

ETHICAL RESEARCH



Sick of poverty: the world's poorer nations have little prospect of affording the drugs their populations need at current commercial prices

When cash is no objective

At a time when even the NHS can't afford the latest drugs, is there any hope for the world's poor countries? Yes, there is – as Janis Smy finds out from an altruistic London-based doctor who is developing a treatment for hepatitis C

When satirist Tom Lehrer lampooned doctors who 'specialise in diseases of the rich', he clearly did not have Prof Sunil Shaunak in mind.

The London-based clinician and academic is powerfully motivated by the global burden of preventable and treatable disease, and is determined to find ways of providing medicines that the poorest people in the world can afford.

At a time when the NHS has to question the use of expensive treatments such as Herceptin and inhaled insulin, the benefits of altruistic research may also extend to those of us in the developed countries.

Prof Shaunak, consultant physician at Hammersmith and Chelsea and Westminster hospitals and professor of infectious diseases at Imperial College, has his sights fixed on hepatitis C, which infects more than 170 million people worldwide, causing a huge burden of chronic liver disease and premature death.

He stands prepared to challenge long-held principles of protein chemistry, to pit his wits against the pharmaceutical giants and to parley with governments.

Hepatitis C is optimally managed by a combination of the broad-spectrum antiviral ribavirin and a form of the immunomodulatory protein interferon-alpha, chemically modified to extend its half-life. The all-important modification involves attaching polyethylene glycol (PEG) polymers to the otherwise relatively small immune protein, making it large enough to withstand rapid metabolism and excretion.

The process, known as pegylation, has proven to be a money-spinner for the pharmaceutical giants, which command high prices for their treatments. Pharmacists at the Hammersmith report that a course of combined hepatitis C therapy for one patient costs about £7,000.

Now Prof Shaunak, in collaboration with Prof Steve Brocchini, a research chemist at the London School of Pharmacy, has developed a new method of pegylation which does not infringe existing patents. The resulting molecule, recently reported in *Nature*, appears to be as effective as the existing product.

Unlike their commercial rivals, however, the collaborators have no intention of growing rich from their discovery.

'People in academic medicine have a choice,' says Prof Shaunak. 'They can use their ideas and creativity to make large sums of money for small numbers of people, or they can look outwards to the global community and make affordable treatments for common diseases.'

The new combined treatment for hepatitis C, using the alternative pegylated interferon, enters fast-track clinical trials in India next year, funded by the Indian government.

Sir Michael Arthur, British High Commissioner to India, applauds the plan. 'The technology transfer agreement is a shining example of how exciting innovations in our best universities can be rapidly turned into new and useful healthcare products,' he says.

Shantha, a pharmaceutical company in Hyderabad, has been granted use of the technology in view of its record in manufacturing affordable healthcare products yet still making enough profit to stay in business. Its version of hepatitis B vaccine costs about US\$1.25 per course, compared with about \$125 charged by the multinationals. It is widely used by developing countries and has been adopted by the World Health Organization.

For Prof Shaunak, the development of the new pegylated interferon alpha molecule is the culmination of a career spent challenging accepted mores. And it's an ethos that began when he was only a junior.

He says: 'When I was a trainee, I was astonished to see how doctors sat in little boxes. The best research was being carried out in these territorial enclaves. I wanted to say outside of the boxes, and look at medicine beyond any individual organ-based system – hence my commitment to infectious diseases.'

His chosen field did not seem to offer the most promising career – infectious diseases were considered to be pretty much conquered. Then AIDS rocked the world, involving not just an initial organism, but also showing how large numbers of immunosuppressed patients could be hit simultaneously by multiple pathogens, opening up the concept of

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multi-drug therapy for infectious disease.

Prof Shaunak moved to the US to specialise in HIV. 'In the UK,' he says, 'HIV is mainly the province of genito-urinary doctors, but in America it is looked at by infectious disease specialists as part of internal medicine.'

The experience opened his eyes to the yawning healthcare divide between rich and poor – and stirred him to find ways to bridge it.

'HIV patients who couldn't pay got no medicines,' he says. 'So if one of our more affluent patients died, we asked the family to return unused HIV drugs, which we reissued to those who would otherwise have no treatment at all. It was breaking all the rules.'

But breaking the rules has become a stock in trade for Prof Shaunak. He cheerfully admits that the crucial step in the new pegylation process would never have been developed had he and Prof Brocchini understood and respected one of the central tenets of protein chemistry.

Previous forms of pegylation involved attaching numerous PEGs to the outside of the interferon, comparable to bubble-wrapping. Prof Shaunak and Prof Brocchini circumvented the existing patents by breaking a disulphide bond in the protein, creating a bridge and using that as an attachment point for PEG.

'Later,' he says, 'we learnt that the disulphide bonds should never be interfered with if you hope to retain biological function. Fortunately, we hadn't read the protein text books.'

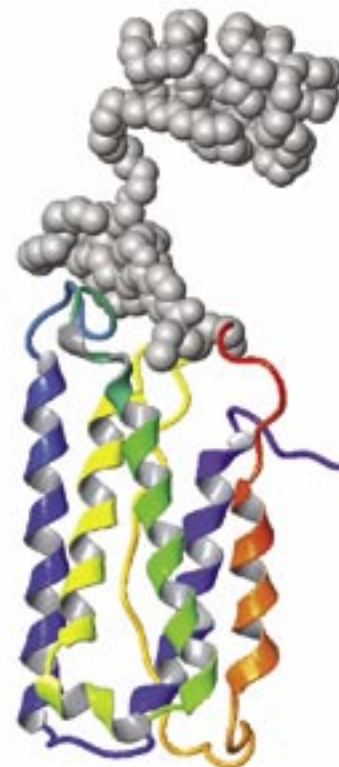
The collaborators are confident that disulphide bond-based pegylation can be used to make affordable versions of other therapeutically useful biological proteins.

Prof Shaunak believes the work will form part of the 'revolution' he believes is about to hit the research environment.

'The pharmaceutical industries haven't done anything to help a large proportion of people around the world,' he says. 'But we live in a global community. The idea that we can ignore what happens in the developing world no longer applies. People already realise that diseases such as bird flu and severe acute respiratory syndrome (SARS), which begin thousands of miles away, can have a big effect on us. We need global solutions to these global challenges.'

He concludes: 'The Make Poverty History campaign is an example of what people can do when they are determined. I hope young doctors now in training will see just how exciting work like this can be.' ■

Prof Shaunak's molecule is an alternatively pegylated interferon that crucially breaks a disulphide bond to create an attachment point for the PEG polymer



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