Cytos' cat and mouse game

By Lev Osherovich, Senior Writer

Cytos Biotechnology AG is aiming to spin out a new company to house an allergy vaccine program that uses Cytos' phage particle technology to tolerize the immune system to an allergenic cat protein. Cytos says that a cat allergy vaccine based on the approach is ready for clinical testing.

Cat allergy results from allergen-specific IgE antibodies, which prompt basophils and mast cells to degranulate and release histamines that lead to inflammation and anaphylaxis. In addition to antihistamines, available palliative remedies include desensitization therapy, which involves subcutaneous injections of an allergen to train the immune system to not make IgE in response to cat dander.

However, conventional desensitization therapy is often ineffective and can reactivate IgE production, leading to severe anaphylactic responses. Cytos has been seeking a way to deliver antigens to tolerance-building innate immune cells without triggering an IgE response.

"Currently, all vaccines against allergies have the problem of inducing anaphylactic reactions," Cytos' EVP and CSO Martin Bachmann told *SciBX*. "In mice and, so far, in human cells, the one we made does not."

The solution to avoiding IgE responses, Cytos found, is tricking the immune system into recognizing cat allergens as viral antigens, which are known to trigger production of protective IgG-type antibodies.

Cytos' approach uses the company's Q β bacteriophage particles to deliver major cat allergen I (1PUO; Fel D1) and toll-like receptor (TLR)-binding adjuvant to innate immune cells.

Making the cat protein "look like a virus" creates a strong immune response that leads directly to IgG production, according Bachmann.

As published in *The Journal of Experimental Medicine*, basophils from human volunteers with cat allergies did not degranulate when exposed to the Q β -Fel D1 complex but did degranulate when treated with Fel D1 alone.¹

In mice, the viral formulation of Fel D1 did not stimulate basophils and mast cell degranulation. Instead, wild-type mice treated with the vaccine complex developed a strong IgG-type antibody response against Fel D1.

These IgG antibodies protected against allergic reactions: mice sensitized to Fel D1 and subsequently vaccinated with the bacteriophage complex did not develop anaphylaxis when rechallenged

with the antigen. Anaphylaxis did occur in control mice that were sensitized but not vaccinated.

Bachmann led the study team.

"The complex of Q β -Fel D1 is a perfect candidate for allergen immunotherapy for cat allergy, but the mechanism of its function is not clear," said Daocheng Zhu, assistant professor of allergy at the **Feinberg School of Medicine at Northwestern University**.

Although the specific mechanism of protection remains murky, Bachmann suspects the IgG-bound antigen activates Fc γ receptor IIb (CD32; FCGR2B), an inhibitory receptor on basophil and mast cell surfaces. As a result, IgE has no effect when it binds these cells. Indeed, unlike wild-type mice, *Fcgr2b* knockout mice were not protected from allergy by vaccination.

Cat's cradle

The challenges in developing an allergy vaccine are twofold: it must avoid activating an immediate IgE response while reprogramming the immune system for long-term tolerance. Although the Cytos vaccine clearly avoided the IgE problem, the question going forward is whether the IgG antibodies elicited by the product will actually induce tolerance to Fel D1 in humans.

"Nobody has been able to show that induction of IgG titers correlates with clinical outcomes" in allergy, said Martin Steiner, CEO of **ImVisioN Therapeutics AG**.

ImVisioN thinks the route to tolerance does not involve changing the types of antibodies generated against an antigen, but rather rebalancing the T cell response. The company's IVN201, a Fel D1-based vaccine, is in Phase II trials for cat dander allergy and is thought to work by enhancing T_{reg} cells that shift the proinflammatory T helper cell type 2 (Th2) response to a more protective Th1 response.

Indeed, whereas Bachmann's paper found that tolerance could arise from changing the antibody response to IgG from IgE, previous research has shown that the type of T helper response caused by allergens is at the root of tolerance.

"It's not surprising that the phage particle technology could produce a more rapid immunogenic effect" than conventional desensitization therapy, said Nolan Sigal, president and CEO of **Tunitas Therapeutics Inc.** "What's surprising is the connection to antibodies."

Tunitas uses technology developed by Andrew Saxon, professor of clinical immunology and allergy at the **University of California, Los Angeles**, to activate FCGR2B.² Tunitas' lead preclinical candidate is a fusion of Fel D1 to an IgG fragment. Sigal said the vaccine works by stimulating FCGR2B to block IgE's activation of mast cells. He thinks the vaccine achieves long-term tolerance by altering T cell responses.

Other players in the allergy vaccine field include **Circassia Ltd.**, which has cat and ragweed allergy vaccines in Phase II, and **MacroGenics Inc.**, which has dual-affinity mAbs targeting FCGR2B in preclinical development for allergy.

Cytos hopes to spin out the new company prior to the start of Phase I testing. Cytos has filed patents covering the vaccine and the

method of phage particle delivery, and the technology is available for partnering.

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COMPANIES AND INSTITUTIONS MENTIONED

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