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A MODERN VACCINE TO TREAT CROHN'S DISEASE

Crohn's disease began in the developed economies of Western Europe and North America about the middle third of the 20th century. Thereafter with plateaus at intervals in some regions it has steadily increased in frequency. The latest information available from Europe shows the disease climbing at about 25% overall in the last 10 years. A similar rise has taken place in North America. The region worst hit is Nova Scotia where 1 in 300 people are now affected. Crohn's disease is spreading worldwide so that it is rising in countries which were formerly thought to be free of the disease. The results of epidemiological research from Stockholm and the Czech Republic as well as from Melbourne at the opposite end of the planet show that the reported increase in Crohn's disease in children in those areas over recent years has averaged about 5 fold per decade.

For an individual person with Crohn's disease the mainstay of treatment is suppression of the immune system with drugs like Prednisolone and azathioprine. Ordinary antibiotics can help. In people with acute flares the newer agent Infliximab usually brings about remission. These treatments work by suppressing the inflammation not by treating the cause of the Crohn's disease so that although the relief they may bring is welcome, relapse is almost inevitable. Research groups in the UK and the Netherlands analysing the world medical literature have found that there has been no statistically significant improvement in the major long-term outcomes in Crohn's disease, like drug dependency or the need for major surgery, over the last 35 years.

From the large picture as well as for individual Crohn's disease sufferers themselves and their families, the conventional strategy of focussing research and treatment almost exclusively on identifying and suppressing disease mechanisms rather than on disease causation is not winning against Crohn's disease, it is losing. A radical change in strategy directing treatment at the cause of the disease is essential. Our research over more than 15 years, which has recently been confirmed by other scientific researchers in Europe and North America, has placed this issue centre stage.

Reliable scientific evidence strongly suggests that most of Crohn's disease is being caused by a bug called MAP…short for *Mycobacterium avium* subspecies *paratuberculosis*. MAP is a proven cause of chronic inflammation of the intestine of different types affecting a wide range of animal species including primates. MAP infection is widespread in domestic livestock and there are wildlife reservoirs. MAP is being transmitted to people in milk supplies as well as from environmental sources such as contaminated waters. MAP is very difficult to detect in humans but when the tests are done correctly almost everybody with Crohn's disease is found to be infected. To put it another way….. almost everybody suffering from chronic inflammation of the intestine (of the Crohn's disease type) ….is infected with a scientifically well characterized multi-host pathogen which has the proven specific ability to cause chronic inflammation of the intestine.

From 1992 I developed anti-MAP treatment using a combination of the antibiotics rifabutin and clarithromycin to which MAP is partially sensitive. The lives of a substantial proportion of people struggling with serious Crohn's disease have been turned around by this treatment and many have been rescued from major surgery. But MAP infections are very difficult to eradicate and this treatment

does not always work. Not everyone responds, and relapses although often mild and containable, do occur. We need new anti-MAP treatments.

Conventional vaccines work by stimulating antibodies in the blood which bind to an incoming bug and prevent people getting sick…hepatitis or pneumonia for example. But conventional preventative vaccines could not get at the MAP bugs in Crohn's disease because the MAP bugs are already hiding inside cells. However, modern vaccines use DNA technologies to arm-up populations of hunter-killer immune 'T' cells. These patrol the body and kill MAP-infected cells together with the MAP they contain. Deleted cells are replaced with healthy ones. So modern vaccines can be used to treat chronic disease. There is already evidence that they may work in hepatitis and in TB which is also caused by a member of the mycobacterium family.

We began work on the anti-MAP vaccine in 2001. We knew that the disease-causing properties of MAP lay in only 5% of its DNA genome. So we used modern bioinformatics and computer programs to focus on this 5% and pick 4 key bits of the MAP bug. Two of these bits sit on the MAP surface and two are released from the bug, so all 4 are 'seen' by the immune system of someone with Crohn's disease.

MAP DNA speaks a slightly different 'language' to human DNA. So over 2002-2003 we synthesised our 4 MAP genes in human DNA-speak and strung them together in a single cassette. In 2003-2004 we inserted this MAP-cassette into 2 harmless carrier viruses called MVA and Ad5 already approved for clinical trial use in TB, malaria and in cancer vaccines. We showed that the MAP-cassette inserts in MVA and Ad5 were stable and worked nicely. Vaccination of mice with Ad5 to prime and MVA to boost produced huge numbers of anti-MAP hunter-killer cells. There were no side effects and all the mice remained quite healthy.

In 2004 - 2005 we tested the vaccination procedure in mice infected with a laboratory strain of MAP. Six months after infection with MAP, sham vaccinated mice had 100-10,000 MAP bugs per gram in their spleens. In the mice which got the real vaccine we could not detect the MAP bug at all in ¾ of them and the bugs were at the lowest limit of detection by a very sensitive DNA test in the others. Mice which had been vaccinated before exposure to MAP infection were also partially protected. Again, none of the mice showed side effects from the vaccine. We have since repeated these studies on two further occasions against a virulent recent disease isolate of MAP and the successful results have been consistently confirmed.

The modern anti-MAP vaccine we have produced is highly effective in treating MAP infection and offers protection against re-infection. Although further laboratory work is currently in progress we are now in a position to begin the rigorous application process for regulatory and ethical approvals for clinical trials in people. The first step is to get the vaccine made under contract according to Good Manufacturing Practice (GMP) and put through rigorous toxicity testing. The total cost of getting the vaccine into human clinical trials is about one million pounds.

We need your help….can you?

Please make cheques payable to "St George's University of London" with RLB0057 written on the back, and mailed direct to Prof. Hermon-Taylor (contact details above). All funds go only for the vaccine. Gift Aid Certificates available. St George's, University of London is a tax exempt charity number X64491.

All the scientific indicators so far say that the vaccine treatment will work. If this is borne out in the human clinical trials we shall at last have a totally new and potentially lasting treatment to offer people with Crohn's disease.