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Advanced therapies: Implementing New Regulations

Consequences for research-based industry

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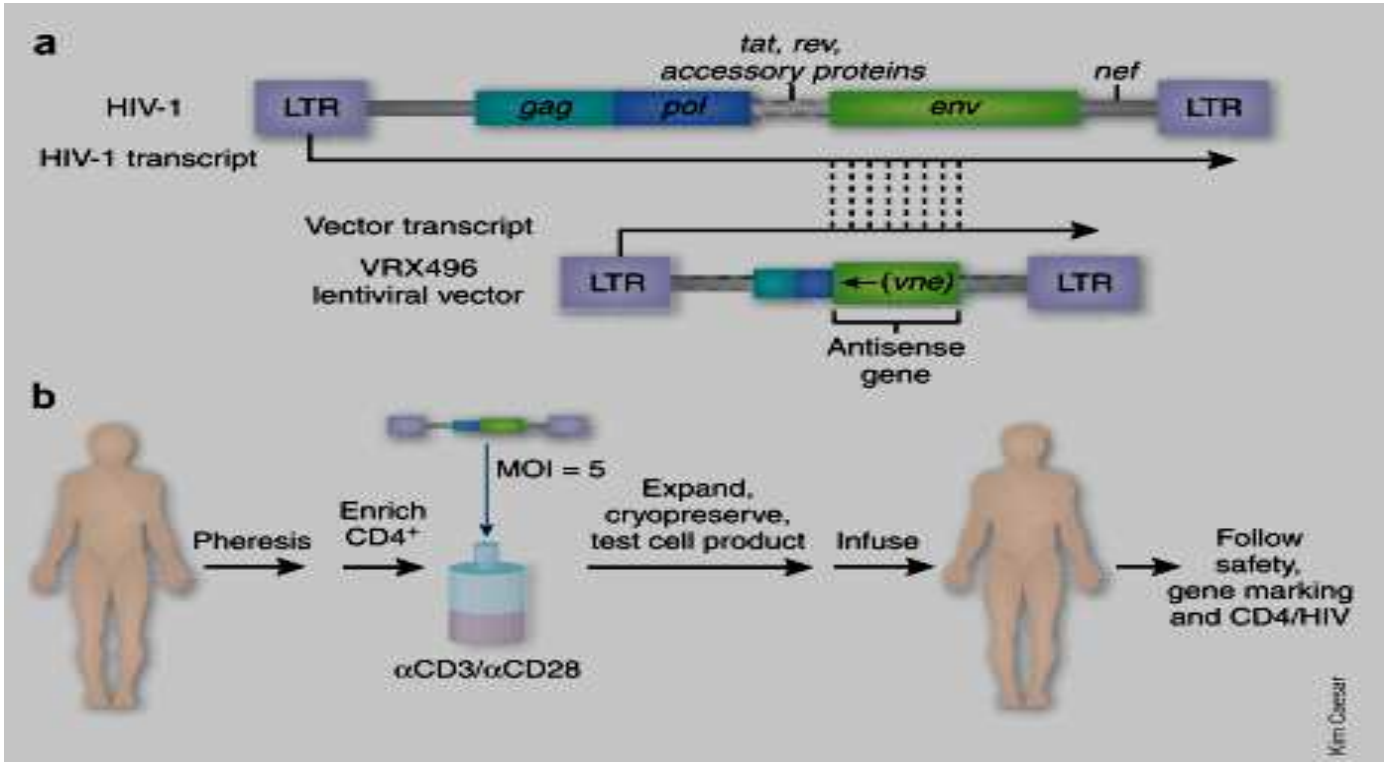
Regulatory Excellence in Europe

B. Levine et al, 2006, PNAS: Gene transfer in humans using a conditionally replicating lentiviral vector



Example: ex-vivo transfer of a therapeutic gene

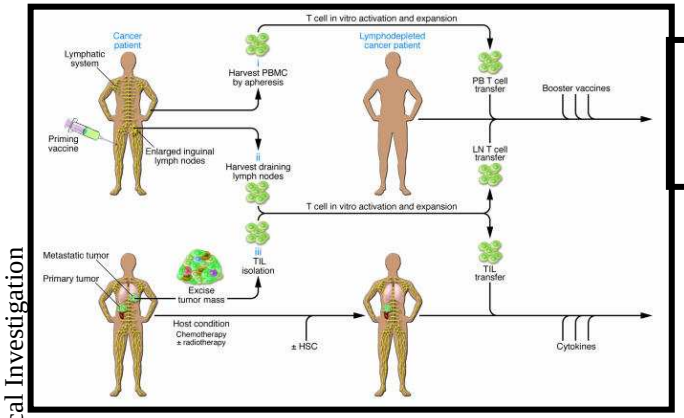
- Example for gene therapy
- Ex-vivo transfer of a therapeutic gene to human cells with its subsequent expression in vivo
- Contract manufacture possible
- New validation and testing paradigms due to low cell counts and technology

Example: ex-vivo transfer of a therapeutic gene

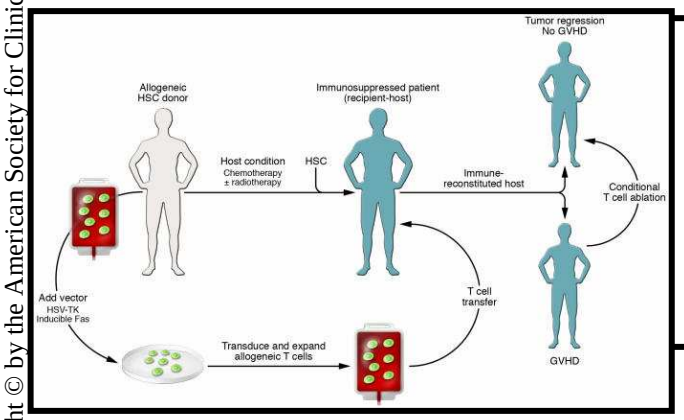
- Animal models for non-clinical safety testing available but immense non-clinical safety package
- Changes to state-of-the-art clinical development of AIDS treatments
  - Dose finding and administration regimen definition
  - Size of cohorts
  - Efficacy endpoints as usual for HIV treatments or not
  - Long-term safety follow up, i.e. 5 to 10 years

Adoptive T cell therapy for cancer in the clinic

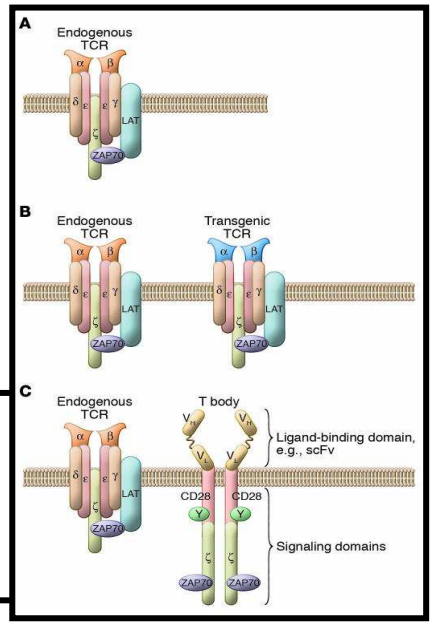
J. Clin. Invest. Carl H. June, et al. 117:1466 doi:10.1172/JCI32446



TIL instead of CTL



Combination approaches using vaccines and adoptive T cell transfer



T cells engineered to express tumor antigen–specific receptors

Example: adoptive T cell therapy

- Example for somatic cell therapy
  - Genetically modified immune cell *per excellence*
  - Personalised medicine
- Induction of retargeted immune reaction to tumors
- Tumor, e.g. melanoma = **patient** specific, even metastasis-specific
- A new cell preparation is required to be developed for the same patient if the transgenic TCR specificity is not fully reactive or has not the right affinity
- These preparations are thus constantly changed even for one patient

Example: adoptive T cell therapy

- Early Phase I stage, use in late stage tumor diseases
- Academic groups or spin-offs
- Problematic animal models
  - Problematic to predict human relevance
  - No commonly accepted PD and lack of relevant toxicity models
  - Variety, discrepancies and controversies
- Centre-based manufacture and treatment
- Sample size and timing prohibit classical manufacturing process validation and release testing approaches

More somatic therapies, more advanced

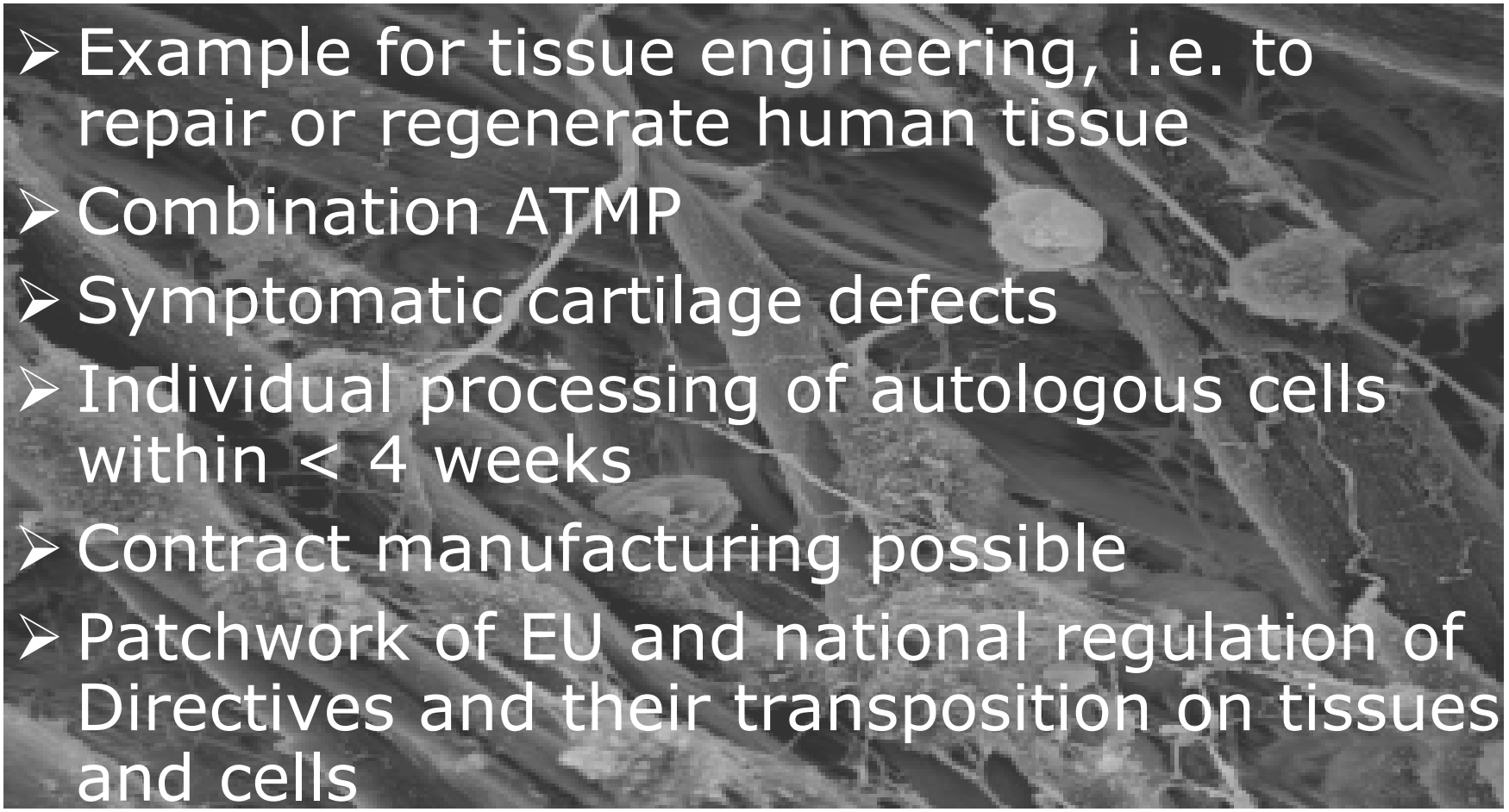
Intramyocardial CD133+ bone marrow stem cell transplantation in chronic heart failure

Prof. Gustav Steinhoff, Department of Cardiac Surgery, Rostock

TK cell therapy enabling haplo-HSCT in high-risk leukaemia

MOLMED S.p.A.

Example: autologous cultured chondrocytes



- Example for tissue engineering, i.e. to repair or regenerate human tissue
- Combination ATMP
- Symptomatic cartilage defects
- Individual processing of autologous cells within < 4 weeks
- Contract manufacturing possible
- Patchwork of EU and national regulation of Directives and their transposition on tissues and cells

Basis: innovative therapeutics

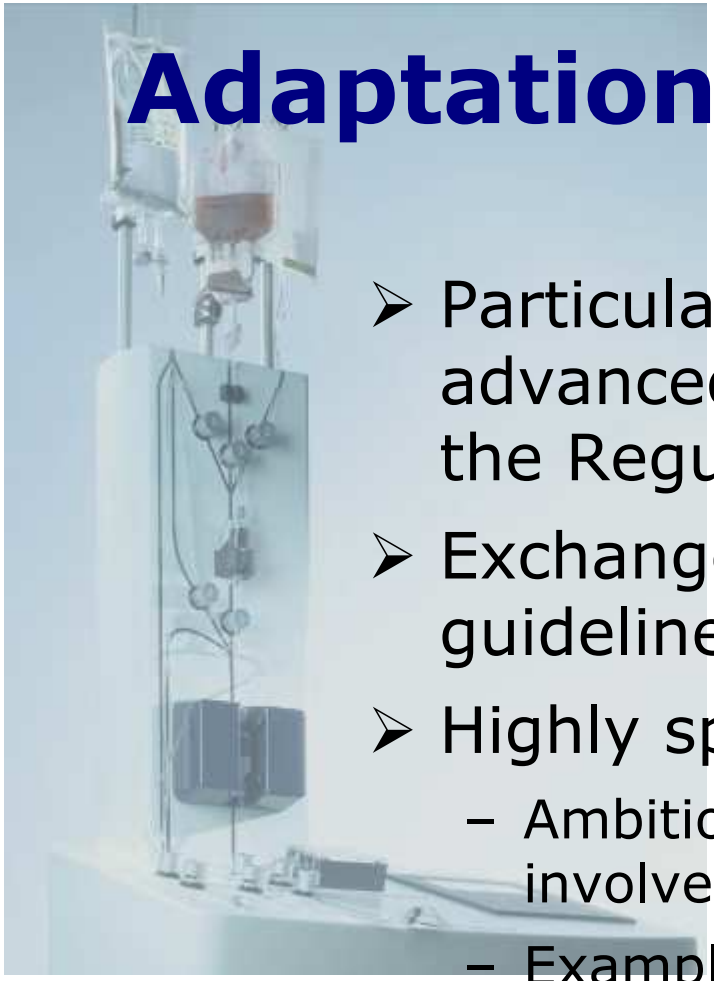
- The primary role of research based industry is ***innovation - to research and develop new medicines***
- Young technology which opens up entirely new treatment modalities
  - including orphan and wide spread diseases
  - seriously debilitating or life-threatening diseases
- Understanding of regulatory principles and their adaptation to these technologies
- Continue to accomplish conversion of basic research results into therapeutic reality

Practice: diversity

- The advanced therapies categories comprise of extremely diverse concepts
- Heterogeneous players in size and topic: gene, cell, tissue
  - Academic clinical research groups
  - Publicly funded consortia
  - SME
  - Big Pharma
- Geographical pattern
- Mixed landscape in industry and learning societies
- Treatment modalities from personalised medicine to conventional commercial product
- Combination of R&D in advanced therapies with service providing activities

Reality: reimbursement

- Innovative concepts require early thoughts on how to familiarise key players with them
  - Previously unknown concepts
  - Combination of technology, surgery and pharmacology
  - Challenge the concept with reality
- HTA considerations and activities start early on in parallel to R&D
- Fully new questions



Adaptation: Manufacture and GMP

- Particular nature of the manufacture of advanced therapies is acknowledged in the Regulation
- Exchange on the content of the specific guidelines, incl. GMP
- Highly specialised and experienced scene
  - Ambitious, aware, interested, prepared, involved
  - Example: CellGenix as a spin-off from the University Medical Center Freiburg
  - First European license for blood stem cells according to GMP and German Drug Law one year after foundation in 1995

Adaptation: Manufacture and GMP

- Many autologous or other forms of individual preparations
- *Hand* and no *mass* or *automated* production
- Process upscale often means transfer of technology to other centres
  - Multiply process and controls
  - Focus on process/technology authorisation
- Constant correlation of phenotype/consistency/clinical performance is challenging

Most challenging: non-clinical models

- It is in our hands to contribute to the common knowledge developing on whether we use artificial or relevant models
  - Anti-tumor somatic cell therapy: no way to predict primary or secondary PD in humans due to multi species-specific, HLA-restricted, xenogeneic antigens and interaction of allo- and auto-antigens in the immune response that is up-regulated by a human cytokine
  - Stem-cell for local use: comprehensive systemic or long-term animal studies when developing treatments for local use only
- Paradigms might change
  - Horse for cartilage repair
  - Cellular treatments
- Critical experience that failures are often not accepted for publication but we need to show failures

Most challenging: non-clinical models

- We need to learn that animal models are relevant when we
  - try to find arguments, not only for success but also for failure
  - do not try to demonstrate absence of toxicity but presence of toxicity
  - balance the likelihood of toxicity with the likelihood of clinical effect
  - consider the species used for PD not being automatically sufficient to study human biology and toxicity
  - consistently collect knowledge

Clinical relevance

- Many ATMP
  - Entirely new concepts and technologies
  - *Seriously debilitating or life-threatening diseases*
  - Cutting edge such as combination of surgery and treatment effects
  - Small patient populations
- Commonly accepted efficacy endpoints applicable?
  - Gene therapy: common surrogate markers of HIV therapies
  - Stand-alone or add-on therapy (tumor vaccine, last-chance treatments or best-practical-care)

Clinical relevance

- Common principles or new paradigms of clinical development, adapted to the clinical development phase
  - Adaptive clinical study design such as combined Phase IIb/III study
  - Risk management rather than very long study duration to obtain adequate number of events
- Potential to use the option of a conditional marketing authorisation
- Be aware that we develop moving targets
  - Partly we should not worry too much on the future
  - Many attempts will not anymore be used in five years' time due to gained experience

Constant exchange to learn

- Unique support by authorities
  - EMEA and EU Commission fully aware of the particular nature of advanced therapies
  - Incentives and procedures
  - PEI as authority with long standing experience via involvement due to legal obligations and practical scientific experience
  - Active and prominent contribution at EU level
- For spin-offs, most of the SMEs are remarkably well prepared and informed
- For smaller academic groups, regulatory know-how implemented into academic background

Constant exchange to learn

- Important to install suitable but permanent support at national level in addition to the CHMP Working Parties to prepare the CP obligations
  - for individual companies
  - for regular cooperation within specialised working group
- Homogeneous interpretation of hospital exemption and its transposition into national law
- Combined ATMP

Constant exchange to learn

- Learn and use common regulatory terminology and principles
  - Acknowledge that regulatory principles do not set hurdles but call for a scientific approach
  - Install a strategy of early and regular contacts to authorities
  - Feel responsible and understand that every explanation of a case is active participation in developing regulatory requirements
  - Recall existing experience in areas such as use of umbilical cord stem cells or blood components

To summarise: Chances

- Regulation of advanced therapies as medicinal products is fully relevant and consequent
- Proven right of existence of regulatory principles
- Understanding and creativity on how to apply them to the various categories of advanced therapies
- Mature system allowing authorities to understand themselves as partners of industry
- Willingness to cooperate and support at all levels

To summarise: Chances

- Scientific advice of various forms
  - to have a good mutual dialogue on the requirements
  - to ascertain that the practical hurdles are taken to the attention of CHMP and CAT
- Best conditions to introduce entirely new concepts into clinical practise - pragmatic but safe - in the interest of patients