**Project title:** Development of a long acting dosage form of penicillin for the prevention of recurrent acute rheumatic fever rheumatic heart disease

**Project summary:**

ARF is a post infectious, immune mediated complication of infection with the bacteria Group A Streptococcus (GAS) that in turn leads to heart damage (RHD).[4] Recurrent GAS infection in patients with previous ARF leads to cumulative heart damage that causes most of the burden of RHD. Penicillin can prevent this recurrent infection and worsening of RHD, but current drug formulations are not appropriate for long term use. ARF and RHD occurs in developing settings where overcrowding, poor hygiene and lack of access to health care leads to frequent and severe GAS infection.[4] ARF occurs most commonly in children and young adults.[5] Consequently, RHD impacts on young adults in their most economically productive years, and through the associated morbidity and premature mortality, has a huge impact on society.[5] There is no cure for established RHD; costly, largely palliative, heart surgery is a last resort.[6] This project aims to prevent the suffering and unnecessary deaths caused by RHD by developing a novel penicillin formulation that will prevent recurrent GAS infection and ongoing heart damage in patients with ARF.

Penicillin is currently administered via monthly, painful intramuscular injections of benzathine penicillin G (BPG) for at least 10 years.[7] This is logistically difficult and expensive, especially in developing world settings. Further, even when regular BPG injections are delivered, the quality and global supply of BPG is sub-optimal.[8] Generic formulations have been associated with lower than expected serum concentrations of penicillin after administration, as well as practical concerns such as blocking in the administering needle.[9, 10] Hence most patients at risk of RHD do not receive adequate penicillin prophylaxis, and patients continue to suffer with, and die of, preventable heart disease.

This project will develop a method of penicillin administration that last for at least 6 months thereby providing a practical, affordable, pharmacologically stable and less painful method of treatment compared to monthly injection, allowing mainenance of adequate serum penicillin levels. For penicillin prophylaxis to be adequate, serum penicillin levels must be maintained above the minimum inhibitory concentration (MIC) of GAS. GAS is exquisitely sensitive to penicillin, and GAS resistance to penicillin has never been reported despite prolonged use in extremely large numbers of people. These features support the theoretical application of long acting, slow release formulations for the secondary prophylaxis of ARF. Our current work is focused on combining penicillin with existing slow release technologies that are being tested in rat models to determine which formulations provide the optimal release kinetics. This application relates to the ongoing clinical development of this technology, namely phase one and two safety studies and pharmacokinetic equivalence studies, followed by phase three efficacy studies. Following this, it is planned that the long acting penicillin formulation would be rolled out to those requiring secondary prophylaxis with phase four studies providing the ongoing surveillance for this technology. Ultimately, a long acting penicillin formulation would revolutionize management of RHD worldwide by vastly increasing the number of patients successfully treated, thereby preventing RHD and ultimately decreasing mortality from this disease.

*As taken from original proposal template, question 5.*
References:


