- Vaccination / Immune system

Flu, cancer, HIV: after Covid success, what next for mRNA vaccines?

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It is one of the most remarkable success stories of the pandemic: the unproven technology that delivered the Moderna and Pfizer/BioNTech vaccines in record time, helping to turn the tide on Covid-19. The vaccines are based on mRNA, the molecule that instructs our cells to make specific proteins. By injecting synthetic mRNA, our cells are turned into on-demand vaccine factories, pumping out any protein we want our immune system to learn to recognise and destroy.

Pre-pandemic, the technology was viewed with scepticism – a clever concept, but not guaranteed to deliver. Now there is growing confidence that mRNA vaccines could have far-reaching applications in tackling diseases from flu to malaria.

Flu

Every February flu scientists take part in an annual ritual: bets are placed at a World Health Organization meeting on which flu strains will dominate the following winter. There are four influenza viruses in circulation, each rapidly evolving so that the previous year's vaccines will have lost efficacy. Manufacturers need at least six months to produce vaccines, a laborious process that involves growing attenuated virus inside millions of chicken eggs. When the flu forecast is on target, vaccines can be 60% effective, but a mismatch between vaccines and circulating strains can result in efficacy as low as 10%.

The holy grail of flu research is a universal vaccine that would work across all four strains and continue to work for their future incarnations as they shuffle their genomes over time. Such a vaccine would need to target the core influenza protein that doesn't change much from strain to strain. But our immune systems do not respond strongly to this part of the virus and so the goal has remained elusive for decades. However, mRNA is so quick and easy to produce that vaccines can be designed to strike many sites simultaneously. "Such a vaccine will likely be able to induce broadly protective responses," said Norbert Pardi, a microbiologist at the University of Pennsylvania. His team is working on a vaccine candidate that will use about a dozen pieces of mRNA and is designed to work across several flu strains. The team hopes to begin human trials in 2023.

Cancer

The HPV vaccine, which protects against the virus that causes most cervical cancers, already averts thousands of cases of cancer each year. In future, scientists hope that mRNA vaccines could be used to vaccinate against cancer itself by teaching the immune system to recognise mutations before they occur, in an entirely new approach to treatment. "We're taking advantage of the known genetic progression of cancer," said Prof Herbert Kim Lyerly, who is working on cancer vaccine technology at Duke University.

His team plans to trial an mRNA vaccine next year in patients with latestage breast cancer, where tumours typically evolve to be unresponsive to drugs by acquiring mutations in specific genes. Again, an advantage of mRNA is the ability to hit multiple targets at once – in this case, a handful of potential mutations. "There's no better surgeon in the world than your immune system to pick off those [mutated cells] in the early stage," said Lyerly.

The first applications, if successful, could extend a patient's life by months by keeping cancer at bay for longer. Eventually it may be possible to prevent cancer in certain high-risk populations such as heavy smokers, where a mutation in a gene called KRAS accounts for up to a quarter of cancers. Malaria

In October the WHO approved the first rollout of a malaria vaccine. But there is scope for improvement, with the RTS,S vaccine reducing severe malaria by 30%. A fundamental challenge is that the malaria parasite has evolved a way of preventing immunologic memory. Even after catching malaria, let alone being vaccinated, people remain susceptible to reinfection, and the disease kills 500,000 people annually, mostly babies and children.

In 2012, Prof Richard Bucala, of Yale School of Medicine, and colleagues discovered that malaria induced this "immune system amnesia" using a protein called PMIF, which kills memory T-cells. Bucala is working on a form of RNA vaccine that would immunise against PMIF.

Studies in mice suggest that blocking the protein allows the immune system to clear malaria quicker, resulting in milder illness and, crucially, future immunity. Bucala has teamed up with scientists at Oxford's Jenner Vaccine Institute to test the candidate, and if results are positive they hope to begin human trials next year.

"Vaccines are desperately needed in the developing world for parasitic diseases that have long depressed economic and societal development of many countries," said Bucala. "RNA has not only enabled the success of our PMIF vaccine but the platform is far less expensive than protein-based vaccines, opening opportunities for a malaria vaccine that have not previously existed."

HIV

"We're going into the fifth decade now of a global pandemic for HIV," said Derek Cain, of Duke University's Human Vaccine Institute. So far, a vaccine has remained out of reach.

Cain's team has focused on a subset of HIV patients (fewer than onethird) who eventually develop specialised antibodies that can neutralise HIV years after infection. By this time there is a huge reservoir of virus in the body, and it is too late to clear the infection. "It's like you find a fire extinguisher but the whole house is on fire already," said Cain. However, if a vaccine could induce these antibodies, the hope is that they could extinguish HIV before it takes hold.

Cain and colleagues have meticulously mapped out the circuitous route taken by the immune system to create these highly specialised antibodies, and as part of a consortium they are concocting a sequence of four or five multi-target mRNA vaccines designed to "recreate the arms race between the immune system and the pathogen".

"We certainly think that an HIV vaccine will be far and away the most complicated vaccine that we've ever had to put into the population," said Cain. "We don't expect it to work 100% or 90% like the Covid vaccines, but even if we can get to 50-60% that would be a success; 70% would be amazing."