

A novel treatment for gonorrhoea in females

Background

Gonorrhoea is the second most commonly reported sexually transmitted infection (STI), affecting over 106 million people each year. Alarming increases in incidence over the past five years (80% in Australia and 67% in the US) has earned gonorrhoea status as an urgent public health threat by both the Center for Disease Control and Prevention (CDC) and the World Health Organisation (WHO). *Neisseria gonorrhoeae*, the bacterium responsible for gonorrhoea infection, is highly variable and exquisitely host-adapted. Its advanced treatment evasion strategies has seen resistance develop against every antibacterial ever used to treat it. The current recommended treatment is dual antimicrobial therapy with ceftriaxone and azithromycin; however, many strains are now resistant to this approach and 'untreatable gonorrhoea' has been reported in several countries. *Neisseria gonorrhoeae* infection does not induce immunity, which means reinfection is extremely common, particularly with behaviour change away from barrier protection with the advent of pre-exposure prophylactics for HIV. Additionally, despite significant investment and research, no vaccines have ever been developed.

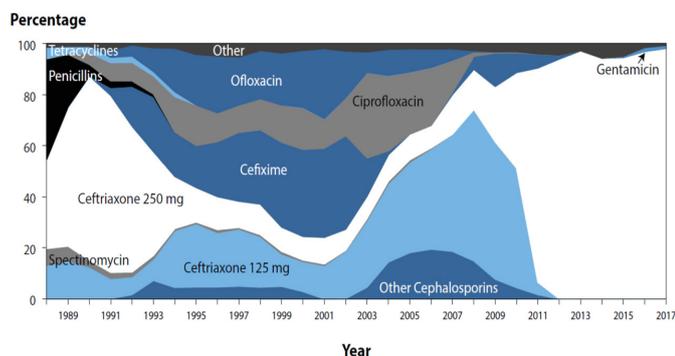
Gonorrhoea affects both men and women in their oral, anal and genital tracts and presents a serious threat to

human wellbeing and quality of life. Alarmingly, up to 80% of female gonococcal cervicitis is asymptomatic and when left untreated can lead to pelvic inflammatory disease (40% of infected women) that can result in severe long-term health implications such as infertility, adverse pregnancy outcomes and devastating neonatal complications. This significant pool of 'silent' infections, particularly when they exist among the sex worker community, are a major driver of recurrent infection in men and women. Additionally, gonorrhoea infection is known to increase the risk of acquiring and transmitting HIV, for both men and women, which is a significant public health risk in its own right.

With the increase of multi-drug resistant (MDR) gonorrhoea and lack of a successful vaccine strategy, there is a critical need for the development of new therapeutics to treat and prevent this intractable disease.

The technology

At the Institute for Glycomics and the Research Institute at Nationwide Children's Hospital, we have discovered that methyl dopa can cure and prevent gonorrhoea infection in women. *Neisseria gonorrhoeae* exclusively exploits complement receptor 3 (CR3), expressed on human cervical epithelial cells, for the colonisation of cervical



Distribution of primary antimicrobial drugs used to treat gonorrhoea among participants, Gonococcal Isolate Surveillance Project (GISP), 1988–2017. Source: Centres for Disease Control and Prevention.

At present, the standard of care treatment for gonorrhoea is a dual antimicrobial therapy (ceftriaxone plus azithromycin). However, many strains of *Neisseria gonorrhoeae* are now resistant to this treatment.

mucosa and continued survival in the host. Blocking the interaction of CR3 and *Neisseria gonorrhoeae* can treat existing infections and also prevent new infections. We have demonstrated in primary human cervical epithelial (Pex) cells, the gold standard pre-clinical model for gonococcal cervicitis in women, that a single administration of low dose methyldopa can treat MDR gonorrhoea within 24–48 hours, by binding with CR3. By acting on the human host, rather than the bacterium, this first-in-class therapeutic provides a unique mechanism of action for the treatment and prevention of gonorrhoea. Importantly, this also means that it is highly unlikely that *Neisseria gonorrhoeae* bacterium will develop resistance to methyldopa.

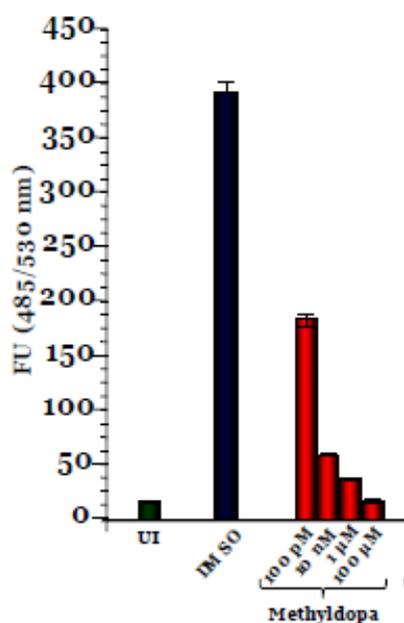
Methyldopa is an off-patent, prescription medication that has been used as a treatment for moderate hypertension in pregnant women for approximately 50 years. It is listed on the WHO List of Essential Medicines and has a well-established, long-term safety record. For this indication, it is typically prescribed as a daily administration of 2–3 grams, to be taken over two to four oral doses for months at a time. Our data suggest that administration of methyldopa for gonorrhoea, will require a much lower dosage, potentially administered over 2–3 days only. Additionally, methyldopa's oral tablet formulation is likely to result in improved patient compliance compared to currently available antibiotics for gonorrhoea, which are delivered via injection.

Gonorrhoea market

The global market for gonorrhoea therapeutics is predicted to reach US\$5.6 billion per annum by 2021. Market growth is strong (CAGR of 2.88%) and could increase rapidly as MDR strains become more widespread. Currently, 97% of countries have reported incidences of gonorrhoea resistance to standard treatment options. Despite significant efforts over the last two decades, development of a vaccine for gonorrhoea has not been successful. Consequently, the market for gonorrhoea therapeutics and prophylactics remains strong, particularly where they can treat MDR strains. Methyldopa may initially enter the market as a high-value product for use as a last line of defence against treatment failures. As resistance to traditional antibiotics grows, and the use of methyldopa as an antibiotic becomes more accepted, it is expected that methyldopa will rapidly secure a significant share of the gonorrhoea therapeutic market as a frontline therapeutic and prophylactic. Uniquely however, methyldopa has an opportunity to hold its market share, by avoiding resistance through its unique mechanism of action.

Competing technologies

Currently, only three new drug candidates are in clinical development for treatment of gonorrhoea: solithromycin (Phase III completed), zoliflodacin (Phase II completed), and gepotidacin (Phase II completed). All of these new treatments target the bacterium. Understanding that *Neisseria gonorrhoeae* bacterium are highly adaptable against antibiotics through rapid mutation and acquisition of foreign DNA, it is likely that resistance to these new technologies will eventuate soon after deployment. Effective, long term treatment for gonorrhoea, globally, will require a diverse drug war chest, comprising drugs that exploit a variety of disease mechanisms. Additionally, a focus on treatments for MDR gonorrhoea will be critical. Methyldopa is unique in this market in its ability to defend human cervical cells against *Neisseria gonorrhoeae* without modifying the bacterium. This positions it as a strong candidate to dominate the gonorrhoea treatment and prophylactic markets.



Fluorometric adherence assay showing effect of methyldopa on *N. gonorrhoeae* strain MS11 adherence to Pex cells. Arbitrary fluorescence units (FU), indicative of bacterial adherence, were recorded at 1 h post-challenge of Pex cells with the green fluorescent protein (GFP)-expressing *N. gonorrhoeae* strain, MS11gfp. A significant dose-dependent decrease in gonococcal adherence to Pex cells was observed in the presence of increasing concentrations of methyldopa.

Opportunities and advantages

Significant advantages can accrue from successful repurposing of an approved therapeutic, particularly where strong mechanisms for differentiation from the original product exist. Methyldopa is an excellent candidate for repurposing and provides the following opportunities:

Differentiated packaging

Reduced dosage and treatment duration for gonorrhoea compared to hypertension allow for new short course packaging.

Differentiated delivery

Methyldopa is currently delivered as an oral tablet. While this would also be effective for the treatment of gonorrhoea, it's likely that product differentiation could be further achieved by reformulating the product as a pessary, topical cream or coated condom.

Limited availability

Currently, methyldopa is not widely prescribed. Despite being the frontline treatment for hypertension in pregnancy due to its safety profile, more efficacious treatments have overtaken its use for hypertension in a non-pregnant population. Many previous manufacturers and marketers of methyldopa have ceased production due to the small market and the drug is in short supply. Given the size of the gonorrhoea market, methyldopa's use for gonorrhoea is likely to rapidly overtake its use as an anti-hypertensive. The ability to freely market this new indication will drive uptake and exclusivity. Additionally, the limited number of manufacturers may allow exclusive supply agreements to be implemented.

Low manufacturing costs

As a long-standing generic, methyldopa manufacturing has been well refined and costs of production are low. This allows for a strong profit margin to be established, particularly where manufacturing and supply chains are already in place.

IP Protection

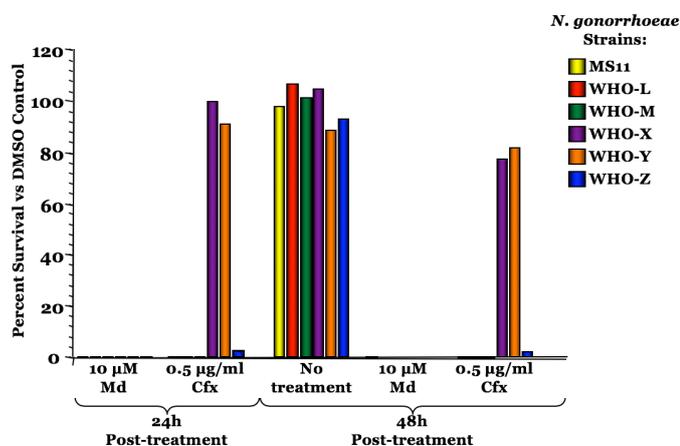
We hold strong IP protection around the use of methyldopa as a treatment and prophylactic for gonorrhoea infection.

Truncated regulatory approval pathway

A considerable body of toxicology, clinical and manufacturing data exists on methyldopa that can be used in submission of a new approval for gonorrhoea under the US FDA's 505(b)(2) regulatory pathway. Similarly, proof of concept activities can readily occur through the Australian TGA's Special Access Scheme. Repurposing significantly reduces the time and cost required to take the drug to market.

Lead candidate for new chemical entity

The new mechanism of action displayed by methyldopa in preventing and treating gonorrhoea provides an exciting opportunity for this drug to be used as a template for a lead optimisation program to develop a separately patentable, new chemical entity for approval under the standard FDA 505(b)(1) regulatory pathway.



The effect of a 48h, single dose, treatment with methylodopa (Md; 10µM) or ceftriaxone (Cfx; 0.5 µg/ml) on multidrug-resistant *N. gonorrhoeae* infection of primary human cervical epithelial cells. Methylodopa had the same effect on all strains tested (n=12); and greater than 99% of gonococcal killing occurred within 24h. None – untreated; WHO – World Health Organization.

Intellectual property

Griffith University and The Research Institute at Nationwide Children’s Hospital have filed a provisional patent application in the United States on the use of ligands to inhibit the interaction of pathogens with CR3-expressing cells, and for treating or preventing the development of infections caused by such pathogens. CR3 is a novel target for methylodopa. The patent specifically exemplifies the use of methylodopa, among other repurposed drugs, for the treatment of gonorrhoea and HIV.

Title: “Agents and methods for modulating pathogen activity”, 62/739025.

Opportunity for partnership

We are now seeking a partner to license this technology. The preferred partner would have the ability to progress this technology through to regulatory approval for this new indication and have manufacture and market access capability and expertise. The proposed licence would take a typical fee and royalty-bearing structure. The research team is accessible for consulting as the technology is progressed through preclinical and clinical development activities.

RESEARCH LEADER

Professor Michael Jennings is Deputy Director and an NHMRC Principal Research Fellow and Research Leader at the Institute for Glycomics. He is a world leading authority on the molecular basis of bacterial infectious diseases, including *Neisseria meningitidis* (meningitis) and *Neisseria gonorrhoeae* (gonorrhoea). Prof. Jennings coordinates the multi-disciplinary team of collaborators who discovered this novel use of Carbamazepine, including; Dr Jennifer Edwards (Research Institute at Nationwide Children’s Hospital) who is a world leader on *ex vivo* model systems for *Neisseria gonorrhoeae*, and Dr Christopher Day (Institute for Glycomics), who is an expert in biophysical analysis and co-developer of novel approaches for drug screening.

ABOUT US

The Institute for Glycomics is a flagship biomedical research institute at Griffith University in Queensland, Australia. The Institute is one of only six of its kind worldwide and has a strategic focus on translating drug and vaccine discovery research in cancer and infectious disease into clinical outcomes. **The Research Institute at Nationwide Children’s Hospital** comprises three research facilities with 12, highly collaborative, theme-oriented Centers of Emphasis that span the spectrum of research important to pediatric health. It is intimately associated with NCH and The Ohio State University (OSU) in Columbus, Ohio. TRI-NCH is consistently ranked as one of the top ten NIH-funded freestanding pediatric research centers in the United States. It is also one of the fastest growing pediatric research institutes in the United States. Both institutions have a strong track record in commercialisation and industry engagement, and our research leaders and business personnel have extensive experience in developing technologies for the commercial market. With a combined total of over 415 multidisciplinary researchers and support staff, the Institute for Glycomics and TRI-NCH are well positioned to deliver tangible clinical solutions for infectious diseases.

CONTACT

Eloise Keefe - Business Manager

E.e.keefe@griffith.edu.au P +61 7 5552 9283