EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Are regulators up to speed to address the challenges of biotechnological medicinal products?
The CAT Work programme 2010-2015

Regulatory Science: Are regulators leaders or followers?
European Medicines Agency 15 December 2010

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Starting with thanks…

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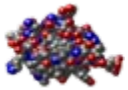
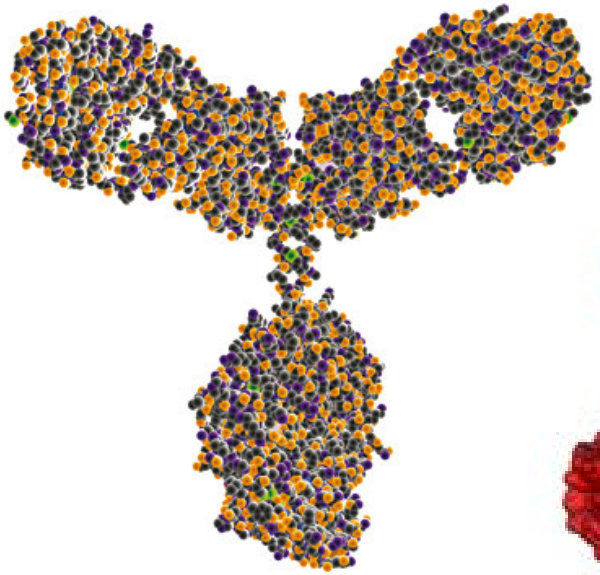
Complexity of biotechnological products

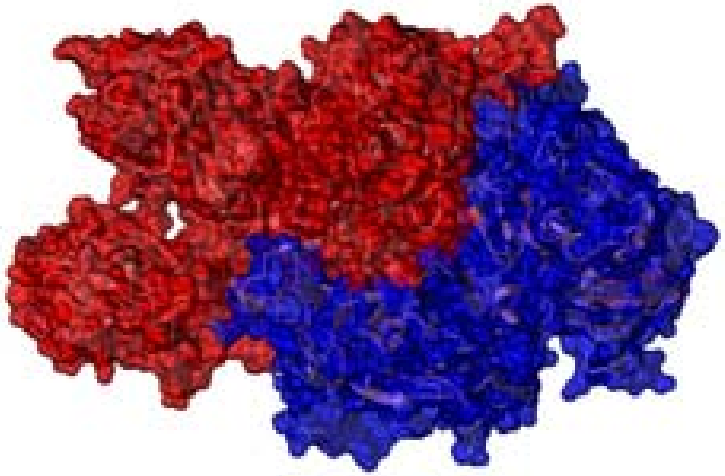


Aspirin
180 Daltons

Insulin
5 700 Daltons



Monoclonal antibody
150 000 Daltons



Coagulation Factor VIII
280 000 Daltons

www.laborjournal.de www.wikipedia.org

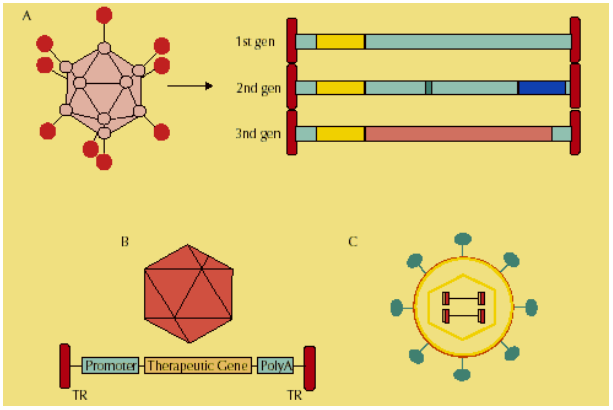
Advanced therapies and their challenges

Gene therapy medicinal products

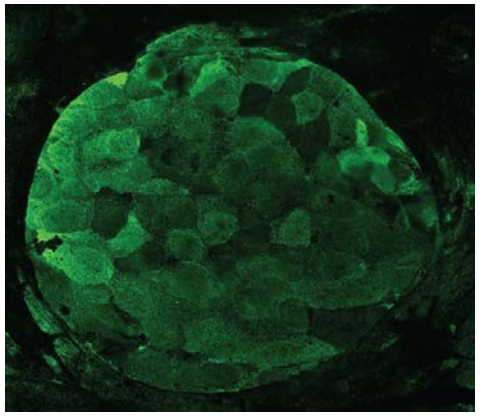
Somatic cell therapy medicinal products

Tissue engineering products

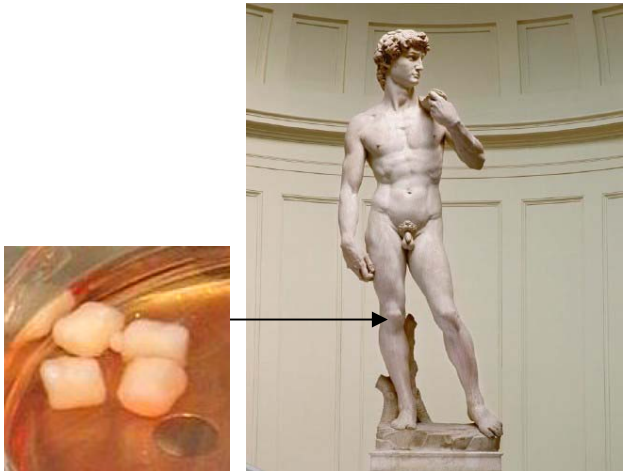
Genetically modified cells



www.heartandmetabolism.org



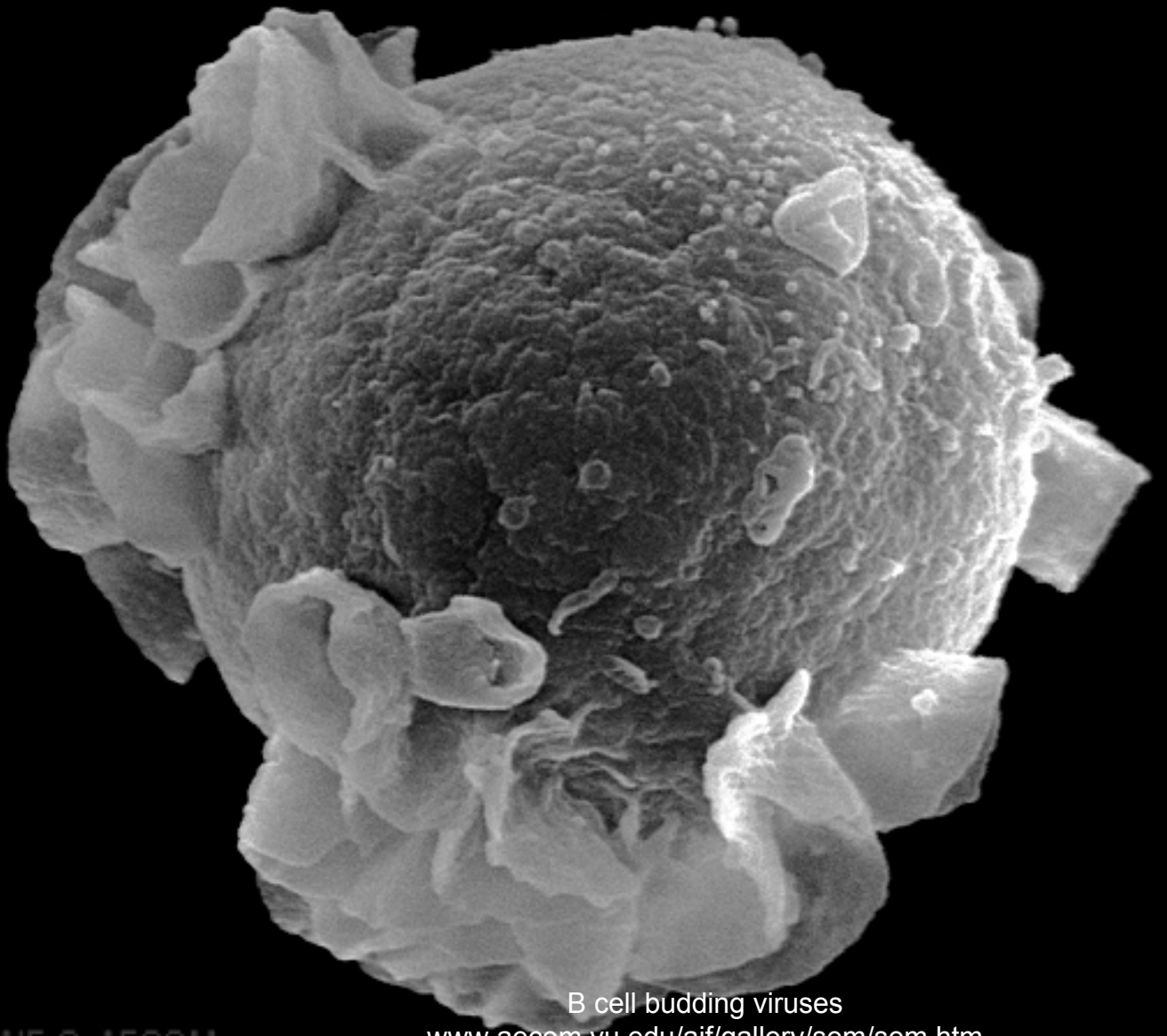
Nat Biotechnol 2005, 23(7)



http://www.cbte.group.shef.ac.uk/

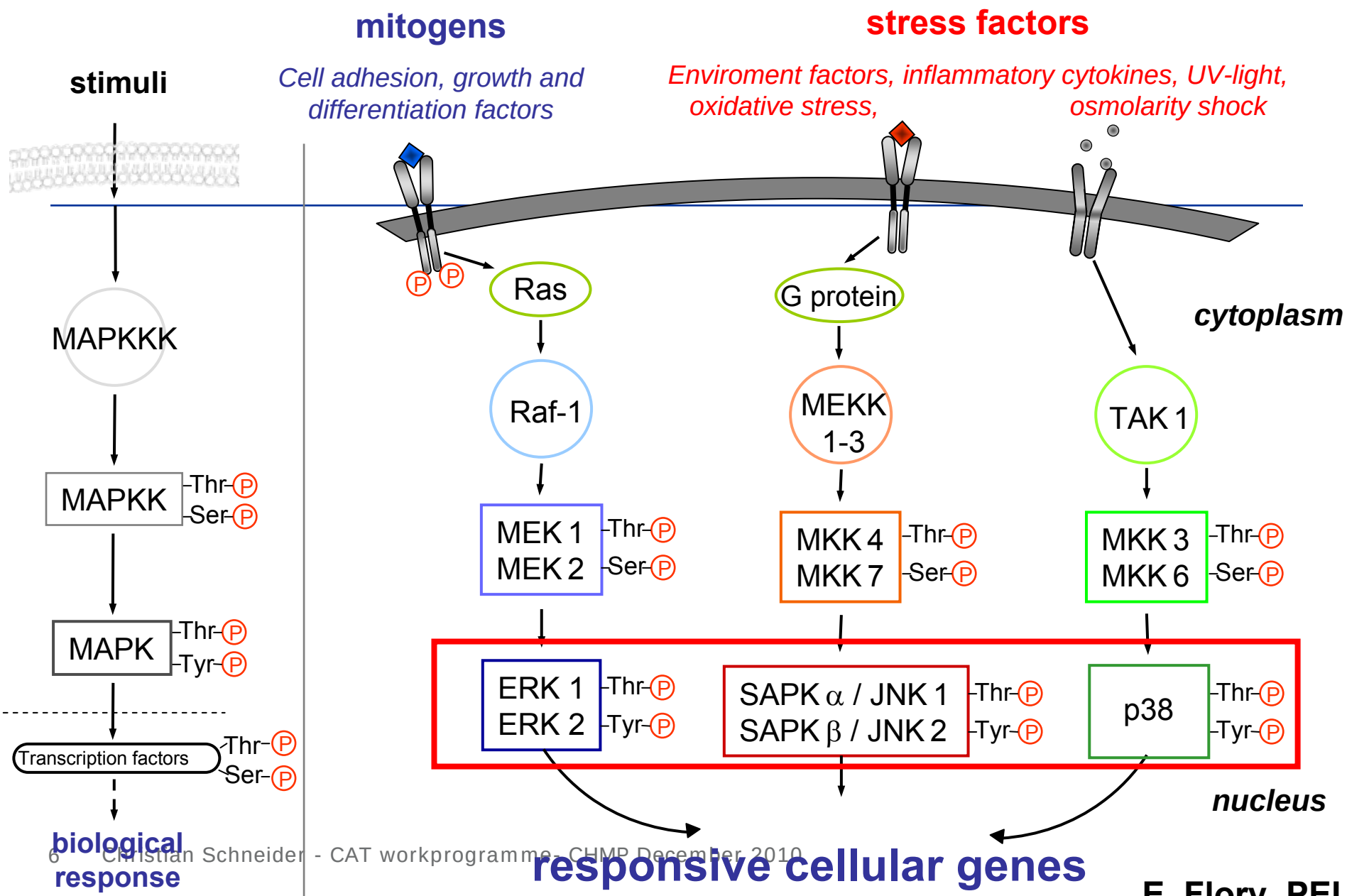
Complexity of Advanced Therapies

monoclonal antibody



B cell budding viruses
www.aecom.yu.edu/aif/gallery/sem/sem.htm

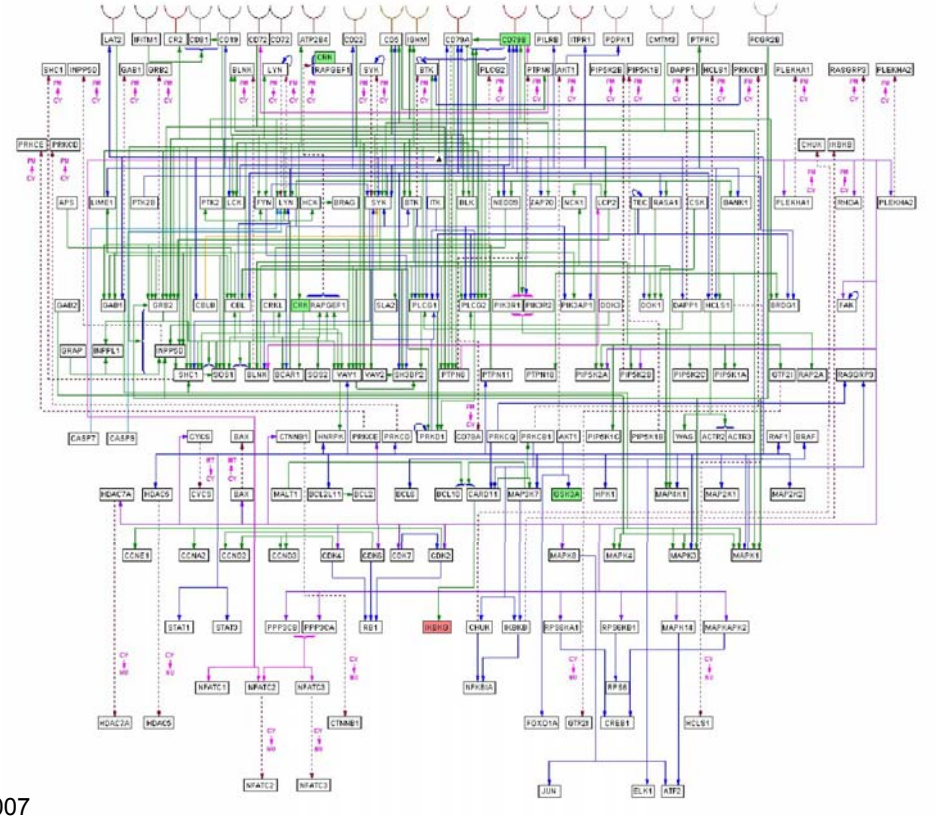
Intracellular MAPK signaling pathways



E. Flory, PEI

Complexity of signalling

Overlap and location of positive and negative modulators of NFk-B signalling identified in a cell-based screen within the T-cell receptor signaling pathway

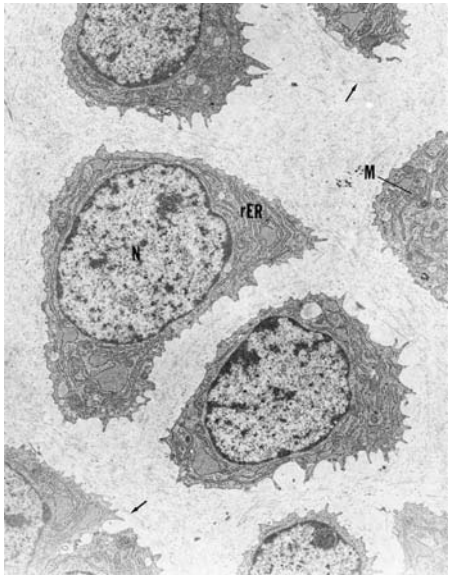


Halsey et al, Genome Biology 2007

Challenges with cell-based products

Cells are complex systems

- Cells are dependent on their (micro-) environment
- Cells are reactive to their environment
- Cell cultures can become heterogeneous
- Cells might de-differentiate (e.g. during longer cell culture)
- Cells might migrate („biodistribution“)
- Cells are fragile and (sometimes) mortal



=> Regulatory consequences:

√ Need for adequate characterization

√ but also necessity to accept limitations

The ATMP Regulation

Committee for Advanced Therapies

- ✓ New Scientific Arena
- ✓ Expertise
- ✓ Beyond Traditional
- ✓ Research

- ► Lack of funds and costly investments
- ► Market (specific and small)
- ► Regulatory barriers

Committee for Advanced Therapies

Why a work programme?

EMA is a key player in the successful implementation of ATMP legislation

- A shared vision to address challenges of ATMPs
- Being empowered to take decisions means taking responsibilities and learn balance

Committee for Advanced Therapies

Why a work programme?

- Understand the environment
  - Provide adequate tools to overcome barriers to translation
    - Guidelines in line with scientific progress

      Is it the product that has to stretch to the guideline
      or is it the guideline that has to be realistic for the product?

10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

Article 29

Transitional period

1. Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

2. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.

3. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in paragraphs 1 and 2 of this Article.

„In God we trust, the rest bring data!“

W. Edwards Deming

Pioneer in Quality Philosophy, W. Edwards Deming is widely held to have been one of the leaders who helped create the Total Quality Movement. Deming's 14 points and his book "Out of the Crisis" are key documents in the development of Quality Systems for Business management. Dr. Deming is best known for his revolution in the quality and economic productions in Japan where from 1950 onward he taught top management and engineers, methods for management of quality. These teachings dramatically altered the economy of Japan. In recognition of his contributions the Union of Japanese Science and Engineering (JUSE) instituted the annual Deming prizes for achievement in quality and dependability of product.
http://www.resourcesystemsconsulting.com/blog/reference/glossary

Efficacy data
(Marketing ≠ Efficacy!)
(„Experience“ ≠ Proof of efficacy!)

Which data can be used?

How to deal with claims like
„No reports on serious adverse events so far, so a very well tolerated and safe product“?

Objective 1

- **To successfully respond to implementation of the provisions of Article 29 of Regulation (EC)1394/2007: assessment of products legally on the EU market**

Know the number and kind of products legally on EU market

Reflect on the criteria for MAA assessment

Proactive dialogue with potential applicants and MSs

Report on the experience to EC and MSs in 2010-2011

Objective 2

- **To facilitate development of ATMP and access to registration procedure**

B) Strengthen dialogue with stakeholders:

•Draft a structured work programme tailor-made for the **specific needs of different parties** (industry, SMEs, Academia, research groups, patients' groups).

•Increase the list of **CAT Interested Parties**

•Engage in dialogue with **charity foundations and trusts** concerning products they are developing .

•Organise a **joint conference** on ATMPs involving EMA/CAT, EFPIA, EBE, EUROPABIO, Learned Societies to share clinical, scientific and regulatory expertise in the field for the benefit of all stakeholders

Objective 3

- **Promote the use of available regulatory procedures and introduce potential improvements**

Provide regular tutorial training / workshop for all stakeholders (including assessors, inspectors)

Developing an European training and education platform for SMEs and Academia

Dedicated assistance for ATMP certification submissions

Objective 4

- To explore possibilities offered by the regulatory procedures to the ATMP field (by improving existing procedures and reflecting on alternative procedures)

Fast track evaluation?

Extend incentives for SMEs to academia, hospitals, trusts and small research groups?

Because the science is evolving fast, on regular basis to screen system to identify potential changes required
(and then engage in dialogue with the European Commission)

Appropriate use of follow-up efficacy system

Objective 5

- **Foster innovation**

Dialogue with EC DG Research

Promote allocation of funds for ATMP research

Reinforce contact with leaders of EU projects on ATMP

Objective 6

- **Promote access and availability to ATMP for EU patients**

Cooperation with CTFG

Dialogue with NCA on 'hospital exemption'

Encourage development of ATMPs for unmet medical needs without alternative treatments.

The CAT as an open-minded scientific player

PERSPECTIVES

OPINION

Challenges with advanced therapy medicinal products and how to meet them

The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat

Abstract | Advanced therapy medicinal products (ATMPs), which include gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered products, are at the cutting edge of innovation and offer a major hope for various diseases for which there are limited or no therapeutic options. They have therefore been subject to considerable interest and debate. Following the European regulation on ATMPs, a consolidated regulatory framework for these innovative medicines has recently been established. Central to this framework is the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA), comprising a multidisciplinary scientific expert committee, representing all EU member states and European Free Trade Association countries, as well as patient and medical associations. In this article, the CAT discusses some of the typical issues raised by developers of ATMPs, and highlights the opportunities for such companies and research groups to approach the EMA and the CAT as a regulatory advisor during development.

Advanced therapy medicinal products (ATMPs) comprise gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products and tissue-engineered products (for legal definitions see BOX 1 and REFS 1,2). They are at the forefront of innovation, offering potential treatment opportunities for diseases that currently have limited or no effective therapeutic options. ATMPs have therefore been subject to considerable interest, but have generated both positive and negative outcomes.

For example, recent publications have suggested that gene therapy for monogenetic diseases could result in long-term beneficial results and may prove to be an effective treatment strategy[3–6]. In addition, cell-based skin substitutes and cartilage products have already been used for more than a decade, and upcoming somatic cell therapy medicinal products and tissue-engineered products might also become efficacious treatment modalities. However, despite their promise and the progress made, ATMPs have sometimes caused clinical problems, which have led to reports in the lay press. For example, although rare, fatalities following gene therapy have been reported, including a lethal systemic inflammatory immune reaction and leukaemia due to insertional oncogenesis[4,7]. Recently, fetal stem cells were reported to cause a brain tumour, suggesting that cell-based medicinal products (CBMPs) also have intrinsic risks that need to be addressed[8].

With the new European regulation on ATMPs[1], a consolidated regulatory framework for these innovative medicines has recently been assembled. Central to this new legislation is the establishment of the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) in London, UK. The CAT is a multidisciplinary scientific committee of experts representing all member states of the European Union and countries from the European Economic Area and the European Free Trade Association (Iceland and Norway are currently represented in the CAT), as well as representatives from patient and medical associations (BOX 2). This independent committee, with a high degree of expertise in both the scientific and regulatory aspects of ATMPs, started its work in January 2009. The CAT gathers dedicated European experts to review the quality, safety and efficacy of ATMPs according to standards established by regulatory authorities, and to debate scientific developments in the field. Information on the declared scientific expertise of the CAT members and alternates (reflecting the expertise required by the regulation on ATMPs) can be found in FIG. 1.

The CAT is responsible for the primary evaluation of ATMP marketing authorization applications (MAAs) for the EMA's Committee for Medicinal Products for Human Use (CHMP). The CAT operates two new regulatory procedures for companies developing ATMPs — the classification procedure and the certification procedure — which are both discussed further below.

The CAT aims to foster innovative medicines while maintaining a high standard of regulatory responsibility. Guidance had already been developed by various EMA and CHMP regulatory groups (for example, the Biologics Working Party, the Gene Therapy Working Party or the Cell-based Products Working Party) before the establishment of the CAT, and through the Scientific Advice Working Party. However, the CAT now combines and complements these activities within a single committee to support the development of ATMPs in Europe.

Marketing authorization of ATMPs requires, as for all medicinal products, that the applicant demonstrates that the product is consistently manufactured to a predefined quality, and that it is safe and efficacious in patients. The CAT recognizes that some ATMPs will require new strategies for their development and scientific assessment. For example, the clinical performance of many types of CBMPs strongly depends on the final performance of the cell preparation administered. Success depends on the rigorous control of the manufacturing process and specifications, which has

Nat Rev Drug Discov 9(3):195-201.

Correspondence

Ouagadougou, Burkina Faso (A-O); and University of Newcastle, Newcastle, UK (SC)

1 Kohli M, de Souza DK. Young Voices demand health research goals. Lancet 2010; 375: 1445–47.
2 Anon. Declaration of the International Students' Meeting on Public Health (ISM-PH4, April 22, 2005), Istanbul, Turkey. http://www.ii-hasak.org/english/work20/ongoing/ismph.pdf (accessed July 22, 2010).

Use of unregulated stem-cell based medicinal products

Advanced-therapy medicinal products (ATMPs) include stem cells, gene therapy, or engineered tissues, and hold promise for a large number of currently incurable diseases. Yet no marketing authorisation has been granted for any stem-cell medicinal products in the European Union.

ATMPs are complex and their evaluation requires specific expertise. For this reason, the Committee for Advanced Therapies (CAT) was established in the European Medicines Agency. The CAT is responsible, among other tasks, for preparing a draft opinion on the quality, safety, and efficacy of ATMPs that follow the centralised marketing authorisation procedure.[1]

The CAT is concerned about a phenomenon known as stem-cell tourism in which severely ill patients travel to clinics around the world where unauthorised stem-cell-based treatments are offered in the absence of rigorous scientific and ethical requirements. Some clinics offer these unauthorised therapies to desperate patients with incurable diseases at a high cost without ethics approval from independent bodies and potentially without documentation of adequate quality standards necessary for the protection of patients' safety.

There are serious concerns about the safety and efficacy of such experimental treatments that use poorly defined stem-cell preparations from a variety of sources. These preparations are often inadequately characterised and they can lack pharmacological or toxicological data from non-clinical studies to establish reasonable evidence of safety and efficacy.[2,3] Generally, there are no peer-reviewed publications to demonstrate their efficacy. The retrospective data analyses that are sometimes found on the clinics' websites lack transparency; hence, such data cannot be properly assessed. However, there are already well documented cases of where so-called stem-cell therapy has resulted in serious adverse effects, including brain tumours,[4] meningitis or other life-threatening infections.[5]

The CAT strongly encourages high-quality research leading to the development of stem-cell-based medicinal products in approved programmes of research and development. Before clinical use, rigorous non-clinical studies should be done to establish the safety and effectiveness.[6]

To ensure the safety of patients involved in clinical research, development of stem cells should comply with the highest standards, as for any investigational medicinal product, under the supervision of statutory regulatory bodies. Those planning the development of such treatments are encouraged to engage in dialogue with the CAT at an early stage of this process.

We declare that we have no conflicts of interest.

For members of the Committee for Advanced Therapies and the CAT Scientific Secretariat see web appendix

Committee for Advanced Therapies and CAT Scientific Secretariat
advancetherapies@ema.europa.eu
European Medicines Agency, London E14 4HB, UK

1 European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF (accessed July 21, 2010).
2 Regenberg AC, Mullikin LA, Schneider R, Mathews DJ. Medicine on the fringe: stem cell-based interventions in advance of evidence. Stem Cells 2009; 27: 2383–89.
3 Barclay E. Stem-cell experts raise concerns about medical tourism. Lancet 2005; 372: 885–84.
4 Committee for Advanced Therapies. Reflection paper on stem cell-based medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500073932.pdf (accessed July 21, 2010).

Patients' information sheets and multicentre studies

Service Users Research Endeavour (SURE) is a patients' representative group at the Liverpool Heart and Chest Hospital, UK. One of our main functions is to check the clarity of patients' information sheets. We would like to bring to your attention what we find to be a lack of consistency in the information sheets that accompany commercial multicentre studies.

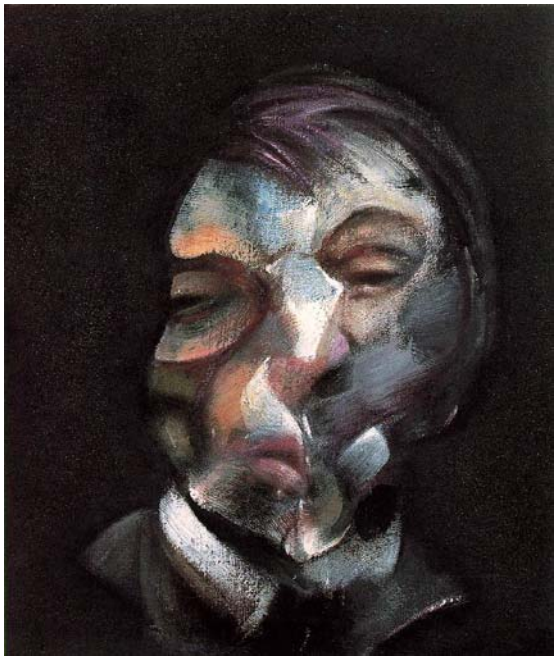
Patients' information sheets should give a fully comprehensive idea of what the study means and what is expected from participating individuals. But they should also be concise and in a language easily understood by patients and laypeople. In May, 2008, the UK's National Research Ethics Service introduced the requirement for a lay summary with each new clinical research application, but there does not seem to be any way of enforcing this requirement. In our experience, when dealing with commercial multicentre studies with a central site responsible for drafting and circulating patients' information sheets, the lay summary is often missing from the submitted documentation.

Our experience with one study led us to write directly to the sponsoring pharmaceutical company. In this case, the patients' information sheet was 18 pages long and written in complicated language that was not very meaningful to a layperson and even less so to a sick patient. The company then produced a one-page lay summary that was clear and informative and very welcome to the SURE group members.

In general terms, lay groups might feel that there is a lack of cooperation from big pharmaceutical companies in the production of lay summaries, but our experience shows that direct communication can have the desired result. However, a direct approach should not be necessary if companies

Lancet 376(9740):514

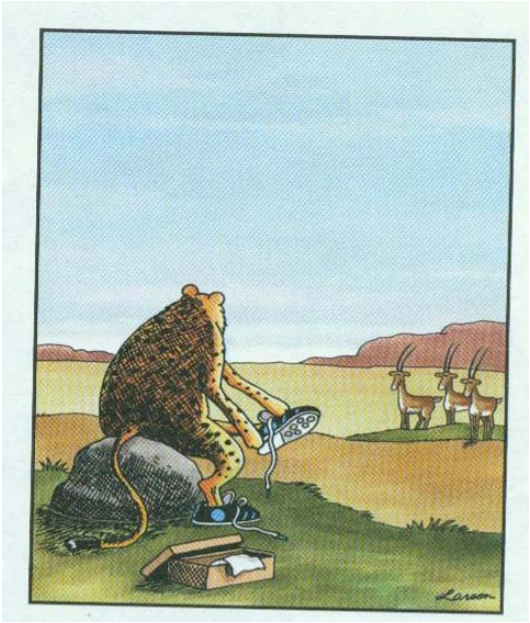
Holistic view:
Step back and look at the entire picture



Francis Bacon
Self portrait
(1971)

Francis Bacon
Portrait
(1979)

…and closing with thanks



Yes, we are up to speed to address the challenges of Advanced therapies medicinal products – the EMA has created an innovative environment!