Update on proposed work relating to microbiological risks associated with stem cell therapy / ATMPs

Background

A meeting was held in February 2012 between interested SaBTO members and representatives of the regulatory bodies, the Medicines and Healthcare products Regulatory Agency (MHRA), Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA), to discuss issues of concern to SaBTO members relating to the regulation of Advanced Therapy Medicinal Products (ATMPs). One issue raised was the perceived risk of prion disease in stem cell lines derived from a UK source, and the potential commercial risk resulting from it.

Independently, members of the UK National Clinical Human Embryonic Stem Cell Forum (NChESF) met with experts in TSE (transmissible spongiform encephalopathies) and tissue banking, to explore the possibilities and implications of TSE infection in stem cells (and other tissues) intended for clinical use. The report of this meeting was circulated to SaBTO members in May, and is attached for reference. The report also constituted a request that SaBTO should formally examine this issue and provide guidance, specifically on 'clinical grade' hESC lines but recognising the applicability of some aspects to human application of other cell and tissue products.

Policy colleagues in the Department of Health who lead on policy relating to stem cell therapies are supportive of the proposal that SaBTO should undertake work in this area.

Context

The House of Lords Select Committee on Science and Technology is undertaking an inquiry into regenerative medicine, under the Chairmanship of Lord Krebs. "The Committee will be looking, in particular, at whether the UK is in a position to facilitate the translation of knowledge from world-leading research to treatments and to benefit from the commercial opportunities that they present. It also seeks to explore how realistic some of the reported claims of regenerative treatments and therapies are, both in the UK and internationally."

A workshop to address the regulation of regenerative medicine, which will cover hESCs and other cell-based therapeutic approaches, is to be held on 30th October this year. The workshop is sponsored by the Medical Research Council, the Economic and Social Research Council, MHRA, the Association of the British Pharmaceutical Industry and the Academy of Medical Sciences. The objective of the workshop is to:

- scope the current regulatory environment in the UK/Europe and its suitability for the current R&D needs for cell-based regenerative medicine;

- identify the key areas of regulatory uncertainty and concern regarding the development of cell-based regenerative therapies; and
- identify the likely needs for the area regarding future scientific progress.

Next steps

The Secretariat is currently arranging an initial meeting of SaBTO members, representatives of the group from whom the request came, policy officials and regulators to consider what the scope of the work should be, and discuss the output and how the work should be addressed.

Questions for SaBTO

SaBTO members are invited to comment on:

- the request for SaBTO formally to consider the issue and provide guidance
- elements which should, or should not, fall within the scope of SaBTO's consideration.

Secretariat
22 August 2012

Report to SaBTO
of NChESF consultation meeting on
TSE infection risk in Human Embryonic Stem Cells for clinical use
Edinburgh on 28th March 2012

Members of the UK National Clinical Human Embryonic Stem Cell Forum (NChESF) who are involved with derivation and banking of human embryonic stem cells from IVF embryos, met in with experts in TSE (transmissible spongiform encephalopathies) and tissue banking, to explore the possibilities and implications of TSE infection in stem cells (and other tissues) intended for clinical use. As noted in the report of the meeting with the regulators re ATMPs (advanced therapy medicinal products) held in Feb 2012, the perception that human tissue products emanating from the UK are at particular risk of TSE contamination could adversely affect marketing of stem cells derived in the UK. TSE contamination and testing was not considered specifically as part of the EU Tissue and Cells Directive, and so far no formal risk assessment has been undertaken.

The meeting was chaired by Dr Glyn Stacey (UK Stem Cell Bank) and short presentations to initiate discussions given by:

- Professor Richard Knight (National CJD Research & Surveillance Unit)
- Professor Jean Manson (Roslin Institute)
- Professor Marc Turner (SNBTS)
- Professor Peter Braude (SaBTO).

Issues addressed were:

- What are prions and why do they matter?
- Trends in risk of TSE in cattle and humans in the UK and elsewhere
- Non-bovine and non-human sources of TSE – emerging issues
- The risk of, and steps taken to avoid, TSE contamination of donated human blood, organ and tissue
- Risks of TSE contamination in gametes and embryos in the general population and amongst IVF patients and donors
- Recommendations on current best practice for testing for vCJD contamination
- Constructing a risk assessment process for TSE contamination in human embryonic stem cell lines.

Following wide ranging discussion the group agreed 13 key conclusions and recommendations that addressed TSE risk (items 2-7) and diagnostic testing (items 8-13).

1. The risk of TSE in clinical grade stem cells is a global issue and should be considered from that perspective; only then should the outcome be applied to a UK position.[1]
2. Maternal transmission (sheep), patient to patient, and transmission between single cells is known although the precise nature of the infectious agent and pathogenesis of the disease are still largely unknown.
3. An asymptomatic BSE/vCJD infection rate of ~1:4000 in the UK population is currently accepted based on existing knowledge.
4. There is an ongoing need for a review of risk from tissues, including in UK stem cell lines. This risk needs to be put in context against other tissues and in other countries.

[1] http://www.guardian.co.uk/science/2012/apr/25/mad-cow-disease-us-mutation; http://weddelswift.com/2012/04/25/bse-case-confirmed-in-usa/

5. The route of exposure is likely to be a key factor in pathogenesis as the risk and incubation period for iatrogenic CJD shortens the closer the target is to the central nervous system.
6. Risks of transmission could be associated with gamete donors, and with gamete processing and its components.
7. Questions still remain about zoonotic potential of new and newly recognised animal TSE since different strains of animal disease can behave very differently.
8. A validated prion screening test is not yet available but a practical position is testing for abnormal prion protein.
9. Tests for prions/TSE are in development (3 current lead candidates) but are still in the academic domain and are oriented primarily towards blood screening applications. The group recognised a need to promote exchange and evaluation of samples between groups, including cells and their derivates as test substrates.
10. There is a need to evaluate test criteria and for closer identification of the infectious agent being tested.
11. Testing of cell banks (product testing) is a more relevant approach than donor screening; an alternative would be testing of startup cells whose provenance should be traceable to low risk inputs/starting materials.
12. Criteria will need to be established for how / whether results should be interpreted with respect to public risk and feedback to the cell donor(s).
13. Banks for generic clinical use should be regarded very differently in terms of testing requirements when compared to banks producing cells for specific indications/products.

General Conclusions and actions suggested:

- The group concluded that there were significant new data on CJD infection.
- The group agreed that a narrative with its recommendations should be drafted for SaBTO.
- The group recommended that SaBTO should be asked to formally examine this issue and provide guidance. This guidance should be specific to the ‘clinical grade’ hESC (human embryonic stem cell) lines now being established, but SaBTO should be encouraged to recognise that there are aspects generic to human application of other cell and tissue products.
- Regarding testing of cell banks of hESC lines: the group agreed that the testing of lines in those centres/banks involved directly in product manufacture would probably need to be more extensive than requirements for those in centres established solely as derivation centres with the intention of providing starting materials for a potentially broad range of human applications.

Participant List

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