SONOMA BIOTHERAPEUTICS

Overview of Autoimmune Diseases and the Treatment Potential of T Regulatory Cells

This paper describes a new type of therapy for patients with Rheumatoid arthritis and hidradenitis suppurativa. It is meant to educate patients about the **immune system** and how the therapy–CAR T regulatory cell infusion–is thought to treat the diseases.

Table of Contents

Autoimmune disease and inflammation: *When good cells go bad*

The immune system is a complex group of cells best known for its role in fighting harmful infections. When our bodies encounter a virus or bacteria, the immune system responds to get rid of the infection. This response involves many different types of cells that work together to destroy the virus or bacteria, as well as any infected cells. After the infection is cleared, the immune system helps our bodies heal.

Sometimes the immune system attacks normal, healthy cells in our bodies. This is the cause of many autoimmune diseases, including those listed below. Autoimmune diseases cause inflammation (pain, swelling, warmth, and/or redness). They can also damage otherwise healthy parts of the body. Some examples include:

- **Rheumatoid arthritis, or RA:** The immune system attacks joints, commonly in the hands and wrists, leading to swelling, pain, and eventual joint damage.
- **Hidradenitis suppurativa, or HS:** The immune system attacks certain areas of the skin, causing painful lumps and sores.
- **Type 1 diabetes, or T1D:** The immune system attacks cells in the pancreas that make insulin, which helps control blood sugar. Uncontrolled blood sugar leads to diabetes.

Causes of autoimmune disease

There are multiple causes of autoimmune diseases and Scientists have identified several risks that may lead to disease. For instance, women have much higher risk of developing autoimmune diseases than men. In fact, 4 out of 5 patients with these diseases are women. A person with a family history of autoimmune diseases is also at higher risk. Finally, the environment can play a role. Exposure to the sun, exposure to pollutants, smoking, and even prior infections can increase the risk of developing autoimmune diseases. Even though the cause is unknown, scientists are beginning to understand how these diseases work.

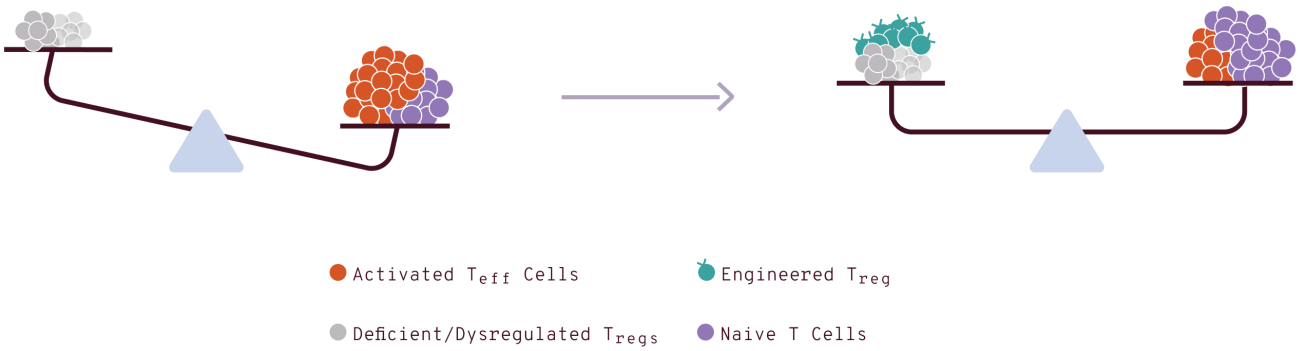
Treating autoimmune disease

Research studies have helped us better understand these diseases. The more scientists learn about them, the better the treatment can be. Early treatments for autoimmune disease focused on decreasing inflammation using drugs such as steroids. These treatments helped the symptoms but did not stop the disease. More recently, scientists have found ways to target the immune system with new drugs. These drugs, such as Humira or Enbrel, have been an improvement in patients with diseases such as RA and Crohn's disease. Unlike earlier treatments, they both decrease inflammation and slow the progression of disease. They can, however, lead to side effects such as making a patient more prone to infection.

New research has shown that using a patient's own cells to treat disease might work even better than current drugs. This strategy has looked promising in laboratory studies. Now, scientists are ready to test these treatments in clinical trials. In a clinical trial, scientists and doctors study new drugs in volunteer patients. During the trial, patients are carefully followed to make sure the drug is safe and effective. Sonoma Bio is working on one of these new drugs. This drug and the clinical trial are explained in more detail in this paper.

Important cell types in autoimmune disease

Immune cells are also known as “white blood cells.” There are many types of white blood cells, including T cells, B cells, Natural Killer (NK) cells, dendritic cells, and many more. Within each of these cell types, there are also further specialized groups of cells. These specialized cells work together, and all play a unique role in defending the body against disease. They also play a large role in autoimmune diseases. For example, 2 types of T cells have been shown to be important in RA and HS - T effector cells and T regulatory cells. T effector cells play a role in making inflammation worse, while T regulatory cells help to calm inflammation. When the balance of these two cells is off, autoimmune disease can result.



T effector, or T_{eff} cells: *Drivers of inflammation*

T effector, or T_{eff} cells play an important role in the immune system. When a person is infected with a virus or bacteria, T_{eff} cells fight the infection. However, in autoimmune disease, these T_{eff} cells mistake healthy cells for something harmful. They then attack healthy tissues, causing inflammation. Many T_{eff} cells can be found in the joints of RA patients. Here, the inflammation leads to swelling, pain, and eventually, damage to the joints. In HS patients, T_{eff} cells in the skin lead to an increase in the number and size of lumps on the skin, and increased swelling and pain.

T regulatory, or T_{reg} cells: *Putting the brakes on inflammation*

Another important subgroup of white blood cells in autoimmune disease is T regulatory, or T_{reg} cells. In contrast to T_{eff} cells, T_{reg} cells can decrease inflammation. T_{reg} cells help to calm the immune system after it has cleared an infection. They also protect healthy tissues from accidental attack by the immune system. In autoimmune disease, T_{reg} cells are not able to stop T_{eff} cells from attacking healthy tissues.

A healthy immune system needs balance

In a healthy immune system, T_{eff} and T_{reg} cells are in balance. In autoimmune disease, this balance is off. T_{eff} cells are overactive and outnumber T_{reg} cells at the site of inflammation. T_{reg} cells may also be dysfunctional and unable to calm inflammation. This imbalance leads to uncontrolled inflammation which damages healthy tissues. Restoring the balance could reverse autoimmune disease. One way to restore balance would be to give a patient more T_{reg} cells to counter the T_{eff} cells. Scientists have been studying different methods to do this, and early results in both animals and humans have been promising.

The first studies of using T_{reg} cells for autoimmune disease were done in the laboratory

Studies in animals have helped scientists learn how T_{reg} cells help control autoimmune disease. These studies use animals with diseases that are like those in humans. In some studies, animals with arthritis received T_{reg} cells. In these animals, there was less inflammation and damaged joints were repaired. In other studies, animals with diabetes that received T_{reg} cells showed no more signs of disease. These early studies showed that T_{reg} cells may be able to improve autoimmune disease.

The first animal studies used “bulk” T_{reg} cells as the treatment. In these studies, scientists take white blood cells out of an animal and separate the T_{reg} cells from all the other cells. Then, the T_{reg} cells are grown in a test tube until there are millions of cells. These cells are then given back to the animals. Once in the blood, the injected T_{reg} cells roam the body. Eventually, some of these cells will end up at the location of inflammation where they can help calm it down. This strategy has shown promise, but it may work better if the T_{reg} cells knew exactly how to get where they’re needed.

More recently, animal studies have used “targeted” T_{reg} cells to treat disease. These studies are like “bulk” T_{reg} studies, except for one big difference. In “targeted” T_{reg} cell studies, scientists modify T_{reg} cells so that they go to the site of inflammation. In mice with arthritis, for example, the modified cells go to the joints. In mice with diabetes, the modified cells go to the pancreas. Both “bulk” and “targeted” T_{reg} experiments led to improvement in disease. However, in the diabetes model, “targeted” T_{reg} cells were even better in improving disease. Based on these studies, scientists learned that we need to develop T_{reg} cells that are targeted to treat each type of disease.

T_{reg} cell therapies have been tested in humans

Given the promising results in animal studies, there is hope that these therapies might work in humans. To date, there have been many studies of T_{reg} cell therapies in humans, though no therapy is FDA approved yet. These clinical trials tested T_{reg} in various diseases such as diabetes and lupus. T_{reg} cell therapies have also been tested in patients who have had liver or kidney transplants. Here, researchers hope the T_{reg} cells will prevent the patient’s immune system from attacking the new organ. These studies have been similar to “bulk” T_{reg} experiments in animals. First, T_{reg} cells were isolated from the patients. Then, the cells were grown in a lab and injected back into the patients. So far, researchers have seen variable results from these studies. Some patients saw some improvement, but others did not, so scientists think more work is needed. One important finding from these studies is that T_{reg} cell therapies are safe and well tolerated. T_{reg} cells also lasted over one year in the blood of the patients who received this therapy.

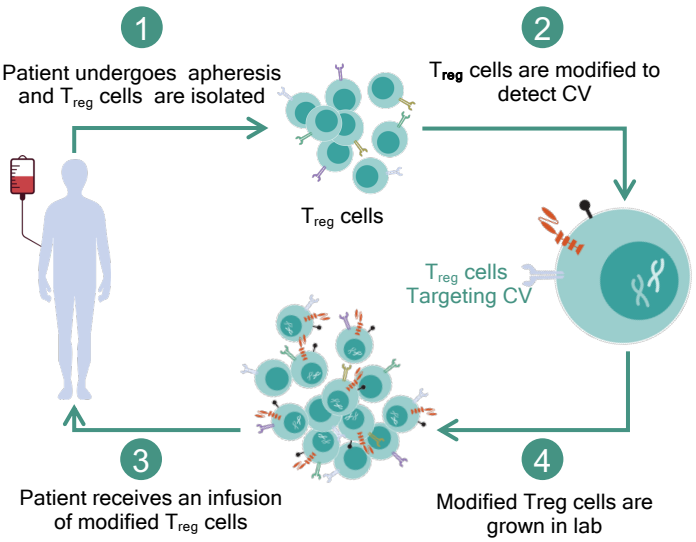
As in animal studies, T_{reg} cell therapies might work better if the cells are targeted. Sonoma Bio has developed technology to alter human T_{reg} cells, targeting them to areas of inflammation. These cells are expected to go to the inflamed joints in patients with RA, and to the inflamed skin in patients with HS.

SBT777101: *A next-generation T_{reg} cell therapy for RA and HS*

In order to tell T_{reg} cells where to go, scientists needed to identify a protein found at the site of inflammation. In studies of the joints of RA patients and the skin of HS patients, scientists detected high levels of a protein called citrullinated vimentin, or CV for short. CV can be found anywhere in the body, but there is much more of it at the sites of inflammation. Sonoma Bio's process of making T_{reg} cell therapies modifies the T_{reg} cells so they can detect CV. Once injected into the body, these cells should go to the place where CV is highest: tissues with high levels of inflammation.

How SBT777101 is made

The process to modify the T_{reg} cells to target sites of inflammation takes several steps. First, blood is taken from a patient, and the T_{reg} cells are separated from all the other cells. Next, a virus is introduced to the T_{reg} cells. This virus is modified so that it cannot spread to other cells in the body or to other people. The purpose of this virus is to deliver instructions to the T_{reg} cells to tell them how to detect CV. These viruses are considered safe and are used in many FDA approved cell therapies. After the T_{reg} cells receive their instructions, they are grown in the lab so that there are enough cells to give back to the patient. At the end of this process, the T_{reg} cells that have been engineered to detect CV are ready for infusion into patients.



Modified T_{eff} cells are already approved for use in patients with cancer

Modification of T_{reg} cells is a newer process and there are no approved drugs yet based upon this technology. However, modifying T_{eff} cells (T cells which *increase* inflammation) has been studied for over 20 years in humans. The FDA has approved several T_{eff} cell therapies for treatment of certain cancers. In patients with cancer, T_{eff} cell therapies go to a tumor and kill cancer cells. T_{eff} cell therapies are also being studied in patients with certain autoimmune diseases such as lupus, where the cells target and destroy a subset of immune cells that contribute to disease.

Differences between T_{eff} and T_{reg} cell therapies

There is one big difference between modified T_{eff} and T_{reg} cell therapies. T_{eff} cell therapies *cause* a lot of inflammation to kill cells such as cancer cells. This inflammation can lead to severe side effects that a doctor must carefully manage. After the cancer cells are killed however, inflammation returns to normal. Treg cell therapies should *calm* inflammation, so scientists do not expect to see the same kind of side effects as T_{eff} cell therapies. As with any medication, there is always some risk of side effects. Sonoma Bio plans to monitor patients closely after they receive the drug in case something unexpected happens.

What will happen in the clinical trials for RA and HS?

The T_{reg} cells in this trial are made specially for every patient, so there are several steps that must happen before receiving the treatment. Below is a description of what will happen throughout the clinical trial.

1. Pre-trial screening

Doctors and researchers at select sites in the United States are offering this trial to eligible patients. Patients must sign consent and meet certain criteria to enter the trial. For both RA and HS, patients must have active disease despite previous treatment. If a doctor feels the patient may qualify for the trial, additional information will be required. The patient will need to have a physical examination and go through their medical history with the doctor. They will also need to undergo several laboratory tests. The results of this screening will be discussed between the doctor, Sonoma Bio, and each patient to decide whether this trial is a good fit.

2. Apheresis

If the patient qualifies for the trial, they will go through a procedure called apheresis. Apheresis is similar to giving blood, except that only the white blood cells are isolated and removed, and the remainder of the blood is returned to the patient. Apheresis is performed at a blood center or specialized clinic. The patient will have 2 IVs inserted into 2 different veins, usually one on each arm. Blood flows from one vein into a machine and then returns to the body through the second vein. The machine separates white blood cells from the patient's blood. This procedure lasts about 2 hours but can vary from person to person. The procedure is simple, well-tolerated, and has been widely used for many years. The patient will not receive any medications or treatments during the procedure.

3. Processing of cells

After apheresis, the white blood cells are shipped to a lab where they are converted into the final drug product as described in the section "How SBT777101 is Made". The manufactured cells will be carefully evaluated by scientists for quality and safety before being shipped back to the clinic. This process will take about 6 weeks from start to finish.

4. Drug infusion

When the product is ready, the patient will come back to the clinic. A doctor will review any changes in medical history, medications, or health status with the patient. If the patient still qualifies, the hospital or clinic will admit them and administer the cells that were specifically made for them. This procedure will take about 30 minutes. Also, before injection, a skin biopsy will be required for patients with HS. A synovial (joint) biopsy is optional for RA patients.

5. Short hospital stay

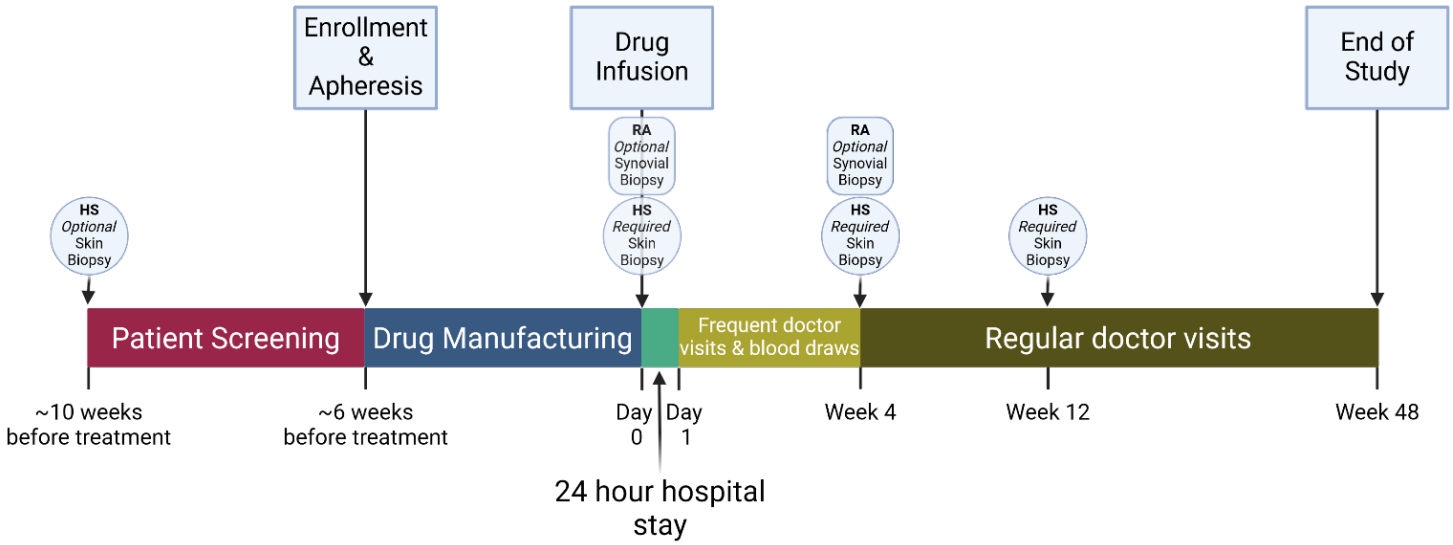
After receiving the product, the patient will be monitored at the hospital for 24 hours. This hospital stay is to ensure there are no harmful reactions to the medication.

6. Follow-up

After the patient goes home from the hospital, they will be closely monitored for one month. This will require frequent visits to the doctor and blood draws. Patients with RA can volunteer for a synovial (joint) biopsy at 4 weeks. Skin biopsies will be required for HS patients at 4 and 12 weeks. These samples are critical to understanding how the therapy is working. After the first month, patients will continue to be monitored for about 1 year. Doctors will watch for side-effects or reactions to the medication. They will also monitor the patient's disease to determine if the drug is working.

7. Long-term follow-up

After the end of the trial, patients will be highly encouraged to participate in a 15-year safety follow-up trial. This long-term follow-up may require phone calls, doctor visits, and/or blood draws. You will be asked to sign a separate informed consent for this safety follow-up trial.



Definitions

Apheresis: A process to isolate white blood cells from the blood. Blood flows from an IV in one arm to a machine that separates the white blood cells from the rest of the blood. The remaining blood flows back into the patient through a second IV in the other arm.

Autoimmune disease: Occurs when a person's immune system attacks healthy, normal tissue. There is currently no cure for these diseases.

CV (citrullinated vimentin): A protein that is found in areas of high inflammation. Sonoma Bio modifies T_{reg} cells so they can detect CV and go to the site of inflammation.

HS (hidradenitis suppurativa): An autoimmune disease of the skin. Results in painful lumps and sores on the skin of HS patients.

Immune system: The immune system is made up of many different types of cells, also called white blood cells. These cells are responsible for protecting our bodies from things like viruses and bacteria. The immune system also plays a role in helping the body heal after an infection or injury.

Inflammation: Pain, swelling, redness, and/or warmth. Caused by certain cells of the immune system, such as T_{eff} cells. It occurs in the joints of RA patients and the skin of HS patients.

RA (Rheumatoid arthritis): An autoimmune disease of the joints. This results in painful, swollen joints, usually in the hands and wrists. If untreated, RA can lead to permanent joint damage.

T_{eff} cells (T effector cells): A type of T cell in the immune system. These cells cause inflammation and are one of the primary cells involved in autoimmune diseases.

T_{eff} cell therapy: A type of drug that uses a patient's own T_{eff} cells as a treatment. T_{eff} cells are isolated from a patient's blood and grown and modified in a laboratory. These cells are then given back to the patient. T_{eff} cell therapies kill harmful cells in the body. Several have been FDA approved for the treatment of certain cancers.

T_{reg} cells (T regulatory cells): A type of T cell in the immune system. These cells help to calm inflammation and can promote healing.

T_{reg} cell therapy: A type of drug that uses a patient's own T_{reg} cells as a treatment. T_{reg} cells are isolated from a patient and grown (and sometimes) modified in a laboratory. These cells are then given back to the patient. The goal of T_{reg} cell therapies is to calm inflammation and are being studied in autoimmune diseases and transplants. No T_{reg} cell therapies are currently FDA approved.

T1D (Type 1 diabetes): An autoimmune disease that is caused by the immune system attacking cells in the pancreas. These cells produce insulin, which helps to control blood sugar, and the destruction of these cells results in diabetes. Type 1 diabetes, also known as juvenile diabetes, usually affects younger people.

All figures created with BioRender.com

If you have any additional questions, please feel free to contact your doctor or Sonoma directly at SBT7101Questions@sonomabio.com