EDISON

Cellular Biomedicine Group

Initiation of coverage

Cell therapy for China and the US

Pharma & biotech

We are initiating coverage on Cellular Biomedicine Group (CBMG), a trans-Pacific cell therapy company developing products in China and the US. It has two ongoing Phase I clinical trials of CD19 chimeric antigen receptor T-cell (CAR-T) therapies for blood cancers in China. Additionally, it is adapting its knee osteoarthritis (KOA) treatment ReJoin as an allogeneic product, AlloJoin, which it hopes to develop in the US after a 2017 or 2018 IND. We arrive at an initial valuation of $191.6m or $13.58 per share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/15	2.5	(12.5)	(1.09)	0.0	N/A	N/A
12/16	0.6	(18.1)	(1.34)	0.0	N/A	N/A
12/17e	0.2	(18.8)	(1.38)	0.0	N/A	N/A
12/18e	0.0	(17.8)	(1.25)	0.0	N/A	N/A

Note: *PBT and EPS are normalized, excluding amortization of acquired intangibles, exceptional items and share-based payments.

Chinese CAR-T trials ongoing

CBMG has two ongoing Phase I studies using its CD19 CAR-T therapy for the treatment of diffuse large B-cell lymphoma (DLBCL) and adult acute lymphoblastic leukemia (ALL). The major Western CAR-T developers Kite and Juno have a have licensed the technology in China, but have not started trials to our knowledge. Data are expected for the CBMG trials around year end 2017.

AlloJoin: Off-the-shelf OA cell therapy

AlloJoin is an allogeneic cell product derived from human adipose-derived mesenchymal progenitor cells (haMPCs). Autologous haMPCs (ReJoin) showed improvement in cartilage growth (p=0.007) in patients with KOA in an early clinical trial positioning them as a potential disease-modifying therapy (although it missed its functional endpoints due to two outliers), of which none exist for OA. The interim results from the AlloJoin Phase I trial (n=18) reported no serious adverse events. The trial is expected to report in H217.

Chinese GMP cell production

CPMG has three GMP-certified facilities in China, which it estimates can provide 10,000 doses of both CAR-T and progenitor cells per year for the Chinese market (export of human cells from China is highly restricted). There are a large number of other Chinese companies developing CAR-T and manufacturing know-how is a key barrier to entry for this technology.

Valuation: $191.6m or $13.58 per share

We arrive at an initial valuation of $191.6m or $13.58 per share based on a risk-adjusted NPV analysis. We estimate AlloJoin as the highest value asset at approximately $94m in value. We expect to update our valuation with the completion of the CAR-T and AlloJoin clinical results in 2017. The company ended Q217 with $27.3m in cash, providing a runway into 2018, and we expect it to require $140m to complete its clinical programs and reach profitability in 2024.

2 October 2017

Price	**US$10.65**
Market cap	**US$150m**

Net cash ($m) at 30 June 2017	27.3
Shares in issue	14.1m
Free float	73.4%
Code	CBMG
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	13.9	26.0	(25.0)
Rel (local)	10.6	21.0	(36.0)

52-week high/low	US$15.0	US$5.3

Business description

Cellular Biomedicine Group (CBMG) is a biotechnology company developing cell-based therapeutics with operations primarily in China. It has completed Phase II clinical trials of ReJoin, an autologous progenitor cell therapy for osteoarthritis, and it is developing a similar allogeneic product (AlloJoin). It has also developed a CD19 CAR-T, which is currently in Phase I testing in China.

Next events

AlloJoin results	H217
DLBCL results	Around year end 2017
Adult ALL results	Around year end 2017

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Edison profile page

Cellular Biomedicine Group is a research client of Edison Investment Research Limited

Investment summary

Company description: China focused cell therapy

Cellular Biomedicine Group is a biotechnology company developing cell-based therapies for cancer and osteoarthritis. The company is domiciled in the US but the majority of its operations occur in China, where it has three manufacturing facilities. The company is developing C-CAR011, a CD19 targeting chimerical antigen receptor T-cell (CAR-T) therapy for the treatment of diffuse large B-cell lymphoma (DLBCL) and adult acute lymphoblastic leukemia (ALL), both of which are in Phase I. It is also developing an autologous adipose derived progenitor cell therapy call ReJoin for the treatment of knee osteoarthritis, which has demonstrated the ability to regrow damaged cartilage in Phase II clinical trials. In addition to development of ReJoin, it has developed an allogeneic version called AlloJoin, which it plans to sell in both China and the US, and it has initiated a Phase I trial.

Valuation: Initiated at $191.6m or $13.58 per share

We arrive at an initial valuation of $191.6m or $13.58 per share based on a risk-adjusted NPV analysis. We estimate that ReJoin has the highest probability of success (40%) because it has demonstrated measurable cartilage regrowth in two Phase II clinical trials. The other programs are more risky with probabilities of success of 15% or 20%, due to the lack of significant clinical data in humans. We expect AlloJoin to have the highest profit potential with over $400m in peak revenue in both the US and China. Our lowest value program is ALL due to the high risk and the relatively low number of ALL patients in China.

Financials: $140m in additional capital needed

CBMG had a loss of $29.2m for 2016, up from $13.8m in 2014 and $21.1m in 2015. This spending increase is primarily due to ramping up of the clinical programs. The company has also invested significant capital building out its manufacturing capacity, although the current footprint should be sufficient for the company to produce all of its needed product in China. The company ended Q217 with $27.3m in cash, which we believe will provide a runway into 2018. Our forecasts predict that the company will need $140m in additional capital before profitability in 2024.

Sensitivities: Clinical risk and the Chinese market

CBMG has the risks typical of an early stage biotech company coupled with a unique set of hurdles associated with its focus on China. The CAR-T programs are modeled with a 20% probability of success due to their early stage of development and current lack of efficacy data. ReJoin is the only product with significant in-human data and demonstrated cartilage regrowth in Phase IIb, although it failed to meet its primary endpoints in this trial. AlloJoin may alleviate the logistics issues and lower COGS compared with ReJoin by switching to an allogeneic system. AlloJoin cells express human leukocyte antigen (HLA) proteins, although this did not trigger rejection in preclinical studies, and rejection is unlikely to have posed a significant risk. The company's autologous programs (CAR-T and ReJoin) are limited to the Chinese market due to a ban on the export of human genetic material, and there are a high number of Chinese companies developing cell therapies, but this risk is somewhat offset by CBMG's established manufacturing know-how. China has broad insurance coverage (97%), but higher levels of reimbursement and access to care are limited to the 38% in urban insurance plans. This is coupled with the requirement that patients prepay out of pocket, and that reimbursement is capped even in the more generous insurance schemes, although this is offset by high levels of cash payers historically. Finally, the $140m in additional capital the company needs to reach profitability in 2024 may result in significant dilution, but this amount is low compared to spending on the development of CAR-T programs alone in Western countries.

Company description: Cells across the Pacific

Cellular Biomedicine Group (CBMG) was founded in 2009 and went public via a merger in 2013. The company has raised approximately $94m from the issuance of stock since inception, and it has used this capital to in-license, acquire, and develop a number of cell-based therapies for cancer and further their development. The company officially has 12 products in development in 14 programs, of which four have advanced to the clinic. These programs are split into two categories: the immuno-oncology pipeline and the stem cell pipeline. The immuno-oncology pipeline consists primarily of chimeric antigen receptor T-cell (CAR-T) therapies licensed from PLA General Hospital in Beijing. The company is also developing Dendristim (formerly referred to as GVAX), a cell-based cancer vaccine, which was licensed from the University of South Florida. The two ongoing immuno-oncology programs are the use of C-CAR011, a CD19 targeting CAR-T, for the treatment of diffuse large B-cell lymphoma (DLBCL) and adult acute lymphoblastic leukemia (ALL). The stem cell pipeline consists of internally developed programs using autologous and allogenic progenitor cells (which include, but are not necessarily limited to, stem cells) derived from adipose tissue for the treatment of osteoarthritis and chronic obstructive pulmonary disease. This includes ReJoin, an autologous treatment for knee osteoarthritis (KOA) that has completed Phase IIb, and AlloJoin, an allogeneic version of ReJoin currently in Phase I. All these programs are targeting the Chinese market. Only AlloJoin will be developed for the US because it is allogeneic and therefore not subject to the limitations on the export of autologous tissue from China. For the purposes of this report, we will focus on the clinical programs, although we may add the preclinical assets to our valuation in the future if more data becomes available.

Exhibit 1: Cellular Biomedicine Group pipeline

Product	Phase	Indication
Immuno-oncology pipeline		
C-CAR011 (anti-CD19)	Phase I	Diffuse large B cell lymphoma
C-CAR011 (anti-CD19)	Phase I	Adult acute lymphoblastic leukemia
Anti-BCMA CAR	Preclinical	Multiple myeloma
Anti-CD22 CAR	Preclinical	Heme malignancies
Anti-CD20 CAR	Preclinical	Chronic lymphoblastic leukemia and non-Hodgkin lymphoma
CD20-CD19 BiCAR	Preclinical	Chronic lymphoblastic leukemia and non-Hodgkin lymphoma
BiCAR (undisclosed target)	Preclinical	Acute myeloid leukemia
PD-1 CAR-T combination	Preclinical	Hematologic malignancies
PD-1 CAR-T combination	Preclinical	Solid tumors
Anti-CD30 CAR	Preclinical	Hodgkin lymphoma
Anti-EGFR CAR	Preclinical	Solid tumors
Dendristim (cancer vaccine)	Preclinical	Non-small cell lung cancer
Stem Cell Pipeline		
ReJoin (autologous haMPC)	Phase II complete	Knee osteoarthritis
AlloJoin (allogeneic haMPC)	Phase I	Knee osteoarthritis

Source: Cellular Biomedicine Group

Manufacturing advantages

Cell-based therapies are a relatively new area of development for major pharmaceutical companies, and the industry is still in the process of identifying efficient manufacturing practices for these products. Allogenic cell therapies require production processes that are similar to other biologics, such as sterile culture conditions. However, manufacturing controls and safety precautions are significant. It is both difficult to maintain consistency with human cell products and non-trivial to assay variance between batches. Also given that these are human cells, there must be protocols in place to ensure the cells do not harbor disease. Because of this, cell products generally must be treated as infectious agents, requiring biosafety controls.

Autologous cell manufacturing presents a truly unprecedented level of manufacturing hurdles, controls and regulatory processes. Each patient requires their therapy to be independently produced in an individual batch with sufficient controls in place to ensure cell purity and prevent cross-contamination. Moreover, therapies such as CAR-T require reagents that themselves face a high degree of scrutiny, such as viral vectors to genetically modify cells.

CBMG has an extensive cell therapy manufacturing footprint in China, which in many ways rivals or exceeds CAR-T market front runners Novartis and Kite Pharmaceuticals. The company currently has three manufacturing facilities (in Beijing, Shanghai, and Wuxi) with 47,300 square feet of capacity, and is currently undergoing expansion with the opening of a new facility in Shanghai, bringing the total capacity to 70,000 square feet. By comparison, Novartis currently has 170,000 square feet of production space and Kite has a 43,500 square foot facility. Additionally, CBMG's CAR-T throughput is high efficiency: all plasmids and viral vectors are produced in house and the company has a high-yield, highly automated cell culture system. This system should enable a high throughput and the company is targeting a capacity of 10,000 CAR-T and 10,000 progenitor cell doses per year. The ongoing Phase I and subsequent clinical trials will be a key indicator of whether these processes can supply a consistent and effective product.

The facilities are currently up to the current good manufacturing practices of the CFDA, and were built to international GMP standards, including ISO (International Organization for Standardization) rated clean rooms. The Chinese authorities are currently formalizing aspects of their 2015 draft guidance on cell therapy production. CBMG facilities are in full accordance with the guidance, and the passage of the regulations should protect the company from low-cost, low-quality competitors. Manufacturing represents a very important aspect of the intellectual property for transgenic cell therapies. Although important, technology patents are not typically blocking for CAR-T therapy, as evidenced by the simultaneous development of this technology at multiple prominent companies. However, the safe and reproducible production of these therapies, which can maintain compliance with regulatory standards, requires a significant development of know-how, and CBMG is ahead of many other companies in this regard.

In April 2017, the company signed a collaboration agreement with GE Healthcare Life Sciences China to open a joint laboratory in CBMG's Shanghai facility. The purpose of the lab is to develop industrial control processes for automated CAR-T and stem cell production. We view this collaboration as a significant vote of confidence for the systems that CBMG has in place.

We expect CBMG's production facilities to provide significantly improved costs of goods over cell therapies produced in the US and Europe. There is a high degree of uncertainty regarding the cost of production for different cellular therapies given the limited experience. Dendreon had a COGS of 59% in its final year as a public company for its cell-based prostate cancer vaccine Provenge, a significant improvement over previous years at 70-77%. With a $93,000 price tag for three injections, this translates to an estimated $18,000 in COGS per dose. We expect CAR-T therapy to be more expensive than Provenge as it requires transgenic modification of the cells and generation of the vectors for this purpose. We expect COGS for CAR-T therapies in the US to reach up to $100,000 per course. Given the significantly lower fixed costs in China, we expect an improvement of at least 50%. We expect similar improvements in COGS (albeit from a lower expected rate in the US and Europe) for ReJoin and AlloJoin produced in China as well.

The Chinese market

With its 1.4 billion inhabitants, China is the largest market in the world. Despite this, it ranks as the 20th largest healthcare market at $640bn, with only $108bn in spending on pharmaceuticals.[1] It has

[1] International Trade Administration

also historically been exceptionally hard for the US pharma industry to penetrate and, in 2015, total US drug exports to China were $2bn. China's reimbursement system is almost entirely public, with 97% of individuals covered. This system has always heavily favored domestic above foreign products, which are typically reimbursed at a better rate.

Chinese citizens are covered under one of three schemes: Urban Employee Basic Medical Insurance (UEBMI), Urban Resident Basic Medical Insurance (URBMI), or New Rural Cooperative Medical Scheme (NRCMS). To complicate matters further, each one of these schemes varies based on local government, with wide variations in benefits. UEBMI is by far the best-funded program and the predominant payer in terms of volume, despite only covering 19% of the population. Reimbursement is 75% for inpatient procedures and drugs, and outpatient costs are typically handled via a medical savings account (MSA), which is mandatory for payees and is financed primarily by payroll taxes.

Exhibit 2: Chinese insurance schemes

Program	Acronym	Fraction of population	Target pop.	Inpatient/outpatient reimbursement	Coverage ceiling
Urban Employee Basic Medical Insurance	UEBMI	19%	Urban employees	55%/50%	6x average local worker's wage
Urban Resident Basic Medical Insurance	URBMI	16%	Urban children, unemployed, disabled	75%/use of MSA*	6x average local disposable income
New Rural Cooperative Medical Scheme	NRCMS	62%	Rural residents	55%/50%	8x average local farmer's income

Source: Yu,[2] Hu and Mossialos.[3] Note: * MSA = medical savings account.

Despite the high number of insured individuals, there are still significant hurdles to receiving care in China. Generally in China, patients pay for medical procedures upfront and then apply for reimbursement, which puts patients with low amounts of disposable income at a significant disadvantage. Additionally, although the NRCMS has had significant success in extending coverage to vulnerable people in China's countryside, this population continues to have issues with access to quality care.

Historically, deficiencies in the public health insurance infrastructure have been met through cash payment. The total out-of-pocket contribution for healthcare costs was 33% in 2011 and the government stated a goal of reducing this amount to 30% by 2018.[2] These expenses have been implicated in the exceptionally high rate of household saving in China at 38% in 2014, the highest in the world.[4] This savings rate has consistently increased since the early 2000s with the ageing population of China. In a given year, approximately 13% of Chinese households experience a catastrophic medical expense, defined as spending of more than 40% of their disposable income,[5] so the need to address significant out-of-pocket medical costs is a common occurrence.

It should be noted that there are significant efforts to expand the offering of private insurance in China, and coverage is growing rapidly. As part of healthcare reforms in 2009, the government encouraged insurance companies to provide health insurance products. Increasing the number of privately covered individuals is a feature of the government's current Five-Year Plan. As of 2013, 6.9% of the population bought private insurance, usually as a supplement to public insurance.[6]

Combined, these factors put a degree of pricing pressure on Chinese healthcare costs, For instance, in July 2017 China's Ministry of Human Resources and Social Security negotiated insurance reimbursement for Herceptin (trastuzumab, Roche) at ¥7,200 ($1,066) per vial,

2 Yu H (2015) Universal health insurance coverage for 1.3 billion people: What accounts for China's success? *Health Pol.* 119, 1145-1152.

3 Hu J and Mossialos E (2016) Pharmaceutical pricing and reimbursement in China: When the whole is less than the sum of its parts. *Health Pol.* 120, 519-534.

4 Organisation for Economic Co-operation and Development

5 Ouyang Y (2013) China tackles illness-led poverty as financing gap grows. *Lancet Onco*. 14, 19.

6 Jin Y, et al. (2016) Determinants of Health Insurance Coverage among People Aged 45 and over in China: Who Buys Public, Private and Multiple Insurance *PLOS One*, 11 e0161774.

compared to a pharmacy price of approximately $3,600 in the US. Without insurance Herceptin is priced similarly to the US.

Knee osteoarthritis

CBMG is currently developing two treatments for knee osteoarthritis (KOA), ReJoin and AlloJoin. Both products are human adipose tissue derived mesenchymal progenitor cells (haMPC), although ReJoin is derived from a patient's own adipose tissue whereas AlloJoin is an allogenic product from the same lineage.

The KOA market

Osteoarthritis (OA) is a degenerative bone disease caused by the progressive degradation of cartilage in joints. The disease is primarily caused by progressive damage to the joint that is insufficiently repaired, although genetic factors can account for approximately half of the disease risk.[7] Other risk factors include obesity, advanced age, occupational stress, menopause, and a history of gout or inflammatory disease. As the disease progresses, the persistent irritation can cause the thickening of the synovium leading to stiffening of the joint, and the formation of bone spurs, which cause pain and limit the range of motion. KOA is the most common form of the disease from an incidence perspective (240 per 100,000 person-years), although the prevalence in the knee is lower than in the hand due to age-related effects. The prevalence of KOA increases from 5% in adults over 25 to 19% of those over 45 in the US,[8] making the disorder one of the most common non-infectious diseases. The prevalence in China is 8.1% of individuals over 45.[9]

First-line treatment for KOA typically includes pain management coupled with behavioral changes to reduce risk factors. Exercise and weight loss are typically prescribed for all individuals presenting with symptoms. Exercise in particular has one of the highest effect sizes for any treatment at 0.52 for improvement in pain, compared to 0.32 for nonsteroidal anti-inflammatory drugs (NSAIDs).[10] The nutritional supplements glucosamine and chondroitin are also effective with effect sizes of 0.61 and 0.52 respectively. Patients who do not respond to over-the-counter NSAIDs can be prescribed cyclooxygenase-2 (COX-2) inhibitors, such as Celebrex (celecoxib, Pfizer). Celebrex had peak sales of $2.9bn in 2013, although this includes other indications such as rheumatoid arthritis and acute pain.

Approximately 15% of patients do not have improvement in pain with over-the-counter NSAIDs or COX-2 inhibitors and are candidates for more invasive treatment.[11] Intra-articular corticosteroids are highly effective treatments (effect size of 0.72) and have a better side-effect profile than oral steroids (which are not recommended for OA). However, the steroids only provide pain relief for a matter of weeks, and are therefore limited to the treatment of acute flairs.[12] Intra-articular hyaluronic acid (HA) injections can also be effective in poorly controlled patients (effect size 0.32). HA is a natural polysaccharide that is a major component of synovial fluid and is responsible for its

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7 Spector TD, et al. (2004) Risk factors for osteoarthritis: genetics. *Osteoarthritis and Cartilage*, 12, 39-44.

8 Zhang Y and Jordan JM (2008) Epidemiology of Osteoarthritis. *Rheum. Dis. Clin. North Am.* 34, 515–529.

9 Tang X, et al. (2016) The Prevalence of Symptomatic Knee Osteoarthritis in China. *Arth. & Rheum.* 68, 648-653.

10 Zhang W, et al. (2007) OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis and Cartilage* 15, 981-1000.

11 Kamath CC, et al. (2003) The Cost-Effectiveness of Acetaminophen, NSAIDs, and Selective COX-2 Inhibitors in the Treatment of Symptomatic Knee Osteoarthritis. *Val. in Health* 6, 144-157.

12 Hepper CT, et al. (2009) The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. *J. Am. Acad. Orthop. Surg.* 17, 638-646.

lubricating properties. Additionally it is an essential component of cartilage where it becomes cross-linked into a rigid matrix that provides structural support to the tissue. In patients with OA, HA is depolymerized and reduced in concentration, significantly reducing its joint protecting properties. Therefore, injections of HA can be used to replace the native synovial fluid in a process termed viscosupplementation. HA injections can provide improvement in KOA symptoms for six months or more. There are several brands of HA for intra-articular injection available. Synvisc is produced by Sanofi and had peak sales of $493m in 2013, and the similar brand Artz (Kaken) peaked in 2011 with sales of $403m. The FDA is currently reviewing the marketing NDA for Zilritta (developed by Flexion Therapeutics), a co-formulation of HA and an extended release formulation of the steroid triamcinolone acetonide. It is worth noting, however, that despite the widespread utilization of intraarticular steroids and HA, neither is currently recommended by the American Association of Orthopedic Surgeons, on the basis of lack of comprehensive efficacy data.

There are a number of surgical options for patients with severe deterioration of the knee cartilage that is inadequately addressed by other therapies. The first-line surgical intervention is often arthroscopy, in which the knee is debrided of loose fragments of cartilage. The procedure is performed on approximately 650,000 Americans per year.[13] However, there have been a number of recent studies that have questioned its effectiveness, and improvement in arthritis symptoms is limited.[14] Microfracture surgery is another arthroscopic option, in which after debridement, numerous tiny fractures are introduced into the bone plate underlying the knee cartilage. This process triggers a healing response in which the damaged bone is covered over with a layer of new cartilage. However, this procedure is generally limited to patients 45 years and younger due to the more limited healing response and worse prognosis in older patients. There are approximately 100,000 microfracture procedures performed per year.[15] The most invasive treatment for KOA is partial or total knee replacement in which the joint is replaced with a prosthesis. Although this procedure is typically reserved for patients with debilitating disease and few other options, there are approximately 700,000 total knee replacements done in the US per year.[16]

Regenerative cell therapy for KOA

A significant limitation on the current state of care for KOA is that the only disease modifying treatments are surgical, and there is a significant need for treatments that can improve the course of the disease without exposing the patient to significant risk. There are a large number of patients in which KOA significantly affects daily function who are unfit for surgery, as well as patients with marginal dysfunction in which the risks of the procedure is not justified. Cell-based therapies have been examined as potential solution to this problem as they pose the potential of regenerating the damaged tissue. These procedures can be roughly divided into three categories: platelet rich plasma therapy, chondrocyte replacement and multipotent cell therapy. Platelet rich plasma therapy involves the injection of plasma depleted of red and white blood cell and enriched in platelets into the synovium. In addition to their role in blood clotting, platelets secrete cytokines and growth factors, and the therapy is thought to reduce inflammation and encourage regrowth through the secretion of these molecules, and has a demonstrated efficacy in clinical trials, albeit with effects deteriorating after six months.[17]

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13 National Center for Health Statistics.

14 Kirkley A, et al. (2008) A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee. *New Eng. J. Med.* 359, 1097-1107.

15 Cole BJ and Kercher JS (2010) Special Issue on Microfracture. *Cartilage* 1, 77.

16 Kurtz s, et al. (2007) Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J. Bone Joint Surg.* 89, 780-785.

17 Patel S, et al. (2013) Treatment With Platelet-Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis. *Am. J. Sports Med.* 41, 356-364.

Chondrocytes are the cells that secrete and maintain cartilage, and these cells become fewer in number as OA progresses. The companies Vericel and Histogenics have developed products based around the isolation, expansion, and re-implantation of a patient's own chondrocytes into lesions in knee cartilage. Treatment using these products requires surgical intervention to directly attach the cells to tissue lesions, and is therefore not a means to avoid surgery. Moreover, these techniques can only be used in patients with relatively small defects. Despite these limitations, generally these procedures show improved tissue regrowth and resolution of symptoms compared to microfracture. Vericel had sales of $38.9m for its Carticel product (a chondrocyte suspension) in 2016. The company's MACI product (chondrocytes cultured on a collagen matrix) was approved in 2016, and Histogenics has a similar supported chondrocyte product called NeoCart in Phase III.

The approach to using multipotent cells is somewhat different. The mechanism by which these cells regenerate cartilage is poorly understood. Multipotent cells (meaning either stem cells or more highly differentiated progenitor cells) have the potential to differentiate into a wide array of tissues. Historically, despite the many promises to the contrary, these cells have shown little ability to differentiate and replace damaged tissue across the wide number of indications they have been tested in. However unlike in many other tissues, there is evidence in animal models that stem cells can engraft into cartilage.[18] Many of the regenerative properties of multipotent cells appear to be tied to their ability to secrete high concentrations of anti-inflammatory and pro-regenerative signaling molecules. Cells used this way for the treatment of KOA can be administered via intraarticular injection, without the need for more invasive techniques. There have been a number of published reports of pilot studies on a small number of patients (under 50) that consistently show improvement in disease symptoms and regrowth of tissue using both patient derived (autologous) and donated (allogeneic) multipotent cells.[19,20] Cytori Therapeutics previously had a Phase IIa/b clinical trial using adipose derived regenerative cells (although not a progenitor cell isolate) in KOA, although this trial failed to meet its primary endpoint of reduction in pain at 48 weeks. There is only one Phase I clinical trial in China for KOA that is sponsored by a healthcare company (Shenzhen Hornetcorn Bio-technology Company) listed on Clinicaltrials.gov, although we have few details on the program. Additionally, there have been some stem cell clinics that have offered stem cell injections for the treatment of KOA, although these clinics are largely unregulated and subject to increasing regulatory pushback after some high-profile cases of malpractice. Otherwise, there is very little research into disease-modifying medical treatments for KOA.

ReJoin clinical results

CBMG is developing ReJoin as an autologous haMPC product for the treatment of KOA. The cells are initially isolated from a patient during liposuction, after which the mesenchymal progenitor cells are separated from the surrounding adipose tissue. These cells are then expanded in tissue culture via the company's proprietary manufacturing techniques, and subsequently reinjected into the affected joints.

Some of the most detailed information available on the chondrogenic potential of this therapy comes from a preclinical study the company published using a rabbit model of KOA.[21] KOA was induced in these animals by surgically transecting the anterior cruciate ligament (ACL), which allowed the joint to deteriorate over six weeks. The study compared the effects of the therapy

[18] Koelling S and Miosge N (2009) Stem cell therapy for cartilage regeneration in osteoarthritis. *Expert Opin. Biol. Ther.* 9,1399–1405.

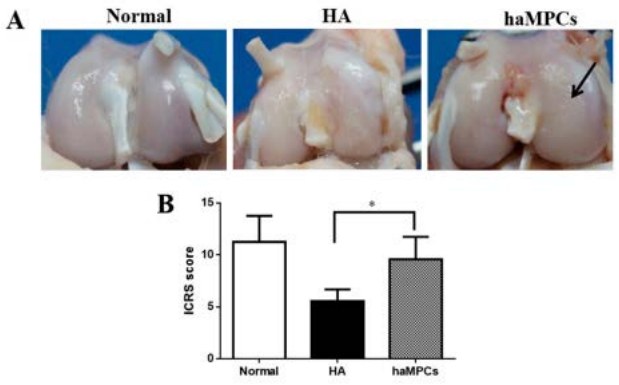
[19] Jo CH, et al. (2014) Intra-Articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee: A Proof-of-Concept Clinical Trial. *Stem Cells* 32, 1254-1266.

[20] Vega A, et al. (2015) Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation* 99, 1681-1690.

[21] Wang W, et al. (2015) Human Adipose-Derived Mesenchymal Progenitor Cells Engraft into Rabbit Articular Cartilage. *Int. J. Mol. Sci.* 16, 12076-12091.

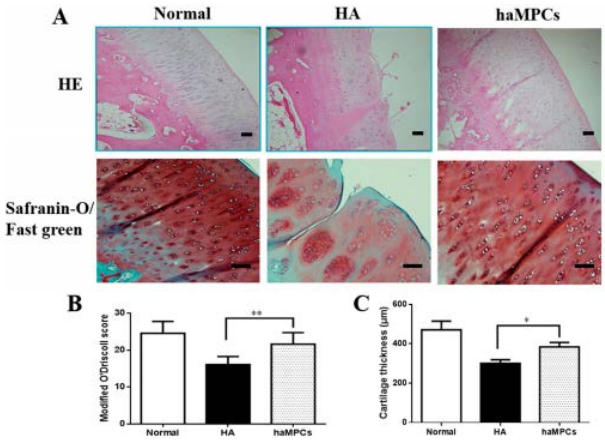
compared to HA injection as a control after 16 weeks. The cell therapy unilaterally showed a statistically significant improvement in lesion size and cartilage thickness when compared to control (Exhibits 3-4). Additionally, when cartilage from the rabbits was stained for human cellular markers, it was shown that the haMPCs had engrafted into the cartilage tissue, confirming that this cell fraction behaves similarly to other multipotent cell therapies and that it has the potential to provide long-term cartilage protection. It should be noted that in this model system the joints of these animals degenerate very quickly over a matter of weeks, as opposed to years in the case of KOA in humans. This may significantly impact the nature of the tissue damage and its ability to respond to cell therapy.

Exhibit 3: haMPCs stimulate cartilage repair in rabbit model



Source: Wang et al. Note: A) haMPC induce the regrowth of cartilage tissue (black arrow). B) International cartilage repair society (ICRS) scores for cartilage regrowth; *p<0.05.

Exhibit 4: haMPCs reduce fissures and increase cartilage thickness in rabbit model



Source: Wang et al. Note: A) Histological stain showing the repair of cracks in cartilage with haMP treatment. B) Modified O'Driscoll histological score of cartilage content;** p<0.01. C) Cartilage thickness in μm; * p<0.05.

The company has performed two clinical trials on ReJoin. The first study was an open-label dose-ranging Phase I/IIa study enrolling 18 patients, performed at Renji Hospital in Shanghai. Patients received two doses of 10, 20 or 50 million cells three weeks apart and were followed for six months. The primary endpoints of the trial were improvement in pain measured on the 11-item Numeric Rating Scale (NRS-11) and improvement in the Western Ontario and McMaster Universities Arthritis Index (WOMAC). WOMAC is a 24-item questionnaire measuring the impact of arthritis on daily function, such as pain while walking or ability to rise from bed or go shopping. Additionally the study measured changes in cartilage volume using MRI, which is the recommended radiographic assessment technique.[22] The study showed significant impacts on all three of these measures when compared to baseline 24 weeks after treatment (Exhibit 5). The improvement in pain (NRS-11) lost statistical significance by the end of the trial, but the improvement in function (WOMAC) and new cartilage was persistent. Additionally, the increase in cartilage volume showed a remarkably linear trend (although the baseline was not disclosed).

Exhibit 5: Results from ReJoin Phase I/IIa trial

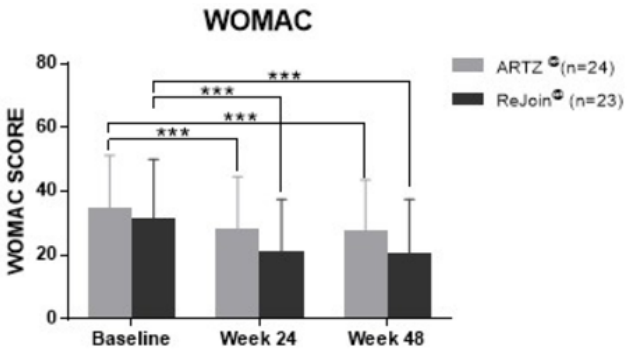
Weeks	NRS-11	p	WOMAC	p	Increase in cartilage (mm^3)	p
Baseline	4.49		34.75		0	
12	2.19	<0.01	25.94	<0.0001	25.71	n.s.
24	2.62	<0.01	20.38	0.0002	53.07	0.026
48	3.62	n.s.	22.77	0.0044	104.23	0.0002

Source: Cellular Biomedicine Group

[22] Conaghan PG, et al. (2011), Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group. *Osteoarth. Cart.* 198, 606-610.

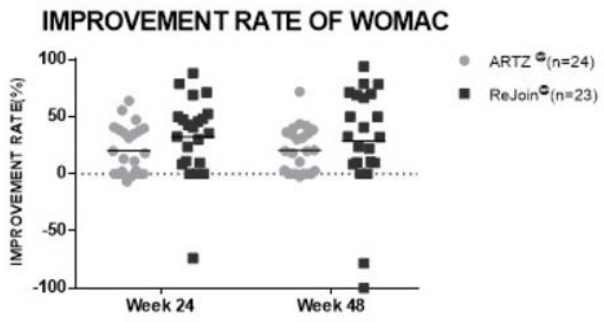
Based on these encouraging results, the company progressed to a 48-person Phase IIb study that compared ReJoin with Artz, a brand of HA viscosupplementation therapy. The trial enrolled patients with grade 1 to 3 KOA (out of 4 on the Kellgren-Lawrence scale). The primary endpoint of the trial was improvement in WOMAC after 48 weeks, with secondary endpoints of pain improvement on the Visual Analogue Scale (VAS) and increase in cartilage volume. Additional data readouts were planned for 24, 72, and 96 weeks. The study showed consistent improvement in WOMAC scores from baseline (p<0.001), and although these scores trended towards larger improvements in the ReJoin arm, the difference from Artz was not statistically significant (Exhibit 6). There were a small number of dramatic outliers in the ReJoin arm based on data provided by the company on the rate of improvement in WOMAC (Exhibit 7). However, we lack insight into the reason behind these outliers and we cannot rule out treatment effects. A higher number of patients saw improvements in WOMAC of over 50% (8 vs 1, p=0.0083) and over 70% (6 vs 1, p=0.036) compared to Artz, although it should be noted that this analysis was done post hoc. ReJoin showed significant improvements over Artz in pain (p<0.02) and in the regrowth of cartilage (p=0.0012) (Exhibit 8). Patients regained or retained almost half a cubic centimeter of cartilage (427mm^3) more than Artz patients.

Exhibit 6: WOMAC scores from ReJoin Phase IIb



Source: Cellular Biomedicine Group. Note: *** p<0.001.

Exhibit 7: WOMAC improvement rate showing outliers from ReJoin Phase IIb



Source: Cellular Biomedicine Group

Exhibit 8: Results from the ReJoin Phase IIb trial at 48 weeks

	VAS improvement	WOMAC improvement	Increase in cartilage (mm^3)
ReJoin (n=23)	47.20%	9.48	302.06
Artz (n=24)	13.65%	6.92	-125.35
p	<0.002	n.s.	0.0012

Source: Cellular Biomedicine Group

The company has not provided a full accounting of adverse events for the two clinical trials, although it has stated that no serious adverse events were reported. The most common adverse events reported in the Phase I/IIa trial were knee pain (50% of patents) and knee swelling (72% of patients), and these were mild to moderate in severity. This result is not particularly surprising given that a bolus is being delivered into the intraarticular space, which is of limited volume. Given that ReJoin constitutes the patient's own cells, we find it unlikely that significant safety concerns should arise.

AlloJoin: Off-the-shelf cells for KOA

Based on the data from the ReJoin clinical trials, the company decided to develop an allogenic product from the same haMPC cell lineage, called AlloJoin, derived from adipose tissue provided by donors. This product removes the necessity to isolate and expand cells from patients as required with ReJoin and has the potential to replicate ReJoin's clinical properties. In the preclinical rabbit study, haMPCs were used allogeneically and fully incorporated into the animals' tissue. It should be noted that these cells did express human leukocyte antigen (HLA) class 1 proteins that are targeted

when foreign tissue is rejected, although it did not seem to pose an issue in the preclinical studies. Additionally, given that the cells constitute a small amount of tissue, unlike stem cell transplants and solid organ transplants safety risks will likely be minor, although it may limit the longevity of the treatment.

AlloJoin also has certain logistic benefits over ReJoin. Autologous cells like ReJoin require the cells to be processed at a medical facility and returned to the patient in a timely manner. AlloJoin, by comparison, would allow for the large-scale production and storage of cells, significantly simplifying the supply chain.

Although AlloJoin improves the scaling and logistics of manufacturing, the company will be unable to leverage its Chinese production capacity outside of that country. The PRC has enacted a series of measures to limit the exploitation of “human genetic resources”, which include any samples that include human DNA. Currently the export of human samples must be made on a case by case basis, and approval is only made quarterly. This effectively makes the exportation of human cellular products from China unfeasible. To this end, the company announced in February that it received a $2.29m grant from the California Institute of Regenerative Medicine (CIRM) to aid in the establishment of cell processing in the US and the filing of an IND with the FDA. The therapy would potentially be eligible for a Regenerative Medicine Advanced Therapy (RMAT) Designation, which would provide increased interaction with the FDA as well as increased review flexibility.

The company is currently performing a Phase I safety study of AlloJoin in 22 KOA patients in China. Similar to the ReJoin Phase I/IIa trial, patients are enrolled in three dosage arms (10, 20 and 50 million cells) and will be followed for up to one year for safety and efficacy (with an interim efficacy readout at six months). The trial has already reported three-month interim safety data (as of December 2016), which showed no serious adverse events. Other reported adverse events were similar to those seen in the ReJoin Phase I/IIa clinical trial, the most common being knee pain (77%) and knee swelling (54%). We expect the full six-month results from the trial to be released in H217.

CAR-T

One of the clearest opportunities for CBMG is to leverage its Chinese cell processing capacity in the realm of CAR-T therapy. CAR-T is an immuno-oncology therapy in which a patient’s T-cells are expanded and transgenically modified to target specific cancer targets. The company is developing a CAR-T product called C-CAR011 targeting CD19 (cluster of differentiation 19), a marker on B-cells, and is testing the product in two ongoing clinical programs: CARD-1 for diffuse large B-cell lymphoma (DLBCL) and CALL-1 for adult acute lymphoblastic leukemia (ALL). The company will be pursuing approval in the Chinese market, as export of the product from China is not possible given that it is human tissue. The technology was initially developed by PLA General Hospital in Beijing, and licensed by CBMG in February 2015, where it was subsequently developed and optimized internally. The technology can be considered a second-generation CAR-T and includes a 4-1BB costimulatory domain, and it uses a lentiviral vector.

CD19 is the most prominent target for CAR-T therapy in the industry. The protein is a marker for immature B-cells (those that are not terminally differentiated into plasma cells), and is present on the abnormal cells of B-cell cancers. Significant effort has been made to study CAR-T therapies in China, and there are no-less than 20 ongoing CD19 CAR-T studies in the country, supported by at least 12 Chinese companies, although these programs are generally early stage, and there is little information on their progress (Exhibit 9). Western companies have also recognized the potential of the Chinese market, and some of the major US players have out-licensed the technology, such as Kite to WuXi AppTec and Juno to Fosun. Novartis has a corporate presence in China, but to our knowledge does not have any CAR-T capacity in the country.

The first CAR-T therapy to be approved in the world was Kymriah (tisagenlecleucel, Novartis) in August 2017 for the treatment of pediatric and young adult patients with ALL at a price of $475,000 per treatment. Additionally, the company announced that it was in discussions with the Centers for Medicare and Medicaid Services (CMS) to develop an efficacy-based billing program, so this price may not reflect the eventual net price per end-user. Kite Pharmaceuticals also has a pending application for approval of its CD19 CAR-T therapy (for the treatment of DLBCL) with an FDA decision expected before 29 November 2017. Gilead announced the intent to acquire Kite and its CAR-T programs for $12bn in August 2017.

Exhibit 9: Selection of CD19 CAR-T programs in China and US

Stage	Product Name	Company	Chinese footprint
Approved	Kymriah	Novartis	No CAR-T*
BLA	Axicabtagene Ciloleucel	Kite Pharma	Licensed to Fosun
Phase II	JCAR017	Juno Therapeutics	Licensed to WuXi AppTec
Phase II	JCAR014	Juno Therapeutics	Licensed to WuXi AppTec
Phase II	Armored CARs	Juno Therapeutics	Licensed to WuXi AppTec
Phase II	JCAR014	Juno Therapeutics	Licensed to WuXi AppTec
Phase II	CTL119	Novartis	No CAR-T*
Phase I	JCAR021	Juno Therapeutics	Licensed to WuXi AppTec
Phase I	Undisclosed	ZIOPHARM Oncology	N/A
Phase I	UCART-19	Cellectis	N/A
Phase I	C-CAR011	Cellular Biomedicine Group	Ongoing in China
Phase I	Undisclosed	Shanghai GeneChem Co	Ongoing in China
Phase I	Undisclosed	Hebei Senlang Biotechnology	Ongoing in China
Phase I	Undisclosed	Sinobioway Cell Therapy Co	Ongoing in China
Phase I	Undisclosed	Wuhan Sian Medical Technology	Ongoing in China
Phase I	CSG-CD19	Carsgen Therapeutics	Ongoing in China
Phase I	Undisclosed	Beijing Doing Biomedical	Ongoing in China
Phase I	Undisclosed	Union Stem cell & gene engineering Co.	Ongoing in China
Phase I	Undisclosed	The Beijing Pregene Science and Technology Company	Ongoing in China
Phase I	Undisclosed	Beijing Sanwater Biological Technology Co	Ongoing in China
Phase I	SDS-19CAR	Innovative Cellular Therapeutics Co	Ongoing in China

Source: Evaluate Pharma, Clinicaltrials.gov Note: *based on best available information.

DLBCL

DLBCL is the most common variety of non-Hodgkin lymphoma, making up approximately 30% of all new cases of the disease. Like other B-cell lymphomas, it is characterized by the proliferation of abnormal B-cells that accumulate in the lymph nodes and destroy their underlying structure. The genetic causes of the disease are diverse and truly it represents an underlying cluster of diseases based on the precise defect and histology. Because of this, the disease can be complex to treat, with widely varying prognoses depending on subtype. For instance, the five-year survival is only 10% when the disease affects bone marrow, compared to over 60% in the disease as a whole.[23] DLBCL is one of the most common hematologic cancers in the Western world, with approximately seven cases per 100,000 in the US. By comparison, the rate in China is much lower: the underlying rate of lymphoma in China is 6.4 people per 100,000,[24] so we estimate a rate of DLBCL of approximately 1.3 per 100,000.

The treatment of DLBCL is similar to other lymphomas and includes a combination of targeted therapy and chemotherapy. The standard of care first-line therapy for the disease is the so-called R-CHOP regimen, consisting of the targeted therapy Rituxan (rituximab, Genentech/Biogen) combined with the chemotherapies cyclophosphamide, doxorubicin, and vincristine, and the immunosuppressant prednisone. Rituxan had $7.3bn in sales in 2016 predominantly due to its use

[23] NIH SEER database.

[24] Chen W, et al. (2016) Cancer statistics in China, 2015. *CA: Can. J. Clin.* 66, 115-132.

in hematologic disorders, although this figure includes other indications such as rheumatoid arthritis and vasculitis.

CBMG initiated a Phase I clinical trial (CARD-1) in China to investigate C-CAR011 for DLBCL in November 2016. The trial is being performed at a single center (Jiangsu People's Hospital) and will enroll 15 refractory DLBCL patients at three ascending doses. The primary endpoint is determination of any dose-limiting toxicities measured 30 days after treatment. The trial should move quickly based on this timeline, with results expected around the end of 2017.

Adult ALL

ALL is similar to DLBCL in that it is caused by the over proliferation of lymphocytes, although unlike DLBCL, these dysfunctional cells accumulate primarily in the bone marrow. In the majority of ALL cases, B-cells or B-cell progenitors overproliferate (so called B-ALL, approximately 75% of cases), although T-cells can be affected in a minority,[25] and therapies such as CD19 CAR-Ts would not be appropriate for these patients. Unlike the vast majority of cancers, ALL afflicts children as well as adults and 30% of ALL cases occur before the age of 15. It is the most common childhood cancer and leading cause of cancer deaths among children despite the fact that the five-year survival rate is high at 90%. By comparison the survival for adult patients is significantly lower at 40% for those aged 25 to 64 and 15% for those 65 and older. The disease is most common in Caucasian populations, but tends to be more aggressive in non-Caucasians. We estimate the incidence of ALL in China at 1.4 per 100,000[24,26] compared to 1.7 per 100,000 in the US.[23]

Treatment for adult ALL is typically combination chemotherapy including an anthracycline (such as doxorubicin) and other chemotherapy drugs such as vincristine, combined with immunosuppression with steroids. A common genetic feature in ALL (and other leukemias) is the formation of the Philadelphia chromosome (25% of ALL cases), and these patients can be treated with Bcr-Abl tyrosine kinase inhibitors such as Gleevec (imatinib, Novartis) or Sprycel (dasatinib, Bristol-Meyers Squibb). Patients who are deemed healthy enough for intensive therapy may undergo hematopoietic stem cell transplants (HSCT).

In January 2017, the company announced that it had begun enrolling patients in a Phase I clinical study (CALL-1) of C-CAR011 at PLA General Hospital. Similar to the DLBCL trial, the primary endpoint will be dose-limiting toxicities. The study will enroll 20 adult patients with relapsed and refractory CD19 positive B-ALL in ascending doses. The company stated that it expects to have data around the end of 2017.

The ALL pilot study

There currently is no in-human data for C-CAR011. However, a previous iteration of the technology (CBM-C19.1) has been evaluated for adult ALL in a published pilot study. [27] The study examined the therapy for the treatment of patients with adult ALL, but it has efficacy implications for other B-cell malignancies such as DLBCL. The study enrolled nine patients with an average of three prior therapies and who had never achieved a minimal residual disease response. Importantly three of these patients had received stem cell transplants, which means that although the T-cells used in the therapy were autologously sourced from the patient, they represent allogeneic tissue.

Four of the nine patients achieved a complete remission (CR) or were minimal residual disease negative (MRD-) for a response rate of 44%. This is significantly less than the 88% CR rate reported by Davila et al. in a 16-person study of relapsed and refractory adult ALL patients

[25] American Cancer Society

[26] Yang C and Zhang X (1991) Incidence survey of leukemia in China. *Chin. Med. Sci. J.* 6, 65-70.

[27] Dai H, et al. (2015) Tolerance and efficacy of autologous or donor-derived T cells expressing CD19 chimeric antigen receptors in adult B-ALL with extramedullary leukemia. *Oncoimmunology* 4, e1027469.

(technology from this study was licensed to Juno).[28] This could potentially be explained due to disease severity as the patients in the Davila study had half as many prior therapies, but it is hard to rule out differences in efficacy. The median overall survival in the C-CAR011 study was 18 weeks at the time of completion, which is better than the median of survival of three months in patients on their third treatment.[29]

However, one of the striking features of this study was the adverse event profile. There were four patients with cytokine release syndrome (CRS), which is to be expected with CAR-T therapy: seven out of 16 patients had CRS in the Davila study. Two patients in the study developed graft vs host disease (GVHD). GVHD is a rare adverse event in CAR-T trials,[30] and has only been observed in one other study that we have been able to find, and at a much lower rate than the current study in line with rates expected for their patient population.[31] It has been seen in animal studies using allogeneic cells,[32] and the two patients who developed GVHD had both previously received HSCT, meaning the T-cells used were not of patient origin. However, other studies such as Davila et al. used patients with prior HSCT without issue. These events could be the result of either the treatment or the design of the clinical trial if sufficient precautions were not taken to exclude patients with a history of GVHD.

Exhibit 10: Patient responses from adult ALL study

Patient	Conditioning therapy	Prior HSCT	CAR-T Dose (m cells)	Response	PFS (weeks)	OS (weeks)	AE (Grade)
1	None	No	220	MRD-	9	>54	CRS (1)
2	Yes	No	360	Progression	0	4	CRS (4)
3	None	No	400	Progression	0	18	
4	None	No	290	CR	0	20	CRS (4)
5	None	No	790	Progression	0	14	
6	None	No	320	Elimination from CNS	>20	>25	
7	None	Yes	530	MRD-	>38	>53	Oral ulcers (1), neurological symptoms (1)
8	None	Yes	250	Hematologic improvement	0	8	Neurological symptoms (1), GVHD (2)
9	Yes	Yes	230	CR	0	>12	CRS (3), GVHD (2)

Source: Dai et al. Note: MRD- = minimal residual disease negative, CR = complete remission, CNS = central nervous system, CRS = cytokine release syndrome, GVHD = graft vs host disease.

The company states that C-CAR011 “represents an advancement” over CMB-19.1, although no details have been provided. It is unclear at this point what aspects of the therapy have changed and if it will have an improved efficacy or safety profile.

Sensitivities

CBMG faces the typical risks of a development-stage biotechnology company, coupled with unique risks associated with its Chinese operational focus. Cell therapies in general pose a high development risk because of the relatively small number of approved products. Of the company’s four clinical stage programs, ReJoin is the only product that has supporting efficacy data in humans, although it failed to reach statistical significance in Phase IIb. Despite this, the therapy demonstrated a capacity to regrow cartilage, which could be leveraged in a future trial design. We

[28] Davila ML, et al. (2014) Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. *Sci. Trans. Med.* 6, 224ra25

[29] O’Brien S, et al. (2008) Outcome of Adults With Acute Lymphocytic Leukemia After Second Salvage Therapy. *Cancer* 113, 3186-3191.

[30] Anwer F, et al. (2017) Donor origin CAR T cells: graft versus malignancy effect without GVHD, a systematic review. *Immunother.* 9, 123-130.

[31] Kebriaei P, et al. (2016) Phase I trials using *Sleeping Beauty* to generate CD19-specific CAR T cells. *J. Clin. Invest.* 126, 3363-3376.

[32] Jacoby E, et al. (2016) Murine allogeneic CD19 CAR T cells harbor potent antileukemic activity but have the potential to mediate lethal GVHD *Blood*, 127, 1361-1370.

expect AlloJoin to show similar efficacy, but there is the possibility of tissue rejection with these allogeneic cells. It is known that haMPCs express HLA proteins, and therefore may be recognized by the host immune system, although this has not been observed in preclinical programs.

There is risk associated with the development of both CAR-T programs, given their early stage and lack of supporting clinical data. The pilot study of the similar CBM-C19.1 in adult ALL showed efficacy in some severely sick patients, but had cases of GVHD. We assume that this was in part the motivation for the development of the next-generation therapy C-CAR011, although the degree to which the new technology can improve efficacy and limit adverse events is yet to be seen.

China is an exceptionally large market, but there are still significant hurdles to utilizing this market. Although insurance coverage is high, a majority are covered under NRCMS, which provides only minimal coverage. Even in the well insured urban population, there are significant headwinds because patients must prepay for care, reimbursement rates are low, and there is a ceiling on reimbursement. However, household savings in China are the highest the world, in part driven by planning for healthcare needs, which offsets some reimbursement risks. We assume that the urban-dwelling Chinese (those covered under UEBMI and URBMI) will have sufficient insurance coverage and personal savings to represent a market for CBMG's products. These factors will have a significant impact on the pricing for CBMG's products, in particular the CAR-T products, which are expected to command high prices relative to other therapies.

There are a large number of companies developing CAR-T therapies in China. CBMG is the only US-domiciled company to have ongoing clinical trials in China, although there are a large number of China-domiciled competitors and the major US CAR-T companies such as Kite and Juno have out-licensed their technology to major Chinese healthcare companies (Fosun and WuXi AppTec). By comparison, there are very few competing cell therapy programs for KOA in China or the US.

The competitive risk of the CAR-T programs is partially offset by CBMG's established manufacturing presence. There is significant intellectual property associated with the manufacturing know-how in a space that generally lacks blocking protections. Additionally, considering the regulatory complexities regarding this technology, the early establishment of this know-how should improve the pathway to approval.

The company had operating losses of $28m in 2016, which are expected to increase with more programs in the clinic. We project that the company will require $140m in additional financing before profitability in 2024, although (and cash raised to date of $94m) this is low compared to the cost for other companies to develop CAR-T alone. For instance, Kite has an accumulated deficit of $427m, and its lead development program was in part funded by the National Cancer Institute.

Valuation

We arrive at an initial valuation of $191.6m or $13.58per basic share. This value was arrived at using a risk-adjusted NPV analysis of the company's four clinical programs based on a series of assumptions. We currently model a launch of C-CAR011 and ReJoin in China, and AlloJoin in the US and China. We currently only include urban Chinese patients covered by UEBMI and URBMI in our model, an estimated 484m lives in 2017. We assume 2% price growth per year in both the Chinese and US markets.

C-CAR011

We give the DLBCL and ALL programs a 20% probability of success, because the earlier version of the product was active (as evidenced by the ALL pilot study), although the current human data on the potency or durability limited.

We assume a launch price of C-CAR011 for both DLBCL and ALL of approximately $84,000. This is a significant discount to CAR-T pricing announced by Novartis at $475,000, and a significant hurdle for patients in the Chinese reimbursement market, but achievable to a degree with a combination of insurance and cash. The DLBCL incidence rate is assumed at 1.3 per 100,000 person years based on reported incidence of NHL of 6.4 per 100,000 in China, of which 30% are assumed to be DLBCL based on data from Western countries. The rate of ALL in China is estimated at 1.7 per 100,000 person years (based on extrapolation of historical rates with the growing baseline incidence of leukemia), of which 75% are expected to be the B-cell type and 70% are expected to be in adults based on Western data. This corresponds to an incidence of 0.7 per 100,000 for adult B-cell ALL.

We expect penetration of 25% for both indications. We expect clinical trials for these programs to be significantly less expensive than trials performed in the US, costing an estimated $30,000 per patient. Finally, we believe that the company can significantly constrain COGS using its efficient manufacturing platform, and we expect COGS in the 15% range.

ReJoin and AlloJoin

We calculate the target market for the KOA products as the refractory KOA patients. In China 8.10% of people over 45 (33.2% of the population) have KOA, of which we assume 15% are refractory to pain medication based on Western data, for a target prevalence of 0.4%. Our calculated prevalence in the US is slightly higher at 0.5% based on KOA of 4.5% in the population over 25 (65% of total) of which 15% are refractory.

We expect ReJoin will be the first product on the market with a 2021 approval and a 2022 launch if the program re-enters the clinic in 2017. We assume a 40% probability of approval, which is lower than standard for programs ready to enter Phase III, because of the lack of statistically significant superiority to viscosupplementation in the Phase IIb clinical trial. We expect that the product will be priced at approximately $10,000 during its launch year, which is around four times the US price of Synvisc. We believe that this price is justified considering it may result in lasting regeneration of cartilaginous tissue and reduce the need for future therapy. We model penetration of 0.5% of the Chinese refractory KOA market, largely limited by it requiring a liposuction procedure. We do not model the product for any market outside China due to the limitation on tissue export. We expect a 250-person Phase III (based on the trial size for Synvisc) costing $20,000 per patient. We expect COGS to be significant at 50%, although this is significantly lower on an absolute basis than the CAR-T therapies because of the increased simplicity in processing non-transgenic cells like haMPC.

We predict a lower probability of success of 15% for AlloJoin because of the lack of data in humans and the potential for tissue graft rejection with its administration. We predict pricing of approximately half that of ReJoin in both China and the US, and several times the penetration (3% in China, 4% in the US). We have included in our calculation cannibalism of ReJoin in China as we expect AlloJoin to replace the ReJoin market if it can produce similar results. We forecast a launch of AlloJoin in 2024 in both the US and China. Our US peak sales estimates are roughly in line with previous peak sales of HA products, which we think is reasonable, considering that it performs at least as well.

We expect to update our valuation with clinical results, and we expect readouts for the AlloJoin, DLBCL, and ALL studies in 2017. We currently do not include any valuations for the company's preclinical assets such as the other non-CD19 CAR-T programs or the Dendristim cancer vaccine. However, we may add these programs to the valuation in the future with more information on the programs. The readouts from the CD19 CAR-T programs may provide validation of the CAR-T manufacturing and development platform, and we expect the anti-BCMA program to be the next to enter the clinic. We may also increase our valuation with further business development activities.

Exhibit 11: Valuation of Cellular Biomedicine Group

Development Program	Region	Prob. of success	Launch year	Peak sales ($m)	Margin	rNPV ($m)
DLBCL	China	20%	2024	181	63%	37.6
ALL	China	20%	2024	102	62%	20.4
ReJoin	China	40%	2022	143	30%	24.8
AlloJoin	China	15%	2024	420	58%	39.9
AlloJoin/Rejoin cannibalism	China					(12.6)
AlloJoin	US	15%	2024	474	47%	54.2
Total						$164.3
Net cash and equivalents (Q217) ($m)						$27.3
Total firm value ($m)						$191.6
Total shares (m)						14.1
Value per basic share ($)						$13.58
Options						1.2
Value per diluted share ($)						$13.29

Source: Cellular Biomedicine Group reports, Edison Investment Research

Financials

CBMG has historically been a loss-making company, and had losses of $29.2m in 2016 and $12.3m for H117. These losses have been steadily increasing over recent years ($13.8m in 2014 and $21.1m in 2015), driven largely by increases in R&D spending ($2.1m in 2014, $7.6m in 2015, $11.5m in 2016). We expect spending to remain at these levels in 2017 but to steadily increase in response to the various products entering Phase III in the 2020 timeframe. The company has historically had a small amount of revenue from consulting services to hospitals on cell therapy development. However, in H117 these revenues totaled less than $200,000, and we do not include this in future forecasts. The company raised $19.1m from stock in 2014 and $19.6m in 2015, which increased to $43.3m in 2016. We believe that the current cash balance of $27.3m should be sufficient to finance operations into 2018 at the current run rate. In June 2017 the company announced a $10m stock buyback program, of which $1.3m was deployed in Q217. We model that the company will need $140m in additional cash to reach profitability in 2024, which we model as illustrative debt: $60m in 2018 and $80m in 2021. The financial burden could potentially be alleviated through the out-licensing of products or production capacity. We believe that the company's manufacturing capacity should be sufficient to support the commercialization of its products in China, although some manufacturing will been needed in the US to support AlloJoin in that market, which we include as approximately $3m in PPE spending before approval.

Exhibit 12: Financial summary

$000s	2014	2015	2016	2017e	2018e
31-December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
INCOME STATEMENT					
Revenue	564	2,505	628	161	0
Cost of Sales	(242)	(1,880)	(860)	(75)	0
Gross Profit	322	625	(232)	86	0
EBITDA	(7,295)	(11,038)	(15,716)	(16,199)	(17,935)
Normalised operating profit	(8,486)	(13,133)	(18,351)	(19,529)	(17,935)
Amortisation of acquired intangibles	(1,428)	(123)	(4,612)	0	0
Exceptionals	0	0	0	0	0
Share-based payments	(2,529)	(7,592)	(5,452)	(5,843)	(5,843)
Reported operating profit	(12,442)	(20,849)	(28,415)	(25,371)	(23,778)
Net Interest	15	42	79	171	109
Joint ventures & associates (post tax)	0	0	0	0	0
Exceptionals	72	630	132	554	0
Profit Before Tax (norm)	(8,399)	(12,460)	(18,140)	(18,804)	(17,826)
Profit Before Tax (reported)	(12,355)	(20,176)	(28,204)	(24,647)	(23,669)
Reported tax	0	729	(4)	(7)	0
Profit After Tax (norm)	(8,399)	(12,460)	(18,140)	(18,804)	(17,826)
Profit After Tax (reported)	(12,355)	(19,448)	(28,208)	(24,654)	(23,669)
Minority interests	0	0	0	0	0
Discontinued operations	(1,493)	(1,684)	(1,001)	106	0
Net income (normalised)	(8,399)	(12,460)	(18,140)	(18,804)	(17,826)
Net income (reported)	(13,848)	(21,132)	(29,209)	(24,548)	(23,669)
Basic average number of shares outstanding (m)	9	11	14	14	14
EPS - basic normalised ($)	(0.97)	(1.09)	(1.34)	(1.38)	(1.25)
EPS - diluted normalised ($)	(0.97)	(1.09)	(1.34)	(1.38)	(1.25)
EPS - basic reported ($)	(1.61)	(1.84)	(2.16)	(1.81)	(1.66)
Dividend ($)	0.00	0.00	0.00	0.00	0.00
Revenue growth (%)	(86.1)	343.9	(74.9)	(74.3)	N/A
Gross Margin (%)	57.1	24.9	-37.0	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Normalised Operating Margin	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	27,590	32,766	27,936	28,517	28,787
Intangible Assets	18,835	23,628	21,771	20,939	20,939
Tangible Assets	1,280	2,769	4,118	5,082	5,352
Investments & other	7,474	6,369	2,047	2,496	2,496
Current Assets	16,095	16,694	40,692	13,021	51,951
Stocks	372	391	0	0	0
Debtors	277	902	453	1,106	1,106
Cash & cash equivalents	14,771	14,885	39,252	10,920	49,849
Other	676	517	987	995	995
Current Liabilities	(4,076)	(3,019)	(2,364)	(3,170)	(3,256)
Creditors	(427)	(261)	(216)	(889)	(974)
Tax and social security	(814)	0	(29)	(29)	(29)
Short term borrowings	0	0	0	0	0
Other	(2,835)	(2,758)	(2,119)	(2,253)	(2,253)
Long Term Liabilities	(453)	(76)	(370)	0	(60,000)
Long term borrowings	0	0	0	0	(60,000)
Other long term liabilities	(453)	(76)	(370)	0	0
Net Assets	39,156	46,365	65,894	38,368	17,482
Minority interests	0	0	0	0	0
Shareholders' equity	39,156	46,365	65,894	38,368	17,482
CASH FLOW					
Op Cash Flow before WC and tax	(7,295)	(11,038)	(15,716)	(16,199)	(14,875)
Working capital	(1,347)	(1,898)	(255)	36	86
Exceptional & other	(1,079)	1,186	104	717	(2,951)
Tax	0	0	0	0	0
Net operating cash flow	(9,721)	(11,751)	(15,868)	(15,446)	(17,741)
Capex	(321)	(6,135)	(2,733)	(3,037)	(3,330)
Acquisitions/disposals	(1,486)	(1,569)	0	0	0
Net interest	0	0	0	0	0
Equity financing	19,141	19,647	43,286	(9,994)	0
Other	(32)	1	0	0	0
Net Cash Flow	7,583	194	24,684	(28,478)	(21,071)
Opening net debt/(cash)	0	(7,595)	(7,709)	(32,077)	(3,745)
FX	13	(80)	(317)	145	0
Other non-cash movements	0	0	0	0	0
Closing net debt/(cash)	(7,595)	(7,709)	(32,077)	(3,745)	17,326

Source: Cellular Biomedicine Group reports, Edison Investment Research

Contact details	Revenue by geography
19925 Stevens Creek Blvd. Suite 100 Cupertino, CA 95014 US +1 408-973-7884 www.cellularbiomedgroup.com	N/A

Management team

CEO: Tony (Bizuo) Liu	Chairman: Terry A Belmont
Mr Liu had been serving as an independent director and chairman of the Audit Committee for CBMG since March 2013 and was appointed as chief financial officer in January 2014. He was appointed as chief executive officer of the company in February 2016. Mr Liu formerly served as the corporate vice president at Alibaba Group, responsible for Alibaba's overseas investments. Prior to joining Alibaba, Mr Liu spent 19 years at Microsoft Corporation where he served in a variety of finance leadership roles. He was the general manager of Corporate Strategy, looking after Microsoft's China investment strategy and corporate strategic planning process.	Mr Belmont has over 20 years of experience in leading major academic and non-academic medical centers and healthcare entities with multi-campus responsibility. Since 2009, Mr Belmont has overseen the UC Irvine Medical Center, the main campus of UC Irvine Health, in Orange, California, and its licensed ambulatory facilities in Orange, Irvine, Costa Mesa, Anaheim and Santa Ana. Prior to joining UC Irvine Medical Center, Mr Belmont served as CEO of Long Beach Memorial Medical Center and Miller Children's Hospital from 2006-09.
CSO: Yihong Yao	**SVP of Clinical Development: Cheng Xiang (Chase) Dai**
Dr Yao is the co-inventor of 26 filed patents relating to tumor classification, degenerative muscle disease and autoimmune disease diagnostics and treatment. He has published over 60 papers in translational science peer-reviewed journals and has authored or co-authored two books on the subjects of inflammatory and autoimmune diseases and genomic biomarkers. In addition to his strong academic background, he has over 15 years of professional experience with pharmaceutical and biotechnology companies, including MedImmune biologics research and development arm of AstraZeneca, and Abbott Bioresearch Center.	Dr Dai is a specialist in cardiology with over 15 years of clinical practice and more than 10 years of corporate experience, including pharmaceutical, biomedical, and executive management as CEO at MedGene Biotechnologies, director for clinical research at China Beike Stem Cell Technologies, medical director, Venturepharm Group Ltd and deputy chief physician in the Cardiology Department at 301 PLA Hospital. Dr Dai has received numerous science and technology awards and published over 30 peer-reviewed scientific papers, filed four patents as a co-inventor and co-authored two books.

Principal shareholders	(%)
Wuhan Dangdai Science & Technology Industries Group	16.09%
Millennium Management LLC	1.34%
Tony Liu	0.91%
Blackrock Inc.	0.66%
Vanguard Group Inc.	0.63%

Companies named in this report

Bristol-Meyers Squibb (BMY), Fosun (HKG:0656), Histogenics (HSGX), Juno (JUNO), KAKEN (TYO:4521), Kite (KITE), Novartis (NVS), Sanofi (SNY), Vericel (VCEL), WuXi AppTec

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