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Cellular Biomedicine Group, Inc. (CBMG-NASDAQ)

CBMG: Initiating Coverage of Cellular Biomedicine Group; Multiple Cell-Based Therapies to Treat Cancer and Degenerative Diseases…

Based on our probability adjusted DCF model that takes into account potential future revenues of the cellular oncology and stem cell therapies, CBMG is valued at $24.00/share. This model is highly dependent upon continued clinical success of the company's pipeline and will be adjusted accordingly based on future clinical results.

Current Price (09/30/19)	$14.98
Valuation	**$24.00**

OUTLOOK

We are initiating coverage of Cellular Biomedicine Group, Inc. (CBMG) with a $24.00 valuation. Cellular Biomedicine Group is a biopharmaceutical company developing cellular therapies to treat cancer and degenerative diseases. The company has a pipeline of CAR-T, TCR, and TIL immuno-oncology development products along with a regenerative medicine program. Clinical trials have initiated for CAR-T products targeting BCMA and CD20 and additional clinical trials for an anti-CD19/CD20 bi-specific CAR-T and an anti-AFP TCR are expected before the end of 2019. China's CDE recently accepted the company's IND such that a Phase 2 clinical trial can initiate for Allojoin®, a regenerative medicine product for the treatment of knee osteoarthritis. In support of the company's role as a leading cell therapy provider in China, in 2018 Cellular Biomedicine Group signed a collaboration agreement with Novartis to manufacture and supply the CAR-T product Kymriah® in China, which included Novartis taking a 9% stake in the company.

SUMMARY DATA

52-Week High	**$20.63**
52-Week Low	**$10.98**
One-Year Return (%)	**-23.10**
Beta	**2.44**
Average Daily Volume (sh)	**33,680**
Shares Outstanding (mil)	**19**
Market Capitalization ($mil)	**$285**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**20**
Insider Ownership (%)	**9**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2019 Estimate	**-5.5**
P/E using 2020 Estimate	**-6.2**

Risk Level	**Above Avg.**
Type of Stock	**Small-Blend**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	0 A	0 A	0 A	0 A	0 A
2019	0 A	0 A	0 E	0 E	0 E
2020					0 E
2021					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	-$0.51 A	-$0.53 A	-$0.56 A	-$0.45 A	-$2.04 A
2019	-$0.51 A	-$0.63 A	-$0.63 E	-$0.64 E	-$2.44 E
2020					-$1.96 E
2021					-$1.82 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Cellular Biomedicine Group, Inc. (CBMG) with a valuation of $24.00. Cellular Biomedicine Group is a biopharmaceutical company developing cell-based therapies for cancer and degenerative diseases, with a focus on the Chinese market. In addition to a full pipeline of development products comprised of CAR-T, TIL, and TCR, along with stem-cell based therapies for the treatment of osteoarthritis, Cellular Biomedicine Group signed a collaboration agreement last year with Novartis for the production of Kymriah® in China. CAR-T products targeting multiple myeloma and non-Hodgkin lymphoma are currently being evaluated in clinical trials and we anticipate additional clinical trials initiating in other indications over the next six to twelve months.

Robust Pipeline with Multiple Cell-Therapy Development Products
Cellular Biomedicine Group has a robust pipeline of products derived from in-house discovery and strategic in-licensing including CAR-T, TIL, TCR, and stem cell products for which we anticipate at least six modalities being in Phase 1 clinical trials by the end of 2019.

Investigator-Initiated Trials to Speed-Up Development Timelines
Cellular Biomedicine Group has begun investigator-initiated trials in China for its CAR-T products in patients with multiple myeloma and non-Hodgkin lymphoma, with additional trials starting later in 2019 and early 2020. These trials are intended to quickly evaluate safety and proof-of-concept in a cost-effective manner before moving to larger trials in China and the U.S. We anticipate initial data readouts from the ongoing trials at the end of 2019 or early 2020.

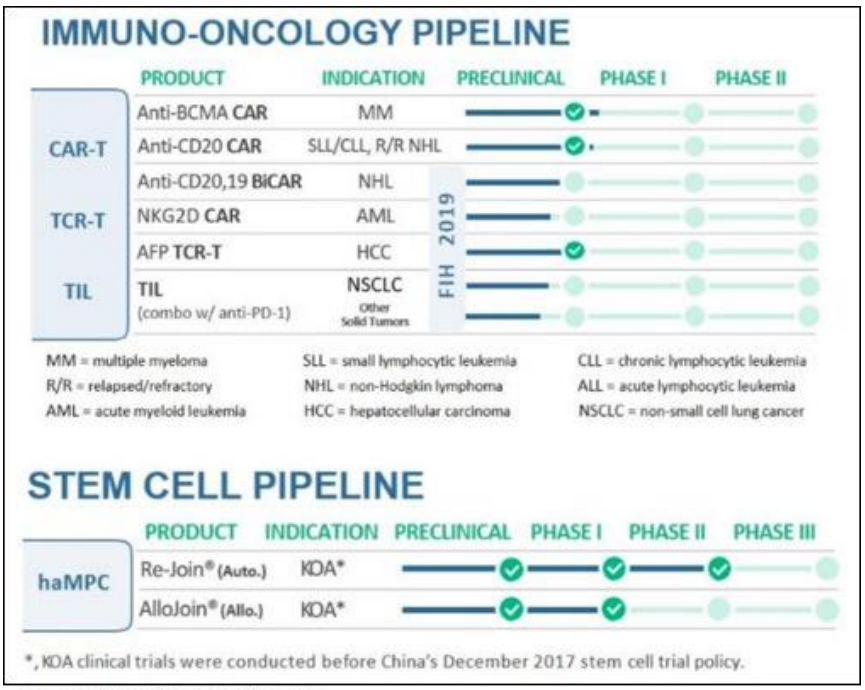
Collaboration with Novartis for Kymriah® in China
In 2018, Cellular Biomedicine Group signed a collaboration agreement with Novartis to manufacture and supply Kymriah® in China. Included in the deal was a $40 million equity purchase from Novartis, which represents a 9% equity stake in the company. Cellular Biomedicine Group will be responsible for manufacturing the product while receiving an escalating single-digit royalty on net product sales of Kymriah® in China, while Novartis will be responsible for distribution, regulatory, and commercialization efforts in China. This deal validates Cellular Biomedicine Group's cell manufacturing technology and we believe puts them at the forefront of cell therapy companies in China.

First-Mover Advantage in China
The company is leveraging its expertise in the Chinese regulatory environment to establish itself as the leader in the Chinese cell therapy market. Very few other companies have the requisite expertise to handle the various compliance, quality assurance, and regulatory issues inherent in the Chinese market while simultaneously working to improve manufacturing timelines for cell therapy clinical trials and commercial launch.

Proprietary Manufacturing Processes for Cellular Therapies
Through collaborations with GE Healthcare Life Sciences and ThermoFisher Scientific, Cellular Biomedicine Group has developed an automated, closed, integrated cell manufacturing system with complete control of the chain-of-custody. The company maintains manufacturing facilities totaling 100,000 ft^2 in Shanghai and Wuxi that meet the quality management systems requirements of ISO 9001:2015, and the facilities of Shanghai and Wuxi sites meet local regulatory standards.

INVESTMENT THESIS

Cellular Biomedicine Group, Inc. (CBMG) is a biopharmaceutical company developing cell-based therapies to treat cancer and degenerative diseases. The company has two main platforms: 1) immune cell therapy for the treatment of both hematologic cancers and solid tumors that utilizes chimeric antigen receptor modified T cells (CAR-T), genetically modified T cell receptors (TCRs), and tumor infiltrating lymphocytes (TILs); 2) human adipose-derived mesenchymal progenitor cells (haMPC) for the treatment of joint diseases. The company initially plans to focus on bringing cell-based therapies to market in China, which is supported by a collaboration agreement signed with Novartis in September 2018 to manufacture and supply the CAR-T therapy Kymriah® (tisagenlecleucel) in China. The company plans to utilize investigator-initiated trials (IITs) in China for evaluating safety and establishing proof-of-concept for the hematologic and solid tumor candidates before potentially expanding to the U.S. for later stage clinical trials. Patient recruitment was recently initiated for Phase 1 clinical trials of an anti-BCMA CAR-T in patients with relapsed/refractory multiple myeloma and an anti-CD20 CAR-T in patients with non-Hodgkin lymphoma. In addition, an IND was recently accepted by China's CDE such that the company can initiate a Phase 2 clinical trial of AlloJoin®.

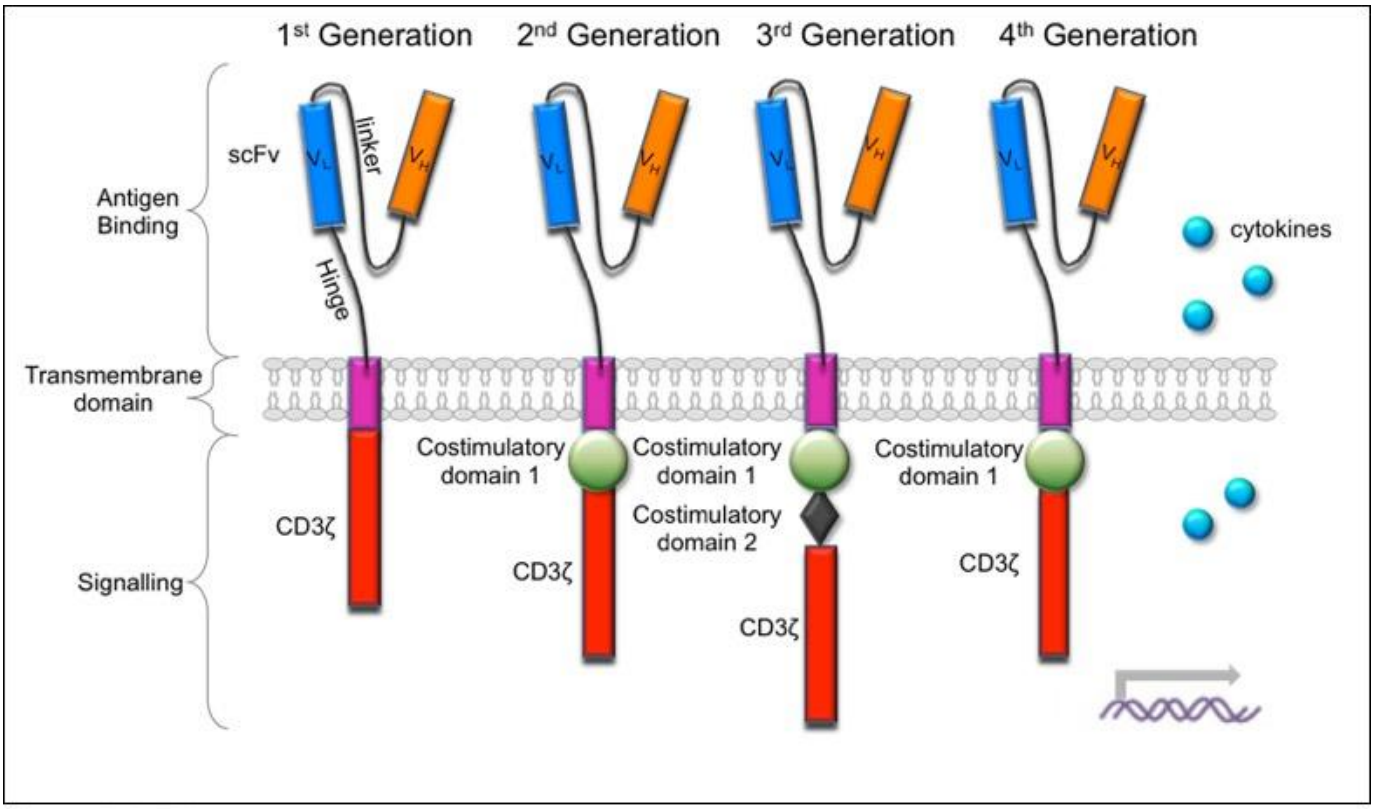


Source: Cellular Biomedicine Group, Inc.

Immuno-Oncology Cell Therapy

CAR-T Therapy

Chimeric antigen receptor (CAR) technology was first described in 1989, in which Israeli scientists expressed the CD3ζ intracellular activating domain linked to an extracellular antibody variable domain targeting 2,4,6-trinitrophenyl (TNP) in T cells causing the release of interleukin-2 in response to TNP-bearing target cells (Gross *et al*., 1989). These 'first-generation' CARs were first tested in humans in the mid-2000's, albeit with disappointing results due to the inability of the CD3ζ domain to sufficiently activate resting T-cells (Lamars *et al*., 2006; Park *et al*., 2007). 'Second'- and 'third-generation' CARs include the co-stimulatory domains CD28 and/or 4-1BB (or OX40 or CD27) and lead to enhanced cytokine production, increased T cell proliferation, and greater anti-tumor efficacy (Carpenito *et al*., 2009). Fourth generation CAR-T cells ('T cell redirected for universal cytokine killing' [TRUCK]) are second generation CARs with an additional gene cassette that contains a cytokine with expression induced by antigen binding (Chmielewski *et al*., 2015).



Source: cellculturedish.com

Kymriah®

The first clinical successes with a second generation CAR-T product utilized an anti-CD19 binding domain and a 4-1BB/CD3ζ costimulatory domain in patients with chronic lymphocytic leukemia (CLL) and pediatric acute lymphoblastic leukemia (ALL) (Porter *et al*., 2011; Grupp *et al*., 2013). Following a license agreement entered into with the University of Pennsylvania, Novartis developed the treatment (Kymriah®) and it has since been approved by the FDA for the treatment of ALL and diffuse large B cell lymphoma (DLBCL).

A Phase 2 clinical trial in pediatric and young adults with ALL served as the basis for the approval of Kymriah® (Maude *et al*., 2018). A total of 75 patients received an infusion of Kymriah® and could be evaluated for efficacy. Patients received a median dose of 3.1 x 10^6 transduced viable T cells per kilogram of body weight. The overall remission rate was 81% at three months, with 45 patients experiencing a complete remission and 21% having a complete remission with incomplete hematologic recovery. The rate of relapse-free survival was 80% at six months and 59% at 12 months.

The most common nonhematologic adverse events were cytokine release syndrome (CRS) (77%), pyrexia (40%), febrile neutropenia (36%), and headache (36%). CRS results from the release of substantial amounts of cytokines into the circulation from activated CAR-T cells and can be one of the most serious adverse events associated with CAR-T therapy. Most patients experience mild flulike symptoms from CRS, however some patients can experience a severe inflammatory syndrome that can ultimately lead to death. Tocalizumab (anti-IL-6 antibody) and corticosteroids are typically used to treat CRS, as these treatments do not appear to interfere with the CAR-T therapy.

Yescarta®

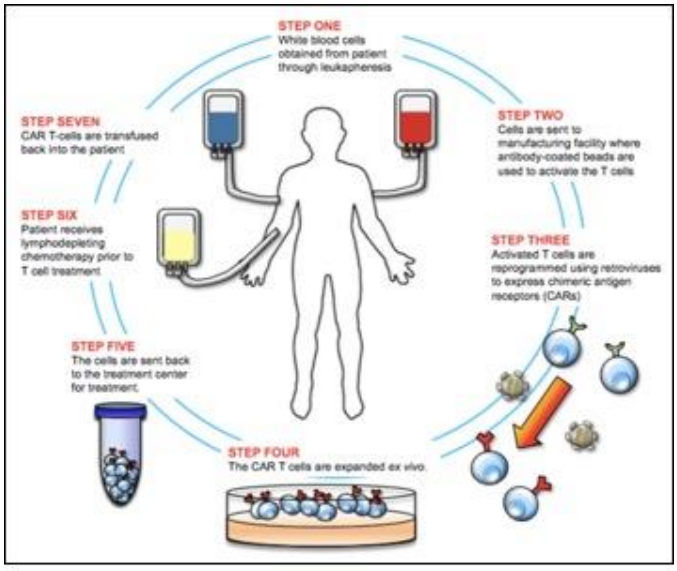
A second CAR-T product containing an anti-CD19 binding domain and a CD28/CD3ζ costimulatory domain was developed by Kite Pharma (since acquired by Gilead), and based on the successful ZUMA-1 trial (Neelapu *et al*., 2017), Yescarta® was approved by the FDA for the treatment of DLBCL, primary mediastinal large B cell lymphoma (PMBCL), and follicular lymphoma.

The ZUMA-1 trial enrolled 111 patients who were treated with a target dose of 2 x 10^6 modified T cells per kilogram of body weight following a conditioning regimen of low-dose cyclophosphamide and fludarabine. Yescarta® was successfully manufactured for 99% of the patients and administered to 101 of them. 82% of patients experienced either a complete (54%) or partial (28%) response, and with a median follow-up of 15.4 months, 42% of patients continued to have a response. The overall survival rate at 18 months was 52%.

The most common adverse events were CRS (93%), pyrexia (85%), neutropenia (84%), and anemia (66%). Most cases of CRS were low grade (37% of grade 1 and 44% of grade 2), however 9%, 3%, and 1% experienced grade 3, 4, and 5, respectively.

CAR-T Manufacturing and Pricing

CAR-T therapy involves a complex manufacturing process that starts with collecting white blood cells from the patient through leukapheresis, activating the T cells, transfecting and reprogramming the T cells with a viral vector, expanding the CAR-T cells *ex vivo*, shipping the cells back to the treatment center, treating the patient with a lymphodepleting chemotherapy, and finally transfusing the CAR-T cells back into the patient. This process takes approximately three weeks from isolation of leukocytes to reinfusion of CAR-T cells.



Source: cellculturedish.com

Kymriah® was initially approved by the FDA in 2017 and Novartis announced that the price would be $475,000 per treatment. Yescarta® was also approved by the FDA in 2017 and Gilead announced that the price would be $373,000 per treatment. Sales of Yescarta® totaled $264 million in 2018. Sales of Kymriah® totaled only $76 million in 2018, which was below all analyst expectations, and was partly due to manufacturing issues that resulted in variability in product specifications. To combat this, Novartis has indicated a plan to automate as much of the CAR-T manufacturing process as possible, including purchasing the cell and gene therapy manufacturer CellforCure, plans to open a manufacturing site in Switzerland to increase capacity in Europe, and signing a collaboration with Cellular Biomedicine Group to manufacture and supply Kymriah® in China.

Kymriah® in China

In September 2018, Cellular Biomedicine Group announced a licensing and collaboration agreement with Novartis to manufacture and supply Kymriah® in China. Included in the deal was a $40 million equity purchase from Novartis at $27.43/share, or approximately a 9% equity stake in the company. In addition, Novartis will receive worldwide rights to certain royalty-free intellectual property related to Cellular Biomedicine Group's CAR-T technology. Cellular Biomedicine Group will be responsible for manufacturing the product while receiving an escalating single-digit royalty on net product sales of Kymriah® in China, and Novartis will be responsible for distribution, regulatory, and commercialization efforts in China. Cellular Biomedicine Group has not indicated when Kymriah® will be available in China, which is partly dependent upon whether a bridging study will be required by regulatory authorities.

Cellular Biomedicine Group CAR-T Pipeline

Cellular Biomedicine Group has four CAR-T products in development for three different hematological cancers.

Multiple Myeloma (MM): This is a cancer of monoclonal plasma cells that derive from post-germinal-center B cells. The disease is characterized by an infiltration of these cells into the bone marrow causing anemia, lytic bone disease, hypercalcemia, and kidney damage from the accumulation of monoclonal immunoglobulins (Kumar *et al*., 2017). The disease is most common in the elderly, with a median age of onset of 69 years (NCI SEER).

When diagnosed, myeloma is classified as either asymptomatic, which only requires clinical observation since early treatment with conventional chemotherapy has shown no benefit, or symptomatic, which should be treated immediately (Kyle *et al*., 2010). Treatment strategies are dictated by age and include induction therapies that are associated with a high rate of complete response followed by maintenance therapies. However, even with the advancements in treatment made over the past 10-20 years, MM remains an incurable disease with a five-year survival rate of approximately 50% (NCI SEER).

The goal of therapy for newly diagnosed patients is the longest possible remission that weighs the benefits of treatment with potential adverse side effects. The International Myeloma Workshop Consensus (IMWC) established response criteria for MM patients and in 2011 updated those criteria to include a deeper level of remission than a complete remission (CR) known as a stringent CR (sCR) (Rajkumar *et al*., 2011). sCR requires both a normalization of serum light chains as well as the absence of clonal plasma cells on a bone marrow biopsy. Even in patients with a sCR, most will still have significant numbers of tumor cells present, otherwise known as minimal residual disease (MRD). While studies are continuing on the optimal method for analyzing MRD, retrospective analyses show that those who are MRD (-) have improved progression free survival (PFS) and overall survival (OS) compared to those that are MRD (+) (Munshi *et al*., 2017; Rawstron *et al*., 2015). The FDA and EMA have released guidelines on the potential use of MRD status as a surrogate marker for OS, and the IMWC has updated its response criteria to include assessment of MRD (Kumar *et al*., 2016). Ongoing studies are attempting to determine the optimal method for MRD assessment such that one day it may be used to help guide treatment decisions.

Currently, the goal of induction therapy is to bring about the longest remission possible. A randomized trial of dexamethasone + lenalidomide (Revlimid®) compared to dexamethasone + lenalidomide + bortezamib (Velcade®) showed the triplet regimen to be superior in terms of overall response rate (ORR; 82% vs. 72%, *P*=0.02), progression-free survival (PFS; 43 vs. 30 months, HR = 0.712 [95% CI 0.56-0.906], *P*=0.0018), and overall survival (OS; 75 vs. 64 months, HR = 0.709 [95% CI 0.524-0.958], *P*=0.025) (Durie *et al*., 2017). This study, along with several others, helped to establish the optimal induction therapy of a proteasome inhibitor + immunomodulatory agent + dexamethasone in patients eligible for a hematopoietic stem-cell transplant (HSCT). This regimen is typically recommended for those younger than 65 with no significant heart, lung, renal, or liver dysfunction.

While the disease will usually relapse for every patient, there is no standardized treatment regimen for relapsed disease, however there are a number of treatment options. The three classes of drugs used in relapsed MM include proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, which are typically used in various combinations along with corticosteroids and various chemotherapeutic agents. Once the patient gets to the third relapse and beyond, the disease is usually refractory to multiple agents and more aggressive. Thus, treatment becomes more difficult but often includes the use of next-generation agents and experimental therapies in clinical trials.

Daratumumab (Darzalex®, anti-CD38 monoclonal antibody) was approved in late line MM as a single agent treatment based on an ORR of 31% and PFS of 4.8 months (Lonial *et al*., 2016). The triplet regimen of daratumumab, pomalidomide (Pomalyst®), and dexamethasone received FDA approval based on a Phase 2 trial showing an ORR of 60% and PFS of 8.8 months in refractory MM patients (Chari *et al*., 2017).

MM is currently a $16 billion market and is dominated by Revlimid®, which had 2018 sales of close to $9 billion, but will lose patent protection in the U.S. in March 2022 (EvaluatePharma). Other top selling drugs include Darzalex® and Pomalyst®, with 2018 sales of $2 billion each (EvaluatePharma). The top selling MM drugs in 2018 are indicated in the following table.

Product	MOA	2018 Sales ($M)
Revlimid®	Immunomodulatory Agent	$8,946
Pomalyst®	Immunomodulatory Agent	$2,040
Darzalex®	anti-CD38 mAb	$2,025
Kyprolis®	proteasome inhibitor	$968
Velcade®	proteasome inhibitor	$915
Ninlaro®	proteasome inhibitor	$561

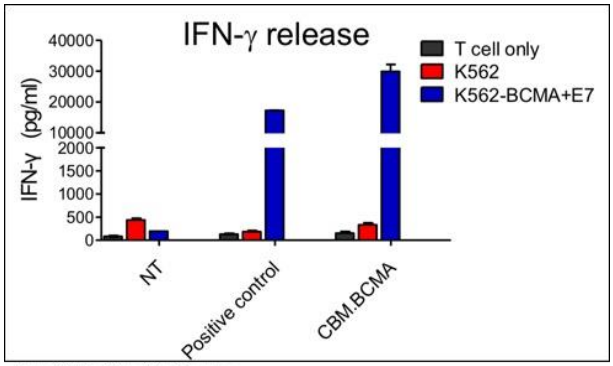
Source: EvaluatePharma / Zacks SCR

CAR-T in MM

A number of CAR-T therapies are in development for the treatment of MM that target the B cell maturation antigen (BCMA). BCMA is required for the survival of long-lived bone marrow plasma cells (Moreaux *et al*., 2004) and it was shown to be expressed on primary myeloma cells, but not normal tissue, of newly diagnosed MM patients (Carpenter *et al*., 2013).

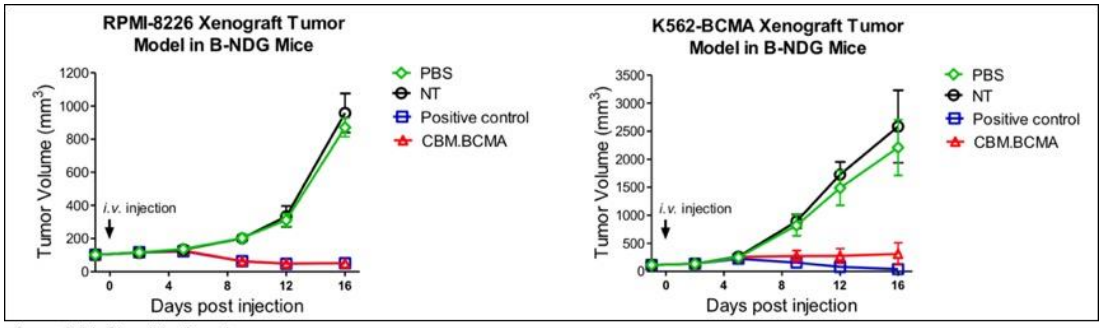
CBM.BCMA

Cellular Biomedicine Group is developing a CAR-T therapy directed against BCMA (CBM.BCMA) for which it has recently initiated a Phase 1 clinical trial in China. The company's BCMA CAR-T product shows similar *in vitro* activity to the anti-BCMA CAR-T product bb2121, which is being developed by Bluebird Bio (BLUE). The following graph shows interferon-gamma (IFN-γ) release by CBM.BCMA is similar to that for bb2121 (positive control) following exposure to K562 cells expressing BCMA.



Source: Cellular Biomedicine Group, Inc.

In addition, CBM.BCMA shows activity on par with bb2121 in two mouse models of MM utilizing different cell lines expressing BCMA.



Source: Cellular Biomedicine Group, Inc.

Cellular Biomedicine Group recently initiated patient recruitment in an investigator-initiated trial (IIT) in China for CBM.BCMA in patients with relapsed/refractory MM and we anticipate topline data from the study before the end of 2019.

bb2121

Bluebird Bio is currently studying bb2121 for the treatment of MM in late stage patients in the pivotal KarMMa (MM-001) trial and will be initiating trials in earlier lines of therapy in 2019. To be eligible for the KarMMa trial, patients must have received three or more prior treatment regimens, including immunomodulatory agents, proteasome inhibitors, anti-CD38 therapy, and were refractory to the last treatment regimen. Patients are being administered 150-450 x 10^6 CAR-T cells following a fludarabine/cyclophosphamide conditioning regimen. The primary endpoint of the trial is ORR. The company has two ongoing Phase 1 clinical trials of bb2121 in refractory MM patients:

- The CRB-401 trial (NCT02658929) is an ongoing study of bb2121 in patients with relapsed/refractory MM. It consists of a dose escalation cohort at four target doses (50, 150, 450, or 800 x 10^6 CAR-T cells) and a dose expansion cohort (150-450 x 10^6 CAR-T cells). Data was recently published for the first 33 subjects administered bb2121 (Raje *et al*., 2019). Results showed an ORR of 85%, including 15 patients (45%) with a CR. Six of the 15 patients who had a CR have relapsed. Median PFS was 11.8 months, which compares quite favorably to the median PFS of 4.8 months and 8.8 months seen in the trials of refractory MM patients discussed previously. A total of 25 patients (76%) had CRS, however only two of those patients were grade 3. Other grade 3 or greater adverse events included neutropenia (85%), leukopenia (58%), anemia (45%), and thrombocytopenia (45%).

- The CRB-402 trial (NCT03274219) is an ongoing study of bb2121 in patients with relapsed/refractory MM that have received three or more prior lines of therapy that included an immunomodulatory agent, a proteasome inhibitor, or were double-refractory to an immunomodulatory agent and a proteasome inhibitor. It is a 3+3 dose escalation study with doses of 150, 300, 450, or 800 x 10^6 CAR-T cells. As of October 2018, 12 patients had been dosed with 150 x 10^6 CAR-T cells. Results showed that 10/12 patients (83%) achieved an objective response, with 3 (25%) complete responses and 6 (50%) very good partial responses or better. CRS occurred in 67% of patients, however only 1 patient experienced grade 3 CRS.

Bluebird is co-developing bb2121 equally with Celgene and will split future costs and profits related to its commercialization in the U.S. Celgene will be responsible for developing and marketing bb2121 in ex-U.S. markets with Bluebird receiving milestones and royalties on sales.

LCAR-B38M

LCAR-B38M is an anti-BCMA CAR-T product that is being developed jointly by Nanjing Legend Biotech and Janssen R&D. It is unique in that instead of a single antigen binding domain, such as for bb2121, it is composed of two different heavy-chain variable domains that target two unique epitopes on BCMA.

- The LEGEND-2 clinical trial is an ongoing Phase 1 study of LCAR-B38M in patients with relapsed/refractory MM (NCT03090659). Patients were lymphodepleted with cyclophosphamide prior to receiving a median of 0.5 x 10^6 CAR-T cells per kilogram body weight in three separate infusions. Out of 57 patients who received treatment, the ORR was 88%, with 39/57 (68%) achieving a CR, 3/57 (5%) achieving a very good partial response, and 8/57 (14%) achieving a partial response. A total of 36/57 (63%) patients were MRD (-). At a median follow-up of eight months, the median PFS was 15 months and median overall survival was not reached (Zhao *et al*., 2018).

- Janssen is conducting a Phase 1/2 clinical trial of LCAR-B38M in the U.S. that includes a Phase 1b dose-escalation portion and a Phase 2 portion utilizing the dose selected in Phase 1 (NCT03548207). Patients in the trial must have received at least 3 prior treatments or are double refractory to an immunomodulatory agent and proteasome inhibitor.

Non-Hodgkin Lymphoma (NHL): This is a group of cancers that develop from either B cells (90% of cases) or T cells (10% of cases) in the lymphatic system. It is estimated approximately 74,000 individuals will be diagnosed with NHL in the U.S. in 2019. The five-year survival rate for NHL patients is approximately 72% (NCI SEER).

NHL constitutes a diverse spectrum of cancers that are classified according to the 2016 WHO classification scheme (Swerdlow *et al*., 2016). The most common subtypes of NHL include diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), Burkitt lymphoma, and peripheral T cell lymphomas (PTCL). Standard of care treatment for DLBCL includes CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab), while other subtypes respond to varying other chemotherapy options with and without rituximab (Armitage *et al*., 2017).

While many advances have been made in the treatment of different NHL subtypes, only approximately 25% of patients with primary-refractory DLBCL respond to second-line treatment (Telio *et al*., 2012), approximately 20% of FL patients will develop progressive lymphoma and have a median OS of less than five years (Jurinovic *et al*., 2016), and responses to treatment for those with PTCL are not as robust as in those with B cell NHLs, with median OS of only approximately 4 years (Escalon *et al*., 2005). Thus, there is a pressing need for more and better treatment options for NHL patients.

The following chart gives an overview of the top selling drugs in NHL, with Rituxan® (rituximab) leading the field with 2018 sales of $5.4 billion (EvaluatePharma).

Product	MOA	2018 Sales ($M)
Rituxan®	anti-CD20 mAb	$5,440
Imbruvica®	BTK inhibitor	$960
Revlimid®	Immunomodulatory Agent	$461
Yescarta®	CAR-T	$264
Gazyva®	anti-CD20 mAb	$252
Adcetris®	ADC	$113
Calquence®	BTK inhibitor	$62

Source: EvaluatePharma / Zacks SCR

CAR-T in NHL

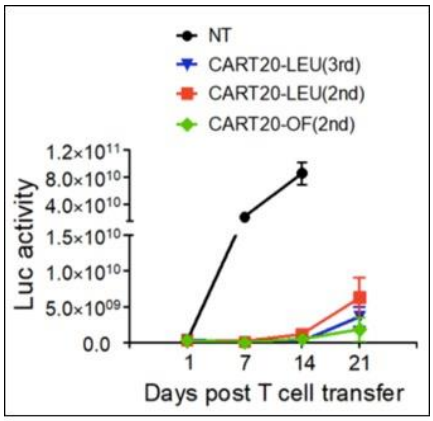
Yescarta® was evaluated in the ZUMA-1 trial, which consisted of a Phase 1 and Phase 2 portion to evaluate its efficacy in patients with high-grade B cell lymphoma. Patients received a lymphodepleting regimen of cyclophosphamide and fludarabine followed by infusion with 1-2 x 10^6 CAR-T cells/kg. Based on the results of these trials the FDA approved Yescarta® for the treatment of DLBCL, primary mediastinal B cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL) in 2017.

- In the Phase 1 portion of the study, seven patients were treated, with one patient experiencing grade 4 CRS and neurotoxicity (Locke *et al*., 2017). The overall response rate was 71% (5/7) with 57% (4/7) of patients experiencing a CR.

- The Phase 2 portion of the study involved two cohorts: cohort 1 for DLBCL and cohort 2 for PMBCL and TFL (Neelapu *et al*., 2017). A total of 111 patients were enrolled, with 101 patients receiving an infusion of CAR-T cells. The ORR and CR were 82% and 54%, respectively. With a median follow-up of 27.1 months the median duration of response was 11.1 months, the median OS had not yet been reached, and the median PFS was 5.9 months (Locke *et al*., 2019). Interestingly, 23 out of the 61 patients with either a PR or stable disease (SD) converted into a CR with no additional treatment, with a median time of conversion of PR to CR of 64 days.

Anti-CD20 and Anti-CD19/CD20 Bi-Specific CAR-T

Based on the success of rituximab (anti-CD20 monoclonal antibody) in treating NHL, Cellular Biomedicine Group is developing both an anti-CD20 and an anti-CD19/CD20 bi-specific CAR-T for the treatment of NHL patients. The company has designed multiple anti-CD20 scFv's for use in a CAR-T construct that show activity in multiple *in vitro* and *in vivo* assays. The following graph shows delayed tumor growth in a mouse model of lymphoma following treatment with different anti-CD20 CAR-T products.



Source: Cellular Biomedicine Group, Inc.

The company recently announced the initiation of a Phase 1 clinical trial that is expected to enroll 12 patients with either DLBCL or small B cell lymphoma who are refractory to anti-CD19 therapy. The trial is taking place at leading research institutions in China.

The potential of an anti-CD19/CD20 bi-specific CAR-T was shown earlier this year through results presented at the 2019 ASCO Annual Meeting. A Phase 1 clinical trial of LV20.19 CAR, which is out of the University of Wisconsin and contains an anti-CD19 and anti-CD20 scFv coupled to CD3ζ and 4-1BB signaling domains, in 17 patients with relapsed or refractory NHL showed an overall response rate of 82% at day 28, including 11 complete responses and three partial responses (NCT03019055). All of the patients who had a complete response remained in remission as of June 2019, with the longest exceeding 1.5 years. Importantly, there were no cases of grade 3 or 4 cytokine release syndrome or grade 4 neurotoxicity. Cellular Biomedicine Group will be initiating a Phase 1 clinical trial of an anti-CD19/CD20 bi-specific CAR-T in the near term.

Acute Myeloid Leukemia (AML): This is the most common form of acute leukemia in adults, with approximately 21,000 individuals expected to be diagnosed in the U.S. in 2019 (NCI SEER). It is primarily a disease of older individuals, with the median age of diagnosis being 67 years in the U.S. (DeSantis *et al*., 2014).

AML is characterized by an abnormal proliferation and differentiation of a clonal population of myeloid stem cells. Large chromosomal rearrangements that result in the production of chimeric proteins can cause the disease through alteration of the normal myeloid maturation process. Genetic mutations are also very common and are seen in >97% of cases (Patel *et al*., 2012).

Eligible patients (typically younger individuals with good performance status and normal creatinine, albumin, and platelet counts) are usually treated with the "7+3" regimen, consisting of cytarabine for seven days and an anthracycline for the first three days. Approximately 60-80% of patients will achieve CR with induction therapy (Büchner *et al*., 2012). Patients who achieve CR are usually offered consolidation therapy in the form of continued chemotherapy and allogenic hematopoietic stem cell transplantation (HSCT). However, even with a high initial response, the majority of patients will relapse and become refractory to treatment, which leads to a five-year overall survival of only 28%.

The following chart gives an overview of the top selling therapies for AML in 2018. Vyxeos® is a proprietary formulation of cytarabine and daunorubicin and had 2018 sales of approximately $100 million (EvalutePharma). Venclexta® was approved for the treatment of AML in Nov. 2018 and is forecast for sales of close to $1 billion in 2024 (EvaluatePharma).

Product	MOA	2018 Sales ($M)
Vyxeos®	Cy+Daunorubicin	$101
Rydapt®	FLT3 inhibitor	$88
IDHIFA®	IDH2 inhibitor	$72
Xospata®	FLT3 inhibitor	$23
Tibsovo®	IDH1 inhibitor	$14

Source: EvaluatePharma / Zacks SCR

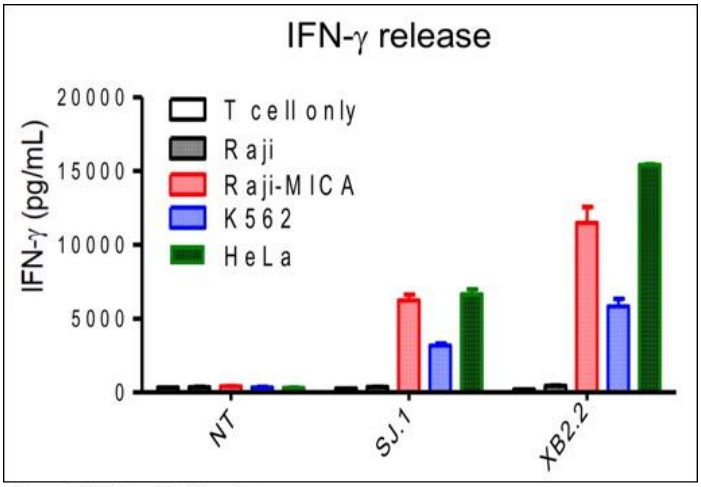
CAR-T in AML

As opposed to ALL and NHL, in which it is possible to target CD19 since the depletion of that antigen is clinically tolerable, there isn't a myeloid equivalent antigen that would result in a clinically benign phenotype, thus increasing the difficulty of developing an effective CAR-T therapy for AML. Some potential targets include FMS-like tyrosine kinase 3 (FLT3), folate receptor b, CD7, CD33, and CD123, however each of those has potential complications including uneven expression and their presence on healthy cells.

NKG2D CAR-T

Given the difficulties associated with finding an AML-specific antigen, an alternative strategy is to manufacture CAR-T cells that express a natural killer (NK) cell receptor that recognizes cancer specific antigens. NKG2D is the best characterized activating NK receptor (Raulet, 2003). It binds to self-proteins that are encoded by distinct genes and expressed as a result of cellular stress, infection, or tumorigenesis while not being expressed by healthy tissue.

Cellular Biomedicine Group is developing a CAR-T product that expresses NKG2D (XB.2.2). As the following graph shows, the lead candidate shows anti-tumor activity as exhibited by interferon gamma release when combined with different tumor cell lines.



Source: Cellular Biomedicine Group, Inc.

Precedent for the use of NKG2D is given by Celyad, which is developing a NKG2D CAR-T product (CYAD-01) for the treatment of relapsed/refractory AML and colon cancer. A 2018 article reported an induced remission in a relapsed/refractory AML patient with the use of CYAD-01 (Sallman *et al*., 2018), thus showing the potential clinical utility of such an NKG2D-based therapy.

T Cell Receptor Technology

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, with over 700,000 individuals affected worldwide, and is the third leading cause of cancer death in the world (ACS). HCC is relatively rare in the U.S. (approximately 42,000 individuals in the U.S. will be diagnosed with HCC in 2019) and other countries where hepatitis infections are not widespread, as most cases of HCC are due to hepatitis infection (both hepatitis B and C). Most cases of liver cancer in countries with low hepatitis rates are due to metastasis of other primary tumors.

A vast majority of HCC cases (>80%) occur in sub-Saharan Africa and in Eastern Asia (El-Serag *et al*., 2012). This is most likely due to the prevalence of hepatitis viruses in these populations. Hepatitis B infection is the dominant risk factor in most areas of Asia and sub-Saharan Africa, with the exception of Japan, where the major risk factor is hepatitis C infection. In China, there are approximately 466,000 new cases of liver cancer diagnosed each year (Chen *et al*., 2016).

HCC most often occurs in the context of a cirrhotic liver, thus patients with cirrhosis typically undergo ultrasonography every six months such that diagnosis of HCC can be made at an early stage. The most effective treatment option for both HCC and the underlying cirrhosis is a liver transplant, and 5-year survival rates higher than 50% can be achieved with this strategy (Forner *et al*., 2012). Unfortunately, most cases of HCC are too advanced once identified to qualify for this procedure.

Current Treatment Options for HCC

Survival time for patients with HCC is entirely dependent on how advanced the disease is when first diagnosed. If found early, liver transplantation offers a potential curative therapy, with 5-year overall survival of 75% and a tumor recurrence rate of less than 15% (Mazzaferro *et al*., 1996). Patients with small tumors and little underlying cirrhosis are eligible for surgical resection. Additional treatment options include local ablative therapies such as radio-frequency ablation (RFA), trans-arterial chemo-embolization (TACE), percutaneous ethanol ablation, and radioembolization.

There is no cure for non-resectable HCC; thus, there exists a significant unmet need for an effective therapy. Chemotherapeutic agents approved for use in non-resectable HCC include sorafenib (Nexavar®), a multi-kinase inhibitor that disrupts signaling in the RAS/MAPK pathway, and lenvatinib (Lenvima®), a multi-kinase inhibitor that targets VEGFR1, VEGFR2, and VEGFR3. Treatment for patients that are refractory to front-line therapy includes regorafenib (Stivarga®), a dual-kinase inhibitor that targets VEGFR2 and TIE2; cabozantinib (Cabometyx®), a multi-kinase inhibitor that targets c-Met and VEGFR2 that was approved in January 2019; and ramucirumab (Cyramza®), a monoclonal antibody that targets VEGFR2 that was approved in May 2019. Even with these treatments, median survival for patients with non-resectable HCC is less than a year. The following chart shows the leading HCC therapies by sales in 2018.

Product	MOA	2018 Sales ($M)
Nexavar®	MAPK inhibitor	$695
Lenvima®	VEGFR inhibitor	$228
Stivarga®	TKI	$60
Opdivo®	anti-PD-1 mAb	$33

Source: EvaluatePharma / Zacks SCR

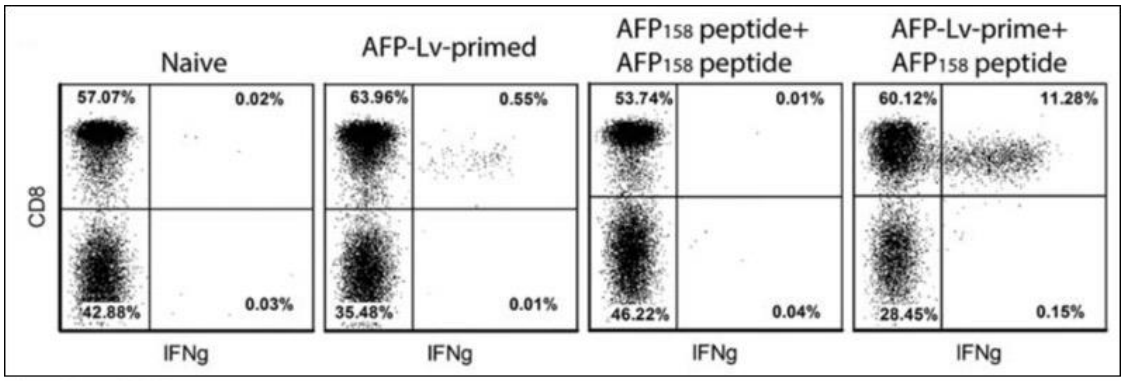
TCRs in HCC

In contrast to CAR-T technology, in which a T cell is transfected with an antibody variable domain linked to the intracellular signaling motifs of a T cell, T cell receptor (TCR) modification involves inserting a cloned TCR into T cells that recognizes a particular tumor associated antigen. The engineered TCR activates the T cell through the same signal transduction machinery as a native TCR (Ahmadi *et al*., 2011).

In 2018, Cellular Biomedicine Group licensed technology from Augusta University that pertained to the production of TCRs specific to α-fetoprotein (AFP) for the treatment of hepatocellular carcinoma (HCC). AFP is a used as a biomarker for HCC as it is expressed by the majority of tumors and the change in AFP level can be predictive of clinical outcome (Vora *et al*., 2009). While vital for the developing fetus, the role of AFP in adult tissues is less well understood, thus making it a potentially useful tumor antigen to target.

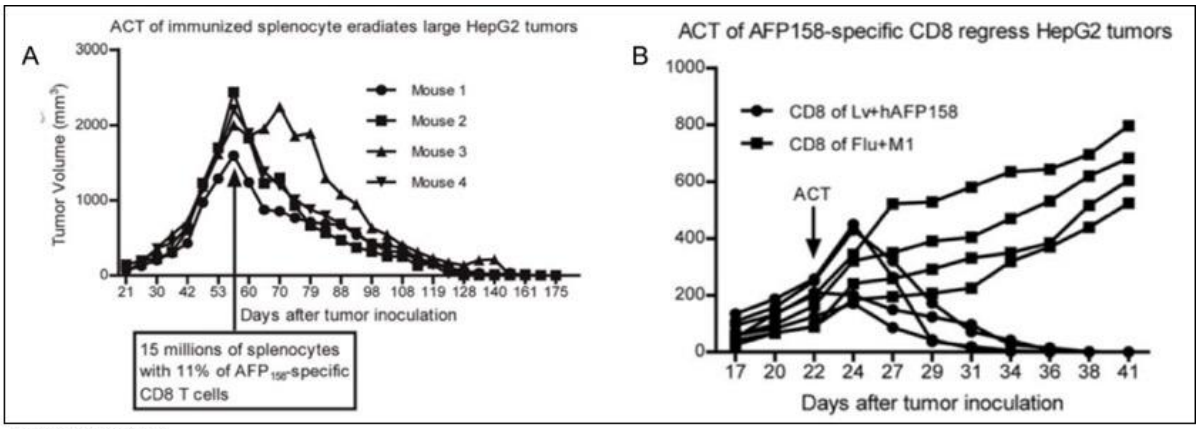
Prior research identified four human leukocyte antigen (HLA)-A2-restricted AFP epitopes that resulted in modest anti-AFP responses (Butterfield *et al*., 2001; Butterfield *et al*., 2006). A TCR specific for $AFP_{158-166}$ was recently cloned, but due to its low affinity it had no antitumor effect (Sun *et al*., 2016). Thus, a new means of identifying high affinity AFP TCRs was necessary in order to identify clones that could be clinically useful.

In an effort to identify high-affinity TCRs for $AFP_{158-166}$, researchers from Augusta University immunized mice with a lentiviral-prime, peptide-boost approach (Zhu *et al*., 2018). Immunization with only a lentivirus expressing AFP or with the $AFP_{158-166}$ peptide resulted in a modest number of CD8+ T cells that recognized $AFP_{158-166}$, however immunizing with $AFP_{158-166}$ peptide following lentiviral-AFP immunization produced a robust number of $AFP_{158-166}$ T cells.



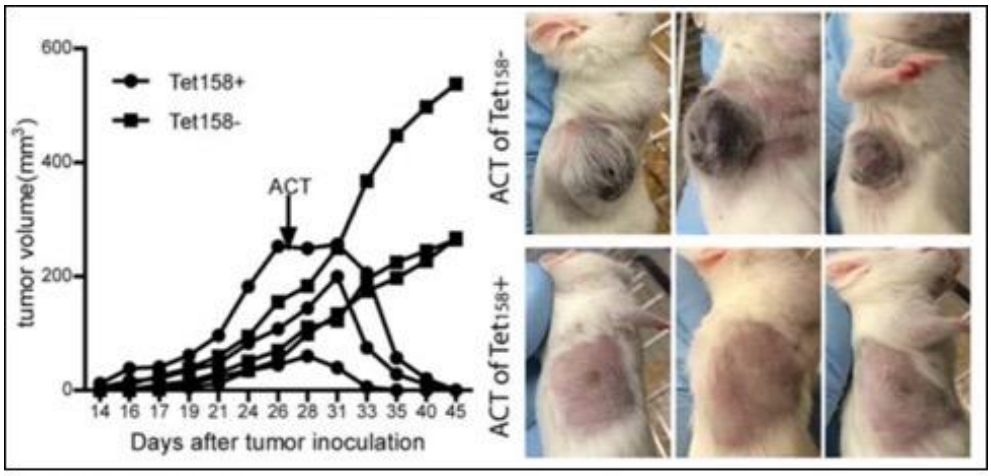
Source: Zhu *et al*., 2018

As shown in the following figure, splenocytes purified from lentiviral-AFP/$AFP_{158-166}$ peptide immunized mice completely eradicated established HepG2 (a human liver cancer cell line) tumors (panel A), but only CD8+ T cells from AFP-immunized mice eradicated HepG2 tumors and not CD8+ T cells from control mice immunized with influenza protein M1 (panel B).



Source: Zhu *et al*., 2018

Mice were then treated with 0.5 million CD8+ T cells that specifically bound $AFP_{158-166}$ and those that did not. The following figure shows tumor growth in mice treated with $AFP_{158-166}$-specific T cells (Tet158+), where the tumor is virtually eliminated, compared to very large tumor growth in mice treated with non-$AFP_{158-166}$-specific T cells (Tet158-).



Source: Zhu *et al.*, 2018

Cellular Biomedicine Group has now cloned different TCRs that bind specifically to $AFP_{158-166}$ and is in the process of identifying potential clinical candidates based on potency and safety. The company has performed a toxicity study of selected TCRs that will include cytotoxicity studies with human primary cells from essential organs, x-scan to identify proteins that may cross-react with the chosen TCRs, and allo-reactivity assays to establish patient HLA selection criteria.

The safety and potential utility of targeting AFP is shown from results obtained by Eureka Therapeutics, Inc. in an ongoing proof-of-concept study in patients with HCC in which Eureka's ET140202 T cell therapy, which contains a human TCR-mimic antibody targeting AFP, demonstrated a favorable safety profile and three out of six patients treated demonstrated tumor regression, including one patient with a complete response. Eureka has recently initiated a Phase 1/2 clinical trial in patients with HCC.

Tumor Infiltrating Lymphocyte Technology

Tumor infiltrating lymphocytes (TILs) are T cells extracted from resected tumor material that are expanded *ex vivo* and re-administered to the patient following a lymphodepletion regimen along with co-administration of IL-2. The first report of the use of TILs dates back to the 1980s in which TILs eliminated established tumors in mouse models (Spiess *et al*., 1987). Since that time, TILs have been used successfully in multiple clinical trials involving patients with metastatic melanoma (Rosenberg *et al*., 2011; Andersen *et al*., 2016) and are starting to be investigated in additional indications.

TILs have certain advantages over other types of adoptive cellular therapy including the fact that the cells are not genetically modified prior to use, since the cells are autologous there is minimal risk for on-target, off-tissue side effects, and the cells target more than one antigen found on the tumors.

The treatment protocol for TILs consists of resecting a portion of a patient's tumor and fragmenting or enzymatically digesting it in the presence of IL-2 to spur proliferation of TILs. Following this growth phase, TILs can be selected for specificity using autologous or HLA-matched tumor cell lines, however more recent studies have shown that this step is not necessary for clinical response (Itzhaki *et al*., 2011). Cells from the initial growth phase are then expanded in the presence of anti-CD3 antibody, IL-2, and irradiated, autologous feeder cells, which ultimately produces up to 1×10^{11} cells in total (Dudley *et al*., 2003). Prior to infusion, patients undergo lymphodepletion with cyclophosphamide and fludarabine and following infusion of TILs patients receive high-dose IL-2 until a maximum tolerated dose is achieved.

Cellular Biomedicine Group has licensed TIL technology from the National Cancer Institute (NCI) that involves selecting TILs for reactivity to neoantigens and using those for treatment. Following the initial cellular expansion,

TILs are tested for reactivity against neoantigens using peptides or tandem minigenes (TMGs) that include mutations identified in the tumor. These neoantigen-reactive TILs are then further expanded before infusion into the patient. Prior results using this approach identified 19 neoantigen T cell reactivities in six different epithelial cancer samples (Yossef *et al*., 2018).

TIL Clinical Efficacy

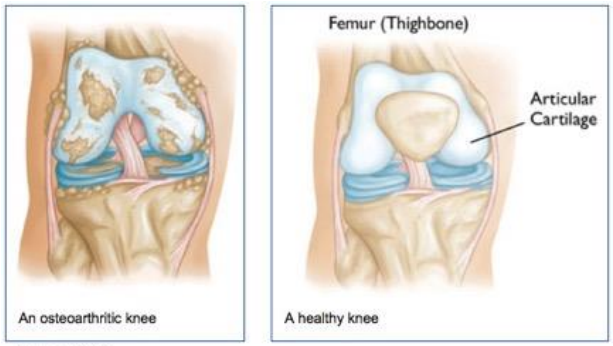
Cellular Biomedicine Group has licensed the rights to utilize neoantigen-reactive TILs in the treatment of NSCLC, head and neck cancer of the oral cavity and pharynx including lip, oral, and nasopharyngeal cancer, stomach cancer, esophageal cancer, and colon/rectal cancer. The isolation of TILs has been shown in patients with NSCLC (Ben-Avi *et al*., 2018), head and neck cancer (Junker *et al*., 2011), and gastrointestinal cancers (Turcotte *et al*., 2014), thus showing that treatment of those cancers is possible with TILs.

Iovance biotherapeutics (IOVA) is developing TIL therapies for melanoma, cervical cancer, head and neck cancer, and NSCLC. The company recently announced updated data on a Phase 2 clinical trial of TIL therapy LN-145 in patients with advanced cervical cancer and TIL therapy lifileucel in patients with advanced melanoma. As of May 2019, 27 cervical cancer patients have been treated with LN-145 with results showing an ORR of 44 percent (3 CR + 9 PR) and with a 7.4-month median follow-up the median durability of response (DOR) hasn't been reached. As of May 2019, 66 metastatic melanoma patients have been treated with lifileucel and results show an ORR of 38 percent (2 CR + 23 PR) and with an 8.8-month median follow-up the DOR hasn't been reached. These results show the promise of TIL therapy in patients who have been heavily pre-treated and who have few treatment options.

Regenerative Medicine

Knee Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis and currently affects approximately 30 million individuals in the U.S. and approximately 57 million individuals in China (Cisternas *et al*., 2016; Fransen *et al*., 2011). It results in a slow degeneration of the joint through a gradual wearing away of the cartilage. OA mostly affects weight-bearing joints (e.g., the hips, knees, and ankles) and results in their progressive deterioration through the degradation of articular cartilage, which is the smooth, white tissue that covers the ends of bones where they come together to form a joint. Articular cartilage is characterized by a very low friction and a high resistance to wear; however, it also has poor regenerative properties. In addition to articular cartilage, the knee joint contains a second type of cartilage called menisci that act as shock absorber pads while joint fluid adds lubrication to the joint.



Source: AAOS

In patients suffering from OA, there is a cartilage failure that leads to a limited range of motion, bone damage, and severe pain. Knee OA (KOA) starts as the lack or loss of articular cartilage and progresses to involvement of the surrounding bone, tissues, and joint fluid. It results in progressive loss of function, including gait, stair climbing, and other physical activities that involve the lower limbs such as walking.

While it has been known to occur in young people, OA typically affects those aged 45 and over and is considered as one of the leading causes of lower limb disabilities among the elderly. In addition, as a result of the major loss

of function and, due to how it limits activity, OA can also result in depression and a loss of independence. There is also a considerable socioeconomic burden on societies and families due to disabilities brought about by OA.

People with KOA experience loss of proprioception, which may affect postural stability and risk of fall. Postural stability is defined as the control over the body's position in space for orientation and balance purpose. Postural stability (static and dynamic balance) is essential during activities of daily living and ambulation. Impaired postural stability is one of the main causes of falls in older adults and constitutes a significant public health problem. It is considered as one of the leading causes of hospital admissions.

As there is no cure for OA, treatment is focused on controlling symptoms and preserving physical function. This is accomplished through a combination of pharmacological and non-pharmacological therapies and ultimately joint replacement therapy.

Even with effective management strategies available, OA is both under-diagnosed and under-treated. This may be due in part to the high co-morbidities associated with OA, with upwards of 90% of OA patients suffering from at least one other chronic condition. OA and cardiovascular disease (CVD) are among the most common dyads seen in clinical practice, with CVD precluding the use of OA therapies – particularly non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, ketoprofen, or diclofenac.

If left untreated, most patients manage the pain associated with OA by limiting physical activities that exacerbate the pain, such as walking. This limitation of physical activity can then lead to poorer overall health, a higher risk of CVD, and worsening of other chronic conditions.

Current Treatment Options for KOA

Treatment options for Knee OA can be divided into two groups: Nonsurgical and Surgical. Nonsurgical treatment options include:

- **Exercise and weight loss**: Weight loss is the first recommendation for patients suffering from KOA, as each extra pound of weight can add 6 pounds of pressure on the knee joint during activity. Muscle strength is another effective means of controlling OA, as the muscles surrounding the knee act as shock absorbers and the stronger the muscles then the more stress they can absorb for the knee.
- **Braces**: Knee braces are available for OA that specifically affects the medial (inside) portion of the knee joint. The braces are custom made and can be quite expensive.
- **Nutritional supplements**: Glucosamine sulfate and chondroitin sulfate are widely used; however, neither of these treatments is regulated by the FDA and we could not find any randomized controlled trials demonstrating superiority of their use over placebo.
- **Viscosupplementation**: This involved the use of Hyaluronic acid injected directly into the cavity around the knee joint. Currently, there are five FDA approved HA injections currently available. Clinical results have been mixed, with only ~50% of patients experiencing symptomatic relief.
- **Cortisone injections**: Injection of cortisone directly into the knee has been shown to be effective for “flares” of arthritis symptoms. However, repeated cortisone injections are known to cause articular cartilage deterioration, thus the injections are used sparingly in the knee joint.
- **Medications**: Anti-inflammatory medications are known to decrease symptoms associated with knee OA. NSAIDs, including aspirin, ibuprofen, and naproxen, are known to be the most effective of the oral medications with stomach irritation being the most common side effect. Less common side effects of NSAIDs include stomach ulceration and renal damage.

Surgical treatment options include:

- **Chondroplasty**: An arthroscopic procedure performed to repair a small area of damage through smoothing of the articulate cartilage. This is only utilized in cases where there is mild-to-moderate cartilage wear.
- **Abrasion/Microfracture**: This procedure is for small areas where there is exposed bone or complete loss of cartilage. The exposed bone is abraded, causing it to bleed and stimulating the growth of fibrocartilage. It has been used successfully in patients who will be receiving a total knee replacement, and can put off the necessity of a total knee replacement for up to 5 years.

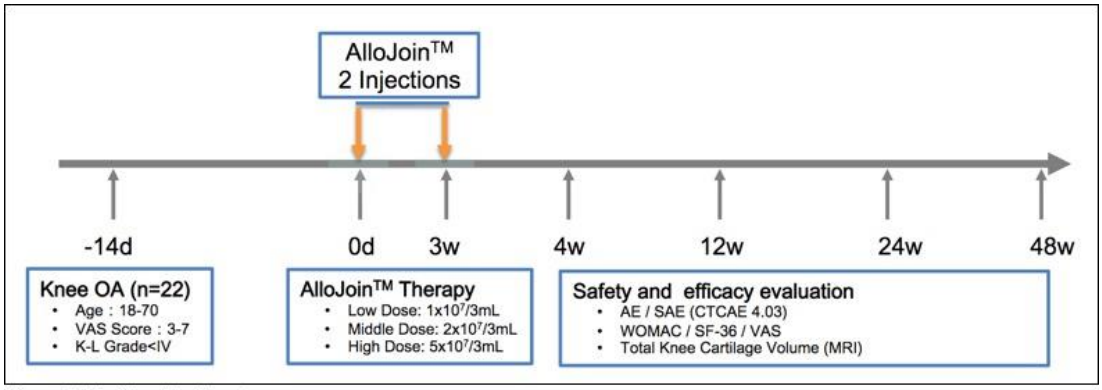
- **OATS procedure**: Osteochondral autograft (or allograft) transplant (OATS) can be performed for both small and large area of full thickness surface cartilage loss. The procedure involves removing a piece of bone that lacks surface cartilage and replacing it with a similar sized piece of bone with intact articular cartilage.
- **Osteotomy**: Patients with knee OA often have arthritis in either the inside or outside portion of the knee, causing a mis-alignment of the knee joint. An osteotomy is performed by wedging open either the tibia or femur and adding bone graft puddy to stimulate new bone growth in the wedged area. The procedure is typically very successful in relieving symptoms and preventing or delaying total knee replacement.
- **Knee replacement**: For severe OA, total knee replacement involves capping the end of the femur and tibia with metal components that recreate the surface of the joint. A plastic spacer is then inserted between the metal pieces to create a smooth gliding surface. Greater than 90% of patients experience a significant or total loss of knee pain. The procedure can cost upwards of $50,000 in the U.S.

The American Academy of Orthopaedic Surgeons (AAOS) published newly revised guidelines for knee OA in 2013 (AAOS, 2013). The most significant change from the previous guidelines issued in 2008 was a strong recommendation against the use of hyaluronic acid viscosupplementation. The reason for this was that a meta-analysis of 14 studies assessing HA injections did not have enough evidence to meet the minimum clinically important improvement thresholds. Another important point from the newly published guidelines was a strong recommendation for the use of NSAIDs.

AlloJoin® and ReJoin™

Cellular Biomedicine Group is developing two cellular therapies for the treatment of KOA, both of which involve the use of human adipose-derived mesenchymal progenitor cells (haMPC). These cells are isolated from adipose tissue obtained via a minimally invasive extraction process that is quick and leaves no scar. The haMPCs are then isolated and expanded before being injected into the knee. ReJoin® uses haMPC derived from the patient while AlloJoin® uses haMPC derived from healthy donors.

AlloJoin®: In 2016, Cellular Biomedicine Group initiated a Phase 1 clinical trial in China to evaluate the safety and efficacy of AlloJoin® in 22 patients with KOA. In 2018, the company announced positive 48-week data, which demonstrated good safety and early efficacy for the prevention of cartilage deterioration. The following chart gives an overview of the trial, with AlloJoin® injections taking place on day 0 and 21 followed by a 48-week follow-up.



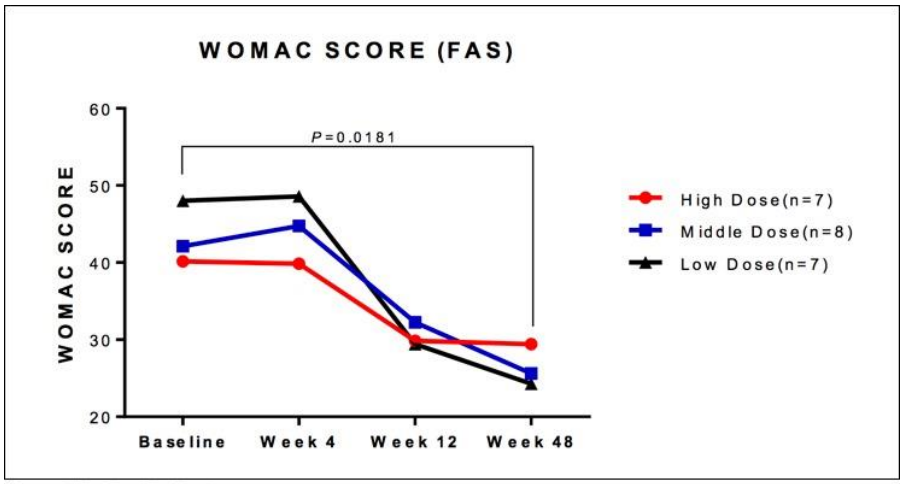
Source: Cellular Biomedicine Group, Inc.

During the trial, all patient's laboratory examinations and vital signs had no significant changes before and after treatment. The following table lists adverse events, which were mostly confined to mild to moderate knee pain and swelling after treatment. The majority of the patients were able to be treated with pain medication and symptoms eased over a few days. No drug-related serious adverse events were reported.

	A (high dose)				B (mid dose)				C (low dose)			
	N	Extent (Grade)	Duration (days)	Outcome	N	Extent (Grade)	Duration (days)	Outcome	N	Extent (Grade)	Duration (days)	Outcome
Knee pain	4	Moderate (3)	13	Remission	4	Moderate (3)	14	Remission	3	Moderate (3)	5	Remission
Knee localized edema					1	Moderate (3)	2	Remission	1	Moderate (3)	20	Remission
Hydrarthrosis					1	Moderate (3)	1	Remission	1	Moderate (3)	1	Remission
Arthrophlogosis					1	Moderate (3)	8	Remission				

Source: Cellular Biomedicine Group, Inc.

The following chart shows the change in pain according to the WOMAC pain scale (Bellamy *et al*., 1988). After 48 weeks of treatment, all three doses showed a statistically significant decrease in pain from baseline. These results are quite comparable to what is seen with treatment of KOA using cyclo-oxygenase-2 selective inhibitors such as celecoxib (Celebrex®) (Sawitzke *et al*., 2010).



Source: Cellular Biomedicine Group, Inc.

In early 2019, the company announced that the China NMPA has approved AlloJoin® as the first stem cell therapy for KOA to be approved to initiate a Phase 2 clinical trial in China under the new Cell Therapy Regulations that were effective since December 2017.

ReJoin®: In January 2016, Cellular Biomedicine Group announced positive results from a Phase 2b trial of ReJoin® in 53 patients with KOA. Results showed a significant improvement in WOMAC score when comparing baseline to 48-week data and the total knee cartilage volume showed a significant increase in patients treated with ReJoin® compared to those treated with ARTZ® (sodium hyaluronate). Pain relief as measured by VAS (visual analog scale) for both the left and right knees showed improvement over baseline as well as a statistically significant effect over ARTZ®.

Financials and Capital Structure

On August 6, 2019, Cellular Biomedicine Group announced financial results for the second quarter of 2019. The company reported no revenue for the second quarter of 2019. R&D expenses for the second quarter of 2019 were approximately $9.1 million compared to $6.2 million for the second quarter of 2018. The increase was primarily due to increased spending on the company's pipeline and expanding U.S. R&D operations. G&A expenses for the second quarter of 2019 were approximately $3.2 million compared to $3.1 million for the second quarter of 2018. Net loss for the second quarter of 2019 was $12.1 million compared to a net loss of $9.2 million for the second quarter of 2018.

Cellular Biomedicine Group exited the second quarter of 2019 with approximately $39.7 million in cash and cash equivalents, not including $17 million in restricted cash. In March 2019, the company raised net proceeds of $17

million following the sale of approximately 1.1 million shares of common stock at $17.00 per share in an underwritten public offering. In January 2019, the company signed a credit agreement for up to 100 RMB (approximately $14.5 million) from China Merchants Bank via a revolving credit line. As of June 30, 2019, all $14.5 million had been drawn under that facility. We estimate the company has sufficient capital to fund operations into the first quarter of 2020.

Risks to Consider

Clinical Risks: Cellular Biomedicine Group does not have any products beyond Phase 1 clinical testing and it will be initiating Phase 1 clinical trials for a number of its development products in the near term. There are no currently approved TIL or TCR products, and while other company's development products in those area have shown promise, there is no guarantee that Cellular Biomedicine Group's products will produce clinically significant results. While other CAR-T products have shown remarkable efficacy in the clinic, there is no guarantee that Cellular Biomedicine Group's CAR-T products will do the same. In addition, CAR-T products are known to be associated with a number of serious adverse side effects, up to and including death. If serious adverse events were to occur during any of the company's clinical trials it would have an adverse effect on the company's share price. Stem cell therapy is a new and as of yet unproven technology for the treatment of OA, thus there is no guarantee that ReJoin® or AlloJoin® will ever be approved for sale.

Regulatory Risk: China's regulatory environment concerning medical treatments is continuing to evolve, and there is no guarantee that the requirements for product approval in China will not continue to change, potentially causing a disruption to product development. In addition, it is unclear how much, if any, of the clinical trial data compiled in China will be accepted by the FDA.

Financing Risk: Cellular Biomedicine Group is not profitable and will require substantial additional capital in order to advance its development products through clinical testing and to approval. We estimate that the company has sufficient capital to fund operations into the first quarter of 2020 due to the fact that there are a large number of clinical trials either currently underway or planned to initiate over the next year, which will cause a rapid depletion of the company's financial resources. There is no guarantee that Cellular Biomedicine Group will continue to be able to finance the company at acceptable terms, and a failure to do so could cause the company to cease development of one or more product programs.

Corporate Structure Risk: The majority of Cellular Biomedicine Group's assets are located in China, where the government continues to exert an enormous influence through various business regulations. It also exerts a significant control over the economy through the allocation of resources, setting monetary policy, and providing preferential treatment to certain industries and companies. The Chinese government does not permit direct foreign investment in stem cell R&D activities; thus, those businesses are operated through local companies (variable interest equity, VIE) with which there is a contractual relationship but no direct equity ownership. While there is no reason to believe the owners of the VIE's that are contracted with Cellular Biomedicine Group would act in an interest contrary to the company's stated mission, if the shareholders of the VIE were to reduce or eliminate their ownership of the VIE entity their interests may diverge from that of Cellular Biomedicine Group.

MANAGEMENT PROFILES

Tony (Bizuo) Liu – Executive Director, Chief Executive Officer, and Chief Financial Officer

Mr. Liu formerly served as the Corporate Vice President at Alibaba Group and was responsible for Alibaba's overseas investments. After joining Alibaba in 2009, Tony held various positions including Corporate Vice President at B2B corporate investment, corporate finance, and General Manager for the B2C global e-commerce platform. He was also Chief Financial Officer for HiChina, a subsidiary of Alibaba, a leading internet infrastructure service provider. Prior to joining Alibaba, Tony 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. Tony was a key leader in the Microsoft corporate finance department during the 1990s as the Corporate Accounting Director. He was well recognized within Microsoft for driving an efficient worldwide finance consolidation, reporting, internal management accounting policy process, and showcased Microsoft's best practices to many Fortune 500 companies in the U.S. Mr. Liu obtained his Washington State CPA certificate in 1992. He 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.

Yihong Yao, PhD – Chief Scientific Officer

Dr. Yao has nearly twenty years of experience in the life sciences industry and academia with strong expertise in clinical biomarker discovery and development, strategy, and personalized medicine. Dr. Yao received his B.S. degree in Biochemistry from the Department of Biochemistry, Fu Dan University, Shanghai, China, a Master's Degree in bioinformatics from Boston University and his Ph.D. in Molecular Biology & Biochemistry from the Department of Biochemistry, University of Kansas. He completed his Postdoctoral Fellowship at Johns Hopkins University School of Medicine. In addition to his strong academic background, he has over fifteen years of professional experience with pharmaceutical and biotechnology companies including MedImmune (biologics research and development arm of AstraZeneca) and Abbott Bioresearch Center. Dr. Yao is the co-inventor of twenty-six filed patents relating to tumor classification, degenerative muscle disease, and autoimmune disease diagnostics and treatment. He has published over sixty 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. Dr. Yao is a frequently invited speaker and panelist for many international conferences on biomarkers, personalized medicine, miRNA, rheumatology, and oncology. Dr. Yao leads Cellular Biomedicine Group's overall scientific research programs in the areas of Immunooncology and inflammatory/autoimmune diseases and is responsible for strengthening the company's Immunooncology platforms and clinical trial design and bioinformatics.

Li (Helen) Zhang – Chief Production Officer

Dr. Zhang is the Senior Vice President of CBMG Technology and Manufacturing. She has more than 30 years' research experience related to tissue, cellular, and molecular biology. After graduating from medical school in 1982, Dr Zhang worked for over 10 years as a pathologist in clinical and instructional capacities. She began her cell and gene studies in 1993 at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin, Germany. Beginning in 1998, Dr. Zhang worked for thirteen years in stem cell (embryonic, fetus and adult) research and gene/cell therapy research at Harvard Medical School. As the associate director of cGMP and laboratory operations at the Harvard Gene Therapy Initiative, Dr. Zhang successfully led a team in providing clinical grade cell therapy and gene therapy products for clinical trials (in accordance with FDA standards) to organizations such as the Harvard Dana Farber Cancer Institute (DFCI), the French company Genethon, and the U.S Muscular Dystrophy Association (MDA). Her team has also provided thousands of cell/gene therapy products to research groups at Harvard and other Ivy League schools for study and research purposes. Dr. Zhang has more than 10 years' experience in cGMP establishment and management, as well as in large-scale manufacturing of clinical grade cell and gene therapy products that meet FDA standards.

VALUATION

We are initiating coverage of Cellular Biomedicine Group, Inc. (CBMG) with a valuation of $24.00. Cellular Biomedicine Group is a biopharmaceutical company developing cell-based therapies for cancer and degenerative diseases, with a focus on the Chinese market. In addition to a full pipeline of development products comprised of CAR-T, TIL, and TCR, along with stem-cell based therapies for the treatment of osteoarthritis, Cellular Biomedicine Group signed a collaboration agreement last year with Novartis for the production of Kymriah® in China. CAR-T products targeting multiple myeloma and non-Hodgkin lymphoma have initiated clinical trials and we anticipate additional clinical trials initiating in acute myeloid leukemia and hepatocellular carcinoma in the near future.

We value Cellular Biomedicine Group using a probability adjusted discounted cash flow model that takes into account potential future revenues from the company's CAR-T, TCR, TIL, and regenerative medicine products. We currently model for Cellular Biomedicine Group to partner each of the assets and to receive a 15% royalty on net sales.

Anti-BCMA CAR-T: We estimate there will be approximately 32,000, 39,000, and 27,000 new cases of multiple myeloma (MM) diagnosed in 2019 in the U.S., E.U., and China, respectively. Cellular Biomedicine Group is currently conducting an investigator-initiated Phase 1 trial for which we expect preliminary clinical data before the end of 2019. We estimate that the company will initiate a Phase 2 trial in 2020, a Phase 3 trial in 2022, and an NDA filing in 2024 with approval in 2025 for each of the three aforementioned regions. Following initial approval in late stage MM, we anticipate approval in earlier stage patients beginning two years following initial approval. We estimate that if successful, the drug would be a blockbuster with peak global sales in excess of $1 billion per year based on the fact that there are currently multiple blockbuster drugs to treat MM. Applying a 15% discount rate and a 33% probability of approval leads to a net present value of $115 million.

Anti-CD20 and Anti-CD19/CD20 Bi-Specific CAR-T: We estimate there will be approximately 74,000, 115,000, and 52,000 new cases of non-Hodgkin lymphoma (NHL) diagnosed in 2019 in the U.S., E.U., and China, respectively. Cellular Biomedicine Group is currently conducting an investigator-initiated Phase 1 trial for the anti-CD20 CAR-T and we anticipate the anti-CD19/CD20 bi-specific CAR-T entering the clinic in the near future. We estimate the company will initiate a Phase 2 clinical trial in 2020, a Phase 3 trial in 2022, and an NDA filing in 2024 with approval in 2025 for each of the aforementioned regions. Just as with MM, following initial approval in late stage NHL, we anticipate approval for earlier stage patients beginning two years following initial approval. We estimate peak global sales in excess of $1.5 billion per year, and when applying a 15% discount rate and a 33% probability of approval leads to a net present value of $138 million.

Anti-NKG2D CAR-T: We estimate there will be approximately 21,000, 31,000, and 31,000 new cases of acute myeloid leukemia (AML) diagnosed in 2019 in the U.S., E.U., and China, respectively. Cellular Biomedicine Group is currently conducting pre-clinical studies and we currently estimate for Phase 1 studies to begin in 2020, a Phase 2 trial in 2022, a Phase 3 trial in 2024 and an NDA filing in 2025 with approval in 2026 for each of the aforementioned regions. We estimate peak global sales in excess of $600 million per year, and when applying a 15% discount rate and a 33% probability of approval leads to a net present value of $41 million.

Anti-AFP TCR: We estimate there are approximately 500,000 individuals with hepatocellular carcinoma (HCC) in China, which we believe is going to be the greatest market opportunity for the company given the very high prevalence of the disease. We currently estimate for the company to initiate a Phase 1 clinical trial in the near term, with a Phase 2 trial in 2021, a Phase 3 trial in 2023, and approval in 2026. If successful, we believe a successful HCC treatment could have peak sales in China of over $500 million. Applying a 15% discount rate and a 33% probability of approval leads to a net present value of $18 million.

TIL: Cellular Biomedicine Group is pursuing non-small cell lung cancer (NSCLC) as a first indication for its tumor infiltrating lymphocyte (TIL) technology. Of the approximately 225,000 and 400,000 individuals who suffer from NSCLC in the U.S. and E.U., respectively, we estimate that approximately 75% of patients are resistant to checkpoint inhibitor therapy, thus representing a sizeable market opportunity. We believe global

peak yearly sales in excess of $2 billion are possible, and when applying a 15% discount rate and a 33% probability of approval leads to a net present value of $102 million.

Knee Osteoarthritis: China currently has approximately 57 million individuals who suffer from knee osteoarthritis, and we conservatively estimate that approximately 10% of them would be open to stem cell therapy. We estimate for a Phase 2 study to initiate in 2020, a Phase 3 study to start in 2022 with approval in 2025. We currently forecast for peak sales of approximately $200 million and applying a 15% discount rate and a 25% probability of approval leads to a net present value of $9 million.

Combining the net present value for each of the company's assets along with the current cash balance leads to a net present value for the company of approximately $458 million. The company has approximately 19.25 million shares, which leads to a valuation of approximately $24 per share.

PROJECTED FINANCIALS

Cellular Biomedicine Group, Inc.	2018 A	Q1 A	Q2 A	Q3 E	Q4 E	2019 E	2020 E	2021 E
CAR-T	$0	$0	$0	$0	$0	$0	$0	$0
TCR	$0	$0	$0	$0	$0	$0	$0	$0
TIL	$0	$0	$0	$0	$0	$0	$0	$0
Regenerative Medicine	$0	$0	$0	$0	$0	$0	$0	$0
Kymriah	$0	$0	$0	$0	$0	$0	$0	$0
Other Income	$0	$0	$0	$0	$0	$0	$0	$0
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$24.2	$6.0	$9.1	$9.0	$9.3	$33.3	$35.0	$40.0
Selling and Marketing	$0.3	$0.0	$0.0	$0.0	$0.0	$0.1	$0.0	$0.0
Impairment of Non-Current Assets	$2.9	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
General & Administrative	$13.2	$3.4	$3.2	$3.5	$3.5	$13.6	$14.0	$14.5
Other (Income) Expense	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($40.5)	($9.4)	($12.3)	($12.5)	($12.8)	($47.0)	($49.0)	($54.5)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$1.6	($0.1)	($0.2)	$0.0	$0.0	($0.3)	$0.0	$0.0
Pre-Tax Income	($38.9)	($9.3)	($12.1)	($12.5)	($12.8)	($47.2)	($49.0)	($54.5)
Income Taxes	($0.0)	$0.0	$0.0	$0.0	$0.0	$0.0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($38.9)**	**($9.3)**	**($12.1)**	**($12.5)**	**($12.8)**	**($47.2)**	**($49.0)**	**($54.5)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($2.2)**	**($0.51)**	**($0.63)**	**($0.63)**	**($0.64)**	**($2.44)**	**($1.96)**	**($1.82)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	17.7	18.2	19.2	20.0	20.0	19.3	25.0	30.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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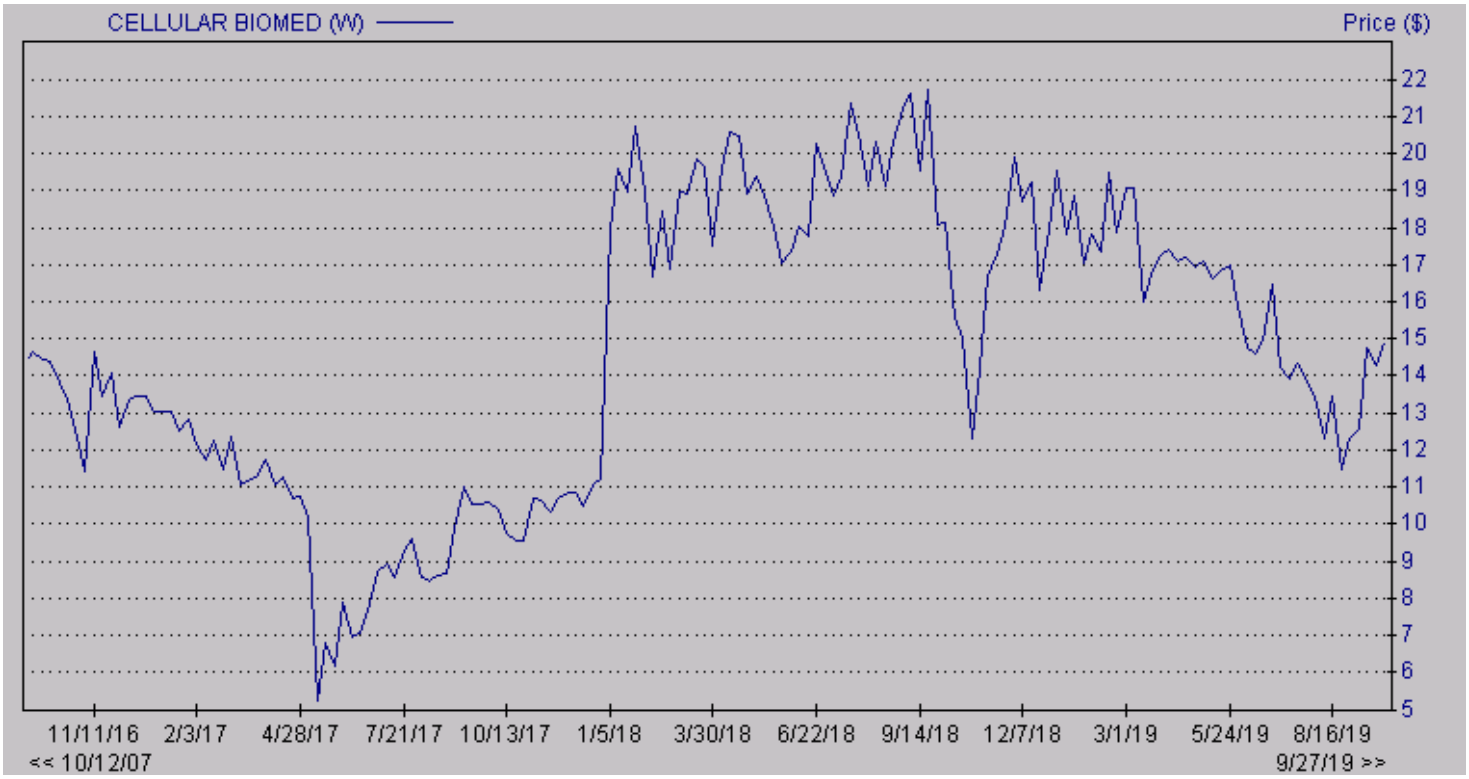
HISTORICAL STOCK PRICE



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