

## Summary

In the United Kingdom, Research in Haematology has a long and distinguished record predicated on a sound scientific approach, but its Development, at least on a regional basis, has been erratic. UK Haematology has benefited from some outstanding basic research by University groups. NHS centres of excellence have emerged in a wide range of specialisms within Haematology. These can often be traced back to individuals or small groups with particular interests who were accommodated and nurtured in the NHS environment, sometimes with strong links to University research groups.

Organisations have provided a unifying force in the evolution of Haematology in the UK; among these the College, the British Society for Haematology and the Medical Research Council, the last through its sponsorship of clinical trials in leukaemia, have been an enduring influence.

In laboratory haematology the mechanisation of analysis and the “kit” mentality have led to technical de-skilling and created an environment that has dampened the enthusiasm of potential experimentalists, so that the ethos of empirical scientific investigation struggles to flourish in a more hostile environment. Furthermore, increasing clinical commitments have resulted in a diminution of the traditional laboratory role of the Consultant Haematologist resulting in lack of time to devote to laboratory based research.

Another impediment to research is delay caused by stringent regulatory controls. Potential investigators must first negotiate the documentary morass encompassing research governance and ethical considerations, health and safety at work legislation, as well as detailed specific requirements for the use of radioisotopes, genetic manipulation and animal models. Whereas most investigators crave simplification of these procedures the demand for documentation appears to be increasing exponentially, as exemplified by the current obsession with HTA, and is smothering research effort.

Lastly, because of the European Working Time Directive and PMETB’s constraints on training time, it has become more difficult to encourage and provide opportunities for trainees to pursue a period of research, leading to a higher degree, outside their training programmes. The College has very successfully persuaded DoH to increase the numbers of trainees in Haematology to cope with the expansion of the specialty but this increase has not fed through to more or better research.

To recapitulate an environment conducive to research it is important to aim for an infrastructure in which clinical and laboratory research go hand-in-hand with training. These should be centred on the existing branches of haematology *viz.* malignant disease, haemostasis and red blood cell disorders and also encourage research in topics such as stem cell research, gene therapy, immunobiology and vascular biology.

### **The College could:**

- **Develop more forcefully its important role in training and workforce planning for both clinical and scientific staff in Haematology**
- **Exploit as much as possible the opportunity presented by the Agenda for Change and Skills for Life to develop a comprehensive strategy for training and workforce planning in Haematology**

- **Encourage the development of national research networks devoted to specific topics in Haematology which would then interact with their European counterparts**
- **Encourage the establishment of training schools in Haematology which would allow greater concentration of trainees in fewer centres in which a research project led to a higher degree**
- **Use the website to highlight major advances and controversies in Haematology, and to provide interesting features such as profiles of investigators which reflect the translational and interdisciplinary nature of modern Haematology**
- **Arrange Meetings/Workshops about translational research with inspirational speakers to encourage the debate on relevant topics for future research in Haematology**

## 1. Introduction

### *Haematology in the UK*

Haematology is a highly developed speciality in the UK and has played a leading role in influencing the discipline of haematology in Europe. It is now recognised by the EU as a monospecialty and EHA has produced a model curriculum based on the one used established by BSH. In practice the majority of EU countries are now closer to our monospecialty model than to the medical speciality model.

UK haematology has a long and distinguished record based on a sound scientific approach. Centres of excellence have emerged in a wide range of specialisms within Haematology. These can often be traced back to individuals or small groups with particular interests who were accommodated and nurtured in the NHS environment, sometimes with strong links to University research groups. If UK haematology is to maintain its leading position, internationally, it must attract, train and support young clinical and non-clinical investigators on an interdisciplinary basis.

### *The role of the College in Research*

The general introduction for Transfusion Medicine by Derwood is excellent:

“The College of Pathologists have recently agreed that research will be one of its four pillars of activity, alongside Workforce, Education and Training, and Standards. The position of Director of Research has been created and the Director chairs the College Research Committee. The aim is to develop a formal three year action plan and each pathology specialty has been charged with developing an R&D strategy outline. The College’s vision is, “To enhance pathology research and the understanding of that research for the benefit of the patient and society at large.” Therefore it was important to survey current research activity, see where future opportunities would present themselves and how these could be usefully exploited. At the same time it is clearly important to improve research education and maximise research opportunities for both doctors and scientists. Finally, through the College’s website and public relations operation the flow of research information, the profile of academic transfusion medicine in the

UK and public awareness of research might be increased. Some pathology specialties such as clinical academic microbiology were facing virtual extinction through changing NHS and university priorities. Whilst Transfusion Medicine research is relatively healthy, there is still a need to strengthen both blood centre and hospital research in certain areas, and also to optimise training for the researchers of the future.” [Derwood Pamphilon, Research and Development in Transfusion Medicine, 2007]

### ***Haematology Research in the UK***

The UK has an outstanding record of scientific innovation. The discipline of Haematology has evolved based on alliances among the NHS, universities and the bodies that fund high quality research. The NHS supports research and development that is relevant to its national priorities and the benefit of patients. University research groups undertake research in a wide range of specialisms within the discipline. The LRF, Wellcome, MRC and CRUK are the largest providers of financial support for research and development.

## **2. Background**

Haematology research has an exemplary record of achievement in basic research and its translation into improvements in the diagnosis, therapy and prevention of disease. The discovery of the molecular basis of the inherited disorders of haemoglobin and enzyme defects has informed our understanding of complex biological processes. Coupled with the development of DNA techniques these advances have provided the framework for the present concept of molecular disease. Several of the scientific discoveries involved in this progression have been recognised by the award of Nobel prizes, and a substantial proportion of these have gone to investigators in the UK. These factors have combined to ensure that Haematology is at the leading edge of molecular medicine.

Imatinib has proved efficacious in the treatment of chronic myeloid leukaemia and is the first of a new class of anti-proliferative drugs, the signal transduction inhibitors. An important factor in its development was the detailed understanding of the biological pathway involving bcr-abl. Application of this paradigm should lead to the identification of small therapeutic molecules for the treatment of other diseases.

Bone marrow transplantation involving haematopoietic stem cells has provided an important platform for the study of stem cell biology. The regenerative capacity of ES cells appears to hold huge potential for the provision of stem cells to devise experimental treatments for many severe disorders. The use of unrelated and mismatched donors has expanded in parallel with increased understanding of the graft versus host/graft versus leukaemia effect and of the utility of donor lymphocytes post-transplant. This research in turn has stimulated greater efforts to understand the function and utility of professional antigen presenting cells, such as dendritic cells, and in their application to cellular immunotherapy.

Thrombosis and haemostasis also have strong foundations in UK Haematology. Huge numbers of patients are affected by venous thromboembolic events. Important areas of research currently include antithrombotic therapy, haemostatic mechanisms in stroke and cancer related thrombosis.

Most clinical trainees specialise in malignant haematology, and most training programs currently provide limited exposure to the non-malignant branches of the subject. In the United States fears

have been expressed over the economic factors that have supported “the apparent wholesale incorporation of haematology into mainstream oncology” (Schaefer, 2004). In the UK there is similar concern that clinical haemato-oncology has proved to be a distraction for other equally or more important aspects of haematological practice and research. In parallel with this trend clinicians who train in haematology spend less time on research with only a small percentage staying on to work in an academic environment.

To ensure the future of Haematology it will be essential to integrate basic research and its translation into therapies across the whole range of serious blood diseases. Whereas most of the research effort remains focussed on malignant disease it is now also important, even essential, to encourage programs in basic research such as stem cell biology, and in the main branches of non-malignant haematology. However, learning from experience gained in malignant haematology this could be assisted by the creation of clinical and research networks which would garner core resources such as tissue banks and promote collaborative research efforts, especially in the rarer disorders. Models for this already exist, for example the scheme devised by the LRF for tissue banking.

### **3. Funding for Research**

Haematology research funding is made up of several components, including the direct spend on research programmes, infrastructure, support services and laboratories. In 2003 the annual spend on **cancer** research in the UK was estimated to be £450 M (Hansard, 2003). Of this sum the largest proportion of the total expenditure was in the field of biological research, although research into aetiology and treatment was also well supported. Cancer research is funded by approximately 250 charities, numerous Government bodies and the pharmaceutical industry (Hansard, 2003).

It is difficult to obtain reliable estimates of expenditure on Haematology research in the UK, but it is probably of the order of £50 to £100 M. The Leukaemia Research Fund (LRF), the MRC, CRUK and Wellcome are major funders.

The LRF, the only large charity in the UK dedicated to researching malignant blood diseases has an annual spend of £23 M. It supports scientists and doctors working in over fifty research centres across the UK. It provides valuable practical help to fundholders through various schemes such as financial and organizational support for Tissue Banks and a service for the production of monoclonal antibodies. The LRF also provides cohesion by organizing specialist scientific meetings.

For CRUK the annual spend on Haematology, as of April 2006, was over £12m. This includes spend on leukaemia, myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease, essential research services and infrastructure underpinning CRUK research teams, as well as direct grant funding.

The British Society for Haematology provides £200 K per year for research in the form of Fellowships, Travel awards and Start-up grants. It jointly funds an annual Project Grant with the LRF. In 2007 BSH funded a Fellowship jointly with the British Society for Haemostasis & Thrombosis and LifeBlood and is currently planning another Fellowship in the area of red blood cell studies.

#### **4. Current Arrangements for Research in Haematology**

It has been estimated that there are over four hundred routine Haematology laboratories which take part in quality assurance schemes and that at least 50 of these are affiliated with research groups which receive funding from external research organisations. Most of the reported high quality research is carried out in centres of excellence which have emerged in a wide range of sub-specialties. These can often be traced back to individuals or small groups with particular interests who were accommodated and nurtured in the NHS environment, sometimes with strong links to University research groups.

A substantial proportion of research effort is driven by clinical trials. This is especially true in the field of leukaemia where successive trials organised by the MRC have revolutionised the treatment of childhood and adult leukaemia. Advances in genomics, particularly in DNA microarray technology are now permitting the study of associations between the expression levels of thousands of genes and clinical outcome in individuals with specific oncogenic lesions. The long term aim of this work is to enable specific treatment for individual patients.

High quality biological research is concerned with mechanism, and haematology is no exception. A thorough understanding of the mechanisms involved in specific disorders particularly as they pertain to structure-function relationships will enable rational drug design with the possibility, in principle, of ultimately treating a large proportion of diseases in which the defects have been identified.

At present many UK groups have the capability of identifying genetic mutations associated with specific disorders, but the implementation of translational research has been slow and few have the collaborations or partnerships required to develop potential therapeutic strategies for the disorders they have defined. A major immediate challenge is to find ways, including funding, for speedier implementation of advances in knowledge to enable better sub-classification and risk stratification of disease at diagnosis. This has the potential to inform patient management decisions and to contribute to greater cost effectiveness of limited resources for treatments. This “near patient” research is under-represented in both research and NHS funding.

#### **5. Constraints**

The emphasis on malignant haematology over the past few decades has resulted in the relative neglect of research in the non-malignant branches of the discipline. This is particularly severe in the areas of red cell studies and haemostasis/thrombosis, where UK investigators made many significant early contributions. As a result there are now relatively few centres which have the capacity to encourage and mentor future investigators in non-malignant haematology.

The College may wish to consider undertaking a role in liaising on training matters between research centres to ensure that all of the sub-specialties are covered. This should include the research training of both medical and scientific staff.

Funding for translational research in non-malignant haematology is sparse.

## 6. Areas for Further Development

### *Organisational issues*

Recent advances in molecular genetic analysis, immunophenotyping and cytogenetics have extended the repertoire of diagnostic tests available for individual patients. In some centres the tests are performed outside the traditional haematology laboratory, for example in core technology units dedicated to particular types of analysis. An integrated approach should be encouraged to facilitate a cohesive research and clinical applications program. This would complement the current development of multidisciplinary approaches to patient diagnosis and management. Of particular importance is the need to encourage trainees to develop research interests which they can maintain, and be of relevance to future clinical commitments.

The College may like to consider providing advice and assistance to centres on the configuration to achieve optimal efficiency. This could take the form of a Workshop or Lectures. An important related topic is the development of **multidisciplinary teams** in both malignant and non-malignant haematology.

At national level there are opportunities to develop larger, more inclusive networks for specific diseases. **The College could encourage the development of such national networks topics in Haematology which would then interact with their European counterparts.**

### *Further topics for investigation*

The American Society of Hematology has produced an agenda for haematology research 2006-2008 based on the views of its 14 scientific committees. The main topics which they consider are:

1. Haematopoietic Stem Cells
2. Normal and pathological haematopoiesis
3. Haematological Malignancies
4. Targeted and Gene Therapies
5. Immunobiology
6. Thrombosis and Vascular Biology

The sub-divisions of these topics are given in detail in Appendix 1, and provide enormous scope for research.

## 7. Research Partners/Collaborators

Haematology research has now reached an exciting conjunction where the underlying causes of disorders can be defined by molecular genetic analysis, and the potential exists to generate rationally designed drugs based on detailed structure-function considerations. Important opportunities therefore exist to forge partnerships between research centres and the pharmaceutical industry.

## 8. Research Training and Education

The logistical need for clinical trainees to specialise in malignant haematology and the trend to place less emphasis on research in training programs has stifled training in non-malignant haematology and

will hinder the development of future academic haematologists. To address this problem it is desirable to create training programs that are less slanted towards cancer and to provide resources specifically directed towards non-malignant haematology. One solution may be to combine training in non-malignant haematology with either **laboratory medicine** or **transfusion medicine**. This should result in the creation of a cadre of investigators who may then choose to proceed to develop academic careers.

At present clinical training programmes do not encourage, or allow time for, trainees to undertake research activities. This means that the majority of future senior consultants will have less understanding of a clinician scientist role in maintaining and developing the status of haematological research within the UK. To counteract this trend, the College should consider playing a constructive role in **training and workforce planning for both clinical and scientific staff** in Haematology. This would involve making sure that trainee posts are aligned with available permanent posts. **Agenda for Change may represent a timely opportunity to develop a comprehensive strategy for training and workforce planning in Haematology.**

Haematology has benefited enormously from its interdisciplinary tradition and it will be important to ensure that training programs are extended to include post-doctoral Biomedical Scientists. They should be encouraged to obtain MRCPath., preferably by the submission of published work, although in some cases it may not be possible for able candidates to develop their portfolio adequately to achieve this goal. They should be helped to develop their careers as Clinical Scientists and, to facilitate this, a transfer route to State Registration as Clinical Scientists should be developed in co-operation with the College, BSH and HPC. The combination of clinicians and scientists with different career paths should enable good communication and enhance the translation of scientific advances into the clinic.

## **9. Promoting Research**

In order to promote research it is important to identify the scale of the tasks that need to be tackled and to communicate effectively to promising investigators, potential funders and the public.

It has been estimated that 110,000 people suffer from malignant blood disorders such as leukaemia, lymphoma and myeloma in the UK at present, and that some 25,000 people are newly diagnosed with conditions every year (LRF). In the United States, which a population four times that of the UK, there are about 500,000 venous thromboembolic events, 1.1 million myocardial infarctions and more than 150,000 stroke deaths annually (ASH, 2006).

Clearly more academic trainees are required. According to a survey conducted by the College at the end of 2006 there are only three academic trainees – 1 in England, 1 in Wales and 1 in Scotland (Fiona Addiscott, Workforce Planning Manager, The Royal College of Pathologists).

Few opportunities, funding and career-wise, are available to encourage scientists, clinical and academic, into research activities in malignant haematology and there are even less in non-malignant haematology. The College can play a pivotal role in collaborating efforts to redress this situation.

### **References**

Agenda for Hematology Research 2006-2008. American Society of Hematology  
[http://www.hematology.org/images/pdf/research\\_agenda\\_2006.pdf](http://www.hematology.org/images/pdf/research_agenda_2006.pdf)

Hansard, 2003.

<http://www.publications.parliament.uk/pa/cm200203/cmhansrd/vo030320/debtext/30320-30.htm>

Schafer AI. The Hematologist: ASH News and Reports; 2004: vol.1, issue 4.

**Acknowledgements**

Derwood Pamphilon, Archie Prentice, Fiona Addiscott (RCPATH.), David Grant (LRF), Ken Mills, Finbarr Cotter, Sandra Irvine, Denis Alexander, Josephine Querido (CRUK)

## **Appendix 1: ASH Agenda for Hematology Research 2006-2008**

[http://www.hematology.org/images/pdf/research\\_agenda\\_2006.pdf](http://www.hematology.org/images/pdf/research_agenda_2006.pdf)

### **1. Haematopoietic Stem Cells**

- Stem cell microenvironment
- Stem cells and ageing
- Stem cell therapy
- Stem cell tracking
- Immunomodulatory effects of stem cell therapy
- Embryonic stem cells

### **2. Normal and pathological haematopoiesis**

- Pathogenesis of anaemia of chronic inflammation
- Actions of haemopoietic growth factors on non-haematopoietic tissues
- Therapeutic potential of haematopoietic cytokines
- Regulation of haematopoiesis

### **3. Haematological Malignancies**

- Molecular profiling of haematological malignancies
- Neoplastic stem cells
- Immune therapies for haematological malignancies
- Treatment of haematological malignancies

### **4. Targeted and Gene Therapies**

- Targeting neoplastic stem cells
- Regenerative medicine
- Cell and Gene Therapy

### **5. Immunobiology**

- Immune recognition
- Mechanisms of immune response
- Normal and abnormal mechanisms of immune regulation
- Transplantation immunology
- Immune therapy
- Innate Immunity
- Lymphopoiesis
- Immune cell trafficking

### **6. Thrombosis and Vascular Biology**

- Antithrombotic therapy
- Early mechanisms of arterial and venous thrombosis
- Animal models for venous and arterial thrombotic disorders
- Genomics, transcriptomics and proteomics
- Cancer related thrombosis
- Thrombosis and vascular disease unique to women
- Stroke