GETTY

TREATMENT

In search of a booster shot

A plethora of therapies can keep the symptoms of allergy under control, but they can't cure. New research aims to prevent allergies from developing in the first place.

BY LAUREN GRAVITZ

In 1911, a British researcher named Leonard Noon attempted to do for hay fever what his predecessors had done for smallpox and rabies. Using small amounts of grass pollen, Noon injected 'pollen vaccines' into people suffering from grass allergy, gradually increasing the amounts to help build up a tolerance to the irritant. A century later, Noon's immunotolerance therapy has matured into a technique widely used by allergists, one that can be tailored for dozens of airborne allergens.

At their worst, such allergens — which cause the sniffing, sneezing and sinus misery also known as rhinitis — rarely cause more than severe annoyance. These days, people who suffer from allergies like pollen, mould, or dust mites have a few more choices than Noon's patients. Over-the-counter antihistamines provide relief for mild cases, while people with more persistent allergies can use prescription corticosteroids to decrease inflammation and keep their sinuses clear. Those with the most severe cases, however, still benefit from allergy shots or a combination of all of the above. The current protocol for allergic rhinitis shots requires injections as often as twice a week, and a course of treatment takes between three to five years to yield a long-lasting effect. But this approach is futile in as many as 25% of sufferers and many hope that a more effective treatment must be possible.

The same airborne allergens which cause rhinitis can also cause a more serious problem: allergic asthma. It's not clear how the conditions are related, but during the past 20 years researchers have shown that serious allergies can evolve into acute asthma, which can require sufferers to have hospital care and is very occasionally fatal. As with rhinitis, most sufferers can control their asthma with existing drugs. The remaining 25%, however, have drawn the eye of drug developers.

WHEN GOOD IMMUNE SYSTEMS GO BAD

Pollen and other airborne allergens should be harmless. But in 20% or more of the world's population, something triggers an immune response. In these over-reactive immune systems, allergens prompt the activation and proliferation of a group of white blood cells known as T helper 2 (Th2) cells, triggering a cascade of events that causes overproduction of a class of antibody called immunoglobulin E (IgE) and leads to inflammation and irritation (see 'Targeting Th2 activity'). In rhinitis, such inflammation causes the classic range of hay fever symptoms. In asthma, inflammation and other unknown culprits — perhaps coupled with a genetic predisposition (see 'Seeking a gene genie', page S10) — cause the airway to remodel and become prone to constriction upon exposure to an allergen. The more researchers learn about the cellular chain of events, the closer they are to determining which links are most vulnerable to intervention[1].

BUILDING TOLERANCE

Most rhinitis treatments focus on variations of the same immunotolerance on which Noon capitalized a century ago. The method exploits the very response that causes allergies in the first place: the body's adaptive immune system, which evolved to remember and attack foreign bodies or antigens after first encounter. With airborne allergies, the adaptive immune system reacts each time it sees an antigen to which it is sensitized (such as mould, cat dander or ragweed pollen). A course of shots, injecting increasing quantities of allergen extracts over many years, can gradually build tolerance in the immune system and prevent it from launching an offensive every time it meets the offending molecules.

This approach is, however, fraught with problems. Shots don't always work, they require a substantial time commitment from a patient, and they bring a rare but inherent danger — after all, people are being injected with the substance to which they are allergic. "It's medieval stuff, in a way," says Mark Larché, an allergist at McMaster University in Hamilton, Ontario. "Allergists still mix up cocktails of extracts in their offices to give to people. There's a weird juxtaposition of a disease-modifying approach with this dark-arts business of using extracts, and people having terrible allergic reactions."

One reason these extract-based cocktails may fail is the omission of particular antigens. "People aren't just allergic to one allergen of dust mites. There can be as many as twenty that are important," Larché says. Although extract makers try to standardize their products, it's a difficult goal. "Studies have shown that some of the most important antigens can be missing," adds Larché, who co-founded the UK-based biotech company Circassia in 2006 to try to improve that hit rate.

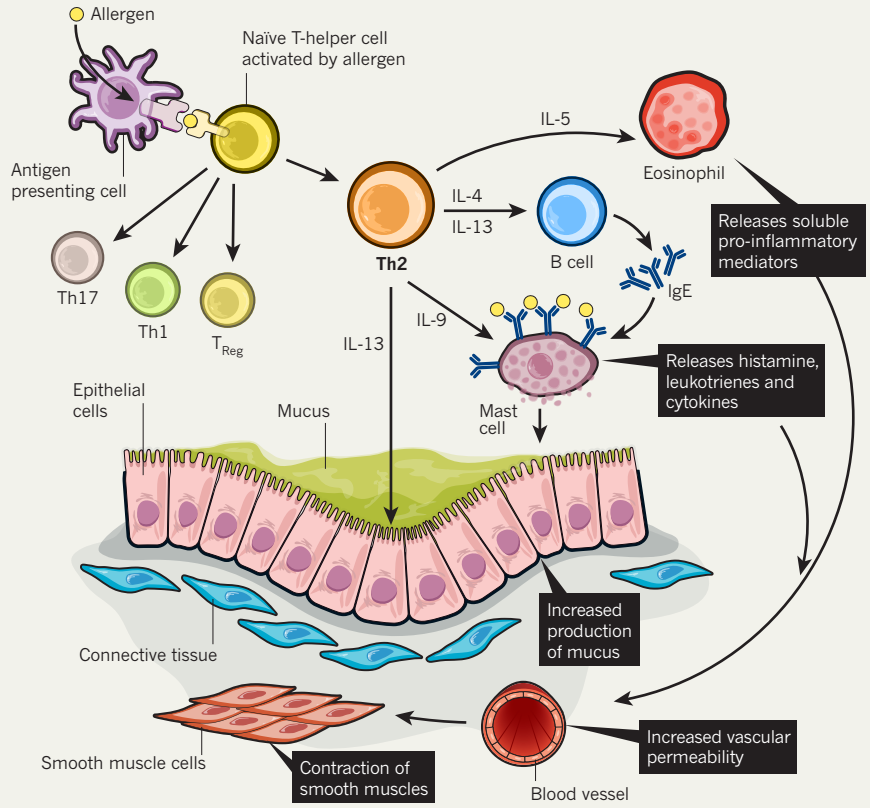
Circassia is one of a few companies working to create a second generation of allergy shots and, from a regulatory standpoint, is perhaps the furthest along. The company's approach is based on identifying specific parts of the allergen molecules, called epitopes, that T cells recognize and interact with. Rather than extracting the whole allergen from pollen or the faeces of dust mites, the company is building synthetic versions of the relevant epitopes that can be put together into a dose that is quantifiable and replicable. "We can ensure our synthetic epitopes are consistent from batch to batch," says Rod Hafner, Circassia's senior vice president of research and development. "And because we're using epitopes that don't interact with [the antibody] IgE, they don't have a risk of anaphylaxis. We get a faster onset of efficacy and it persists much longer."

Circassia is developing products for four of the most common allergens: cat, ragweed, dust mite and grass pollen. Early data suggests that, at least for cat allergies, 4 shots given 4-weeks apart are enough to prevent symptoms for at least a year. The company is moving the cat-allergy product into phase III trials, aiming for regulatory approval by 2015, and expects that the ragweed trials could come a year later.

Rudolf Valenta, an allergist at the Medical University of Vienna, is approaching the allergic rhinitis problem from a different angle. Valenta is also interested in creating homogenous synthetic vaccines, but he wants to take it a step further into diagnostics. He and his colleagues developed an allergen library, with DNA fragments from different antigens that could be placed on a protein chip. Then, from just a single drop of a patient's blood, the chip can rapidly detect which molecules a patient is allergic to. "The beauty is that in just a few minutes you can record the complete reactivity profile of a

TARGETING Th2 ACTIVITY

How the cytokines produced by Th2 cells stimulate inflammation – and hence offer therapeutic targets



Target	Mode of action	Example (In development at)
Immunoglobulin E	IgE increases allergen uptake by antigen-presenting cells, priming the immune system for attack against the allergen. Anti-IgE therapies aim to prevent it from binding to the antigen-presenting cells.	Lumiliximab (Biogen Idec) Anti-IgE vaccine (Pfizer, United Biomedical)
Mast cells	Mast cells release histamine, cytokines and other immune-system mediators that promote vascular and smooth-muscle changes, increase mucus, and recruit additional inflammatory cells. Blocking their activation could prevent downstream effects.	R343 (Rigel)
Th2 Cytokines (e.g. IL-4, IL-5, IL-13)	Cytokines produced by Th2 cells orchestrate allergic inflammatory responses. Numerous approaches take aim at specific cytokines in order to improve the Th1 to Th2 ratio.	Mepolizumab (GlaxoSmithKline) MEDI-528 (Medimmune) IL-13 MAB (GlaxoSmithKline)
Toll-like receptors (e.g. TLR9)	TLRs are immune-cell specific receptors. Different ones regulate different aspects of the immune response, and the hope is that stimulating the appropriate TLR will promote a more appropriate balance of Th1 to Th2 cells.	CYT003-QbG10 (Cytos vaccine) IMO-2134 (Idera Pharmaceuticals)

patient against hundreds of allergy components," Valenta says.

Valenta and his colleagues are using the data to build molecules called recombinant hypoallergens. They take an allergen, pluck out the peptides that don't induce an immune attack and attach them to carrier molecules from the hepatitis B virus. When injected, instead of triggering production of IgE, these hypoallergens stimulate production of another antibody, called IgG, that prevents IgE from binding and thereby keeps the patient safe[2]. "In a study where we applied the vaccine components to the patients' skin, we saw no reaction at all," Valenta says. These vaccines have the potential to induce no side effects.

Ultimately Valenta envisions an entire system in which a protein chip determines each patient's allergy profile, and then a series of vaccines is tailored to match these specific sensitivities. For now, though, his team is still working one allergy at a time. In collaboration with the Vienna-based biotech company, Biomay, they are about to begin a 3-year phase II trial, testing their approach with a vaccine made of 4 different grass–pollen antigens.

STAYING A STEP AHEAD

A growing number of studies indicate that children with allergic rhinitis are at higher risk of developing allergic asthma. No one is precisely sure how allergic rhinitis can be a catalyst for the development of asthma. One theory gaining credibility suggests that overactive immune cells, triggered by a response to airborne allergens, damage the epithelial and smooth muscle cells that line the lungs' airways. In regeneration, the epithelium and smooth muscle grow back abnormally, leaving the lungs increasingly vulnerable to attacks of inflammation and airway obstruction, particularly when the immune system encounters the allergens that caused the initial attack.

Some scientists, therefore, wonder if it might be possible to stop allergic asthma before it starts. The key will be to identify children most at risk, and intercede before the process becomes irreversible.

One study, led by Christian Möller at Umeå University in Sweden, observed 117 children with pollen allergies for over 10 years. Half of the children were 6–14 years old when the trial began, received a 3-year course of allergy shots for grass and/or birch pollen; the other group received a placebo. Seven years later, the researchers found that the risk of developing asthma was nearly halved for the children receiving the allergy shots, confirming the hypothesis that early treatment of rhinitis could very well stop the onset of asthma[3].

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A related, 4-year study, set to conclude at the end of 2011, aims to determine if allergy prevention, of both rhinitis and asthma, can start even earlier. Led by Patrick Holt, an immunologist at the University of Western Australia in Perth, it follows young children — between 18 months and 30 months old when the study began — who were beginning to show signs of allergic disease. Each day for one year, the children received just a few drops of a mixture of dust mite, cat and grass pollen extracts under their tongue. "It's not immunotherapy, because they weren't yet sensitized," says Holt, who leads the cell biology division at the university's Telethon Institute for Child Health Research. "We wanted to expose their mucosa to allergens that are important in their environment in order to drive the process of mucosal tolerance, a natural process through which individuals can escape sensitization[4]."

The more researchers understand about immune cascades, the more they can hone their attack.

SCULPTING THE IMMUNE RESPONSE

Once allergic asthma develops, it can prove a difficult beast to tame. When long-acting corticosteroids fail — as they do in about 25% of allergic asthma cases — there are not many alternative treatments. Part of the reason these cases are so intractable is that researchers still don't fully understand the precise cause and effect of the disease. In fact, most researchers are coming around to the belief that allergic asthma is not a single disease but a cluster of similar symptoms generated by a variety of underlying causes. "Asthma is a garbage-can term," says Sally Wenzel, director of the Asthma Institute at the University of Pittsburgh Medical Center. "The definition of asthma is incredibly broad."

Unlike the allergic rhinitis approach of immunotolerance, most allergic asthma approaches use a tactic known as immunomodulation, which aims to interrupt the cellular cascade that leads to the overabundance of IgE. "Immunology is maturing to the point where we have a much bigger, more complete picture. And it could be a false dawn, but it's an exciting period in this area of science," says Roberto Solari, head of respiratory biology at GlaxoSmithKline (GSK), based in London.

The more researchers understand about immune cascades, and which cells are involved, the more they can hone their attack. Some approaches aim for the top of the chain, altering the proportion of the various T helper cells among the white blood cells. Since different types of white blood cells drive different immune-response pathways, the hope is that stimulating Th1 immunity could muzzle the allergy-prone Th2 activity. But this approach has its drawbacks. "The problem with targeting something that high up," says Thomas Casale, chief of allergy and immunology at Creighton University in Omaha, Nebraska, "is that you'd likely affect other processes that might be important, increasing susceptibility to infections or lowering your ability to fight infections." With that concern in mind, other researchers are aiming further down the cascade, trying to eliminate the Th2 products that stimulate inflammation, such as particular interleukins (IL-4, IL-5, IL-13). Some are even attempting to eliminate what those products target, such as the white blood cells called eosinophils or IgE itself[5].

Not only does asthma range in severity, even patients with similar disease severity can have very different characteristics or phenotypes. And different phenotypes will respond better to some interventions than others, depending on which point in the immune cascade a drug is targeting. The only anti-IgE drug to hit the market so far is a monoclonal antibody called omalizumab, which was approved in the United States in 2003, but only works for the roughly one-third of intractable allergic asthma cases in which IgE levels fall within a narrow range. (Omalizumab appears to be effective for allergic rhinitis, but the cost, which can surpass US$20,000 per year, is beyond the means of most sufferers. "Although allergic rhinitis has a high prevalence, it's not going to kill you," says Casale.)

Omalizumab is likely to be the first of many drugs that will be aimed at specific subsets of allergic asthma. Multiple therapeutics, which takes aim at a variety of molecules in the Th2 cascade, are in various stages of clinical trials. The interleukins produced by Th2 cells drive different elements of the inflammation process (see 'Targeting Th2 activity') and two in particular, IL-5 and IL-13, have proven particularly attractive targets; GSK completed a phase III trial of anti-IL-5 mepolizumab in 2010. But these, too, are showing promise only in very small subsets of patients. People with high levels of eosinophils in the mucus of their lower airways appear to benefit from anti-IL-5 therapy, whereas people with high levels of a blood protein called periostin seem to be helped most by anti-IL-13.

"In the past, we've treated asthma with the medicines we have. But in the future, we need to define those diseases better, define the patients better, and target therapies to those stratified patients," says GSK's Solari. "This is where 21st century medicine needs to go." ■

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