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**From the President
Professor John Bell PMedSci**

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Dear Professor Goldman,

Transplantation Research Integration in Europe (TRIE) consultation

The Academy of Medical Sciences welcomes the opportunity to respond to the TRIE consultation on cross-European transplantation research priorities. Our Fellowship represents a wealth of experience in cell and solid organ transplantation from across the continuum of basic, translational and clinical research.

As a champion of academic medicine the Academy wishes to express its support for the TRIE initiative. Transplantation is a crucial part of the European research agenda and, in many circumstances, further cross-border collaboration would be helpful.

We raise two issues that cut across transplantation research in Europe. First, the need to control the homogeneity of immunosuppressive protocols and clinical management practices across European Centres. Second, the timing of investment; early support may promote the field of transplantation, but could come before real breakthroughs are made and may not be the most efficient use of limited resources. We address the specific topics raised in the consultation letter below.

Standardisation and validation of immune biomarkers to predict and monitor outcomes

The large number of samples needed to clinically validate immune biomarkers is likely to require cross-European collaboration, although this approach is not necessarily appropriate for all aspects of this issue. Large, accessible and high-quality banks of DNA and RNA serum will be needed and it is crucial that each sample is accompanied by detailed and prospective clinical information. In this respect, much can be learned from the experiences of the Immune Tolerance Network in the USA.

The lack of a reliable and reproducible 'gold standard' test is a particular barrier to standardisation and validation. In its absence, there is a danger that the 'standard' test of one year will be superseded by the next. Clear evidence is needed that the standards chosen are appropriate, to avoid infrastructure being developed prematurely. We consider standardisation and validation of biomarkers to be of medium to high priority and, while implementation could be challenging, it could be tackled in the next five years.

The study of pharmacogenetics to optimize graft outcomes

Investigation of this topic would need to be genome wide, to include DNA samples from recipients and donors, and incorporate detailed clinical information. High-level bioinformatics input would be needed for both the power calculations in designing the study and for the analysis of data.

In the absence of compelling evidence of long-term graft benefit, which would require investigation of many patients on controlled regimens over long periods of time, clear evidence is needed of cost-effectiveness before infrastructure and funding is established. It may be that the pharmaceutical companies that produce the drugs used in transplantation are better placed to pursue this topic because they are well organised and have strong incentives to continue only the most promising lines of inquiry.

The scale that could be achieved in a European-wide study in this area would make implementation more likely, although in other respects it is unclear how a cross-European programme would add value. It may be some years before the results of this proposal are rolled out clinically. Where possible, TRIE should consider building on existing resources. There are also opportunities to link this proposal with the biomarkers topic.

Design of a roadmap for high-risk patients

Currently there are not enough high-quality clinical trials of high-risk patients. Different centres use different protocols, making comparison and collaboration more challenging. Cross-European working would offer major benefits, particularly across ABO blood groups and for uncommon transplants to highly sensitive patients, where researchers in individual countries may not be able to enrol enough subjects.

Implementation is likely to be difficult, given the variety of factors contributing to risk status. It should be noted that algorithms and guidelines for particular groups of patients may have already been developed independently by particular sub-disciplines within the transplant community. The Academy believes that this topic is relevant to a particular section of the patient population and is of medium to high priority.

Novel cell-based therapies for hematopoietic stem cell and organ transplantation

Novel cell-based therapies are at a relatively early stage of development and it may be some time before their implementation. There is some concern that they may be labour intensive, expensive and logistically challenging. Debate is also needed about their sustainability if not properly commercialised and regulated.

The implementation of the pre-clinical work in this area would be cost-effective and should be taken forward. However, while cell-based therapies may provide proof-of-principle for targeting particular pathways, they may not offer a long-term solution. Clinical trials will be expensive but could be undertaken if well designed. A cross-

Europe approach would be suitable, as more coordination is needed between centres already conducting this sort of research. Networks may be a useful method of rolling out therapies. However, barriers created by recent European legislation will need to be surmounted if greater collaboration is to be achieved.

Innovative training programmes for physicians and scientists

Robust training programmes for clinicians and scientists are always a feature of good medical practice. While training programmes could be implemented quickly, there are questions about how this is best achieved. Each country within Europe has a different training programme for physicians. It would therefore be useful to have common standards of accreditation and validation. The European Society for Organ Transplantation has already undertaken work in this area. However, exchange programmes are not always a necessary component of cross-European training efforts.

As highlighted by the Academy's reports on '*Systems Biology*' and '*Safer Medicines*', expertise in the use of *in vivo* animal models has been in decline due to increasingly complex regulation, escalating costs and animal activism. Training of both clinical and non-clinical medical scientists in this area is therefore a high priority. TRIE may wish to look to PhD schemes funded by the Wellcome Trust as part of the '*Integrative Animal Physiology Initiative*' for guidance on how such programmes might be rolled out across Europe. For clinicians, there might be opportunities within existing training fellowship schemes earmarked for work on transplantation, similar to those conducted in collaboration with the medical royal colleges of radiology or surgery, within the Cancer Research UK Clinical Fellowship scheme.

There is a serious shortage of transplant surgeons throughout Europe and it is important that more clinicians are attracted to and trained in this discipline. Surgeons should therefore be included alongside physicians and scientists in the title of this topic. A continuing problem for surgeons seeking entry into academic transplantation in the UK, and possibly across Europe, is the burden of rigid clinical training requirements.

Other topics

Other topics TRIE may wish to consider taking forward include:

- Development of robust methodologically sound randomised controlled trials in areas not supported by industry.
- Improving the quality and quantity of donor organs and developing innovative organ preservation systems.
- Brokerage between pharmaceutical companies and European regulatory bodies, particularly with regard to the relative value of drugs used to control acute or chronic rejection.
- Promoting novel approaches to induce transplantation tolerance and to develop biomarkers to detect tolerance.
- Research into cell transplantation into the joints.

We would be delighted to expand on any of these points or provide further assistance if required.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'John Kim', written in a cursive style.

Cc: Professor Kathryn Wood FMedSci