

Setbacks rattle allergy vaccine frontrunners, but hopes remain

Two British drug companies, focused on a new class of protective immunotherapies for severe allergy, suffered clinical disappointments in the same week. First, Circassia Pharmaceuticals announced on June 20 that its cat allergy vaccine, Cat-SPIRE, fared no better than placebo in a large phase 3 trial, triggering a strategic review of the Oxford company's entire pipeline. Then, Allergy Therapeutics revealed on June 27 that the phase 2 dose-finding trial of its grass pollen product, Grass MATA MPL, failed to determine an appropriate dose to take forward into phase 3 development, forcing the Worthing, UK-based company to run another study and delaying the start of pivotal US testing.

Given the strong cat-allergen-tolerizing benefits observed in phase 2 testing of Circassia's vaccine, the recent results came as a surprise to many allergy specialists (*Nat. Biotechnol.* **31**, 371–372, 2013). “The problem is not the products,” says Lawrence DuBuske from George Washington University School of Medicine in Washington, DC, who consults for Allergy Therapeutics and has been a trial investigator for both biotechs. “The problem is how the products are being assessed.”

For decades, the only immunotherapy available to allergy sufferers was a series of 50 or more injections, each containing a tiny volume of allergen extract to help tolerize the immune system. Many patients eventually experience long-lasting relief in this way. But a full course takes three to five years, the injections are painful, and—worst of all—come with a danger of anaphylactic shock.

In 2014, the US Food and Drug Administration (FDA) approved the country's first sublingual allergy tablet: Oralair, made by Antony, France-based Stallergenes Greer for grass-pollen-induced allergic rhinitis (*Nat. Biotechnol.* **32**, 405, 2014). Grastek from the Kenilworth, New Jersey-based drug giant Merck for grass pollen followed, then a ragweed allergy therapy from Merck called Ragwitek. But the tablets still have to be taken on a daily basis for years. And in the US, sales have been sluggish, in part, experts say, because of physicians' reluctance to stop administering the more profitable injections. In late July, Merck decided to end its partnership with Denmark's ALK-Abello and give back the North American marketing rights to Grastek, Ragwitek and another tablet for dust mite allergy.

Both Circassia's and Allergy's vaccines promise a speedier route to tolerance. The immunotherapies involve only four injections administered over the span of weeks to months, not years, a convenience that prompted ana-



The feline allergen Fel d 1 is produced mostly in cat saliva and sebaceous glands.

lysts to anticipate big things for both. With the recent trial hiccups, however, “I certainly think the market will be more wary,” says Martin Hall, a life sciences analyst at Hardman & Co. in London.

Circassia's Cat-SPIRE contains a mixture of seven peptides from Fel d 1, the main cat allergen, which is produced in feline saliva and sebaceous glands. Circassia designed the synthetic peptides by identifying stretches of amino acids within the Fel d 1 protein sequence that bind major histocompatibility complex class II on antigen-presenting cells and can prompt allergen-specific T cells to differentiate into regulatory T (T_{reg}) cells. The selected epitopes thus induce T_{reg} cells that prevent the inflammatory cascade responsible for allergic symptoms—hence the name SPIRE, short for synthetic peptide immuno-regulatory epitopes. Importantly, the peptides are too small to cross-link the IgE antibodies on mast cells that spark unwanted reactions to the treatment, thereby enabling higher doses of the immunotherapy without fear of side effects.

In phase 2 testing, Circassia gave its immunotherapy to individuals with cat allergy exposed to a defined level of cat dander in an enclosed exposure chamber. When challenged in this way, participants who received the full course of four shots of Cat-SPIRE experienced a reduction in rhinoconjunctivitis symptoms that lasted for a year or more compared with people who received a placebo. For the phase 3 trial, Circassia decided to test its product in a more real-world scenario, and it's in the study

design and patient selection where many allergists think the company got into trouble.

To be eligible for the Circassia trial, participants had to test positive on standard allergy tests, as well as exhibit a baseline of allergic symptoms. However, because symptoms typically come and go, this requirement might have “skimmed off people who are at their peak [allergy response], and you're going to have regression toward the mean,” says Harold Nelson, an allergist-immunologist at National Jewish Health in Denver, who led the trial. “That method of selection sets itself up for everybody getting better,” even those on placebo.

Indeed, at the end of the year-long, 1,245-person phase 3 Cat-SPIRE trial, all groups experienced a 60% improvement—including the placebo group. The endpoint was a composite measurement of allergy symptoms and how much rescue medication individuals used, according to top-line data released by Circassia.

Linda Cox, an allergy specialist at the University of Miami Miller School of Medicine at Holy Cross Hospital in Ft. Lauderdale, Florida, who served on the data and safety monitoring board for the trial, points to another inclusion criterion as a potential problem. Participants had to live in a home with a cat and spend a minimum of eight hours each day indoors. But, she says, “it's well known in the allergy world that people who live with a cat long enough will be tolerized—it's a crude natural immunotherapy.”

A better patient population, Cox argues, would be immune-naïve individuals with

Table 1 Short-course immunotherapies in active clinical development

Company (location)	Product	Allergy	Technology	Stage of development
Circassia Pharmaceuticals (Oxford, UK)	Cat-SPIRE	Cat	Synthetic peptide immuno-regulatory epitopes	Phase 3 follow-on study ongoing in North America, Europe and Russia
Circassia Pharmaceuticals	HDM-SPIRE	House dust mite	Synthetic peptide immuno-regulatory epitopes	Phase 2 field study ongoing in North America, Europe and South Africa
Circassia Pharmaceuticals	Birch-SPIRE	Birch	Synthetic peptide immuno-regulatory epitopes	Phase 2 challenge study wrapping up in Canada
Allergy Therapeutics (Worthing, UK)	Grass MATA MPL	Grass	Allergoids, microcrystalline tyrosine, monophosphoryl lipid A	Phase 1 safety study of higher doses ongoing in the US; phase 2 dose-ranging study with conjunctival challenge planned for Europe in 2017
Allergy Therapeutics	Pollinex Quattro Birch	Birch	Allergoids, microcrystalline tyrosine, monophosphoryl lipid A	Phase 3 study to start in Europe in 2017
Allergy Therapeutics	Acarovac MPL	House dust mite	Allergoids, microcrystalline tyrosine, monophosphoryl lipid A	Phase 1 study to start in Europe in 2016
Anergis (Epalinges, Switzerland)	AllerT	Birch	Contiguous overlapping peptides	Phase 2 field study published in May 2016 (<i>J. Allergy Clin. Immunol.</i> 138 , 162–168, 2016)
Biomay/Vienna	BM32	Grass	Peptide carrier fusion	Phase 2 dose-scheduling study ongoing in Europe. Phase 3 study to start in Europe in 2017
Astellas (Tokyo) Immunomic Therapeutics (Rockville, Maryland)	ASP4070	Japanese cedar	LAMP-based DNA vaccine	Phase 1 safety study wrapping up in Japan

severe cat allergies, who generally avoid coming into close contact with cats because exposure causes debilitating symptoms and distress. “It’s the people who say, ‘I can’t go visit my mother because I’m wheezing within five minutes’ or ‘Every time I go to my girlfriend’s house I’m having swelling and itching’—that’s the population that you’re interested in seeing how this drug behaves.”

Experts are quick to emphasize that the Circassia trial failure should not doom the entire field of peptide-based allergy vaccines. “I’m not sure it’s an intrinsic problem based on the efficacy of the short peptides,” says François Spertini of the Lausanne University Hospital, who founded Epalinges, Switzerland-based Anergis to commercialize a different peptide strategy, one that uses long and linear peptides to achieve immunogenicity without adopting the three-dimensional shape needed to bind IgE.

But Rudolf Valenta, an allergist at the Medical University of Vienna, says that peptides alone are not enough. “What you must understand,” he says, “is that they are only addressing T cells with this approach, and the injection of the peptides will not induce the production of allergen-specific IgG antibodies,” which, he argues, are needed to prevent IgE activation in response to the allergen (as opposed to the therapy). That’s why Valenta, in collaboration with a Viennese company called Biomay, is developing recombinant fusion proteins that elicit an allergen-specific IgG response that blocks IgE binding.

For its part, Circassia is now reviewing the full phase 3 dataset for the cat allergy trial and will provide a portfolio update on September 27. The magnitude of the placebo response “has not been seen before at that level,” says CEO Steve Harris, “and we’re continuing our inves-

tigations.” However, the biotech has already stopped development of its SPIRE-based treatments for grass and ragweed allergies in light of the trial flop. Phase 2 trials of the company’s therapies for house dust mite and birch allergies continue.

Allergy’s product Grass MATA MPL (which is known as Pollinex Quattro Grass in Europe, where it’s already available on a pre-approval basis when physicians make requests on behalf of specific patients) relies on a different mechanism from Cat-SPIRE. The vaccine consists of allergen extracts from Timothy grass modified with glutaraldehyde to enable quick immune-priming but at the same time reduce IgE-binding capacity to avoid allergic side effects. The resulting ‘allergoids’ are mixed with a special size-optimized form of the amino acid tyrosine that slows the product release at the site of injection. This creates a kind of depot to prolong the vaccine’s activity and to enhance tolerability. And whereas most allergy shots use aluminum salts as an adjuvant, Allergy Therapeutics’ product takes advantage of a detoxified lipopolysaccharide obtained from the *Salmonella minnesota* bacterium, called monophosphoryl lipid A (MPL), to further stimulate immunity.

A decade ago, Allergy Therapeutics conducted a phase 3 study of Grass MATA MPL in more than 1,000 subjects, led by DuBuske. The treatment was well tolerated and, compared to placebo, provided a 13% average reduction in a combined symptom–medication score during the peak grass pollen season in the full study population. But the therapy got ensnared in regulatory red tape after a trial participant developed a rare neurological condition called transverse myelitis. In 2007, the FDA

imposed a clinical hold on Grass MATA MPL and two other immunotherapies from Allergy Therapeutics that were in clinical development at the time, as the agency conducted a review of all products involving the MPL adjuvant.

It took five years for Allergy Therapeutics to get the hold lifted. And by the time it did, the company set out to boost that 13% efficacy rate even higher. So, it went back into phase 2 to try higher doses of Grass MATA MPL, using an environmental exposure chamber—the FDA’s preferred methodology—to assess doses that were 2- and 3.6-times the previously tested treatment.

The higher doses proved safe, but the data were inconclusive on which one offered the best allergy protection. “There was not a clear pattern,” says company CEO Manuel Llobet. “I cannot tell you why. The fact is we were not able to pick the best dose because there was no consistency between the responses to the different doses.” According to Llobet, Allergy now plans to run another dose-finding study in 2017 using an eye-drop challenge test, an approach that worked to help the company find a preferred dose for its Pollinex Quattro Birch, a short-course immunotherapy in development in Europe for treating birch tree allergies. Phase 3 testing for Grass MATA MPL will likely be pushed back to 2018.

Meanwhile, other short-course immunotherapies are moving ahead, too (Table 1).

And even with the recent clinical setbacks, most allergy experts remain upbeat. “We have the science behind us,” says DuBuske, “and it’s just going to be a matter of doing the right model, finding the right dose and moving forward.”

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