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A Survey of Current Landscape in Regenerative Medicine

- Fast Evolving Field Albeit Accompanied by High Risk -

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〈Summary〉

○ Regenerative medicine has tremendous therapeutic potential and may well be the next frontier for medical breakthroughs. Many diseases are poorly served with existing therapeutic modality and are in urgent need for new ways of intervention. With the advancement in iPS cells and adult stem cells, regenmed has made major progresses and may rise to meet the medical needs.

○ However, regenmed field carries high risks – both clinical and financial. On the clinical side, disappointments in the past suggest enthusiasm should be tempered until definite data emerge. Small uncontrolled phase I/II studies are only signal generating, rather than definite proof of concept. Many regenmed companies have short financial runways and thus funding is a bottleneck. The funding environment and valuation for cell therapy companies are much better in Japan than the U.S. and Europe.

○ In terms of therapeutic area, CV disease is the most promising as a number of products are in the mid-late stage development. CNS is a bit early, but several diseases (such as AMD, MS, and Parkinson's disease) seem to be quite amenable to regenmed approach. For wound care and orthopedics, regenmed products haven't become main stream, but some exciting products are in development. Several regenmeds are in early-mid stage studies in autoimmune diseases and diabetes. Combining gene therapy and cell therapy has the promise of curing certain diseases. Finally, cell therapy in cancer is also promising.

○ For pharma R&D, iPS cells are very useful for drug toxicity testing and disease modeling. Therefore, iPS R&D tool providers may have a bright future.

○ In a similar way to the orphan drug industry, we need several successful "high flyers" to catapult the regenmed industry to the center stage of medicine. Therefore, it is critical for leaders to succeed and prosper just as Genzyme blazed the trail in the orphan drug world. Then others will follow.

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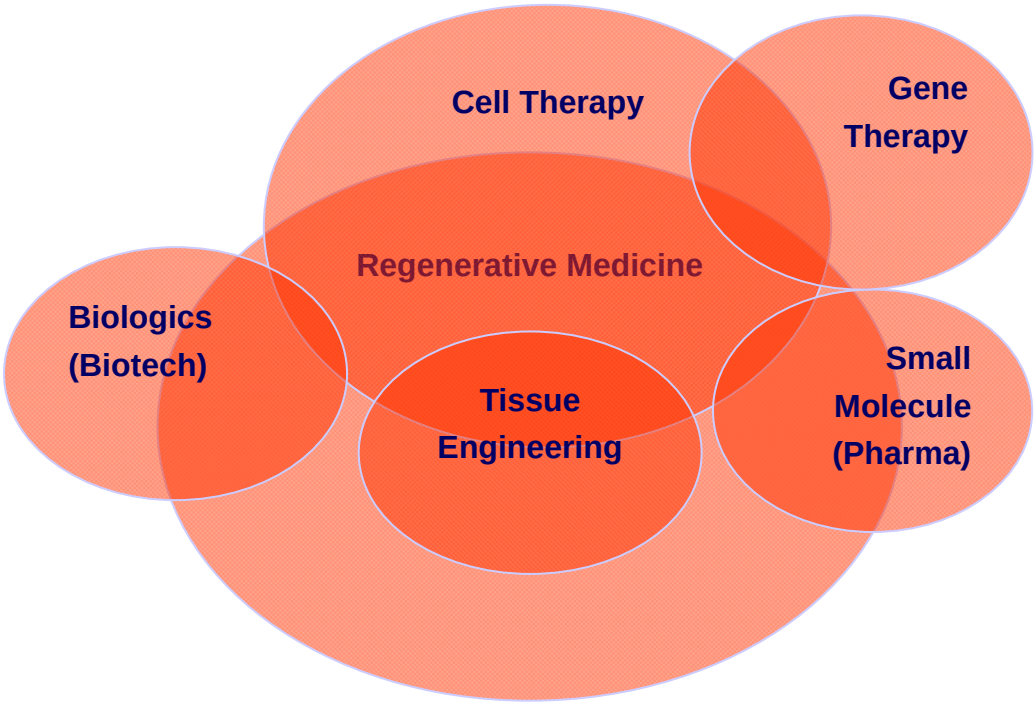
1. Introduction

Regenerative medicine involves using engineered cells, tissues, biomaterial scaffold, growth factors, or combinations of them to help human body augment, repair, replace or regenerate organs and tissues that have been damaged by disease. Regenerative medicine or Regenmed is a very broad, multi-disciplinary field involving stem cells, bioengineering, gene therapy and other cutting edge technologies (see Figure 1). Regenmed represents a whole new dimension of medicine as it holds the promise not only to alleviate the disease burden but to fundamentally repair the damage by replacing or replenishing with healthy cells or tissues.

Figure 1 Scopes of Regenerative Medicine



Source: Compiled by MHBK/IRD based on 2013 Regenerative Medicine State of the Industry Briefing by ALLIANCE for Regenerative Medicine

Cell therapy is a key component of Regenmed. The invention of iPS cells by Dr. Shinya Yamanaka has ushered in a new era in stem cell research. Stem cell field is booming. However, regenmed is not only restricted to stem cells,

recently field has moved away from the notion of introducing cells into the body that would integrate and create replacement tissue, towards using cells or biologics as a means to provide signaling through paracrine effect or direct anti-inflammatory effects. Because of this signaling effect rather than the replacement effect, cells don't need to permanently engraft to deliver the therapeutic benefit. So in this sense, cells function as a drug delivery capsule that contains many potential therapeutic agents whose effects are often not entirely known. In some cases, it may not even be necessary to deliver cells themselves, but instead growth factors embedded on a biomaterial might be enough.

Although regenerative medicine and cell therapy have great potential, the field has had many setbacks and is considered high risk. Oftentimes, cell therapies have promising phase II data that cannot be replicated in phase III studies. One example is Prochymal for GvHD developed by Osiris/Genzyme. The robustness of phase II data of cell therapy is often in question as the trials are typically small, not double-blind, placebo-controlled. In the stem cell field, some companies have gone bankrupt or are close to bankruptcy. Existing companies are often struggling to raise money. Perhaps the rollercoaster experience of stem cell companies can be best illustrated by wound care companies Advanced Tissue Sciences and Organogenesis. Both went bankrupt, and then their products came back to life and now generate annual sales of over $100mn. Dendreon's experience of Provenge is another example of the volatility typically accompanying regenmed companies.

Despite the risky nature of regenmed companies, we believe the field holds great promise long-term. In general, in cardiovascular diseases, regenerative medicine programs are transitioning from phase II to phase III studies. Areas such as heart failure and MI are especially promising. In CNS area, most programs are still in proof of concept (POC) stage. Promising CNS diseases for regenmed include retinal pigment epithelial cells (dry AMD), oligodendrocyte (MS) and dopaminergic neurons (Parkinson's disease). In wound care and tissue repair applications, there are several approved cell therapies for wound care with exciting clinical data being generated. In orthopedic applications, there are commercial products as well as promising programs in development.

In addition to therapeutic applications of cell therapy, iPS or other stem cells can be good tool in pharmaceutical R&D. Having a cell line recapitulating the disease state, i.e., "disease in a dish," is very helpful in screening

compounds for that disease. It may be particularly useful for repurposing existing drugs. iPS-derived cells are also useful in drug toxicity testing. For example, the U.S. FDA has proposed to use assays with iPS-derived cardiomyocytes in lieu of human thorough QT clinical trials to test compounds' cardiotoxicity. Companies focused on iPS cells such as ReproCell in Japan and Cellular Dynamics in the U.S. could benefit from wide-spread use of iPS cells in drug R&D. So we think the near-term winner of regenmed may be the tool suppliers for stem cell research and pharmaceutical R&D.

A. Different Types of Stem Cells

There are several main sources of stem cells (see Table 1).

Table 1 Different Types of Stem Cells

Cell Type	Tissue Source(s)	Cell Potency	Differentiation Potential	Proliferation potential
Pluripotent stem cells				
Human Embryonic Stem Cells (hESCs)	Embryonic	Pluripotent	Theoretically to any cell types	Unlimited
Induced pluripotent stem cells (iPSCs)	Somatic cells (e.g., fibroblast)	Pluripotent	Theoretically to any cell types	Unlimited
Adult stem cells				
Hematopoietic stem cells (HSCs)	Bone marrow	Multipotent	Blood cells	Limited
Mesenchymal Stem Cells (MSCs)	Bone marrow, adipose tissue, umbilical cord blood (UCB), peripheral blood	Multipotent	Bone, cartilage, adipose, muscle, pancreatic beta cells	Limited
Adipose stem cells (ASCs)	Fat tissue	Multipotent	Various	Limited
Neural Stem Cells (NSCs)	Brain, spinal cord	Multipotent	Neurons, astrocytes, oligodendrocytes	Limited

Source: Compiled by MHBK/IRD based on public reports

Human embryonic stem cells (hESCs) have the longest history. The first isolation of embryonic stem cell line was reported in the journal Science by American scientist James Thomson in 1998. Because of their pluripotency (can differentiated into any cells in the body), and ability to divide endlessly, hESCs have vast potential in regenerative medicine. However it has also raised substantial concerns. Firstly, the source of the hESCs is from human embryo, which has led to criticisms on ethical ground and strong federal regulatory oversight. Secondly given its pluripotency and unlimited division potential, there is concern that hESC may continue to grow in an uncontrolled fashion to form cysts and tumors in the body. The dreaded term is teratomas, which are disorganized tumors containing cells from all three embryonic germ layers. Teratomas contain undifferentiated stem cells and are highly malignant. The concern over teratoma is a significant safety roadblock for the clinical development of hESCs. So far, clinical development of hESCs has progressed slowly. In late 2011, due to a lack of adequate funding, hESCs pioneer Geron halted the world's first clinical trial using hESC-derived cells for spinal cord injury and announced its exit from the hESC field. Currently there are only a few remaining companies working on hESCs-derived stem cells, including Advanced Cell Technology

(running the only clinical trial using hESCs-derived RPE cells), BioTime (consolidated IPs of several ESC companies), and California Stem Cell Inc. (developing hESC-derived stem cells for drug research). None of these companies uses hESCs directly in therapies. Rather, they use hESC-derived cells that are already destined to differentiate into certain target tissue. Advanced Cell Technology uses hESCs-derived RPE cells. BioTime's PureStem human embryonic progenitor cells are already destined to differentiate into certain tissues. Presumably, the restricted differentiation potential could afford these therapies with better safety.

With the isolation of human iPS cells from human somatic cells in 2007 and the award of 2012 Nobel Prize to Dr. Yamanaka, iPS cells have emerged as one alternative to hESCs. Like hESCs, iPS cells are also pluripotent, i.e., they can theoretically differentiate into any cell types in the body. Recently, it has been shown in some instances scientists can directly reprogram human somatic cells into other cell types without going through the intermediary iPS state. It is still subject to a lot of scientific debate the similarities and differences between iPS cells and hESCs. As iPS cells don't go through the fertilization process of hESCs, they may have different telomere maintenance, mitochondrial content and genomic imprinting. As iPS cells can be made from diseased tissue, iPS cells are very useful in drug research to recapitulate the disease condition as "disease in a dish." In general, iPS cells can be very useful for drug screening (compound repurposing), in vitro toxicity testing, etc. For the research applications of iPS cells, ReproCell in Japan and Cellular Dynamics in the U.S. have successfully completed their respective IPOs this year.

We can perhaps draw comparisons to other major discoveries in biology in recent years (see Table 2). A comparison to another recent major breakthrough in biology (RNA interference) suggests a cautious approach is warranted. The significance of discovery of RNA interference (RNAi) perhaps can be considered on par with iPS cells. After its discovery, RNAi quickly attracted huge investment from pharma with Merck and Roche leading the charge. But a few years later, Roche exited from the field and Merck shut down its dedicated RNAi R&D facility. The applications of iPSCs in therapeutics are still evolving and are in early phase. In comparison, we believe in the near-term iPSC technology has big potential in research field in a similar fashion to the PCR technology (see Table 2), which has created billions of dollars of economic value in the research tool market.

Table 2 Comparing iPS to Other Major Breakthrough in Biology

Technology	Year of Nobel Prize Award	Deal Year	Deal Description	Deal Result
PCR and site-directed mutagenesis	1993	1991	Roche licensed the PCR technology from Cetus Corp. for $300mn upfront payment and additional royalties;	Roche received economic return of many folds over its initial investment
RNA interference	2006	2006	Merck acquired Sirna for $1.1bn.	Merck shut down RNAi facility in 2011.
		2007	Roche agreed to pay Alnylam up to $1bn with $331mn upfront for the non-exclusive license of its RNAi technology.	Roche terminated its effort to discover RNAi based therapy in 2010.
iPS Cell	2012			

Source: Compiled by MHBK/IRD based on public information

Developing iPS cells for therapeutic use is still early. The benefit of using iPS cells in the clinical is no-brainer – unlimited supply, minimal immune rejection as it is an autologous therapy, etc. However, there are many open questions regarding the genetic engineering involved in the reprogramming process and the resulting iPS cells. For example, some studies have found a high mutation rate in iPS cells, often in oncogenes and tumor suppressor genes, thus raising the risk of cancer. The pluripotent nature of iPS cells also raises cancer concern. Researchers have to make sure their cells derived from iPS cells are pure and don't have further differentiation potential. Teratoma is the number one risk factor in iPS cells just as it is for ESCs. There are also concerns over epigenetic memory of the reprogramming as DNA methylation patterns are not reprogrammed. Another potential problem is the different genetic imprinting in female iPS cells. Despite these concerns and many unanswered questions, the field has advanced to approach clinical testing of iPS cells in several diseases. A number of iPS-cell derived therapies are in preclinical development (see Table 3). Recently a panel of the Japanese Ministry of Health, Labor and Welfare gave a green light to clinical research involving iPS cells. Japan's government-backed research institute Riken has just started the world's first clinical study using iPS cells for the treatment of age-related macular degeneration. For the treatment protocol, skin cells will be collected from patients, induced into iPS cells, reprogrammed into RPE cells, grown into a cell sheet and then implanted into patients' retina. A Riken venture company Retina Institute Japan will try to develop and eventually commercialize iPS-derived therapy for AMD. Another Japanese company Megakaryon Corporation is developing iPS-derived platelets. The U.S. company Advanced Cell Technology (ACT) is also developing iPS

cell-derived platelets in the pre-IND stage. Platelets are believed to be a low risk use of iPS cell technology because they don't have nuclei and can be irradiated to destroy any remaining DNA. Thus, there is less risk to develop tumors. Some researchers are developing iPS cell-derived dopaminergic neurons for Parkinson's disease, oligodendrocyte precursor cells for multiple sclerosis, and Keratinocytes for a rare skin disease called RDEB (see Table 3).

Table 3 Selected iPS cell-based therapy initiatives

Institution	Cell Type	Disease indications	Current Stage
Advanced Cell Technology	Megakaryocytes (for platelets)	Refractory thrombocytopenia, leukemia, aplastic anemia	Pre-IND
RIKEN (Japan)	Retinal pigment epithelium	wet Age-related macular degeneration	Japan Health Ministry Panel gave okay to start clinical trial
Stanford University	Keratinocytes	Recessive dystrophic epidermolysis bullosa (RDEB)	Pre-IND stage; clinical trial could begin in mid-2014
Kyoto University with Megakaryon Corp. (Japan)	Megakaryocytes (for platelets)	Thrombocytopenia with leukemia, or requiring bone marrow or cord blood transplantation; cancer	Phase 1/2 planned for 2014 or 2015
University of Rochester	Oligodendrocyte precursor (OP) cells	Multiple sclerosis	Planning 2015 trial using tissue-derived cells; later will test human iPS cell-derived OP cells
NIH	Dopaminergic neurons	Parkinson's disease	Preclinical; IND filing in late 2014 possible
Kyoto University (Japan)	Dopaminergic neurons	Parkinson's disease	Clinical trial could being at end of 2015
Bascom Palmer Eye Institute, University of Miami	Retinal ganglion cells	Glaucoma & other optic neuropathies	Moving into GMP production, preclinical toxicology studies
University of Minnesota	Keratinocytes and hematopoietic grafts	RDEB	Preclinical animal models
Instituto Leloir (Argentina)	Dopaminergic neurons	Parkinson's disease	Proof of concept
Columbia University; with New York Medical College and Stony Brook Medicine	Three-dimensional skin equivalents from fibroblasts and keratinocytes	RDEB	Proof of concept

Source: Compiled by MHBK/IRD based on Ken Garber, Nature Biotechnology June 2013

In the stem cell field, adult stem cells such as mesenchymal stem cells (MSCs) have made big strides in therapeutic applications. The Australian company Mesoblast demonstrated MSCs don't induce severe immune reactions if given allogeneically. Allogeneic delivery of stem cells is very important in the industrialization of stem cell therapy as autologous therapy involves cumbersome procedures that are often limiting the wide adoption of such therapy. MSCs can be expanded in vitro in large numbers and packaged "off-the-shelf" to deliver to patients. Thus manufacturing will be akin to traditional pharmaceutical manufacturing and gross margins will be similar as well. The vast majorities of current stem cell therapies involve adult stem cells such as MSCs.

Regenerative medicines in different stages of development

According to Alliance for Regenerative Medicine (ARM), there are 250 companies developing cell or tissue-based therapies. Top 15 regenerative medicine products generated $460mn sales in 2010, $730mn sales in 2011 and $900mn sales in 2012. According to Stem Cell Summit 2012, sales of regenerative medicine are expected to surpass $6bn in 2020. Most currently marketed cell therapies are used for wound care and orthopaedic applications (see Table 4). However, the bigger opportunities lie in cardiovascular and neuronal applications. In early-mid stage development (see Table 5 and Table 6), there are many therapies targeting broad therapeutic areas with large commercial potential:

- Cardiovascular diseases: Myocardial Infarction, Congested Heart Failure, Vascular Disease/Critical Limb Ischemia.
- Neurological Injury & Diseases: Stroke, Amyotrophic lateral sclerosis, Parkinson's disease, Multiple Sclerosis, Cerebral Palsy, Spinal Cord Injury.
- Ocular Diseases: Age-related Macular Degeneration, Stargardt's Macular, Retinitis Pigmentosum, Glaucoma.
- Cancer: solid tumor and haematological malignancies.
- Inflammatory diseases: diabetes, IBD, GvHD, RA, Lupus.
- Renal disease: acute kidney injury, choric kidney disease.

Table 4 Commercially Available Cell Therapy Products

Company Name	Products	Description	Indication	Market Cap ($mn)
Allosource	AlloStem	Stem cell bone growth substitute	Bone graft	
Alphatec Spine	PureGen	Osteoprogenitor Cell	Spine repair	
Altrika	MySkin, CryoSkin	Matrix with live cells	Wound care	
BioDlogics	BioDfence patch	Allograft derived from amniotic tissue	In vivo wound covering	
Avita	ReCell Spray-On Skin	Autologous cell	Wound care	
BioDlogics	BioDfactor, BioDfence	Allograft derived from human placenta	Wound care	
Terumo (Harvest Technologies)	Smart PReP platform	Platelet rich plasma (PRP)	Orthopedics, cosmetics,	$9,025
Cytomedix	Platelet rich plasma (PRP)	AutoloGel; Angel cPRP system	Orthopedics, Wound care	$38
Dendreon	Provenge	Dendric cell therapy	Prostate cancer	$404
Fibrocell	LAVIV	Isolate, purify and regenerate autologous fibroblast for reinjection	Cosmetic	
Genzyme / Sanofi	Carticel, Epicel	Autologous chondrocytes,	Cartilage repair, Wound care	
Nuvasive	Osteocel (bought from Osiris for ~$90mn in 2008)	Allograft bone matrix retaining MSCs and osteoprogenitors	Orthopedics	$1,104
Kinetic Concept	GRAFTJACKET	Human dermal tissue graft	Wound care such as DFU	
Organogenesis	Apligraft; GINTUIT	Bilayered tissue-engineered skin; allogeneic cellular sheet	Venous ulcer, diabetic foot ulcer (DFU); Oral soft tissue regeneration	
Osiris Therapeutics	Grafix wound healing matrix; Ovation cellular repair matrix	Three-dimensional matrix that contain MSC and other cells	Wound care, bone repair	$570
Orthofix	Trinity Evolution	Allograft with stem cells	Orthopedics	$382
Shire	Dermagraft	Dermal tissue engineered skin	Diabetic foot ulcer	£13,170
TiGenix	CondroCelect (not approved in the U.S.)	autologous chondrocytes	Cartilage and osteocondral lesions	€ 37

Source: Compiled by MHBK/IRD based on list from "2013 Regenerative Medicine State of the Industry Briefing" by ALLIANCE for Regenerative Medicine Public Company Reports.
Note: Blue = Orthopedics, Pink=wound care, No color = other

Table 5 Regenerative Products in Mid- to Late- Stage Clinical Development

Company Name	Technology	Products	Indication	Market Cap ($mn) if Public
Allocure	MSC	AC607	Acute kidney injury	
Avita Medical	ReCell® Spray-On Skin	Autologous cell therapy	Skin defects (wound, cosmetics)	$36
Aastrom	Autologous bone marrow derived stem cell		Critical limb ischemia (CLI) and dilated cardiomyopathy (DCM).	$10
Athersys	Multipotent adult progenitor cells (MAPC)	MultiStem®	IBD (ph II partnered with Pfizer), Ischemic stroke (ph II), GVHD, AMI	$103
Amorcyte (NeoStem)	Autologous bone marrow derived, CD34 positive selected stem cell product	AMR-001	AMI (phase II)	$178
Avita Medical	Autologous cell therapy	ReCell® Spray-On Skin	Skin defects (wound, cosmetics)	
AxoGen	(ECM) processed from human peripheral nerve tissue.	Avance® Nerve Graft	peripheral nerve discontinuities	
Cytori	Adipose derived stem and regenerative cells (ADRCs)	Celution System	Refractory heart failure, AMI, vascular delivery, Breast recon and soft tissue	$145
Harvard Apparatus Regenerative Technology Inc.	Tissue / organ regeneration	InBreath hollow organ bioreactor, scaffold	Regenerative trachea for transplantation	
Healthpoint (S&N)	Alogeneic living human cell suspension	HP802-247	Venous Leg Ulcers	
ISTO Technologies	Juvenile cartilage cell	DeNovo® ET	knee cartilage repair	
Mesoblast	Adult mesenchymal precursor cells (MPCs)	Revascor	CV and Neurovascular (partnered with Teva), Spine lumbar fusion, Degenerative disc disease (DDD), Diabetes	AUD 1,739
Osiris	Preparation of mesenchymal stem cell for direct injection into knee	Chondrogen	Meniscus regeneration; OA	$570
TiGenix	Expanded allogeneic adipose-derived stems cells (eASCs)	Cx601 in Phase III; Cx611 in Phase IIa; Cx621	Perianal fistulas in Crohn's disease, RA, autoimmune disease	€ 37

Source: Compiled by MHBK/IRD based on list from "2013 Regenerative Medicine State of the Industry Briefing" by ALLIANCE for Regenerative Medicine Public Company Reports.
Note: Blue = Orthopedics, Pink=wound care, Green= CV, Yellow=neuronal, No color = other

Table 6 Regenerative Products in Early- Stage Clinical Development

Company Name	Technology	Products	Indication	Market Cap ($mn) if Public
Advanced Cell Technology	hESC, iPS	Retinal pigment epithelium program	Stargardt's Macular dystrophy (ph I), dry AMD (ph I)	$179
Capricor	Cardiac stem cells	Cardiosphere-derived cells (CDCs)	MI (ALLSTAR phase I/II trial using allogenic cell under way)	
Cellerant	Myeloid Progenitor Cells	CLT-008	Engraftment in cord blood transplants (ph I), neutropenia (ph I)	
DiscGenics	Human disc derived stem cells		Degenerative disc disease	
Fate Therapeutics	Ex vivo and In vivo modulation of stem cells; iPCS	ProHema (cord blood derived stem ell)	Hematological malignancies	$128
InVivo Therapeutics	Polymer-based device for SPI		Spinal cord injury	$120
Priuristem	PLX (PLacental eXpanded) cells	PLX-PAD	PAD (Critical limb ischemia, Intermittent claudication)	$195
Q Therapeutics	Glial progenitor cells	Q-cell	Multiple sclerosis, ALS	
Pathfinder Cell Therapy	Pathfinder Cells ("PCs")		Diabetes, CV, renal disease	$2
ReNeuron	CTX neural stem cell line	ReN001	Stroke	
Tengion	Tissue enginerring using autologous progenitor cells	Neo-Urinary Conduit Neo-Kidney Augment	Cystectomy patients, CKD patients	$2
Tissue Genesis	Adipose-derived stem cell	Adipose-derived stem cell-coated vascular graft	PAD	
StemCells	Human neural stem cells	HuCNS-SC	Spinal cord injury, PMD, AMD	$73
ViaCyte	Proprietary pancreatic endoderm cells, delivery system	VC-01	Diabetes	
Cardio3 Biosciences Juventas	The Cardiopoiesis Platform (adult stem cell into heart cells) Stromal cell-Derived Factor-1 (SDF-1)	C3BS-CQR-1; C3BS-GQR-1 (protein) JVS-100	CHF; AMI Heart failure and critical limb ischemia	

Source: Compiled by MHBK/IRD based on list from "2013 Regenerative Medicine State of the Industry Briefing" by ALLIANCE for Regenerative Medicine Public Company Reports.
Note: Blue = Orthopedics, Green= CV, Yellow=neuronal, No color = other

B. Financing for Regenerative Medicine Companies

Except for a few leading companies (e.g., Mesoblast, Osiris), financing often seems to be a struggle for regenerative medicine companies. Poor returns in the past remind investors of the significant downside in investing behind novel but yet unproven regenerative medicine technologies. Of the over 70 biotech companies that have gone public on NASDAQ since 2008, on average share has gone up by almost 60% post IPO. By our account, there are five regenmed companies that completed IPOs in this period – Bioheart, Tengion, Bluebird bio, Cellular Dynamics, and Fate Therapeutics. Bioheart has lost almost all its value since its IPO in 2008. Tengion has lost almost 90% of its value since the IPO in April 2010. Bluebird Bio has done well since IPO although its focus on orphan drugs and unique gene therapy approach are big contributing factors to its strong share performance. Cellular Dynamics completed its IPO in late July and is up ~40% from the

IPO price. It is focused on services instead of developing therapeutics. Fate Therapeutics had to significantly cut IPO price from the original $14-16 per share to $6 per share to complete the IPO.

Another notable phenomenon is the big difference in valuation between western and Japan listed regenerative medicine companies. ReproCell and Cellular Dynamics are direct competitors in the iPS cell market. These two companies even went public around the same time (see Table 7). However the difference in aftermarket performance has been huge. ReproCell share traded at 18,300 yen at the close in Tokyo on June 28th, 472 percent above its IPO price of 3,200 yen. The shares went untraded for two days after listing on Osaka's JASDAQ exchange on June 26 after buy offers outnumbered sell orders by as much as 10-to-1. Meanwhile Cellular Dynamics had a first-day stock return of -21%. Although since the IPO date, the valuation of these two companies has converged somewhat, the difference in valuation is still huge with ReproCell having a valuation of more than three times that of Cellular Dynamics. We note the stem-cell driven valuation jump in Japan is not limited to ReproCell. The pharmaceutical company Dainippon Sumitomo had also experienced share jumps due to its acquisition of U.S. biotech Boston Biomedical, which developed a cancer stem cell targeted therapy. The implication of this difference in public appetite for regenerative medicine companies is perhaps for Japanese companies to use the cheaper financing (with much lower cost of capital) to buy U.S. stem cell assets. On the other way, some western stem cell companies may consider dual listing in Japan to tap into the groundswell of investor interest.

Table 7 Difference in Valuation between Two Competitors in iPS Cells

Company Name	Listing exchange	Market Cap ($mn) if Public	IPO Date	IPO Price	Amount raised ($mn)	Current share price	2012 Sales	Share performance since IPO
ReproCell	JASDAQ	$894	6/26/2013	¥3,200	¥4,149	¥1,982	$4.20	-38%
Cellular Dynamics	NASDAQ	$268	7/25/2013	$12.00	$46.2	$18.11	$6.58	51%

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

C. M&A and Corporate Alliances for Regenerative Medicine Companies

Because of the harsh financial environment, many M&As in regenerative medicine / cell therapies involved consolidation of technology platforms (see Table 8). In terms of big pharma's interest, so far only a few large pharma have tentatively tapped into this field. These pioneers include Shire, Teva (through Cephalon), Celgene, Pfizer etc. We believe to kindle wide-spread enthusiasm from big pharma for regenmed, there has to be clear commercial successes. One precedent is orphan drug biotech industry. 10-15 years ago, no big pharma is interested in orphan drugs. But with companies such as Genzyme, Shire, BioMarin and ViroPharma demonstrating the commercial potential of orphan drugs, big pharma have turned around. Sanofi acquired Genzyme for $20bn in 2011. Currently almost every big pharma is interested in orphan drugs and orphan drug companies often enjoy rich valuations. For regenmed field to fully blossom, it requires the successes of leaders such as Mesoblast, which has generated the most impressive data across many therapeutic areas. If Mesoblast can show similar efficacy in phase III studies, it will be able to bring significant profits to it and its partner Teva. The commercial success will then propel many other pharma companies to look at M&As for the remainder of the regenmed field.

Table 8 Notable M&A and Alliance Deals in Regenerative Medicine

Acquirer	Target	Date	Amount $mn)	Highlights
ThermoGenesis	TotipotentRx	Jul-13	12.5mn shares of ThermoGenesis (~$18.6mn)	Merger of ThermoGenesis (a manufacturer of systems for processing cells and tissues) and TotipotentRx (a developer of formulations for cell-based therapy)
Celgene	Tengion	Jul-13	$15mn upfront payment for certain options	$15mn upfront for right of first negotiation on Tengion's Neo-Kidney Augment program, exclusive option to acquire certain assets and warrants on stock.
Smith & Nephew	Healthpoint Biotherapeutics	Nov-12	$782mn	S&N acquired all assets from this wound care company which markets Collagenase Santyl® ointment and have in phase III development of a novel cell therapy, HP802-247.
Shire	Pervasis	Apr-12	$2.5mn upfront plus a potential $169.5mn earn-outs	Shire receives phase II Vascugel (endothelial cells on a matrix used to improve arteriovenous access grafts for hemodialysis patients with end-stage renal disease).
Cytomedix	Aldagen	Feb-12	$16mn upfront, plus ~$0.25 in potential earn-outs	Cytomedix receives three early-stage programs based on use of autologous stem cells identified by the enzymatic surface marker ALDH. Earn-outs tied to success of phase II ALD401 in ischemic stroke.
Neostem	Amorcyte	Jul-11	$10mn	Neostem receives the autologous bone marrow-derived AMR001, a CD34 and CXCR4 positive selected stem cell therapy designed to preserve heart muscle function post-AMI, then set to enter phase II.
Shire	Advanced Biohealing	May-11	$750mn	Shire receives the approved product Dermagraft (fibroblasts for diabetic foot ulcers) as well as other wound healing assets.
TiGenix	Cellerix	Feb-11	$88mn	Merger of two cell therapy-oriented firms, bringing orthopedics - oriented TiGenix adipose tissue-derived stem cell programs for immunological diseases and treatment of fistulas.
Astellas	Cytori	Dec-10	$10mn equity investment	$10mn investment in equity at a premium price in return to option and observation rights
Teva (Cephalon)	Mesoblast	Oct-10	$130mn upfront for licensing, $220mn for 20% equity stake, $1.7bn in regulatory milestones	Cephalon (now Teva) licensed global commercial rights of mesenchymal precursor stem cell (MPC) therapies for cardiovascular and CNS diseases, hematopoietic stem cell transplantation for cancer.
Osiris	Genzyme	Nov-08	$130mn upfront, up to $500mn development and regulatory milestones, up to $250mn sales milestones	Licensed commercial rights to Prochymal and Chondrogen outside of U.S. and Canada

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

2. Regenerative Medicine Players by Therapeutic Focus

With active research in many clinical applications of regenerative medicine, which area is more likely to have breakthroughs? In this section we will explore major clinical applications of regenerative medicine. As this is pretty much still an evolving field, we are only seeing tentative signs of clinical promise. Definite proof of clinical value can only come from well-designed phase III studies.

A. Cardiovascular – Exciting Cell Therapies Approaching Critical Stage of Development

Many companies are developing regenerative medicine for cardiovascular diseases such as congested heart failure, myocardial infarction, vascular disease/Critical Limb Ischemia, etc. There are huge unmet medical needs in cardiovascular disease. CV ailment is the most prevalent disease in the world. It is estimated that in the U.S. one in four people have cardiovascular disease and the prevalence will increase to one in three people by 2025 due to the aging population. CV conditions such as heart failure have heavy disease burden and economic cost. There are over six million people in the U.S. with heart failure. Heart failure patients admitted to hospitals have high readmission rate (half will be readmitted within 6 months) and poor life expectancy (one third will die within a year). Pharmacotherapy for heart failure is largely ACE inhibitors, which is very inadequate. There is no new drug approved for heart failure for the last twelve years and the current drug pipeline doesn't offer much hope either. Treating heart failures with medical devices such as heart pumps is expensive and has complications. So there is a particularly high unmet medical need for heart failure. Fortunately a number of companies are developing regenerative medicine for this dire condition. As few good options exist for severe heart failure patients, as a new modality, cell therapy offers new promise. Already we are seeing some early signs of efficacy of cell therapy in heart failure.

For heart attack (myocardial infarction), there are a million cases of heart attacks in the U.S. per year. There is highly unmet medical need to help patients with MI to recover damaged heart muscle and to regain full heart function.

There are variations in the technology employed for CV diseases – sources of stem cell, autologous vs. allogeneic (Capricor is making a transition from

autologous to allogeneic); intracoronary delivery (infused in the coronary artery such as Capricor) vs. intramyocardial injection (injected to the heart muscle often by NOGA Myostar catheter); delivery of highly purified cells or a mixture of cells (Mesoblast uses a homogeneous cell population for therapy while companies such as Aastrom and Cytori administer a mixture of cells). Stem cell therapies have shown some encouraging albeit early clinical efficacy in CV diseases, particularly in heart failure and MI. Several different sources of stem cells being developed for cardiovascular diseases have shown promising results (see Table 9).

Table 9 Examples of Different Stem Cells Being Developed for CV Conditions

Types of Cell	Indication	Trade (company) name	Year reported	Data Summary
Autologous bone marrow-derived mononuclear cells (BMMNCs)	AMI		2011	Intracoronary delivery prevents remodeling after AMI. BMMNC also reduced the incidence of death, recurrent MI and stent thrombosis.
Autologous BMMNCs	AMI		2011	5-year results of the TOPCARE-AMI trial showed sustained left ventricular ejection fraction improvement.
Autologous BMMNCs	Chronic ischemic cardiomyopathy		2012	Phase II FOCUS-CCTRN trial investigated the efficacy of transendocardial delivery of BMMNCs in patients with chronic ischemic cardiomyopathy. Exploratory analyses showed an improvement in LVEF was associated with bone marrow CD34+ and CD133+ progenitor cell counts.
Autologous BMMNCs	Chronic ischemic cardiomyopathy		2011	TAC-HFT trial showed transendocardial delivery of MSCs or BMMNCs led to improved cardial contractility and decreased infarct size.
Autologous bone marrow-derived CD34+ stem cells	AMI	AMR-001 (Neostem)	2011	A small, dose-escalation study post MI reported improved perfusion and infarct size reduction, which is correlated with the quantity and mobility of the infused CD4+ cells.
Adult mesenchymal precursor cells (MPCs)	Heart failure	Revascor	2011	In a 60-patirnt trial, Major Adverse Cardiac Events (MACE) were significantly reduced in Revascor-treated patients over 22 months follow-up (p=0.036). Cardiac mortality was also significantly reduced.
Bone marrow-derived allogeneic MSCs	AMI	Prochymal (Osiris)	2011	Infusion within 7 days of acute MI significantly reduced cardiac hypertrophy, stress-induced ventricular arrhythmia, heart failure and rehospitalization.
Autologous and allogeneic bone marrow-drived MSCs	Ischemic cardiomyopathy		2012	The POSEIDON trial compared autologous and allogeneic bone-derived MSCs in patients with ischemic cardiomyopathy. Both cell types are safe and demonstrate potential regenerative bioactivity. The study is considered a general endorsement for the benefits of allogeneic MSC.
Autologous cardiac-derived stem cells that express c-kit.	Heart failure	Cardiac stem cells	2011	Phase I SCIPIO trial demonstrated c-kit+ CSC is safe and effective at improving left ventricular systolic function and reducing infarct size in patients with chronic ischemic cardiomyopathy.
Cardiosphere-derived cells	AMI	Cardiosphere-derived cells (Capricor)	2012	Phase I CADUCEUS trial showed a reduction in scar mass (28% by 6 months and 42% by 12 months) and an increase in viable heart mass, regional contractility and regional systolic wall thickening at 6 months after cell therapy (and 1.5-3 months after MI).
Adipose tissue-derived MSCs	AMI	ADRCs (Cytori)		A phase II study of autologous adipose-derived stem and regenerative cells via intracoronary delivery in AMI patients (ADVANCE study) was initiated in September 2012, with data available as early as YE 2015.
Adipose tissue-derived MSCs	Ischemic heart disease	MyStromalCell		The MyStromalCell trial is currently ongoing. It is a randomized, double-blind, controlled study investigating VEGF-A-stimulated adipose tissue-derived MSCs.

Source: Compiled by MHBK/IRD based on Ivonne H Schulman and Joshua M Hare, “Key developments in stem cell therapy in cardiology” in “World Stem Cell Report 2012.”

Specifically, a number of companies are developing stem cell therapies for cardiovascular diseases (see Table 10).

Mesoblast

Mesoblast is the leader in regenerative medicine. It is the company to watch to gauge the overall status of the industry. It has leading clinical programs in multiple therapeutic areas. Mesoblast has demonstrated encouraging clinical data in four programs – heart failure, spinal disc repair, spinal fusion and bone marrow transplants. In addition, it has generated encouraging efficacy in animal models for diseases such as diabetes and rheumatoid arthritis. The company is pursuing development of its MPC (mesenchymal precursor cell) technology for a dozen indications. Mesoblast was founded in 2004 based on technology from South Australia's Hanson Institute to isolate adult mesenchymal precursor cells using magnetic-activated cell sorting with MPCs' surface markers. Mesoblast showed importantly that its MPCs don't trigger immune response when given allogeneically. Like other cell therapy, the precise mechanism of action for MPCs is unknown and is likely to be pleiotropic. Consistent with current understanding of cell therapies, the mechanism of MPCs is unlikely to be dependent upon them permanently engrafting and functioning as replacement cells. Rather, MPCs are likely to carry out their therapeutic benefits through paracrine, anti-inflammatory, or other signaling effect.

As Mesoblast is an Australia-based company, it was not well known in the U.S. until the U.S. pharma company Cephalon signed a major deal with Mesoblast in December 2010. In that deal, Cephalon paid $130mn upfront payment and made a $220mn equity investment (for a 20% stake) in exchange for worldwide rights in cardiovascular and neurological diseases. In October 2011, Teva acquired Cephalon. Following a pipeline review in December 2012, Teva reaffirmed its commitment to the Mesoblast alliance. Because of the rich licensing deal with Cephalon, Mesoblast has been well funded. To further build a cash war chest, in March 2013, Mesoblast raised AUD$170mn via a private placement of its share, which was an unheard-of amount in the regenerative medicine industry.

Of all the clinical programs Mesoblast is running, the most impressive data for the commercially most significant indication is generated for its Revascor MPC program in heart failure. Revascor is a single-dose of MPCs injected to the heart via myocardial catheter. Mesoblast conducted a 60-patient, randomized, placebo-controlled phase II trial for CHF. Extensive data was presented at American Heart Association meeting in November 2011. In the study, Revascor elicited minimal host immune

reactions. Major Adverse Cardiac Events (MACE) were significantly reduced in Revascor-treated patients over 22 months follow-up (p=0.036). MACE risk over time was reduced by 78% in Revascor-treated patients vs. controls (p=0.011), with 60-90% risk reduction seen at every MPC dose. Cardiac mortality was significantly reduced in Revascor-treated patients compared with controls over a mean follow-up of 22 months (2% vs 20%, p=0.02). Highest dose of Revascor™ completely prevented any deaths or episodes of heart failure hospitalization after three years follow-up, while 30-40% patients on placebo experienced events. Revascor also demonstrated improvements in cardiac remodeling and patients' daily function in terms of longer 6-minute walk.

Based on the impressive data in phase II study, Teva has recently initiated a 1,700-patient phase III trial in CHF with primary end point being reduction in MACE rate and hospitalization. If Teva can replicate the phase II data in phase III, Revascor could become a multi-billion dollar product. Teva will have an interim look at the efficacy data in 2H 2014. The final result of the study is likely not expected until 2016 or later.

Terumo (Harvest Technologies)

Terumo's U.S. subsidiary Harvest Technologies is developing autologous BMAC (bone marrow aspirate cells) for multiple cardiovascular conditions. It is running a phase III pivotal study in critical limb ischemia with final data expected likely in 2015. The study will enroll 210 patients in 25 centers. Patients will be randomized 2:1 for BMAC and placebo. BMAC has accumulated the most clinical experience among cell therapies for cardiovascular conditions (it has been given to over 200 patients around the world). It has generated promising results in multiple phase II trials. Beyond CLI, Terumo is also running a phase I studies in heart failure and enhanced coronary artery bypass grafting (CABG).

Capricor

Capricor is developing Cardiosphere Derived Cells/CDCs for post MI recovery and heart failures. CDCs are harvested autologously from endomyocardial biopsy, and then grown to the therapeutic dose. CDCs are delivered via intracoronary artery infusion to patients. CDCs are not cardiomyocytes and they disappear from the heart after certain period of infusion. They are likely to exert the function by recruiting stems cells to the infarct site. In a small clinical trial named CADUCEUS published in the February issue of *Lancet*, infusing these cells significantly decreased scar

size and generated new myocardium at six months in post-MI patients. Recognizing the cumbersome nature of autologous therapy, Capricor is transition to an allogeneic approach and is running a phase I/II trial in post MI patients to recapitulate what it found in the CADUCEUS trial with allogeneic CDCs. It has been found that these allogeneic cardiac stem cells are very easy to expand in vitro. Capricor is also starting a phase I trial in heart failure. If the post MI trial is successful, Capircor is likely to partner with a large company for phase III program in the post MI setting. The trial could begin in 2016 with 2-year MACE as the endpoint.

Cytori is developing autologous adipose-derived cells for cardiovascular diseases. Cytori is different from other cell therapy companies in that it doesn't manufacturer the cells directly. Rather it sells the instrument (called Celution) and consumables for harvesting and processing adipose-derived stem and regenerative cells (ADRCs). ADRCs contain a large number of different cell types including adult stem cells, endothelial progenitor cells, leukocytes, endothelial cells, and vascular smooth muscle cells. Cytori is running a 45-patient U.S. phase II study (ATHENA) in chronic myocardial ischemia with data expected as early as late 2013. If the data is positive, Cytori will run a phase III study to support its PMA application. Cytori is running a 216-patient pivotal study (ADVNACE) in Europe for acute MI.

Aastrom

Aastrom also 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 II a study, Ixmyelocel-T is delivered either through intramyocardial delivery to the myocardium via thoracotomy or through endocardial injections delivered via NOGASTAR® endomyocardial catheter. In both delivery routes, safety was found to be similar to the control group. 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. Aastrom is currently conducting a phase II study in ischemic-DCM patients. Aastrom has discontinued the development of Ixmyelocel-T for critical limb ischemia (CLI).

Amorcyte, a subsidiary of Neostem, is developing autologous bone marrow derived, CD34 positive stem cell therapy AMR-001, in a phase II study for the prevention of major adverse cardiac events following acute myocardial

infarction (AMI). In an early phase I study, AMR-001 showed good efficacy.

Athersys is developing MultiStem (allogeneic stem cell obtained from bone marrow) for AMI. A 150-patient phase II trial is ongoing.

Table 10 Stem Cell Products Developed for CV Indications

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage (most adv. Program)	Market Cap ($mn) if Public
Mesoblast	Revascor	Adult mesenchymal precursor cells (MPCs)	Allogeneic	CV (CHF, AMI, Chronic angina) and Neurovascular (both partnered with Teva), T2DM, Spine lumbar fusion, eye disease, bone marrow transplant	III (CHF)	AUD 1,739
Terumo (Harvest Technologies)	BMAC	Bone marrow aspirate cells	Autologous	Critical limb ischemia (CLI), Heart failure, enhanced CABG surgery.	Ph III (CLI); Ph I (CHF)	$9,025
Cytomedix	ALD-301; ALD-201	ALDHbr bone marrow stem cells	Autologous	Critical limb ischemia (CLI); Ischemic heart failure	II	$38
Cytori	Celution System	Adipose derived stem and regenerative cells (ADRCs)	Autologous	Acute Myocardial Infarction, Refractory heart failure due to chronic myocardial ischemia, vascular delivery, Breast recon and soft tissue	II (U.S. CHF); III (Europe, AMI)	$145
Aastrom	Ixmyelocel-T	Autologous bone marrow derived stem cell	Autologous	Heart failure - dilated cardiomyopathy (DCM).	II	$10
Amorcyte (NeoStem)	AMR-001	Autologous bone marrow derived, CD34 positive selected stem cell product	Autologous	AMI (phase II)	II	$178
Athersys	MultiStem®	Multipotent adult progenitor cells (MAPC)	Allogeneic	AMI	II in 2014	$103
Capricor	Cardiosphere-derived cells (CDCs)	Cardiac progenitor cells	Autologous / Allogeneic	MI (ALLSTAR phase I/II trial using allogenic cell under way)	I/II	
Cardio3 Biosciences	C-Cure; C3BS-CQR-1; C3BS-GQR-4	The Cardiopoiesis Platform (adult stem cell into heart cells)		CHF; AMI	II	$81
Cesca	SurgWerks	Autologous cells isolations from bone marrow or peripheral blood	Autologous	CLI, AMI	I	$17
Juventas	JVS-100	Stromal cell-Derived Factor-1 (SDF-1)	NA	Heart failure, critical limb ischemia, AMI	II	
Pluristem	PLX-PAD	PLX (PLacental eXpanded) cells	Allogeneic	PAD (Critical limb ischemia, Intermittent claudication)	I	$195
Tissue Genesis	Adipose-derived stem cell-coated vascular graft	Adipose-derived stem cell; Icellator Cell Isolation System	Autologous	PAD	I	
Celgene	PDA 002	Human placental-derived stem cells	Allogeneic	PAD with diabetic foot ulcers	I	$60,404
Pathfinder Cell Therapy		Pathfinder Cells ("PCs")	Allogeneic	Diabetes, MI, renal disease	Preclinical	$2

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

B. CNS

CNS therapeutics is one of the riskiest therapeutic areas. A number of companies are working on cell therapies for neurological Injury or degenerative diseases, such as stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS), Spinal Cord Injury (SCI), age-related macular degeneration (AMD) etc. A variety of cell types and approaches are used. (see Table 11). A couple of companies are using autologous cells such as Brainstorm and Cytomedix. Many companies are using allogeneic approach. Some companies are developing neural stem cells for CNS conditions. There are several types of brain-resided stem cells (see Figure 2). Q Therapeutic uses glial progenitor cells rather than the neural stem cells used by Neuralstem, ReNeuron and StemCells. A couple of companies including InVivo Therapeutics and AxoGen are developing acellular material-based implants to treat nerve injury. Overall, to our knowledge, no clear human efficacy data has been shown for these therapies Athersys and Cytomedix are running placebo-controlled phase II studies in stroke. We will see data over the next year.

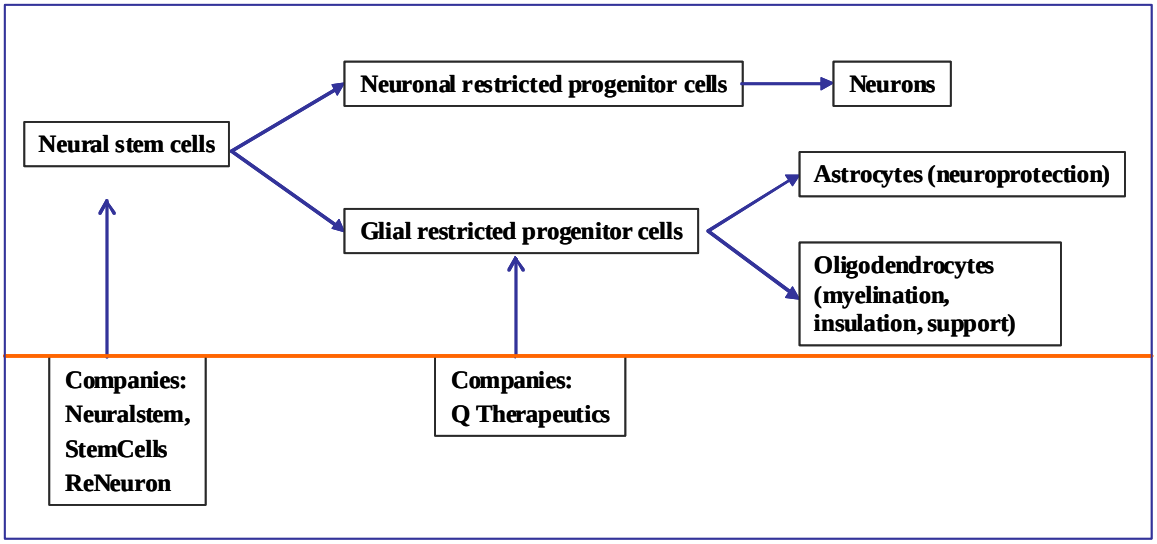
Last year saw excitement over using hESC to treat ocular diseases. A study published in Lancet by Advanced Cell Technology reported two patients, one with Stargardt's macular dystrophy and the other with dry age-related macular degeneration, showed improvements in their vision for up to 4 months after receiving the cell therapy. No safety concerns such as abnormal cell growth, teratoma, rejection or inflammation were observed. As retina is an immune privileged area, there is limited immune response to injected cells. Potential market for dry AMD is very large. Using stem cell-derived RPE (retinal pigment epithelium) cells for AMD is one of the most interesting areas in regenerative medicine. Both Advanced Cell Technology and BioTime are developing human embryonic cell-derived RPE cells for dry AMD. StemCells, Inc. is developing purified human neural stem cells for dry AMD. As we mentioned earlier, world's first clinical study using iPS cells will be initiated in Japan for the indication of AMD. Using iPS cells for AMD has the advantage of being patient-derived, and therefore reduces the necessity for immunosuppression. Beyond AMD, advances have also been made for using hESCs in cornea repair, although so far the data has been restricted to in vitro models.

Table 11 Stem Cell Products Developed for CNS Indications

Company Name	Products	Technology / Cell Type	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if Public
Advanced Cell Technology	MA09-hRPE	Human embryonic stem cells	Allogeneic	Dry AMD	I/II	$179
Athersys	MultiStem	Multipotent Adult Progenitor Cells (MAPC)	Allogeneic	Stroke	II	$103
AxoGen	Avance® Nerve Graft	(ECM) processed from human peripheral nerve tissue.	Allogeneic	peripheral nerve discontinuities		
BioTime	OpRegen, OPC-1	Human embryonic stem cells	Allogeneic	AMD, SCI	I planned	$203
BrainStorm	NurOwn	Messenchymal stem cells	Autologous	ALS	II planned	$34
Celgene	PDA-001/ cenplacel-L	placenta-derived stem cells	Allogeneic	Stroke, MS, ALS	II (stroke)	$60,404
Cytomedix	ALD-401	ALDHbr bone marrow stem cells	Autologous	Stroke	II	$38
InVivo Therapeutics		Polymer-based implant device	NA	SCI		$120
Mesoblast	MPC	Adult mesenchymal precursor cells (MPCs)	Allogeneic	Parkinson's, stroke, wet AMD (phase II)	Preclinical	AUD 1,739
Neuralstem	NSI-566	Human spinal cord derived neural stem cells	Allogeneic	ALS, SCI, Stroke	II planned	$189
Q Therapeutics	Q cells	Somatic glial progenitor cells	Allogeneic	Multiple sclerosis, ALS	I planned	
ReNeuron	ReN001	CTX neural stem cell line	Allogeneic	Stroke	I	$63
Stemedica Cell Technologies	Stemedyne- RPE; Stemedyne -NSC Stemedyne -MSC	Stem cells processed in a low oxygen (ischemic tolerant) environment	Allogeneic	Dry AMD; Alzheimer's; Stroke	I/II	
StemCells	HuCNS-SC	Human neural stem cells	Allogeneic	Spinal cord injury, PMD, Dry AMD	I/II	$73
Celgene	PDA 001	Human placental-derived stem cells	Allogeneic	Stroke, MS, ALS	Phase II, Phase I	$60,404

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

Figure 2 Different Types of Brain-resided Stem Cells



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

C. Wound care and tissue/organ regeneration

Chronic wounds affect 6.5 million people in the U.S. It is estimated over $25bn is spent on treating chronic wounds in the U.S. every year. Chronic wound is often secondary to diseases such as diabetes and obesity. With the rising prevalence of such primary diseases and the aging population, prevalence of chronic wound is expected to grow substantially. One estimate (from BioMedGPS) put the global wound care market at $6bn in 2012 and projects it to grow at 6% CAGR over the next five years. There are four types of chronic wounds – arterial ulcers, venous ulcers, pressure ulcers, and diabetic foot ulcers (see Table 12 for prevalence data for major types of wounds).

Table 12 Prevalence and Market Potential of Major Types of Wounds

Prevalence and market potential of major types of wounds	
Pressure Ulcers	Worldwide (excluding developing countries where estimation is difficult) 7.4 million pressure ulcers. 2.5 million pressure ulcers are treated in the U.S. in acute care facilities alone.
Diabetic Ulcers	In the U.S., 23 million people (7.8% of the population) suffer from diabetes. 25% of all diabetics will develop a diabetic foot ulcer. Approximately 71,000 non-traumatic lower-limb amputations were performed in people with diabetes in 2004. Recurrence rate of diabetic foot ulcers is 66%.
Venous Ulcers	In the U.S., prevalence is approximately 600,000 annually. In individuals 65 years and older, affects approximately 1.69% of the population.
Acute Wounds	40 million inpatient surgical procedures performed in the U.S. in 2000, 31.5 million outpatient surgeries.
Scarring and Fibrosis	Potential $12 billion market.
Burns	450,000 burn injuries receive medical treatment in the U.S. each year.

Source: Compiled by MHBK/IRD based on Sen CK, et al. Human Skin Wounds : A Major and Snowballing Threat to Public Health and the Economy, Wound Repair and Regeneration, 2009 Nov-Dec; 17(6): 763-771; Medtech Insight June/July 2013

Wound care is an emerging specialty of medical practices. According to expert, there are three periods of wound treatment. Prior to 1997, doctors just used simple topical treatment like Gauze to manage chronic wounds. From 1997-2001, first-wave of biologic-based products such as Regranex, Dermagraft and Apligraph were introduced with a lot of excitement. But that followed with a period of confusion and disappointment. We are currently standing in front of perhaps another era of next-generation products.

There are currently a large number of cell-based therapies on the market or in development for wound care (see Table 13). Some products have demonstrated exciting data. Recently Osiris stopped trial early for Grafix in diabetic foot ulcer (DFU) due to overwhelming efficacy. In the 131-patient trial, 62% patients receiving Grafix achieved complete wound closure at 12 weeks compared to 21% patients who received conventional therapy. In another instance, the

Israel-based company MacroCure is developing CureXcell, which is a cocktail of allogeneic white blood cells to treat hard-to-heal wounds. In a non-randomized controlled Phase IV trial in Israel, CureXcell achieved an average closure rate of 70% for chronic hard-to-heal wounds, which compared favorably to advanced products that have closure rate of 30-50%. MacroCure is currently conducting a randomized, double-blind and placebo-controlled phase III trial with 400 patients in U.S. Canada and Israel.

A few companies are involved in tissue and organ regeneration. Tengion's technology takes patient's own cells, grow them to tissues or organs in bioreactors and then implant them back to the same patients. Tengion is currently running a phase I trial for its Neo-Urinary Conduit for bladder cancer patients undergoing cystectomy. It will also start clinical trial this year for its Neo-kidney Augment product. Harvard Apparatus Regenerative Technology Inc. tried to spin off from parent company Harvard Biosciences via an IPO early this year. But the IPO was cancelled. The company has developed a 3D Bioreactor to grow Hollow Organs, Bronchus, Trachea & Blood vessels.

Table 13 Regenerative Products Developed for Wound Care and Tissue Repair

Company Name	Products	Technology (cell/tissue/biologic type)	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if
Shire	Dermagraft	Dermal tissue engineered skin	Allogeneic	Diabetic foot ulcer	Commercial	£13,170
Organogenesis	Apligraft	Bilayered tissue-engineered skin	Allogeneic	Venous ulcer, diabetic foot ulcer (DFU)	Commercial	
Healthpoint (S&N)	Regranex gel	Gel containing PDGF		Diabetic foot ulcer	Commercial	$6,852
	HP802-247	Allogeneic living human cell suspension of keratinocytes and fibroblasts	Allogeneic	Venous Leg Ulcers	Clinical development	
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	Commercial	$570
Altrika	MySkin, CryoSkin	Matrix with live cells	Autologous	Wound care	Commercial	
BioDlogics	BioDfence patch	Allograft derived from amniotic tissue	Allogeneic	In vivo wound covering	Commercial	
Cytomedix	AutoloGel; Angel cPRP system	Platelet rich plasma (PRP)	Autologous	Orthopedics, Wound care	Commercial	$38
Fibrocell	LAVIV	Isolate, purify and regenerate autologous fibroblast for reinjection	Autologous	Cosmetic	Commercial	$146
Genzyme / Sanofi	Epicel	Autologous epidermis	Autologous	Burn	Commercial	$96,774
Kinetic Concept	GRAFTJACKET	Human dermal tissue graft	Allogeneic	Wound care such as DFU, venous ulcers and pressure ulcers	Commercial	
TEI Biosciences	SurgiMend; SurgiMend PRS; PriMatrix; etc.	Biologic matrix derived from fetal bovine dermis		Soft tissue repair and reinforcement in surgery	Commercial	
Avita Medical	ReCell® Spray-On Skin	Autologous cell therapy	Autologous	Venous leg Ulcers, burns, scars	Commercial (Europe), Clinical trial in the U.S.	
Intercytex	ICX-RHY (VAVELTA®)	A suspension of human dermal fibroblasts (HDFs) to be injected into skin	Allogeneic	skin, hair regeneration; Epidermolysis Bullosa; Scar Contractures; Acne Scarring	Commercial (Europe), Phase II trials	
MacroCure	CureXcell	Injection of a cocktail of white blood cells including monocytes/macrophages, neutrophils, and lymphocytes.	Allogeneic	Hard to heal wounds such as lower extremity chronic wounds in patients with diabetes, pressure ulcers and post-surgical wounds.	Phase III	
Tengion	Neo-Urinary Conduit™, Neo-Kidney Augment™	Organ regeneration platform to create neo-tissues and neo-organs. Progenitor cells.	Autologous	Delay dialysis and kidney transplant in advanced CKD patients; bladder cancer patients undergoing cystectomy	Phase I (Neo-Urinary conduit); Pre-IND (Ned Kidney)	$2
Harvard Apparatus Regenerative Technology Inc.	InBreath hollow organ bioreactor, scaffold	Tissue / organ regeneration	Autologous	Regenerative trachea for transplantation	Clinical trial	

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

D. Orthopedics

Stem cell-based products have also found applications in spine and orthopedic applications. It was estimated the 2011 U.S. sales of stem cell products as bone replacement were around $130mn and were growing at 20+% per annum. Two major stem-cell based bone grafts on the market are Osteocel Plus from NuVasive and Trinity Evolution from Orthofix. Both are demineralized bone matrix (DBM, which serves as the scaffold) containing stem cells and growth factors. PureGen from Alphatec Spine and AlloStem from Allosource are two other similar products. To our knowledge, the benefit of having the stem cell in the bone graft is unproven. So although these products have grown nicely, they haven't taken the center stage in bone graft market. One notable project in development for spinal fusion is NeoFuse MPC product from Mesoblast. In a phase II study in lumbar spinal fusion, NeoFuse demonstrated comparable success rate as bone autograft. If NeoFuse can replicate the data in a phase III trial, it could substitute the gold standard bone autograft in spinal fusion as there won't be a need for a second surgical procedure to harvest the bone. In April 2013, Mesoblast reported preliminary efficacy data of MPCs for intervertebral disc repair. A single dose injection of MPCs led to a significant reduction in back pains and improvement in function at 6 months of follow up. 71% patients achieved the pre-specified success criteria, compared to 20% and 30% for the two control arms.

A number of chondrocyte-based products are marketed for cartilage repair, including Carticel from Genzyme and CondroCelect from TiGenix. Cartilage repair is expected to grow into a big market as many aging adults suffer from sports injuries or natural course of aging. Histogenics is a notable company. Histogenics came into being as a result of a merger of two cartilage repair companies – Histogenics and ProChon Biotech. The merger allowed the company to establish a broad platform for cartilage repair and concentrate resources on the most promising asset NeoCart. Following the merger, Histogenics raised $12mn financing and then in July 2012, it did a recapitalization and raised $49mn to fund the phase III study of NeoCart. NeoCart is produced 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 will have a better chance of making a difference in patients. NeoCart has

generated impressive clinical data, which showed superiority to standard of care microfracture on multiple metrics. It is currently in a phase III study to demonstrate its efficacy. Besides NeoCart, Histogenics has in development of VeriCart, which is collagen scaffold that the orthopedic surgeon implants into a cartilage defect to stimulate cartilage regeneration. There are a number of other companies working on regenerative approaches for cartilage and meniscus repair.

Table 14 Regenerative products for Spine and Orthopedics

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if Public
Nuvasive	Osteocel (bought from Osiris for ~$90mn in 2008)	Allograft bone matrix retaining MSCs and osteoprogenitors	Allogeneic	Spinal fusion	Commercial	$1,104
Orthofix	Trinity Evolution	Allograft with stem cells	Allogeneic	Spinal fusion	Commercial	$382
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	$9,025
Cytomedix	Angel cPRP system	Platelet rich plasma (PRP)	Autologous	Orthopedics	Commercial	$38
Genzyme / Sanofi	Carticel,	Autologous chondrocyte implantation	Autologous	Cartilage repair,	Commercial	
TiGenix	CondroCelect (not approved in the U.S.)	Autologous chondrocyte implantation	Autologous	Cartilage and osteocondral lesions	Commercial	€ 37
BioTissue Technologies AG	BioSeed®-C, CHONDROTISSUE®	3-dimensional chondrocyte graft; Scaffold material for cartilage repair	Autologous	Cartilage repair	Commercial (Europe)	
ISTO Technologies	DeNovo® ET	Juvenile cartilage cell	Allogeneic	knee cartilage repair	Phase III	
Mesoblast	NeoFuse MPC product	Adult mesenchymal precursor cells (MPCs)	Allogeneic	Spinal fusion, Degenerative disc disease (DDD)	Phase II	€ 1,739
Histogenics	NeoCart	Autologous chondrocytes grown in DBM ex-vivo	Autologous	Cartilage repair	Phase II	
TissueGene	TG-C	human chondrocytes engineered to produce the therapeutic growth factor TGF-ß1	Allogeneic	Cartilage, bone regeneration	Phase II	
Osiris	Chondrogen; Cartiform	Preparation of mesenchymal stem cell for direct injection into knee; Viable cartilage mesh	Allogeneic	Meniscus regeneration; OA; Acute Cartilage Injury	Phase II, Phase I	$570
Cesca	SurgWerks	Autologous cells isolations from bone marrow or peripheral blood	Autologous	Osteoarthritis, bone fusion	Phase I	$17
DiscGenics	Injectable Discogenic Cell Therapy (IDCT)	DiscGenics technology to isolate human disc stem cells	Allogeneic	Degenerative disc disease (DDD)	Preclinical	
BioRestorative Therapies Inc.	brtxDISC™	MSCs delivered via proprietary cannula	Autologous	Degenerative disc disease (DDD)	Preclinical	
Orteq	Actifit® meniscal implant	biodegradable, synthetic scaffold made from proprietary polymer		Meniscus repair	Phase II	
Nanotope		peptide amphiphiles that form a substrate that directs surviving cells to re-grow damaged tissue				

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

E. Diabetes

Diabetes is a huge medical problem around the world. According to IDF (International Diabetes Federation) Diabetes Atlas 2012 update, there are estimated 371mn people living with diabetes worldwide and the number is projected to grow to 552mn by 2030. An estimated $471bn is spent on treating diabetes in 2012 and it will increase to over $565bn in 2030. Although huge strides have been made recently in pharmacological therapy, the Holy Grail, which is to restore the functional pancreatic islet cells, remain unaddressed. Several regenerative treatments are being developed for diabetes (see Table 15). Mesoblast is currently conducting a phase II study in diabetes and just initiated another phase II trial in diabetic nephropathy. The phase II trial in diabetes will report data in second half 2013.

Another notable company with especially ambitious approach is ViaCyte. It 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. The Encaptra® drug delivery system holds and protects the PEC-01 cells, and helps them differentiate into functional islet beta cells. VC-01 can be then implanted into patients subcutaneously.

Table 15 Regenerative Medicine Being Developed for Diabetes

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if Public
Mesoblast	MPC	Adult mesenchymal precursor cells (MPCs)	Allogeneic	Type 2 Diabetes	Phase II	AUD 1,739
Osiris	Prochymal	Bone marrow-derived allogeneic MSCs	Allogeneic	Type 1 Diabetes	Phase II	$570
Neostem (Athelos)		Treg cells	Allogeneic	Type 1 Diabetes	Phase I	$178
Athersys	MultiStem®	Multipotent adult progenitor cells (MAPC)	Allogeneic	Type 1 Diabetes	Preclinical	$103
ViaCyte	VC-01	Cell-device combination product encapsulates the PEC-01 pancreatic precursor cells derived from a human embryonic stem cell line in the ENCAPTRA implantable drug delivery system.	Allogeneic	Type 1 & 2 Diabetes	Preclinical	

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

F. Autoimmune Diseases

Autoimmune diseases such as GvHD, RA, IBD could be amenable to cell therapy as cells can have immunomodulatory effects to dampen autoimmune diseases. Several regenerative treatments are being developed for autoimmune conditions (see Table 16). Of these, Prochymal from Osiris has the most clinical experience. Prochymal had very favorable phase II results in GvHD and Osiris was able to sign a very rich deal with Genzyme to license Prochymal and Chondrogen in November 2008 (for countries outside of the U.S. and Canada: $130mn upfront, up to $500mn development and regulatory milestones, up to $150mn sales milestones). However, a pair of phase III trials of Prochymal in GvHD both for the refractory population and first-line population failed to meet primary endpoint. Osiris share price tanked as a result. In March 2012, Osiris received approval from Health Canada for refractory Crohn's disease in pediatric patients. In June, Osiris also received approval from New Zealand for acute GvHD in children. Notwithstanding these two approvals, in September 2012, Genzyme (acquired by Sanofi) returned worldwide commercial right for Prochymal back to Osiris. The Prochymal experience suggests caution is needed in assessing the data of cell therapy for autoimmune disease.

Athersys partnered with Pfizer for inflammatory diseases of IBD. Phase II trial in ulcerative colitis will report data in 2H2013. One program that has shown encouraging safety and efficacy recently in the clinic is Cx611 from TiGenix. Cx611 is allogeneic adipose tissue derived expanded stem cells (eASCs) administered to patients via IV infusion. In April 2013, TiGenix reported encouraging results from a phase IIa study in refractory rheumatoid arthritis patients. Although the trial size was small and patients enrolled were quite heterogeneous, Cx611 preliminarily showed efficacy in very refractory RA patients while patients on placebo showed no benefit.

Table 16 Regenerative Medicine Being Developed for Autoimmune Diseases

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if Public
Osiris	Prochymal	Bone marrow-derived allogeneic MSCs	Allogeneic	GVHD, Crohn's disease	Phase III	$570
TiGenix	Cx601, Cx611	allogeneic adipose tissue derived expanded stem cells (eASCs).	Allogeneic	Rectal fistula in Crohn's disease, RA	Phase III, Phase II	€ 37
Athersys	MultiStem®	Multipotent adult progenitor cells (MAPC)	Allogeneic	GvHD, IBD (partnered with Pfizer)	Phase II	$103
Celgene	PDA-001 / cenplacel-L	placenta-derived stem cells	Allogeneic	Crohn's disease, RA	Phase II, Phase I/II	$60,404
Neostem (Athelos)		Treg cells	Allogeneic	GvHD, steroid-resistant asthma	Phase I	$178
Mesoblast	MPC	Adult mesenchymal precursor cells (MPCs)	Allogeneic	RA, Asthma, pulmonary fibrosis	Preclinical	AUD 1,739

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

G. Combination of Cell and Gene Therapy in Orphan Diseases and Cancer

Combining gene and cell therapy has the promise of fundamentally cure certain diseases. With better vector design and better targeting diseases caused by single-gene defects, gene therapy has made big progresses recently. In November 2012, UniQure received the world's first approval of a gene therapy product (Glybera) in Europe for the condition of lipoprotein lipase deficiency. The approval of Glybera may be a harbinger for a lot more successes to come in the field of gene therapy. Combining gene and cell therapy could be particularly potent. The process of ex vivo transduction is conceptually simple – isolate autologous cells (often hematopoietic stem cells), manipulate these cells ex vivo by transduction with correct gene (or slightly modified and enhanced gene), re-infuse these cells back to patients, then hopefully these infused cells will permanently engraft and correct the defects. This ex vivo delivery of gene therapy has the benefit of not subjecting patients to systemic administration of retrovirus-based gene therapy and therefore is safer. This autologous approach is also safer than allogeneic stem cell transplant due to lower risk of immune rejection. There are a number of examples of combining cell and gene therapy (see Table 17).

One example of this application is for the related orphan diseases sickle cell disease and beta thalassemia. Both diseases are caused by defects in beta globin gene. Bluebird bio has just begun phase I study of LentiGlobin therapy for these two orphan indications. A researcher group at University of California, Los Angeles' Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research has also developed a similar therapy for sickle cell disease, which will begin phase I study in early 2014.

Another application is in cancer. Chimeric Antigen Receptor (CAR) modified T-cells have shown great promise in hematological cancer. Research finding in CLL (chronic lymphocytic leukemia) by Carl June at U. Penn published in 2011 in New England Journal of Medicine led to wide media coverage. Research has shown CAR modified T-cell therapy can cure diseases such as CLL and ALL (acute lymphoblastic lenkemia). Transducing cytotoxic T cells with CARs will make them continuatively activated and supercharged to attack malignant cancer cells. Similar ex vivo transduction approach can be used to make CAR modified T-cells. Just in this case, cytotoxic T cells rather than hematopoietic stem cells are isolated from patients and transduced ex vivo with CAR genes. Celgene and Bluebird bio have entered into a collaboration to use Bluebird bio's

technology to manipulate autologous T cells ex vivo to treat cancer.

Another notable application is in AIDS. Sangamo Biosciences is developing an autologous ZFN-CCR5-modified T-cell product (SB-728-T) to treat HIV. HIV strains require two coreceptors on T cell surface to enter into the cell – CD4 and CCR5 (for most HIV strains). It was discovered that a group of people with a particular mutation in CCR5 have a truncated and nonfunctional CCR5 protein on their T cells that renders the cells resistant to HIV infection. These individuals don't get AIDS despite repeated exposure to HIV. Sangamo uses its zinc finger gene editing technology to engineer this particular naturally occurring mutation in CCR5 in T cells isolated from AIDS patients. Then these modified T cells are re-infused back to patients. Sangamo is currently running a phase II study. If proven to be successful, this approach could cure AIDS.

Another application is to use genetically modified iPS cells to treat the rare skin condition recessive dystrophic epidermolysis bullosa (RDRB, see Table 3). RDEB is a result of a single, loss-of-function mutation in a collagen gene. A group of researchers at Stanford University biopsy the patients' own fibroblasts, reprogram them into iPS cells, genetically correct the monogenic defect, differentiate these cells into keratinocytes, assemble these cells into skin grafts, and finally graft it onto affected areas in patients. The researchers may start phase I study in 2014.

Table 17 Examples of Combining Cell and Gene Therapy

Institution	Approach	Disease indications	Current Stage	Market Cap ($mn) if Public
Bluebird bio	Ex vivo manipulation of autologous blood cells by gene therapy	beta thalassemia, sickle cell disease	Phase I	$543
Bluebird bio (partnered with Celgene)	CAR-T (chimeric antigen receptor activated T cells)	Hematological cancer	Preclinical	
Sangamo Biosciences	ZFN-CCR5-modified T-cell product (SB-728-T)	AIDS	Phase II	$675
Stanford University	Gene therapy to correct genetic defects ex vivo	Recessive dystrophic epidermolysis bullosa (RDRB)	Pre-IND stage; clinical trial could begin in mid-2014	

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

H. Combination of Cell and Immuno Therapy in Cancer

With promising data for immune checkpoint inhibitors, cancer immunotherapy is all the rage currently. AstraZeneca just acquired Amplimmune for $225mn upfront and up to $275mn development milestones despite its most advanced program is already partnered with GSK. Combining cell (sometimes stem cell) therapy with immunotherapy can be very powerful in cancer (see Table18).

- Several companies including Argos, ImmunoCellular, Prima BioMed, and Northwest Biotherapeutics are developing variations to Dendreon's Dentritic cell based therapy.
- Several companies are engineering T cells with modified TCR and CARs for cancer. Autologous chimeric antigen receptor (CAR)-modified T cells have shown curative effects in CLL and ALL. Carl June's breakthrough research has gathered broad media coverage. Novartis has taken the lead by partnering with U. Penn. Recently Celgene formed an alliance with Bluebird bio to use its technology to develop CAR-T.
- A number of companies are working on improved hematological stem cell transplant (HSCT). HSCT is limited by the availability of the matched donor and has high toxicity (and mortality rate). But HSCT is a curative treatment for some hematological cancers. Companies including Fate Therapeutics, Immunovative Therapeutics and Kiadis Pharma are developing improved HSCT.
- A number of companies are developing cancer vaccines based on cancer cells. For example, NewLink Genetics and NovoRx are developing cancer vaccines using modified cancer cells. Historically, cancer vaccine field has seen many failures. For example, GVAX from Takeda/Cell Genesys (formulation of two off-shelf prostate cancer cell lines) failed phase III clinical trials in 2008. However, further analysis of one of the failed trials showed some survival benefit of GVAX manifested later in the trial. It remains to be seen if the modifications by NewLink and NovoRx can lead to better immune response and positive results in clinical trials.

Table 18 Cancer Programs That Combine Cell and Immuno Therapy

Company Name	Products	Technology / cell type	Autologous / Allogeneic	Indication	Stage	Market Cap ($mn) if Public
Dendreon	Provenge	Dendritic cells loaded with prostate cancer antigen	Autologous	Prostate cancer	Commercial	$404
ImmunoCellular	ICT-107, ICT-121, ICT-140	Dendritic cells loaded with cancer antigen	Autologous	Glioblastoma vaccine; Recurrent Glioblastoma; Ovarian cancer	II, I, Preclinical	$136
Prima BioMed	CVac™ cell therapy	Dendtritic cells loaded with mucin-1-MFP, novel adjuvant	Autologous	Ovarian cancer	III	$42
Argos	AGS-003, AGS-004, AGS-009	Arcelis immunotherapy (self dendritic cells transfected with amplified tumor RNA)	Autologous	Renal cell carcinoma, HIV, Lupus	III, II, I	
Northwest Biotherapeutics	DCVax®	DCVax Dendritic Cell Immunotherapy	Autologous	Prostate, Other solid tumors	II, I	
Adaptimmune		Engineered TCRs and CARs	Autologous	Myeloma, Ovarian cancer, Hepatic cancer, synovial sarcoma, Melanoma, HIV	I/II	
Bluebird bio / Celgene	CAR-T	Chimeric antigen receptor activated T cells	Autologous	Hematological cancer	Preclinical	$543
Coronado Biosciences	CNDO-109	Tumor activated NK cells	Allogeneic	AML	IIa	$237
Cell Medica	Cytorex; Cytovir	cytotoxic T lymphocytes (CTLs) targeting tumor or viral antigen	Autologous, Allogeneic	Cancer; CMV infection	II (CMV infection)	
Fate Therapeutics	ProHema	Hematopoietic stem cells isolated from cord blood	Allogeneic	Hematological cancer	II	
Immunovative Therapeutics	AlloStim	"Mirror Effect™" Technology. T-Stim	Allogeneic	Allogeneic transplant for hematological cancer	I/II	
Kiadis Pharma	ATIR, Rhitol, Reviroc	Transplantations from partially matched (haploidentical) donors	Allogeneic	HSCT, Steroid-resistant GvHD, reducing relapse after autologous GvHD	I/II	
CEL-SCI Corporation	Multikine	Leukocyte Interleukin, Injection		Head & Neck cancer	III	$25
NewLink Genetics	algenpantucel-L (pancreas), tergenpumatucel-L (lung)	HyperAcute Immunotherapy	Allogeneic	Pancreatic cancer, Non small lung cancer	III, II	$468
NovaRx	Lucanix, Glionix	NSCLC cell lines gene-modified to block the secretion of TGF-β; Glioma cell lines blocked for TGF-β immunosuppression	Allogeneic	Non small cell lung cancer;	III, I	

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

3. Conclusion and outlook

Regenerative medicine has tremendous therapeutic potential and may well be the next frontier for medical breakthroughs. Despite the great potential, regenmed industry has not yet delivered on its promise. Solid progresses have been made and many regenmed companies are ploughing ahead. The industry is urgently in need of breakthrough therapies that can unequivocally demonstrate the clinical value and commercial success of regenmed. That is why it is important for leaders such as Mesoblast to succeed. The key risks for the industry are both clinical and financial. On the clinical side, developing regenmed can be compared to the development of other advanced technologies in the past such as recombinant protein, antibody, anti-sense, RNAi, gene therapy, etc. In gene therapy, the unfortunate death of Jesse Gelsinger in 1999 cast a deep freeze over the field. It was not until late 2012 when the world first saw the approval of a gene therapy product. Premature testing with pluripotent stem cells such as hESC or iPS cells may lead to similar tragedy. The second risk is financial. Currently the majority of regenmed companies are enduring a harsh financing environment with venture financing almost non-existent and IPO window largely closed. Although there are funding agencies such as California Institute of Regenerative Medicine (CIRM), small business innovation research (SBIR) grant, and the friendly funding environment in Japan, in general it is tough for the majority of players outside of Japan to obtain financing on good terms. Over half of publicly traded regenmed companies have less than 1 year's operating cash on their balance sheets (see Table 19). How much financial runway regenmed companies have is often in question. There seems to be huge difference in funding and valuation for stem cell companies between Japan and western markets. Therefore there perhaps exists an opportunity to arbitrage – either for Japanese players to use low cost-of-capital financing to buy western asset, or for western companies to tap into financing in Japan.

Overall we found as a reflection of the early stage of the industry, there are many different approaches in regenmed, ranging from autologous to allogeneic, from well-characterized cells to mixture of cells, and many different sources of cells and the ways of processing these cells. In terms of therapeutic area, cardiovascular area is the most mature as a number of companies are in the mid-late stage development. CNS is a bit early, but several diseases in CNS (such as AMD, MS, and Parkinson's disease) seem to be quite amenable to regenmed approach. For wound care and orthopedic applications, although there are already a large number of regenmed

products on the market, the commercial products often don't have convincing clinical data to demonstrate their superiority over alternative therapies (or enough clinical differentiation to persuade wide adoption). Therefore, regenemed remains in the fringe rather than the center of these two areas. However, new products in development could change the current situation and put regenmed at the center stage in wound care and orthopedics.

In terms of large pharma's interest, so far only a few large pharma have tentatively tapped into this field. These pioneers include Shire, Teva (Cephalon), Celgene, Pfizer, etc. Beyond pharma, medical device and wound care companies often have presence in regenmed. However it hasn't become a main driver of their businesses.

As in other medical field, clearly the ultimate success of the industry will be driven by clinical data instead of media hype. Over the next five years, we will be watching important data readouts from a number of mid-late stage companies. Regenmed has the potential to transform medicine as some conditions (such as CHF, MI, dry AMD, etc) are poorly served by drugs and device therapies, and clearly another treatment modality is urgently needed. The market is certainly huge. It will be up to the regenmed companies to demonstrate their products' clinical value, robustness of the manufacturing, and commercial viability in terms of reimbursement/pricing.

While data is the watch word for therapeutic use of regenmed, we see promising applications of iPS cells in drug R&D. iPS cells can be used to create "disease in a dish", which is very useful for drug screening. iPS-derived cells (such as cardiomyocytes) are also useful in drug toxicity studies. With the high inherent risk in therapeutic use of stem cells, maybe the tool suppliers such as iPS cell suppliers are a safer bet to exploit the economic potential of regenerative medicine.

Table 19 Valuation of Publicly Traded Regenmed Companies (excluding cancer)

10/10/2013 Company name	Market Cap (USD in mn)	EV (USD in mn)	Price ($USD)	52-wk Hi	52-wk Low	% 52-wk High	Sales 2012	Sales 2013E	Net Income 2012	Net Income 2013E	Net Cash	YTD return
NASDAQ Composite Index			3752	3818	2837	98%						24%
NASDAQ Biotechnology Index			2099	2233	1339	94%						47%
NYSE Arca Biotechnology Index			2021	2247	1398	90%						31%
Mesoblast Limited	$1,646	$1,348	5.19	7.14	4.00	73%	$30	$16	-73	-58	289	-2%
ReproCELL, Inc.	$894		20.22	37.96	16.12	53%	$4					NA
Sangamo Biosciences Inc.	$675	$628	11.35	13.20	4.92	86%	$19	$23	-22	-26	47	89%
Osiris Therapeutics, Inc.	$570	$543	17.37	27.40	6.55	63%	$12	$26	-11	-11	27	93%
bluebird bio, Inc.	$543	$314	23.48	36.25	21.06	65%	$0	$21	-24	-24	229	NA
Medipost Co Ltd	$454	$420	64.48	96.30	49.92	67%	$28	$34	2	5	33	NA
MiMedx Group, Inc.	$439	$435	$4.98	$7.73	$1.81	64%	$26	$58	-8	2	4	30%
Organovo Holdings, Inc.	$433	$420	5.80	8.50	1.80	68%	$0	$0	-44		13	123%
Cellular Dynamics International, Inc.	$268	$365	17.98	24.11	9.50	75%	$7		-22		22	
MolMed S.p.A.	$209	$192	0.94	0.98	0.52	96%	$0	$7	-29	-26	17	
BioTime, Inc.	$203	$202	3.61	5.02	2.67	72%	$0	$0	-21		14	15%
Pluristem Therapeutics, Inc.	$195	$141	3.39	4.10	2.47	83%	$1	$1	-15	-19	54	6%
Neuralstem, Inc.	$189	$186	2.74	3.02	0.88	91%	$1		-10	-13	4	152%
Advanced Cell Technology Inc.	$179	$178	0.07	0.10	0.05	70%	$1		-29		2	24%
Neostem, Inc.	$178	$166	6.98	9.89	5.00	71%	$34	$14	-54	-34	11	17%
Fibrocell Science, Inc.	$146	$126	3.90	7.20	3.03	54%			-23		21	4%
Cytori Therapeutics, Inc.	$145	$157	2.22	4.55	2.09	49%	$15	$14	-32	-30	-12	-21%
Fate Therapeutics, Inc.	$128	$187	7.03	9.19	6.06	76%	$7		-14		-2	
Athersys, Inc.	$103	$84	1.87	2.42	0.95	77%	$8	$4	-15	-29	19	76%
ReNeuron Group plc	$100	$94	0.06	0.07	0.03	81%	$0	$0	-10		5	180%
StemCells Inc.	$73	$59	1.46	2.50	1.37	58%	$1	$1	-28	-24	14	-11%
AxoGen, Inc.	$72	$87	4.20	6.25	2.25	67%	$8	$12	-9		-15	56%
BioLife Solutions, Inc.	$57	$67	0.81	0.88	0.14	92%	$6	$7	-2	-1	-11	138%
TiGenix N.V.	$50	$45	0.39	1.42	0.26	28%	$6	$9	-27	-17	0	-57%
Cytomedix, Inc.	$38	$40	0.37	0.90	0.36	41%	$10		-20		-2	-49%
Brainstorm Cell Therapeutics Inc.	$34	$31	0.20	0.27	0.15	73%	$0	$0	-3		3	-11%
Avita Medical Limited	$34	$24	0.10	0.15	0.09	69%	$4	$3	-8	-8	10	-13%
Living Cell Technologies Limited	$26	$22	0.07	0.11	0.04	67%	$0	$0	6		4	46%
International Stem Cell Corporation	$24	$28	0.24	0.41	0.13	59%	$0	$0	-10		1	20%
ThermoGenesis Corp.	$17	$10	1.04	1.60	0.61	65%	$0	$0	-5		7	24%
VistaGen Therapeutics, Inc.	$11	$16	0.50	0.95	0.50	53%	$0	$0	-12		-6	-32%
Aastrom Biosciences, Inc.	$10	$49	0.22	1.58	0.22	14%	$0	$0	-29	-20	4	-83%
Total	**$8,143**	**$6,663**				**66%**						**31%**

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

<List of Abbreviations>

AKI	Acute Kidney Injury
ALS	Amyotrophic lateral sclerosis
AMD	Age-related Macular Degeneration
ARM	Alliance for Regenerative Medicine
CHF	Congested heart failure
CKD	Chronic kidney disease
CLI	Critical Limb Ischemia
CNS	Central Nervous System
CV	Cardiovascular
DFU	Diabetic foot ulcer
ESC	Embryonic stem cells
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
GvHD	Graft versus host disease
hES	Human embryonic stem cells
IBD	Inflammatory bowel disease
iPS	Induced pluripotent stem cells
IRD	Industry research division
M&As	Mergers and Acquisitions
MHBK	Mizuho Bank
MI	Myocardial Infarction
MS	Multiple Sclerosis
MSC	Mesenchymal stem cells
PAD	Peripheral artery disease
PMD	Pelizaeus-Merzbacher Disease
POC	Proof of concept
RA	Rheumatoid arthritis
RPE cells	retinal pigment epithelium cells
SCI	Spinal cord injury

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