticals in Japan



Note: JNDA: Japanese New Drug Application
Source: L.E.K. research and analysis

to manufacturers with limited global development capacities, the requirement of safety and efficacy through PMS creates an ongoing operational burden after approval, with meaningful PMS implementation barriers (e.g., lack of clinical and financial incentives, as patients can have access to the marketed drugs without the risk of being assigned to the placebo cohort, and are not competitively incentivized compared to foreign geographies). More importantly, manufacturers following the conditional approval path are faced with a significant financial and reputational risk if the RM therapy turns out to be unsafe or not effective.

From a clinical operations perspective, hospitals are becoming increasingly experienced with RM clinical trials requirements. However, some therapy-specific operational issues remain challenging to accommodate, and hospitals expect close manufacturer involvement and support. Additionally, the number of medical institutions that will ultimately be providing such therapies is likely to be limited.

In the near future, RM therapies without an appropriate comparator standard of care are likely to be priced using a cost-plus method. However, the cost-plus pricing method may not fairly grasp the true value of RM, nor reflect some of those therapies' idiosyncratic nuances, such as the one-time treatment option of some therapies. Moreover, the current premium system may not be sustainable for highly expensive gene therapies, given the already expensive base price.

Despite the prescriptive pricing rules, a "black box" component of the Ministry of Health, Labour and Welfare's (MHLW) negotiation process and a high risk of policy-level backlash involving sudden changes to pricing rules, especially for high-priced RM therapies, remain significant. For example, since 2017, the MHLW has been increasingly issuing "optimal use guidelines" at time of reimbursement or retrospectively, to ensure innovative drugs are provided to the most appropriate patients, and to effectively limit use of the high price/volume drugs. For example, guidelines have been released for Kymriah limiting its use to patients under 26, among other significant limitations. Stipulations can also include biomarker levels, patient history, past treatment(s) tried, medical facility criteria and physician criteria/certifications. Since April 2019, innovative drugs with high peak revenue forecasts (i.e., >JPY 10 billion peak revenue forecast for new drugs and >100 billion revenue for existing drugs) may be subject to new Health Technology Assessment pricing revisions, with a maximum downward adjustment of 15%.

Payers are another audience that biopharma companies and biotechs may have to navigate in Asia

Traditional reimbursement systems, geared toward provision of chronic care, are unable to cope with the high costs of gene and cell therapies. In the U.S. for example, the treatment for Kymriah, which is indicated for advanced lymphoma and pediatric leukemia, costs USD 375,000-475,000. Yescarta, indicated for adults with large B-cell lymphoma, is priced at USD 373,000. Luxturna, indicated for a specific type of inherited retinal dystrophy, is priced at USD 850,000, and Zolgensma, a lifesaving gene therapy for pediatric spinal muscular atrophy, costs USD 1.5 million per patient. For the APAC market, the cost of Kymriah is estimated at USD 413,000 in Australia and USD 306,000 in Japan.

Given the nascent stage of these technologies and the lack of long-term follow-up data, there are differing views among stakeholders on what constitutes reasonable price levels for these therapies, and on whom the burden should fall.

Payers in particular have different data needs and interests that go beyond the safety and efficacy required by regulators (e.g., cost-effectiveness, economic value). Consequently, companies will have to work with payers early on to ensure that appropriate data is collected during and after clinical trials, and develop new payment models.

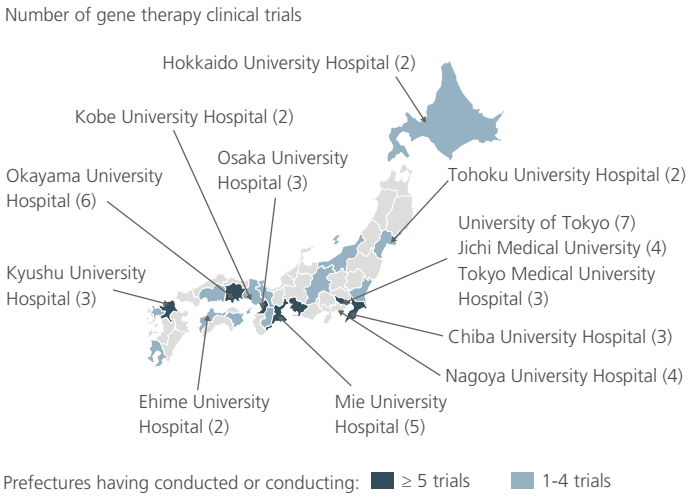
In grappling with these challenges, biotechs may be better served by launching their RM therapies first in the U.S. given the greater degree of regulatory scrutiny and evidence collection, ensuring patient safety, and safeguarding the brand from any undesirable public relations that might arise post-marketing in more lax markets.

The Asian clinical landscape is underdeveloped and presents a number of barriers for entrants, but also major opportunities to differentiate

Asia's clinical development environment presents tremendous opportunities for global RM developers. However, given the nascent nature of the RM development landscape, bringing a novel RM therapy to patients for trials and eventual commercialization presents its own set of challenges, among which are the inherently unique and complex protocols, the trial design and patient recruitment, and the significant planning and coordination required across the various stakeholders.

The lack of standard procedures also contributes to the challenging clinical development landscape in Asia. This becomes more important as the product advances through clinical stages, as the higher number of sites required in later phases could make it more difficult to closely coordinate with the biotechs and ensure consistency in materials handling.

Figure 8
Institutions involved in Japan's 64 gene therapy clinical trials (1995-2018)



In Japan, ~30 hospitals located in multiple prefectures participated in gene therapy clinical trials between 1995 and 2018 (Figure 8), offering developers a number of clinical site options to choose from, subject to compliance. Moreover, Japan boasts a strong network of physicians and key opinion leaders (KOLs) that can support data creation, once provided with appropriate training and support from biopharma companies and biotechs.

In the context of patient recruitment, access to properly designed and executed patient registries can be a powerful tool for gaining access to patients, particularly considering that RM therapies often target less prevalent diseases for which recruitment can be challenging. As such, Japan has recently enacted several initiatives aimed at supporting secondary use of disease registries to achieve cost-effectiveness in clinical studies, such as the Clinical Innovation Network. Ongoing initiatives include the improvement of data anonymization and interoperability, and the promotion of new technologies in healthcare data. These are expected to increase data acceptability to support real-world post-marketing performance of a product, as well as to reduce trial timelines and costs.

From cell handling to cryologistics, RM's clinical and logistical hurdles cannot be overstated. By catering to the specific requirements of these advanced therapies, development partners such as contract research organizations (CROs) and CDMOs that have the required know-how are likely to help reduce costs and timelines required for project setup (Figure 9), particularly for smaller biotechs that lack in-house knowledge and capabilities. At present, given the high level of unmet needs, the bourgeoning RM pipeline and changing biopharma needs are likely to create tremendous growth opportunities in the CDMO/CRO space in Asia.

There are opportunities for players along the supply chain, which, compared to Europe and the U.S., is also underdeveloped

Besides RM therapy developers, the ecosystem of players fulfilling the RM value chain includes CDMOs, enabling tech providers (e.g., cell banks, culture media and automation technologies providers) and third-party logistics companies offering ultra cold chain solutions to transport cells between locations during the cell harvest, manufacturing and distribution processes.

Figure 9
Case Study: Timeline and cost comparison between manufacturing in-house and outsourcing to CDMO* (Phase II setting)

Stage and scope	Cost [expressed as normalized cost units]		Timeline [months]	
	In-house	Outsourced	In-house	Outsourced
Project setup Commissioning of cleanroom, quality control laboratory and ancillary facilities; staffing CDMO project team	312	5	9	2
Technology transfer Training at the academic site and CMO staff training; GMP documentation transfer/implementation; materials sourcing	280	50	7	4
Implementation and performance qualification Qualification and validation of cleanroom and equipment, analytical methods, manufacturing process, and shipping	242	126	6	5
GMP manufacturing Capacity for up to six lots/month (monthly fee includes three lots, with each additional lot charged individually)	40/month	21/month	6	6
Total setup and monthly ongoing costs	834 setup plus 40/month	181 plus 21/month	28	17

Note: *For academic research laboratory spun out biotech planning for a Phase II clinical trial that involves 36 patients over the course of six months
Source: BioProcess International; L.E.K. analysis

Manufacturing processes for RM therapies share a number of similarities to those for biologics. However, complications arise when it comes to cell acquisition (if not procured from cell banks), expansion and differentiation. All of these processes will require significant investments if they are to be developed in-house. CDMOs offer an attractive alternative, particularly for small biotechs that lack expertise, capacity or resources to commercialize products on their own. This approach also makes sense from a risk management perspective, as the rapid pace of innovation in the RM sector could potentially lead to the obsolescence of initial technologies, making in-house investment prospects risky. However, due to the surge in RM clinical activity, RM biotechs face up to two years before they can access capacity at existing CDMOs.

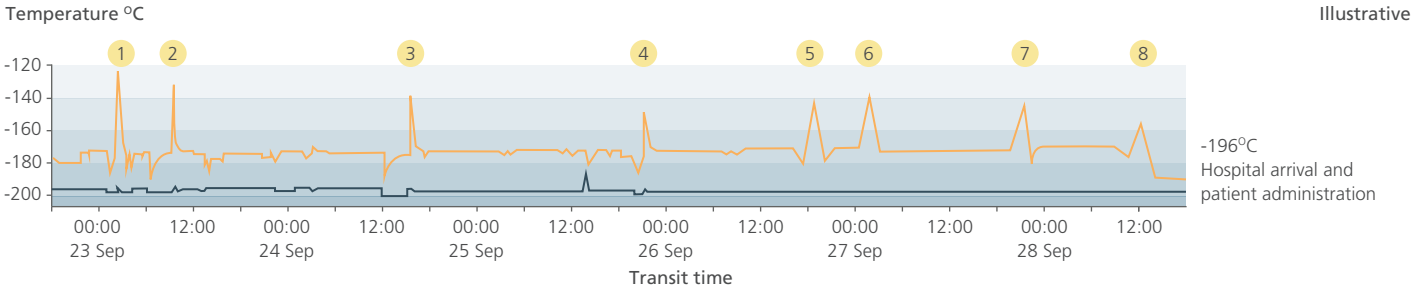
"There are no regulatory reasons why the cells cannot be shipped across different countries. Some countries may require some customs clearance, but as long as appropriate documents are made, the transport of cells is possible."
— Technical director of bio-manufacturing, Global CDMO

Developers could also opt for decentralized manufacturing and subsequently transporting RM therapies to points of care, as there are no regulatory hurdles for centralizing manufacturing abroad. However, the cost advantage could be offset by high transportation and compliance costs, and would likely further amplify the need to solve the product's logistical hurdles.

Labor and facility costs are expected to be the primary concerns for manufacturing cell therapy products, followed by resourcematerials and quality control procedures. Our work with biotechs in Asia and abroad has highlighted that key challenges arise from the lack of standard procedures. One key enabler is the advent of automation and improved workflow technologies, which could greatly drive down the cost of therapy manufacturing. Critically, automation considerations will need to be addressed early on during clinical trials, as any process changes would be arduous, time consuming and costly, and might inadvertently limit the product's scalability and commercial potential.

As cell therapy products consist of metabolically active mammalian cells, which require oxygen and nutrients to remain viable and potent, they are naturally more susceptible to adverse temperature events (Figure 10) during handling and shipping. Autologous cell therapy products, for example, involve a complex chain of custody, from cell collection from the patient through shipping, incorporation into the drug-manufacturing process, storage and distribution back to the patient, all of which must be done within a very tight window of time and temperature. Therefore, cell therapy products typically need to be delivered just in time

Figure 10
Dry shipper temperature log



Adverse temperature event typically anticipated

1. Removed from storage at the distribution center and placed in a container (dry shippers) for transfer to a clinical site
2. Transferred from the controlled-rate freezing unit to the manufacturer's temporary storage unit
3. Left the manufacturing facility (removed from temporary storage and placed in a container, then loaded on a truck)
4. Removed from the container it was transferred in and placed in a storage container at a distribution center
5. Removed from the transfer container and either placed in a controlled-rate thawing unit or a storage unit at the clinical site pharmacy
6. Removed from storage in the pharmacy and placed in a cryocart for transfer to the patient bedside
7. Transferred from the cryocart to a thawing or processing unit
8. Removed from the thawing unit and placed on a tray, awaiting administration to the patient

Source: Fisher BioServices, L.E.K. analysis

to the point of care, or stored at cryogenic temperatures (-60°C to -150°C) to preserve the cells in a metabolically inactive state. This is generally manageable during clinical trials but becomes a significant challenge at the commercial scale. While developers could implement those capabilities in-house, outsourcing to third-party vendors is a more common approach.

Furthermore, different cell therapy products have different formulations, which call for different storage and handling arrangements (Figure 11). Hence, product-level capacity planning and logistical solutions must be thought through within the same RM modality.

On the other hand, gene therapy products consist of nucleic acids that are either naked or packaged in a variety of different vectors and drug delivery systems (viral, lipid nanoparticles, etc.). As such, they are inherently more stable than cells and can leverage existing logistics infrastructures for biologic drugs.

In the U.S. and EU, several cryologistics providers are already capable of supporting allogeneic cell therapy products, with 24-48 hours' of domestic shipment coverage, while storage is mainly handled by manufacturers. Increasingly, cryologistics providers are entering the storage marketplace by establishing their own warehousing services. The case for Japan and China is, however, different, as ultra-cold chain logistics are not well established yet. In Japan, biotechs typically distribute through pharmaceutical wholesalers. However, for the commercialization of Temcell in Japan, ultra-cold chain logistics were jointly developed by JCR and Medipal (one of the big four wholesalers), as there were no preexisting players. In Asia, this market remains generally underserved compared to the U.S. and EU.

Healthcare providers eager to provide RM therapies to their patients would need to carefully assess whether their existing infrastructure and processes can uphold the high quality standards of these scientifically complex and novel therapeutics. Appropriate facilities for the harvesting and delivery of RM therapeutics, ultra-cold storage, and tight control systems need to be implemented, as errors could have dire consequences. Additional knowledge and expertise will also need to be acquired by care delivery agents, through proper training, and and will likely need greater involvement and support from the manufacturer than would be typical for small molecules or biologics.

"The bigger issue is what happens at the treatment site. Most places don't have the facility to store the regenerative therapies. Also, processes required at the point of care have to be simple, robust and straightforward — they should always understand the ramifications of the process. Formulation and therapy delivery should be as simple as possible and preferably comparable to injections."
— Head of R&D, Cell Therapy Biotech

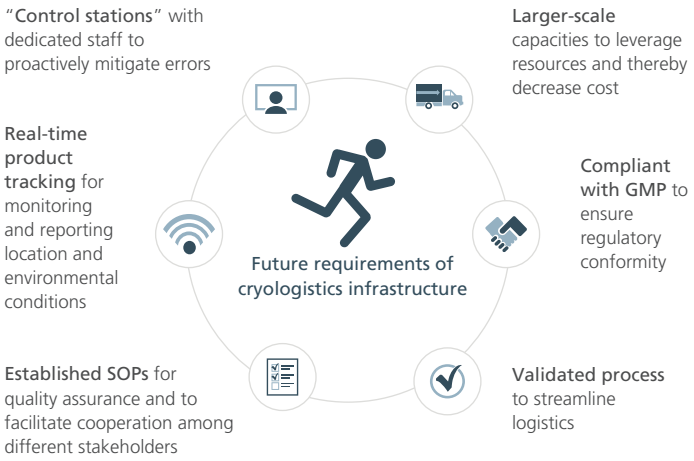
Although great scientific, manufacturing and logistical advancements have been made in recent years in the EU and U.S., the supply chain for RM therapies in Asia is still largely underdeveloped and will need to go through a similar systematic organization and standardization. Investments may need to be large, but the complexity of this challenge (Figure 12) only highlights the size of the prize for those participants that are able to sufficiently address the host of unique manufacturing and logistical challenges when delivering gene, cell and tissue engineering therapies to patients in Asia.

Figure 11
Variation of storage requirements of different regenerative medicine therapies

Regenerative medicine	Modality	Type	Storage requirement
Alofisel (darvadstrocel)	Adipose SC	Allogeneic	15°C-25°C
ChondroCelect	Chondrocytes	Autologous	15°C-25°C
Stemirac	Bone-marrow derived MSC	Autologous	-80°C
Prochymal (remestemcel-L)	MSC	Allogeneic	-135°C
Provenge (sipuleucel-T)	Dendritic cells	Autologous	2-8°C

Source: L.E.K. research and analysis; company websites

Figure 12
Future requirements of cryologistics infrastructure



Note: SOP: Standard Operating Procedures
Source: L.E.K. interviews and analysis

A final consideration for utilizing CDMOs is that biotechs will need to have scientists who can facilitate the technology transfer, as well as bioprocessing experts and quality control personnel to audit manufacturing processes regularly.

Biotechs should look to provide physician training and hospital infrastructure support in addition to typical commercial activities

Scientifically complex products (in which we include RM therapies require a higher level of customized support, given the complexity of the information to be delivered and of the patient cases typically encountered. It should be noted that as the complexity of information to be delivered and the level of support physicians require in using the products increase, medical science liaisons (MSLs) should be deployed separately from promotion efforts to provide medical information and support, typically in the launch phase but also across the product life cycle, particularly for complex disease areas and wherever patient support services are offered. Physicians expect different information and support along the product life cycle, some of which can be delivered through non-medical representative (MR) channels.

Commercialization of cell therapy products is likely to be limited to centers of excellence, due to the complex nature of the products, and should ensure manufacturers will have better control over products and can better avoid adverse events. The limited number of treatment centers and specialists will mean that biotechs will require fewer MSLs and smaller sales forces, more comparable to that for (ultra) orphan drugs.

The commercialization pathway for RM therapies will, however, bring new challenges. Biotechs should look to follow a five-step process to effectively commercialize their products in Japan (Figure 14). The first step should involve generating a consensus view by aligning with KOLs and academic societies on treatment guidelines and regulations upon entry.

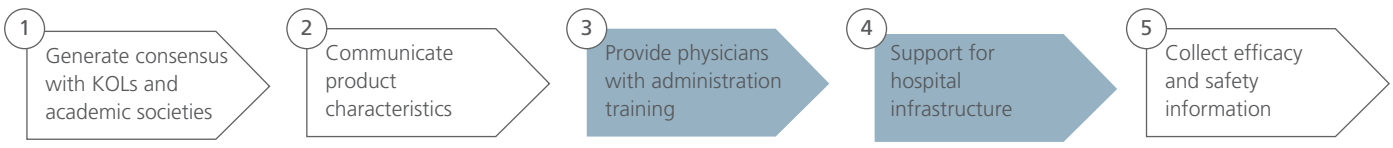
Biotechs should next effectively communicate their products' characteristics to physicians, ensuring they have the latest and most accurate information for their therapies.

Another key consideration, particularly for cell therapies, is that physicians will need well-designed trainings on how to administer therapies to patients. The clinical delivery of cell and gene therapies is more complex and multidisciplinary than pills or biologics. Biotechs should consider supporting and providing resources for specialist institutions that will be responsible for RM therapy certification systems.

As we noted earlier in this article, RM therapies have very specific, and different, product-by-product infrastructure requirements. Biotechs should therefore be prepared to support the development of processes for storing and delivering therapies safely in different patient settings. This should include support for perioperative and surgical procedures.

The final consideration in our five-step process is to conduct PMS for all patients receiving RM therapies. This is particularly important for any therapies that may have skipped Phase III trials, in which case PMS becomes a requirement.

Figure 13
Five-step process: Commercial activities recommended for regenerative medicine therapies



Unique to cell therapy

Source: L.E.K. interviews and analysis

Checklist and priorities for different RM players

In recent years, RM therapies have demonstrated huge potential in reshaping the treatment paradigm, especially in rare diseases and oncology. The recent approvals for Kymriah, Yescarta, Luxturna and Zolgensma have demonstrated the rising acceptance of these therapies. While the growth opportunities are significant, important challenges still remain on the Asian horizon.

For RM therapies to be successfully commercialized, the right infrastructure and network of service providers must be in place. This involves different kinds of enabling technology and service providers, including cryologistics providers, CMOs and cell banks. While Japan and South Korea are relatively advanced in these areas, there is still room for development compared to the U.S. and EU markets.

We believe the logical next steps for market participants will include the following:

- Biopharma checklist and priorities:
  1. Work closely with regulators in each country to understand, in detail, requirements and how they will vary for each of your individual therapies
  2. Begin preparations earlier than usual, and do not wait until near the launch of your RM therapies to conduct standard activities for small molecules and biologics.Understand the large-scale distribution and commercialization requirements for your products
  3. Develop new business models that should be customized for each country
- CDMO/CRO checklist and priorities:
  1. Build a network of hospitals that can support RM development in each market
  2. Work with biotechs to standardize manufacturing protocols
  3. Work with logistics companies to understand requirements for individual products, particularly handling products at the site of care
- Supply chain vendor checklist and priorities:
  1. Plan the development of cryologistics infrastructure and capabilities, including monitoring systems for each key market
  2. Work with potential clients to standardize processes and protocols for different categories of RM therapies

Technical advantages and challenges of RM modalities

The technical advantages and challenges of different RM modalities vary significantly, and consequently these modalities lend themselves to addressing different types of diseases and therapeutic areas. In the table below we have outlined further details for each.

Modality	Advantages	Challenges
AAV	• Natural tropism of specific serotypes toward specific tissues (e.g., AAV9 for neuronal tropism, AAV1 for airway tropism) • Negligible risk of insertional mutagenesis (do not integrate into the host genome) • Replication incompetent without helper virus (such as adenovirus) • Can bypass immune response due to capsid engineering	• Limited duration of therapeutic effect (~6-12 months); dilution in dividing cells drives the need for re-dosing • Limited by load capacity to shorter genomic sequences (<5kb) and weaker promoters • Unable to be delivered repeatedly as it is likely to trigger an immune response after first administration
LVV	• Permanently incorporate DNA into the genome to form a new integrated therapeutic DNA molecule and replicate with host DNA; able to transduce both dividing and quiescent cells • Broad tropism, targeting various tissues • Ability to contain larger payloads (~8kb) • Replication incompetent as the components necessary for virus production are split across three or four plasmids	• Higher risk for insertional mutagenesis (random integration) as it integrates the DNA into the host genome • Unable to be delivered repeatedly as it is likely to trigger an immune response after first administration
NVP	• Able to transfer larger genes compared to viral approaches • Less immunogenic compared to viral vectors, hence it can be delivered repeatedly • Much longer shelf life of over nine months without any performance degradation	• Limited duration of therapeutic effect (high expression for a few days, followed by a milder expression that can last months); dilution in dividing cells drives the need for re-dosing • Requires drug delivery systems (DDSs) which are yet to be optimized for in vivo use • In its naked form, efficacy limited to certain tissues (e.g., smooth muscle with cell-to-cell communication), and no targeting properties
mRNA	• Efficacious as protein replacement therapy for loss-of-function diseases • Avoids the inherent risk of insertional mutagenesis associated with integrative gene therapy	• Limited duration of therapeutic effect (1-2 weeks) depending on protein half-life • Requires DDSs, which are yet to be optimized for in vivo use • Mild cytotoxicity can be observed at some therapeutic doses
siRNA	• Addresses monogenic diseases caused by gain-of-function mutations • Highly selective targeting of specific nucleic acid sequences • Can be continuously expressed by an engineered plasmid vector	• Limited duration of therapeutic effect (1-2 weeks) • Requires DDSs to increase stability against nuclease digestion and allow the use of lower concentrations • Susceptibility to degradation by nucleases • Saturation of the endogenous RNAi machinery by exogenous siRNA can disrupt natural cellular processes • miRNA-like off-target effects
miRNA	• Used for miRNA replacement therapy for cancer treatment • Enable regulation of entire signaling networks within the cells • More durable effect from miRNA compared to siRNA	• Limited duration of therapeutic effect (1-2 weeks) • Less specificity toward the target, increasing the risk of off-target effects
ASO	• Highly selective targeting of specific nucleic acid sequences • Pharmacokinetics well understood, involving a rapid distribution to all peripheral tissues in vivo, and a slow metabolism	• Requires DDSs to increase stability against nuclease digestion and allow the use of lower concentrations • Heavy chemical modifications necessary for stability can affect efficacy • Mild to moderate toxicities from binding to the off-target RNA, or immune stimulation
sgRNA	• Disease-modifying treatment due to permanent genome editing	• Risk of off-target effects • Cas9 toxicity in vivo
hESC	• Natural pluripotency • Indefinite replication	• Raises ethical concerns due to the destruction of a human embryo

Modality	Advantages	Challenges
iPSC	• Circumvents ethical issues around the use of hESC • Enables potential for disease modeling • More potential clinical applications compared to MSC • Allows off-the-shelf business models based on single donor-derived cells	• Highly dependent on enabling technologies • Lacks established protocols for differentiation, resulting in high product variability • High risk of mutagenesis
MSC	• Low immunogenicity/suitable for unmatched allogeneic transplantation • Easily isolated in large quantities due to availability in various tissues (e.g., bone marrow, cartilage, fat, dental pulp) • Used for a wider range of systemic diseases (e.g., autoimmune disorders, graft-versus-host disease, sepsis) and endogenous tissue regeneration, due to their immunomodulatory effect and paracrine secretions	• Exogenously administered MSC show poor survival and engraftment rate • Limited to applications in immunomodulation and tissue engineering of the mesodermal lineage only • Mechanism of action not clearly understood • Risk of undesired homing in the lungs
HSC	• Relevant for certain blood and bone marrow cancers and autoimmune diseases • Can be mobilized from bone marrow to bloodstream using G-CSF cytokines, which makes them readily accessible for collections and ex vivo genetic modification	• Challenging ex vivo expansion
Progenitor cells	• Can multiply in large numbers, while being lineage-committed • Easier to culture and maintain in vitro; less chance of unwanted mutations	• More difficult to collect due to lower availability • Limited potency and replication capability compared to multi- and pluripotent SCs
CAR-T	• Can be autologous or allogeneic (off-the-shelf based on engineered single donor-derived cells) • Higher specificity compared to other therapeutic options (e.g., chemotherapy) • Inclusion of suicide genes allows control of the proportion of infused cells (and their antitumor activity) in vivo using an inducing agent	• Low penetration of solid tumors • Targets limited by the number of tumor-specific cell-surface antigens • Cytokine storm side effects • Off-target effect due to cross-reactivity
TCR	• Can recognize intracellular tumor-related antigens • More direct tumor cell killing and immunostimulatory effect	• Off-target effect due to cross-reactivity
TIL	• Able to penetrate solid tumors, which other types of cells typically cannot	• Short-lived effect due to deactivation by tumor micro-environment • Off-target effect due to cross-reactivity • Chronic inflammatory side effects
Acellular scaffolds	• Provides an environment for new tissue regeneration • Can be designed with tightly controlled parameters (porosity, degradation rate, etc.)	• Occasional adverse effects (inflammation, swelling)
Ex vivo tissue-engineered constructs	• Uses ex vivo expanded autologous cells • Good medium- to long-term results • Typically used for matrix-associated autologous chondrocyte transplantation	• Occasional adverse effects (inflammation, swelling)

Endnotes

[1] Statistics by Country for Genetic Disease — https://www.rightdiagnosis.com/g/genetic/stats-country.htm.

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Ray Fuji is a Partner and the Representative Director of L.E.K. Consulting's Japan practice and is a member of L.E.K.'s Global Leadership Team. He has more than 17 years of experience directing consulting engagements focused on corporate strategy development, mergers and acquisitions, operational and organizational issues, and performance improvement. Ray has advised a diverse range of clients across a broad range of industries that include pharmaceuticals, medical technologies, diagnostics, consumer products, financial sponsors, industrial products, and travel and leisure.

Prior to joining L.E.K., Ray was a financial advisor with Lazard Frères and Lehman Brothers. He started his career as a management consultant with PricewaterhouseCoopers and joined Johnson & Johnson as a manager after completing his MBA program. Ray earned his Bachelor of Arts in biology from Washington University in St. Louis, and he received his Master of Business Administration from the Olin School of Business at Washington University. He is a native of Japan and fluent in English and Japanese.

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Prior to joining L.E.K., Yuta worked at Japanese consulting firms in Singapore and Tokyo, supporting Japanese and multinational companies in their growth strategy and business development in the Asia-Pacific region. He earned a bachelor's degree from International Christian University in Tokyo and a Master of Science degree from Tokyo University. Yuta also spent time as a researcher at the University of California, Berkeley, studying cell and molecular biology.

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