PROCORE - FRANCE/HONG KONG JOINT RESEARCH SCHEME
COMPLETION REPORT

Project Reference Number

F-HK17/10T

Project Title

Non-invasive diagnosis of liver fibrosis and cirrhosis in patients with nonalcoholic fatty liver disease with transient elastography (Fibroscan) and serum biomarkers

Particulars

	Hong Kong team	French team
Name of Project Co-ordinator (with title)	English: Dr Vincent Wai-Sun Wong Chinese: 黃煒燊醫生	Professor Victor de Lédinghen
Name of Co-Investigator (if any)	English: Henry Lik-Yuen Chan Chinese: 陳力元 English: Angel Mei-Ling Chim Chinese: 詹美玲	Julien Vergniol
Institution or Institutional affiliation	[ ] CityU [ ] HKU [✓] CUHK [ ] HKUST [ ] HKBU [ ] LU [ ] HKIEd [ ] PolyU	[ ] CEA [ ] INRA [ ] CNRS No. [ ] INRIA [ ] INFREMER [ ] INSERM No. [✓] University of Bordeaux [ ] Others:
Other project team members (if any)	N/A	N/A

Funding Period

	1st year	2nd year (if applicable)
Start Date	January 2011	N/A
Completion Date	December 2011	N/A

Objective(s) as per original application

1. To assess the accuracy of FibroTest, FibroMeter and the ELF panel to diagnose advanced liver fibrosis and cirrhosis in patients with NAFLD
2. To develop an algorithm combining liver stiffness measurement by transient elastography and serum biomarkers (FibroTest, FibroMeter and/or the ELF panel) to improve the accuracy to diagnose advanced liver fibrosis and cirrhosis in patients with NAFLD

i) Outline of proposed research and results obtained

In 2010, this collaborative group published a landmark paper on the use of transient elastography (Fibroscan) in patients with nonalcoholic fatty liver disease (NAFLD) (*Hepatology* 2010;51:454-62). The test is accurate and reproducible in detecting advanced liver fibrosis and cirrhosis. However, measurements often fail in obese patients because ultrasound wave cannot be transmitted to the liver parenchyma. With this background and the support of the PROCORE Scheme, the collaborative group set out to solve this unmet need.

First, we tested the use of the new Fibroscan XL probe for liver stiffness measurement. XL probe uses low frequency ultrasound to gain access to deeper liver tissue. Thus, the liver parenchyma of obese patients can also be assessed. We demonstrated that valid measurements could be obtained by XL probe in 94% of patients with body mass index over 30 kg/m^2, compared to 74% when the original M probe was used. Among patients with valid measurements by both the M probe and XL probe, we showed that both probes had similar overall accuracy in diagnosing advanced liver fibrosis and cirrhosis, using liver histology as the gold standard.

Furthermore, we have also completed XL probe measurements and paired liver biopsies in 193 NAFLD patients. Valid measurements were obtained in 95% of cases. We determined optimal cutoff values to diagnose advanced fibrosis and cirrhosis in this group of patients. The manuscript is currently under review.

Apart from that, we have tested a number of serum biomarkers. Among them, cytokeratin-18 fragments and fibroblast growth factor-21 had the highest accuracy in identifying patients with nonalcoholic steatohepatitis, the active form of NAFLD. The areas under receiver-operating characteristics curves of cytokeratin-18 fragments and fibroblast growth factor-21 were 0.91 and 0.84 for the diagnosis of NAFLD, and 0.70 and 0.62 for the diagnosis of nonalcoholic steatohepatitis, respectively. Work on the combined use of transient elastography and serum biomarkers is under way.

ii) Significance of research results

Traditionally, liver biopsy is required for determining the severity of liver diseases. However, liver biopsy is invasive, labor intensive and not welcomed by patients. Our new work on transient elastography and serum biomarkers provides important data on the non-invasive diagnosis of advanced fibrosis and cirrhosis in patients with chronic liver disease. This can effectively identify patients at risk of developing liver-related complications. As a result, timely monitoring and treatment can be provided. Based on our estimation, 30-60% of liver biopsies may be avoided when these non-invasive tests are used in clinical practice.

iii) Research output

Full papers (Please see attachments):

1. **de Lédinghen V**, **Wong VW**, **Vergniol J**, Wong GL, Foucher J, Chu SH, Le Bail B, Choi PC, Chermak F, Yiu KK, Merrouche W, Chan HL. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan®. J Hepatol 2012;56:833-9. (Impact factor 9.33)
2. Shen J, Chan HL, Wong GL, Choi PC, Chan AW, Chan HY, **Chim AM**, Yeung DK, Chan FK, Woo J, Yu J, Chu WC, **Wong VW**. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. J Hepatol 2012;56:1363-70. (Impact factor 9.33)

Conference abstracts:

1. Shen J, Chan HL, Wong GL, Choi PC, Chan AW, **Chim AM**, Yu J, **Wong VW**. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. Oral presentation at Digestive Disease Week, San Diego, USA on 22 May 2012.

(Although the biomarker work was performed only in the Hong Kong cohort and was supported mainly by the General Research Fund (project 477710), the French group provided important ideas and comments during the meetings supported by the PROCORE Scheme.)

iv) Potential for or impact on further research collaboration

With the support of the PROCORE Scheme, the French and Hong Kong groups have established strong collaboration. We have planned a number of new projects that will have major impact on clinical practice and the medical literature.

1. We have established a network of 6 major centers in Fibroscan research. Based on combined data, we will derive algorithms for the interpretation of Fibroscan results for individual liver diseases.

2. Both the French and Hong Kong groups have installed the state-of-the-art Fibroscan machine with controlled attenuation parameter for the estimation of hepatic steatosis. We hypothesized that accurate diagnosis of nonalcoholic steatohepatitis is possible by combining liver stiffness measurement and controlled attenuation parameter. Analysis will be performed based on our NAFLD cohorts.

3. Fibroscan measurements have been shown to predict the risk of liver cancer in patients with viral hepatitis. Its predictive role in NAFLD has not been established. Since both groups have been following large and well-characterized NAFLD cohorts over the years, we are at a unique position in determining the utility of various non-invasive tests of liver disease in prognostication.