Q&A

Angela Christiano: More than skin deep

Angela Christiano, a molecular geneticist at Columbia University in New York City, was diagnosed with the autoimmune disease alopecia areata around 25 years ago. Since then, she has been unpicking the mechanisms behind this form of hair loss. She spoke to *Nature* about the long-neglected condition, and progress towards a cure.

What sets alopecia areata apart from other types of hair loss?
This type of alopecia is special because it's an autoimmune disease. A healthy hair follicle exists in a state called immune privilege, meaning it's shielded from recognition by the immune system. In alopecia areata, the follicle loses that protection. For reasons that are not yet known, the follicle mistakenly signals for immune cells called T cells to come and attack it. But, unlike other forms of hair loss in which follicles can become permanently scarred, the follicles in people with alopecia areata can recover if the immune attack stops.

How much of this was known when you began your alopecia research?
When I was diagnosed with the condition in 1996, just after finishing my postdoc, I couldn't believe how little research had been done. No one could tell me what caused alopecia areata. It was assumed to be an inflammatory skin disease. Physicians prescribed steroids, and when drugs were approved for a skin disease, such as atopic dermatitis, they would be tested for my condition, too. But, as my team learnt from genetic studies, the pathways causing alopecia areata are more closely related to autoimmune diseases such as rheumatoid arthritis and type 1 diabetes.

Why was the condition so neglected?
It is considered a cosmetic problem, and therefore, not important. It does not cause pain, and there's no comorbidity. But that dismisses the reality of its impact on people with the condition. Alopecia areata is the only form of hair loss that affects children and young adults. And because it affects the eyelashes and the eyebrows, as well as the top of the head, it brings a lot of stigma. People often feel they've lost their personality. I've always had great support from people who are affected, but from some colleagues there was hesitation.

What have you learnt about the genetics of alopecia areata?
The condition is polygenic — many genes are involved. We have genotype information from more than 5,000 people, and from that database we identified 14 genetic regions that contribute to the disease. Similar research for autoimmune conditions such as Crohn's disease has found many more linked genes, but researchers had many tens of thousands of people to look at — we were lucky to find as many genes as we did with our small sample.

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The most significant region we identified contains HLA genes, which tells you it is an autoimmune disease, as do several other genes we found that are shared with rheumatoid arthritis and type 1 diabetes. But one region — the second strongest contributor that we saw — is unique to alopecia areata. It contains ULBP genes, and we think that upregulation of this region could trigger the signal that hair follicles put out to attract T cells. Another gene, *STX17*, is involved in pigmentation of hair; we now know that T cells prefer to attack pigmented hair follicles that contain melanin, rather than grey hairs.

How has this fed into your search for therapy?
It's been a multidisciplinary effort. Once we found evidence of several susceptibility genes, we had to turn to immunology. Raphael Clynes, an immunologist with a focus on type 1 diabetes at Columbia, suggested we try a drug that disrupts the JAK pathway, one of the main intracellular signalling systems. By 2012 there were two JAK inhibitor drugs on the market that were mainly used to treat rheumatoid arthritis and a type of cancer called myelofibrosis. We tested them in mice with alopecia and found that the drugs revived inactive hair follicles when used orally or topically (L. Xing *et al. Nature Med.* **20**, 1043–1049; 2014). The mice started to show regrowth in four weeks. We moved to human trials in 2016, and now a number of major drug companies are developing JAK inhibitors for alopecia areata. Approval from the US Food and Drug Administration could come in the next two years. This would be a real milestone, because no drug has been approved specifically for alopecia areata.

Where do you want to go next?
In trials, the disease often comes back when people stop taking the drugs, and some people do not respond to JAK inhibition at all. So we really want to find a permanent solution. One option might be to try to destroy the memory cells that replenish the T-cell population. We can lower T-cell activity with JAK inhibitors, but it might be possible to clear enough T cells to get rid of the disease altogether. We're also about to start a clinical trial of faecal transplants in people with alopecia areata. This is based on research that suggests that the community of microbes that live in the gut could affect the disease.

What we're afraid of, honestly, is that people will look at JAK inhibitors and call it a job well done. It couldn't be more different — one therapy is not enough. We still need to find more options that we can turn to. Our biggest challenge is going beyond just treatment, we really want to go for a cure.

Interview by Laura Vargas-Parada
This interview has been edited for length and clarity.