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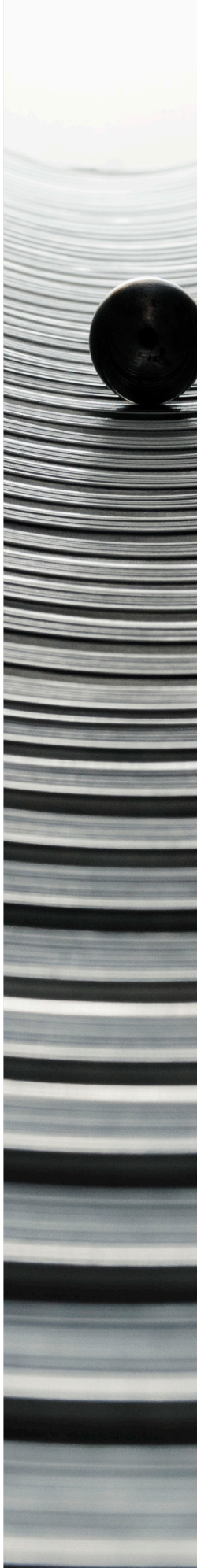
INVESTMENT MANAGEMENT



Counterpoint Global Insights

CAR-T Therapy

EDGE | AUGUST 2020

WELCOME TO THE EDGE.
Morgan Stanley Investment Management's Counterpoint Global shares their proprietary views on a big idea that has the potential to trigger far-reaching consequences—ideas such as blockchain, autonomous vehicles, machine learning and gene editing.

Counterpoint Global's long-term ownership mindset emphasizes perspective, insight and thinking across categories, while our investment process focuses on identifying unique companies with sustainable competitive advantages. Through The EDGE, we share our framework for thinking about change and our process for recognizing patterns that may drastically alter the investment landscape over the longer term.

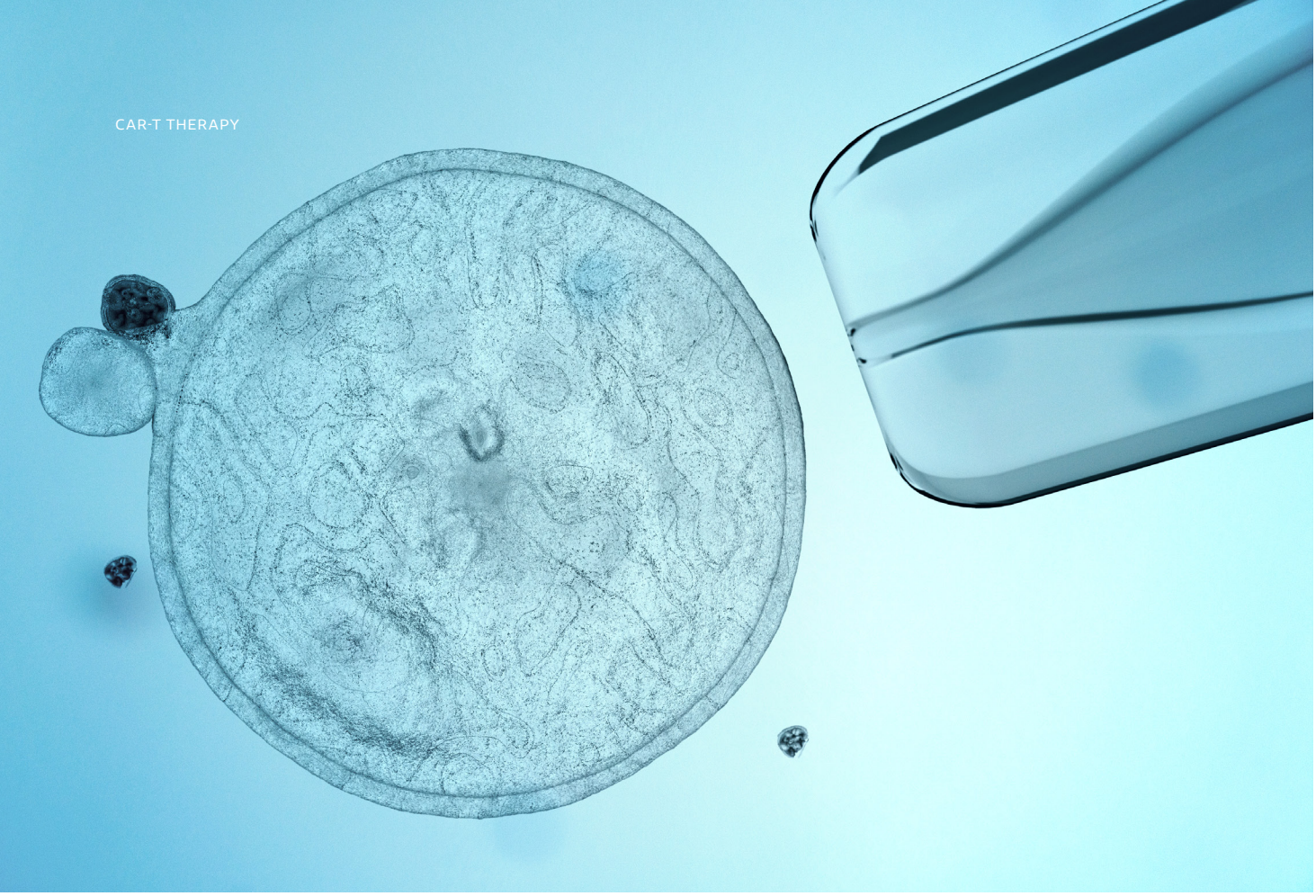
This work complements our team's more traditional, fundamental research to create a framework for long-term investing that is grounded in intellectual curiosity and flexibility, perspective, self-awareness and partnership.

Stem cell based cellular therapy

Genetically engineered cellular therapy is one of the most complex cancer therapies ever invented and has forever changed the survival outcome expectations for patients with blood cancer. Chimeric antigen receptor T (or CAR-T) cell therapy programs the patient's own immune system to attack cancer. Tumor immunologists long hoped that the immune system could be a key to curing cancer and after years of toiling in the lab, CAR-T therapy finally made this dream a reality. But despite demonstrating impressive results in blood cancers, this first generation therapy has low utilization because of high costs, complexity of treatment, and severe toxicities.

The next generation of cellular therapy has the potential to revolutionize cancer treatment. Cellular therapy based on stem cells could disrupt the current marketplace by decreasing costs and increasing the addressable market, while mimicking the impressive survival statistics we currently see with first generation therapy in patients receiving late-line treatment.

The natural immune response is complicated. A healthy immune system requires the intricate coordination of



multiple components. This system is prone to breakdown, which can lead to the development of various illnesses that include cancer. CAR-T cell therapy seeks to simplify this process by genetically engineering a patient's own cells to efficiently and effectively target and eliminate cancer. Doctors do this by removing T cells, our body's foremost fighter, from a cancer patient. They then genetically engineer the cells to express a key (or a receptor) that specifically recognizes a tumor's lock (or antigen) (*Display 1*). The genetically-engineered cells are returned to the patient. Meeting their match triggers the cells to carry out cellular processes that kill the tumor cells. Because this manufacturing process is lengthy, inconsistent, and complex, patients unable to wait for this therapy's development have limited success.

While the clinical results have been staggering (doubling to tripling the response to standard therapy, *Display 2*), initial uptake of approved therapies has been underwhelming. We believe that next generation cellular therapy will need to overcome three key challenges to increase access and expand the market potential. First, cellular therapy has failed in solid tumors (non-blood or liquid tumors) which remain an unmet medical need and represent over 80% of cancer deaths. Second, high costs of therapy and complex manufacturing are a hindrance to use. Lastly, severe toxicities including an immune response triggered whole-body attack (known as cytokine release syndrome) and neurotoxicity have plagued early generations of therapy. The cost of treating side effects, unwanted or unexpected events or reactions to a drug, and lengthy hospital stays create a financial burden.

> Stem cell based cellular therapy is disruptive because it has the potential to address the main challenges of first generation therapy while maintaining the impressive survival rate observed in cancer patients receiving late-line treatment.

Multiple next-generation approaches are under development that address the issues with first generation therapy and have the potential to revolutionize cancer treatment. A second generation approach uses CAR-T cells that are manufactured ahead of time from healthy donors rather than the bespoke manufacturing of the cells of an ill cancer patient. This approach is known as allogeneic CAR-T therapy and is disruptive because it has the potential to reduce complexity, time to treatment, and accessibility.

As promising as allogeneic CAR-T is, the fact remains that healthy donors are inherently diverse, making therapy inconsistent and irreproducible.

To overcome this hurdle, scientists pursuing a third generation CAR-T can use stem cells which allow for the development of a well-characterized,

uniform, and ready-to-use cellular therapy. The upfront drug discovery and development is complex for cellular therapy based on stem cells but advances in genomic sequencing and editing techniques have made this technology more viable in cancer treatment. We believe the use of stem cells could convert a complicated therapeutic process into a manageable product. This would lower the cost of therapy and expand the addressable market.

Here's a sketch of how cellular therapy based on stem cells works. Scientists begin with healthy donors and create induced pluripotent stem cells (iPSC). These are cells, often taken from the skin, that have been reprogrammed back to an embryonic-like state to enable the development of a renewable source of any type of human cell. The starting material, uniform iPSC, is engineered with properties of interest using genetic editing techniques. At this stage of development, scientists can use sequencing technology to fully characterize the genetic code of the cells. This allows them to create a known and uniform product.

Stem cell based therapy differs from first generation therapy, which uses cancer patient's cells, and second generation therapy, which uses the inconsistent and diverse cells of healthy donors. Scientists can differentiate expanded stem cell lines into immune cells of interest, including classical T cells (the T in CAR-T) or different cell types that can potentially mitigate safety issues. The cells can then be produced at commercial scale to create a consistent clinical supply that is available for easy administration at any hospital.

First generation cellular therapy has so far been unsuccessful in dealing with solid tumors. Treating solid tumors likely requires multiple genetic changes and therefore numerous steps in genetic engineering. Because stem cell based therapy can be edited and thoroughly examined, scientists can include many complex editing steps without increasing the risk of the inappropriate changes that lead to unwanted cellular effects. This is unlike first and second generation therapy development, where only a finite number of changes can be reliably supported and the final product is diverse rather than uniform. Stem cell based therapy therefore has the potential to be effective for both blood and solid tumors.

First generation therapy takes up to three weeks to manufacture and often fails quality control measures. Approximately 15-20% of patients do not receive their treatment in a normal clinical setting. As this therapy generates a product for each patient on a one-for-one basis, it does not scale.

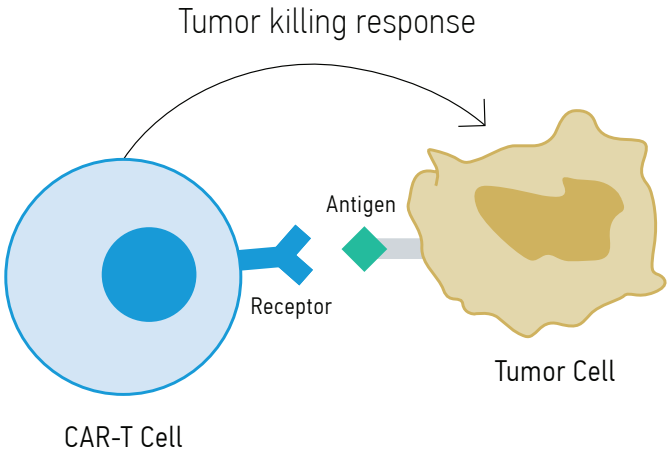
Stem cells are essentially unlimited, as one batch can be expanded and stored to form a renewable and reliable supply chain for therapy development.

Stem cell based therapy does scale because it can develop an effectively infinite number of doses available for administration at any hospital. This has the potential to double gross margins as compared to the current therapy.

While the initial engineering and development of the therapeutic product based on stem cells is complex, the

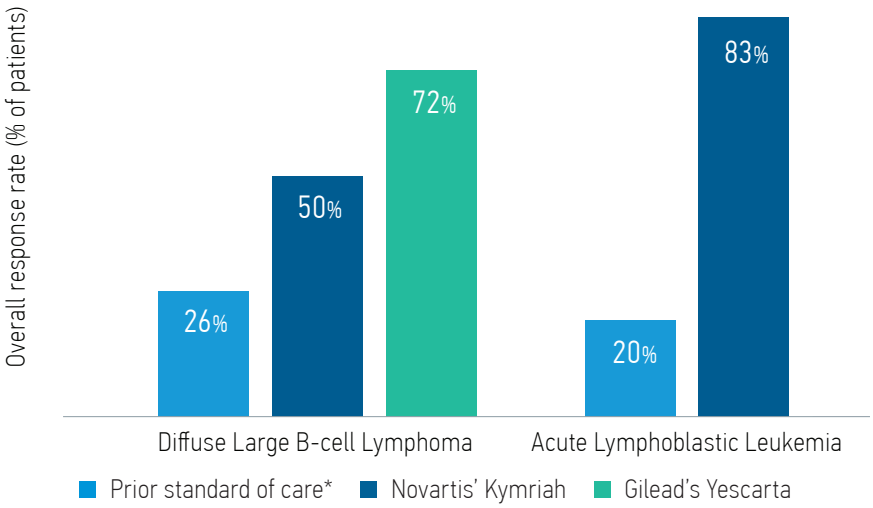
DISPLAY 1

Schematic representation of CAR-T cell interacting with a tumor cell expressing the correct antigen



DISPLAY 2

Published response rates for approved CAR-T therapy in liquid cancers



Source: Package insert for approved drugs.

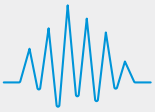
* Standard of care = SCHOLAR-1 study in DLBCL, CLO-212 study in ALL

subsequent manufacturing and delivery to patients is easy and convenient. By decreasing the complexity of manufacturing and increasing scalability, stem cell based therapy increases access to therapy and lowers the cost substantially.

CAR-T therapy can be a financial drain because of the high costs of side effects and lengthy hospitalization stays. This limits adoption in outpatient settings (which is potentially better for reimbursement) and earlier lines of therapy (which is a larger total addressable market). First generation CAR-T therapy also has a black box warning for fatal or life threatening side effects. The ability to develop stem cells into any cell type, including a non-T cell therapy, may mitigate the previously observed safety risks without compromising efficacy. That said, the potential risk of long-term use of stem cells is unknown.

We believe there are five key challenges that stem cell based therapy will need to overcome. First is efficacy. Stem cell based therapy needs to demonstrate survival and response results comparable to a personalized stem cell therapy. The first of these products is currently in clinical trials after more than a decade of research and development. Second is safety. We do not know the long-term risks of using stem cell based therapy. Whether these cells could spontaneously de-differentiate (return to their pluripotent state) and develop cancer remains an unanswered question. Third is regulatory risk. How long would it take for physicians, patients, and regulators to get comfortable with this therapy? Doctors may have to monitor patients long term for unwanted side effects, which would add to the lifetime cost and burden of therapy. Fourth is the longevity of therapy. Since this therapy is made from a foreign substance (unlike one's own immune cells), the patient's immune system may reject it. It is an open question as to whether the low persistence of therapy would diminish the therapy's ability to potentially prevent a hypothetical cancer recurrence. However, it could allow for another dose of therapy, which could have therapeutic benefits. Lastly is commercialization. The ability to scale manufacturing at a reasonable cost remains a major barrier, but we believe that the industry's continuous learning may allow it to overcome this challenge.

First generation cellular therapy has had impressive results and changed the survival statistics for blood cancer patients with no other options.



OTHER DISRUPTORS

Other themes the team is currently researching include

- Blockchain
- Autonomous vehicles
- Machine learning
- Automation/robotics

We believe stem cell based therapy has the potential to become a ubiquitous and disruptive product to treat both blood and solid cancer patients. Stem cell based therapy creates an inexpensive, eternal drug source that may simplify cellular therapy manufacturing and delivery. This therapeutic opportunity solves the main issues of earlier generation therapy such as an inability to tackle solid tumors, manufacturing complexity, high costs, and safety concerns. Stem cell based therapy ensures broader market accessibility while potentially curing cancer patients. Though drug development is still in its infancy, we believe stem cell based therapy may have enormous potential.

Counterpoint Global

New York

INVESTORS	RESEARCH RESPONSIBILITIES	YEARS OF EXPERIENCE	YEARS WITH FIRM	YEARS WITH TEAM
DENNIS LYNCH	Lead Investor, Head of Counterpoint Global	29	25	25
SAM CHAINANI	Head of Counterpoint Global~ New York, Technology	27	27	23
JASON YEUNG	Health Care	26	21	19
ARMISTEAD NASH	Business Services, Software	23	21	19
DAVID COHEN	Consumer	35	30	24
ALEX NORTON	Consumer, Industrials, Technology (ex Software)	28	23	23
MANAS GAUTAM	Head of Global Endurance, Generalist	11	8	8
ANNE EDELSTEIN	Health Care	12	5	5
ABHIK KUMAR	Software, Media	14	4	4
JENNY LEEDS	Healthcare	7	4	4
JOSHUA JARRETT	Director of Research, Generalist	18	3	3
RUOBING CHANG	Internet	11	7	3
ALEKS SAMETS	Payments	3	3	3
BETH FIFER	Health Care	11	2	2
MUHAMMADRAZA PANJU	Internet	4	2	2
PETE STOVELL	Generalist	29	2	2
MICHAEL MORITZ	Generalist	5	1	1
CONSILIENT RESEARCH				
MICHAEL MAUBOUSSIN	Head of Consilient Research	37	3	3
DAN CALLAHAN	Consilient Research	18	3	3
DISRUPTIVE CHANGE RESEARCH				
STAN DELANEY	Big Ideas, Emerging Themes	22	22	19
SASHA COHEN	Big Ideas, Emerging Themes	6	6	6
JUSTIN AMEZQUITA	Big Ideas, Emerging Themes	3	3	3
VASILEIOS PRASSAS	Big Ideas, Emerging Themes	9	2	2
SUSTAINABILITY RESEARCH				
THOMAS KAMEI	Head of Sustainability Research, Internet	11	11	11
DERRICK MAYO	Sustainability Research	18	9	2
CLIENT RELATIONSHIP & BUSINESS MANAGEMENT				
MARK TODTFELD	Chief Operating Officer	28	18	4
KERRY ANN JAMES	Head of Client Relations, Portfolio Specialist	26	6	2
PRAJAKTA NADKARNI	Portfolio Specialist	19	16	12
MICK MORAN	Portfolio Specialist	9	9	1
MCKENZIE BURKHARDT	Portfolio Specialist	20	20	20
XAVIER SALAZAR	Portfolio Analyst	5	5	1
KATHRYNE DOWNS	Portfolio Specialist ~ Global Endurance	11	11	1
EARL PRYCE	Portfolio Administrator	23	23	16
CHAYSE MORGAN	Portfolio Administrator	3	3	3
ERICA CASARENO	Portfolio Administrator	1	1	1
AMBER YANG	Business Management	13	5	2

Asia

Global, International, Asia

KRISTIAN HEUGH Lead Investor, Head of Global Opportunity

- 13 Investors
- 6 Portfolio Specialists
- 1 Portfolio Operations Analyst

"Investor" refers to an analyst or portfolio manager of Counterpoint Global.
Team members may change without notice from time to time. Years of Experience listed above refers to Industry Experience.
Years of Experience, Years with Firm and Years with Team are as of September 2023.

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Dubai: MSIM Ltd (Representative Office, Unit Precinct 3-7th Floor-Unit 701 and 702, Level 7, Gate Precinct Building 3, Dubai International Financial Centre, Dubai, 506501, United Arab Emirates. Telephone: +97 (0)14 709 7158).

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