

WHAT ARE THE SCIENTIFIC CHALLENGES FACING THE DEVELOPMENT OF EFFECTIVE VACCINES AGAINST PATHOGENS WITH HYPER VARIABLE GENOME SEQUENCES?

Since using the first vaccine in 1796, Edward Jenner has in effect saved more lives than anyone else in history. Not bad for a man who, despite ensuring that his method did work, didn't actually know *how* it worked.

Fast-forward two hundred-odd years, and we are now facing the next big hurdle in immunology: the illusive ever-changing pathogens which mutate right from under our noses and the medical treatments we throw at them. This is the territory we aim to claim from giants such as HIV and malaria. But how?

Vaccines protect us from pathogens by training our immune systems. The word 'pathogen' originates from the Greek *pathos*, suffering, and is used for things such as bacteria, fungi, viruses and protozoa which cause disease.

Without vaccines, our body is constantly playing a risky memory game. When our bodies encounter a pathogen for the first time, it takes some time for our white blood cells to recognise that there's *something* dangerous there and what proteins (AKA antigens) the *something* is made up of. They then have to make the necessary antibodies, Y-shaped molecules which latch onto the antigens so they become like two pieces of a jigsaw puzzle. If all goes well, and the pathogens are neutralised, some of our white blood cells become memory cells; if they recognise the antigens in the future, they'll be able to fight the pathogens quickly and easily, before we develop symptoms.

As a rule, vaccines safely recreate this scenario by injecting us with a dead or weakened pathogen. That way the pathogens don't put up much of a fight, but it still allows our white blood cells to flex their metaphorical muscles, and for the memory cells to be created as a stockpile for the future.

But what if a pathogen mutates? Fortunately for us, some of them—such as measles, polio and tetanus—don't change that much. But some do, so much so that our body doesn't recognise them again and the normal style of vaccines won't work. Take HIV for example, the most terrifying foe. It replicates *very* rapidly and copies its genes *very* carelessly. In fact, the genome of any two HIV viruses can differ by almost 50%.

And so we stumble upon the Achilles' heel. Not everything in the pathogen can change, at least not without being seriously detrimental to the pathogen. Some antigens are evolutionarily conserved because they are absolutely fundamental. For instance, HIV contains an imaginatively-named antigen called gp120 which is vital in allowing the virus to replicate. If a certain HIV virus mutates so it doesn't have gp120, then there's no replication and a dead end for that particular virus. If it does have the antigen, then that could be its downfall: perhaps a vaccine of gp120 antigens is all that's needed?

There have been attempts at this sort of vaccine, but they had been largely fruitless until the recent appearance of a possible light at the end of the tunnel. In 2009, an HIV vaccine trial in Thailand appeared to have reduced the risk of infection by 30%. It's clearly not enough for launching a full-blown campaign, but it's a refreshing result after many failed attempts. Scientists are still analysing the secret of the vaccine's success, but it seems that one element of this is the fact that not only did it exploit the importance of the gp120 antigen, but it also worked in tandem with another attack line.

Viruses replicate by sabotaging human cells, turning them into miniature virus-making factories. Some white blood cells have the specific task of destroying these infected cells, but are not always successful. The 2009 vaccine contained a hybrid of canarypox and HIV which posed no real danger to the humans in the trial, but tricked the white blood cells into launching a full-scale search for the aforementioned 'factories'. Perhaps the secret is to develop a detailed understanding of this particular trial, magnify the parts of the mechanism that worked and apply the technique to other diseases in order to develop effective vaccines.

But the plot thickens further. A key problem seems to be that the evolutionarily conserved antigens tend to be well-hidden in the virus, so even if they're *there*, it's hard for our body to find out. Researchers will have to develop an efficient way of overcoming this hurdle.

There's also another pathway to a solution, somewhat thornier and less well-trodden. It's known that white blood cells can produce less specialised, 'one-size-fits-many' antibodies which can work for several different antigens. Coaxing the white blood cells into producing these skeleton keys is a difficult matter, but if we find an efficient way of doing this, it may just be the secret weapon we've been looking for.

And thus we conclude a whistle-stop tour of a modern conundrum. Taming such diseases as HIV, malaria and even influenza is a daunting task. But fortunately for us, it seems that years of research may finally be coming together to form the beginnings of a solution.