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Creating markets & marketing strategies

Newsletter

August 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 "Why is CAR-T Therapy a Hot Topic Today? Part 1." 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 2.

Read on to learn more about this topic and other current news. The next newsletter will be published on September 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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Commercializing a Product?

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 sympton 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 270 mile bike ride through 3 states (MA, CT and NY) starting at Boston College and finishing in Greenwich, CT. There were 45 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 fundraiser goes until October. I would like to thank you in advance for your dontaion. 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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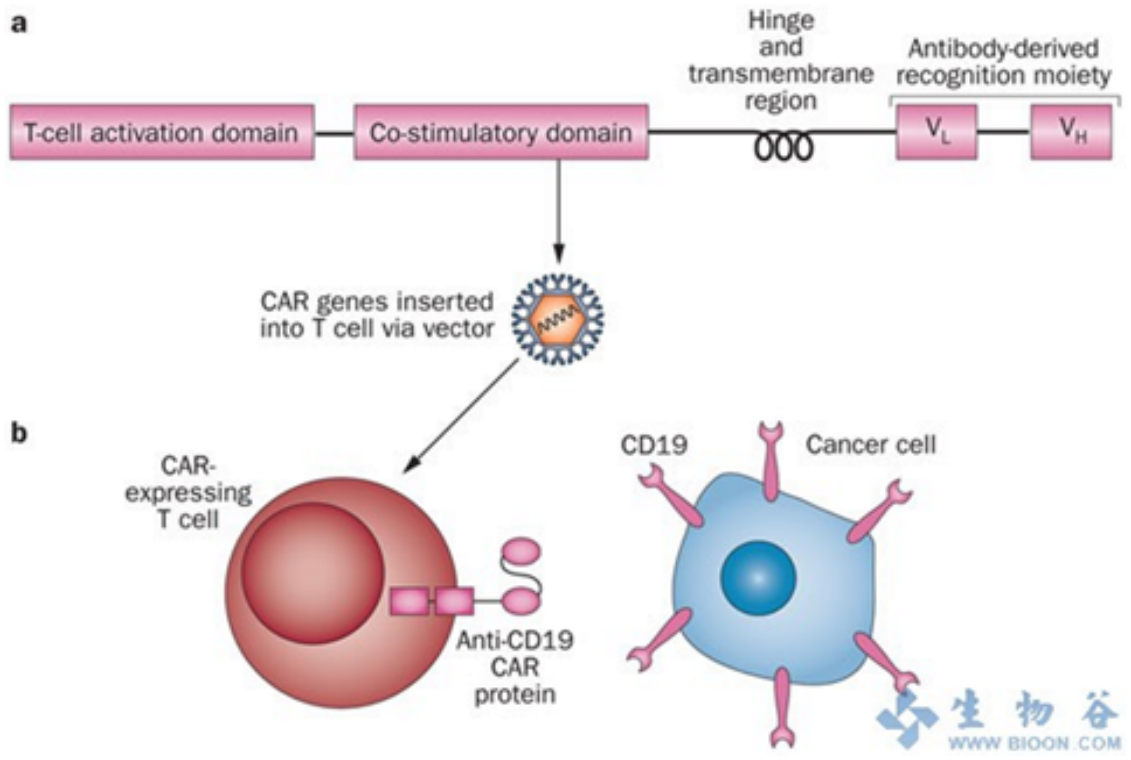
Why is Chimeric Antigen Receptors T cell (CAR-T) Therapy a "Hot Topic" Today? Part 2



An anti-CD19 CAR-expressing T cell recognizing a CD19+
Source: Kochenderfer et al., Nature Reviews Clinical Oncology 10, 267-276, doi: 10.1038/nrclinonc.2013.46

Last month, I covered: 1) The types of immuno-oncology (IO) therapy; 2) Roadblocks to cellular therapies; 3) What are CAR-T cells and how do they work; and 4) How well does CAR-T therapy works. If you haven't had a chance to read it, click here.

This month, I will cover: 1) What is the side effect profile; 2) Why CAR-T therapies will be expensive; 3) Does CAR-T therapies justify the cost? and 4) Questions still facing the CAR field?

What is the side effect profile?

One of the potentially lethal side effect with CAR-T therapy is cytokine release syndrome (CRS) which involves elevated levels of several cytokines including interleukin (IL)-6 and interferon γ. Clinical symptoms include fever, hypotension, respiratory insufficiency and neurological changes such as delirium, global encephalophathy, aphasia and seizure like activities/seizure. This particular side effect was not evident in mice models, and was presented only when it was infused into humans.

There were several cases of CRS at Children's Hospital of Philadelphia (CHOP) with significantly elevated levels of IL-6 which made the patients extremely ill. After a cytokine blockade failed, one 8 mg/kg dose of an IL-6 receptor antagonist, Tocilizumab, and the IL-6 levels returned to normal. IL-6 is a classic feedback loop mechanism possessing a network effect and one needs to interrupt multiple nodes or block the IL-6 mechanism to halt this toxicity.

It was also found that by measuring the percentage of bone marrow blast (BMB) (%), defined as disease burden, correlates with the severity of CRS for children. Those with no disease burden are characterized as having BMB below 50%, and those with disease burden (yes) have greater than 50% BMB. Those who have a "yes" for disease burden have a greater likelihood and severity of CRS. It is more advantageous to deploy therapy in patients with a low burden of disease resulting in less toxicity. The more BMB, the more severe the CRS. This could be also applied to adults as they have a mature immune system compared to children who are still developing their immune system.

Why CAR-T therapies will be expensive

People want to live longer with a better quality of life. To achieve this, scientist have gone into uncharted waters in understanding the etiology or mechanism of action of diseases which is not an easy feat. In order to achieve this, drug development has gotten longer and longer and therefore, more and more expensive. On average, according to a 2013 study published by Tuft's Center for the Study of Drug Development, it takes 11 (range 10-15) years to develop a drug from research to approval

with a cost on average of $2.6 billion dollars.

IO therapy is far more complex than small or large molecule. Scientists understand how our immune system works, but not thoroughly enough to know how the immune system will react when one starts to manipulate the human immune system.

In order to administer CAR-T therapy, scientists had to figure out the following steps to manufacturing this therapy:

1. Depending on the type of cancer, design a CAR with the best external and internal signals (Signal 1 and Signal 2); and
2. Design it with the best viral vector to transmit the gene to the T-cell and proliferate;
3. Get the CAR-T cells to expand ex. vivo in order to infuse it back to the patient;
4. Get the reprogram cells to expand in the host and persist for unlimited amount of time in order for the patient to remain cancer free;
5. Collect T-cells from the patient;
6. Reprogram the patient's T-Cell to CAR-T cells;
7. Infuse it back into the patient.

All these steps takes an extraordinary amount of scientific knowledge, experimentation and time for each individual. This is truly personalized medicine. CAR-T therapy is uncharted territory and no one knows whether this will work for every individual even if it is using an individual's own immune system.

	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.			

Comparison Study of three different CAR-T Therapies for ALL and CLL.

In the comparison study of SKMCC, NCI, and UPenn for leukemia, the therapy worked for ALL in a small number of patients, but not very well for CLL. The expression of CAR-T cells only lasted for 30 days in the SKMCC and

NCI which may account for why the response rate was poor for CLL. However, even with an expression rate of greater than 4 years in the UPenn study, the overall response rate was 57% vs. 90% with ALL.

For patients who achieved a partial response or is nonresponsive to the CAR-T therapy, doctors and scientists have to figure out why the patient didn't have a complete response. It may mean going back to the drawing board in designing a different CAR, using a different viral vector, or using a different type of T-cell. This path adds on cost to the CAR-T therapy. Or they may decide to either add another drug or go with a different class of agents.

In calculating the cost to produce this therapy, because the process described has be done separately for each individual, it becomes very costly. Production cost only comes down when there is economy of scale, and with CAR-T therapy, there is no economy of scale since it's personalized to each individual. The cost of this therapy can only be determined by the biotech company that is actually developing the CAR-T therapy.

This is the dilemma. Society wants personalized medicine yet who is going to pay for the cost of personalize medicine? Insurance providers will not pay for CAR-T therapy because it is unproven by regulatory standards right now as well as their standards, the side effect profile is risky even though it can be remedied and it is very expensive. Today, most insurance companies will only pay for the standard treatments and only when all therapies fail, will the insurance company consider adoptive cellular therapy with special circumstances.

Does CAR-T therapies justify the cost?

The obvious answer is "yes." If one can use their own immune system to fight cancer, this is ideal and the therapy would be a one dose cure as oppose to traditional treatments including checkpoint inhibitors, another IO therapy, where the patient would have to take the drug/biologic for a specific period of time and hope the cancer is eradicated. Any inhibitor, is only viable for a limited period of time compared to a programmed T-cells which could be expressed for an unlimited time period.

In non-CAR-T therapy, the cancer could return and the same or different drug/biologic would have to be administered again similar to a maintenance therapy vs. a cure which is less expensive in the long run. And as each episode of a relapse occurs, the odds of survival is diminished

significantly because the body gets weaker and the cancer get smarter in terms of resistance.

But the real answer relies on the payer. The insurance company will not pay for a new therapy unless it is proven that CAR-T therapy works and is a cure, by their standards, not just FDA approval, it's safe and it saves the insurance company money. But in order to determine this, health economic data must be collected over a determined length of time to demonstrate not only efficacy and safety, but the therapy saves the company money compared to standard treatment which many times are generic versions of the drug or biosimilar of a biologic.

If the insurance company won't cover the therapy, and the patient or family wants the therapy, they will have to pay for it. If the patient can afford to pay for it, they will. But most patients and families can't afford it and they will have to rely on standard treatment and hope for the best.

Questions still facing the CAR field?

The development of CAR-T therapy is at the beginning of its era. There are still many questions facing the CAR field:

- Persistence: Correlates with outcome?
- Is long term persistence of CAR cells desired?
- Which approaches give durable persistence of CAR-Ts?
- What is the best vector to introduce the CAR: retroviral, lentiviral or non-viral vectors?
- scFv or endodomain construction?
- What is the optimal T cell type and composition of the infused product?
- How can checkpoint therapy and Car T therapy be combined?

In addition to questions facing the CAR field, there are clinical questions such as degree of disease burden, pre and post infusion therapy that can affect how well the CAR-T therapy works.

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Closing Thoughts

It has been established that CAR-T therapy can work thus far as a cure in some patients. But the design of the CAR can be very complex and is critical since the choice of co-stimulatory signals will determine whether or not an immune response is induced (CD28) and for inhibiting an immune response (CTLA 4 and PD1):

1. Inadequate co-stimulation can weaken host defenses leading to infection of cancer.
2. Inappropriate co-stimulation can lead to allergy, autoimmunity and graft rejection.
3. Inadequate co-inhibition leads to autoimmunity or autoinflammatory disease.
4. Inappropriate co-inhibition leads to immunologic exhaustion.

It's a fine balance between the design of the CAR-T cells as well as clinical influences such as disease burden or pre-therapy in order for this therapy to work. There are two main questions that still need to be answered: 1)Why do some patients only have a partial or no response? Is it T-cell exhaustion, something else, or a combination of things; and 2) Why doesn't CAR-T work on solid tumors? Are T-cell better at locating circulating cancer cells passively vs. actively honing in on solid tumors and what can be done to make them active? These questions need to be answered in perfecting this therapy.

The issue of cost is always a topic at hand as to who is going to pay for these advance therapies. But the better question to ask is what is the cost to the healthcare system for drugs each time they don't work on a patient just because they are cheaper and what is the cost to the patient who has to suffer through these failures when one dose of a CAR-T therapy could have cured the patient?

If the allogenic CAR-T cells can work just as well as autogenic CAR-T cells, the cost of therapy will definitely decrease. Currently, there are two companies, Cellectis, a French company and Kite Pharma, a Boston based company working on allogenic or donor CAR-T therapies.

Until we change the mindset of everyone to foster preventive care, have patient's take responsibility of their own health, embrace the notion of treating the right patient with the right drug, with the freedom of advance

technology being covered by insurance, and foster the expectation that not everything has to be treated with a machine gun when a pistol will achieve the same outcome, the cost of healthcare will continue to be out of control.

Once CAR-T therapy is perfected, the word "cure" will replace "remission" which was fiction 20 years ago. The industry will find a way to perfect allogenic T-cells to be as efficacious as autogenic T-cells and therefore the cost will be less expensive to more patients will have access to it. But insurance has to be willing to trust that people will use it appropriately in order to get broader experience with this therapy.

The advances in technology scientists have made today is extraordinary, where cancer may be cured permanently. We have the technology, healthcare professionals should be able to use this technology freely.

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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