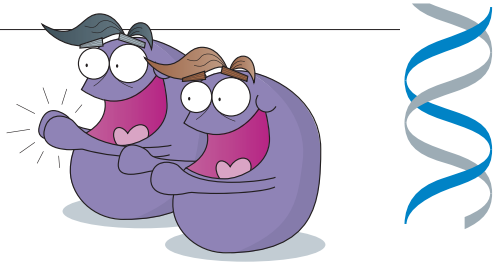
GENOME WATCH

A 'clap' for *in silico* studies



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This month, Genome Watch discusses the importance of *in silico* studies for the investigation of *Treponema pallidum* and *Neisseria gonorrhoeae*, two sexually transmitted pathogens for which few genetic tools are available.

The sexually transmitted diseases gonorrhoea and syphilis are difficult to study owing to our inability to grow and maintain the causative agents, *Neisseria gonorrhoeae* and *Treponema pallidum*, respectively. This led to several experiments that are today considered to be "outrageous and abhorrent" (REF. 1). In one such study in the 1940s, medical researchers from the US health service infected hundreds of prisoners, soldiers and mental patients in Guatemala with syphilis and gonorrhoea without the subjects' permission; this study came to light only recently and drew an official apology from the US government. These experiments were intended to further our understanding of the mechanisms of disease transmission and the effects of penicillin treatment on the disease.

Currently, syphilis and gonorrhoea are abundant in several parts of the world. There have been marked advances in our knowledge of the microbiology and molecular biology of the two causative organisms since the days of the study in Guatemala, but the *in vitro* manipulation of these pathogens remains limited. However, information from the genome sequences of *T. pallidum* subsp. *pallidum* str. Nichols[2] and *N. gonorrhoeae* str. FA 1090 can help overcome the growth and isolation problems and provide a foundation for further studies.

The recent emergence of antibiotic-resistant strains of these pathogens has focused syphilis and gonorrhoea research on the identification of drug targets and vaccine candidates. For example, a computational study used different databases and bioinformatics tools to find essential *N. gonorrhoeae* genes and proteins with no similarity to human sequences, identifying six potential drug targets and three vaccine targets based on their metabolic-pathway distribution, cellular localization and role in virulence[3]. The drug targets include fructose-1,6-bisphosphate aldolase (which plays a part in metabolic pathways such as glycolysis, the pentose phosphate pathway, and the fructose and mannose pathways), the putative two-component system transcriptional response regulator PtsN (which is unique to *N. gonorrhoeae*), tryptophan synthase α-chain, indole-3-glycerol phosphate synthase and anthranilate phosphoribosyltransferase. Vaccine targets identified in the study include the assembly protein, PilF, and putative pilin protein, PilV, of the type IV pilus, which is associated with bacterial adhesion, aggregation, invasion, host cell signalling, surface motility and natural transformation. Proteins that had previously been tested as vaccine targets are PorB, outer-membrane phospholipase A, transferrin-binding protein A (TbpA) and TbpB; T cell-stimulating protein A (TspA) and TspB of *Neisseria meningitidis* have been patented as vaccine candidates.

Similarly, a comparative genomic analysis revealed important differences between the Lys-tRNA synthetases of *T. pallidum* and other spirochetes (which belong to class I) and the Lys-tRNA synthetases of their eukaryotic hosts (which belong to class II)[4]. As no protein structure was available for this protein, an *in silico* structural model was generated and proposed by the authors as an interesting template for specific drug design[5]. However, further computational docking and high-throughput screening experiments will be required in order to extract more useful information.

The drug-resistant strain *T. pallidum* subsp. *pallidum* str. Chicago was recently sequenced[6] using short-read Illumina technology. This strain was first isolated in 1951 and has been passaged through animals fewer times than the Nichols strain, which was isolated in 1912; long-term passage can affect antigenic variation, immune escape and persistence of the pathogen. Compared with the Nichols strain, the Chicago strain has 44 single-nucleotide substitutions, 21 deletions (a total of 30 nucleotides), and 75 insertions (a total of 1,303 nucleotides). The sequence and annotation of the Chicago strain genome should facilitate and encourage the use of this strain for addressing questions concerning the pathogenesis of syphilis.

The information gained from a genome sequence will also simplify the protocols of drug trials, as it allows the initial trials to be done *in silico*, with less risk for patients. Most *in silico* analyses require experimental validation, but they are still an advance for the identification of potential drug and vaccine targets in syphilis and gonorrhoea research.

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Competing interests statement
The author declares no competing financial interests.