METHOD FOR IDENTIFICATION OF SOFOSBUVIR RESISTANT PATIENTS

Identification of patients with Genotype 3 chronic HCV infection with a reduced likelihood of response to sofosbuvir-based therapies

Key benefits
- Identification of patients with Genotype 3 chronic HCV infection with a reduced likelihood of response to sofosbuvir-based therapies
- Test may be performed on a biological sample from the subject such as blood, plasma, biopsy or cell sample
- A knowledge of viral variants may influence treatment choice and be of particular importance in patients who have failed therapy

Background
Chronic HCV infection is common affecting nearly 100 million people worldwide. The nucleotide sofosbuvir (sold under the brand name Sovaldi among others) is the backbone of many therapies but patients with genotype 3 (40% of HCV infections) respond slightly less well, leading to European guidelines advocating augmented therapy for such patients.

Sofosbuvir is an inhibitor of the hepatitis C virus polymerase and is the main therapeutic drug for the treatment of genotype 3 HCV. It is usually combined with another drug, typically an NS5A inhibitor such as daclatasvir or velpatasvir and around 90% of patients are cured.

The Problem
However, some patients do not respond to sofosbuvir-based therapies and it is not clear whether re-treating such patients with extended duration of therapy will be beneficial or not. New, sofosbuvir-free, antiviral therapies are available and a test that would identify which patients were unlikely to respond to sofosbuvir would be of huge clinical value.

For patients (with genotype 3 HCV) who have not responded to sofosbuvir (many tens of thousands per year) testing prior to re-treatment is likely to be recommended given that therapy is around US$40,000-US$50,000. A pre-treatment test costing US$1000 that avoided futile therapy would be financially very attractive and be highly cost-effective.

The invention
We have identified novel polymorphisms within the HCV Polymerase protein, HCV NS5b) which reduces the response to sofosbuvir based therapies. Identification of viruses containing these polymorphisms may allow more effective stratification of treatment.

Project Development and Results
In the BOSON clinical trial of sofosbuvir and ribavirin with or without pegylated interferon (Foster GR et al., Gastroenterology 2015;149:1462-70), patients with cirrhosis who had one of the identified mutations - the A150V variant - had a reduced response to therapy (71% achieved an SVR) compared to patients who did not have this variant (88%).
Patients with HCV Genotype 3 from the English early access programme who did not respond to sofosbuvir based antiviral therapies were phenotyped using the QMUL ‘capture-fusion’ assay. A group of patients who did not respond to therapy had a reduced response to sofosbuvir in this assay and sequencing showed the majority of such patients had a polymorphism at positions 150 and 206 in the polymerase protein. These mutations were introduced into viral replication systems and the changes in sofosbuvir sensitivity are shown below.

There was a marked reduction in the efficacy of sofosbuvir in replicons containing the listed mutations and combinations of mutations had a marked impact on response.

These data indicate that a knowledge of the presence of these viral variants may influence treatment choice and this may be of particular importance in patients who have previously failed therapy with current drug regimens.

A patent has been filed to protect the test referenced in the header.

**Link to inventor website:**

[https://www.qmul.ac.uk/blizard/all-staff/profiles/graham-foster.html](https://www.qmul.ac.uk/blizard/all-staff/profiles/graham-foster.html)

**We are seeking either licensing partners or companies developing Hep C drugs who require to assay patient for precision medicine therapy**