2019 Prince Mahidol Award winners announced

The prizes, given annually for achievements in medicine and public health, have gone this year to scientists working on hepatitis C virus and trachoma. Talha Burki reports.

Heidelberg University Hospital

Ralf Bartenschlager

London School of Hygiene & Tropical Medicine

David Mabey

On Nov 21, the winners of the 2019 Prince Mahidol Awards were announced. Ralf Bartenschlager (Heidelberg University, Heidelberg, Germany) received the prize for medicine for his work on the hepatitis C virus, which paved the way for the direct-acting antivirals that have transformed treatment. The prize for public health went to David Mabey (London School of Hygiene & Tropical Medicine, London, UK) for his work on trachoma, an infection targeted for elimination by 2020.

Bartenschlager started working on hepatitis C virus in the early 1990s. As a postdoctoral researcher, and later with his team, he characterised the NS3 protease and the NS5B polymerase, viral enzymes that are the targets of the antiviral drugs in clinical use today. His team also sought a system to replicate the virus, but the solution was a long time coming. First, they discovered that they were working with an incomplete genome. Even after the genome was restored, the virus would not replicate. It had acquired mutations that were stymieing the process. Charles Rice, at the time a researcher at Washington University School of Medicine, developed a consensus genome. But it still did not replicate in cell culture.

"The replication of the virus in cell culture was so inefficient that we needed a method to enrich for very rare replication events", explains Bartenschlager. They stripped down the genome to the parts necessary for replication and inserted a gene that conferred resistance against a particular toxic drug. Only cells in which replication of the viral RNA, plus the additional gene, had occurred at a high level would be able to survive treatment with this drug. In the first generation of replication, there were just 20–40 such cells out of 10 million. But that was enough.

"It was the breakthrough to finally get the system up and running", said Bartenschlager. The viral RNAs that had successfully replicated had specific mutations. Moreover, certain single cells supported viral replication better than others. "By plugging the mutations back into the genome and using the more supportive cells, it was possible to jump start the replication process", Bartenschlager told *The Lancet*. The work gave drug development researchers a means to study the effect of particular compounds on the hepatitis C virus in liver cells.

> **"'It was a real team effort by the entire community to get to this stage'…"**

The direct-acting antivirals that were then developed can cure more than 90% of patients, and have been used to treat millions of people. "It was a real team effort by the entire community to get to this stage", said Bartenschlager. "But the job is not done. For global elimination, there is a lot of ground to cover in terms of making treatment available; for preventing people from contracting the virus, there is a need for a vaccine."

When Mabey started working on trachoma in the early 1980s, the best available treatment was 6 weeks of tetracycline ointment administered twice a day in both eyes. Try giving that to a small child. "People had lost interest in trachoma", recalls Mabey. "It was a hugely important cause of blindness, but hardly anyone was working on it." The optimism that had attended the advent of a potential vaccine had evaporated after disappointing trial results. Mabey wanted to understand why the vaccine had failed. He started studying the immune response to *Chlamydia trachomatis* infection, the cause of trachoma.

In the mid-1980s, a new oral antibiotic entered the market. "A single dose of azithromycin was enough to cure genital chlamydia; we wanted to see if the same thing would happen for trachoma", said Mabey. He co-authored a 1993 paper showing that azithromycin was equivalent to the full course of standard treatment. But the people most in need lived in areas endemic for trachoma. "If you only treated individuals with active trachoma, they would soon be re-infected", explains Mabey. What if you treated the whole village? In 1999, Mabey and others showed that community-wide treatment with azithromycin decreased *C trachomatis* infection.

In their 1993 paper, Mabey and colleagues had concluded that "azithromycin used on a wide scale could transform trachoma control programmes". WHO subsequently pledged to eliminate trachoma as a public health problem by 2020. After a request from Joe Cook of the Edna McConnell Clark Foundation, which funded Mabey's studies, Pfizer agreed to donate the azithromycin. More than 800 million doses have since been distributed. The number of individuals living in trachoma-endemic areas, and so at risk of blindness, has fallen from more than 1·5 billion in 2002, to 142 million today. The 2020 target will be missed, but Mabey reckons there is a good chance trachoma will be eliminated by 2030. "Trachoma is a disease of poverty, and it has horrible consequences", Mabey told *The Lancet*. "If we manage to eliminate it, and we sustain the gains, it will be a wonderful victory for public health."

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