

Novel drugs help reset dysfunctional immune systems

- Autoimmune or allergic conditions are caused by dysfunctional immune responses, leading to excessive inflammation within the body.
- One way to treat these diseases is to directly target the overactive immune system.
- Dr Roly Foulkes, Chief Scientific Officer at Revolo Biotherapeutics in the UK, highlights new candidate drugs which encourage cells to differentiate into regulatory cells rather than inflammatory cells.
- This prevents the immune system entering overdrive and may improve long-term management of autoimmune conditions.

Scientists have identified over 80 different autoimmune conditions, including type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and lupus. Autoimmune conditions occur when the body recognises its own tissues as something foreign and mounts an immune response against them.

As part of this process, immune cells called dendritic cells display small portions of proteins on their surface. These small parts of the protein are called antigens, and they are used to educate the immune system as to what may be a danger to the body. Normally the antigens are from sources, such as bacteria, rather than the body, but in the case of autoimmune diseases, the body's own antigens are seen as a threat.

The antigens presented on the surface of the dendritic cells – a type of antigen-presenting cell (APCs) – are recognised by another type of immune cell called a T cell. There are different types of T cells, including those that regulate immune responses and those that drive inflammation and tissue destruction.

To treat inflammatory conditions, such as autoimmune conditions and allergies, drugs must be able to put the overactive immune system back into balance.

Chaperone proteins lend a helping hand

Dr Roly Foulkes, CSO of Revolo Biotherapeutics, UK, and his team work to understand the mode of action of two biologic therapeutics derived from naturally occurring chaperone proteins. They are called IRL201805 (derived from Binding Immunoglobulin Protein – BiP) and IRL201104 (derived from Chaperonin 60.1), or 1805 and 1104 for short.

Chaperone proteins have an important intracellular job in protein folding, modification, and transportation. Many chaperones are called heat shock proteins (HSPs) and were first discovered in bacteria, where they assist microorganisms to live and adapt in harsh environments.

But not all chaperones act exclusively within cells. Revolo Biotherapeutics found that some chaperone proteins had immune-modulating functions outside of cells. These apparent changes in extracellular 'moonlighting' functions are diverse and can influence the metabolic and immune regulatory pathways in immune cells they directly bind to, such as dendritic cells, promoting their tolerogenic (immune tolerance) features.

This makes the candidate chaperone proteins ideal treatment options to promote a healthy immune response and restore balance within tissues of the body. This often involves tolerogenic effects, which occur when the immune system tolerates the presence of particular antigens.

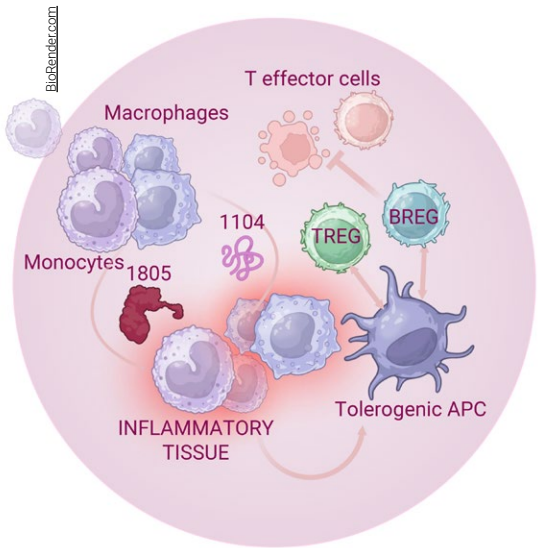
Managing inflammatory conditions

The team at Revolo Biotherapeutics have already tested chaperone proteins 1104 and 1805 for use in several different inflammatory diseases, including food and pollen allergies, rheumatoid arthritis, and other immune-mediated conditions, such as eosinophilic oesophagitis.

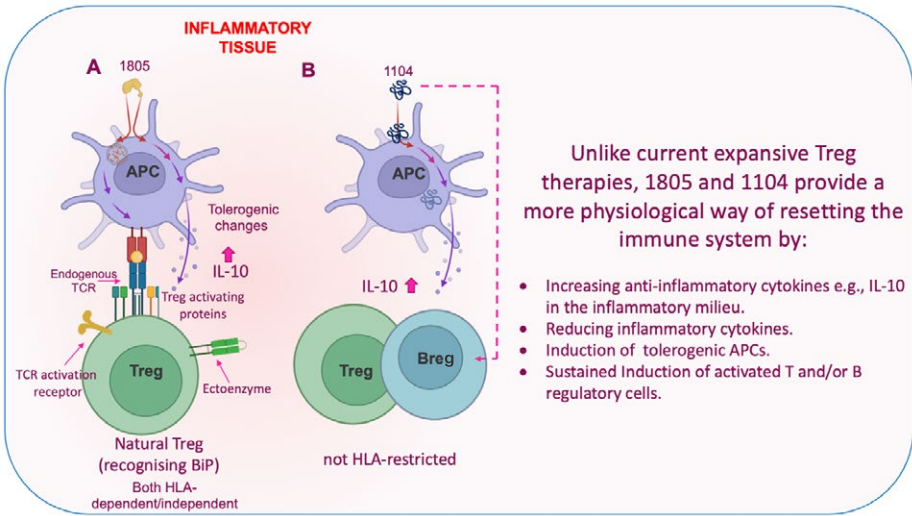
Globally, approximately 5% of adults and 8% of children are affected by food allergies. Foulkes explains that in preclinical food allergy models, administration of protein 1104 led to a marked reduction in allergic symptoms. In addition, the drug may be able to work prophylactically, indicating that it is capable of resetting the immune system before the allergic effects occur.

The research team have also just completed an allergen sensitive study in a group of 60 people, in association with Professors Stephen Till, King's College London, and Mohamed Shamji, Imperial College

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Chaperone molecules 1104 and 1805 bind to APCs, promoting changes in their immune tolerogenic features.



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London. They are currently evaluating the safety and efficacy of using 1104 in this cohort of patients.

In addition to food allergies, Foulkes highlights other studies which have shown the immune-modulating potential of 1104 and 1805. The molecules interact with immune cells, which in turn pass on immune-suppressive properties to nearby regulatory T cells (Tregs) and regulatory B cells (Bregs).

Eosinophilic esophagitis (EoE) is a swallowing disorder with no current cure. One feature of the disease is infiltration of immune cells into the oesophagus, followed by progressive inflammation and fibrosis. Revolo Biotherapeutics has collaborated with Professor Evan Dellon, University of North Carolina, USA, to run a clinical study in EoE consisting of a placebo group and two treatment groups receiving different doses of

1104. The results of the study showed 1104 met its primary endpoint, a reduction in esophageal eosinophil infiltration. Moreover, the treatment with 1104 led to an increase in Tregs and Bregs, a finding that has not been reported before for any other therapeutic in EoE.

A clinical trial has also been completed in patients with rheumatoid arthritis with a single dose of 1805. It was effective in reducing disease activity scores up to 12 weeks, and this correlated with an increase in activated Tregs. A second larger phase II trial is currently planned.

Both candidate chaperones may target not one but multiple immune regulatory pathways common to many inflammatory and autoimmune diseases. In collaboration with Professor Carl Goodyear, University of Glasgow, UK, Foulkes has shown that 1805 selectively targets gene signalling in immune cells from autoimmune patients compared to cells from healthy donors. He is also working with Professor Tariq Ahmad, Exeter University, UK, to see if these new generation of immune resolution promoting chaperone-derived molecules may be effective at treating a number of gastrointestinal chronic inflammatory diseases such as ulcerative colitis.

Drug development

Drug candidates 1805 and 1104 both aim to achieve long-term disease remission with less frequent dosing compared to current therapies, without suppressing the immune system directly. Existing treatments which do cause immune suppression can leave a patient vulnerable to other illnesses, such as infection.

The proteins 1805 and 1104 are able to bind to antigen-presenting cells, such as dendritic cells, where they have a direct impact on the body's tolerogenic capacity. In addition, the proteins can indirectly promote the immune suppressive activities of regulatory T cells.

Both molecules have the potential to return an out-of-balance immune system to its normal state, putting patients into long-term disease remission, without the significant side effects seen with current chronic therapy. Foulkes hopes to lead further trials to explore how 1805 and 1104 may aid remission of other inflammatory diseases, such as food allergies and inflammatory bowel disease.

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Personal response

How did you become interested in the biopharma industry?

I have always been interested in how medicines can treat serious diseases. My initial interest was in how key endogenous factors control high blood pressure. I soon realised a key feature of the human immune system is its ability to be modified leading to effective treatments for human diseases.

How does Revolo Biotherapeutics' approach differ from other companies?

At Revolo, our approach is to utilise the regulatory immune response to re-balance deleterious inflammatory events through the physiological activation of regulatory T and B cells by acting upstream in the immune cascade using chaperone molecules to regulate the immune system. This is very different from other approaches, where companies target single downstream mediators, such as cytokines, with some level of relief, but with limited clinical benefit.

What are the next steps in developing chaperone proteins for clinical use?

Revolo Biotherapeutics have completed an efficacy phase 2 study in eosinophilic

esophagitis and seasonal allergic rhinitis with 1104 and a single study with 1805 in rheumatoid arthritis (RA) patients. We are planning additional studies in EoE, food allergy, RA, and ulcerative colitis, as these chaperone-derived drugs are likely to have utility in a range of allergic and autoimmune diseases. This will potentially confirm the power of chaperones to control excessive immune activation through effects on multiple cells and processes.

How else could we harness the power of chaperone proteins?

The restoration of immune tolerance for the treatment of these inflammatory diseases is very novel and ground-breaking, and chaperone-based proteins may reduce long-term chronic inflammation and reset immune balance in numerous diseases.

What advice would you give someone moving into the field of biotherapeutics?

Biotech is so rewarding and exciting and it provides a means to use your scientific training and skills to make a real difference in patient care in a number of as yet, incurable diseases.

Details



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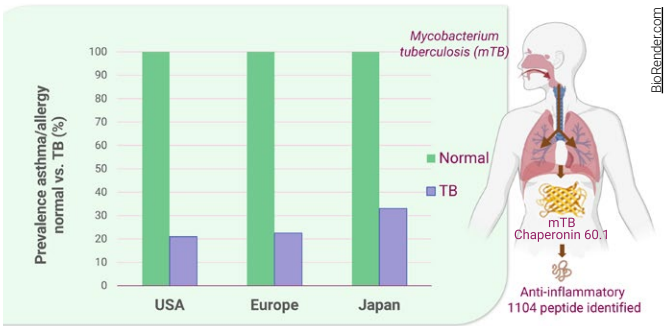
Bio

Dr Roly Foulkes has worked in the pharma industry for more than 30 years. He was at Celltech/UCB for 25 years as head of immunology and inflammation, followed by a number of biotech consulting roles. He became CSO of Revolo Biotherapeutics in 2018.

Further reading

Eggleton, P, et al, (2023) The therapeutic mavericks: Potent immunomodulating chaperones capable of treating human diseases. *Journal of Cellular and Molecular Medicine*, 27(3), 322–339.

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1104 is a peptide derived from a 60.1 chaperonin of the tuberculosis (TB) causing bacterium, *Mycobacterium tuberculosis* (mTB). TB infection is correlated with up to a 70% reduction in allergy development. 1104 can reset the immune system from an inflammatory to a non-inflammatory state.

Drug	Disease	Discovery	Pre-clinical	Phase 1	Phase 2	Phase 3	Disease prevalence
IRL201805	Rheumatoid arthritis						446/100,000
	Inflammatory bowel disease						321/100,000
IRL201104	Eosinophilic esophagitis						57/100,000
	Grass Pollen allergy						30,000/100,000
	Food allergy						5000/100,000

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