Challenges with Advanced Therapy Medicinal Products

First Workshop on Advanced Therapy Medicinal products (ATMP) at the European Medicines Agency 3rd April 2009

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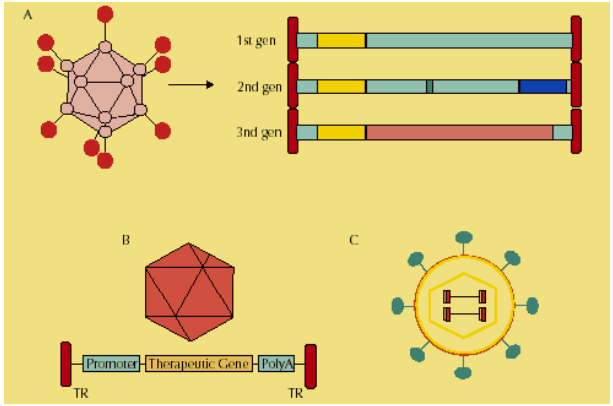
Advanced therapies and their challenges

Gene therapy medicinal products

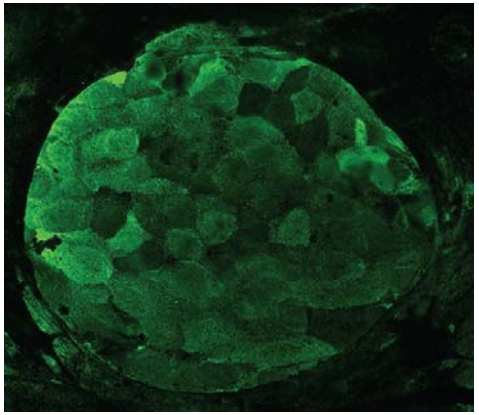
Somatic cell therapy medicinal products

Tissue engineering products

Genetically modified cells



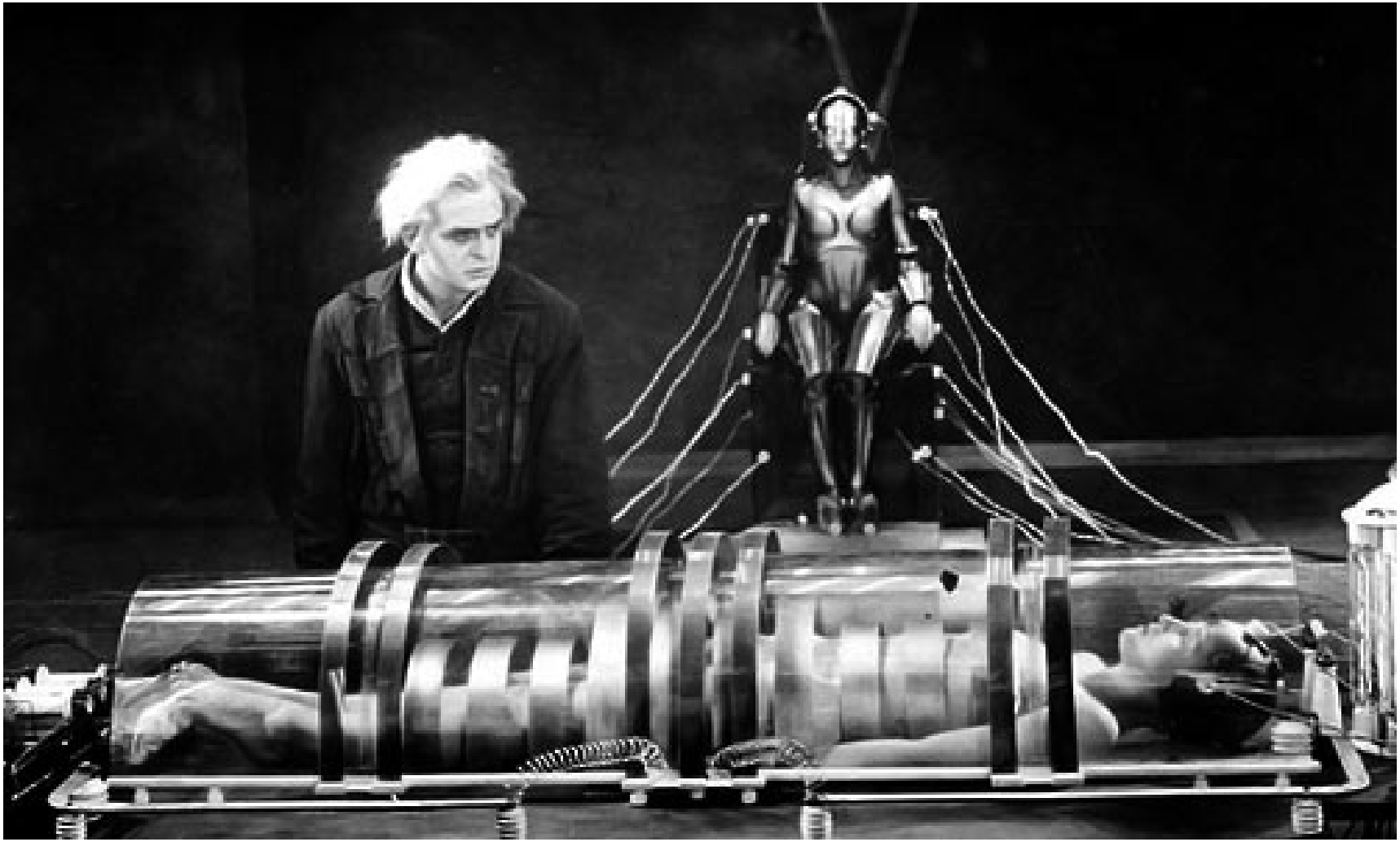
www.heartandmetabolism.org



Nat Biotechnol 2005, 23(7)

www.biomed.brown.edu

Advanced Therapies: Science Fiction?



Clinical Trial Applications with CBMP

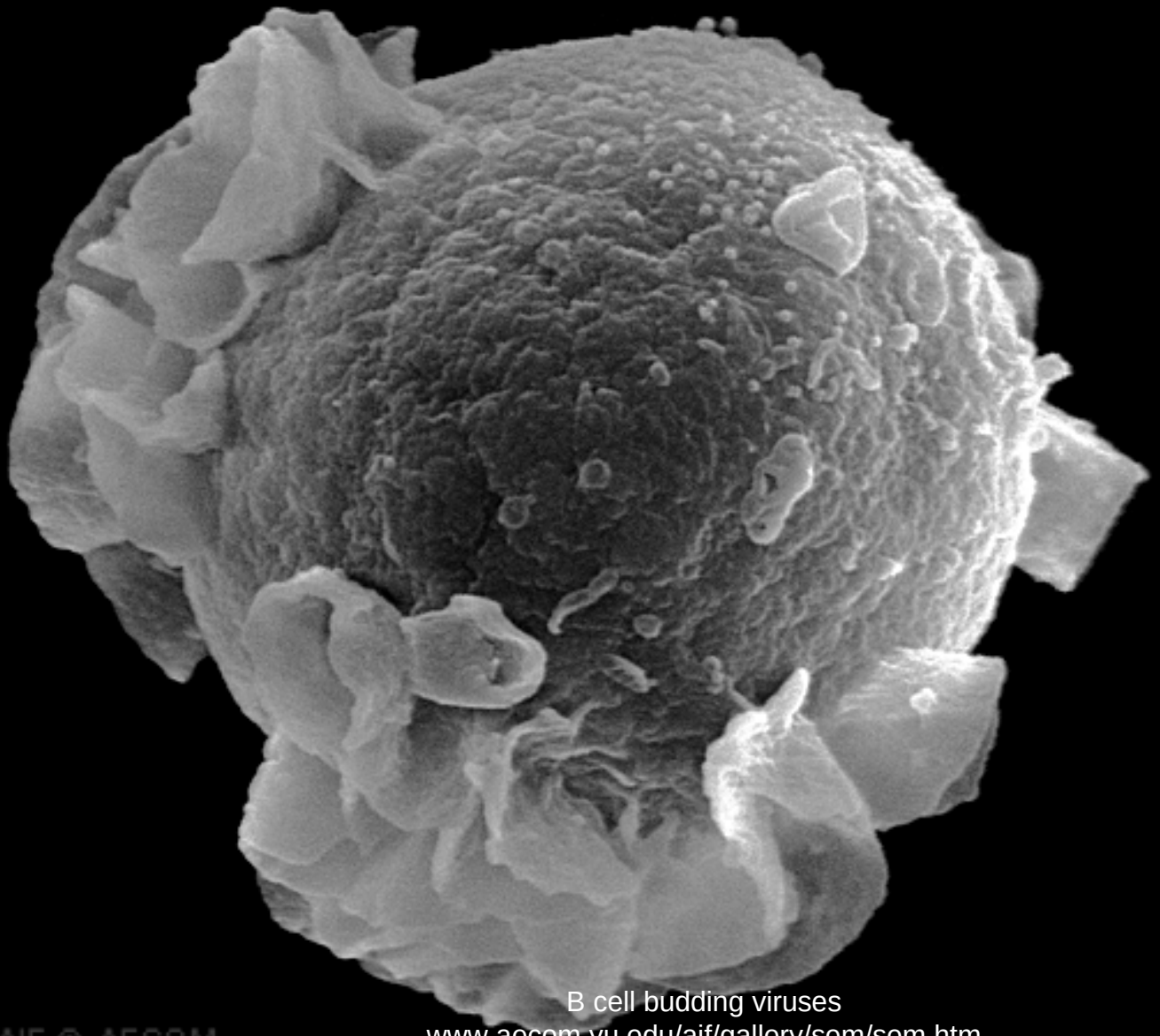
Somatic cell therapy MPs ***(trials / original products)***	***3Q 2005*** ***(25 / 13)***	***3Q 2006*** ***(73 / 59)***	***3Q 2007*** ***(132/112)***
Cancer immunotherapy	3	23	45
Cardio-vascular	4	17	31
Skin/liver/lung/eye/diabetes/intestine/bone TE	5	12	28
Neurological	1	4	5
Lymphohistiocytosis (HLH)	–	1	1
AIDS	–	1	1
Infertility	–	1	1
	13	**40**	**112**

Eudra CT: 3Q 2005 to 3Q 2007

E. Flory, PEI

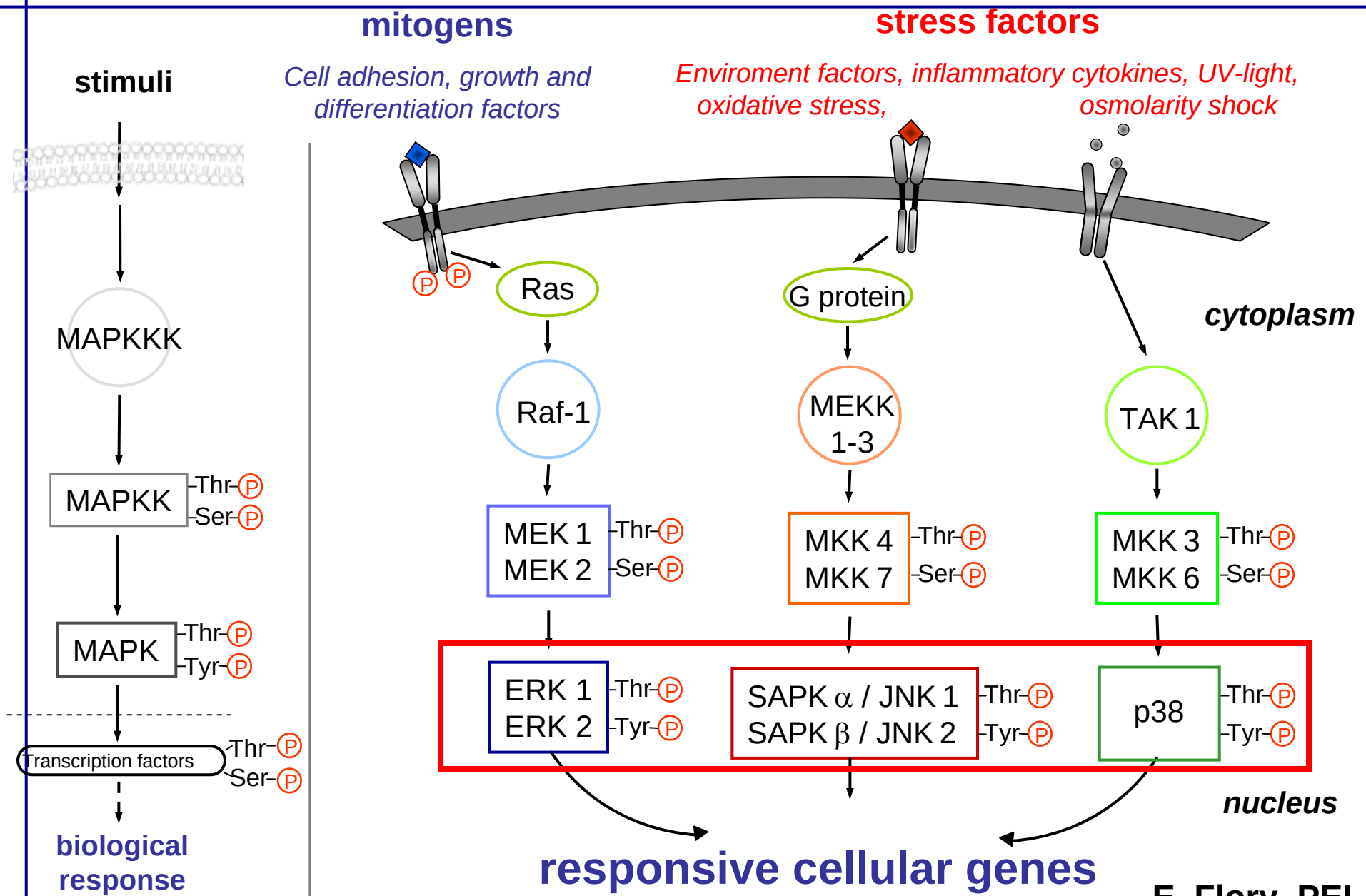
Complexity of Advanced Therapies

Fab Fragment of a
monoclonal antibody



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

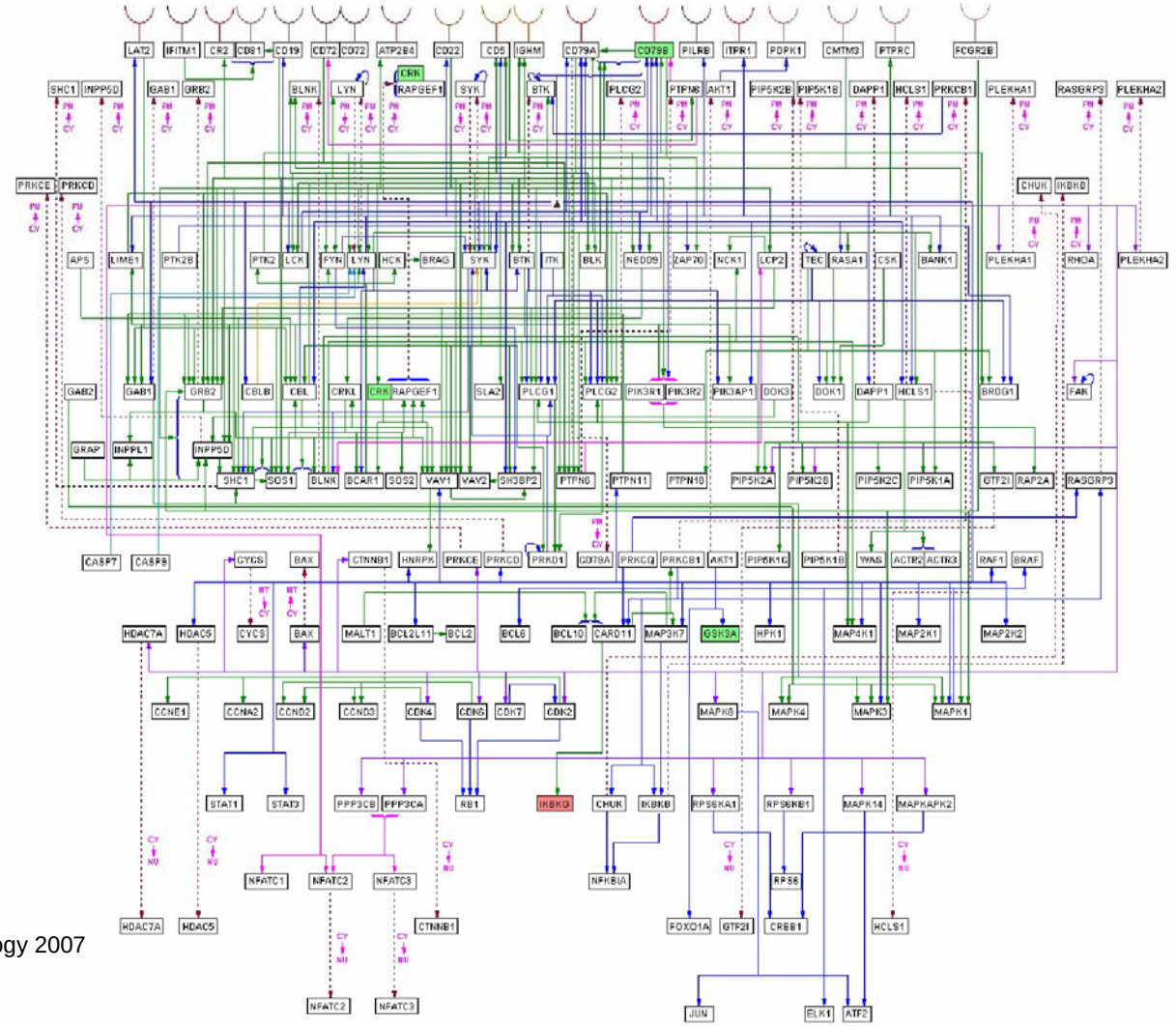
Intracellular MAPK signaling pathways



E. Flory, PEI

Complexity of signalling

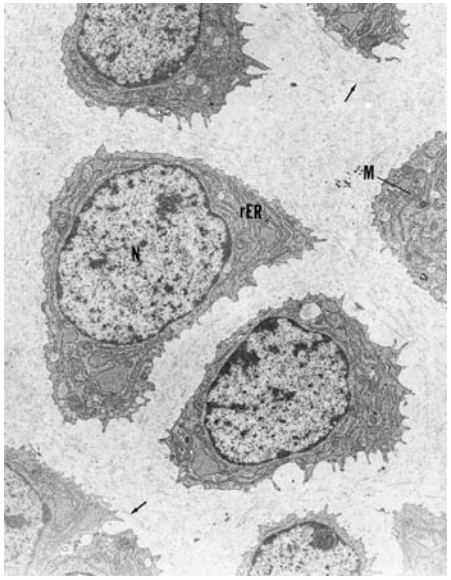
Overlap and location of positive and negative modulators of NFk-B signalling identified in a cell-based screen within the T-cell receptor signaling pathway



Halsey et al, Genome Biology 2007

Challenges with cell-based products

- **Cells are complex systems**
  - **Cells are dependent on their (micro-)environment**
    - Species-specificity
    - Disease-specificity
  - **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**



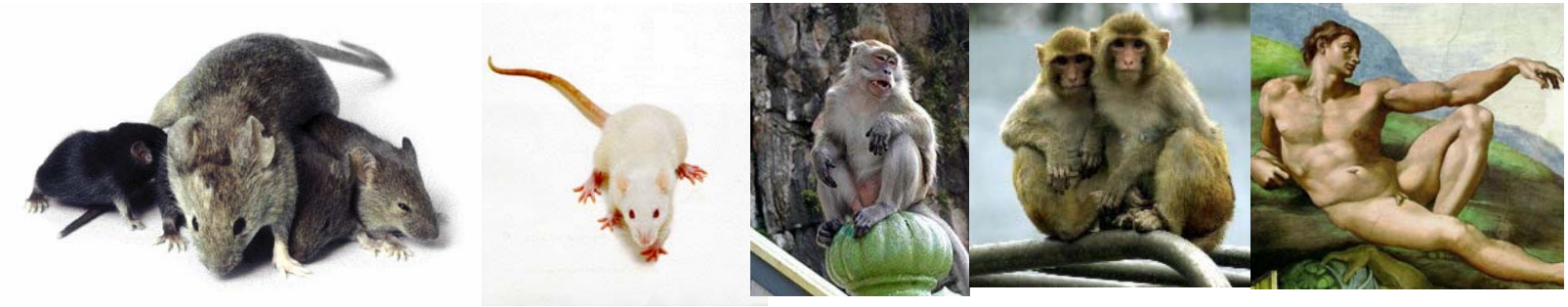
=> Regulatory consequences:

√ Need for adequate characterization

√ but also necessity to accept limitations

Challenges with cell-based medicinal products

- **Non-clinical evaluation**



A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)*.

*NfG on preclinical safety evaluation of biotechnology derived pharmaceuticals (CPMP/ICH/302/95; ICH S6)

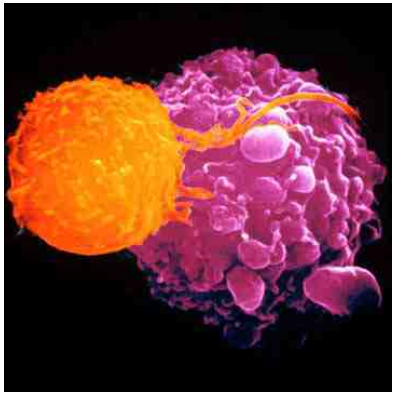
- **Cell surface molecules (receptors, integrins,…)**
- **Secreted factors like cytokines**

Example: Engineered killer T cells

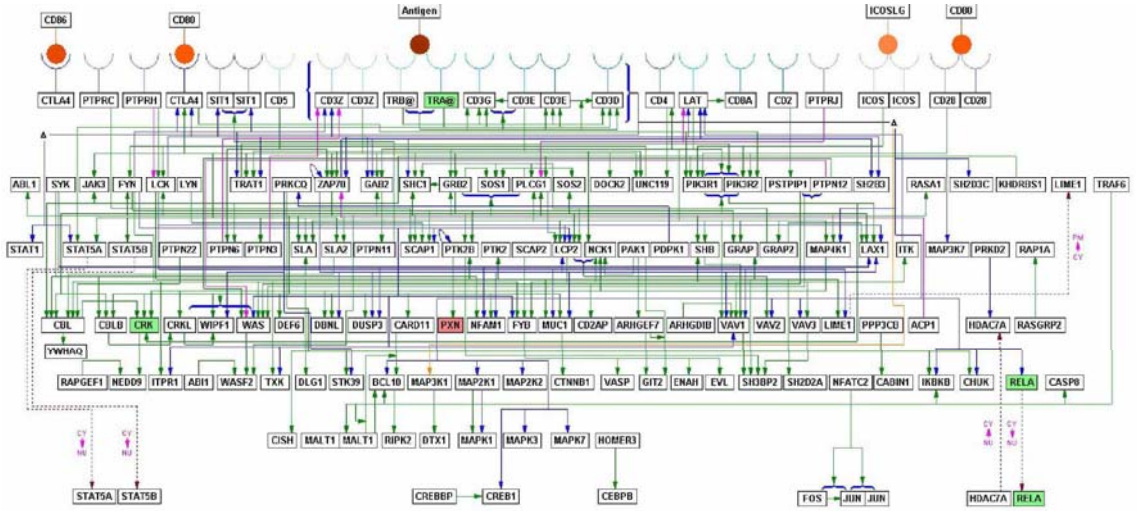
www.jdaross.cwc.net/cellmediated_immunity.htm

Challenges with genetically modified cells

- **Example: Genetically modified T cells directed to attack tumour cells**
  (transduced with tumour-specific TCR)

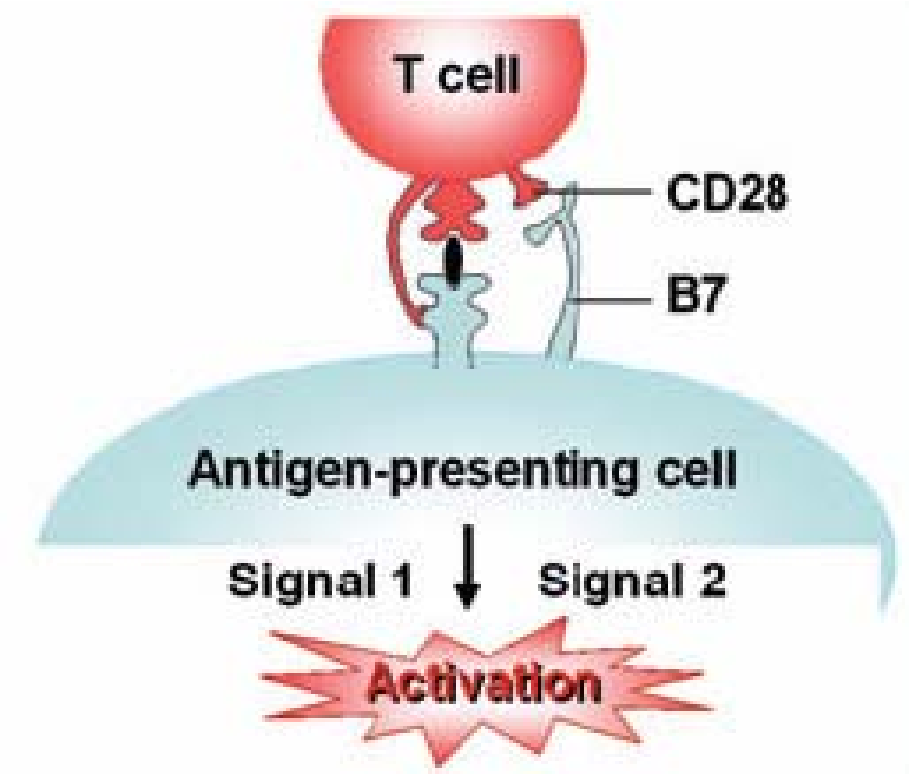


  - **CD8+ T cells are highly potent killers**
  - **Around 20,000 active genes,**
    (including T cell receptor, cytokines, chemokines, their receptors,…)
  - **Complex interactions of signalling pathways, e.g. NFκB**



Halsey et al, Genome Biology 2007

T cell activation



Schneider CK et al, Nat Biotechnol 2006, 24(5)

T cell recognition is „degenerate“

Hypothesis of „molecular mimicry“ in the pathogenesis of autoimmunity

= a T cell cross-reacts with a self-antigen

Pecularity of the T cell receptor (TCR):

Ligand-TCR interaction is not as specific as for antigen-antibody binding („degenerate“ recognition)

=> several similar sequences can bind and activate the T cell

Example: Activation of MBP-specific T cell clones by microbial peptides

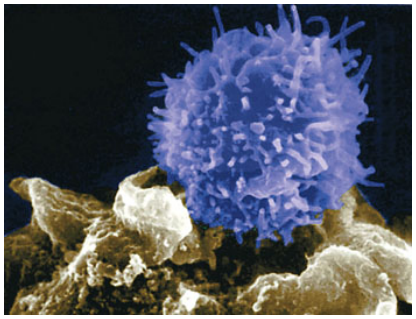
Species	Protein	Amino acid sequence
Homo sapiens	**Myelin Basic Protein**	**ENPVVHFFKNIVTPR**
Human Papilloma Virus 7	L2 Protein	IGGR**VHFFK**D**I**SPIA
Herpes Simplex Virus	UL15 Protein	FRQL**VHF**VRDFAQLL
Adenovirus Typ 12	ORF	DFE**VV**T**F**L**K**DVLPEF
Pseudomonas aeruginosa	Phosphomannomutase	DRLLML**F**A**K**DV**V**SRN

Wucherpfennig et al, J Clin Invest 1995, 100(5)

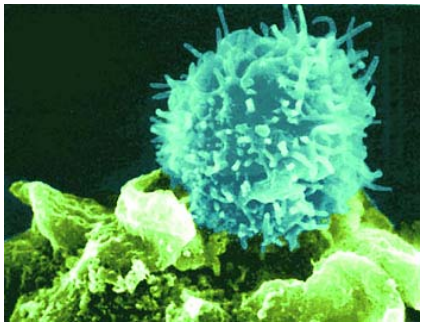
Challenge: Non-clinical toxicology

- **Toxicity of advanced therapies aiming at augmenting T cell activation**
  - **Genetically modified T cells (tumour-specific TCR)**
  - **Tumour vaccines based on viral vectors expressing modified tumour antigens for enhanced antitumour activity**
  - **Engineered antitumoural T cells with modified T cell receptors for enhanced antitumoural activity**
- **The main concern is cross-reactivity with physiological tissue**
- **Challenge: No sufficiently informative non-clinical model at all!**

The „homologous“ model



Human engineered T cells with human T cell receptor



Mouse engineered T cells with mouse T cell receptor

Challenge: Non-clinical toxicology

- **Testing of the product itself in animals not relevant**
  - **T cells will not recognize anything (will only recognize in context with corresponding human MHC molecule)**
  - **A mouse model transgenic for the corresponding MHC molecule also not sufficiently predictive: Cross-reacting antigens are entirely different („man is not mouse“)**

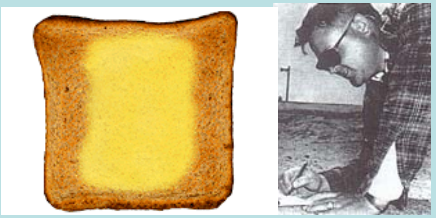
- **Testing in a homologous model likewise not relevant**

  - Engineered mouse T cells recognizing mouse tumour antigen in a mouse MHC context

  => cross-reactivity not sufficiently informative

How to solve this?

Murphy's laws



„If anything can go wrong, it will.“

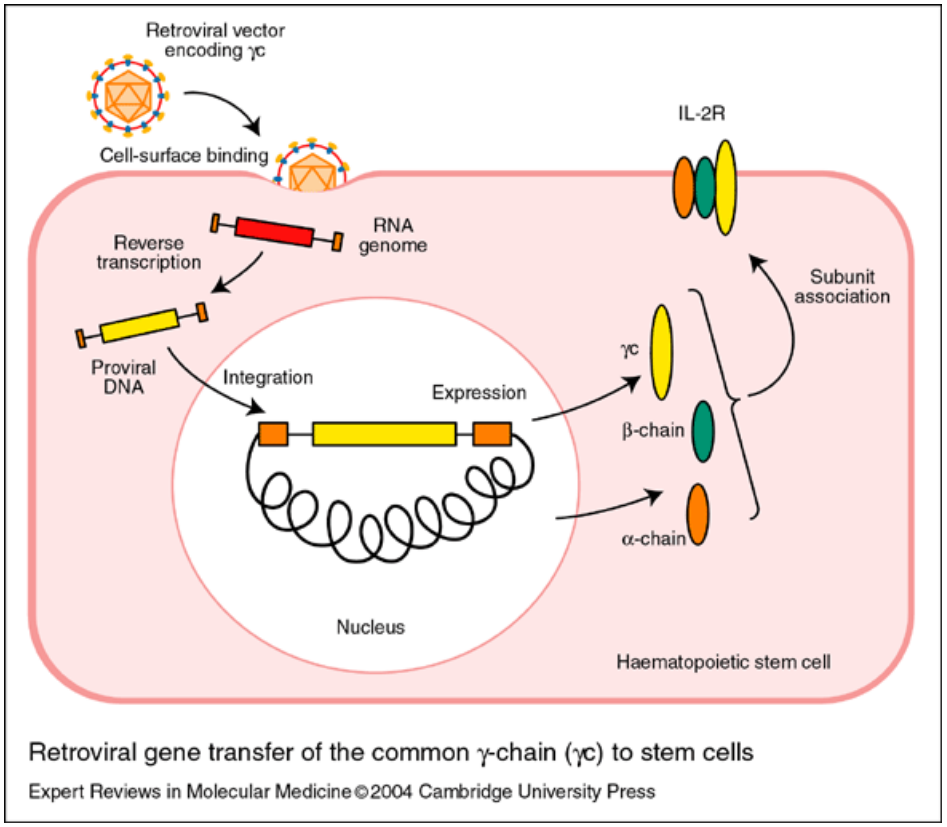
„If you perceive that there are four possible ways in which something can go wrong, and circumvent these, then a fifth way, unprepared for, will promptly develop.“

„Left to themselves, things tend to go from bad to worse.“

- **Employ risk-based approach**
- **Implementation of relevant (additional) safety endpoints in the clinical trials**
  - **„You will only see what you are looking for“**
  - **Also based on theoretical consideration**
- **Appropriate starting „dose“**
- **Take information from comparable products, knock-out mice** (can be valuable, since gene is knocked out completely)

Challenges with gene transfer medicinal products

Gene transfer medicinal products



Retroviral gene transfer of the common γ-chain (γc) to stem cells

Vector-related issues clearly to be distinguished from effects mediated by expression of the gene

= added complexity as compared to biotechnological products of having additional test components (vector, genetic material)

Clinical challenges with gene transfer

- **„How to target only the target“**
  - **Gene transfer medicinal products which substitute for an organ or tissue-specific gene defect, but with multilocular occurrence (skin, muscle, bone,…)**
    - How to administer locally to ensure desired local distribution?
    - Impact on patient when administered multilocally (more than 20 injections per patient etc.)
    - Impact of additional devices on safety (e.g. tissue damage and enhancement of immunogenicity?)
  - **Where to administer locally when gene product replaces a metabolic dysfunction (e.g. clearing serum levels of certain metabolites) => might be done anywhere („local bioreactor“), but where?**
- **Possibility / Necessity for re-administration?**

Clinical challenges with gene transfer

- **How to control the clinical trial?**
  - **For proof-of-principle**
    - Patient as own control
      (comparing pre- and post treatment) might be acceptable, depending on the effect size / severity of the defect / historical data)
  - **For pivotal trial**
    - Control group usually required to distinguish effect of gene defect correction from usual best supportive care (e.g. dietary measures for metabolic conditions)
      => gene transfer usually represents a monotherapy, not an add-on to standard of care
- **How to blind the trial?**
- **How to measure clinical outcome?**
  - **For many gene defects there is no available treatment and thus no validated clinical endpoints.**

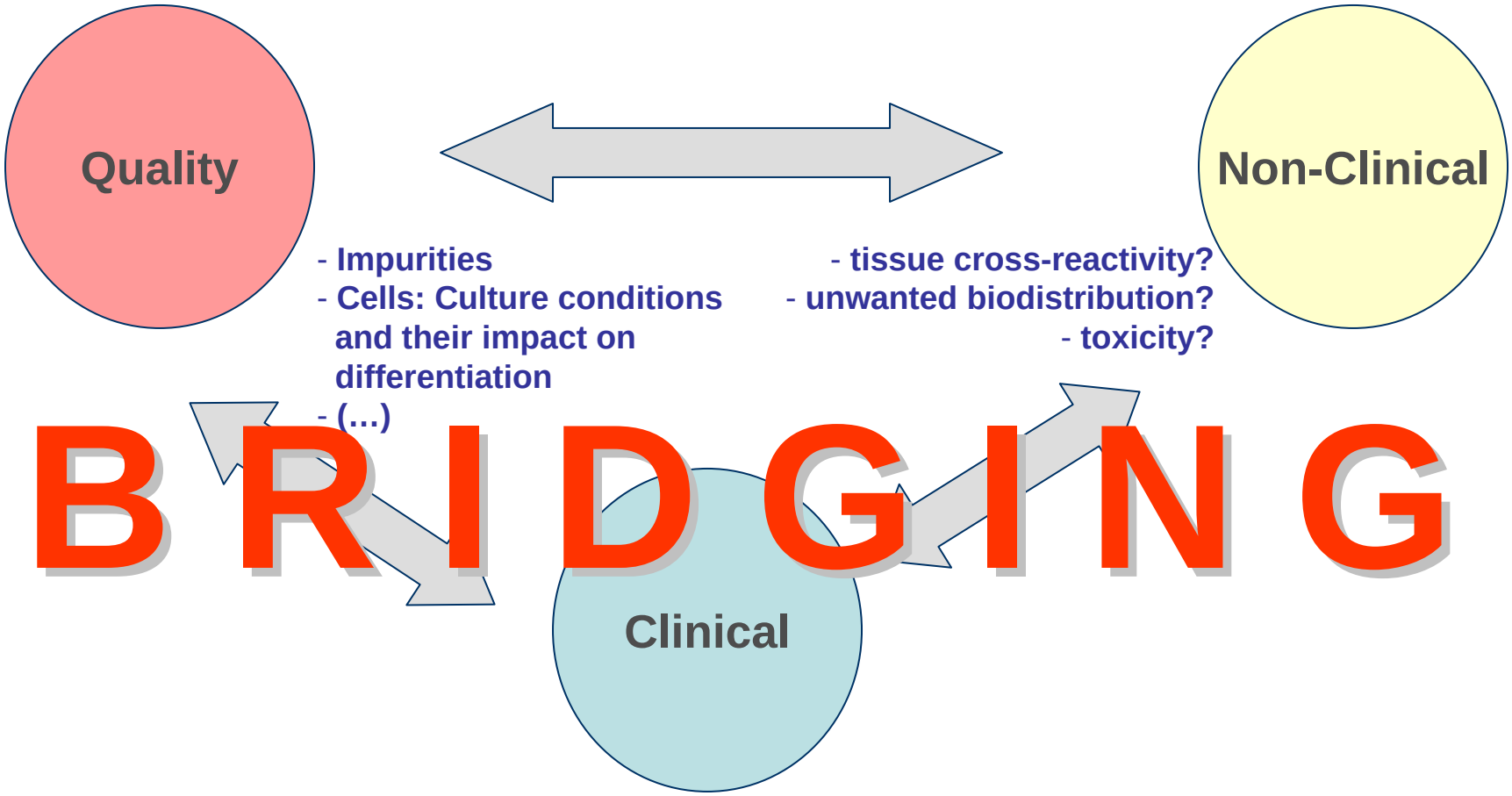
Borders to ethics

- Important: Adverse events that are to be expected must be seen in the light of the benefit
  - Even for integration / tumourigenicity!
    (e.g., gene therapy for a severe disease that would take a lethal course within the first years of life)
- Patients‘ unmet medical need vs. need for evidence
- Importance of long-term follow-up and risk management
  - Legislation: Opens possibility to long-term follow-up of efficacy => important e.g. for tissue engineering products, where efficacy might be apparent only after many years
- Autologous product: Who is the owner? The patient?

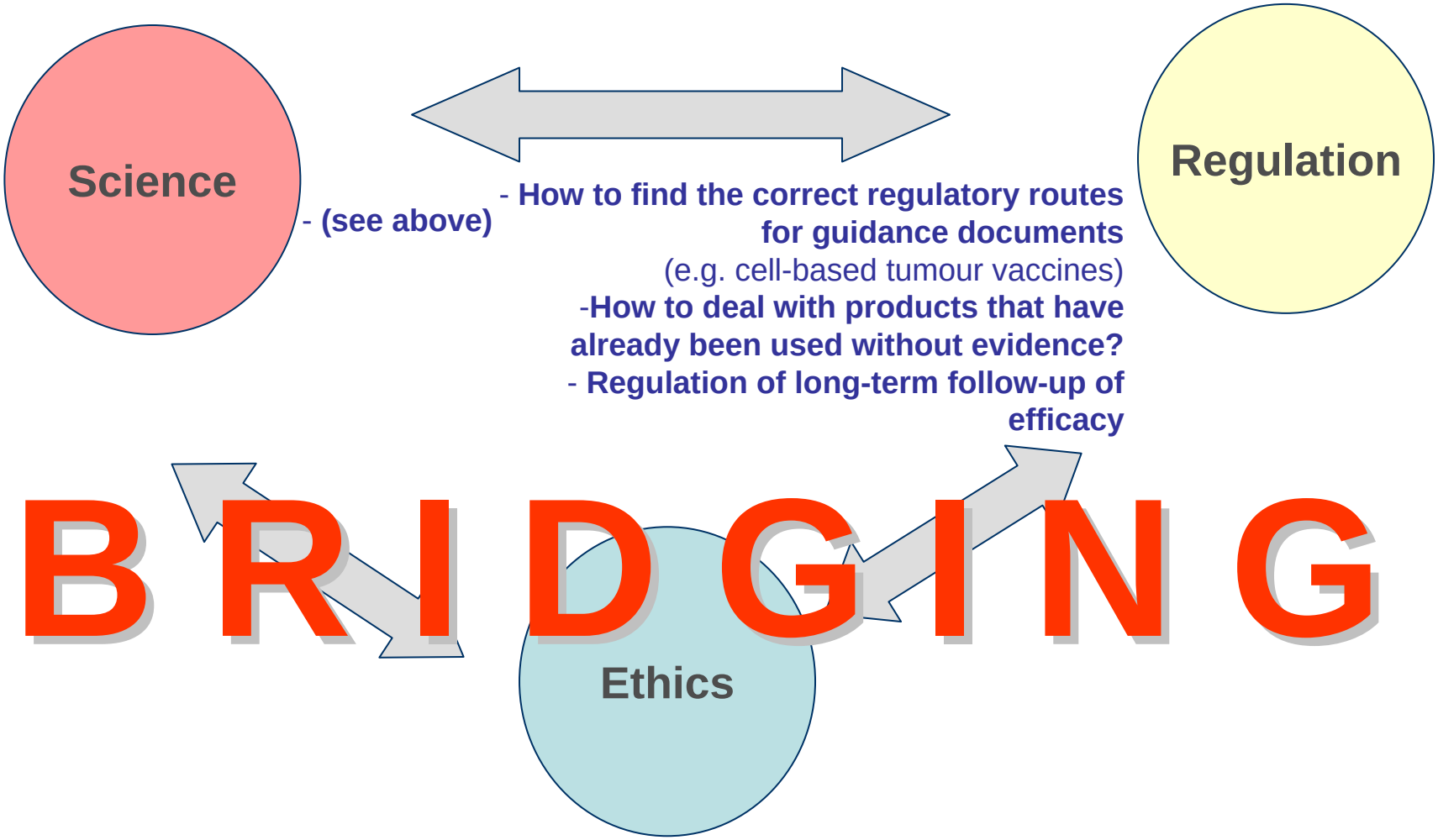
Why we have a CAT

http://www.poster.net/conger-cydney/conger-cydney-cat-fish-8300191.jpg

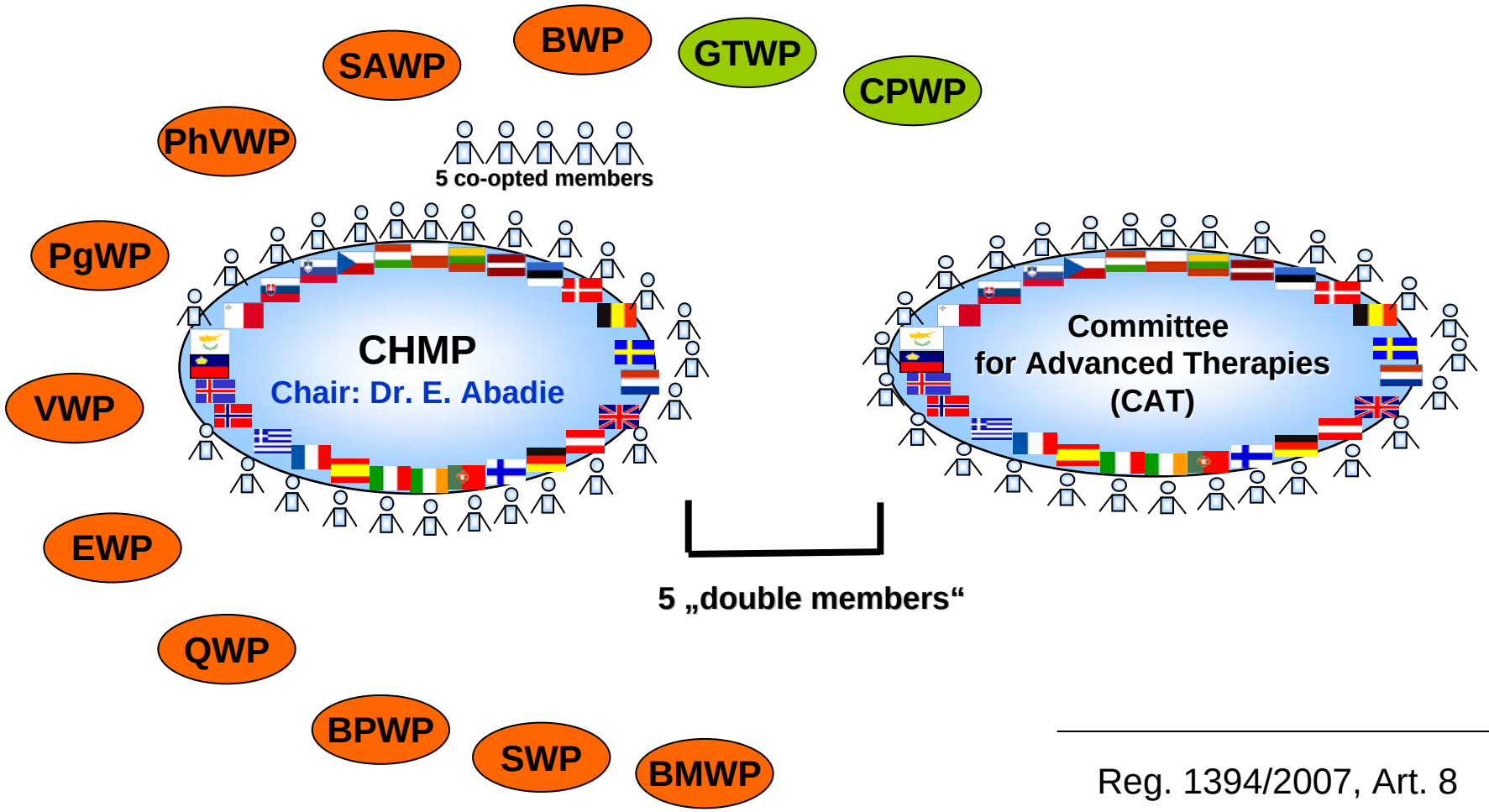
Advanced Therapies are „threesome“



Advanced Therapies are „double-threesome“

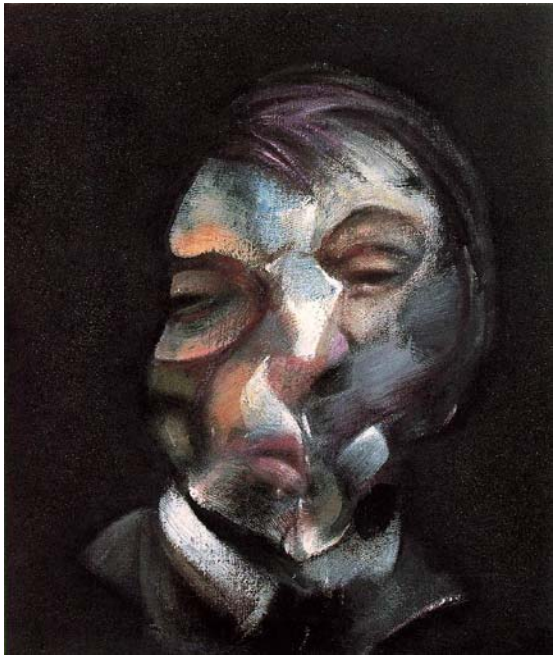


The Committee for Advanced Therapies (CAT)



Reg. 1394/2007, Art. 8

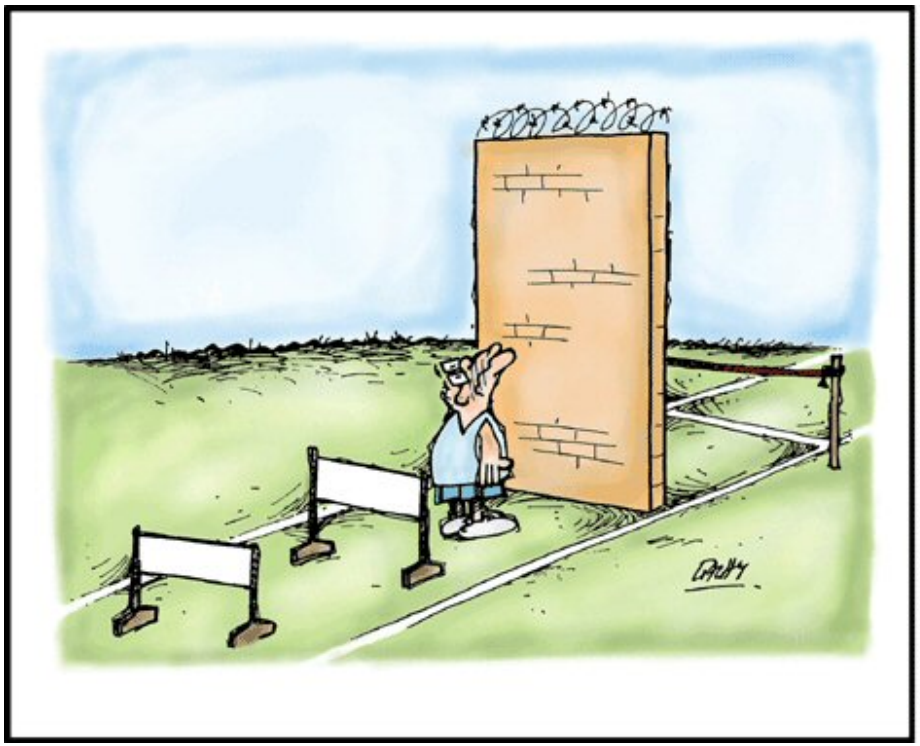
Holistic view:
Step back and look at the entire picture



Francis Bacon
Self portrait
(1971)

Francis Bacon
Portrait
(1979)

Challenge: Balanced view



Hurdles should neither be too high…

…nor too low.

To develop an ATMP is not an excuse for an immature dossier or to neglect regulatory standards.