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An Updated Look at Regenerative Medicine

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〈Summary〉

○ Following our initial report on regenerative medicine in October 2013, cell and gene therapy field has made major strides. In this updated report, we take another snapshot of the industry and examine the recent past, current status and what the future may hold.

○ Pharmaceutical innovation is a slow process. It often takes many years for a project to go from an idea to a drug. Sometimes enough technical advances accumulate to a threshold level to enable the development of a breakthrough medicine. To complete the loop, clear clinical data is needed to validate the underlying technology advances. We believe in regenerative medicine, gene therapy and the related field of oligonucleotide therapy have cleared important technical hurdles and proved their mettle in the clinic.

○ The incorporation of new AAV-vectors in gene therapy has ushered in a golden era of gene therapy. From neurodegenerative CNS disease, hemophilia, hemoglobinopathy, to genetic-caused eye diseases, gene therapy has generated groundbreaking data, even promising of a cure. Although commercial success has so far been lacking, we believe it is a matter of time before we see the first blockbuster gene therapy product. Given the complex logistics and higher cost, regenerative medicine need to show transformative effect on disease rather than incremental benefit. Gene therapy is a prime example of how a one-time therapy can have huge and lasting impact on patients' lives.

○ In the cell therapy area, with the exception of CAR-T therapy, the clinical trial experience over the last four years has been mostly disappointing. We have seen some tentative signs of efficacy but not the transformative efficacy expected from the promise of regenerative medicine. Therefore, outside of more established areas such as HSCT, wound care and orthopedics, we would still characterize cell therapy as waiting for clinical validation.

○ In this report, as an extension to gene therapy, we also discussed the field of nucleic acid-based drugs. Both ASOs and siRNAs have passed important technical hurdles and proven their clinical utility by developing groundbreaking medicines. But some platform safety risk remains. mRNA is emerging as a new treatment modality. mRNA vaccine is a well-suited application, but its development is still in early days.

Executive Summary

- We published an overview report on regenerative medicine in October 2013. Over the last four years, the landscape has evolved considerably. In this report we update the progresses of regenerative medicine and try to separate the wheat from chaff in the field.
- In cell therapy, while CAR-T has clearly emerged as a winner, traditional in vivo cell therapies have had plenty of disappointing clinical news. Outside of established areas such as HSCT, wound care and orthopedics, we would still characterize traditional cell therapy as waiting for clinical validation. Further developing cells into tissues before giving to patients seems to overcome some hurdles of cell therapy. Another trend we see is future cell therapy is likely to be dominated by iPSC derived cells instead of adult stem cells or ES-derived cells that are in current clinical development. We continue to be enthusiastic about the prospect of combining genetic engineering and cell therapy. In the future genetically engineered, iPSC derived cells may become 'super' cells to treat human diseases.
- The incorporation of new AAV-vectors in gene therapy has ushered in a golden era of gene therapy. From neurodegenerative CNS disease, hemophilia, hemoglobinopathy, to genetic eye diseases, gene therapy has generated groundbreaking data. Although the data often come from a small number of patients, the dramatic treatment effect is very impressive. We believe gene therapy is well poised to make big impacts on the clinical outcomes of many patients. Gene therapy may be the most exciting area of regenerative medicine. While big pharma have been lukewarm about cell therapy (outside of CAR-T), they are warming up to gene therapy and have entered into a number of acquisitions or technology licensing deals with gene therapy companies.
- We included in their report a review of nucleic acid based drugs. Although they may not be considered regenerative medicine in the traditional sense, they bear characteristics of advanced therapies and are related to gene therapy. Nucleic acid based drugs have overcome important technical hurdles in recent years. After forty years of development and the success of Spinraza, ASO has been proven to be an effective treatment modality. siRNA development lags behind ASO but the success of patisiran has validated the siRNA approach. We believe although two potentially blockbuster oligonucleotide drugs have been developed, some platform risks of ASO and siRNA remain. We have also seen a number of setbacks in developing oligonucleotide drugs. mRNA therapeutics is emerging as a new therapeutic modality. It is particularly suitable for developing vaccines especially personalized vaccines like neoantigen vaccines for cancer. But developing mRNA therapeutics is still in early days and will likely go through its up-and-downs as the technology and pipeline mature.
- In conclusion, revolutionary technical improvements have occurred in CAR-T, gene therapy, oligonucleotide drugs, which are enabling development of breakthrough drugs. No doubt they will be important treatment modalities in the future. As stated in our October 2013 report, we still characterize the traditional cell therapy in high-risk but high-reward areas as waiting for clinical validation.

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Glossary and Abbreviations

Abbreviations	
AAV (vector)	Adeno associated virus (vector)
ADA-SCID	Adenosine deaminase deficiency - severe combined immunodeficiency
AMD	Advanced macular degeneration
AMI	Acute myocardial infarction
ARM	Alliance for Regenerative Medicine
ASH (Conference)	American Society of Hematology (Conference)
ASO	Antisense oligonucleotide
AZ	AstraZeneca
BLA	Biologics license application
CAR-T (Therapy)	Chimeric Antigen Receptor T-cell Therapy
CMS	The Centers for Medicare & Medicaid Services
CMV	Cytomegalovirus
CNS	Central nervous system
CV	Cardiovascular
ES (cells)	Embryonic stem (cells)
FDA	Food and Drug Administration
GalNAc	N-Acetylgalactosamine
GSK	GlaxoSmithKline
GvHD	Graft versus host disease
Fka	Formerly known as
HSCT	Hematopoietic stem cell transplantation
IBD	Inflammatory Bowel Disease
IP	Intellectual Property
IPO	Initial Public Offering
iPSC	Induced pluripotent stem cell
IND	Investigational New Drug (application)
LNP	Lipid nanoparticle
MACE	Major adverse cardiac event
MPS disease	Mucopolysaccharidosis disease (orphan lysosomal storage disease)
mRNA	Messenger RNA
MSC	Mesenchymal stem cell
NK cells	Natural killer cells
PDUFA date	The Prescription Drug User Fee Act date (for drug approval)
NK cells	Natural killer cells
RA	Rheumatoid arthritis
Regenmed	Regenerative medicine
RMAT	Regenerative Medicine Advanced Therapy (designation)
RNAi	RNA interference
siRNA	Small interfering RNA
SMA	Spinal muscular dystrophy
SPA	Special protocol assessment
TA	Therapeutic area
TTR amyloidosis	Transthyretin amyloidosis
VEGF	Vascular endothelial growth factor

Source: Compiled by MHBK/IRD based on public company reports

I. Introduction

A. Introduction

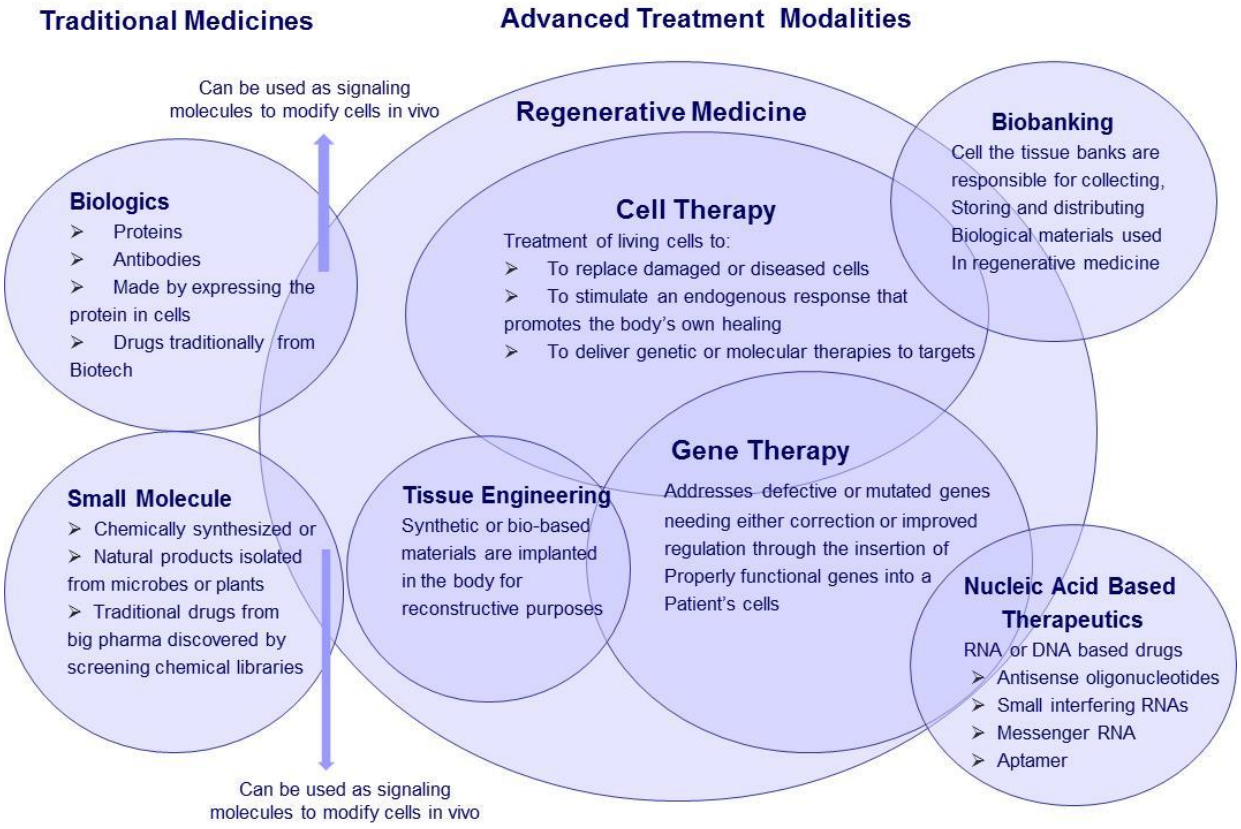
In October 2013, we published a report titled "A Survey of Current Landscape in Regenerative Medicine[1]." In that report we characterized the regenerative medicine field as novel and promising but required clinical validation. Over the last four years, numerous companies have reported important clinical data or passed key regulatory milestones. Therefore a clearer picture has emerged. As most have expected, engineered T cell therapy (CAR-T) has become an unquestioned success. In August, FDA approval of Kymriah for blood cancer acute lymphoblastic leukemia (ALL) and its manufacturer Novartis set a price of $475,000 for a course of therapy. Gilead acquired CAR-T company Kite Pharma for $11.9bn in August and received FDA approval for Yescarta in October. Gene therapy has also been a tremendous success. Companies such as Spark Therapeutics, bluebird bio, BioMarin, uniQure and Sangamo reported exciting data in Inherited Retinal Disease, β-thalassemia, Sickle Cell Disease, Hemophilia, and other genetically inherited diseases. However, for cell therapies in the traditional sense (not modified T cells to treat cancer), there have been many failures but just one or two ultimate successes. So we believe cell therapy in many high-risk but high reward areas is still waiting for clear clinical validation. In this report we provide an update of regenerative medicine by examining recent technological progresses and clinical experiences in cell therapy and gene therapy. As an extension of gene therapy, we also take a look at the exciting field of nucleic acid based drugs. We believe these advanced treatment modalities have tremendous potential in tackling diseases poorly served by traditional small molecule and antibody drugs. However, clinical proof is needed in some areas to validate the underlying technology and the therapeutic approach.

B. Background of Regenerative Medicine

Regenerative medicines by definition are treatments to regenerate or restore functions of damaged or diseased tissues. It represents a new paradigm in human health as it has the potential to resolve medical needs by addressing the underlying causes of diseases. Therefore regenerative medicines often have curative potential. Regenerative medicines go beyond traditional treatment modalities such as small molecule or protein drugs and into the realms of advanced treatment modalities such as cell therapy, gene therapy, tissue engineering and nucleic acid based therapy (see Figure 1). In this report, we discuss the two main components of regenerative medicine - cell therapy and gene therapy. As an extension of advanced treatment modality we also discuss nucleic acid based drugs.

[1] https://www.mizuhobank.co.jp/corporate/bizinfo/industry/sangyou/pdf/mif_141.pdf.

Figure 1 Illustration of the Scope of Regenerative Medicine



Source: Modified by MHBK/IRD based on 2013 Regenerative Medicine Annual Report by Alliance for Regenerative Medicine

C. U.S. Regulatory Updates – RMAT Designation

The U.S. Congress passed the 21st Century Cures Act in December 2016. Section 3033 of the Act (called Accelerated Approval for Regenerative Advanced Therapies) created the Regenerative Medicine Advanced Therapy (RMAT) designation[2]. This designation provides sponsors with increased regulatory interaction and guidance with the FDA, potential eligibility for priority review, and opportunity for accelerated approval. In order to qualify, product candidates must be deemed a regenerative medicine therapy. The law stipulates that regenerative medicine therapies include "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products." FDA has taken a broader view on the definition of regenerative medicine by including gene therapy. On August 30, FDA described the approval of CAR-T therapy for acute lymphoblastic leukemia as the first "gene therapy" approved in the U.S.[3]

[2] https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm
[3] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm

On November 16, 2017, FDA unveiled a general framework for the development and review of regenerative medicine products and regulation of the clinical use of regenerative products. The released framework includes two final guidances and two draft guidances. The two final guidances provide clarity on which products are except from FDA regulations[4], and how FDA defines "minimal manipulation" and "homologous use.[5]" The first draft guidance[6] clarifies regulatory pathways for devices used in the recovery, isolation, or delivery of Regenerative Medicine Advanced Therapies (RMAT). In the second draft guidance[7], FDA explains how it might consider regenerative medicine products for expedited review pathways, including Fast Track, breakthrough therapy and RMAT designations, as well as accelerated approval and Priority Review[8].

The second draft guidance titled "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" is the most significant for the regenerative medicine industry. According to this draft guidance, RMAT has characteristics of both breakthrough designation and accelerate approval pathway in the U.S. Its definition and features are better understood if compared to the breakthrough designation (see Table 1).

- RMAT enjoys all the benefits of the fast track and breakthrough designations, including early and close interaction with the FDA.
- The efficacy bar to qualify for breakthrough designation is higher than RMAT. RMAT products must provide preliminary clinical evidence demonstrating the potential to address unmet medical needs for that disease or condition. In contrast, breakthrough designated products must demonstrate "substantial improvement on a clinically significant endpoint over available therapies." According to the draft guidance, "as opposed to breakthrough designation, the RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies."
- Products with RMAT designation may be eligible for accelerated approval. Accelerated approvals are often based on surrogate endpoints but companies need to conduct post-market studies to show benefits on ultimate endpoints to win final approval. According to the draft guidance, post-approval requirements for RMAT-designated product may be fulfilled from sources other than the traditional confirmatory clinical trials. The post-market requirements may involve confirmatory clinical trials, patient registries, electronic health records, or other data collection. In formulating the draft guidance, FDA retains great flexibility and will determine the requirements on a case-by-case basis.

[4] https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf
[5] https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM585403.pdf
[6] https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM585417.pdf
[7] https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM585414.pdf
[8] Biocentury Extra, November 16, 2017

- In terms of pre-approval requirements, FDA also maintains substantial flexibility for itself by leaving the requirements vague. In the draft guidance, FDA mentioned innovative trial designs and novel endpoints. FDA encourages sponsors of RMAT to have early discussion about clinical trial requirement. But FDA didn't set a specific bar for what constitutes "preliminary clinical evidence" sufficient for approval.
- A product with RMAT designation may be eligible for priority review if supported by clinical data at the time the market application is submitted. But the priority review benefit is not automatically granted to RMAT-designated products.

Table 1 Comparison of the Key features of Breakthrough and RMAT Designation

	Breakthrough Therapy Designation	Regenerative Medicine Advanced Therapy Designation
Statute	Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act
Qualifying criteria	A drug that is intended to treat a serious condition, **AND** Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug is a regenerative medicine therapy, AND the drug is intended to treat, modify, reverse, or cure a serious condition, AND preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition
Features	• All fast track designation features, including: ▪ Actions to expedite development and review ▪ Rolling review • Intense guidance on efficient drug development, beginning as early as Phase 1 • Organizational commitment involving senior managers	• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements
When to submit	With the IND or after and, ideally, no later than the end-of-phase 2 meeting	
FDA response	Within 60 calendar days after receipt of request	
Designation Rescission	Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria	

Source: FDA draft guidance "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions"

It is helpful to compare the early approval schemes of the three major pharmaceutical regulatory bodies (see Table 2). Japan has the easiest pathway for approval of cell therapy. Japan's PMD Act (The Act on Pharmaceuticals and Medical Devices) allows for conditional & time-limited authorization of regenerative medicine products based on clinical data that confirm safety and are likely to predict efficacy (see Table 2). Sponsors are required to submit confirmation efficacy and safety data to support full approval within seven years of marketing. The RMAT designation doesn't lower the preapproval efficacy requirements as much as PMD Act does in Japan. During the legislative process, FDA and the Alliance for Regenerative Medicine beat back attempts to allow marketing of certain cell-based therapies based solely on small Phase II trials. Then FDA Commissioner Robert Califf co-authored an article in The New England Journal of Medicine, in

which he wrote, "the assertion that existing standards for regulatory approval are too rigorous for stem-cell therapies results largely from a lack of familiarity with the available pathways for developing cellular therapy products and from the lack of a systematic, facilitated approach to assembling the clinical data necessary to support the licensure of stem-cell therapies produced by individual practitioners at different sites." Recently FDA declined to approve Vericel's RMAT-designated Ixmyelocel-T to treat heart failure due to Ischemic Dilated Cardiomyopathy (DCM) based on a phase 2 trial and requested a larger trial. This is an example of FDA not lowering approval standard for RMAT-designated products.

Table 2 Evolving Early Approval Schemes by Three Major Regulators

Type	US	EU	Japan
Orphan	Priority review Orphan designation	Accelerated review Orphan designation	Priority review Orphan designation
Conditional	Accelerated approval for serious or life threatening illnesses	Conditional MA MA under exceptional circumstances	Conditional & Time-limited approval Approval for oncology drug, Orphan drug
Priority	RMAT Breakthrough therapy & Fast track designation (Rolling submission)	PRIME Pilot project on adaptive path (Rolling submission)	SAKIGAKE Forerunner review assignment

Source: "Regulation of Regenerative Medicine in Japan" by Dr. Yoshiaki Maruyama, Office of Cellular and Tissue-based Products, PMDA, Japan

FDA's Center for Biologics Evaluation and Research (CBER) reportedly has received 30 requests for RMAT designation and has granted 7 of the 26 it has acted on. A list of companies that have received RMAT designations is shown in Table 3.

Table 3 Companies That Have Received RMAT Designation

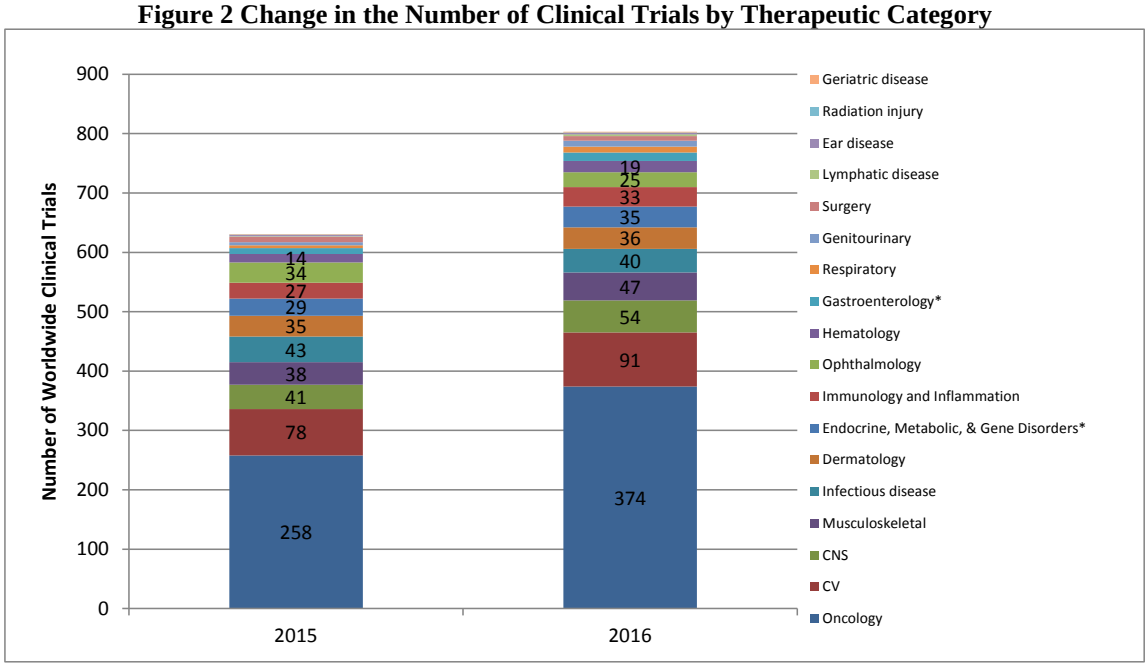
Date	Company	Therapy	Stage	Mechanism	Indication
3/27/2017	Humacyte	Humacyl	Phase 2	Human acellular vessel (HAV)	Vascular access for hemodialysis
4/17/2017	Enzyvant	RVT-802	Preregistration	Allogeneic thymic tissue	Primary immune deficiency from complete DiGeorge Syndrome
5/2/2017	jCyte	jCell	Phase 2b	Human retinal progenitor cells (hRPCs)	retinitis pigmentosa (RP)
5/10/2017	Vericel	ixmyelocel-T	Phase 2b	Autologous mesenchymal stromal cells and macrophages from bone marrow	Heart failure due to ischemic dilated cardiomyopathy (DCM)
7/19/2017	Mallinckrodt / Stratatech	StrataGraft	Phase 3	Skin graft	Severe burn
9/20/2017	Kiadis Pharma	ATIR101	Phase 2	Donor lymphocyte infusion	Prevent infection in HSCT patients
10/2/2017	Asterias Biotherapeutics	AST-OPC1	Phase 1/2	Oligodendrocyte progenitor cells derived from human embryonic cells	Spinal cord injury

Source: Compiled by MHBK/IRD based on public company reports

D. Industry Statistics

According to ARM (Alliance for Regenerative Medicine) 2016 annual report[9], at the end of 2016, there were 804 ongoing clinical trials for regenerative medicine worldwide, representing 21% growth from 2015. Most of the growth came from oncology clinical trials (see Figure 2). In terms of therapeutic category, oncology has the lion's share by having 47% of the total, followed by CV, CNS, Musculoskeletal, Infectious Diseases, Dermatology, etc. (see Figure 3). In terms of technology, 425 trials are for gene & gene-modified cell therapy, 533 for cell therapy and 20 for tissue engineering. In terms of stage of development, 68 trials are in phase III, 475 trials in phase II and 261 trials in phase I.

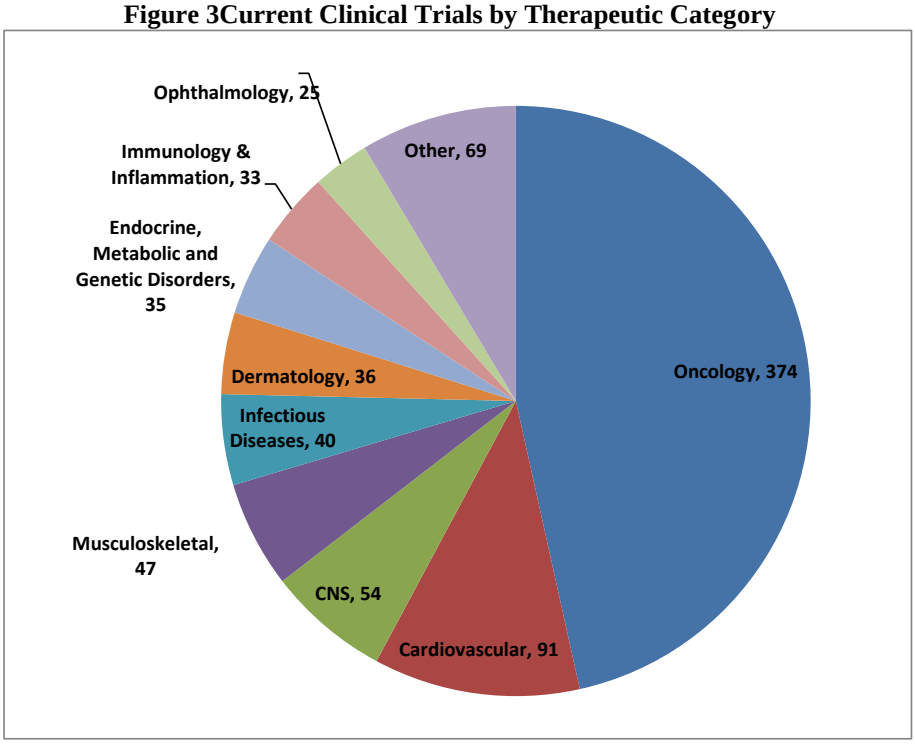
Figure 2 Change in the Number of Clinical Trials by Therapeutic Category



Source: Alliance for Regenerative Medicine 2016 Annual Data Report; *Note: ARM didn't disclose 2015 clinical trial numbers for Gastroenterology and Endocrine, Metabolic & Gene Disorders so the 2015 numbers were based on our estimates

[9] https://alliancerm.org/sites/default/files/ARM_2016_Annual_Data_Report_Web_FINAL.pdf

Figure 3Current Clinical Trials by Therapeutic Category

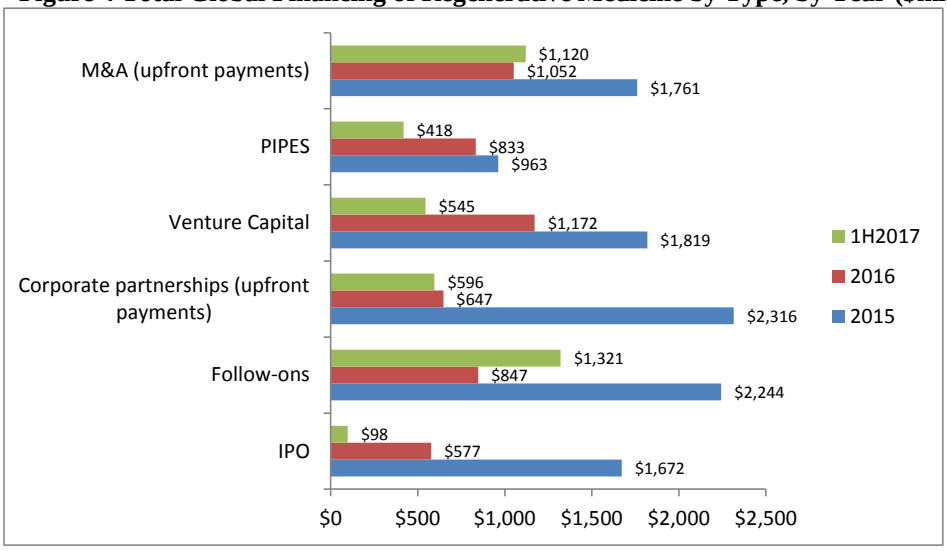


Source: Alliance for Regenerative Medicine 2016 Annual Data Report

E. Financing for Regenerative Medicine

To fund R&D programs, regenerative medicine companies have a strong need for continued cash infusion. Biotech financing in general has declined substantially from the peak 2015 levels. Regenerative medicine companies cannot escape this trend. However, judged from the amount of financing in the first half of 2017, regenerative medicine companies have raised a healthy sum compared to 2016 (see Figure 4). Gilead's $11.9bn acquisition of Kite Pharma in 2H2017 will boost 2017 M&A figure dramatically.

Figure 4 Total Global Financing of Regenerative Medicine by Type, by Year ($mn)



Source: Alliance for Regenerative Medicine, 2Q2017 Quarterly Data Report

Regenertive medicine companies have raised substantially funding through U.S. IPOs (see Table 4). Companies that have gone public are concentrated in promising areas such as cancer cell therapy, gene therapy, gene editing, and nucleic acid therapeutics. Post IPO performance has been uneven but leaders have delivered stellar returns.

- Kite pharma returned almost 10x for its IPO investors as the company was taken over at $180 a share. The Kite Pharma buyout is a watershed moment for regenerative medicine. Shares of many cell therapy companies jumped in sympathy. Some companies promptly raised funding. However, we view the Kite Pharma takeout as a one-off deal in the industry. In our view, the deal was driven more by the strong interest from a committed buyer than by near-term financial returns of underlying asset. For the deal to generate positive financial returns, Gilead needs to take a very long-term bullish view of the underlying CAR-T technology. We are not sure other big pharma with less deep pocket than Gilead but more urgent need to fill the commercial pipeline will do similar deals.
- Gene therapy companies such as Spark Therapeutics and AveXis have delivered stellar clinical data and strong share performance.
- Gene editing companies such as Editas, Intellia and CRISPR only had a short history in the public market, but so far their shares have been holding up nicely.

However there are laggards too:

- After their clinical programs failed, Celladon and Mirna became public shells for reverse mergers.
- For companies slow to progress their clinical programs or fail to show good clinical data, shares tend to languish.

Table 4 U.S. IPO History of Regenerative Medicine Companies

Ticker	Company Name	Category	IPO Date	IPO Price Low	IPO Price High	IPO Price	Share Offered	Fund Raised ($mn)	Market Cap ($mn)	Return To Date
NITE	Nightstar Therapeutics	Gene therapy	9/27/2017	13.0	15.0	14.0	5.4	75.0	389	-4%
TOCA	Tacogen	Gene therapy	4/13/2017	10.0	12.0	10.0	8.5	85.0	218	18%
CRSP	CRISPR Therapeutics	Gene editing	10/19/2016	15.0	17.0	14.0	4.0	56.0	751	34%
BOLD	Audentes	Gene therapy	7/20/2016	14.0	16.0	15.0	5.0	75.0	847	91%
AVXS	AveXis	Gene therapy	2/11/2016	19.0	21.0	20.0	4.8	95.0	3,145	395%
EDIT	Editas Medicine	Gene editing	2/3/2016	16.0	18.0	16.0	5.9	94.4	1,068	53%
WVE	Wave Life Sciences	Nucleic acid therapy	11/11/2015	15.0	17.0	16.0	6.4	102.4	1,056	140%
VYGR	Voyager Therapeutics	Gene therapy	11/11/2015	15.0	17.0	14.0	5.0	70.0	460	3%
DMTX	Dimension Therapeutics	Gene therapy	10/22/2015	14.0	16.0	13.0	5.5	71.5	100	-54%
MIRN	Mirna Therapeutics	Nucleic acid therapy	10/1/2015	13.0	15.0	7.0	6.3	44.1		
RGNX	RegenxBio	Gene therapy	9/16/2015	17.0	19.0	22.0	6.3	138.6	877	29%
NK	NantKwest	Cancer cell therapy	7/28/2015	20.0	23.0	25.0	8.3	207.5	401	-81%
CYAD	Celyad	Cancer cell therapy	7/19/2015			68.6		100.0	330	-51%
ADAP	Adaptimmune	Cancer cell therapy	5/6/2015	15.0	17.0	17.0	11.3	192.1	698	-57%
NTLA	Intellia Therapeutics	Gene editing	5/5/2016	16.0	18.0	18.0	6.0	108.0	750	-1%
CLLS	Cellectis	Cancer cell therapy / Gene editing	3/25/2015			41.5	5.5	228.3	863	-30%
ONCE	Spark Therapeutics	Gene therapy	1/29/2015	19.0	21.0	23.0	7.0	161.0	1,699	99%
JUNO	Juno Therapeutics	Cancer cell therapy	12/19/2014	21.0	23.0	24.0	11.0	264.0	5,413	87%
BLCM	Bellicum	Cancer cell therapy	12/18/2014	15.0	17.0	19.0	7.4	140.6	295	-55%
KITE	Kite Pharma	Cancer cell therapy	1/15/1900	15.0	16.0	17.0	7.5	127.5	11,900	959%
AGTC	AGTC	Gene therapy	3/27/2014	13.0	15.0	12.0	4.2	50.4	65	-70%
QURE	uniQure	Gene therapy	2/5/2014	13.0	15.0	17.0	5.4	91.8	534	2%
CLDN	Celladon	Gene therapy	1/30/2014			8.0	5.5	44.0		
DRNA	Dicerna	Nucleic acid therapy	1/30/2014			14.0	6.0	84.0	163	-49%

Source: Compiled by MHBK/IRD based on public company reports. Note in this list, we included cell therapy companies, adoptive cancer cell therapy companies, gene therapy companies, gene editing companies and companies developing nucleic acid based medicine.

II. Cell Therapy

A. Background of Cell Therapy[10]

Cell therapy involves using stem cells or adult/somatic cells to treat human diseases. Stem cells are distinct from adult/somatic cells by two properties – long-term self-renewal and the ability to differentiate into various specialized cells. In comparison, adult/somatic cells are terminally differentiated cells residing in specific organs to perform designated functions. Adult cells such as muscle cells, blood cells or nerve cells do not normally replicate themselves.

It is helpful to look at how cells are increasingly differentiated during embryonic development (see Figure 5). At the highest echelon is totipotent embryonic stem cells found in fertilized egg within a couple of cell divisions after fertilization. Totipotent embryonic stem cells can give rise to all types of differentiated cells found in an organism plus the supporting extra-embryonic structures of the placenta. Fertilized egg develops into early embryo, where embryonic stem cells are found. Embryonic stem cells (ESC) are pluripotent, i.e., they can differentiate into any types of differentiated cells in the body. ESCs also have the ability to renew themselves long-term. As human ESCs (hESCs) are derived from human embryos which are left over from in-vitro fertilization procedures, their uses carry moral and ethical issues. In addition, because of the potent renewal and differentiation abilities of hESCs, they can lead to formation of unusual solid tumors called teratomas in animals. Therefore, hESCs are not used directly in the clinic and instead are further differentiated into more restricted stem cells before used to develop therapeutics.

As human embryo further develops, it forms three germ layers (see Figure 5). The out layer called Ectoderm contains stem cells that give rise to the nervous system, sensory organs, skin, and related structures. The Innermost layer called Endoderm contains stems cells that differentiate into lungs, other respiratory structures, and digestive organs. The middle layer Mesoderm gives rise to bone, muscle, connective tissue, kidneys, and related structures. The stem cells in these three specific germ layers are restricted to differentiate into cells only in that particular lineage therefore they are called multipotent (in contrast to pluripotent of hESCs). There are further layers in the hierarchy of multipotent stem cells. In each germ layer, further differentiated stem cells give rise to specific cell types of the tissue where they typically reside. These stem cells are referred loosely as adult stem cells or somatic stem cells. Examples of adult/somatic stem cells include:

- Hematopoietic stem cells reside in bone marrow and give rise to all kinds of blood cells.

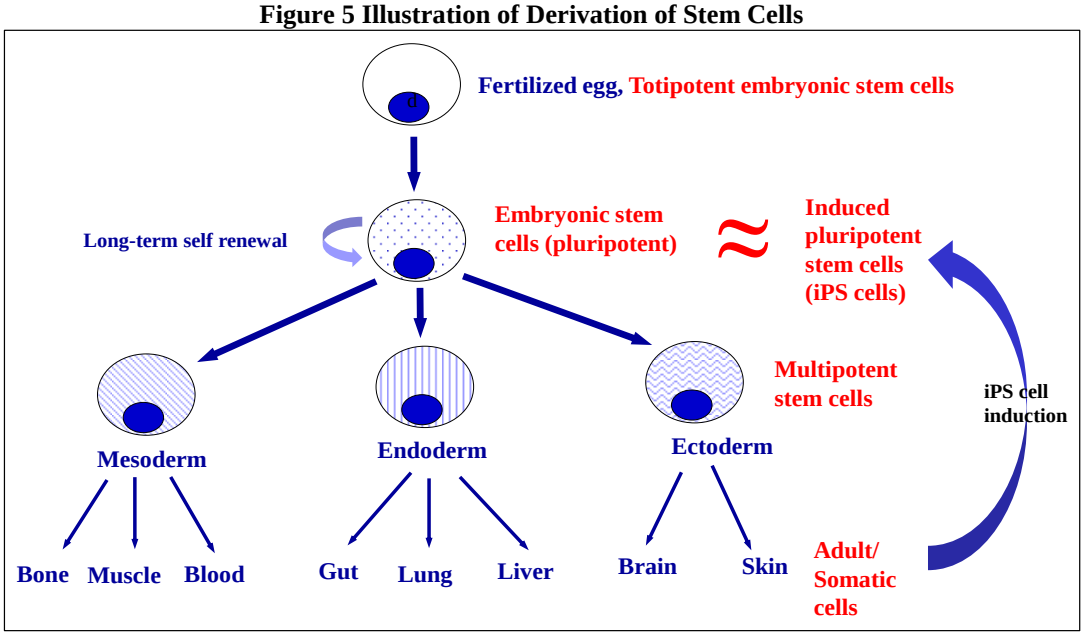
[10] For a more detailed introduction of stem cell therapy, please refer to "Stem Cell Basics" website by National Institute of Health (https://stemcells.nih.gov/info/basics/1.htm).

- Mesenchymal stem cells are present in many adult tissues. Those from the bone marrow give rise to bone cells (osteoblasts and osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and stromal cells that support blood formation.
- Neural stem cells in the brain give rise to neurons, and cells supporting the neurons (astrocytes and oligodendrocytes).
- Epithelial stem cells in the lining of digestive tract give rise to digestive cells.
- Skin stem cells in the basal layer of the epidermis and at the base of hair follicles give rise to skin cells (keratinocytes) and hair follicles.

So far, cell therapy has mostly used adult/somatic stem cells. Hematopoietic stem cells have been used successfully for decades to treat cancer. There have been many clinical trials of mesenchymal stem cells and other adult stem cells. Terminally differentiated adult/somatic cells are sometimes used in cell therapy. For example, Histogenics is developing NeoCart for cartilage repair. NeoCart is an implant of autologous cartilage cells expanded in vitro and embedded in a collagen scaffold.

Adult cells (such as skin fibroblast) can be genetically reprogrammed in vitro back to an embryonic stem cell-like state called induced pluripotent stem cells or iPSCs (see Figure 5). iPSCs can be differentiated into various adult somatic cells, which can be used as therapeutics. Autologous cell therapy using cells derived from iPSCs has huge potential in cell therapy. But to our knowledge, iPSC derived cell therapeutics is still in early-stage development as no patients are in clinical trial in the U.S. and just a handful of patients are in clinical trial in Japan.

Figure 5 Illustration of Derivation of Stem Cells



Source: Illustrated by MHBK/IRD

B. Recent Progresses of Cell Therapy

A large number of cell therapy programs have reported important clinical data. The majority of them failed due to a lack of adequate efficacy (see Table 5). To our knowledge, there was only one success of a cell therapy in a placebo-controlled phase III trial - TiGenix's Cx601 for complex perianal fistula in patients with Crohn's disease. Cx601 is allogeneic adipose-derived stem cell product. In a phase III trial conducted in Europe, Cx601 significantly separated from placebo on efficacy endpoint – remission rate of 51.5% vs. 35.6% at 24 weeks with p value of 0.021. Takeda has licensed the ex-U.S. rights to Cx601. Takeda is expected to launch Cx601 in Europe in 1H2018. As a result of the negative clinical news flow, cell therapy companies outside of oncology are trading at low valuations (see Table 6).

Going forward, we don't see many incoming critical data releases for cell therapies (see Table 7). One anticipated clinical readout is Histogenics' NeoCart for repairing knee cartilage damage in mid. 2018. NeoCart is an engineered implant using autologous cartilage cells harvested from non-weight-bearing cartilage surface of the patient's femur. NeoCart has a high likelihood success in our view as the product uses cells that are (1) destined for specific function (chondrocytes for cartilage), (2) autologous (low risk of immune rejection), (3) are grown in a collagen scaffold under conditions that simulate cartilage environment (therefore cells are protected in the scaffold and adapted to the environment), (4) MACI, a somewhat similar product from Vericel, had positive phase 3 results and was already approved by the FDA.

Table 5 Clinical Trial Results of Cell Therapy (Excl. Cancer)

Company	Time	Disease	Data description	Results
Positive trials				
Mesoblast	Jun-15	Diabetic nephropathy	Phase II	Positive
TiGenix	Aug-15	Complex perianal fistula in Crohn's disease pts	Phase III	Positive
Mesoblast	2015	Chronic low back pain	Phase II	Postive
Mesoblast	Feb-16	RA	Phase II	Positive
Negative trials				
Cytori	Jul-17	Scleroderma hand dysfunction for Habeo	Phase III	Missed efficacy endpoint
Capricor	May-17	Heart attack	Phase II	Missed efficacy endpoint
Stemcells Inc.	May-16	Spinal cord injury	Phase II	Terminated trial due to efficacy
Celyad	2016	CHF	European P III	Chart-1 trial failed
Mesoblast/Teva	2015	CHF	1st interim analysis of P III	Teva terminated the joint development for heart failure.
Vital Therapeutics	Aug-15	alcohol-induced liver decompensation (AILD)	Phase III	Failed to show efficacy
Macrocure	Aug-15	Venous leg ulcer	Phase III	Phase III failed futility analysis
Stemcells Inc.	Jun-15	Dry AMD	Phase I/II	Failed
Athersys	Apr-15	Stroke	Phase II	Failed to meet primary endpoint
Smith & Nephew	Oct-14	Venous leg ulcer	Phase III	Failed to show efficacy
Cytori	Aug-14	Refractory CHF	Phase II (Athena)	Halted due to safety
Athersys	May-14	Ulcerative Colitis	Phase II	Failed to show efficacy
Cytomedix	May-14	Stroke	Phase II	Failed
Neostem	Nov-14	Acute MI	Phase II	Missed efficacy endpoint
Trials with mixed data				
ReNeuron	Dec-16	Stroke	Phase II	Mixed (missed 3-month endpoint)

Source: Compiled by MHBK/IRD based on public company reports

Table 6 Valuation and Financials of Cell Therapy Companies (excl. cancer)

12/14/2017 Company name	Ticker	Market Cap ($mn)	EV ($mn)	Price ($USD)	Sales 2016	Sales 2017E	Net Income 2016	Net Income 2017E	Net Cash
NYSE Arca Biotechnology Index	^BTK			4201					
MiMedx Group, Inc.	MDXG	$1,331	$1,295	$12.15	$246	$322	12	37	37
AxoGen, Inc.	AXGN	$907	$909	26.70	$41	$59	-14	-11	-2
MEDIPOST Co., Ltd.	KOSDAQ:A078160	$646	$640	83.51			-4		6
Healios K.K.	TSE:4593	$684	$635	14.33	$5.7		-4.5		48
Mesoblast Limited	ASX:MSB	$484	$422	1.04	$19	$3	-4	-78	63
TiGenix NV	ENXTBR:TIG	$300	$275	1.09	$15	$15	4	-37	24
BioTime, Inc.	BTX	$296	$290	2.32			34		17
MolMed S.p.A.	BIT:MLM	$271	$258	0.59	$25		-15		14
Athersys, Inc.	ATHX	$202	$173	1.68	$17	$3	-15		28
Osiris Therapeutics, Inc.	OTCPK:OSIR	$197	$154	5.85					43
ReproCELL, Inc.	JASDAQ:4978	$190	$138	2.97	$5.7		-4.5		48
Fate Therapeutics, Inc.	FATE	$194	$139	4.37			-33	-41	54
Pluristem Therapeutics Inc.	PSTI	$150	$129	1.43			-23	-29	21
Organovo Holdings, Inc.	ONVO	$152	$101	1.38	$1	$4	-39	-39	51
Asterias Biotherapeutics, Inc.	AMEX:AST	$116	$99	2.25	$1		-35	-30	17
ReNeuron Group plc	AIM:RENE	$86	$25	0.03			-16	-27	61
BioLife Solutions, Inc.	BLFS	$77	$74	5.73	$8	$11	-7		3
Capricor Therapeutics, Inc.	CAPR	$43	$43	1.62	$4		-19	-16	0
Histogenics Corporation	NasdaqCM:HSGX	$45	$33	1.85	$0		-16	-26	12
Avita Medical Limited	ASX:AVH	$54	$51	0.05	$3	$5	-6	-10	3
Cesca Therapeutics Inc.	KOOL	$29	$31	2.68	$12	$0	-19		-3
Caladrius Biosciences, Inc.	NasdaqCM:CLBS	$33	-$27	3.45	$32	$0	-33	-19	59
Fibrocell Science, Inc.	FCSC	$15	$10	0.67			-15		12
Hemostemix Inc.	TSXV:HEM	$21	$16	0.06			-3		4
Living Cell Technologies Limited	ASX:LCT	$11	$6	0.02			-2		6
Neuralstem, Inc.	CUR	$32	$18	2.23			-21		14
Cytori Therapeutics, Inc.	CYTX	$8	$17	0.24	$15	$8	-22	-18	-9
VistaGen Therapeutics, Inc.	VSTA	$26	$26	0.00		$1	-47	-13	2
International Stem Cell Corporation	OTCPK:ISCO	$7	$9	1.61	$7	$8	-1	-6	-2

Source: Compiled by MHBK/IRD based on data from Capital IQ

Table 7 Upcoming Milestones for Cell Therapy Companies (Excl. Cancer)

Company	Program	Stage	Indication	Event
Mesoblast	MSC-100-IV	Phase 3	pediatric steroid-resistant acute GVHD	2H17
TiGenix	CX601	EU MAA	Complex perianal fistula in Crohn's disease	EMA approval 2H17
Mesoblast	MPC-150-IM	Phase 2b	end-stage advanced CHF	1Q18
Histogenics	NeoCart	Phase 3	Knee cartilage damage	Mid. 2018

Source: Compiled by MHBK/IRD based on public company reports

Due to the lack of clinical successes outside of CAR-T therapy, big pharma have been mostly absent from doing deals in traditional cell therapy (see Table 8). Two biopharma have divested their cell therapy businesses. In January 2014, Shire divested the Dermagraft wound care business to Organogenesis and wrote off $650mn of the $750mn it spent to acquire it less than three years ago. Also in 2014, Sanofi divested the former Genzyme cell therapy products with sales of $44mn to Aastrom (now called Vericel) for only $6.5mn. A few cell therapy companies such as Celyad and Caladrius have repositioned themselves to cancer. However in the case of Caladrius, phase III trial of the oncology program it acquired was later on terminated.

In the following pages, we will review recent clinical trial results and current status of cell therapies by therapeutic areas.

Table 8 Cell Therapy Deals (Excl. CAR-T deals)

Acquirer / Licensee	Target / Licensor	Date	Amount ($mn)	Highlights	Japan deal
Hitachi Chemical	PCT from Caladrus	Mar-17	$75	Acquired the cell CMO business PCT from Caladrius (80% remaining stake)	√
Cytori	Azaya Therapeutics	Jan-17	$2	Acquired nanoparticle technology	
Integra LifeSciences	Derma Sciences	Jan-17	$204	Amniotic tissue for wound and burn	
Mallinckrodt	Mesoblast	Dec-16	4.99% equity for $21.7mn	Option to license two of Mesoblast's programs - back pain and GvHD	
Allergan	LifeCell	Dec-16	$2,900	Acellular dermal matrices, Alloderm and others for soft tissue repair and surgery	
Celgene	Evotec	Dec-16	$45mn upfront, up to $250mn milestone payments	Exclusive R&D collaboration - iPSC-based drug screening for neurodegenerative diseases	
Bayer/Versant	BlueRock	Dec-16	$225	Invested $225mn series A funding. Allogeneic cell for PD and heart disease	
Mitsubishi Tanabe	TissueGene	Nov-16	$24mn upfront plus $410mn milestone payments	MTP licensed TissueGene's Invossa™ for degenerative osteoarthritis for the Japanese market.	√
Mallinckrodt	Stratatech Corp	Aug-16		StrataGraft regenerative skin tissue and skin technology. Sales of $29mn.	
Takeda	TiGenix	Jul-16	€25mn upfront, €355mn royalties	ex-U.S. license of Cx601 for perianal fistulas in patients with Crohn's disease	√
J&J	ViaCyte	Feb-16	NA	Following an option deal in 2014, J&J combined its BetaLogics unit with ViaCyte.	
Healios	Athersys	Jan-16	$15	Partnered Multi-stem for stroke in Japan	√
Astellas	Ocata Therapeutics	Nov-15	$379	Cell therapy for ophthalmology conditions	√
Integra	TEI	Jun-15	$312	Regenerative products for wound care and soft tissue reconstruction.	
Chugai	Athersys	Mar-15	$10	Chugai licensed MultiStem for development in Japan for stroke.	√
Celgene	Mesoblast	Apr-15	$45mn equity investment	Right of first refusal to certain MSC programs.	
Fujifilm	Cellular Dynamics	Mar-15	$307	iPS derived cells for research.	√
Nikon	Lonza	Mar-15		Collaboration for Cell and Gene Therapy Manufacturing in Japan	√
Celyad (Cardio3)	Celdera Medical	Jan-15	$10mn upfront, $50mn milestone	Acquired OnCyte CAR-T programs from Celdera Medical.	
Janssen (J&J)	ViaCyte	Aug-14	$20	Right to a trasanction around VC-01 for Type 1 Diabetes	
Novartis	Gamida	Aug-14	$35mn for a 15% equity stake and an option to acquire the company for $165mn cash in 2015. Milestone pmt of $435mn.	Technology to harvest and expand stem cells from umbilical cord blood. Clinical programs include bone marrow transplantation for hematological cancers, sickle cell disease and thalassemia.	
Vericel (formerly called Aastrom)	Sanofi (Genzyme) cell therapy and regenmed	Apr-14	$6.5	Include three autologous cell therapy products: Carticel, Epicel and matrix-induced autologous chondrocyte implant, or MACI. Aastrom will also acquire manufacturing and production facilities.	
Caladrius (Neostem)	California Stem Cell, Inc.	Apr-14	$34 upfront, up to $90mn milestone payment	Melapuldencel-T is an irradiated autologous in vitro proliferating melanoma cell line loaded onto an autologous dendritic cell combined with GM-CSF. CSC will start phase III study under SPA for its Melanoma Dendritic cell vaccine in 2014.	
Sobi (Swedish Orphan Biovitrum)	TiGenix	Apr-13	NA	Licensed CondroCelect to Sobi. CondroCelect sales grew 25% to €4.3mn in 2013. Sobi will pay 22% royalty for first year and 20% thereafter for the ten -year licensing period.	
TC BioPharm	Medinet	Mar-14		TC Biopharm licensed cell technology of Medinet for development in Europe.	√
Organogenesis	Shire's Dermagraft business	Jan-14	No upfront, Pay up to $300mn if Dermagraft sales reach certain goal by 2018	Shire sold the Dermagraft business it acquired three years ago. Recorded $650mn in loss for the sale. The business has been under pressure after Medicare cut reimbursement. Shire has abandoned its plan for establishing a regenerative medicine unit.	
Janssen biotech (J&J)	Capricor	Jan-14	$12.5mn upfront for the option to license. Milestone payment up to $325mn.	J&J received an option to license Capricor's cardiosphere cells. J&J can exercise the option within six months of the availability of ALLSTAR phase II data.	
Intrexon	Medistem	Dec-13	$26 ($6mn in cash and $20mn in stock)	Intrexon which is focused on synthetic biology acquired Medistem which develops Endometrial regenerative cells. This deal will add to Intrexon's platform.	
Mesoblast	Osiris' MSC therapeutic business	Nov-13	$35mn upfront, $15mn in 6 months, up to $50mn regulatory milestones, plus royalties	Acquired Prochymal for Crohn's disease and GvHD, acquired Osiris' entire IP on MSC, inherited partnership with JCR in Japan.	

Source: Compiled by MHBK/IRD based on public company reports

C. Cardiovascular

Cardiovascular disease is a huge potential market for cell therapy. We reviewed a number of cell therapies in mid-late stage clinical development in our report published in October 2013. Since then, a large number of such trials have reported data, which are mostly negative (see Table 9). Baxter terminated the phase III RENEW trial prematurely due to strategic reasons. The RENEW trial showed a preliminary signal for efficacy. Trials from Athersys, Neostem, Cardio3, Capricor failed to meet primary efficacy endpoints. Cytori terminated the trial due to adverse events. Mesoblast's phase III heart failure is ongoing but partner Teva backed out of license and returned rights to Mesoblast. A recent academic review of landmark studies using bone-marrow derived cells, mesenchymal stem cells or presumed cardiac progenitor cells also showed little or negligible treatment effect on cardiac function[11].

Table 9 Recent Clinical Trial Results of Cell Therapy in CV Conditions

Company Name	Products (Trial)	Technology / cell type	Autologous / Allogeneic	Indication	Stage	Result date	Results	Market Cap ($mn) if Public
Athersys	MultiStem	Multipotent adult progenitor cells (MAPC)	Allogeneic	AMI	II	4/17/2015	Failed to meet primary endpoint in a phase II trial.	
Baxter	RENEW trial	Intramuscular (IM) delivery of purified autologous CD34+ stem cells	Autologous	Refractory angina	III	2016	Study terminated prematurely due to strategic reasons. 112 of the planned 444 patients were enrolled. Therapy was found to be safe and showed some, albeit not statistical significant, efficacy.	$35,262
Caladrius (formerly Neostem)		AMR-001 (Autologous bone marrow derived, CD34 positive selected stem cell product)	Autologous	AMI	II	November-14	Failed to meet primary endpoint in a phase II trial.	$33
Capricor	CAP-1002 (ALLSTAR)	Cardiosphere-derived cells (CDCs)/ Cardiac progenitor cells	Allogeneic	MI	II	May-17	Interimu analysis of phase II ALLSTAR trial showed futility. J&J declined to exercise licensing rights.	$43
Ceylad (formerly Cardio3 Biosciences)	C-Cure (Chart-1, Chart-2)	Bone marrow stem cells reprogrammed into cardiomyocytes (through the cardiopoiesis platform)	Autologous	Congested heart failure (CHF)	III	June-16	Missed primary endpoint but met statistical significance in a subset of patients	$330
Cytori	Celution System (ATHENA)	Adipose derived stem and regenerative cells (ADRCs)	Autologous	Refractory CHF	II	August-14	Put on clinical hold due to reported cerebrovascular events.	$8
Mesoblast	MPC-150-IM	Adult mesenchymal precursor cells (MPCs)	Allogeneic	CHF	III	Ongoing	Teva returned the rights in June 2016 after the first interim analysis. Passed an interim futility analysis in April 2017, in which no safety concern was raised.	AUD 631
Terumo (Harvest Technologies)	BMAC	Bone marrow aspirate cells	Autologous	Critical limb ischemia (CLI)	III	Trial completed	Study completed but results unknown	$16,608
Vericel (formerly Aastrom)	Ixmyelocel-T (ixCELL-DCM)	ixmyelocel-T (mesenchymal stromal cells and alternatively activated	Autologous	HF due to ischemic DCM	II	April-16	The 126-patient study met primary endpoint compared to placebo (p=0.03)	$169
TiGenix	ALLOCSC-01	Cardiac stem cells	Allogeneic	AMI	I/II	Mar-17	Safe. Preliminary indication of efficacy by showing a larger reduction in in one pre-specified subgroup	$300

Source: Compiled by MHBK/IRD based on public company reports

Mesoblast – Took on the Heart Failure Trial On Its Own

Mesoblast is pursuing the development of its mesenchymal lineage adult stem cells (MLCs, also called MPC or Mesenchymal Precursor Cell) technology in a variety of indications. The precise mechanism of action for MPCs is unknown and is proposed to deliver therapeutic benefits through paracrine effect (i.e., secreting pro-growth and repair proteins such as growth factors, chemokine, VEGF, etc).

[11] "Heart regeneration and repair after myocardial infarction: translational opportunities for novel therapeutics." By Cahill, Choudhury and Riley, Nature Review Drug Discovery, October 2017. Volume 16 pages 699 - 717.

Mesoblast is running a large phase III study of its MPC-150-IM for congested heart failure. MPC-150-IM is a single-dose of MPCs injected to the heart via myocardial catheter. Prior to the initiation of phase III study, Mesoblast conducted a 60-patient, randomized, placebo-controlled phase II trial for CHF. In the study, MPC-150-IM elicited minimal host immune reactions. On the efficacy side, Major Adverse Cardiac Events (MACE) were significantly reduced in MPC-150-IM -treated patients over 22 months follow-up (p=0.036). MACE risk over time was reduced by 78% in treated patients vs. controls (p=0.011), with 60-90% risk reduction seen at every MPC dose. Based on this result, Mesoblast's former partner Teva initiated a 1,700-patient phase III trial in CHF with primary end point being reduction in MACE rate and hospitalization. But in June 2016, after the first interim analysis, Teva terminated the partnership with Mesoblast. Mesoblast took over the program and streamlined its business to free up financial resources to support the phase III study. Enrollment of the trial is reduced from the original 1,700 patients to 600 patients. In April 2017, Mesoblast announced that MPC-150-IM passed a pre-specified interim futility analysis of the efficacy endpoint in the trial's first 270 patients, and the trial will go to completion. In addition to this phase III study in severe CHF patients, Mesoblast is also conducting a phase 2b multi-center study in 159 NYHA Class III/IV patients who have end-stage advanced CHF in North America. Result of this study will be available in 1Q2018 and if positive, could support an accelerated approval.

Terumo – Marketing the First Cell-based CV Product

In September 2015, Terumo announced that its autologous skeletal myoblast sheet was conditionally approved as a cellular or tissue-based product in Japan. This approval is notable as it is the first product approved in Japan under the conditional approval pathway. Autologous skeletal myoblast sheets are cultured from a patient own thigh muscle and transplanted to patient's heart under the open chest surgery. Terumo has been conducting research on cell sheets since 2007. So this break-through commercial product is long time in the making. Terumo set a price of $15,000 for one application of the heart sheet.

Vericel (formerly Aastrom) –A RMAT Designation Didn't Help Quick Approval

Vericel (formerly known as Aastrom) demonstrated promising data in CHF for its Ixmyelocel-T autologous cell therapy. Ixmyelocel-T contains mesenchymal stromal cells and macrophages purified from bone marrow and then expanded in vitro. In the phase IIa study, safety was found to be similar to the control group and Ixmyelocel-T led to a significant reduction in MACE (major adverse cardiac event) rate in the ischemic DCM (Dilated Cardiomyopathy) cohort via the catheter delivery. In March 2016, Vericel reported positive top-line results from phase IIb ixCELL-DCM clinical trial of Ixmyelocel-T in patients with heart failure due to Ischemic Dilated Cardiomyopathy (DCM). This 126-patient, placebo-controlled trial met its primary endpoint with patients in the ixmyelocel-T group having a 37 percent reduction in all-cause deaths, cardiovascular hospitalizations, or unplanned outpatient and emergency department visits to treat acute decompensated heart failure during the 12 months following treatment compared to

the placebo group (p=0.0344). The primary endpoint was driven by a reduction in both all-cause deaths (3% for Ixmyelocel-T vs. 18% for placebo) and cardiovascular hospitalizations (38% vs. 47%) respectively. Ixmyelocel-T received RMAT designation from the FDA in May 2017 to treat heart failure due to DCM. It has also received orphan drug and fast track designation from the FDA earlier. Following a Type B meeting with FDA on September 29, 2017, Vericel disclosed FDA requested the company to conduct at least one additional well controlled clinical trial to support an ixmyelocel-T BLA filling. Vericel further stated it has no plan to fund the trial itself unless it can find a partner. We believe this is an example of FDA not lowering regulatory hurdle for RMAT designated products.

BioCardia – Phase III Trial of Autologous Bone Marrow Derived Mononuclear Cells Ongoing

BioCardia is developing CardiAMP—autologous minimally processed bone marrow cells from a patient's own cells in a pivotal trial for CHF. In the CardiAMP procedure, first 60cc of bone marrow is drawn from the iliac crest (hip bone) of the patients, then the cells are processed point of care at patients' bedside to select mononuclear bone marrow cells and finally cells are injected into the heart tissue by BioCardia's own Helix transendocardial delivery system. In a small phase II study, CardiAMP was shown to be safe and have some preliminary efficacy (efficacy was a secondary endpoint in the study). BioCardia is conducting a 250-patient phase III study in heart failure with results expected in 2019. Beyond CardiAMP, BioCardia is also developing CardiALLO —allogeneic culture expanded mesenchymal bone marrow cells from a universal donor for heart failure. BioCardia is expected to file U.S. IND in 4Q2018 for CardiALLO.

TiGenix – Preliminary Data for AlloCSC-01 for AMI

TiGenix is developing allogeneic cardiac stem cells ALLOCSC-01 to treat acute myocardial infarction (AMI). In March 2017, TiGenix reported top-line, 1-year data from the phase I/II CAREMI trial in acute myocardial infarction (AMI). The trial enrolled 51 patients with AMI and left ventricular dysfunction, of which 35 received a single intracoronary administration of AlloCSC-01 and 16 patients received placebo. Patients were treated within the first week post-AMI. The study met all safety objectives, demonstrating that allogeneic cardiac stem cells can be transplanted safely through the coronary tree. On efficacy side, a larger reduction in infarct size was found in the AlloCSC-01 arm in a prespecified subgroup of patients with poor long-term prognosis.

D. CNS

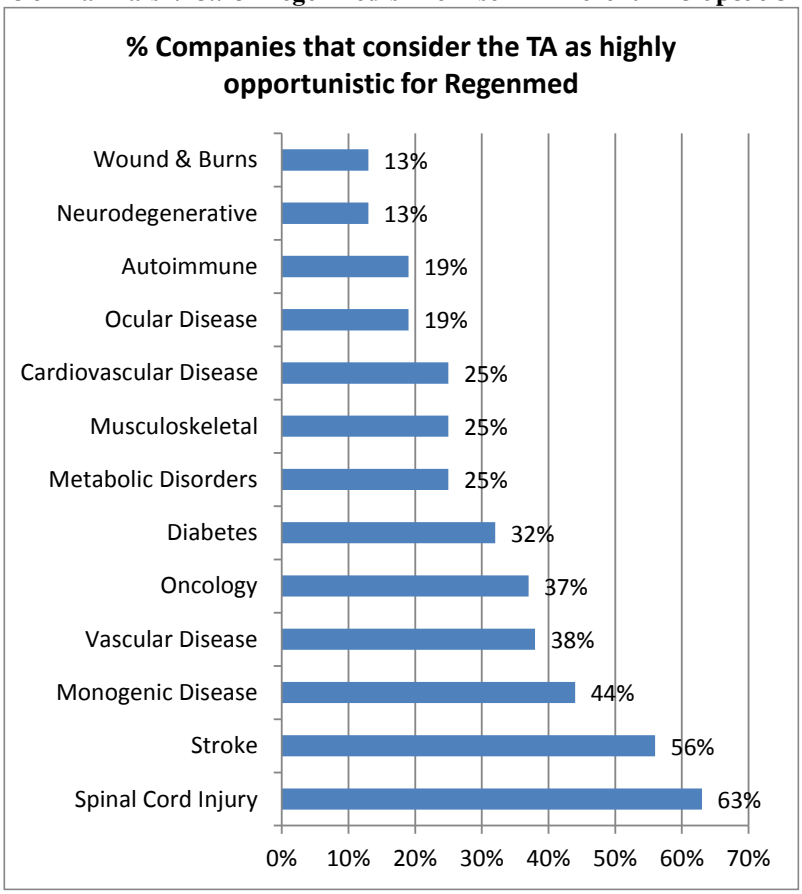
CNS represents one of the highest unmet medical needs. Alliance for Regenerative Medicine did a survey of 16 pharma and large-cap biotech companies to gauge their interest in regenmed (results were published in 2014 ARM annual report). In the survey, CNS conditions such as stroke and spinal cord injury were pointed out as areas where regenerative medicine could make the most impact (see Figure 6). But at the same time, CNS therapeutics is one of the riskiest therapeutic areas in drug development. This really proves true to form as a large number of regenmed CNS trials have failed over the recent years (see Table 5). A number of companies are venturing forward with advanced clinical programs for stroke, traumatic brain injury, AMD, etc. (see Table 10). We believe as drug development in CNS has been so challenging, programs with ambivalent phase II results probably will have a hard time to succeed in phase III. Even programs that have generated quite positive phase II data in CN sometimes fail in phase III trials. However as the unmet medical is so large, if the late-stage trials turn out to be successful, the potential market is huge. In CNS cell therapy, AxoGen is an interesting company as its approach of using tissue engineering to repair damaged peripheral nerve represents a low-risk approach.

AxoGen

AxoGen is focused on repairing peripheral nerve damages. It markets four major products for the $1.5bn extremity nerve repair market (see below). These products provide structural support to provide a good milieu for injured nerves to regenerate on their own. In this sense, these products can be considered low-hanging fruits in CNS therapies.

- Avance® Nerve Graft is a processed human nerve allograft for bridging severed nerves. The human nerve allograft is decellularized and processed resulting in a surgical implant with the natural structural pathways to guide axon regeneration. In a large clinical study called RANGER, Avance® Nerve Graft was shown to lead to overall recovery rate of 84-87%, comparable to autograft outcome but without its associated complications and significantly superior to manufactured conduit.
- AxoGuard® Nerve Connector is a minimally processed, extracellular matrix derived from porcine small intestine submucosa (SIS) designed as a coaptation aid for tensionless repair of transected or severed peripheral nerves.
- AxoGuard® Nerve Protector is a minimally processed, intact extracellular matrix derived from porcine small intestine submucosa (SIS) designed to wrap and protect injured peripheral nerves.
- Avive™ Soft Tissue Membrane is a minimally processed human umbilical cord membrane that can be used as a resorbable soft tissue covering to separate tissue layers.

Figure 6 Pharma's View of Regenmed's Promise in Different Therapeutic Areas



Source: Alliance for Regenerative Medicine 2016 Annual Data Report

Table 10 Regenerative Products Being Developed for CNS Indications

Company Name	Products	Technology / Cell Type	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if Public
SanBio (DSP)	SB623	Bone marrow derived MSCs	Allogeneic	Stroke, traumatic brain injury (TBI)	II	$1,357
AxoGen	Avance® Nerve Graft; AxoGuard nerve protector	(ECM) processed from human peripheral nerve tissue.	Allogeneic	peripheral nerve discontinuities	Market	$907
BioTime	OpRegen, OPC-1	Human embryonic stem cells	Allogeneic	Dry AMD	I/II	$296
Athersys	MultiStem	Multipotent Adult Progenitor Cells (MAPC)	Allogeneic	Stroke	III	$202
BrainStorm Cell Therapeutics	NurOwn	MSCs harvested from bone marrow, expanded and induced into NTF secreting MSCs	Autologous	ALS	III will start in 2017	$74
ReNeuron	ReN001	CTX neural stem cell line	Allogeneic	Stroke	III will start in 2017	$64
InVivo Therapeutics	Neuro-Spinal scaffold	Polymer-based implant device	NA	Spinal cord injury	IDE trial ongoing	$31
Stemedica Cell Technologies	itMSCs	Mesenchymal stem cells processed in a low oxygen (ischemic tolerant) environment	Allogeneic	Ischemic stroke, Alzheimer's disease, TBI	I/IIa	

Source: Compiled by MHBK/IRD based on public company reports

E. Wound Care

Wounds care is an established market for regenerative medicine. There are a number of commercial products available for conditions such as diabetic foot ulcer, venous ulcers, pressure ulcers, surgical wounds, burn, etc. (see Table 11). *Meddevicetracker* forecasts the global tissue-engineered skin replacements/substitutes market totaled about $725.8m in 2015 and is expected to grow at 6.4% CAGR to reach $991.9mn by 2020. US sales accounted for 93.5% of skin-replacement revenues, followed by European sales, accounting for 4.7%, and countries outside of the US and Europe accounting for only 1.8% of sales. Reasons for low adoption outside of the U.S. include cultural aversion to using cadaveric tissue, risk of disease transmission, and limited reimbursement.

According to *Meddevicetracker*, Acelity (now Allergan)'s AlloDerm Regenerative Tissue Matrix is the market leader with a 35.1% share and $254.9m in sales in 2015. Organogenesis ranked second by having 21% share. MiMedx followed as the third by having ~19% share. Integra Lifesciences is another major competitor in wound care. In January 2016, Integra LifeSciences received FDA approval for its Omnigraft dermal regeneration matrix to treat diabetic foot ulcers. Integra has generated solid clinical data to support Omnigraft in the FOUNDER trial. In the study, Omnigraft users achieved a wound closure rate of 61% compared to a 45% closure rate at 12 weeks. Omnigraft requires fewer applications than some other competitors and is gaining share in the market place. We note other new innovations haven't fared as well. Despite promising results in early studies, MacroCure's CureXcell and Healthpoint (Smith & Nephew)'s HP802-247 failed in late-stage trials. Currently Osiris is conducting a phase III trial of its OTI-15-01 program to treat diabetic foot ulcer. Another notable phase III program is Mallinckrodt's StrataGraft. StrataGraft is an allogeneic skin graft used to treat severe burn and has received RMAT designation.

Table 11 Commercial Products for Wound Care

Company Name	Products	Technology (cell/tissue/biologic type)	Autologous / Allogeneic	Indication
Allergan (formerly owned by Acelity)	AlloDerm regenerative tissue matrix	Human accelular dermal matrix	Allogeneic	Burn, general surgical, periodontal, and plastic reconstructive procedures, hernia repair.
Wright Medical	Graftjacket (ortho application of AlloDerm)	Human dermal collagen matrix	Allogeneic	Repair bone, tendon and ligamentous tissue
Organogenesis	Dermagraft	Dermal tissue engineered skin	Allogeneic	Diabetic foot ulcer
Organogenesis	Apligraft	Bilayered tissue-engineered skin	Allogeneic	Venous ulcer, diabetic foot ulcer (DFU)
Osiris Therapeutics	Grafix wound healing matrix; Ovation cellular repair matrix	Three-dimensional matrix that contain MSC, fibroblasts and epithelial cells.	Allogeneic	Wound care, burn, bone repair
MiMedx	EpiFix	Dehydrated, non-viable cellular amniotic membrane	Allogeneic	Wound care such as DFU, venous ulcers and pressure ulcers
Integra	Omnigraft	Matrix made from silicone, cow collagen, and shark cartilage	Bioengineered product	Diabetic foot ulcers, burn,
Integra	AMNIOEXCEL	Dehydrated human amniontic membrance	Allogeneic	Wound care
Integra	PriMatrix	Fetal bovine dermis derived acellular dermal matrix	Xenograft	Wound care
Altrika Ltd.	MySkin, CryoSkin	Matrix with live cells	Autologous	Wound care
Vericel	Epicel	Autologous epidermis	Autologous	Burn
Avita Medical	ReCell® Spray-On Skin	Autologous cell therapy	Autologous	Venous leg Ulcers, burns, scars

Source: Compiled by MHBK/IRD based on public company reports

There have been a number of recent M&A deals in the wound healing market (see Table 12). One type of deal is for big pharma to shed underperforming or non-core wound care assets. Examples include Shire's divestiture of Dermagraft to Organogenesis (while incurring $650mn loss) and Sanofi's divesting former Genzyme cell therapy products to Vericel. Another type of deal is for existing players to consolidate, including Integra's acquisitions of Derma Sciences and TEI LifeSciences, and Organogenesis's acquisition of Dermagraft. Another major deal was Allergan's acquisition of LifeCell to enter into regenerative medicine business. LifeCell's products AlloDerm and Strattice Tissue Matrices are commonly used in breast reconstruction and abdominal wall surgeries respectively. They have synergies with Allergan's focus on aesthetic and plastic surgery.

Table 12 Recent Deals in Wound Care

Acquirer	Target	Date	Amount ($mn)	Sales	EV/Sales
Integra LifeSciences	Derma Sciences	Jan-17	$204	$89	2.3
Allergan	LifeCell (AlloDerm)	Dec-16	$2,900	$450	6.4
Integra LifeSciences	TEI Biosciences	Jun-15	$312	$64	4.9
Vericel	Genzyme cell therapy business	Apr-14	$6.5	$44	0.1
Organogenesis	Dermagraft (Shire)	Jan-14	Up to $300mn milestone		

Source: Compiled by MHBK/IRD based on public reports

F. Orthopedics

A number of stem cell-based products are on the market to treat orthopedic conditions such as spinal fusion, cartilage defects, etc. (see Table 13). But their adoption has been modest so far. To gain wider adoption, sponsors need to conduct robust studies to demonstrate clinical benefits of their products. Currently a number of companies are conducting phase III studies, which should provide such evidence (see Table 13). Prime examples include:

NeoCart from Histogenics

NeoCart is an autologous implant manufactured by seeding a type-I collagen matrix scaffold with autologous chondrocytes and then growing it in a high-pressure bioreactor that mimics the natural environment of cartilage. NeoCart is implanted into patients six weeks following arthroscopic cartilage biopsy. As what is implanted into patients is grown cartilage instead of just chondrocyte cells (as in the case of Carticel from Genzyme), it may have be more efficacious in patients. NeoCart has generated impressive phase II clinical data, which showed superiority to standard of care microfracture on multiple metrics. In a 30-patient phase II study, 76% patients on NeoCart responded to therapy compared to 22% of patients treated with microfracture in one year with p value less than 0.05. This improvement was carried over to 2 years and 3 years. The ongoing NeoCart phase III study will recruit 249 patients (170 on NeoCart arm and 79 on Microfracture arm) and is conducted by special protocol assessment (SPA). Histogenics finished enrollment in 2Q2017 and is targeting top-line data readout and BLA filing in 3Q2018. Vericel's MACI is a similar product to NeoCart and it has reported positive phase III results. Therefore, we believe NeoCart phase III program should be relatively low risk.

TG-C from TissueGene

A notable company working in osteoarthritis is TissueGene. TissueGene is a U.S. biotech company but is majority own by Kolon Life Sciences in South Korea. TG-C is an allogeneic cell therapy of human chondrocytes that have been genetically modified to produce the anti-inflammatory factor TGF-ß1. It is in a U.S. phase III study to treat patients with osteoarthritis. TG-C has generated robust efficacy and clean safety data in U.S. placebo-controlled phase II trial as well as in a phase III trial conducted in South Korea. The product has received approval in South Korea and is branded as Invossa. In November 2016, Mitsubishi Tanabe Pharma licensed the Japanese market right of Invossa from Kolon Life Sciences by paying $24mn upfront as well as $410mn milestone and double-digit royalty. We believe the licensing agreement is a solid endorsement of the clinical profile of TG-C.

MPC-06-ID (NeoFuse MPC) from Mesoblast

Mesoblast is currently conducting a phase III study of its allogeneic MPC (mesenchymal precursor cell) therapy (code-named MPC-06-ID) for chronic low back pain due to disc degeneration. Mesoblast has generated positive phase 2 data prior to the initiation of phase 3 trial.

At both 6 and 12 months, a reduction in pain from baseline of 50% or more, was seen in 59.3% of the MPC-06-ID group, 44.8% of the 18 million MPC group, 18.8% of the saline group, and 15.8% of the HA (Hyaluronic acid) group.

Table 13 Regenerative products for Spine and Orthopedics

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage
Nuvasive	Osteocel (bought from Osiris for ~$90mn in 2008)	Allograft bone matrix retaining MSCs and osteoprogenitors	Allogeneic	Spinal fusion	Commercial
Orthofix	Trinity Evolution	Allograft with stem cells	Allogeneic	Spinal fusion	Commercial
Alphatec Spine	PureGen	Osteoprogenitor Cell Allograft	Allogeneic	Spinal fusion	Commercial
Allosource	AlloStem	Adipose derived MSC product seeded on a demineralize 3D scaffold	Allogeneic	Spinal fusion	Commercial
Terumo (Harvest Technologies)	Smart PReP platform; BMAC	Platelet rich plasma (PRP); Bone marrow aspirate cells	Autologous	Orthopedics, cosmetics,	Commercial
Genzyme / Sanofi	Carticel	Autologous chondrocyte implantation	Autologous	Cartilage repair	Commercial
Vericel	MACI	Expanded chondrocytes on porcine collagen membrane	Autologous	Cartilage repair	Commercial
TiGenix	CondroCelect	Autologous chondrocyte implantation (ACI)	Autologous	Cartilage and osteocondral lesions	Commercial in EU, US PIII
Histogenics	NeoCart	Autologous chondrocytes grown in DBM ex-vivo, implant into knee	Autologous	Cartilage repair	Phase III
TissueGene	TissueGene-C	human chondrocytes engineered to produce the therapeutic growth factor TGF-ß1	Allogeneic	Degenerative arthritis / knee osteoarthritis	Phase III
Mesoblast	MPC-06-ID (NeoFuse MPC)	Adult mesenchymal precursor cells (MPCs)	Allogeneic	chronic low back pain due to disc degeneration	Phase III
Isto Biologics	RevaFlex (DeNovo ET)	Decellularized juvenile cartilage scaffolds are implanted in defect	Allogeneic	knee cartilage repair	Phase III
Tetec AG	NOVOCART 3D	Autologous cells are mixed with novocart (novel 3D collagen matrix) and implanted into patients	Autologous	Cartilage repair	Phase III
Medipost Co. Ltd.	CARTISTEM	Human umbilical cord mesenchymal stem cells are mixed with biopolymer solution	Allogeneic	Cartilage repair	Phase I/II
Cytori	ECCO-50 (Celution device)	Intra-articular injection of Celution processed adipose-derived regenerative cells	Autologous	Osteoarthritis	Phase I in U.S., Available in Japan
StemGenex	SVF injection	Injection of stromal vascular fraction (SVF) fat	Autologous	Cartilage repair	Observational

Source: Compiled by MHBK/IRD based on public company reports; Development pipeline for cartilage defects and osteoarthritis was referenced from "A Road Map to Commercialization of Cartilage Therapy in the United States of America." TISSUE ENGINEERING Volume 22, Number 1, 2016. The list excludes university-sponsored research studies.

G. Diabetes

The Holy Grail of treating diabetes is to restore or replenish functional pancreatic islet cells. If stem cells-derived functional human islet cells can be safely and permanently implanted in to diabetic patients, then a potential cure of diabetes is possible. A couple of companies are working on this approach. The task is quite complex. Human stem cells need to be differentiated into pancreatic beta cells and then encapsulated in an implant device to protect them from host immune system while preserve the flow of proteins. As a result of the high technical hurdle, the progress has been slower than hoped in our view.

ViaCyte

ViaCyte is developing a cell-device combination that functions as replacement pancreas. ViaCyte engineers pancreatic endoderm cells derived from a single human embryonic stem cell line to produce an unlimited supply of beta cell precursors (PEC-01). PEC-01 cells are encapsulated in ViaCyte's Encaptra® drug delivery system to become the end product VC-01. VC-01 can be then implanted into patients subcutaneously. The Encaptra® drug delivery system holds and protects the PEC-01 cells. It is designed to prevent immune rejection by surrounding PEC-01 cells with a semi-permeable, protective membrane. ViaCyte has demonstrated in pre-clinical models that the unique combination of these cells with this device results in rapid and extensive growth of blood vessels around the device, providing a plentiful oxygen source and rapid distribution of insulin to the body. In August 2014, ViaCyte signed an option deal with Janssen Research & Development LLC (Janssen). For $20mn upfront payment, Janssen received the right to evaluate a transaction related to the VC-01™ combination product that ViaCyte is developing for type 1 diabetes. Then in February 2016, ViaCyte and J&J further decided to join forces in developing beta cells in a deal where ViaCyte acquired the assets of Johnson & Johnson's diabetes-focused venture, Janssen BetaLogics.

Semma Therapeutics

Semma Therapeutics was founded based on technology licensed from Harvard Professor Douglas Melton, who discovered a method to differentiate human embryonic stem cells or iPS cells into functional, insulin-producing beta cells in the laboratory. The final step of differentiation from pancreatic progenitors into fully functional insulin-secreting beta cells in vitro has been a biggest hurdle until Professor Melton's lab found the solution. Semma Therapeutics is relying on this technology to develop beta cell implants to treat Type 1 diabetes.

H. Autoimmune Diseases

Autoimmune diseases such as graft versus host disease (GvHD), Rheumatoid Arthritis (RA), inflammatory bowel disease (IBD) could be amenable to cell therapy as cells can have immunomodulatory effects to dampen autoimmune diseases. In September 2015, JCR received full approval of HEMCELL HS Injection (formerly known as Prochymal) for GvHD in Japan. It is the first allogeneic regenerative medicine approved in Japan. HEMCELL HS Injection has a long development history. It was originally developed by Osiris Therapeutics, sold to Mesoblast, which then out-licensed Japanese right to JCR. Along the way, the therapy has accumulated enough clinical data to support its efficacy and safety.

A number of regenerative treatments are being developed for autoimmune conditions (see Table 14). One notable success of using stem cells to treat autoimmune related conditions is Cx601 from TiGenix. Cx601 is allogeneic adipose tissue derived expanded stem cells (eASCs) administered locally to treat perianal fistula in Crohn's disease. We note Cx601 is not used to treat an autoimmune disease, but to treat a complication of autoimmune disease. Cx601 has demonstrated efficacy and safety in a well-controlled phase III study. In the study, patients receiving Cx601 had complete remission rate of 51.5% vs. 35.6% of placebo at 24 weeks with a p value of 0.021. TiGenix has submitted for European approval and a launch in Europe is expected in 1H2018. TiGenix has initiated a U.S. phase III study under special protocol assessment. In July 2016, Takeda licensed rights outside of the U.S. with an upfront payment of €25mn and an equity investment of €10mn.

Another notable program for autoimmune disease is Mesoblast's MPC-300-IV. MPC-300-IV contains 300 million Mesenchymal Precursor Cells (MPCs) which are given intravenously. Mesoblast released phase II results of MPC-300-IV for the treatment of refractory RA in February, 2017. In the study, a single intravenous MPC infusion in biologic refractory RA patients caused no serious adverse events and resulted in dose-related improvements in clinical symptoms, function, and disease activity.

Mesoblast is developing MSC-100-IV in a 60-patient open label Phase 3 trial as a front-line therapy for children with steroid-refractory acute GvHD. Mesoblast expects to fully read out trial results during 2017. In December 2016, Mallinckrodt Pharmaceuticals entered into an option deal with Mesoblast. Mallinckrodt made a $21mn equity investment in Mesoblast in exchange for a 9-month option to license two of Mesoblast's candidates, MPC-06-ID in the treatment or prevention of moderate/severe chronic low back pain (CLBP) due to disc degeneration and MSC-100-IV in the treatment of acute graft versus host disease (GvHD). We haven't heard Mallinckrodt's decision to exercise the option.

There have been setbacks of giving stem cells systemically to treat autoimmune conditions. For example, Athersys' MultiStem (Multipotent adult progenitors) cell therapy failed in a phase II

placebo-controlled study in ulcerative colitis in April 2014. In the study conducted jointly with partner Pfizer, MultiStem was shown to be safe but didn't show significant efficacy. Celgene conducted a phase II study of its PDA-001 (placenta-derived stem cells) in Crohn's disease. The study was concluded in 2014 but we haven't seen the results or any recent update on the program.

Table 14 Regenerative Medicine Being Developed for Autoimmune Diseases

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage
TiGenix (Takeda OUS right)	Cx601	Allogeneic adipose tissue derived expanded stem cells (eASCs).	Allogeneic	Perianal fistula in Crohn's disease	Filed in Europe, III global
TiGenix	Cx611	Allogeneic adipose tissue derived expanded stem cells (eASCs).	Allogeneic	Sepsis	Phase I/II
Mesoblast (JCR markets in Japan)	TEMCELL HS Inj. (Prochymal)	Bone marrow-derived MSCs (originated by Osiris)	Allogeneic	GVHD, Crohn's disease	Market in Japan for GVHD, Phase III
Mesoblast	MPC-100-IV	Mesenchymal Precursor Cells (MPCs)	Allogeneic	GVHD, Crohn's disease	Phase III
Mesoblast	MPC-300-IV	Mesenchymal Precursor Cells (MPCs)	Allogeneic	RA; Diabetic nephropathy/ Type 2 diabetes	Phase II
Celgene	PDA-001 / cenplacel-L	placenta-derived stem cells	Allogeneic	Crohn's disease	Phase II (still active?)

Source: Compiled by MHBK/IRD based on public company reports

I. Adoptive Cellular Therapy for Cancer – A Rising Tide Lifts All Boat

Adoptive T cell therapy or CAR-T (Chimeric Antigen Receptor T cell) therapy passed two milestones in 2017. On August 30, FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL). Interestingly, FDA called the approval a historic action for approving the first "gene therapy" product in the U.S.[12] Novartis priced Kymriah at $475,000, a level lower than some observers expected. As another payer-friendly step, Novartis will enter into pay for performance agreement with CMS for Kymriah, in which Novartis will only get reimbursed when patients achieve response after one month's treatment. Another major milestone was Gilead's acquisition of Kite Pharma for $11.9bn on August 28. Kite Pharma' CAR-T drug, Axi-Cel is waiting for FDA approval for defused large B cell lymphoma (DLBCL). In paying $11.9bn, Gliead clearly has taken a long-term view of the potential of CAR-T therapy. While CAR-T therapy has delivered miraculous efficacy in conditions such as ALL, DLBCL and Multiple Myeloma, whether the ultimate market size justifies the acquisition price remains to be determined.

[12] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm

To reach the current state of nirvana, CAR-T therapy has gone through some valleys along the way. Since the start, the therapy has been burdened with severe side effects such as cytokine release syndrome (CRS) and neurotoxicity such as cerebral edema.

- Perhaps the bleakest moment came in November 2016 when Juno placed its lead program JCAR015 in phase II ROCKET adult ALL trial on clinical hold due to two patient deaths related to cerebral edema. Juno subsequently terminated the program. But fast forward one year, Juno is advancing JCAR017 nicely along for DLBCL and its stock has more than recouped the loss as a result of the JCAR015 setback.

- So far, all CAR-T therapies in late-stage development use engineered autologous T cells. Cellectis is developing off-the-shelf, allogeneic UCART (Universal Chimeric Antigen Receptor T-cells). However in September 2017, FDA placed UCART123 ongoing Phase 1 study on clinical hold. The clinical hold was initiated after Cellectis reported one fatality in the clinical trial where one patient developed grade 5 CRS, together with a grade 4 Capillary Leak Syndrome. FDA lifted the clinical hold in November 2017.

A large number of biotech companies are working on adoptive cellular therapy for cancer (see Table 15). So far for CAR-T therapy, CD19 is the most validated target as it is the target for Kymriah, axi-Cel and JCAR017. BCMA has also become a validated target as demonstrated by bluebird bio and China's Nanjing Legend Biotech. In hematological oncology, other targets such as CD22, CD38, CD123 are also used. There are many innovative next-generation CAR-T technologies in development, including CAR-Ts with on-off switches (e.g., Bellicum), dual or multiple-targeting to improve specificity and reduce antigen loss-led escape (e.g., Autolus, Celyad), and antibody-coupled CAR-T (e.g., Unum).

As CAR-T therapy can only target cell surface antigens, CAR-T therapy cannot work in solid tumors. Tumor cells often don't have unique surface markers for CAR-T to target and they instead present tumor associated intracellular antigens as a part of MHC complex, which is only recognized by TCR (T cell receptors). All the major CAR-T companies also pursue TCR therapy. Companies such as Adaptimmune specializes in developing TCR engineered T cell therapies. In September 2017, GSK exercised its option to license Adaptimmune's NY-ESO-targeting, SPEAR T-cells program. The program has generated promising phase I data in synovial sarcoma.

Table 15 Adoptive Cellular Therapy for Cancer

Company (Partners)	Ticker	Market Cap ($mn)	Program	Target	Indication	Stage
CAR-T cell therapy						
Novartis	SWX:NOVN	$197,246	Kymriah (CTL 019)	CD19;	ALL; CLL, DLBCL, MM; FL, MCL	Approved; Phase II; Phase I
Kite / Gilead	KITE	$11,900mn acquisition price	Axi-Cel; KTE-C19; KITE-585	CD19; CD19; BCMA	DLBCL; ALL, MCL, CLL; Multiple myeloma	Filed for DLBCL; Phase I-III; Phase I
Juno / Celgene	JUNO	$5,413	JCAR-017; JCAR014; JCAR018;	CD19 CD19 CD22 BCMA	NHL; NHL, CLL; ALL, NHL; Multiple myeloma	Pivotal trial; Phase I; Phase I; Phase I
bluebird bio /Celgene	BLUE	$8,474	BB2121	BCMA	Multiple Myeloma	I/II
Cellectis / Pfizer /Servier	ENXTPA:ALCLS	$1,016	UCART19; UCART123	CD19; CD123	ALL; AML, BPDCN	I; I (on clinical hold)
Ziopharm / Intrexon / Merck KGaA	ZIOP	$624		CD 19; CD33	Leukemia/lymphoma; AML	I
Celyad	CYAD	$389	CYAD-01	NKG2D ligands	Hematological malignancy	I
Bellicum	BLCM	$295	BPX-601	PSCA	Pancreatic	I
Mustang Bio	MBIO	$300	MB-101; MB-102	IL13Rα2; CD123	Glioblastoma multiforme; AML	I; I
Autolus			AUTO3; AUTO2	CD19/CD22; BCMA/TACI	ALL/DLBCL; Multiple Myeloma	I
Unum Therapeutics			ACTR087	Rituximab	R/R NHL	I
Poseida Therapeutics				BCMA; PSMA	Multiple Myeloma; Prostate cancer	Preclinical
Engineered TCR T cell therapy						
Kite / Gilead	KITE	$11,900	Multiple	MAGE A3/A6, HPV16 E6 & E7, etc.	Solid tumors	I
Juno	JUNO	$5,413	Multiple	WT-1, MUC16, ROR1, Lewis Y	Solid tumors	I
Adaptimmune / GSK	ADAP	$698	NY-ESO T cell	NY-ESO; MAGE A4, A10, AFP	Synovial sarcoma, Other; Solid tumors	I/II
Bellicum	BLCM	$295	BPX-701	PRAME	AML/MDS	I
MediGene	XTRA:MDG1	$326	MDG1011; TCR-IIT	PRAME; MAGE-A1	AML/MDS/MM; Multiple myeloma	CTA submitted
Immatics / MD Anderson			ACTolog, ACTengine, ACTallo	Various	Various	Preclinical
Takara Bio			MAGE-A4	MAGE-A4		I
Cell Medica / Cell and Gene Therapy Catapult				WT1		I
TCR^2 Therapeutics			TRuC			Preclinical
Non genetically modified T cells						
Iovance Biotherapeutics (formerly Lion Biotechnologies)	IOVA	$632	LN-144, LN-145	Patients TILs	Metastatic melanoma, Cervical, Head and Neck cancer	II, II
Atara Biotherapeutics	ATRA	$450	ATA129	Allogeneic CTL targeting EBV	Post HSC transplant lymphoproliferative disorder	II
NK Cell Therapy						
NantKwest	NK	$401	aNK		Hematological malignancy	I
Fate Therapeutics	FATE	$194	FATE-NK100		AML, solid tumors	I

Source: Compiled by MHBK/IRD based on public company reports

J. iPSC – Stem Cell Therapy of the Future

Nearly all of the clinical programs described in the sessions above are based on adult stem cells, embryonic stem cells or adult immune cells. To our knowledge, there is no active iPSC cell therapy trial in the U.S. yet. The versatility of iPSC cells is very appealing. iPSCs can be differentiate into many cell types of the body and the resulting cells can be used to treat various diseases. In addition, iPSC cells could significantly expand the use of autologous cell therapy. Therefore we believe in the long term, iPSC will become the predominant cell therapy format

In a landmark deal, Bayer and Versant Ventures joined forces to launch stem cell therapy company BlueRock Therapeutics with $225mn series A financing in December 2016.[13] BlueRock has licensed extensive iPSC IP from academic and industry partners in the U.S., Japan and Canada. The basic iPSC intellectual property (IP) was invented by Nobel Prize winner Dr. Shinya Yamanaka of Kyoto University and licensed from iPS Academia Japan Inc., which manages iPSC IP. Initial focus will be on cardiovascular, neurological and other conditions. For CV, an initial program will be regenerating heart muscle in patients who have had a heart attack (myocardial infarction, MI) or are suffering from chronic heart failure. In CNS, an initial program is to use regenerated dopaminergic neurons to treat Parkinson's disease.

Besides BlueRock, many other companies are working on iPSC therapies. For example, Fate Therapeutics is using iPSC to derive CD34+ hematopoietic stem cells, which can be then differentiated to immune cells for treating patients.

Besides therapeutic use, iPSC derived cells can be used in drug screening. For example, Evotec and Celgene announced a major collaboration where Celgene will use Evotec's iPSC platform to screen drugs for neurodegenerative diseases such as Amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.

[13] http://www.press.bayer.com/baynews/baynews.nsf/id/Bayer-Versant-Ventures-Join-Forces-Launch-Stem-Cell-Therapy-Company-BlueRock-Therapeutics-USD

III.Gene Therapy

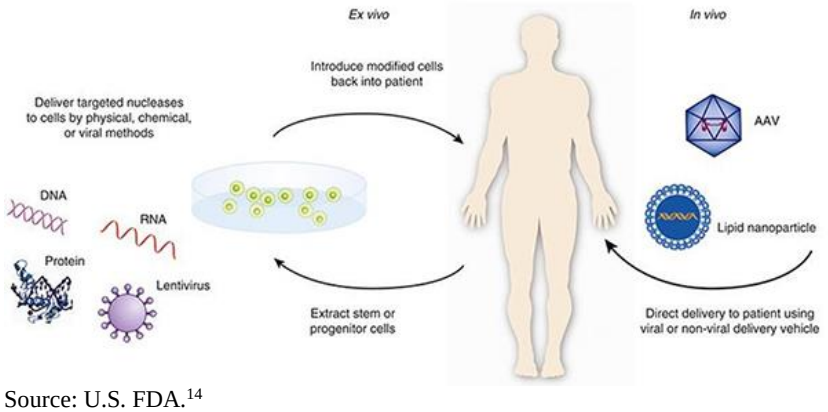
A. Background of Gene Therapy

According to the U.S. FDA, human gene therapy is the administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use. There are around 30,000 genes in human body. Sometimes monogenetic defect directly causes a specific disease. In such cases, reintroducing a foreign copy of the correct gene inside the corresponding cells or editing the resident gene in the genome can treat the underlying disease. A gene therapy can also inactivate a disease causing gene or introduce a new or modified gene to treat disease. As gene therapy or gene editing addresses the fundamental genetic cause of a disease, it has curative potential.

There are two ways of introducing foreign DNA into the body (see Figure 7). One is the in vivo approach whereby DNA encapsulated in viral particle or nanoparticle is given either systemically or specifically into the targeted tissue. The vector carried gene will find its way to the target cells, merge into the cells, getting into nucleus, transcribed into messenger RNA, and then translated into protein to carry out function. The second approach is ex vivo whereby cells are isolated from patients, transduced with DNA/RNA in vitro, and then infused back to the patients. Prime examples of ex vivo gene therapy are CAR-T (chimeric antigen receptor (CAR) T cells) therapy and modified hematopoietic stem cell therapy.

For in vivo gene therapy, the difficulty of delivery of gene can be both a curse and a blessing. While more cumbersome than systemic delivery, injecting DNAs into specific target tissues such as the brain or eye can ensure high tissue-specific expression and avoid toxicity from systemic exposure. Ex vivo gene therapy is also a more complicated form of delivering, but it ensures high transduction rate and also avoids systemic exposure. Retroviral vectors were used in delivering gene therapy in the past. But as they integrate into genome, they can cause cancer. Adeno associated virus (AAV) is a non-pathogenic and non-integrating virus. AAV vectors are emerging as the vector of choice for in vivo gene therapy.

Figure 7 Illustration of Two Types of Gene Therapy



Source: U.S. FDA.[14]

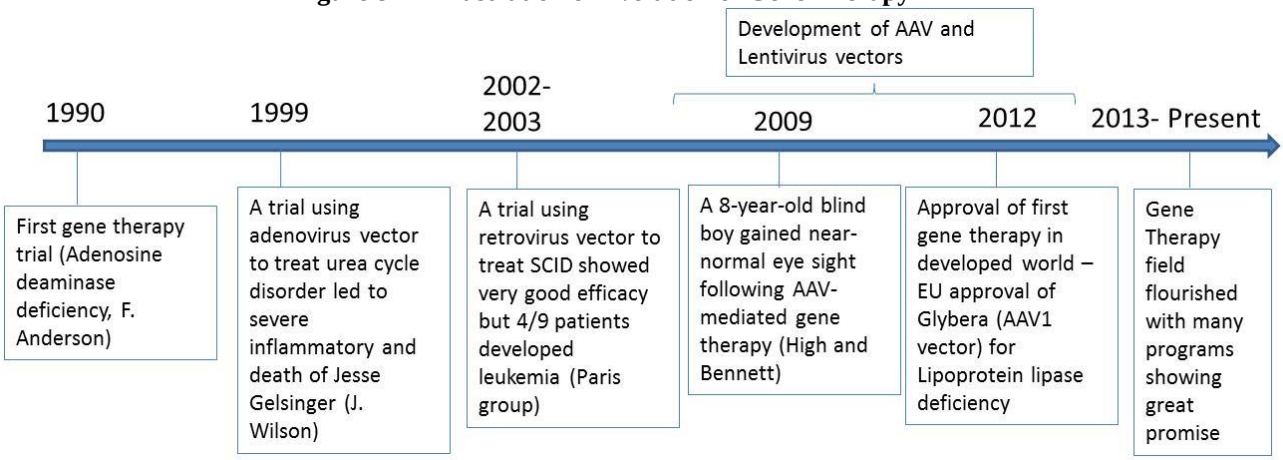
B. Recent Progresses of Gene Therapy

Gene therapy has come a long way over the last two decades (see Figure 8). Gene therapy first captured public's excitement and imagination in 1990 when a child suffering from severe combined immunodeficiency was reportedly successfully treated. However gene therapy field ground to a halt in 1999 after a patient named Jesse Gelsinger died while undergoing gene therapy. In 2003, FDA halted gene therapy trials using retroviral vector as it was found to cause leukemia due to insertions of the retroviral vector. Despite the "nuclear winter" of gene therapy from 1999 to the late 2000s, scientists, especially researchers at University of Pennsylvania and The Children's Hospital of Philadelphia (CHOP), persevered in researching new gene therapy vectors and delivery technology. In 2009, Corey Haas, an American child with a rare eye diseases caused by missing a retinal pigment protein was treated by gene therapy at The Children's Hospital of Philadelphia and gained normal vision. This therapy was later developed by Spark Therapeutics as Luxturna, which is currently awaiting FDA approval with PDUFA date on January 12, 2018.

In 2012, EU approved uniQure's Glybera as the first gene therapy product approved in the developed world. While the €1mn treatment Glybera was ultimately withdrawn from the market due to a lack of commercial adoption, the Glybera approval was a harbinger of a boom for gene therapy. Since then, a number of companies have demonstrated exciting clinical data of gene therapy in a diverse array of diseases including retinal disease, hemophilia, beta hemoglobinopathies (beta-thalassemia and sickle cell disease), CNS disease (spinal muscular atrophy and Parkinson's disease), and orphan diseases. In this section, we look at the current state of gene therapy and its promising future.

[14] https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm

Figure 8 An Illustration of Evolution of Gene Therapy



Source: Compiled by MHBK/IRD based on public reports

C. Technology Advances That Underpin the Gene Therapy Boom

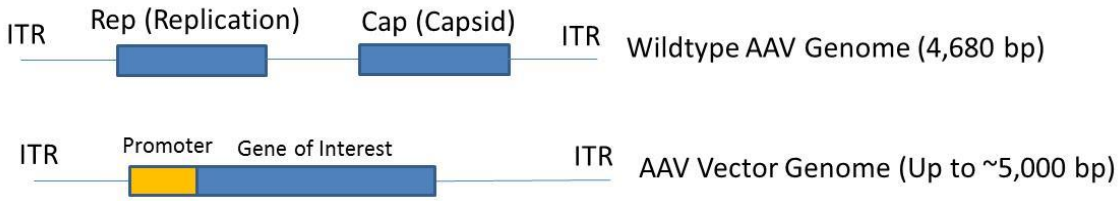
Replacing the defective gene in diseased tissue to treat the underlying disease is a simple and compelling concept. However implementing gene therapy has not been straight forward as drug developers faced a number of hurdles. Issues of the gene therapy programs included host immunogenicity to viral vector, delivery to targeted tissue, transfection efficiency, level and persistence of gene expression once the DNA is inside the cell, and potential tumorigenic effect of integrating vectors. Over the last decade, researchers such as Dr. James Wilson at the University of Pennsylvania have made important breakthroughs in discovering viral vectors for gene therapy. The new portfolio of viral vectors can ameliorate many problems gene therapy programs have encountered in the past. The main workhorse of today's gene therapy is Adeno-Associated Virus (AAV). Dr. Wilson discovered many novel AAVs that have desirable properties, including AAV7, AAV8, AAV9, AAVrh10 and over 100 other novel AAV vectors (this is in comparison to AAV1-6, which are generally considered old AAV vectors). The biotech company Regenxbio licensed this portfolio of novel AAV vectors from Dr. Wilson and named them NAV (Novel Adeno-Associated Virus) Vectors.

Compared to adenovirus vectors, AAVs have much lower immunogenicity and are not pathogenic in human, therefore are very safe. As shown in Figure 9, recombinant AAV basically gutted viral proteins and replaced them with transgene under a promoter. Such an AAV vector construct cannot replicate on its own and also cannot integrate into genome. Therefore unlike retroviral vector there is little risk of oncogenic potential.

The new AAV vectors have higher and longer-term expression compared to AAV1 and AAV2. NAV also offers higher transfection efficiency and potential better tissue accessibility and selectivity. For example, AAV9 can cross blood-brain barrier to reach CNS. AAV8 is effective in delivering genes to retina and liver. Both AAV8 and AAV9 are good at targeting skeletal

muscles. In addition, Regenxbio claims NAV is easier and thus cheaper to manufacture. Besides AAV capsids, other advances have made, such as promoters that drive higher gene expression tissue specificity. All of these advances have enabled the development of gene therapies currently in the clinical development. There are over 180 AAV-vector based gene therapy trials ongoing[15].

Figure 9 Illustration of AAV Vector



Source: MHBK/IRD

The discovery of CRISPR-Cas9 system has ushered in a new era in gene editing. In contrast to traditional gene therapy where a piece of foreign DNA is introduced to diseased cells to replace the defective gene, gene editing uses DNA homing/recognition mechanism and endonucleases to edit the defective gene in the genome. Therefore, gene editing is supposed to correct the genetic defects while leaving nothing behind. Gene editing can be used to knock out genes, insert genes or replace genes. Along the line, its efficacy declines as the tasks get more complicated. There are three main technologies for gene editing (see Table 16). Zinc finger perhaps has the longest history, followed by TALEN. CRISPR/Ca9 is the newest technology and due to its ease of use has attracted widest adoption. Companies involved in gene editing have grown in leaps and bounds. Since May 2016, three CRISPR/Ca9 companies – Intellia Therapeutics, Editas Medicine, and CRISPR Therapeutics - have gone public, each with market cap around $800mn. European company Cellectis also listed its shares in the U.S. in March 2015. However we note the enthusiasm of gene editing is not unchecked. For example, in a paper published in *Nature Methods* this May, researchers at Stanford University found CRISPR/Cas9 could cause wide-spread unintended mutations in mouse genome. CRISPR-Cas9 players have raised significant doubt over the conclusion of the study. But nonetheless the potential off-target effect of CRISPR-Cas9 will need to be watched for.

[15] http://www.wiley.com//legacy/wileychi/genmed/clinical/

Table 16 Comparison of Three Main Types of Gene Editing Technology

Gene Editing Tool	Zinc finger nuclease	TALEN	CRISPR/ca9
DNA guide	ZF transcription factor	Transcription activator-like (TAL) protein	20 nucleotide guide RNA sequence
Endonuclease	Fok1	Fok1 or other	cas9
Advantages	Binding is very specific	Binding is very specific	May not be very specific
Disavantages	Time consuming to engineer the ZF protein	Time consuming to engineer the TAL protein	Quick and easy to design the guide
IP	Dominated by Sangamo		Complicated, litigations among the top-three players
Companies	Sangamo	Cellectis	CRISPR Therapeutics
		bluebird bio	Editas Medicine
			Intellia Therapeutics
			Caribou Biosciences
			Horizon Discovery

Source: Compiled by MHBK/IRD based on public reports

D. Key Players in Gene Therapy and Their Clinical Experience

Table 17 lists publicly traded gene therapy companies. Many companies on the list have delivered exciting clinical data in a variety of diseases. In the following pages we review key players in specific therapeutic areas and the clinical data that underpins the current excitement over gene therapy.

Table 17 Publicly Traded Gene Therapy Companies

12/14/2017	Market Cap	EV	Price	Sales					EV/Sales
Company name	($mn)	$mn		2016	2017E	2018E	2019E	2020E	2020E
BioMarin Pharmaceutical Inc.	$15,571	$15,480	$88.72	$1,117	$1,306	$1,488	$1,727	$2,042	7.6
bluebird bio, Inc.	$8,474	$7,900	$183.80	$6	$39	$27	$71	$299	26.4
Juno Therapeutics, Inc.	$5,413	$4,495	$44.51	$79	$100	$79	$226	$639	7.0
AveXis, Inc.	$3,145	$2,770	$98.42	$0	$0	$20	$184	$376	7.4
Spark Therapeutics, Inc.	$1,699	$1,222	$45.74	$20	$9	$95	$269	$432	2.8
Sangamo Therapeutics, Inc.	$1,395	$1,158	$16.55	$19	$36	$56	$57	$72	16.0
Editas Medicine, Inc.	$1,068	$806	$24.45	$6	$15	$17	$26	$25	32.0
Cellectis S.A.	$1,016	$730	€ 28.27	$54	$37	$39	$38	$28	25.7
Regenxbio Inc.	$877	$710	$28.15	$5	$9	$9	$10	$30	23.7
Audentes Therapeutics, Inc.	$847	$691	$28.73	$0	$0	$0	$0	$238	2.9
CRISPR Therapeutics AG	$751	$497	$18.74	$5	$11	$24	$0	$109	4.5
Intellia Therapeutics Inc.	$750	$527	$17.73	$16	$27	$38	$39	$49	10.8
Abeona Therapeutics Inc.	$748	$692	$16.10	$1	$1	$1	$20	$237	2.9
Adaptimmune Therapeutics plc	$698	$466	$7.26	$14	$42	$52	$16	$42	11.0
uniQure N.V.	$534	$466	$17.40	$25	$12	$14	$13	$9	54.0
Voyager Therapeutics, Inc.	$460	$334	$14.16	$14	$9	$11	$16	$23	14.6
Nightstar Therapeutics Plc	$389	$319	$13.46						
Bellicum Pharmaceuticals, Inc.	$295	$213	$8.49	$0	$0	$1	$25	$139	1.5
Tocagen Inc.	$218	$131	$11.80	$0	$0	$0	$55	$78	1.7
GenSight Biologics S.A.	$144	$72	€ 6.17	$3	$5	$2	$32		
Adverum Biotechnologies, Inc.	$140	-$47	$3.13	$1	$2	$1	$1	$1	
Lysogene S.A.	$87	$63	€ 4.85	$2	$2	$2	$2	$3	
AGTC	$65	-$61	$3.58	$47	$44	$31	$28	$49	

Source: Compiled by MHBK/IRD based on public reports

1. CNS

There is a huge unmet medical need for neurodegenerative diseases. Traditional small molecule or antibody drugs haven't proven to be effective due to access issues or failure to address the underlying etiology. Using gene replacement or gene knock-down technology directly delivered to the brain seems to be the best solution for such intractable diseases. Although the delivery can be invasive (involves injection into the brain or into the spinal columns of patients), gene therapy can directly address the underlying cause of neurodegenerative disease. There are a number of gene therapy programs in the clinic (see Table 18). Clear proof-of-concept data have been shown by pioneers in the field.

AxeXis

AveXis reported perhaps the most exciting clinical data in gene therapy. In the devastating disease of spinal muscular dystrophy (SMA), AveXis showed a single IV administration of AVXS-101 (SMN1 gene on AAV9 vector) could lead to significant improvements in clinical outcome. In the study, 15 patients were treated at two dose levels (3 at low dose and 12 at high dose). All 12 infants treated at high dose remain alive and event free. 15 out of the 15 kids reached 13.6 months event-free. 9 out of 9 treated patients reached 20 months event free, compared with 8% of untreated children who typically would be alive by this point without major breathing support. In addition to favorable clinical outcome, infants on therapy were also able to achieve significant developmental milestones such as head control (11/12 patients), rolling (9/12 patients), sitting with assistance (11/12 patients). Such milestones improvements were considered unprecedented in this patient population. Given the striking results compared to natural history data, FDA has given AveXis breakthrough designation for this therapy. FDA will allow AveXis to conduct a single-arm, pivotal study in spinal muscular atrophy Type 1 that uses natural history of the disease as a comparator, and only enrolls 15-20 patients. While AVXS-101 is given intravenously for SMA type 1 patients, AVXS-101 will be given via intrathecal delivery in the less severe SMA Type 2 patients. A trial in SMA Type 2 is expected to start in late 2017.

Voyager Therapeutics

In September 2017, Voyager Therapeutics reported phase Ib results of VY-AADC01 for Advanced Parkinson's Disease (PD), which clearly demonstrated the proof of concept. VY-AADC01 supplies the key enzyme responsible for breaking down L-dopa into dopamine to postsynaptic neurons and thus restores advanced PD patients' response to L-dopa treatment. It is directly injected into the affected brain region under the guidance of intra-operative MRI. The trial tested three dose levels of gene therapy AADC01 with five patients in each cohort. The lowest dose cohort conveniently served as a control for the two higher dose cohorts. In the study, VY-AADC01 showed dose-dependent coverage of the targeted brain region (Putamen), AADC activity, decrease in PD medicine, and improvement in PD symptoms. On the safety side, infusions of VY-AADC01 have been well-tolerated with no vector-related serious adverse events (SAEs).

Abeona Therapeutics

Abeona Therapeutics is using AAV9 vector-based gene therapy to treat MPS IIIA/B (Sanfilippo A/B) diseases. Sanfilippo patients miss key lysosomal enzymes to break down complex sugars called glycosaminoglycans (GAGs). As a result, the substrate GAG (heparan sulfate) accumulates in a patient's lysosomes and cause neurological toxicity. ABO-102 delivers the missing SGSH gene to treat Sanfilippo A while ABO-101 delivers the missing NAGLU gene to treat Sanfilippo B. Abeona has reported promising proof-of-concept data for ABO-102, which showed dose and time-dependent reductions in CSF heparan sulfate levels, reduction of heparan sulfate level in urine, decreases in liver volume and preliminary signs of neurocognitive benefit.

While biomarker data is quite promising, long-term neurocognitive improvement is likely to be the important for FDA approval.

Lysogene

Founded in 2009, Lysogene is also developing a gene therapy for Mucopolysaccharidosis type IIIA (MPS IIIA), or Sanfilippo syndrome Type A. Lysogene's LYS-SAF302 gene therapy uses AAVrh10 vector to deliver the SGSH gene to the brain via intracerebral injection. Lysogene plans to initiate pivotal trial in January 2018.

Tocagen

Tocagen is a unique company developing gene therapy for cancer. Its lead program Tocagen uses its proprietary retroviral replicating vector to deliver cytosine deaminase to tumor cells. Patients are then given oral Toca FC, which is an inert pro drug that is converted to chemo drug 5-FU by cytosine deaminase. 5-FU has a short half -life and kills tumor cells in the rumor microenvironment. Tocagen has generated promising phase 2 data of this therapy for recurrent high-grade glioma and is conducting a phase 3 study in this indication. Tocagen's retroviral replicating vector gene therapy platform preferentially delivers genes to fast-dividing cancer cells. It can be utilized to deliver to cancer cells a variety of anti-cancer factors such as antibody fragments, immune agonists, siRNA, and cytokines.

Table 18 Notable Gene Therapy Programs for CNS Diseases

Company	Market Cap	Product	Vector	Gene / Delivery	Indication	Stage	Milestone
AveXis	$2,908	AVXS-101	AAV9	SMN1 (IV)	SMA Type 1	Phase 1/2	Initiate pivotal trial in 2017
Voyager Therapeutics	$482	VY-AADC01	AAV2	Amino acid decarboxylase (AADC), (MRI guided injection into brain)	Parkinson's disease	Phase 1	Initiate pivotal trial in YE17
		VY-SOD101		RNAi targeting SOD1 mRNA (intrathecal injection)	ALS	Preclinical	
		VY-HTT01		RNAi targeting mutant HTT mRNA (MRI guided injection into brain)	Huntington's disease	Preclinical	
		VY-FXN01		FXN gene (intrathecal or intravenous injection)	Friedrich's Ataxia	Preclinical	
Abeona Therapeutics	$610	ABO-102	AAV9	SGSH (IV infusion)	MPS IIIA /Sanfilippo syndrome type A	Phase 1/2	
		ABO-101	AAV9	NAGLU (IV infusion)	MPS IIIB /Sanfilippo syndrome type B	Phase 1/2	
Lysogene	$110	LYS-SAF302	AAVrh10	SGSH (N-sulfoglycosamine sulphohydrolase), (Direct injection in brain)	MPS IIIA /Sanfilippo syndrome type A	Phase 1/2	Pivotal trial starts in 1Q18
		LYS-GM101	AAVrh10	Beta galactosidase I	GM1 gangliosidosis	Preclinical	
uniQure	$225	AMT-130	AAV5	miHTT (DNA encoding anti-sense to Huntingtin mRNA)	Huntington's disease	Preclinical	Start P1 in 2018
Regenxbio	$995	RGX–111	AAV9	IDUA	MPS I	Phase 1	
		RGX–121	AAV9	IDS	MPS II	Preclinical	
Agilis		AGL-AADC		AADC (injection into brain)	AADC deficiency	Phase 2	
		AGL-FA		FXN gene (injection into brain)	Friedrich's Ataxia	Preclinical	
Tocagen	$212	Toca 511 & Toca FC	Retroviral replicating vector (RRV)	Cytosine deaminase (CD)	Recurrent high-grade glioma	Phase 3	

Source: Compiled by MHBK/IRD based on public reports

2. Hemophilia and Hemoglobinopathy

Gene therapy is expected to be the disruptive technology in treating hemophilia. If the data holds up in later-stage trials, a potential cure of some hemophilia patients appears to be within reach.

Hemophilia B

There are two main competitors in developing Factor IX gene therapy for hemophilia B. Spark Therapeutics in partnership with Pfizer is developing the Padua variant of Factor IX gene for Hemophilia B. The Padua variant is a rare mutation of Factor IX gene found in a family in Italy. This variant has 8-9x the normal activities of Factor IX. Spark Therapeutics has treated ten patients treated at the 5x 10^{11} vg/kg dose. Every patient in the group achieved 16-79% normal Factor IX activity. Importantly these ten patients had no bleed in the year after gene therapy and nine of the ten patients had not taken Factor IX concentrates to prevent or control bleeding event. Such a clinical result represents almost a cure of Hemophilia B. Pfizer has taken over the development of the program and will initiate a pivotal study. uniQure is developing a AAV5 vector based gene therapy of wild-type Factor IX in its AMT-060 program. In the five patients treated at high dose (2x 10^{13} vg/kg), average Factor IX activity was 5.1%. These patients also showed a reduction in bleed. uniQure is switching from AMT-060 to AMT-061, the latter of which is a Padua variant of Factor IX gene therapy. AMT-061 and AMT-060 are identical in structure apart from two nucleotide substitutions in the coding sequence for FIX. An analysis of nonhuman primate data shows AMT-061 at 2x 10^{13} vg/kg dose may lead to mean FIX activity of approximately 30 to 50 percent of normal. FDA has allowed uniQure to initiate a pivotal trial of AMT-061 in 2018. In announcing this essential substitution of AMT-060 with AMT-060, uniQure closed the gap with Spark Therapeutics and saw its share jump over 50%. Besides Spark Therapeutics and uniQure, Sangamo is developing a gene editing approach to insert Factor IX gene in the albumin locus of genome.

Hemophilia A

The hemophilia A market is more crowded than hemophilia B as there are five programs in the clinic. BioMarin's BMN 270 is by far the furthest along. In July, BioMarin presented exciting data at the ISTH (International Society on Thrombosis and Haemostasis) meeting. In the 7 patients treated at the 6x10^{13} vg/kg dose , AAV5-FVIII produced sustained mean and median FVIII levels of 104% and 89% respectively over 1 year of observation. 75-80% of the 7 patients achieved factor level in the 50% and 150% range, which is considered normal factor levels. Impressively, annualized bleed and factor VIII use rates for 4E13 and 6E13 vg/kg were zero. With such exciting data, BioMarin plans to initiate two phase 3 studies by the end of 2017. Each study will test each active dose of BMN 270 in 40 patients for one year with four years of follow-up. Spark Therapeutics, Sangamo (in partnership with Pfizer), Shire and Dimension Therapeutics also have FVIII gene therapy in the clinic, but their programs are in earlier stage compared to BioMarin. Spark Therapeutics is expected to report phase 1/2 data in 2017.

Hemoglobinopathy

As demonstrated by bluebird bio, ex vivo gene therapy is a promising approach to treat beta thalassemia and sickle cell disease. Bluebird bio's LentiGlobin BB305 therapy uses lentiviral vectors to transduce a variant of β hemoglobin gene ex vivo to hematopoietic stem cells. LentiGlobin has shown promising data in β thalassemia. Presented at ASH (American Society of Hematology) conference in 2016, a study found 8 out of 8 treated with the non- $\beta^0\beta^0$ (less severe) patients were transfusion-free at 12 months. For 5 patients with the $\beta^0\beta^0$ genotype, there is a ~65% median reduction in transfusion volume and frequency.

Table 19 Notable Gene Therapy Programs for Hemophilia and Hemoglobinopathy

Company	Market Cap	Product	Vector	Gene / Delivery	Indication	Stage	Milestone
uniQure / Chiesi	$534	AMT-061	AAV5	Factor IX (Padua gene variant)	Hemophilia B	Phase 1/2	Initiate pivotal trial in 2018
Spark Therapeutics	$1,699	SPK-9001 (Pfizer)	AAV-SPK100	Factor IX (Padua gene variant)	Hemophilia B	Phase 1/2	
Sangamo	$1,395	SB-FIX	AAV6	Use ZFN to insert Factor IX gene in albumin locus (gene editing)	Hemophilia B	Phase 1/2	
St. Jude	NA		AAV8	Factor IX	Hemophilia B	Phase 1/2	
BioMarin	$15,571	BMN 270	AAV5	Factor VIII	Hemophilia A	Phase 1/2	Initiate 2 P3 trials in YE17
Spark Therapeutics	$1,699	SPK-8011	AAV2	Factor VIII	Hemophilia A	Phase 1/2	
Sangamo	$1,395	SB-525 (Pfizer)	AAV6	Factor VIII	Hemophilia A	Phase 1/2	
Shire	$44,361	SHP654	AAV8	Factor VIII	Hemophilia A	Phase 1/2	
Dimension Therapeutics	$1	DTX201 (Bayer)	AAVrh-10	Factor VIII	Hemophilia A	Preclinical	
BLUE	bluebird bio	$8,474	LentiGlobin	Beta globin gene or a hybrid A-gamma/beta globin (ex vivo gene editing)	Beta thalassemia; Sickle cell	Phase 3; Phase 1/2	P3 started in '17
Sangamo	$1,395	ST-400		ex vivo gene editing	Beta-thalassemia	Preclinical	
		BIVV-003		ex vivo gene editing	Sickle Cell Disease	Preclinical	

Source: Compiled by MHBK/IRD based on public reports

3. Eye Diseases

The compartmental nature of the eye makes it quite suitable to gene therapy as gene therapy can be given by local injection and will induce minimal immune reaction. A number of companies are developing gene therapy for eye disease and one product is approaching the market (see Table 20).

Spark Therapeutics

Spark Therapeutics is the flagship company in the group. Spark Therapeutics was founded based on pioneering work done at Children's Hospital of Philadelphia. It was able to successfully bring RPE65 gene therapy Luxturna through phase III study and file a BLA. Luxturna replaces the defective RPE 65 gene in the photoreceptors of the eye. RPE65 deficiency is often found in children with certain inherited retinal dystrophy diseases such as Leber Congenital Amaurosis (LCA) and retinitis pigmentosa (RP). As patients with RPE65 especially suffer poor vision under

lowly light levels, Spark Therapeutics designed a maze to measure patients' ability to navigate under various lighting conditions. The phase 3 trial clearly hit the primary endpoint. At 1 year, 93% of patients achieved a gain in functional vision and 72% achieved the maximum improvement. As a secondary endpoint, visual acuity was improved but not at a significant level (p=0.17). Spark Therapeutics' second ophthalmology program is SPK-7001 for patients with choroideremia. Choroideremia is a slowly progressive inherited retinal disease caused by inherited mutation in the CHM gene that encodes the Rab escort protein-1 (REP1). In May 2017, Spark Therapeutics reported some preliminary data for this program. While the program was found to be safe, it is unclear if it was demonstrated to be efficacious – "as of the March 29, 2017 data cutoff, interim efficacy analysis of the first 10 participants in the Phase 1/2 clinical trial did not show consistent and conclusive evidence of effect at the duration of follow-up in later-stage participants." But Spark Therapeutics did mention some signs for efficacy – "non-significant differences between the injected and control eye were observed on one or more endpoints in four of the 10 participants in favor of the injected eye."

Nightstar Therapeutics

Founded based on technology licensed from Oxford University, UK-based Nightstar Therapeutics is also developing REP1 gene therapy for choroideremia. According to its F1 filing, as of June 30, 2017, a total of 50 patients have been treated with NSR-REP1, consisting of 32 patients across four clinical trials that have completed at least one-year follow-up. Only 6% (6/31) treated patients experienced a loss of visual acuity of more than 5 letters after one year's follow-up vs. 13% of historical control. There were five hyper-responders (defined as a gain in visual acuity of greater than 15 ETDRS letters). Based on the data, Nightstar Therapeutics plans to initiate a phase 3 STAR study in 1H2018. The study will enroll 140 patients with a diagnosis of CHM due to REP1 mutations as confirmed by genetic testing. The primary endpoint of the STAR trial is to measure the proportion of patients with an improvement of at least 15 ETDRS letters from baseline in visual acuity at 12 months post-treatment. Study results are expected in 2020.

Regenxbio

Regenxbio originally licensed a portfolio of novel AAV vectors (AAV7, AAV8, AAV9, AAVrh.10 and others) from Dr. James Wilson lab at The University of Pennsylvania. It then sub-licensed the novel AAV vectors to many major gene therapy players. It stands to earn up to 10% royalties from the licensing of its NAV technology. Rengenxbio is also developing its own proprietary pipeline. A lead program is anti-VEGF Fab gene therapy to treat wet AMD. The program is only in phase 1 so there is scant data. The market for wet AMD is large and well defined. Adverum (formerly Avalanche Biotech)'s gene therapy for wet AMD gene therapy program has struggled to demonstrate consistent efficacy. However, Regenxbio's AAV8 vector has much higher expression than Avalanche Biotech's AAV2 vector, which should help on efficacy.

GenSight Biologics

The French company GenSight Biologics is developing gene therapy for a rare, rapidly progressing blindness disease called Leber's hereditary optic neuropathy (LHON). In a phase 1/2 trial in LHON, ND4 gene therapy GS010 showed a net gain of +15 letters in treated eye vs. untreated eye. GenSight is running with phase 3 studies for GS010 with recruitment completed and data readout expected in 1H2018. If the trial is successful, GenSight will be able to deliver the second gene therapy after Spark Therapeutics for rare eye diseases.

AGTC

AGTC in partnership with Biogen is developing gene therapy for X-linked retinoschisis (XLRS) and X-linked retinitis pigmentosa (XLRP). In addition, it is also developing gene therapy for Achromatopsia and a few other ophthalmology indications.

Table 20 Notable Gene Therapy Programs for Eye Diseases

Company	Enterprise Value ($mn)	Product	Vector	Gene	Indication	Stage	Milestone
Spark Therapeutics	$1,222	Luxturna / voretigene neparvovec	AAV2	RPE65 (subretinal injection)	RPE65 mediated Inherited retinal dystrophies (IRD)	BLA	PDUFA date January 12, 2018
		SPK-CHM	AAV2	CHM	Choroideremia	Phase 1/2	
Nightstar Therapeutics	$319	AAV2-REP1	AAV2	REP-1	Choroideremia	Phase 1/2	Phase 3 starts in 1H2018
		NSR-RPGR	AAV	retinitis pigmentosa GTPase regulator (RPGR)	X-Linked Retinitis Pigmentosa	Phase 1	
Regenxbio	$710	RGX–314	AAV8	Anti-VEGF Fab (subretinal injection)	wet AMD	Phase 1	
GenSight Biologics	$72	GS010	AAV2	ND4	Leber Hereditary Optic Neuropathy	Phase 3	Phase 3 data in 1H2018
			AAV2		retinitis pigmentosa	Preclinical	
AGTC	-$61	XLRS (partner Biogen)	AAV	RS1	X-Linked Retinoschisis	Phase 1	
		XLRP (partner Biogen)	AAV	RPGR	X-Linked Retinitis Pigmentosa	Phase 1	
		ACHM	AAV	CNGB3 / CNGA3	Achromatopsia	Phase 1	
Adverum Biotech (fka Avalanche biotech)	-$47	AVA-101 (Discontinued)	AAV2	sFLT-1 (a naturally occuring VEGF inhibitor)	wet AMD	Phase 2a (Discontinued)	
		ADVM-022	AAV.7m8	aflibercept	wet AMD	Preclinical	IND 2018

Source: Compiled by MHBK/IRD based on public reports

4. Muscle, Liver and Other Orphan Diseases

A number of companies are developing gene therapies to treat muscle and liver orphan diseases (see Table 21). These programs generally just got into clinical trials and are in early stage. But clinical data is coming. Audentes will report preliminary data for its MTM1 gene therapy to treat a neuromuscular disease called X-linked myotubular myopathy by the end of this year. Regenxbio will report some data for its LDL receptor gene therapy to treat homozygous familial hypercholesterolemia (HoFH). Dimension Therapeutics will report initial data for OTC deficiency by year-end. So far these companies have reported promising data in animal models – e.g., Audentes in dogs and Regenxbio in mice.

Dimension Therapeutics is developing AAV8 based gene therapy for metabolic orphan diseases associated with liver. It has two programs - OTC gene therapy for OTC deficiency, an X-linked, urea cycle disorder, and glucose-6-phosphatase gene therapy for an inborn error of glucose metabolism called Glycogen Storage Disease Type Ia. Highlighting the potential value in gene therapy for orphan diseases, a bidding war erupted for Dimension Therapeutics recently. Dimension Therapeutics was initially focused on gene therapy for hemophilia. After its program for hemophilia B failed in early 2017, its share dropped to $1.20 per share (translate into market cap of $30mn enterprise value of -$17.5mn). On August 25th, Regenxbio announced a deal to acquire Dimension Therapeutics for $3.41 per share in stock. Subsequently, the rare disease company Ultragenyx submitted a proposal to acquire Dimension at $6 per share in cash, which translates into ~$100mn enterprise value. This $6 price represents a premium of 400% to Dimension's unaffected share price as of August 24, 2017.

Benitec is combining gene therapy and RNA interference in an approach called DNA-directed RNA Interference (dd-RNAi). Its lead program BB-301 to treat oculopharyngeal muscular dystrophy will go into clinic next year. In BB-301, the transgene contains the replacement PABPN1 gene as well as genes encoding siRNAs responsible for silencing endogenous aberrant proteins.

Adverum will bring two gene therapy programs for orphan conditions into the clinic. These two programs use well-validated targets to treat monogenic diseases of alpha-1 antitrypsin deficiency and Hereditary Angioedema.

Table 21 Notable Gene Therapy Programs for Muscle, Liver and Other Orphan Diseases

Company	Market Cap	Product	Vector	Gene	Indication	Stage	Milestone
Audentes Therapeutics	$768	AT132	AAV8	MTM1 (Myotubularin)	X-linked myotubular myopathy	Phase 1/2	Preliminary data YE2017
		AT342	AAV8	UGT1A1	Crigler-Najjar syndrome Type 1	Phase 1	
		AT982	AAV9	GAA	Pompe disease	IND 1H18	
		AT307	AAV9	CASQ2	CPVT	IND 2017	
Regenxbio	$643	RGX–501	AAV8	LDL receptor	Homozygous familial hypercholesterolemia (HoFH)	Phase 1	Data YE2017
Benitec Biopharma	$29	BB-301	AAV	PABPN1 gene plus shRNA genes	Oculopharyngeal Muscular Dystrophy	Preclinical	IND 2H18
AAVLife					Friedrich's Ataxia	Preclinical	
Dimension Therapeutics (now a part of Ultragenyx)		DTX301; DTX401	AAV8	OTC; G6Pase	OTC deficiency; Glycogen Storage Disease Type Ia (GSDla)	Phase 1/2; Preclinical	Preliminary data YE2017 for OTC program
Adverum Biotech (fka Avalanche biotech)	-$47	ADVM-043	AAVrh10	Alpha-1 antitrypsin	A1AT Deficiency	Preclinical	IND YE 2017
		ADVM-053	AAV	C1-esterase inhibitor	Hereditary angioedema	Preclinical	IND 2018

Source: Compiled by MHBK/IRD based on public report

E. Potential Risks of Gene Therapy

While gene therapy is a very promising field, needless to say, it carries high risk. There are several categories of risk for gene therapy.

1. Technical and clinical Risk

We have seen many clinical failures of gene therapy in the past.

- For example, prior to the promising data by Voyager Therapeutics, at least nine gene therapy trials in Parkinson's disease have failed to show sufficiently robust clinical efficacy or found a clear path toward regulatory approval.[16] For example, after reporting lackluster phase 2 data for PD gene therapy CERE-120, Ceregene was acquired by Sangamo for only $1mn. CERE-120 was a gene therapy to deliver neurturin, a neurotrophic factor, to the brain.
- In hemophilia, Dimension Therapeutics reported mixed data for its hemophilia B program DTX101 in early 2017 and subsequently terminated the program. While efficacy was seen, 5 out of 6 patients saw elevation in liver enzymes. We note current gene therapy programs often use steroid prophylaxis to reduce the risk of liver enzyme elevation. However whether the liver risk can be eliminated remains to be seen.
- In eye disease, specifically wet AMD, Avalanche Biotech's phase 2a trial of AVA-101 (sFLT-1 gene, a naturally occurring VEGF inhibitor) delivered lackluster data and the program was discontinued. A similar program of sFLT-1 gene therapy for wet AMD from Genzyme/AGTC also has been discontinued.
- In CV disease, Celladon's heart failure gene therapy Mydicar failed to meet its primary and secondary endpoints in a phase 2b trial called CUPID2. CUPID2 is a randomized, double-blind, placebo-controlled, trial evaluating a single intracoronary infusion of the cardiovascular gene therapy agent MYDICAR (AAV1/SERCA2a) versus placebo added to a maximal, optimized heart failure drug and device regimen. Much of its former billion-dollar market cap was lost and Celladon became a shell for reverse merger. But the Mydicar program was taken over by a company called Theragene Pharmaceuticals for further development.

2. Manufacturing Risk

AAV gene therapy involves complex manufacturing process to make live viruses. Therefore this is a high requirement for manufacturing. Gene therapy companies have chosen to either investing in the manufacturing capacity in house or rely on external contract manufacturing organizations (CMOs). CMOs are lowering the manufacturing hurdle for small companies. For example, Brammer Bio is the CMO partner for Abeona Therapeutics and Lysogene for manufacturing their gene therapy products.

[16] "Parkinson's Disease Gene Therapy: Success by Design Meets Failure by Efficacy." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3944322/

3. Commercial Risk

Gene therapy is unique when compared to other therapies because it is given only once to patients. This is a result of immunogenicity concern of repeated dosing. This one-treatment therapy doesn't fit the current drug reimbursement system which is basically pay-as-you-go. Insurers don't want to pay the high price tag for one-time therapy upfront because: (1) it is quite a large sum upfront, (2) they don't know how long the benefit from gene therapy will last, (2) patients switch insurance plans so insurance companies cannot stand to benefit from patients' better health for their life time. Therefore, there have been hot discussions of new payment model for gene therapy products. For example, recently in the wake of FDA approval of Novartis' Kymriah (CAR-T therapy for ALL) as the first gene therapy in the U.S., Dr. Steve Miller, the chief medical officer of Express Scripts, wrote in a blog to advocate for a new payment model for gene therapy[17]. In Kymriah's case, Novartis set a price of $475,000 and agreed to outcome-based payment, i.e., it will not collect payment unless patients respond to Kymriah. We note although the outcome-based payment model is a start, it doesn't fundamentally address the longitudinal mismatch of drug benefit vs. payment. Eventually drug companies may need to find a way to get paid in installments over the life-long period that gene therapy delivers benefits.

This lagging of payment model innovation vs. gene therapy innovation creates a commercial risk for gene therapy companies. We note the first two gene therapy launches were failures. uniQure and its commercial partner Chiesi pulled Glybera from the European market due to a lack of reimbursement and demand for the $1mn therapy. GSK struggled with its European launch of Strimvelis for the rare immune system disorder ADA-SCID and is divesting its rare disease portfolio. In Stimvelis' case, the disappointing launch came even after GSK agreed to pay-for-performance deals for the $665,000 therapy.

It will be interesting to see how the market will accept pricing for Spark Therapeutics' Luxturna next year. We have seen pricing estimate as high as $750,000 for one eye. Whether the insurers will agree to reimburse at that high level is a question mark.

We note in some areas where there is existing expensive therapy, gene therapy is likely to have an easier time to get reimbursed. In such cases, gene therapy will replace existing cost rather than adding to the total cost. One example is hemophilia. Factor therapy for a hemophilia patient can cost up to $400,000 per year, which makes gene therapy looks like a bargain. In SMA, Biogen's Spinraza costs $750,000 for the first year of treatment ($375k per year afterwards). The high-price tag didn't hinder its adoption. Biogen reported Spinraza sales of over $200mn in a quarter. So if AveXis's SMA gene therapy is approved, it already gets a very good benchmark for pricing.

[17] http://lab.express-scripts.com/lab/insights/drug-options/gene-therapy-holds-great-promise-but-big-price?ec_as=db138d292871411bbd079095a66ceab4

F. Deals in Gene Therapy

Big biopharma have shown different enthusiasm for gene therapy. So far Pfizer, Bayer, Biogen and Gilead have been the most active in making acquisition or doing licensing deals in gene therapy (see Table 22).

Table 22 Selected Deals in Gene Therapy

Acquirer	Target	Date	Amount $mn)	Therapeutic areas
Ultragenix	Dimension	Sep-17	$90mn acquisition	Gene therapy for rare diseases
Gilead	Kite Pharma	Aug-17	$11.9bn acquisition	CAR-T Therapy
Lonza	PharmaCell	Jun-17	Acquisition for an undisclosed amount. Annual sales of €11mn.	Cell and gene therapy CMO
Pfizer	Sangamo	May-17	$70mn upfront, $475mn in milestones	Preclinical gene therapy for hemophilia A
Pfizer	Bamboo Therapeutics	Aug-16	Acquired for $193mn upfront and $495mn milestone payment	Neurovascular (DMD) and CNS
Biogen	UPenn	May-16	Up to $2 billion multi-year alliance for gene therapy and gene editing	Eye, skeletal muscle and the central nervous system (CNS).
Avalanche Biotech	Annapurna Therapeutics	Feb-16	$105.6 merger	Combine Avalanche's ophthalmic disease gene therapy with Annapurna's gene therapies for rare diseases
Bayer	CRISPR Therapeutics	Dec-15	Bayer invests $335mn in a JV with CRISPR Therapeutics	Gene editing to treat blood disorders, blindness, and congenital heart disease
Biogen	AGTC	Jul-15	$124mn upfront, $1.1bn in milestones	Gene therapy for ophthalmic diseases XLRS and XLRP
Roche	4D Molecular Therapeutics	Apr-15	Undisclosed	Develop AAV vectors for gene therapy.
BMS	uniQure	Apr-15	$100mn near-term payment, including $50mn at closing	Cardiovascular disease including the S100A1 program in congested heart failure.
Genzyme (Sanofi)	Voyager Therapeutics	Feb-15	$100mn upfront, including $65mn in cash and $30mn equity investment	AAV gene therapies for CNS disorders.
Biogen	TIGET	Jan-15	$5mn upfront	Hemophilia
Amgen	Kite Pharma	Jan-15	$60mn upfront, $525mn milestone per product	CAR-T Therapy
Novartis	Intellia	Jan-15	Undisclosed upfront payment, equity stake	CRISPR gene editing to engineer CAR-T and hematopoietic stem cells
Novartis	Caribou	Jan-15	Funding to Series A financing	CRISPR gene editing for research
Pfizer	Spark Therapeutics	Dec-14	$20mn upfront, additional milestone payment of $260mn	Hemophilia B program SPK-FIX (IND 1H2015)
Janssen Biotech	Transposagen Biopharma	Nov-14	$292mn in upfront and milestone payment per program	Gene editing technology to create CAR-T Therapy
Bayer	Dimension Therapeutics	Jun-14	$20mn upfront, additional milestone payment of $232mn	AAV gene therapies for Hemophilia A
Pfizer	Cellectis	Jun-14	$80mn upfront, $185mn milestone per product	CAR-T Therapy
Regeneron	Avalanche Biotech	May-14	Upfront and milestone up to $600mn	Ophthalmology, including right for first negotiation for AMD gene therapy AVA-101
Baxter	Chatham	Apr-14	$70mn acquisition	Hemophilia
Chiesi Farmaceutici	uniQure	Jul-13	$22mn upfront, additional $18mn equity investment	European commercialization of Glybera for LPLD and co-development for Hemophilia B
Celgene	bluebird bio	Mar-13	Undisclosed upfront payment and $225mn milestone per product	CAR-T Therapy

Source: Compiled by MHBK/IRD based on public reports

IV. Nucleic Acid Based Therapy

A. Background of Nucleic Acid Based Drugs

Nucleic acid based drugs are drugs based on nucleic acid such as DNA or RNA. It is an emerging treatment modality. As illustrated in Figure 10, genetic information stored in the form of DNA is transcribed into messenger RNA or mRNA, which then moves from nucleus to the cytosol where it is translated into protein. Protein is the manifestation of genetic information as it ultimately carries out cellular functions. Current pharmacopeia contains almost exclusively of small molecule or protein/antibody drugs targeting protein (see Figure 10). Nucleic acid based drugs go up one level to target mRNAs. We discuss three main forms of nucleic acid based drugs in this report.

a) Antisense oligonucleotides (ASOs)

ASOs are short single-strand DNA molecules. There are mostly two kinds of ASOs that inhibit the targeted mRNA. First as illustrated in Figure 10, ASOs bind to targeted mRNA. RNase H recognizes the DNA-RNA duplex and cleaves the mRNA, which leads to its degradation. This is the traditional way of how ASOs inhibit mRNA. Second class of ASO doesn't require RNase H and works by causing alternative splicing of mRNA through steric blocking the mRNA. The two approved ASO drugs Exondys 51 for Duchene muscular dystrophy and Spinraza for spinal muscular atrophy belong to this alternative splicing ASO category.

b) Small Interfering RNA (siRNA)

Fire and Mello received Nobel Prize in 2006 for their discovery of RNA interference. In RNA interference, long double-stranded RNAs are cut by an enzyme called Dicer to form siRNAs. siRNA is a double-stranded RNA duplex. Upon binding to the RNA-induced silencing complex (RISC), the two strands are separated. The antisense strand binds to the target mRNA. Then the RISC associated with the antisense strand degrades the target mRNA. siRNA is catalyzed by the efficiency RISC cleavage machinery. Thus it is considered to be a more potent mechanism than ASOs inside the cell. The discovery and development of siRNA lags ASOs by two decades. So siRNA drugs borrow heavily from the lessons learned from developing ASO drugs.

c) mRNA Therapeutics

mRNA therapeutics simply entails delivery mRNA inside the cell, where it will use host cellular translational apparatus to translate into proteins. The translated proteins will carry out the therapeutic function.

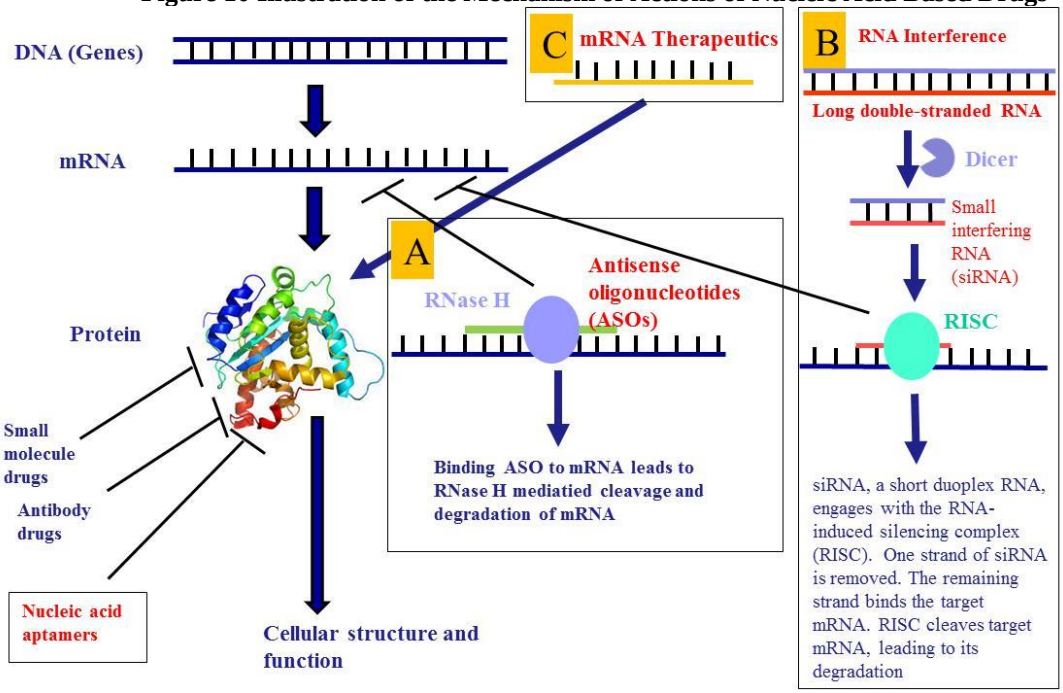
d) Other Nucleic Acid Based Drugs

There are a few other classes of nucleic acid based drugs. One is aptamer. Nucleic acid aptamers are short, single-stranded DNA or RNA molecules that bind to protein targets

(see Figure 10). Aptamers form defines structures due to the complementary base pairs. The three-dimensional structure is capable of recognizing and modulating specific sites of protein target. Aptamers have been in development for many years as a small molecule alternative to antibody. The first approved aptamer drug is Macugen for wet advanced macular degeneration. But due to inferior efficacy, Macugen was quickly made obsolete by antibody drugs targeting the same target VEGF (vascular endothelial growth factor). So at least from the first experience, aptamer couldn't match antibody drugs' potency and specificity.

MicroRNAs (miRNAs) are small single-stranded naturally occurring RNAs expressed from introns of the genome. miRNAs are regulators of the expression of many genes. The single-stranded miRNAs form hairpin loops, which are cleaved by Dicer to form dsRNA. Also as in siRNAs, dsRNA uses the RISC complex to silence the target mRNA. In addition to RISC-mediated mRNA cleavage, miRNA can also bind to mRNA to inhibit protein translation. Unlike siRNA where the binding to target is 100% complementarity, the binding of miRNA to target is imperfect and is not tight. Thus one miRNA can regulate many genes' expression.

Figure 10 Illustration of the Mechanism of Actions of Nucleic Acid Based Drugs



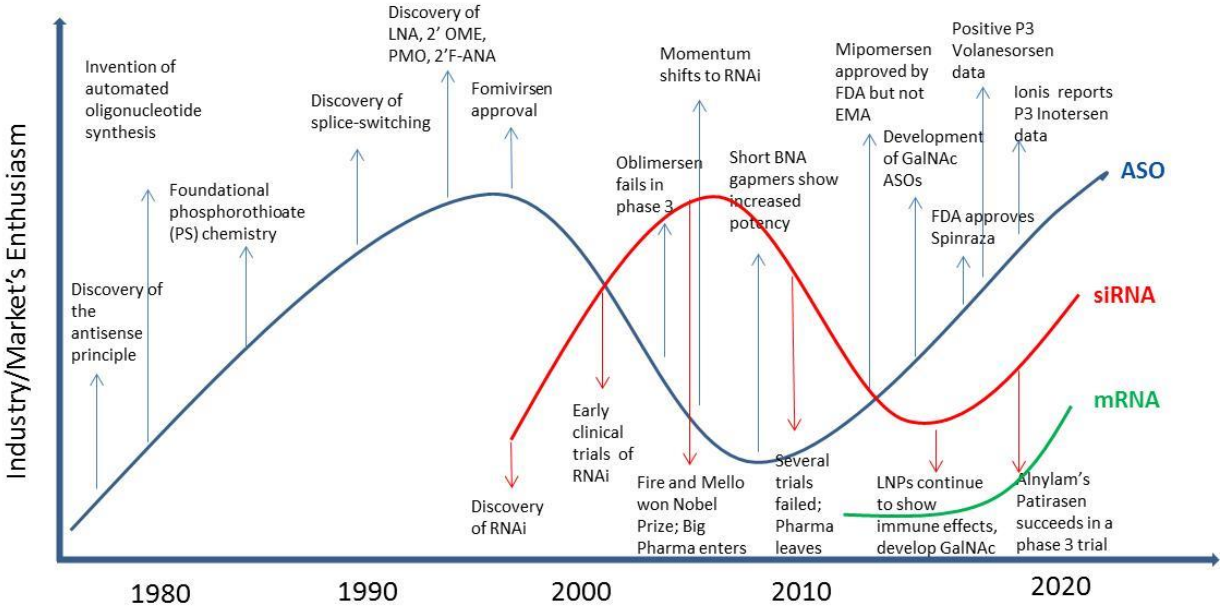
Source: Illustrated by MHBK/IRD

B. Recent Progresses of Nucleic Acid Based Drugs

Nucleic acid (NA) based drugs hold great promise in drug development. Here we define nucleic acid-based drugs as oligonucleotide drugs and the newly emerging mRNA based drugs. Oligonucleotide drugs include antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), microRNAs, aptamers and others. A key advantage of oligonucleotide-based drugs is their targets can be specified by the base sequence. In the post-genomic era, oligonucleotide based drugs can be theoretically applied to any targets, even difficult targets not amenable to traditional pharmaceutical intervention. The success of an oligonucleotide drug depends on its sequence design (picking the right sequence and right target) and pharmacokinetic properties of the delivery. While designing the right sequence seems to be relatively straight forward (if the target is biologically validated), the key hurdle has been the delivery to the specific tissue for NA drugs to work on their targets.

Figure 11 juxtaposes the development timeline of ASOs , siRNAs and mRNAs. The development of ASOs predates the development of RNAi by two decades. ASO mechanism was discovered in 1978 when Zameinik and Stephenson demonstrated an oligonucleotide that is antisense to a viral RNA could reduce protein translation and viral replication. In comparison, Fire and Mello discovered RNA interference (RNAi) in 1998. The 20-year head start of ASOs means many innovations in the ASO field can be applied to RNAi. The development of mRNA as therapeutics only gathered steam this decade, led by Moderna and others.

Figure 11 Illustration of Evolution of ASOs, siRNA and mRNA



Source: MHBK/IRD modified from Khvorova and Watts, "The chemical evolution of oligonucleotide therapies of clinical utility." *Nature Biotechnology* 35, 238–248 (2017), March 2017. For a good illustration of how oligonucleotide drug technology evolved along with oligonucleotide companies, please refer to Khorkova& Wahlestedt, "Oligonucleotide therapies for disorders of the nervous system." *Nature Biotechnology* 35, 249–263 (2017), March 2017.

C. Antisense Oligonucleotides (ASOs)

Since its discovery as potential therapeutics in 1978, ASO technology has gone through several iterations. While we cannot find standard definition, there are roughly three generations of ASO chemistry. Each generation generally increases the potency by 10 fold vs. the earlier generation (see Table 23).

1. First generation ASO is based on phosphorothioate (PS) chemistry. PS ASOs need frequent administration and large doses, which makes them inconvenient and less tolerable.

2. Second generation ASOs achieve improved stability and high potency by including 2'-modified and conformationally constrained nucleotides. 2' modification examples include 2'-*O*-methyl (2'-OMe), 2'-*O*-methoxyethyl (2'-O-MOE), 2'-fluoros (2'-F), and 2'-F-ANA. Constrained nucleotides include Locked nucleic acid (LNA) and "constrained ethyl" (cEt). However as the sugar modified RNA-like nucleotide cannot elicit RNase H cleavage of complementary RNA, a "gap" of PS DNA is incorporated in the middle of ASO which offers a window for RNase H cutting. This is the so-called gapmer ASO. Ionis specifically calls MOE Gapmer as Gen. 2.0 and cET containing Gapmer as Gen. 2.5 (see Table 23).

3. Third generation ASOs are conjugated ASOs to facilitate specific tissue and cell uptake. Ionis called it LIgand-Conjugated Antisense (LICA) Technology. The predominant form of LICA is triantennary N-acetyl galactosamine (GalNAc) conjugation. GalNAc is an amino sugar that is a natural ligand for the asialoglycoprotein receptor expressed on hepatocytes. Thus, GalNac can be applied to many oligonucleotides to specifically target liver. The discovery of GalNAc conjugate is a major breakthrough in oligonucleotide drugs. GalNAc conjugation increases the potency of gen. 2 and 2.5 ASOs by 10x in the liver. Currently a large number of clinical programs use GalNAc conjugates (see Table 24). Another new generation of oligonucleotide drugs is stereopure oligonucleotide being developed by Wave Life Sciences. Stereopure oligonucleotides have been shown in in vitro studies to be more efficacious and stable than stereomixture oligos.

Table 23 Comparisons of Different Generations of ASO Technology

ASO Technology	Attributes	Human dose (mg/week)
Gen 1.0 *Phosphorothioate*	•Add stability; •Improves distribution to tissues	1200-3500
Gen 2.0 *MOE* Gapmer	• Increases potency; • Increases stability; • Reduces non-specific toxicities	100-400
Gen 2.5 *cEt* containing Gapmer	• Increases potency and therapeutic index • Expands range of targets and tissues	20-80
Ligand conjugated Gen 2 Gapmer	• Facilitate specific tissue and cell uptake • Higher potency	4.5-20
Ligand conjugated Gen 2.5 Gapmer	• Facilitate specific tissue and cell uptake • Higher potency	1-2

Source: Compiled by MHBK/IRD based on presentation from Ionis Pharma

Table 24 Clinical Programs based on GalNAc Conjugates

Drug	Company	Mechanism and chemistry	Target	Disease	Development
Revusiran	Alnylam	siRNA	Transthyretin (mutant and wild type)	Hereditary ATTR amyloidosis	Withdrawn
Fitusiran	Alnylam	siRNA	Antithrombin	Hemophilia	Phase 2
Inclisiran	Alnylam	siRNA	PCSK9	Hypercholesterolemia	Phase 2
IONIS-APO(a)-LRx	Ionis	ASO	Apolipoprotein A	Very high apolipoprotein a	Phase 2
IONIS-ANGPTL3-lRx	Ionis	ASO	Angiopoietin-like 3	Mixed dyslipidemias	Phase 2
RG-101	Regulus	anti-miR	miR-122	Hepatitis C virus infection	Phase 2
ALN-CC5	Alnylam	siRNA	Complement component C5	Complement-mediated diseases	Phase 1/2
ALN-AS1	Alnylam	siRNA	Aminolevulinic acid synthase	Hepatic porphyrias, including acute intermittent porphyria	Phase 1
IONIS-HBV-LRx	Ionis	ASO	HBV genome	HBV infection	Phase 1
RG-125	Regulus	anti-miR	miR-103 and miR-107	Nonalcoholic steatohepatitis; type 2 diabetes and pre-diabetes	Phase 1

Source: Khvorova and Watts, "The chemical evolution of oligonucleotide therapies of clinical utility." *Nature Biotechnology* 35, 238–248 (2017), March 2017.

Concurrent with the advancement of oligonucleotide technology, biotech industry has made substantial progress in moving pipeline forward. There are five oligonucleotide-based drugs already approved in the U.S. (see Table 25). Ionis CEO Stan Crooke called the FDA approval of Kynamro (mipomersen) in 2013 "the end of the beginning" for antisense. While Kynamro failed to achieve substantial sales, its approval marked the maturation of antisense technology and presaged a rapid advancement of antisense pipeline. In 2016, Exondys 51 and Spinraza, two alternative splicing ASOs, were approved. The development of Spinraza is especially noteworthy both in terms of its stellar clinical profile in the dire orphan disease spinal muscular dystrophy (SMA) and its commercial success. In the second quarter on the market, Spinraza already generated $200mn in sales.

Table 25 FDA Approved Oligonucleotide Drugs

Brand (Generic name)	Year of FDA approval	Company	Indication	Peak Sales	Mechanism	Comments
Vitravene (fomiversen)	1998	Ionis / Novartis	CMV Retinitis in HIV patients	NA	Phosphorothioate (PS) antisense oligo targeting mRNA of HCMV	Novartis pulled this drug from the market due to a lack of demand
Macugen (pegapatanib)	2004	Eyetech / OSI /Pfizer	Wet AMD	$185mn in 2005	Aptamer inhibitor to VEGF	After Lucentis was approved in 2006 for wet AMD, Macugen sales declined precipitously as its efficacy is inferior to Lucentis.
Kymamro (mipomersen)	2013	Genzyme / Ionis	Hypercholesterollemia (HoFH)	NA	PS substituted antisense oligo targeting mRNA of apolipoprotein B-100	Black box warning for hepatotoxicity. It failed to generate material sales due to inferior clinical profile.
Exondys 51 (eteplirsen)	2016	Sarepta	Duchenne Muscular Dystrophy	$1bn	Antisense for alternative splicing (exon skipping)	Good launch after a controversial accelerated approval by the FDA.
Spinraza (nusinersen)	2016	Biogen / Ionis	Spinal Muscular Atrophy	$2bn+	Antisense oligo that binds pre mRNA of SMN2 gene for alternative splicing	Very strong launch after approval in December 2012. 2Q17 sales exceeded $200mn.

Source: Compiled by MHBK/IRD based on public reports

As with any other therapeutic modality, there were failures in antisense drug development. We note there were at least three failures of ASOs in cancer – PKCα ASO Affinitak from Ionis and Eli Lilly, bcl-2 ASO Oblimersen from Genta, clusterin ASO Custirsen from OncoGenex. Often multiple pathways are at work to drive cancer. Therefore blocking one plausible target may not have big effect. Outside of cancer, ASOs have a fairly high probability of success (POS) with regard to efficacy, but safety concerns may linger. This year, Ionis reported positive phase 3 results for Inotersen (TTR ASO) for TTR Amyloidosis. Although the study met efficacy endpoint, safety observation was noted – 3 serious adverse events for thrombocytopenia (including one death) and 4 patients discontinued due to renal toxicity. Either because of these safety observations or its shift in priority, GSK declined to exercise its right to license Inotersen. Ionis plans to submit for approval and market Inotersen on its own.

Ionis and Akcea reported positive phase 3 results of Volanesorsen (ApoCIII) for Familial Chylomicronemia syndrome (FCS). In one study, Volanesorsen-treated patients had 77% reduction in triglyceride vs. 18% mean increase with placebo. There was also a corresponding decrease in incidence of pancreatitis attacks and abdominal pain. Ionis and Akcea plan to file BLA this year.

Besides aforementioned programs, Ionis has built a very rich pipeline, spanning cardiovascular, severe and rare, cancer, metabolic and other diseases. ASO technology really blossomed under the pioneering leadership of Ionis. For a complete list of Ionis pipeline and its pharma partners, please refer to its corporate website - http://www.ionispharma.com/pipeline/.

D. Small Interfering RNAs (siRNAs)

The discovery of RNA interference in 1998 attracted huge academic and industry interest. As Fire and Mello received the Nobel Prize in physiology or medicine in 2006, interest in RNAi reached a peak. Big pharma made major deals in RNAi - Novartis' partnership with Alnylam in 2005, Merck's $1.1bn acquisition of Sirna in 2006, Roche's $1bn ($331mn upfront) partnership with Alnylam in 2007 and AstraZeneca's $400mn partnership with Silence Therapeutics in 2007. But as pharma realized efficacy, safety and most importantly delivery issues of RNAi, they exited the field. Pfizer and Roche exited RNAi in 2010. Roche sold its RNAi assets to Arrowhead in 2011. Novartis divested its RNAi assets to Arrowhead in 2015. Merck divested what was left of Sirna to Alnylam for $175mn in 2014. So RNAi field dropped to a nadir in 2014/2015 (see Figure 11).

But RNAi leader Alnylam persevered. Alnylam and other industry players have made important breakthroughs in the basic siRNA technology, especially regarding delivery. Alnylam has focused its development efforts on using GalNAc to deliver siRNA to the liver to treat rare and liver diseases. It has gone through three generations of its GalNAc delivery technology (see Table 26). ESC-conjugates have higher stability compared with STC-conjugate and thus are given at much lower does, which results in greater potency and durability with lower exposure. ESC+ conjugate further improves upon ESC conjugate by increasing specificity and thus reducing off-target side effect such as liver toxicity. Alnylam's research has found most of the liver toxicity of siRNA is due to off-target binding of the siRNA, which is dependent on its sequence. ESC+ uses chemically modified nucleotides within the seed region of the antisense strand to lower the chance for off-targeting binding. We note most of Alnylam's current pipeline uses its ESC-Conjugate. But next wave of INDs will use ESC+ Conjugates.

Table 26 Evolution of Alnylam's GalNAc Delivery Technology

Generation	First Generation	Second Generation	Third Generation
Technology name	STC-Conjugate	ESC-Conjugate	ESC + Conjugate
Description	• Standard Template Chemistry GalNAc conjugate • SC administration	• Enhanced Stability Chemistry GalNAc conjugate • SC administration	• Enhanced Stability Chemistry ↑ Specificity GalNAc conjugate • SC administration
Stage	First generation GalNAc conjugate, initial human POC	Second generation GalNAc conjugate, Human POC, greater potency and durability with lower exposures	Next generation GalNAc conjugate with further improvements to specificity and therapeutic index
Examples	Revusiran	• Fitusiran • Inclisiran • Givosiran • ALN-TTRSC02 • ALN-GO1 • ALN-CC5 • ALN-HBV	• 2018 INDs and CTAs

Source: Alnylam investor presentation "2017 RNAi Roundtable: Platform advances in RNAi Therapeutics," given on August 23, 2017

We believe with the improved technology and maturing pipeline, the siRNAi field is on the up-swing again, but it is not of the woods yet. The recent clinical experience has been mixed (see Table 27). In October 2016, Alnylam stopped Revusiran development after an imbalance in cardiac death was detected in the phase 3 trial and the data monitoring committee concluded benefit-risk profile of the trial was unfavorable. Revursiran is based on the old STC-GalNAc technology. As such it was given at much higher doses than the newer technology. Alnylam reported the dose exposure of one year treatment of revusiran is equivalent to 70 years' exposure of patisiran delivered by lipid nanoparticle (LNP), and to 12-140 years' exposure of ESC-GalNAc conjugates.

The recent success of Alnylam's patisiran for TTR Amyloidosis (polyneuropathy) in the phase 3 APOLLO trial was a watershed moment for siRNA therapy. Patisiran not only demonstrated overwhelming efficacy but also good safety. In the 225-patient pivotal trial, patisiran met primary endpoint of change in mean modified Neuropathy Impairment Score +7 (mNIS+7) with a big statistical margin ($p = 9.26x10^{-24}$). Patisiran also met all the secondary endpoints. On the safety side, adverse events occurred in 96.6% of the patisiran group vs. 97.4% for placebo. Serious adverse events were less common for patisiran than placebo (36.5% vs. 40.3%). The rate of discontinuation due to treatment was 7.4% for patisiran vs. 37.7% for placebo. The rate of discontinuation due to adverse events was 4.7% for patisiran vs. 14.3% for placebo. Common adverse events that were more common in patisiran arm were peripheral edema (29.7% vs. 22.1%) and infusion reaction (18.9% vs. 9.1%). While the patisiran clinical data is very impressive, as it is based on LNP technology licensed from Arbutus Biopharma rather than Alnylam's ESC-GalNAc technology, its success is not yet a wholesale validation of Alnylam's new technology platform. LNPs historically have a checked record for immune activation, especially with chronic use. LNP has to be given with steroids. Most of the oligo industry has shifted away from LNP delivery to GalNAc based delivery. So the success of patisiran is particularly remarkable.

Alnylam's current clinical siRNA pipeline is based on ESC GalNAc. Of these programs, data has been mixed (see Table 27). The Medicines Company reported promising phase II data for Inclisiran for hypercholesterolemia. But other ESC GalNAc based clinical programs had encountered bumps on the road. Liver enzyme elevation is a potential concern for GalNAc delivered siRNA, although it is asymptomatic at low doses. Alnylam's next-generation ESC+ GalNAc is promised as having much improved liver safety than ESC GalNAc.

Table 27 Recent Clinical Experience of siRNA Programs

Date	Program	Target / Indication	Company	Technology	Outcome	Clinical Results
9/26/2016	DCR-MYC; DCR-PH1;	Cancer; Primary Hyperoxaluria	Dicerna	LNP	Negative	MYC program failed to pass efficacy hurdle. Dicerna will focus on its GalXC technology platform for rare diseases, chronic liver diseases, cardiovascular disease and viral infectious diseases.
9/28/2016	ALN-AAT	Alpha-1 antitrypsin deficiency (AATD)	Alnylam	ESC GalNAc	Negative	Halted development after Phase I/II resulted in three patients with liver enzyme elevation at the highest dose. But dose-dependent knowdown was observed. Alnylam will focus on follow-on molecule ALN-AAT01.
10/5/2016	Revusiran	ATTR amyloidosis with cardiomyopathy	Alnylam	STC GalNAc	Negative	Peripheral neuropathy and elevated blood lactate were observed in phase 2 extension study, which triggered an interim analysis by the data monitoring committee of the phase 3 ENDEAVOUR trial. DMC recommended suspension of dosing as it found a lack of favorable benefit-risk profile. Alnylam discontinued the program after its analysis showed an imbalance of cardiac-related death. However Alnylam's later analysis found the imbalance in death was likely due to chance.
11/10/2016	ARC-520	HBV	Arrowhead	EX1 delivery	Negative	FDA put ARC-520 on hold due to death in non-human primates toxicity studies. Later in the month, Arrowhead discontinued EX1 delivery RNAi programs in HBV and AAT. Arrowhead will focus on subQ administered and extra-hepatic RNAi-based development programs.
11/15/2016	Inclisiran	PCSK9 for hypercholsterolemia	Alnylam / The Meidicines Company	ESC GalNAc	Positive	ORION -1 Phase 2 study showed excellent efficacy and clean safety.
9/7/2017	Fitusiran	Anti-thrombin III (AT3) for Hemophilia	Alnylam	ESC GalNAc	Mixed	In September 2017, Alnylam suspended dosing in a phase 2 trial of fitusiran after a patient died due to thrombosis. FDA lifted the clinical hold in December 2017 to allow the trial to proceed. Partner Sanofi is planning a comprehensive phase 3 development program for Fitusiran.
9/20/2017	Parisiran	ATTR amyloidosis with polyneuropathy	Alnylam	LNP	Positive	Patisiran showed overwhelmingly positive efficacy data and good safety data.

Source: Compiled by MHBK/IRD based on public reports

The recent renaissance in ASO and siRNA hasn't escaped the attention of big pharma as a number of them have inked deals in this field (see Table 28). Big pharma are particularly interested in using ASOs or siRNAs to target lipid disorders. Lp(a) and APOCIII are hot targets. Novartis, Amgen and Pfizer have all signed deals for these targets.

Table 28 Recent Deals of ASO and siRNA

Date	Licensor	Licensee	Assets	Economics / Deal Structure
5/5/2016	Wave Life Sciences	Pfizer	Broad collabration of Wave's stereopure oligonucleotide technology in metabolic disease. Pfizer will select five research programs as a part of this collaboration, one of which is APOCIII.	$30mn in equity investment and $10mn upfront payment. Up to $871mn in milestone payment. WAVE will advance up to five programs from discovery through to the selection of clinical candidates, at which point Pfizer may elect to exclusively license the programs and undertake further development and potential commercialization
9/29/2016	Arrowhead	Amgen	Two cardiovascular programs - RNAi ARC-LPA and another undisclosed program.	$21.5mn equity investment and $35mn in equity payment and up to $617mn in milestone payments for the global license.
11/10/2016	BMS	Nitto Denko	Phase 1b asset ND-L02-s0201 (siRNA for HSP47) in development for advanced liver fibrosis	$100mn upfront for the global license
1/6/2017	Ionis / Akcea	Novartis	Phase I/IIa-stage cardiovascular disease candidates AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. Both programs use GalNAc conjugated ASOs (LINA).	$100mn equity investment and $75mn upfront for an option to license at the end of phase II.
1/9/2017	Silence Therapeutics	Arrowhead	NA	Silence Therapeutics acquired $9.6mn Arrowhead stocks, which amounts to 8.4% of the company. Silence Therapeutics wants to use the equity stake to facilitate discussions with Arrowhead for technology/business collaborations.
10/18/2017	Alnylam	Vir Biotech	ALN-HBV02 siRNA program for HBV	Unspecified upfront and equity. $1bn plus milestone payments.

Source: Compiled by MHBK/IRD based on public reports

Currently the majority of siRNAs in clinical development are originated by Alnylam and most of Alnylam's programs use GalNAc conjugate to delivery to the liver. The industry has largely moved to GalNAc. Arrowhead has abandoned its old DPC (dynamic polyconjugate delivery) platform in favor or subcutaneous GalNAc. Dicerna has also recently shifted its focus to GalNAc delivered therapy to treat rare diseases, chronic liver diseases, cardiovascular diseases and viral infectious diseases. LNPs (Lipid nanoparticles) have been out of fashion as LNPs elicit immune activation and have to be given with steroids. However if the current GalNAc delivery encounters toxicity issues, the industry may move back to LNPs. Interestingly the first real success of siRNA drug patisiran uses LNP delivery. Patisiran will be the first siRNA drug approved and it has blockbuster potential. Alnylam licensed the LNP technology for patisiran from Arbutus Biopharma. Arbutus is developing siRNAs for HBV using its LNP delivery technology. In October 2017, Arbutus attracted $116mn strategic investment in the form of preferred convertible stock from Roivant Sciences.

Beyond GalNAc or LNP delivery to the liver, some companies are working on delivering naked siRNA to other organs either through local delivery or specifically targeting kidney (see Table 29). Quark Pharma is developing naked siRNAs. It exploits naked siRNA's renal clearance to deliver siRNAs to the kidney. Quark's QPI-1002, a siRNA targeting p53, is designed to protect

p53-triggered apoptosis in kidney cells that are undergoing some stress (either kidney transplant or acute kidney injury). Quark's second program QPI-1007 is a siRNA targeting caspase-2. It is given via intravitreal injection to treat a complication of cataract surgery called NAION (non-artertic ischemic optic neuropathy).

Table 29 Selected Clinical Stage siRNA-based RNAi Therapeutics

Company	Agent	Delivery formulation	Indication	Development stage
Alnylam	Patisiran (ALN-TTR02)	LNP	Familial amyloidotic polyneuropathy	Phase 3
Quark	QPI-1002 (I5NP)	Naked siRNA	Post-kidney transplant, Post-cardiac surgery	Phase 3 Phase 2
Quark	QPI-1007	Naked siRNA	NAION	Phase 2/3
Sylentis (in Madrid)	SYL1001	Naked siRNA	Dry-eye syndrome	Phase 2 complete
Alnylam / Sanofi Genzyme	Fitusuran (ALN-AT3)	GalNAc conjugate	Hemophilia A&B	Phase 2
Alnylam	Givosiran (ALN-AS1)	GalNAc conjugate	Acute hepatic porphyrias	Phase 3 pending
Alnylam	Cemdisiran (ALN-CC5)	GalNAc conjugate	PNH and aHUS	Phase 2
The Medicines Company / Alnylam	Inclisiran (PSCK9si) (ALN-PSCsc)	GalNAc conjugate	Hypercholesterolemia	Phase 2
Benitec	BB-401 (EGFR)	Intratumoral injection of plasmid	Head and neck cancer	Phase 1/2
RXi Pharmaceuticals	RXI-109	Cholesterol conjugate	Dermal scarring after surgery, Retinal scarring	Phase 2 Phase 1
Arbutus Biopharma	ARB-1467 (TKM-HBV)	LNP	Chronic hepatitis B infection	Phase 2
Alnylam	ALN-TTRsc02	GalNAc conjugate	ATTR amyloidosis	Phase 1
Alnylam	ALN-GO1	GalNAc conjugate	Primary hyperoxaluria	Phase 1
Alnylam	ALN-HBV	GalNAc conjugate	Hepatitis B	Phase 1
MD Anderson Cancer Center	siRNA-EphA2-DOPC	LNP	Advanced solid tumors	Phase 1

Source: Modified based on Ken Garber, "Worth the RISC?" Nature Biotechnology, Volume 35, Number 3, March 2017

E. mRNA as Therapeutics

mRNA-based therapeutics is emerging as a hot field. Notable improvements of mRNA technology were made in academia, which attracted venture capitalists and other sponsors to fund startups. Over the recent years, mRNA has attracted an estimated $2.5 billion from partnerships and investments from pharmas and VCs. Flush with capital, companies such as Moderna are leading the charge of developing mRNA as therapeutics. Currently there are around a dozen of mRNA-based programs in early clinical development. Most of these programs are vaccines. Over the next two years, we should see proof of concept data from this batch of clinical programs which will infer the prospect of mRNA therapeutics.

1. Advances in mRNA Technology

If technology hurdles can be solved upfront, mRNA can be a faster and cheaper way of producing therapeutic proteins than recombinant technologies. Instead of engineering and producing proteins in expensive manufacturing plants, mRNAs coding for the therapeutic protein can be given to patients on demand. mRNA has even more advantages in situations of delivering multiple protein therapeutics (such as antibody mixtures) or personalized protein therapeutics (such as cancer neoantigen). Conceptually a leader such as Moderna can invest billions of dollars upfront to overcome hurdles in mRNA delivery, then the mature technology

can be applies at low cost across a variety of indications. While the hurdles for mRNA therapeutics remain daunting, the technology has improved over the years[18].

- There has been substantial improvement in the stability and expression of mRNA. mRNA engineering that helps on this regard includes adding 5' cap and 3' poly(A) tail to the mRNA, codon optimization, CpG optimization, incorporation of modified bases, secondary structure manipulation, providing 5' and 3' untranslated elements, etc. It appears the industry has made great strides in improving mRNA stability.
- Naked mRNA causes innate immune reactions. Researchers have found substituting modified bases can 'de-immunize' the mRNA. For example, substituting pseudouridine for uridine and 5-methylcytidine for cytidine lower mRNA's immunogenicity and improves translation efficiency.
- Another issue is mRNA manufacturing. Being able to make stable mRNA goes a long way towards ensuring its ease of manufacturing. Several mRNA companies have built factories and shown they can produce GMP-grade material. In addition, a number of contract research and manufacturing organizations (CDMO) are available to manufacture GMP mRNA for third parties.
- mRNA expression level is another hurdle. One innovation to boost expression level is the addition of viral replicase in the coding region of mRNA, which makes the mRNA self-amplifying. The RNA-dependent RNA replicase co-opts the host machinery and allows mRNA to copy itself. But such mRNA is not infectious because it is delivered by LNP nonviral system and doesn't have viral structural proteins. In a sense, self-amplifying mRNA is like an adjuvant for mRNA based vaccines. Both GSK and BioNTech are using alphavirus replicase for their mRNA constructs.
- Delivery of mRNA to the targeted tissue and getting into right cells is a major hurdle. LNPs (lipid nanoparticles) are often used as delivery vehicle. Systemic delivery of mRNA therapeutics adds another layer of complexity although proof of concept has been demonstrated by expression of Erythropoietin (EPO) and other proteins in animal models. Most of the current mRNA programs are vaccines that use local delivery such as intramuscular and intradermal injection. Even for a non-vaccine project, Moderna/AZ's VEGF-A mRNA therapy for cardiovascular disease is delivered locally. Ethris is expected to start clinical trial for CFTR mRNA therapy for cystic fibrosis. The therapy is given via inhalation, again taking advantage of local delivery.

[18] Laura DeFrancesco, "The 'anti-hype' vaccine" Nature Biotechnology, Volume 35, Number 3 p193-197. March 2017

2. mRNA Pipeline and Deals

The overwhelming majority of mRNA pipelines are for vaccines (see Table 30). Vaccine is the most suitable application for mRNA because of (1) local delivery and (2) the immunogenicity of mRNA is actually good for vaccines. Two types of mRNA vaccines are under development. First is the traditional vaccine for infectious diseases. mRNA specialists Moderna and CureVac are developing mRNA vaccines against viral pathogens such as rabies, Zika, influenza, CMV, etc. Traditional vaccine heavyweights such as Sanofi and GSK also invested in mRNA-based vaccines for infectious diseases. In 2011 Sanofi Pasteur partnered with CureVac. GSK has in-house mRNA technology. It has a self-amplifying RNA vaccine against Zika virus in preclinical development.

Another major application of mRNA is cancer vaccines. Cancer is a tricky area for vaccine. Historically with one exception, the vast majority of cancer vaccines in development have failed. Already we have seen two failures from mRNA vaccines this year. In January, CureVac reported its mRNA vaccine for prostate cancer (CV9103) didn't show survival benefit in a phase IIb trial. CV9103 is an intradermal mRNA vaccine targeting six antigens overexpressed in prostate cancer cells. In February 2017, a phase 3 trial of Argos Therapeutics' kidney cancer mRNA vaccine AGS-003 was discontinued for futility. AGS-003 is a dendritic cell vaccine loaded with patient tumor derived mRNA. While vaccine alone may not work in treating cancer, as vaccines may convert the tumor from non-inflamed to an inflamed state, combining it with checkpoint inhibitors or other immune-oncology modulators may lead to good clinical results. mRNA is very suitable for developing cancer antigens as vaccines because (1) mRNA can be used quickly to design highly personalized vaccine, (2) multiple cancer antigens can be incorporated into one product. Recognizing the potential of developing mRNA-based cancer vaccines, Merck partnered with Moderna, Roche/Genentech and Sanofi partnered with BioNTech, and Eli Lilly partnered with CureVac. Please see Table 31 for a list of corporate deals for mRNA therapeutics.

Moderna is also developing mRNAs for non-vaccine use. One program in phase 1 is VEGF-A mRNA therapy for cardiovascular diseases such as heart attack. It is given via local injection. Another program is IL12 intratumoral injection for cancer immunotherapy. We note in both cases, local delivery is used.

Table 30 RNA Vaccines in Clinical Development

Company	Drug	Indication	Stage of development
BioNTech	Lipo-MERIT	Melanoma	Phase 1
BioNTech	IVAC mutanome	Melanoma	Phase 1
BioNTech	TNBC-MERIT	Triple-negative breast cancer	Phase 1
CureVac	CV9104	Prostate cancer	Phase 2 failed
CureVac	CV9202 plus radiation	NSCLC	Phase 1
CureVac	CV7201	Rabies	Phase 1
CureVac	CV8102	RSV, HIV, rabies	Phase 1 rabies
CureVac	CV9103	Prostate cancer	Complete
Moderna	mRNA 1851	Influenza H10	Phase 1
Moderna (DARPA funded)	mRNA1388	Chikungunya	Preclinical
Moderna (BARDA funded)	mRNA 1325	Zika	Phase 1/2
Moderna	mRNA1440	Influenza H7	Phase 1
Moderna and Merck	mRNA 4157	Cancer (personalized)	Preclinical
Moderna	mRNA-1647	CMV	Preclinical
Moderna	mRNA-1653	HMPV/PIV3	Preclinical
Argos	AGS-003	RCC	Phase 3 failed
Argos	AGS-003	NSCLC	Phase 2
Argos	AGS-0004	HIV/AIDS	Phase 2
GSK and Vaccine Research Center at NIH	Self-amplifying RNA vaccine	Zika	Preclinical

Source: Laura DeFrancesco, "The 'anti-hype' vaccine" Nature Biotechnology, Volume 35, Number 3 p193-197. March 2017

Table 31 Selected Deals in mRNA Therapeutics

Date	Company	Partner	Indication	Terms	Upfront	Milestones $Mn	Profit sharing
Oct-17	Eli Lilly	CureVac	Cancer	$50mn upfront and €45mn equity investment, up to $17bn milestone to develop 5 cancer	$50; €45	$1700	Royalties
Aug-17	Astra Zeneca	ethris GmbH	Respiratory	€25 million upfront and is eligible for milestones under the 5-year deal	€25	ND	ND
Jan-17	Shire plc	RaNA Therapeutics Inc.	Cystic fibrosis, urea cycle disorders	RaNA acquired Shire's MRT mRNA platform; former Shire employees will move to RaNA	Equity in RaNA	ND	Royalties
Dec-16	Takeda	Arcturus Therapeutics	NASH and other GI disorders	Utilizing Arcturus' wholly-owned therapeutic delivery platform LUNAR™ and UNA Oligomer chemistry for NASH and GI disorders.	ND	ND	ND
Sep-16	BioNTech AG	Genentech Inc. / Roche	Cancer	Partners will develop individualized cancer vaccines, share development costs. BioNTech has an option to co-promote undisclosed programs in U.S. and Europe	$310	ND	Shared for some undisclosed
Jul-16	Moderna Therapeutics Inc.	Vertex Pharmaceuticals Inc.	CF	Three-year deal to discover and develop CF therapies; Moderna will lead discovery; Vertex will lead and fund development and commercialization	$40	$275	Royalties
Jun-16	Moderna Therapeutics Inc.	Merck & Co. Inc.	Cancer	Partners will test individualized cancer vaccines in combo with Merck's Keytruda pembrolizumab; Moderna will lead development through POC after which Merck has option to advance to late-stage development and the companies will share	$200	ND	50/50, Moderna has option co-promote in U.S.
May-16	BioNTech AG	Bayer AG	Veterinary diseases	Undisclosed	ND	ND	ND
Jan-16	Moderna Therapeutics Inc.	AstraZeneca plc	Cancer	Partners will discover and develop two immuno-oncology programs; Moderna will develop through IND; AZ will run early clinical studies and partners will share costs of late clinical development	ND	ND	50/50 in U.S., royalties ex-U.S.
Nov-15	BioNTech AG	Sanofi (Euronext:SAN; NYSE:SNY)	Cancer	Partners will discover and develop up to five cancer immunotherapies; BioNTech has an option to co-promote two products in U.S. and Europe	$60 (A)	$300 per program (up to $15B)	Royalties
Oct-15	Arcturus Therapeutics Inc.	Ultragenyx Pharmaceutical Inc. (NASDAQ:RAR	Rare diseases	Arcturus will discover therapies against two targets; Ultragenyx has option to up to eight more targets and will develop and commercialize resulting products	$10	$156 per program (up to $16B)	Royalties
Jan-15	Moderna Therapeutics Inc.	Merck & Co. Inc. (NYSE:MRK)	Viral infections	Three-year deal to discover and develop antiviral vaccines; Moderna will synthesize vaccines against four viruses; Merck will lead discovery, development and commercialization of up to five products	$100	ND	Royalties
Sep-14	CureVac AG	Boehringer Ingelheim GmbH	Non-small cell lung cancer (NSCLC)	CureVac granted BI exclusive, worldwide rights to CV9202, a Phase I vaccine that codes for six antigens in NSCLC	€35 ($45.3)	€430 ($556.4)	Royalties
Jan-14	Moderna Therapeutics Inc.	Alexion Pharmaceuticals Inc.	Rare diseases	Alexion received 10 product options to develop and commercialize mRNA therapies. Alexion will lead discovery, development and commercialization; Moderna will design and manufacture mRNA	$125	ND	Royalties
Oct-13	CureVac AG	Johnson & Johnson	Influenza	CureVac will develop flu vaccines using Crucell's antigen sequences	ND	ND	ND
Mar-13	Moderna Therapeutics Inc.	AstraZeneca plc	Cardiovascular, metabolic and renal, cancer	Five-year deal to discover and develop therapeutics against cardiometabolic and cancer targets; AZ has option to up to 40 products, will lead development and commercialization; Moderna will design and manufacture mRNA	$240	$180	Royalties
11-Nov	CureVac AG	Sanofi	Infectious diseases	Sanofi has option to prophylactic and therapeutic vaccines against five pathogens; in 2014 exercised first option and extended others	ND	€150.5 ($203.5) per pathogen, up to €752.5 ($1B)	Royalties

Source: Compiled by MHBK/IRD based on public reports and BioCentury data

F. Players in Nucleic Acid Based Therapeutics

Each of the three areas of nucleic acid based therapeutics is dominated by a leading player. The rise or fall in each area is directly reflected by the performance of that leading player. Ionis' strong performance clearly signaled the acceptance of ASOs. The recent strong performance by Alnylam driven by the success of the phase 3 patisiran trial is a validation of siRNA. In the mRNA therapeutics field, it is still early days but leader Moderna has raised an unprecedented amount of private funding and is progressing multiple therapies into the clinic. There is strong "Co-opetition" among players in nucleic acid based drug development. Advances in delivering ASOs have been readily applied to siRNAs. mRNA development will undoubtedly borrow technologies from forerunners of ASOs and siRNAs. Some companies are developing multiple modalities under one roof. For example, Wave Life Sciences is applying its stereopure oligonucleotides to both ASOs and siRNAs. Sometimes companies have come together to start new companies. For example, Ionis and Alnylam pooled their resources together to start microRNA company Regulus. But as technology matures, increasingly companies will compete not only on intellectual property front, but also on commercial front. Alnylam's ATTR siRNA patisiran is a directly competitor to Ionis' ATTR ASO inotersen. Both agents have reported positive phase 3 results. The result seems to favor the hypothesis that once getting into cells, siRNAs could be more potent than ASOs. Industry observers may have expected better safety for ASOs than siRNAs in general and inotersen than patisiran in particular. However it appears the reverse is true in this specific case. Thrombocytopenia and renal observations were cited as a part of the inotersen trial and Ionis' partner GSK exited from the partnership. Patisiran has higher rate of injection site reactions but no other notable severe side effect related to immune response or liver toxicity has been noted.

The number of companies in the ASO and siRNA space has declined over the years. The majority of the financial resources is concentrated at top players (see Table 32). Among private companies, Moderna and BioNTech have vast financial resources. Moderna reportedly has raised $2.2bn in funding since its founding. It reportedly has $1bn in cash on its balance sheet. BioNTech is the largest private biotech in Europe and is majority owned by the family office of pharmaceutical billionaire Andreas Strüngmann.

Companies such as Sarepta, Akcea and The Medicines Company are product companies instead of platform companies. Some mid-sized platform players have gained more financial resources by partnering with other deep-pocketed players. For example, Wave Life Sciences partnered with Pfizer and Arbutus raised $116mn financing from Roivant Sciences.

For smaller companies with less resource, we believe there could be more consolidations. Merging some of the smaller players carries several benefits: (1) bring more technology under one roof to gain more technical capabilities; (2) save on corporate overhead; (3) for some private companies to go public through reverse mergers. We are seeing such deals happening. For

example, Translate Bio (formerly known as RaNA) acquired Shire mRNA Therapeutics platform in January 2017.

Table 32 Selected Players in Nucleic Acid-Based Therapeutics

Company	Technology	Mkt Cap ($mn)	EV ($mn)	Cash ($mn)	Ticker
Alnylam	siRNA	$12,455	$11,657	$948	ALNY
Ionis	Antisense	$6,543	$6,220	$1,011	IONS
Sarepta	Antisense	$3,400	$2,813	$618	SRPT
The Medicines Company (Licensed PCSK9 siRNA from Alnylam)	siRNA	$1,969	$2,403	$209	MDCO
Akcea Therapeutics (Inois spinoff)	Antisense	$1,293	$1,007	$286	AKCA
Wave Life Sciences	Antisense, siRNA	$1,066	$905	$168	WVE
Idera Pharma	Antisense	$364	$299	$65	IDRA
Arbutus Biopharma (fka Tekmira)	siRNA	$245	$169	$88	ABUS
Arrowhead Research	siRNA	$235	$171	$66	ARWR
Silence Therapeutics	siRNA	$186	$146	$39	AIM:SLN
Dicerna	DsiRNA	$158	$158	$76	DRNA
Benitec	ddRNAi	$32	$21	$12	BNTC
Regulus	micro RNA	$99	$47	$71	RGLS
Rxi Pharma	siRNA, antisense	$15	$9	$5	RXII
PhaseRx	mRNA for ERT	$6	$6	$5	PZRX
Arcturus Therapeutics	mRNA; lipid delivery				ARCT
Quark Pharma	siRNA				
Solstice Biologics	siRNA				
Moderna	mRNA				
BioNTech	mRNA				
CureVac	mRNA				
ethris	mRNA				
eTheRNA N.V.	mRNA				
Noxxon	Spiegelmer aptamer				
Translate Bio (fka RaNA Therapeutics)	lncRNAs, mRNA				
MiNA Therapeutics	saRNA				
Acuitus Therapeutics	mRNA delivery				

Source: Compiled by MHBK/IRD based on public reports and data from Capital IQ

V. Conclusions and Future Outlook

Regenerative medicine holds the promise of delivering transformative cure to certain intractable diseases. Traditional pharmaceuticals such as small molecule and protein drugs are often ineffective in treating degenerative diseases. New treatment modalities such as regenerative medicine stand to make a big difference in such difficult conditions. Regulators worldwide have recognized the potential of regenmed and have introduced more friendly regulatory pathways. But instead of lowing bar for everyone, we believe regulators and industry should perhaps raise the bar so more resources can be dedicated to therapies that have the greatest treatment effect. Due to the cost and logistics hurdles, regenmed is not well suited for delivery of incremental benefit. The effect size needs be large to justify the cost.

In this report, we used this yardstick to look for breakthroughs in regenmed. We surveyed three areas. In cell therapy, beyond the amazing advancement of CAR-T therapy and some established areas such as HCSC, wound care and orthopedics, we believe so far the clinical experience has been disappointing. In our view, there needs to be more work to understand the true mechanism of the experimental cell therapy. Perhaps a step in the right direction is tissue engineering. If the cells are further developed into tissues-like structures and then given to patients, there is a higher chance the cells will perform the role envisaged by the drug developer. Such examples include Histogenics and Axogen. Another direction in cell therapy is to use genetically modified cells. CAR-T is a prime example. While most cell therapies in clinical development use adult stem cells or ES derived cells, we believe in the future iPSC will be the predominant cell source. Combining iPSC and genetic engineering may produce the most potent cell therapy.

The incorporation of new AAV-vectors in gene therapy has ushered in a golden era of gene therapy. The 2012 EU approval of Glybera was a major turning point for gene therapy. With the FDA formally put gene therapy under regenmed, gene therapy is the prime example of the transformative potential of regenmed. From neurodegenerative CNS disease, hemophilia, hemoglobinopathy, to genetic-caused eye diseases, gene therapy has generated groundbreaking data, even promising of a cure. Although commercial success has so far been lacking, we believe it is a matter of time before we see the first blockbuster gene therapy product. We believe more big pharma will include gene therapy technology in their drug development platform.

We included in their report a review of nucleic acid based drugs. Although they may not be considered regenerative medicine in the traditional sense, they bear characteristics of advanced therapies and are related to gene therapy. Nucleic acid based drugs have overcome important technical hurdles in recent years. With the success of Spinraza, ASO has been proven to be an effective treatment modality. siRNA development lags behind ASO but the success of patisiran from Alnylam has validated the siRNA approach. We believe although two blockbuster oligonucleotide drugs have been successfully developed, some platform risk (especially regarding siRNA) will linger, which can only be resolved by additional clinical experience.

Following on the heels of oligonucleotides is mRNA therapeutics. mRNA is well suited to produce proteins on demand and has found many applications in vaccine development. However we believe developing mRNA therapeutics is still in early days. Clinical data emerging in the next couple of years will inform us of its potential.

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