

The killer in our midst: fighting to end tuberculosis

Helen McShane and Helen Fletcher, of the Jenner Institute, Oxford, discuss their Wellcome Trust-funded work towards a new TB vaccine.

HM: TB remains a really major cause of both mortality and morbidity throughout the world: approximately nine million people develop TB every year throughout the world and approximately two million people die every year.

The original TB vaccine is called BCG and BCG is live attenuated *Mycobacterium bovis*. So this is a weakened form of the strain of microbacteria that infects cattle. This vaccine has been used for almost a hundred years; it was first developed in 1921 and it is widely used throughout the world, particularly in the developing world, where it's given at birth. When BCG is given at birth it is good at conferring protection against TB meningitis and systemic forms of TB, i.e. forms of TB outside of the lungs. But what BCG doesn't do is protect well against lung disease either in children or in adolescents or adults.

HF: One in four people in Europe used to die from TB, it was the 'white plague'. I became more interested in the human immunology side of it and wanting to do something to sort of actively help towards perhaps cure or reducing death and disease from TB.

HM: What we've been doing in Oxford over the last 12 years is developing a new vaccine that's designed to be given after BCG to enhance the protective efficacy of BCG. We have taken one of the most immunodominant antigens from BCG, called antigen 85A – that's the antigen that's contained in the new vaccine MVA 85A. So when you give BCG, you develop an immune response to all those antigens, and what we're doing with the new vaccine is focusing the immune response on one particular antigen which is very immunodominant and amplifying and we hope making better the immune response to that particular antigen.

The Wellcome Trust funded what was probably the most risky step, which was taking the vaccine from the laboratory models through into the very first clinical trials, and it was that funding and the success in those early trials that have really led to the expansion to the programme that we have today. One of the most exciting moments was when my postdoc first showed me the plate that we used to look at the immunogenicity one week after we vaccinated the first three subjects. And what he showed me was incredibly strong immune responses, which were five to ten times higher than the immune responses we were expecting to see in that first clinical trial.

South Africa has probably the highest rate of TB disease anywhere in the world, and that's not just HIV-related and it's not just poverty related, as clearly there are other areas of the world with equivalent levels of poverty and HIV infection but yet not equivalent levels of disease.

In the last three months what we've done is start a big phase IIb efficacy trial in South African infants. And what this trial will do is look at 3000 babies born in South Africa who will all receive BCG, and half of them will get the new vaccine and half of them will get a placebo control vaccine, and we will follow those babies up for two years and look at the rates of TB disease in both arms of the trial, in the vaccine arm and the placebo arm.

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HF: The most difficult thing I find about the work we do is not knowing whether this vaccine is actually going to protect or not and we try our hardest to predict whether the vaccine's going to protect and learn about the cell types that are induced by the vaccine but we're not going to know for another two to three years.

HM: We now have a collaboration with Aeras Global TB Foundation who will help us take forward the development of this vaccine and Emergent BioSolutions, with whom we've formed a joint venture, the Oxford–Emergent Tuberculosis Consortium. Those three agencies are all working together to really take forward this vaccine.

HF: We are the leading laboratory in the world in terms of TB vaccine development. I feel really proud that we have paved the way and we've pushed vaccine development forward.

HM: If this vaccine works to stop people getting TB then potentially this vaccine could have a huge impact both in terms of reducing deaths and reducing disease throughout the world from TB.

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