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Drug companies flock to supercharged T-cells in fight against autoimmune disease

Researchers target suppressive cells to keep the body from attacking itself.

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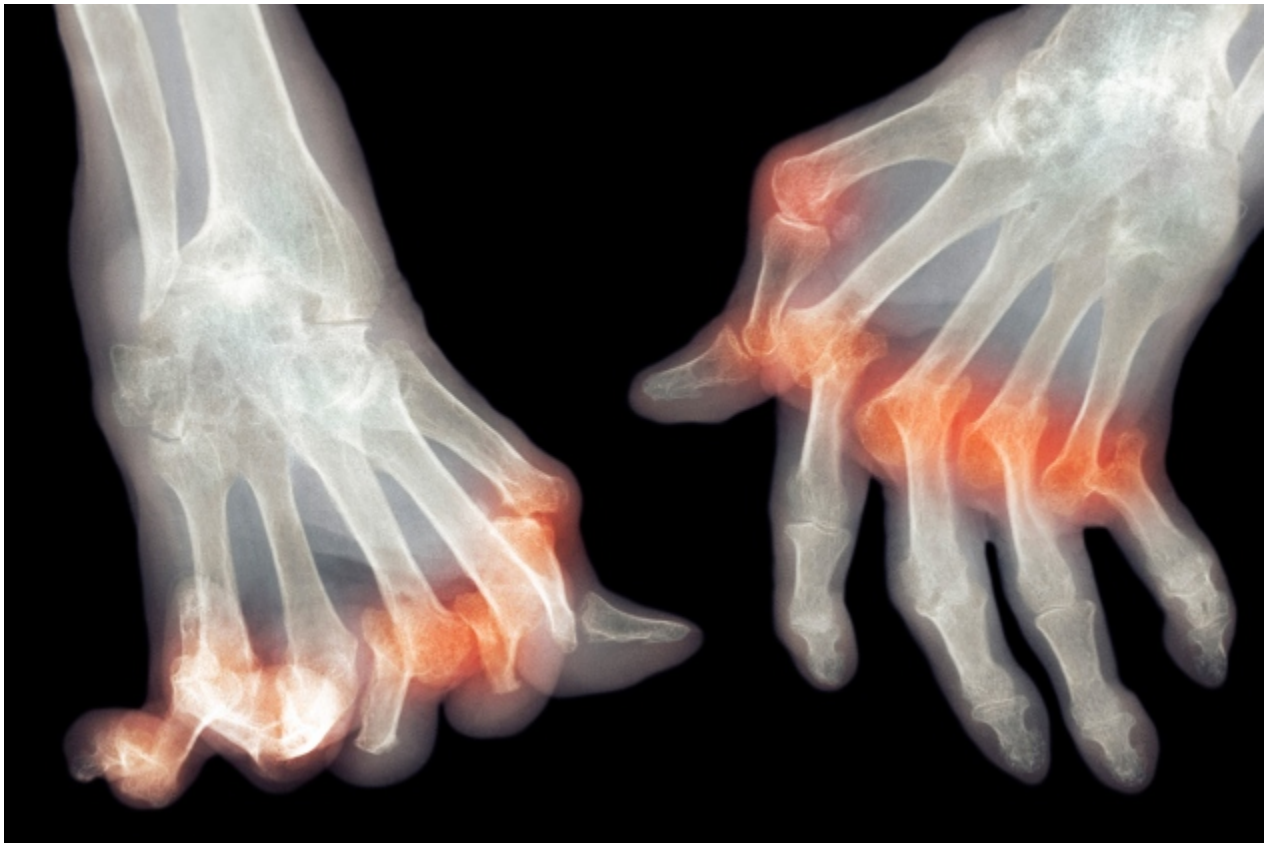

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Rheumatoid arthitis is an autoimmune condition that causes chronic joint inflammation.

Researchers in both academia and industry are turning to immune-suppressing cells to clamp down on autoimmune disorders, and the effort is building to a fever pitch.

On 24 July, pharmaceutical firm Eli Lilly of Indianapolis, Indiana, announced that it would pay up to US$400 million to support the development of a drug — which entered clinical trials in March — that

stimulates these cells, called regulatory T cells. And in January, Celgene of Summit, New Jersey, announced plans to buy a company working on a similar therapy for $300 million.

Other companies, from tiny biotechs to pharmaceutical heavyweights, are also investing in an approach that could yield treatments for a variety of disorders caused by an immune attack on the body's own cells. Such conditions include type 1 diabetes, lupus and rheumatoid arthritis.

"It's a field that's just, like, crazy," says David Klatzmann, an immunologist at Pierre and Marie Curie University in Paris, who has been studying regulatory T cells and advises a Paris company called ILTOO Pharma. "The competition is coming very hard. It's going to be exciting to see where it goes."

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Booster molecule

T cells are often thought of as key foot soldiers in the immune system's battle against foreign invaders. But there are many kinds of T cell, each armed with a different set of skills. Regulatory T cells serve to dampen immune responses — rather than attack invaders — and are important for preventing autoimmunity.

People with disorders caused by an autoimmune attack often also have reduced levels of regulatory T-cell activity, leading scientists to suspect that bolstering such cells could reduce the immune system's attack on the body.

To boost these cells, many researchers — now including those at Lilly and Celgene — are turning to a molecule called interleukin-2 (IL-2). High doses of IL-2 stimulate the 'effector' T cells that attack invaders, and in 1992, US regulators approved the treatment for some people with cancer, to prompt immune responses against the tumours. But low doses of IL-2 — roughly ten times lower than those used to treat cancer — instead stimulate regulatory T cells, and have relatively little effect on effector T cells.

This observation was made in the 1990s, but some researchers resisted the idea of using IL-2 to treat people with autoimmune disorders, even at low doses. The high doses used in cancer treatment are

notoriously toxic, and can be fatal. “Initially, lots of people were so afraid to use it,” says Di Yu, an immunologist at the Australian National University in Canberra. “They have some bitter memories of IL-2.”

Molecular tweaks

Gradually, a handful of promising small clinical trials have begun to overcome those concerns. And in 2011, a pair of studies provided the first clinical evidence that the approach could work. One of these was in graft-versus-host disease[1], a condition that can occur when transplanted bone marrow produces immune cells that attack its new host, and the other was in an autoimmune disorder caused by hepatitis C virus infection[2]. Researchers have also launched other studies in type 1 diabetes and lupus. The lower doses seem, so far, to be much safer than the doses used for cancer treatment.

Even so, there are still concerns about how specific the IL-2 treatment can be — any potential stimulation of effector T-cell responses in a patient who is already undergoing an autoimmune attack could be dangerous. “It’s a robust field, but a challenging field,” says Jeffrey Bluestone, an immunologist at the University of California, San Francisco, who has advised several companies on regulatory T-cell projects. “It's still unclear that you can get a regulatory T-specific response without any other effects.”

Instead, many companies are interested in tweaking IL-2 to make it more specific. Lilly’s $400-million investment went to Nektar Therapeutics, a biotech company in San Francisco, California, that has produced chemically modified IL-2 that is less likely to bind to effector T cells. Delinia, the company that Celgene bought, which is based in Cambridge, Massachusetts, was developing a mutated form of IL-2 that has a similar effect.

Other researchers are investigating possible cell therapies, for example extracting regulatory T cells from a patient's blood, expanding and activating the cells in the laboratory, and then reintroducing them into the patient. Another approach, still in the early stages of development, is to engineer regulatory T cells taken from the body to help the cells better recognize the molecules that are provoking an autoimmune response and to shut that response down.

And basic researchers are still discovering more about the biology of regulatory T cells that could aid the development of future therapies. Hongbo Chi, an immunologist at St. Jude Children’s Research Hospital in Memphis, Tennessee, has been studying how the metabolism of regulatory T cells differs from that of other T cells. And Alexander Rudensky, an immunologist at the Memorial Sloan Kettering

Cancer Center in New York City, and his colleagues, this year reported a new subset of regulatory T cell that may have a more specific function[3].

Although Chi is not directly seeking out new drugs, he has noted industry's enthusiasm with interest. "It's really encouraging to see those therapeutics go into clinical trials," he says. "That motivates us basic researchers to understand the mechanism."

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2. Saadoun, D. *et al*. *N. Engl. J. Med.* **365**, 2067–2077 (2011).
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