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Creating markets & marketing strategies Newsletter

July 15, 2016

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

We have a new mobile friendly newsletter. Love to receive your feedback.

Last month I covered "2016 Translational Imaging Symposium Highlights." If you missed last month's article, click here to read it. This month's newsletter will cover, Why is CAR-T Therapy a Hot Topic Today? Part 1.

Read on to learn more about this topic and other current news. The next newsletter will be published on August 15th.

We encourage you to share this newsletter with your colleagues by using the social media icons at the top, or by simply forwarding this newsletter or use the link at the bottom of this newsletter. Should you or your colleagues want to join my mailing list, click on the icon below or scan the QR code.

Please email me, Regina Au, if you have any questions, comments, or suggestions.

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If you are developing a product and have not conducted the business due diligence to determine commercial viability or success, contact me for an appointment. For successful commercial adoption of your product or looking to grow your business, contact me for an appointment.

For more information on our services, click on the links below:

Product Development
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To Cloud Compute, or Not to Cloud Compute?

I am pleased to announce that my article "To Cloud Compute, or Not to Cloud Compute?" on the Pros and Cons of using Cloud Computing and Storage has been published in *Innovations in Pharmaceutical Technology (IPT)* Journal, July 2016, pages 32-35 © Samedan Ltd. To read an electronic version, click here.

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14th Annual Tri - State Trek for amyotrophic lateral sclerosis (ALS)

Many scientist from academic institutions and pharma/biotech companies such as Sanofi-Aventis, Biogen and ALSTDI (nonprofit company raising money for research), have been doing research for a long time (14th annual Tri-State Trek) to develop a treatment/cure for ALS (Lou Gehrig's Disease), but as of this date, there is no long term treatment for ALS. The only drug on the market, Rilutek®, increases the survival rate by only 2-3 months. This neuro-degenerative disease attacks certain cells in the brain and spinal cord needed to keep our muscles moving and affects mostly men. The average survival rate from the first symptom of ALS is 2 - 5 years.

The Tri-State Trek is a 3-day bike ride fund-raising event for ALS that took place June 24- 26, 2016. This event entailed a a 270 mile bike ride through 3 states (MA, CT and NY) starting at Boston College and finishing in Greenwich, CT. There were 454 participants, about half were riders and the other half were crew members supporting the riders, the event and those who suffer from ALS.

This is my second year volunteering as a crew member since I am not an avid rider and I decided to not only be a donor to support this worthy cause, but to be a donor/fundraiser. I normally wouldn't post a fundraiser in my newsletter, but since it is a worthy cause, it's science/medical and I'm participating, I decided to include it. If you believe in this cause and would like to donate (any amount is appreciated), please click on my fundraising page here. This year's fund raiser goes until October. I would like to thank you in advance for your donation. For more information on ALS, click here.

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The Ascent of Precision Medicine

I am pleased to announce that I was interviewed to identify the trailblazers in personalize medicine for an article entitled "The Ascent of Precision Medicine" in PharmIQ. To read the article, click here to log in (free).

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Why is Chimeric Antigen Receptors T cell (CAR-T) Therapy a "Hot Topic" Today?

Immuno-oncology (IO) is the buzz word today and it has everyone doing IO research. There are many different types of IO and CAR-T is one of the cellular therapies. Why are IO and CAR-T buzzing today? If we look back at the history of cancer treatment, the survival rate was measured in months which according to oncologist was a lot back then because the mortality rate in most cancers was 100%. However, with most traditional chemotherapies, the drugs were not well tolerated because they would kill both cancerous and healthy cells that lead to major side effects, such as loss of hair, nausea and vomiting, and risk of infection. Survival was better, but not much better depending on the type of cancer and the patient's own genetic and physiological make-up.

Scientists have tried to solve the targeting problem by utilizing the patients' own immune system to aid in recognizing and killing the cancer cells, rather than healthy cells and keep the cancer cells at bay. Scientists have tried and are still developing drugs that fall into two categories of IO;

1) Checkpoint therapies - which includes cytokine therapy, therapeutic vaccine (dendritic cell vaccines), antibody drug conjugates, and tumor specific T cell; and

2) Adoptive Cell Transfer (ACT) therapies - tumor infiltrating lymphocytes (TILs) from tumor mass that is excised, and gene transfer methods: Chimeric Antigen Receptors (CAR) T cells and TCR (T cell receptor) T cells for blood.

Checkpoint therapies currently on the market are Merck & Co.'s

pembrolizumab (Keytruda®), and Bristol Myers Squibb's (BMS) nivolumab (Opdivo®) for specific types of cancers and have made significant inroads with some patients becoming cancer free. Both Keytruda and Opdivo are human monoclonal antibodies that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 that inhibits the body's immune response, including anti-tumor immune response. BMS' second monoclonal antibody ipilimumab (Yervoy®) binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86, that also inhibits T-cell activation and proliferation.

Here are the roadblocks to cellular therapies according to Stephen Grupp, MD, PhD, Director of Translational Research, Center for Childhood Cancer Research, The Children's Hospital of Philadelphia. See Table 1.

Roadblocks to Successful Cellular Therapies	
Problem	**Solution**
Targeting - CD19+ tumor cell or B cell both express CD19 so the T cell can't recognize the tumor cell. Getting T cells which previously couldn't recognize cancer cells and force T cells to recognize cancer cells	Need T cell recognition therapies: CAR or TCR which scientists have been developing and there are a number of CAR clinical trials worldwide.
Expansion Ex. Vivo - making these cells for each patient is complicated and making these cells expand outside of the cell culture or ex vivo. Expansion in host - getting "programmed" T cells to expand in the human body and not disappear like proteins. We know how an effector T cell response works, cells have to proliferate enormously to go from a small number of precursor cells to a large number of effector cells and then have a memory response. Requires an enormous amount of T cells.	Need GMP cell culture approach. Need to use a lot of young T-cell that are not exhausted due to the expansion. This has not been proven yet.
Persistence - getting "programmed" T cells to remain in the body for a long term affect.	Need to use central memory T cell that will recognize the cancer cells for a long time. This has not been proven yet.
Effector: Target ratio - create efficient effector cells for clinical trials which requires expansion.	Need evidence for efficiency and safety in Phase I, not just safety.
CAR- Chimeric Antigen Receptors, TCR - T cell receptor, GMP - good manufacturing practice	

Table 1.

For the purpose of this topic, we will focus on Adoptive Cell Transfer and specifically CAR-T cells as an introduction. A CAR gene has two major components, an external receptor that recognizes an antigen binding site on the cancer cells and an internal component, or signaling/expression that

directs the T cell to the cancer binding site and is inserted into a T cell via a retrovirus or lentivirus vector. See Image 1.

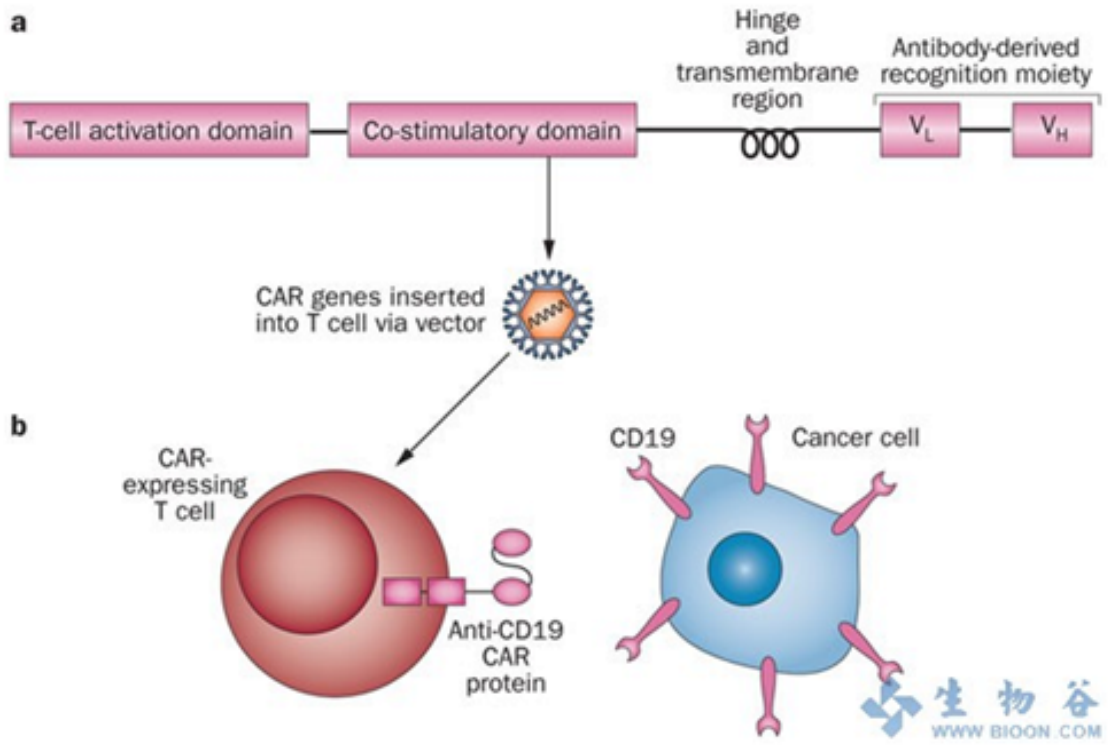

Image 1. An anti-CD19 CAR-expressing T cell recognizing a CD19+. Source: Kochenderfer et al., Nature Reviews Clinical Oncology 10, 267-276

Scientists have been working on CAR-T cells for over a decade and developed the first generation of CAR-T back in 1991 for HIV. This first generation CD4/CD8z (CD4/CD8 T-cells) + CD3 zeta chain (to generate an activation signal in T lymphocytes), CAR-T for HIV (CD4) using a retrovirus went into clinical trial in 1997, the CAR-T persists now for 10 years.

The second generation of CAR-T uses a single chain fragment variable (scFv) or antibody fragment as the external component designed with the internal signaling CD28 or 4-1BB (CD137) + CD3 ζ-chain. Immunologists found that they needed two (2) signals; Signal 1 for activation and Signal 2 for survival and T cell proliferation. These co-stimulatory signals are CD28 (Signal 2) and 4-1BB or Ox40 (Signal 1) + CD3 ζ-chain.. They also believe that the microenvironment plays an important role in the immune system. See Image 2.

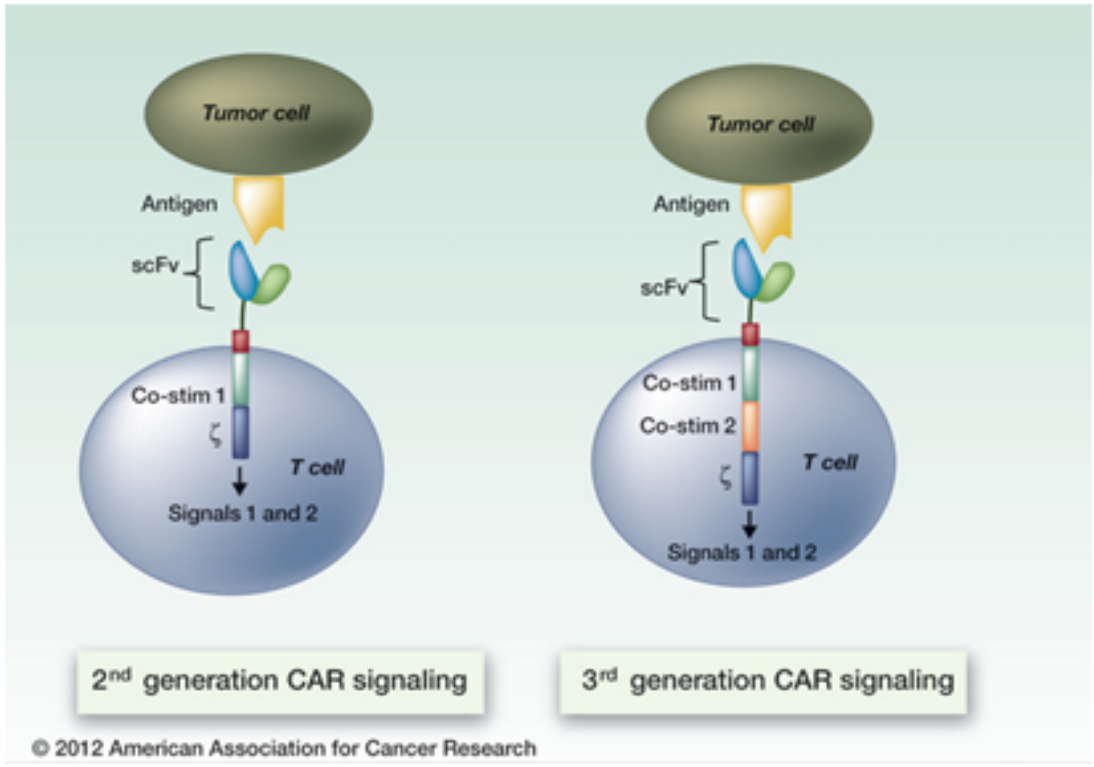

Image 2. Second and third generation CAR signaling
Source: National Cancer Institute.

So how does this therapy work logistically? To make these cancer-fighting T-cells or CAR-T cells, T cells are first collected from the patient and then modified as in image 2 to recognize an antigen binding site on the cancer cells. It usually takes 2 and 1/2 to 3 weeks to insert the gene and grow cells. Once this is accomplished the modified T cells are then infused back into the patient, called autologous therapy.

Once it is infused back into the patient these "programmed" T-cells can multiply and persist for a long time (called "living drug"), they are capable of destroying any cells that have the target antigen.

This disruptive technology of modifying T-cells is sort of similar to monoclonal antibody therapy, as it does use a fragment of an antibody, but has more potency and persistence - as living cells that can persist in the body, as opposed to antibodies (proteins) that are active for a limited time.

How well does it work? Dr. Carl June, Richard W. Vague Professor of Immunotherapy and Professor of Pathology & Laboratory and Medicine Director of Translational Research Programs, University of Pennsylvania, is one of the foremost leaders in CAR-T therapy presented his work at the Royal Society scientific programme on October 6th, 2015 highlighting some of the results of his CART-T therapy. He also emphasized that the design of

the CAR-T is very important as well as which vector you choose.

In designing CD19 for Leukemia, he compared different CAR-T therapy from Memorial Sloan Kettering (MSKCC) to National Cancer Institute (NCI) to UPenn (Carl June). See Table 2.

	MSKCC	NCI	UPenn
Design	CD28 - 19-28z	CD28 - FMC63-28Z	4-1BB - CD19-BB
Vector Expression	Retrovirus Approx. 30 days	Retrovirus Approx. 30 days	Lentivirus > 4 years
CR in ALL	90%	80%	90%
CR in CLL	0/8		4/14
PR in CLL ORR in CLL	0/8 0%		4/14 57%
CR- complete response, ALL - acute lymphocytic leukemia, CLL - Chronic lymphocytic leukemia, PR - partial response, ORR - overall response rate.			

Table 2.

For ALL, this is the type of data that's got everyone very excited about CAR-T therapy. Even though the results for CLL were not as successful, it's a more complex disease to tackle and many companies are focusing on this area. Emily Whitehead, the first pediatric patient with ALL treated with CAR-T therapy was a complete responder in 2012. She remains cancer free for 3 years so far. President Obama announced the Precision Medicine Initiative and Emily was invited to White House in January of 2015 as a successful example of Precision Medicine or Personalized Medicine.

Due to these promising results there are as of September. 16, 2015, 77 CAR-T trials being conducted around the world (48 in US, 8 in UK, 20 in China) and Professor June believes China will outpace the US in clinical trials.

While the CAR-T therapy looks very promising, there is still work to be done to perfect this therapy because as with any type of therapy, there will be side effects and other challenges. Next month, I will cover the advantages and the challenges of this therapy and review what scientists are doing to overcome these challenges.

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Closing Thoughts

Adoptive cellular therapies or CAR-T looks very promising and the goal is to achieve complete response to this therapy. While the data for CR is good for ALL, the numbers are still small and the issue of side effects still needs to be addressed. In addition, while CAR-T therapies are moving towards personalized medicine, manufacturing becomes an issue as manufacturing cost goes down as quantity goes up and you can't achieve this with individualized therapy. This is one of the reasons that CAR-T therapies are so expensive. I will cover this in more detail in my August newsletter, so stay tuned.

Developing a CAR-T therapy and trying to develop your value proposition and target product profile for commercial success? Email me or call me at 1-781-935-1462 for an appointment.

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