The Future of Immunity

By Professor Robin May

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For this year's lecture series, I am trying a different format of transcript. Rather than a long-form written document, which has been largely rendered obsolete by the ability to transcribe from the YouTube recording, this handout is a brief summary of the key topics in the lecture, together with some more extensive suggestions for extra reading. As ever, we would be delighted to hear your thoughts on this new approach!

Over the course of this lecture series we have explored immunity in all its many guises: human immunity, plant immunity and even computer immunity. In this final lecture, we consider where the future of immunity may lie. Will human ingenuity triumph, creating a disease-free future in which we live for hundreds of years and the concept of an 'infection' is consigned to the history books? Or will pathogens take the upper hand and eradicate humanity in an untreatable pandemic?

Immune Evolution – the story so far

Considering the future of immunity means first reflecting on the past. Humans have evolved alongside myriad pathogens for millennia. Until the discovery of vaccines and antibiotics, the only factors that influenced an individual's survival in the face of an infection was their ability to evade infection in the first place or, failing that, their inherited genetic ability to fight off the causative pathogen. Since infectious diseases have been the primary cause of death for humans over most of our evolutionary history, evolutionary theory would predict that immunity genes are likely to be under intense selective pressure. And, just as predicted, that is exactly what modern genetic analyses reveal. In fact, genome sequencing of both living humans and ancient human remains reveals that the fastest evolving genes in our genome are almost all connected to immune function – testament to the critical role that the immune system has played in shaping modern humans.

In extreme cases, genomics can even reveal specific 'selection events' in relatively recent evolutionary history. During the 14th century, a terrible infection swept across Europe – the disease we now know as the bubonic plague or Black Death. Modern estimates suggest a mortality rate of between 30-60%, with entire villages being exterminated within weeks. Such devastation is a potent evolutionary force and, as a result, we can see a clear 'genetic signal' in the survivor population, with several gene variants rising rapidly in frequency within a generation. Modern laboratory analysis shows that many of these directly contribute to the body's ability to fight off the bacterium that causes bubonic plague (*Yersinia pestis*) – a remarkable, if grisly, testament to the power of evolution.

Yesterday's genes, today's impact

Fortunately, today we have more tools at our disposal to help tackle infections without relying solely on natural genetic variation. Vaccines, antibiotics, disinfectants, protective clothing and modern sanitation have all helped to dramatically reduce the threat of lethal infection. And yet, despite all of these measures, genetic variation is still a major contributor to our susceptibility to infection. Work during the Covid-19 pandemic identified a number of gene variants that render carriers more likely to develop severe, life-threatening symptoms. Happily, however, the same approach also highlights new ways to treat these symptoms– for instance, by identifying drugs that target the genes that drive enhanced susceptibility and thereby reduce the severity of the infection. As genome sequencing becomes ever cheaper and faster, this kind of 'personalised treatment' is likely to become more widespread and perhaps one day will become commonplace for guiding treatment of everything from chest infections to athlete's foot.

Taking Control of Immune Evolution

We are all the remarkable survivors of millions of years of natural selection, in which our ancestors were fortunate enough to have a genetic 'menu' that conferred a survival advantage over all the millions of similar humans who died along the way. Consequently, our genomes are the product of an extraordinary history of evolutionary selection. Within the last generation, however, human innovation has opened the door to the possibility of modifying our genomes without relying solely on natural selection.

The discovery of genetic engineering and, more recently, genome editing via the CRISPR/Cas9 system means that DNA can be modified with extraordinary precision. In 2024, the UK became the first country in the world to approve a human medicine based on using this technique to modify human genes – in this case to 'correct' a human mutation that leads to hugely debilitating blood disorders. The power of this approach is not limited to blood disorders, however. In principle, gene editing could be used to modify genes implicated in everything from viral susceptibility to autoimmunity. At the moment, this approach is both very costly and relatively limited in scope, but as the technology develops it may soon become feasible to tackle relatively complex immune disorders in this way. Such an approach offers huge medical benefits, but also raises equally huge ethical questions – not least, the question of when, if ever, it would become acceptable to make heritable genetic changes that might cure a disease permanently, but would also modify the human genome forever.

Immunity is not just for infections

Perhaps the most exciting goal for the future of immunity, though, is not just its ability to tackle infections, but its potential to address some of the most significant non-infectious threats to human health. In recent years we have seen the introduction of a range of immune-based approaches to cancer therapy. In some cases these are designed to reduce the rate of infections that predispose to cancer later on (such as the human papilloma virus vaccine, which protects against cervical cancer), whereas others are designed to 'retrain' the immune system to identify and remove cancerous cells (E.g. the T-VEC vaccine which targets skin cancer). As we learn more about how to effectively design such approaches in a way that stimulate immune destruction of cancer cells whilst leaving healthy cells unharmed, we may ultimately reach a point where vaccination can help prevent or treat many of the most common cancers. Perhaps, in the not-too-distant future, childhood vaccination courses will include a selection of vaccines aimed at protecting them from adult cancers as well as childhood infections.

A Brave New World of Immunity

Despite more than one hundred years of research and a vast number of immunological discoveries, the complexity of the immune system means that we have still only scratched the surface of its capabilities. By combining immunological understanding with powerful genetic tools, scientists are beginning to create therapies that have the potential to tackle some of our most feared diseases. It is now possible, at least in theory, to engineer immune cells to dampen inflammatory responses, enhance pathogen detection, seek out and destroy cancer cells and perhaps even to stop the progression of neurodegenerative diseases like Alzheimer's or Parkinson's. So perhaps the real challenge for the future of immunity is not what we can do with immunity, but rather how we ensure that these pioneering therapies are available to all those that need them…

Key topic in the lecture	**Further reading**
Detecting evolutionary selection in the human genome	Home | David Reich Lab
How infections have shaped modern human populations	Natural selection and infectious disease in human populations | Nature Reviews Genetics
Genetic variation and resistance to Covid-19	Association of genetic polymorphisms with COVID-19 infection and outcomes: An updated meta-analysis based on 62 studies - ScienceDirect GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19 | Nature
Emerging infections and pandemic potential	Home page | CEPI
Genetic polymorphisms and autoimmunity	The genetics and epigenetics of autoimmune diseases - ScienceDirect

Viral vector vaccines	Understanding Six Types of Vaccine Technologies | Pfizer Viral vectored vaccines: design, development, preventive and therapeutic applications in human diseases | Signal Transduction and Targeted Therapy
Self-propagating vaccines	Full article: Self-disseminating vaccines for emerging infectious diseases
Cancer vaccines	Vaccines to treat cancer | Cancer Research UK
Vaccines and immunotherapies against neurodegenerative conditions	Alzheimer's treatments: What's on the horizon? - Mayo Clinic