The ethics and regulation of cell and tissue therapies in the UK

Prof. Mark Lowdell – UCL Medical School, UK

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What is an ATMP?

- Specifically, an ATMP is a biological medicinal product which is either:
  - A somatic cell therapy medicinal product (Part IV of Annex I to Directive 2001/83/EC)
  - A tissue engineered product as defined in Article 2 1 (b) of the AMP Regulation

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What are the specific regulations covering cell therapies?

- 2001
  - 2001-83-EC Medicines Directive
  - Substance includes human blood and blood products
  - transplant application to human somatic cells
- 2004
  - Clinical trials directives enacted - include "substantially modified somatic cells" as IMP for the first time. GMP manufacture required plus MA (IMP) and Qualified Person
- 2006
  - Tissues & Cells Directives enacted in UK
- 2007
  - ATMP regulations published
  - Procurement of starting material regulated by HTA and requiring licence
  - "Nonsubstantial" defined
  - Inclusion of HEI for one-off, non-ATMP products
- 2008-120-EC amended 2001-83-EC to included ATMP

Where to start the academic development process?

The decision tree for "medicinal" vs. "non-medicinal" – MS CA not EMA

- Is the product going to be procured/produced and used in a single surgical procedure?
  - BMNC in coronary artery bypass graft?
- Is the product going to be used homologously?
  - What is non-homologous?
  - Adipose cells for synovial fat pad regeneration?
- Is the product "substantially" modified?
  - Immunologically/physiologically/metabolically

ATMP cell therapy trials at RFH & UCL

- "Studies" – not trials
  - CMV-specific immune regeneration post HSCT – Ph III and Ph III
  - Allogeneic MSC infusions for severe GVHD – Ph III
  - ProT4 DL for relapse post allog HCT – Ph III multicentre
- Clinical trial
  - Autologous tumour lysate pulsed DC in paediatric glioma – Ph I
  - Retinal pigmented epithelial (RPE) derived from hESCs in Strangarianas – Ph II
  - Allogeneic primed NKT cell therapy for AML – PhII
  - ASCAT – Phil
  - MSC-Trial – Phil & Phil
- First-in-man – not trials
  - Autologous stem cell seeded cadaveric tracheal transplant
  - Autologous stem cell-derived cell seeded biocompatible tissue structure for tracheal transplant
  - Autologous stem cell-derived cell seeded biocompatible tissue structure for nasal reconstruction

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Can ATMPs be delivered to GMP in academia?

3-D tissue-engineered ATMPs at UCLP

Should ATMPs be developed in academia?

ATMP development is largely academic

- Reality
  - Academia is driving ATMP development but "held back" by regulation (?)
  - Commercialisation of ATMP will be ESSENTIAL for maximum treatment availability
  - Commercialisation DOES NOT require marketing authorisation
  - Current trials legislation is aimed at MA

- Government needs
  - Protection of the public
  - Increased academic output
  - Increased industrial development of ATMP
  - Increased GDP from ATMP

The ATMP stakeholders

The virtuous circle

- Academic clinician
- Industry
- EU commission
- University/hospital (OMO)
- Patient

All are interdependent:
1. Clinician wants to innovate treatments and NEEDS patients
2. University NEEDS high impact publication and IP but not to fund phase III trials for MA
3. Industry NEEDS clinician to innovate and University to support proof-of-principle
4. University NEEDS Industry to buy its IP and commercialise it after clinical trials
5. Governments NEED to ensure patient safety and maximum availability of novel therapies and commercialisation
6. Patients need access to new safe and effective treatments from Clinicians AND Industry

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Why is this a question of ethics?
- ATMP phase I is rarely (never?) in healthy volunteers
- Tissue/cell procurement invasive procedure
  - Morbidity/mortality
  - Patients put at risk of untested medicine
- Academic investigators planning Phl
  MUST have a plan for development to MAA if successful

Why is this a question of ethics?
- Early phase trials require academic GMP manufacture –
  - Too much PD required for CMO –
    - Diverse scientific and technical expertise
    - Wide range of analytical equipment
    - Assay development
- Academic trials now likely to be phase II
  - Data likely to be used for MAA
  - PD needed from Phl-Phl
- Academic GMP MUST be fit to tech transfer to CMO
- Academic GMP staff must participate in tech transfer

Can academic GMP units do this?

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What are the wider ethical issues?

• Transplant organ
  – Philanthropic donation
  – Public sector supply
  – Very limited regulation
  – No proof of concept
  – No proof of efficacy
  – Lifelong immunosuppression

• Recellularised liver scaffold
  – Regulated as a medicine
  – Complex & expensive manufacture
  – Formal clinical trials
  – No need for immunosuppression
  – Private sector supply
  – Philanthropic donation?

Guiding principles on human cell, tissue and organ transplantation

“The need to cover legitimate costs … accepted as long as the human body and its parts as such are not a source of financial gain”
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Do we need human scaffolds?

Xenogeneic integration

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**Does current clinical trials legislation address the ethical issues specific to ATMPs?**

- In clinical trial the product must meet the PSF
  - What if it fails to meet the dos?
  - What if the viability is too low?
  - What if the label has a non-critical typographical mistake?
- If these are not critical to safety should they prevent administration of the cell medicine?
  - YES: The EU IMP regulations in EUDRALEX are sacrosanct and are there to protect patients from dangerous or fraudulent treatments
  - NO: the patient or donor (or both) went through significant morbidity and/or risk of clinical harm to provide the cell/tissue starting material to make this product and the criteria for dos/effectability are poorly supported by pre-clinical data

If the product fails to meet the PSF how should it be released?

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**Is current clinical trials legislation appropriate for ATMPs?**

- Intended to result in a MA
  - A fixed manufacturing process which delivers a reproducible product with established safety profile and efficacy
- ChondroCelect – first ATMP with MA in EU
- Questions
  - What proportion of ATMPs in development are "patient-directed"?
  - Is the traditional MA-route appropriate for most or even many of these?
  - What about supply as "un-licensed" medicines? – HEC or Specials
    - Re-imbursement for manufacture – not for product
    - No advertising of product
    - No clinical trials (??) – No IMPO
    - Existing pharmacovigilance process
    - Exportable
    - How do you prove efficacy?
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How might we improve the pipeline for ATMPs which should obtain MA?

- Legislation level
  - Facilitate phase III trials
  - More precise definition of the quality requirements for an IMPD
  - Acceptance that animal models may be inappropriate
  - Recognise that this field is important for EU GDP but is currently ~90% academic-led
  - Support small academic GMP facilities (move to FDA risk-based approach?)
  - Increase availability of EDEM reagents for manufacturing
- EU university and funding body level
  - Invest in translational research beyond F-I-M
  - FIM is "cheap" and gets high impact publication (unethical?)
  - Phase II trial needed before commercial funding likely so no early "spin outs"
  - GMP & GQP resources needed for academics (radical limitation of this work?)
- Academic PIs
  - Open exchange of SOPs and reagent qualifications
  - Frank and honest reporting of non-trial F-I-M results (data registry?)

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Are F-I-M as specials/HEC – “Phase 0” ethically acceptable?

Use of compassionate-case ATMP in preclinical data for clinical trial applications

- Safety and traceability primary concern
- No intention to obtain registration
- Driven by risk assessment
- Licensed by MHRA
- Full GMP
- No IMPD/No QP
- Full pharmacovigilence

EMA Jan 2012 – “CAT should reflect, when non-clinical studies are requested, on how far the experience from similar products and, if available, previous clinical experience can be taken into account”

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ATMP development

New ATMP

First-In Man application (academic) &

Phase I/II clinical trial (academic > industry)

& Phase III trials

(industry > academic)

Academic GMP production or

Hospital GMP production or

CMO GMP production (payment for manufacture but NOT for the product)

UK Specials Legislation affords this

Not commercialisable but clinically justified
(e.g., tissue-engineered trachea)

Phase II & Phase III trials

Not commercialisable but clinically justified
(e.g., tissue-engineered trachea)

Academic GMP production or

Hospital GMP production

Near-patient and stage production
(industry with hospital/academia
with GMP MA for a licensed product)

ACT HuES retinal epithelial cells

Promethera – hepatic stem cells

Cytori ADVANCE etc.

Off-the-shelf delivery (Industry)

Drug development (industry)

Marketing authorisation (industry)
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Does the system work?

What happens if we don’t regulate patient-specific ATMPs?

- Unregulated, potentially fraudulent and potentially dangerous regenerative medicines
- FDA warning letters
  - TCA Cellular Therapies (Aug 15, 2011)
  - Intelicell Biosciences (Mar 13, 2012)
  - Thomas E Young LLC (Apr 20, 2012)
  - Lancôme (Sep 7, 2012)
  - Celltex Therapeutics (Sep 24, 2012)
  - Texas Applied Biomedical Services (Sep 24, 2012)

Does the system work?

- Unregulated, potentially fraudulent and potentially dangerous regenerative medicines
- Diabetes stem cell treatment - in Europe
  - Adult Autologous Stem Cell Therapy program to treat a variety of conditions
  - Patient receives 200 – 300 billion stem cells that in turn mean a trillion "plain" cells
  - The reserve of the stem cells, almost lost for the last 15 – 20 years, is restored. New and active cells displace the old and damaged ones

Does the system work?

- 200 billion = 500 times the max clinical dose!
- 200 billion cells will cost £200-400K and take 30 months!!!!

MSC differentiation into insulin-producing cells in vitro

Ezquer et al., 2014 Stem Cell Research & Therapy, 4: 227

*... the feasibility and scalability of such attempts for achieving the final goal of large-scale β-cell replacement are still questionable. Any efforts at replacing β-cells will require an additional approach for dealing with recurrent autoimmunity.
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Conclusions

- Regulation of cell therapies as medicines IS ESSENTIAL – embrace it and use it – don’t fear it
- Reg1364 has improved the EU situation but more needs to be done
- ATMP development in EU MUST address commercially viable AND non-commercial products
  – Partnerships ALREADY required for development AND delivery
- A network of GMP-compliant academic/hospital units is being established across EU which work to same (higher?) standards as “industry”
- HEC could be operationally improved by exclusion of products competing with licensed ATMPs (Mhra position)
- Legislators, regulators, funding bodies, universities and commercial sector must work together to develop this field WITH PATIENTS
- Success requires openness and partnership with regulators