

SUMMARY REPORT OF THE IDRN RESEARCH STRATEGY WORKSHOP IN HEPATITIS

Summary Report of the Infectious Disease Research Network's Research Strategy Workshop in **HBV, HCV and HCV/HIV co-infection** conducted October 14, 2002 at the Royal College of Pathologists, 2 Carlton House Terrace, London, SW1Y 5AF

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Pre-amble

1. The Infectious Disease Research Network (IDRN), continuing its series of research strategy workshops in infectious diseases, invited members of the research community with an interest in hepatitis research to an all-day workshop.
2. Dr. Philip Mortimer (Director, Virus Reference Laboratory, Public Health Laboratory Service, Colindale) and Prof. Howard Thomas (Professor of Medicine, Imperial College of Science, Technology and Medicine) co-chaired the meeting.
3. The aims of the meeting were to define pan-London collaborative research projects in the field and to take the first steps in establishing project development groups that would meet to design protocols and plan the project.

Attendees

Name	Institution	Department
Alsowmely, Dr. A	UCL	Research Student
Atkins, Dr. Mark	St. Mary's & Chelsea & Westminster	
Babiker, Professor Abdel	MRC	HIV & Infections
Banatvala, Professor Janga	GKT	Emeritus Professor
Bartlett, Professor Chris	UCL	GUM
Bertoletti, Dr. Antonio	UCL	Hepatology
Brown, Miss Alison	CDSC	HIV
Cubitt, Dr. David	GOSH	
Darbyshire, Professor Janet	MRC	Director
Dunn, Dr. David	MRC	HIV & Infections
Dusheiko, Professor Geoffrey	UCL	Medicine
Evans, Dr. Barry	CDSC	HIV & STI Division
Forton, Dr. Daniel	ICSM	Affiliated Member
Foster, Dr. Graham	ICSM	Hepatology
Gibb, Dr. Diana	MRC	HIV & Division of Infections
Gilson, Dr. Richard	UCL	GUM
Goldin, Dr. Robert	ICSM	Histopath
Hall, Professor Andrew	LSHTM	Infections & Tropical Diseases
Harris, Dr. Helen	PHLS	Immunisation Division
Hayward, Dr. Andrew	UCL	PCPS
Hughes, Mr. Nigel	British Liver Trust	
Ijaz, Dr. S	PHLS	
Jacobs, Professor Michael	UCL	Hepatology
Johnson, Professor Anne	UCL	PCPS
Judd, Miss. Ali	ICSM	Social Science & Medicine
Karayianis, Dr. Peter	ICSM	Medicine
King, Dr. Vicki	DoH	Blood Borne Viruses

Lee, Professor Christine	RFH	Haematology
Machell, Ms. Tania	Hep. C Resource Centre	
Main, Dr. Janice	ICSM	Genitourinary Medicine
Mangtani, Dr. Punam	LSHTM	Infections & Tropical Diseases
Mieli-Vergani, Professor Giorgina	KCL	Institute of Liver Studies
Mohsen, Dr. Abdul Hadi	KCL	HIV/GU Medicine
Mortimer, Dr. Phillip	PHLS	Hepatitis & Special Projects Unit
Naoumov, Dr. Nikolai	UCL	Hepatology
Newell, Professor Marie-Louise	ICH	Paediatric Epidemiology & Biostatistics
Norris, Dr. Suzanne	KCL	Hepatology
Qirbi, Mr. Naseeb	LSHTM	Infections & Tropical Diseases
Ramsay, Dr. Mary	PHLS	Immunisation Division
Steel, Miss Katherine	IDRN	Network Development
Teo, Dr. Chong Gee	CPHL	Hepatitis & Special Projects Unit
Thomas, Professor Howard	ICSM	Medicine
Thursz, Dr. Mark	ICSM	Faculty of Medicine
Tong, Dr. William	GSTT	Infection
Williams. Professor Roger	UCL	Hepatology
Yee, Mr. Leland	LSHTM	Infections & Tropical Diseases
Zuckerman, Dr. Jane	RFH	Travel Medicine

Programme

9:00 Introduction

Aims of the workshop and deliverables

09:15 Session 1 - HBV

HBV vaccines

Dr. Jane Zuckerman

Treatment of chronic hepatitis B

Dr. Nikolai Naoumov

Acute and chronic hepatitis B in London: viral and host heterogeneities

Dr. Chong Gee Teo

10:45 Coffee

11:00 Session 2 - HCV

Epidemiology/natural history of HCV including genetic/viral prediction of progression and response to treatment

Dr. Mark Thursz,

CNS manifestations of HCV

Dr. Dann Forton

Treatment of chronic HCV

Dr. Graham R. Foster

12:30 Session 3 - HCV/HIV co-infection

HCV/HIV co-infection in haemophilia

Prof. Christine Lee

13:00 Luncheon

14:00 Parallel plenary sessions (I) and conveners

Molecular epidemiology of HBV – Dr. Mark Atkins
Treatment of chronic hepatitis B - Prof. Geoff Dusheiko
Treatment of HCV - Prof. Janet Darbyshire
Prevention of HCV – Dr. Richard Gilson

15:30 Afternoon tea

16:00 Parallel plenary sessions (II) and conveners

Vaccines for HBV – Prof. Jangu Banatvala
HCV/HIV co-infection - Dr. Janice Main
Epidemiology/natural history of HCV - Prof. Roger Williams
CNS manifestations of HCV - Dr. Dann Forton

17:30 Round-up

Rapporteur feedback from plenary sessions
Debate on possible projects
Selection of a two projects for fast-track development
Formation of initial subgroups for protocol development
Network support offered to selected projects

18:30 Close of meeting

Research targets identified by speakers

HBV vaccines

Dr. Jane Zuckerman identified a large number of research targets for HBV vaccine studies or areas where improvements could be made:

- Infant and adolescent immunization
- Colleague's comprehension of HBV serology
- Failure to complete the therapy of neonates
- The importance of the recognition of high risk groups by colleagues and of how such groups should be immunized, including the consideration of compliance of patients
- Defining non-response in terms of serology can be problematic
- How non-response can be overcome
- Debate over correlates of protection, e.g. antibody titre levels
- Estimating the prevalence and incidence of non-response
- Adjuvants to existing vaccines could be studied in non-responder populations
- Different schedules could be studied to identify those that produce similar efficacy in terms of protection but which are associated with better compliance (e.g. a primary course over three weeks, rather than a longer course)
- High risk groups should be targeted, e.g. those that change sexual partners frequently, travelers, expatriates, missionaries, immigrants, drug-users and health care workers

- Evidence to support a policy of universal vaccination for HBV
- What constitutes adequate explanation to parents?
- Study of the sustained efficacy of vaccines, e.g. measuring cellular response in studies over longer periods, as opposed to using antibody correlates of protection in short studies as conducted by pharma
- Studies of the priming of the cellular response and the duration of memory

Treatment of chronic hepatitis B

Dr. Nikolai Naoumov emphasized the following research targets for collaborative focus:

- How to combine antivirals and immunostimulants appropriately in different population groups in London so as to improve treatment response. Cost, toxicity and drug interactions could also be considered. Dr. Naoumov and Dr. Bertolotti (Institute of Hepatology) would be pleased to lead such a project
- Defining treatments specific to a patient based on their aminotransferase levels
- Examining whether various combination therapies produce a better sustained response in terms of clearance (and not only a better initial response) than monotherapy
- Investigation into the effect of timing of different treatment components on treatment response

Acute and chronic hepatitis B in London: viral and host heterogeneity

Dr. Chong Gee Teo highlighted that:

- The prevalence of acute hepatitis B is ~600 cases per year. Approximately one third of acute hepatitis B in South-East England is due to HBV PV, a prisoner variant of HBV of genotype D. This variant, occurring originally in prisoners in North-West England and Yorkshire, is now also found in London.
- The incidence of chronic hepatitis B is more than 6000 cases per year and that these cases are predominantly in immigrants. There is a high density of ethnic minorities in London, with up to 50% of immigrants living in the capital.
- Approximately 5% of HIV patients are HBV co-infected and that these co-infected patients constitute a highly infectious reservoir of HBV. This group also causes difficulties for detection, as mutant variants occur that are not detected by commercial kits.
- Intravenous drug users share needles in London
- Healthcare worker-associated hepatitis B is significant
- There is diversity in variants, in transmission rates, in response to vaccination and response to treatment

Comments to this session included that:

- As no data were available on transmission from patients to health-care workers, if health-care workers were to be tested (in order to be able to continue practicing), should not patients also be tested?
- If awareness amongst high-risk groups is raised about hepatitis B, should not walk-in clinics be set up to enable such groups to be tested?

Prediction of progression and treatment response in HCV

Dr. Mark Thursz discussed the evidence for linearity of the rate of development of fibrosis over time and factors affecting the rate of progression to cirrhosis, e.g. those infected at a younger age showed a slower rate of progression. Dr. Thursz exposed the following research needs and recommended the use of Bayesian statistics in the development of models:

- Model (multivariate) to predict a patient's expected fibrosis rate, to be able to inform treatment choices
- Model to predict the response to treatment

CNS manifestations of HCV

Dr. Daniel Forton described NMR-diagnosed raised choline levels specific to hepatitis C patients (as opposed to those with hepatitis B or controls) and that such spikes are similar to those seen in HIV patients. Responders to treatment have reduced choline level whereas in non-responders raised levels remain.

Due to the difficulties associated with examination of the post-mortem brain and the potential for artifactual findings therefrom it was recommended to look at quasispecies. Data exists suggestive of there being a distinct CNS infection, with IRES mutants gaining entry to the CNS. Such entry may be significant in terms of persistence and response to treatment, due to the CNS providing a sanctuary.

The following foci were suggested for collaborative effort:

- Cognitive and MRS studies in patients with mild hepatitis C pre- and post-treatment
- Collecting data from post-mortem brain material

Treatment of hepatitis C

Dr. Graham Foster discussed the current optimum treatment recommendation of pegylated interferon plus ribavirin, identified gaps in treatment knowledge and, based on these gaps, argued that:

- Patient selection based on the current NICE guidelines may not be relevant for *pegylated* interferon, as the guidelines were written based on treatment with interferon plus ribavirin.
- Currently unstudied groups (those excluded from pharma drug trials) – children, those with acute hepatitis C, active intravenous drug users and patients with renal deficiencies – should be the focus for the IDRN.
- Most importantly, the treatment of patients with advanced cirrhosis should be investigated with a view to giving recommendations as to how best to treat these patients
- Different treatments and treatment durations should be investigated in hepatitis C of genotypes 2 and 3
- Alternative treatments could be examined that are cheap, potentially beneficial and unlikely to be investigated by pharma, i.e. amantadine and NSAIDs.

HCV/HIV co-infection in haemophilia

Prof. Christine Lee described the routes of co-infection due to blood products, indicating that most was due to blood products containing factor VIII concentrate. Although some co-infected patients clear HCV naturally, Prof. Lee emphasized the severity of co-infection with a greater increase between the 1970s and 1990s in hepatitis C viral load compared to the increase in mono-infected patients and with the higher death rate and liver-related death rate.

The focus for research should involve cohort studies and require:

- The development of databases

Research Strategy Workshops

Collaborative projects were proposed in the following fields. For further details of projects please contact the IDRN Co-ordinating Centre:

HCV/HIV co-infection and the epidemiology/natural history of HCV

Chaired by: Prof. Roger Williams

Risk factors in acute HCV/HIV, treatment response in chronic HCV/HIV and the natural history of hepatitis C.

Prevention of HBV/vaccines for HBV

Chaired by: Prof. Jangu Banatvala & Dr. Philip Mortimer

Prophylaxis during pregnancy in HBV carrier mothers, providing evidence to underpin when healthcare workers treated to suppress HBV and HCV carriage could resume work, understanding non-response to HBV vaccines, accelerated HBV immunisation of infants of carrier mothers, evaluation of multivalent HBV vaccines in paediatrics and expansion of an existing feasibility study of administering HBV vaccine to schoolchildren/adolescents to provide evidence to support universal vaccination.

Treatment of hepatitis B and C

Chaired by: Prof. Janet Darbyshire, Prof. Geoff Dusheiko & Prof. Howard Thomas

Examination of the appropriate duration of therapy for different patient types of a LAM + ADEF treatment regime, European study evaluating delayed pegylated interferon treatment in acute HCV, risk/benefit analysis of pegylated interferon plus ribavirin vs. placebo in patients with cirrhosis, trial of treatment regimes in paediatrics, community study of different regimen to assess practical outcome in intravenous drug users, creation of clinical trial infrastructure, trial of priming regimen in children with chronic HBV infection.

Taking forward projects

Participants

In the follow-up to the meeting, participants expressed their interest in contributing to the development of particular projects and were put in touch with one another.

Projects prioritized by delegates for IDRN support

Post-workshop delegates recorded scores, based on three criteria, to select a few projects that the IDRN should support fully in the developmental stages.

Criteria

Criterion 1: How relevant the project is to the public's health or future health, scored on a scale from 1-5, with 1=not at all relevant and 5=highly relevant

Criterion 2: How dependent the project is on (at least) a London-wide collaborative approach in order to reach its recruitment target, scored on a scale from 1-5, with 1=not at all dependent, 5=completely dependent.

Criterion 3: How feasible is it that the project would obtain funding? Scored on a scale from 1-5, with 1=not at all feasible, 5=completely feasible.

Projects selected

The projects scoring most highly on the basis of the three criteria combined were those relating to the: Natural history of HCV, treatment response in chronic HCV/HIV co-infection and risk factors in acute HCV/HIV.

Support offered to selected projects

Support offered by the IDRN, aiming to support project quality and reduce start-up times for multi-centre work, is as follows:

- Assistance in identifying relevant inter-disciplinary expertise in London (this researchers' database will also be available online by January 2003)
- Distribution of protocol drafts to IDRN members for comment regarding study design, ethical or practical concerns and, as the protocol is finalised, for recruitment estimates
- Identification of external peer-reviewers to comment on study design.
- Provision of a central meeting place (IDRN financed & arranged) for protocol development groups to meet in London on a quarterly basis.
- Provision of a suggested collaborative research framework to facilitate collaborations and the work process flow.
- Grant application and ethics submissions preparation.
- Hosting a project start-up meeting after a project has received its own funding but before recruitment begins.
- Communication facilitation through virtual means also, by way of an extranet for each protocol development group on the IDRN website (being developed in 2003).

Support offered to other projects

Although with its current capacity in-house the IDRN cannot offer full backup support to all of the collaborative proposals, the importance of many of the issues raised is recognized. The IDRN proposes, therefore, to:

- Report and discuss the results of this workshop to and with research funding groups, including the Department of Health
- Assist in identifying relevant inter-disciplinary expertise to support the development of collaborations
- On request to open a dialogue with industry for relevant proposals