Interviews

EMJ had the pleasure of speaking to two key opinion leaders, Hugh Sampson and Mário Morais-Almeida, in interviews exploring key developments in the field of allergy and immunology. Sampson reflects on his unexpected path into food allergy research and shares his expert perspective on advancing oral immunotherapy, including the role of biologics like omalizumab in improving safety and accessibility. Meanwhile, Morais-Almeida highlights major shifts in allergy care since the 1990s, from the rise of molecular diagnostics to the impact of biologic therapies in respiratory diseases, and offers a forward-looking view on personalised approaches in allergic rhinitis and the influence of environmental factors.

Featuring: Hugh Sampson & Mário Morais-Almeida

Hugh Sampson

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Q1 What initially drew you to the field of allergy and immunology, and how did your focus come to centre on food allergic disorders?

I got interested in immunology before I even went to college. I had a cousin who did a fellowship with Robert Good, a pioneer in the field of immunodeficiency diseases, and he had told me a lot about it. I got quite excited about the field of immunology once I got to medical school and then into my residency. I was always intrigued by various immunodeficiency diseases, and really looked forward to going into the field of clinical immunology.

When I got to Duke University, Durham, North Carolina, USA, which is where I did my fellowship, my mentor really wanted me to look more at allergy, and I, to be honest, never wanted to do allergy. I never even thought I would think about doing food allergy. However, there was a very nice Emeritus Professor who kept telling me how important food allergy was, and maybe I should look at it. I was doing basic research at the time, and one of my findings brought the train of research that I was doing to a bit of a halt. I started looking at food allergy and Charlie May, at the University of Colorado Medical School in Denver, USA, had, just a couple of years

previously, published on double-blind, placebo-controlled food challenges. It brought science to the field of food allergy, which at the time nobody really considered to be a science.

So, I started doing it, and when I began doing these food challenges and looking at it a little bit more, I became very interested. Then, as would happen, my middle daughter ended up having an egg allergy, so I got to see a little bit of it first-hand and just got more intrigued with it as I got more and more involved.

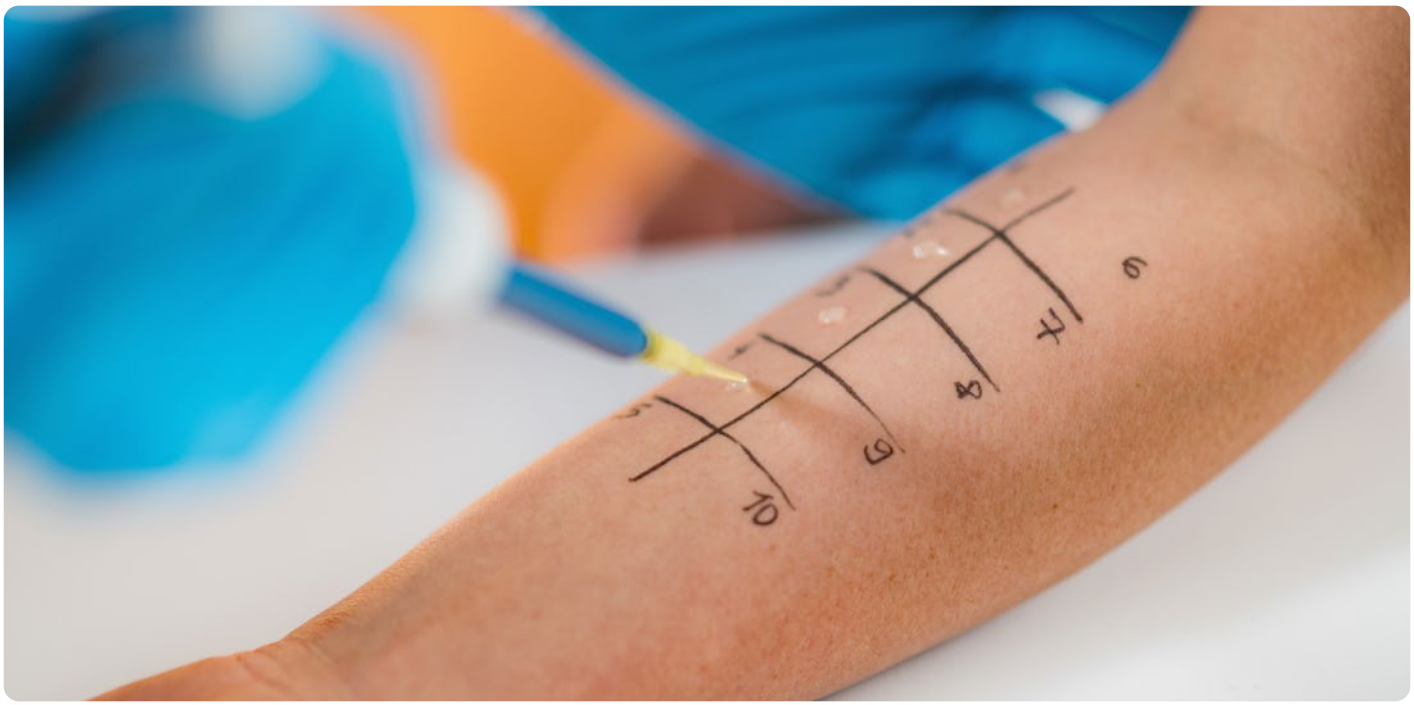
Q2 Oral immunotherapies (OIT) have shown promise in increasing tolerance to food allergens, but they also come with risks and challenges. What do you see as the key advancements needed to make OIT safer, more accessible, and better tailored to the diverse needs of patients with severe food allergies?

I think the work that's been done in oral immunotherapy has been very good. I've spent most of my career telling people they need to avoid food, so it's nice that we finally have something we can do proactively.

The problem with what we see with oral immunotherapy is that there is a high adverse reaction rate, and also it takes a lot of time out of your day. When you initiate the therapy, there are many visits to the physician's or allergist's office as you increase your dose. There's a lot of time required by the parents and the child to go to these different sessions, and that takes about 6 months in most cases.

Also, here in the USA, you're supposed to wait 2 hours before you do any exercise, before you have a hot shower, and you have to be careful about taking certain medications like aspirin and non-steroidal anti-inflammatories. If you get sick, you have to decrease your dose. There's just a lot of interference with your daily life to do oral immunotherapy; however, it does allow you to desensitise the patient, so that if they were to ingest a peanut, for example, they would be able to ingest small amounts of it without having any problem, which is certainly a good thing.

I think one of the biggest things that we have to do is figure out a way to be able to give it more rapidly. One of the things that we've done studies on, and other people have done studies on, is using omalizumab, which is an anti-IgE monoclonal antibody that raises what we call your threshold of reactivity, or the amount of that particular food it takes to cause an allergic reaction. Using that in conjunction with oral immunotherapy, we can get them up to maintenance dose much more quickly, with about a third of the number of adverse reactions. That, in a way, is a step forward, but we're going to have to find other ways to be able to do it much more rapidly. People have thought about modifying the protein, taking out some of the allergenic components of that food protein. So far, we've done very well in our mouse models, and I always tell people, I've cured most mice of peanut allergy and milk allergy, but many of these



methods don't quite translate into humans yet. There's a lot to learn.

The one thing that I've really been encouraged by is that when I started in this field, there were only a couple of us working in food allergy, and now it's one of the most prominent areas in allergy. When we go to national meetings, a third to a half of the presentations are related to food allergy, which never happened before. There are now dozens of companies that are interested in coming up with different forms of therapy for food allergy. I think the field is very promising, we have a lot yet to learn, but I think we're definitely going in the right direction.

I think having something like oral immunotherapy, while we certainly want to do much better than that, is at least allowing us to offer patients something. One more thing that I'm very excited about is some of the early findings looking at doing oral immunotherapy in very young children, like 1–3-year-olds. We're finding that by starting at that early age, we may actually be curing some of their allergies, making them go permanently into remission, which you don't often see when you do oral immunotherapy in older patients.

I always tell people, I've cured most mice of peanut allergy and milk allergy, but many of these methods don't quite translate into humans yet

Q3 With the growing body of research around biomarkers and immunological markers, how do you envision their role in predicting responses to OIT for severe food allergies?

The whole area of biomarkers is also a really interesting area, and that comes largely from a lot of the basic research that's been going on. With better understanding of what the immune mechanisms are that lead to food allergies, we're finding things that better tell us what's happening and how we can predict things.

Our lab has been very interested in something called epitope profiling. What that means is we look specifically at where the IgE antibody attaches to a food. For example, peanuts are made up of several different proteins, and we can now measure those clinically. We see that, for example, in peanuts, the two proteins that seem most important are what we call Ara h 2 and Ara h 6, and what we're doing with this epitope profiling is looking at exactly where the antibodies are attaching to this Ara h 2 protein. By doing this with colleagues who are experts in biostatistics and machine learning, we are able to generate algorithms that help us predict ahead of time what's going to happen when we do immunotherapy.

We've done this now with both milk and peanut. We have looked at the way a certain patient's allergic antibodies see a protein and are able to tell whether they're going to have a successful time with oral immunotherapy, meaning they may even obtain what we call sustained unresponsiveness, or a more long-term remission. The advantage to that is that when we start talking to patients about oral immunotherapy, for example, and knowing how much time that's going to take out of their life, if you have somebody who's likely to have a very good response, they might be much more willing to undergo oral immunotherapy than someone where you can say, you know, this just doesn't look like it's going to work for you.

Then people are looking at more biologic assays, where we look at the response of basophils and mast cells in lab experiments, which show what kind of response we get there. That, and the epitope profiling, are allowing us to get a better handle on not only how people are likely to respond but also give us some idea of how much food they might be able to tolerate before experiencing a reaction. One of the things we've learnt is that when you are food allergic, there are some people who will react to the most minute amount of that particular food, and there are other people who could eat one or maybe even two peanuts and not react, but if they ate more, they would have an allergic reaction. Some of these biomarkers are helping us identify these people, and again, where that may be important is if you know you can ingest the full peanut without having a reaction, it's not so likely that small contaminating amounts will make you react. Therefore, that would definitely change your lifestyle, as you might be much more willing to go out to restaurants or go to your friend's house and things like that. You still need to be cautious, but a small mistake wouldn't end up with you having an allergic reaction.

I think these biomarkers are going to help us in prediction, but then we're also trying to identify biomarkers that tell us, at the end of some form of therapy, how likely you are to be protected without having to do a food

challenge in order to know how much they have to ingest before a reaction will occur.

Q4 How do you think genetic factors or microbiome analysis might improve patient stratification, and what advancements are needed to translate these findings into clinical practice?

Well, I'll admit this is not my area of expertise, but I think one of the things we clearly see is that food allergy does have a genetic component, although it's largely environmentally dependent. The reason we know that is because we've been involved in things like twin studies where you have identical twins. If it was all genetics, the two of them should have exactly the same thing happen, and yet we don't see that.

The other thing is, we know that when we look at the prevalence of food allergy, it really seemed to start increasing in the late 1990s and early 2000s, and there's been a tripling of peanut allergy, for example, in that period of time. Something like that is not genetically controlled; it's too short of a time period. Genetics takes years and years, but there certainly is a component, and there certainly have been some genes that have been identified that seem to correlate with those people likely to go on to have a particular food allergy.

> **Food allergy does have a genetic component, although it's largely environmentally dependent**

But we have a whole lot more to learn. Food allergy is something that is most likely what we would call a multi-gene disorder. It's not just one gene causing the problem, there's a whole bunch of them that get together in a certain environmental situation, and when that combination hits you end up with that food allergy. We have a lot to learn there; the research is going on, and I think it will get better.

The whole microbiome story is fascinating, and I think there's a lot of really interesting work going on now. There are real strides going forward in looking at potential probiotics that may be used to actually help prevent the development of food allergy.

A number of investigators on both sides of the ocean have been very involved in this area and have identified what they call certain 'communities of bacteria' that people have who are more likely to develop a food allergy.

The one thing that's been very clear, as in very young children, is that the bacteria in your gastrointestinal (GI) tract is incredibly important in helping you develop a normal immune system. For example, one of the studies that we're hoping to finish up in the next month or so has been looking at babies born by caesarean (C) section. We've known for a long time that babies born by C-section have a higher rate of allergy, food allergy, autoimmune disease, and some other types of disorders. The feeling has been that because these babies don't come through the birth canal, they don't get the appropriate bacteria from the mother. They tend to get bacteria from the skin or the hospital environment. So, a colleague of mine conducted a study where they demonstrated that by doing vaginal seeding, or taking a swab from the mother's vaginal canal and swabbing a baby who was born by C-section, with it at birth, their microbiome, or the bacteria

in their GI tract, looks much more like a baby born vaginally.

The study we've been doing is taking babies born by C-section and randomly assigning them to get the vaginal seeding with the material from the vaginal canal versus babies getting placebo. We're looking to see whether that is sufficient to prevent the development of allergy or the early forms of allergy. I'll be very excited to see how that turns out as we have a month left to get the final patient in, and then we get to start analysing all the data. In the USA now, 35% of babies are born by C-section, so that's a huge number of babies that are put at higher risk. If we can do something as simple as this swabbing, or vaginal seeding, to prevent a lot of that allergy, that would be a tremendous step forward in our health system.

This is a fascinating area, and I think that over the next several years there will be more of these studies. They've been doing this using probiotics, giving babies active bacteria. There are even studies now where they're looking at giving faecal material, that's obviously been cleaned up, but you give this faecal material from people with normal bacteria to individuals who have food allergy to see if they can modify their immune system or their response from the bacteria in the GI tract to help treat some of these food allergies.

I think in the next 5 years we're going to see some really interesting studies, but the thing that's so fascinating to me is the fact that these bacteria that live in your GI tract have so much power over how your immune system develops. It's probably also the same with the bacteria on our skin. That's another area that's just being started to be looked at, and there's so much to come in that area.

Q5 Based on a recent paper you co-authored entitled 'Epicutaneous Immunotherapy for the Treatment of Peanut Allergy', what do you consider to be the most significant implications of EPIT for clinical practice, particularly in terms of its suitability for younger children compared to current therapies such as oral immunotherapy?

So, for full disclosure, I consult for the company that did that, DBV Technologies, so I could have some bias. The thing that really intrigued me about this is the idea that you can put this really minuscule amount of peanut protein in a patch on somebody's back on a daily basis and bring about this big change in the immune system.

When I started out in my career, I did a lot with atopic dermatitis, which is the allergic, itchy rash babies and older people get on their skin, and I had never really considered how immunologically potent the skin is. It's really an immune organ, and the concept of being able to do something through the skin in a way that can bring about a big change in food allergy was really intriguing.

Simply putting on this patch, which is a little disc that contains a very small amount of a peanut protein, daily for 3 years will expose a patient to the equivalent of one peanut over the 3-year period. That's how little it is. What they've been able to show, especially in very young children (1–3 years old), is that it's highly effective in damping down or turning off the immune response to peanuts. With that, a study was published a couple of years ago showing that it met their primary endpoint, which was protection from reacting to a challenge following therapy, or a certain amount of peanut during therapy.

The part that I find interesting, though, and which in a way I would expect based on how the immune system of the skin works, is that it takes longer to do that. So, children who went through that study were offered a chance to go on a second year of the patch, which they did. After the second year, it showed that even more of the children were able to tolerate larger amounts of peanut protein without reacting. Then they were offered a third year. Now, 3 years on, about two-thirds of those children who were still in the study were able to eat the entire challenge dose without a reaction; this was around 15 peanuts. Overall, about 85% of the children had significant improvement in their peanut allergy. During that period of time, they got major protection from reactions to peanuts.

The thing that's nice about epicutaneous immunotherapy is you see much less in the way of adverse reactions, partly because you're putting it on the skin, and I won't go through all the immunology, but it basically doesn't go through the bloodstream, it goes through the lymphatic system. It's not exposing all these mast cells in basophils to the protein, and therefore, you see much less in the way of adverse reactions, and you don't have to modify it up and down for illness or activities. Parents do the patch at home after the first visit; there's no need for multiple visits, there's no restriction on exercise and showers, and all this other kind of stuff. It's just a much easier way to do it, much less of an interference on a patient's daily life.

To me, it's a potentially exciting way to be able to treat a patient and get a good result. It does take longer than it would with oral immunotherapy, but it's also much less in the way of adverse reactions and in the long-term reach comparable results. That's an exciting way to get started, and my big push is in the 1–3-year-olds, because that's when the parents have much more control anyway, and the results appear to be much better.

Q6 The dual allergen exposure hypothesis presents a fascinating paradox: how the skin can mediate both sensitisation and desensitisation to food allergens. Based on your findings in the paper titled 'The riddle of response to cutaneous allergen exposure in patients with atopic dermatitis', what do you see as the most critical factors influencing whether cutaneous allergen exposure leads to tolerance or allergy, particularly in patients with atopic dermatitis?

That's a great question. I think we're still trying to get all allergists to understand what the difference is. Typically, what happens if you have what I'll call normal, uninflamed skin, or non-irritated skin, and you get a food protein on your skin, or dust mites or pollens, is you become tolerant to that protein just the way you would if you ingest something orally.

If you ingest food, typically, your immune system ensures you become tolerant to it. If you put the food on normal, non-irritated skin, it will also lead to tolerance induction. Where the problem comes in is if the skin is inflamed, such as in atopic dermatitis, or if it's irritated. The latter occurs in part due to our "overwashing" of babies and the change in soap composition, as there are higher amounts of surfactants in those soaps today. This is because it cleans better, but it also damages and irritates the skin a bit, causing what we call the keratinocytes to release "alarmins." Keratinocytes are the cells that make up the outer layer of the skin to protect you and respond to the external environment.

This responsiveness probably evolved during times when we used to have parasites attack our skin, and when you have what you call a "danger signal," they release something called alarmins, which are cytokines. Cytokines tell other cells: 'This is bad, we've got to react against it.' With parasites, IgG responses that we use against bacteria weren't potent enough, so we evolved IgE, which is like a cannon instead of a pistol. It's a major response. Unfortunately, this system has now redirected its response to things that it shouldn't. When the skin is irritated and you get those proteins on the skin, you may develop an IgE-mediated response, which can lead to allergy.

One of the things I don't think we appreciated was how much food protein there is in our environment. Gideon Lack, King's College London, UK, is the one that put forward this dual allergen exposure. One of the things his group did was look at the amount of peanut protein in the house dust of British families, and found very high levels of peanut protein. Babies with this irritated skin are exposed to these proteins, peanut, egg, and milk, in house dust, but also on the hands of the parents and their siblings. They're getting this exposure. One of the questions, especially one that I always had when I started out, was how were these infants becoming peanut allergic when they weren't ingesting any peanut? We didn't realise that it was the environmental peanut on the skin that was leading to this allergy. So, if the skin was totally normal, if it's not irritated, you're going to tolerise. It's not going to be a problem. Most of the kids we see with food allergy have a history of atopic dermatitis, and because they're getting this exposure to allergens on inflamed skin, they develop food (or other) allergies.

There's also something we call the 'atopic march', which is where children who start out with atopic dermatitis end up eventually getting allergic rhinitis and oftentimes asthma. Part of that, again, is due to the fact that they're getting these proteins, dust mites, cat dander, dog dander, all these other proteins on their skin, which is then leading to allergic responses. Previously, we hadn't appreciated this dual role, that if things are all normal, it goes one way but if the skin is inflamed, you have these alarmins secreted, which make it go the other way.

The one thing I always found sort of funny, I'm not sure my patients' parents did, but occasionally we see people who are allergic to Brazil nuts. We don't eat much in the way of Brazil nuts in the USA, whereas in the UK, you have much more exposure to Brazil nuts. So, sometimes, when I find a young child who is allergic to Brazil nuts, I ask the parents, 'Oh, have you lived in England?' More than 50% of the time they say 'Yes'.

Additionally, cashew, to us, is the new peanut, because cashew, at least in the USA, and I know in Australia and the UK as well, has become much more available, and people use it a lot more. So, we're seeing much higher rates of cashew allergy now. In Australia, there was a study published not too long ago showing cashew allergy is just about as common as peanut allergy in young children.

Q7 What key changes or advancements do you anticipate in the field of oral immunotherapies for food allergies in the near future?

One of the biggest problems we see now is that when I started, which was a long time ago, I spent most of the time showing people they weren't reactive to many foods. They might be sensitised, meaning they would have a positive skin test or a positive blood test, but if they ingested it, they were totally fine. Usually, we would find that children would react to one food and occasionally two foods. Today it is almost the reverse. I almost never find somebody who only reacts to a single food.

This multi-food allergy is becoming a real problem, which suggests that we have to come up with methods to be able to treat many food allergies at one time.

Now, some people are looking at doing things like what we call multi-food oral immunotherapy, where you treat them with a whole group of foods. Omalizumab, an anti-IGE antibody, can decrease their reactivity to the particular food, and then you can try to treat them orally with many foods at once, or eventually you might be able to do it with a with a patch or sublingually. But this will still be a pretty onerous process.

A lot of people are now looking at ways to try to turn off mast cells or try to be able to block the development of the IgE antibody in a more global way, not just to be food-specific. It's going to require that we really understand much better how these allergic reactions happen. Again, we see people who have IgE antibodies to peanuts, who don't react to peanuts, and we're still trying to figure out exactly why they're different. We'll have people with very high levels of certain foods and have no problem. We have other people who have really small amounts of IgE, say, peanuts, that we can detect in their serum and yet have terrible reactions. There's still a lot we have to learn about it.

As we understand these mechanisms better and better, I think we have to really be looking at more global ways to dampen the allergic response and, like I said, there are a lot of companies now that are also involved in this. I'm pretty optimistic that at some point we're going to come up with a more multi-allergen approach that will enable us to treat these people who really have multiple food allergies.

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