

# From the bench to the bedside

*Attendees at UCD's Charles Institute Seminar Series heard a presentation from Prof Anne Marie Tobin on insulin resistance and obesity in psoriasis and hidradenitis suppurativa, as well as the role of certain cells in these conditions*

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. The seminars were broadcast to attendees with a special interest in dermatology in other locations, who accessed the talks remotely via an audio-visual link.

Attendees at the series heard a presentation from Prof Anne Marie Tobin, Clinical Associate Professor at the School of Medicine in Trinity College Dublin and Consultant Dermatologist in Contact Dermatology at Tallaght University Hospital, Dublin. She delivered a talk titled 'From Bed to Bench — Insulin Resistance/Obesity in Psoriasis and Hidradenitis Suppurativa (HS): The Role of iNKT and MAIT Cells'. Prof Tobin runs a clinic at Tallaght Hospital to treat patients with these debilitating conditions and she drew on data from a number of studies in which she has conducted research to shed light on the implications of dysregulation of iNKT and MAIT cells in psoriasis and HS.

Prof Tobin presented a number of interactive case studies and invited clinical opinions from attendees on a variety of presentations of dermatology conditions and their aetiology. "Psoriasis is an incredibly interesting disease, both in terms of looking after the patients clinically, and also in the research on the condition, and there are a number of reasons for that," she told the attendees. "One is the protean manifestations of psoriasis — it can occur in the skin, the nails, there may be joint involvement, there can be a palmoplantar psoriasis subtype, and there can also be ocular psoriasis. It's very rare to encounter such a wide range of varied manifestations.

"It is also a very interesting disease immunologically," she continued. "There can be intense inflammation where patients can be red from head to toe, they are treated, the inflammation recedes and there is no scarring — it never leaves a scar and that's an incredibly unusual thing immunologically, to have that degree of insult without scarring."

She also pointed out that psoriasis is also very interesting from a psychological point of view: "These patients can come to you covered from head to toe [in inflamma-

tion], but yet they rarely complain; these patients can be remarkably stoic... but if you clear their inflammation and their psoriasis begins to return, their tolerance is completely gone and they cannot cope with that, so these patients really are fascinating psychologically."

#### Treatment interventions

How psoriasis patients are treated has also seen significant change, she told the seminar, particularly in terms of how therapeutic interventions have progressed. "When I started treating these patients, the only treatments we really had were phototherapy, methotrexate and ciclosporin. Then, serendipitously, along came the TNF inhibitors. They were proven to work, but they were developed for other inflammatory disorders, such as inflammatory bowel disease, and were subsequently seen to also work in psoriasis.

"Now, that has been completely turned on its head," she continued. "The IL-23 biologics were actually first developed for psoriasis, and now they are spun-out to other inflammatory disorders. The same goes for the anti-IL-17s — they were developed to treat psoriasis. That has led to the development of a whole gamut of research into psoriasis and its pathogenesis, potentially being able to offer patients clearance of their disease... it has been incredible to be involved in this, both at a clinical level and a research level in psoriasis."

Prof Tobin went on to outline research in which she has been involved and told the seminar: "There is a very clear correlation between insulin resistance and psoriasis. We now know that cardiovascular disease, for example, metabolic disease, is a highly inflammatory systemic state and that has resulted in a change, even in how cardiovascular disease is managed," she explained. "

Prof Tobin also pointed out that obesity and insulin resistance are known to be comorbidities and risk factors for HS and psoriasis. A key factor in both obesity and insulin resistance is dysregulation of the innate immune system, particularly dysregulation of the invariant natural killer T (iNKT)-cells and mucosal associated invariant T-cells, she added, in patients with HS and psoriasis.

"That's relevant because natural killer cells and iNKT cells are very important in cancer prevention — obese people have a higher risk of certain solid-organ cancers," she continued. "In fact, they also have an increased risk of melanoma, so they seem to have this immune dysregulation that predisposes them to more infections, but it also seems



Prof Anne Marie Tobin

to be elevating their cancer risk." In obese people, it was also found that natural killer and iNKT cells were enriched in omental fat. "That's very relevant because in the past, fat was considered to be an inert substance, almost like cladding," she explained. "Now we know that fat is actually really active immunologically."

She also outlined results of research into clearing psoriasis using phototherapy and told the seminar: "After phototherapy, we found that patients' iNKT cells never reached the same level of controls [than previously]."

#### 'The new psoriasis'

Prof Tobin described how HS is being regarded as "the new psoriasis" and she provided an outline of some of the patient profiles commonly treated in her clinic. "We are seeing more and more of these patients in our clinic — HS is unlike psoriasis, in that it is a really intense inflammatory condition," she said. "It starts off with patients getting boils under their arms. The patient will feel itchy as these boils begin to form, the boils come up, they burst and the pain goes away. But if left untreated or if HS becomes progressive, boils can become abscesses and the two join-up together and then sinus tracts develop. If it progresses further, there can be marked scarring," she explained.

"It typically affects women and patients in their 30s, and three things drive it — a family history, as around one-third of HS patients have a family history; smoking; and being overweight... We again looked at insulin resistance and we found that if overweight was driving this condition, there was going to be a huge level of insulin resistance," said Prof Tobin. "But what we also found were high rates of Framingham risk — 5 per cent of these patients in their 30s had a greater than 20 per cent risk of heart attack in the next 10 years. Those are extremely high risk rates in a relatively young population."

With regard to the microbiome, Prof Tobin explained: "All microbiome work on skin to date has been done using swabs, but it has been shown that you get quite a different result from biopsies, so we really need to be doing both biopsies and swabs," she said. "This is interesting, because it ties-in very nicely to what we are doing in HS, so we collected all the samples from a microbiome study in HS and these are being analysed at

the moment... we have taken biopsies from lesions, uninvolved skin and swabs, and we also got the microbiome, which was a really elegant job of collecting samples from patients, and we also took nasal swabs," she explained, adding that results are currently awaited.

Collecting the microbiome was made possible because it is mapped and because of RNA sequencing technology, she explained. However, perhaps more important was the role of data analytics. "This is because you generate so much data from studies like these that the analysis has somewhat lagged behind the technology. You really need a good biostatistician to work on this type of study."

#### Obesity and disease

During a lively Q&A session, Prof Des Tobin asked whether the increasing rates of obesity among the general population have "moved the dial" in terms of psoriasis incidence. If a person is obese and has a genetic propensity from the human leukocyte antigen associations, a person is more likely to have a manifestation of psoriasis, and indeed potentially, more severe psoriasis. "There is also an association between metabolic syndrome and obesity — we can 'join those dots', but given the dramatic change to the human diet, which has dramatically altered our gut microbiome, possibly resulting in changes to our skin, is there any observed likelihood of increased incidence of skin disease increasing because of that lifestyle shift?" he asked.

Prof Anne Marie Tobin replied: "That is the general theory, but it has not been proven as yet. The theory is that because the gut microbiome has changed, there is a loss of a certain degree of protection at the epithelial barrier," she said. "You then get what's almost like a 'backwash' effect that translates to other organs."

Prof Des Tobin responded by describing a theory that "some autoimmune diseases may have had their first 'flag-waving' via an immune response to a plant protein, in the context of an anti-gliadin protein," he said. "This connectedness between 'you are what you eat' [and immune responses] is increasingly interesting."

*RELIFE has had no input into the content of this article or series of seminars*