2024 Superconvergence biorevolution series: Training the immune system to fight cancer

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Key Takeaways

- The immune system is powerful and it has an interesting capacity to 'remember' past infections.
- The immune system is remarkably effective at identifying and neutralizing the impact of many pathogens.
- CAR-T therapy has resulted in some strong effectiveness to treat certain cancers of the blood.
- Researchers are studying different aspects of CAR-T in order to further refine whether it may be used on certain incurable solid tumours and even autoimmune diseases.

When constructing our Biorevolution strategy, we worked alongside futurist Dr Jamie Metzl, who is a member of the World Health Organization's expert committee on human genome editing. We believe that we are on the precipice of a remarkable period, which could last a few decades, where we challenge and ultimately evolve how we do things, such as:

- How we handle human health care
- How we grow food for an expanding global population
- How we generate novel materials, chemicals and energy from biological sources
- How we think about storing massive amounts of data with higher density and fidelity than we have in the past

Dr Metzl recently published the book *Superconvergence: How the Genetics, Biotech, and AI Revolutions will Transform our Lives, Work and World*. Over the summer, we will publish a series of blogs that draw attention to some of the ideas presented in the book.

The bottom line

Thematic investing, in a sense, is about storytelling. Superconvergence does a great job conveying the narrative behind the WisdomTree BioRevolution ESG Screened Index.

Your immune system is powerful

It's incredible to consider the power of the human immune system. I can remember catching chickenpox when I was five years old. While it was annoying at the time, my parents kept repeating the story that you catch it now, and you never get it again. I didn't realise it, but it was a good example of how vaccines work.

The immune system has a built-in 'memory.' Once it encounters a particular pathogen, usually a bacterium or virus, specific cells can 'remember' these so-called invaders and respond more effectively in subsequent encounters.

Unfortunately, even if we tend to get chickenpox only once, when we investigate why we can get the common cold many different times, we realise that the pathogens can mutate. Technically, with the common cold, we are getting many different variations of a substantially similar infection. This is also why so much attention was paid to the different mutations of the virus during the COVID-19 pandemic.

What is CAR-T therapy?

It's incredible how our collective human understanding of diseases and the immune system has evolved. In the late 1800s, two significant discoveries triggered the path to our current understanding[1]:

- Elias Metchnikff identified phagocytic cells, which can attack invading pathogens.
- Emil Behring and Paul Ehrlich identified antibodies that can neutralise microbial toxins.

Now, it's one thing to have that initial understanding of the immune system and quite another to consider giving the immune system instructions to do specific, useful things.

Here, we can introduce the concept of 'Chimeric Antigen Receptors', the 'CAR' in CAR-T therapy.

From *Superconvergence*:

Our T-cells, a foundation of our natural immune systems, differentiate between our own cells and those of dangerous foreign invaders. These cells function like hall monitors in a restrictive elementary school, always on the lookout for who shouldn't be there. But instead of sending the perceived intruders back to class, they release enzymes knocking them out and make a note to keep a wary eye out should they ever come back. To take advantage of this naturally occurring process as a gene therapy, a person's blood is drawn and the T-cells are extracted and then genetically enhanced to more strongly express the chimeric antigen receptors (CARs) giving them disease-fighting superpowers. After the patient's other T-cells have been depleted by chemotherapy, these enhanced cells, with added genetic targeting instructions, are reintroduced with an increased ability to repopulate. There are many variations on this theme.

In a high-profile 2022 trial, a British teenager from Leicester named Alyssa, who was suffering from an aggressive cancer, T-cell acute lymphoblastic leukemia, in which her immune cells were attacking each other and who was not responding to other interventions, was treated with modified immune cells taken from a donor.

Reengineering the donor's T-cells to replace Alyssa's malfunctioning ones required editing the donor's T-cells to disarm their natural targeting mechanism so they wouldn't attack Alyssa's body, removing a chemical identifier on the donor T-cells so the new cells could evade detection, and giving the donor cells an additional ability to be impervious to a specific chemotherapy drug. The modified donor T-cells were then edited to attack the specific genetic marker of the patient's malfunctioning T-cells. After the modified donor cells were introduced, Alyssa had another bone marrow transplant so the modified cells could repopulate in her body. It was a painstaking and expensive process but, incredibly, it worked. So far, the cancer cells have cleared from Alyssa's body.

We'd note that—while any success in fighting cancer is exciting—as is the case with many of the developments discussed in Superconvergence it feels like CAR-T therapies are on the cusp of a potentially massive breakout of different use cases. However, success is far from guaranteed, and we must respect the complexity of the underlying biological processes.

A new line of attack on childhood brain cancer?

Now, besides having read *Superconvergence*, the catalyst that led to my wanting to write this article was seeing the following title to an article in the journal *Nature*[2].

This Childhood Brain Cancer is Incurable—But Immune Therapy Holds Promise: CAR-T therapy, which harnesses a person's own immune cells, racks up some astonishing success stories against deadly brain tumours in children.

The article notes that a five-year-old in Seattle, Washington, has received 70 CAR-T treatments and counting and that the growth of a diffuse midline glioma (brain and spinal tumour) has been held in check. Doctors are actively seeking to determine why, and, for the time being, the result of this single case is more of an outlier. At least so far, the results observed across a broader trial have not yielded as much success. Still, we are discussing a type of cancer for which there aren't really any other options.

CAR-T treatments have yielded better results in treating blood cancers than in treating solid tumours, such as those found in the lungs or the brain. With these types of tumours, the therapy needs to be able to deal with different mutations of the cancer cells and deliver a sort of 'penetration effect' to go beyond the top layer of the tumour itself.

Possible applications in autoimmune diseases

A different article published in Nature Biotechnology indicated two rather interesting studies regarding other possible use cases for CAR-T therapies[3]:

- The first clinical findings, published in March 2024, showed that CAR-T cells can deplete problematic immune system B cells in progressive multiple sclerosis.
- In June 2024, a phase 1 study in patients with systemic lupus erythematosus was presented by iCell Gene Therapeutics at the European Alliance of Associations for Rheumatology Congress in Vienna. It showed that a CAR-T therapy eliminated all autoantibodies in 11 out of 12 treated patients.

With mRNA, we all recognise the efficacy in terms of the COVID-19 vaccine, but it really represents a platform upon which many different therapies can be built. Maybe CAR-T, characterised by being further along in the treatment of certain blood cancers, will also be able to showcase a broader set of use cases.

We are excited to see how things continue to evolve in this space.

[1] Source: Kaufmann SHE. Immunology's Coming of Age. Front Immunol. 2019 Apr 3;10:684. doi: 10.3389/fimmu.2019.00684. Erratum in: Front Immunol. 2019 Jun 06;10:1214. doi: 10.3389/fimmu.2019.01214. PMID: 31001278; PMCID: PMC6456699.
[2] Source: Ledford, Heidi. “This Childhood Brain Cancer is Incurable—But Immune Therapy Holds Promise.” Nature. Volume 631. July 25, 2024.
[3] Source: Harrison, Charlotte. “CAR-Ts Sweep Into Autoimmunity.” Nature Biotechnology. Volume 42, July 2024.

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