Advanced Therapy Medicinal Products: Challenges and Opportunities Beyond Traditional Pharmaceuticals

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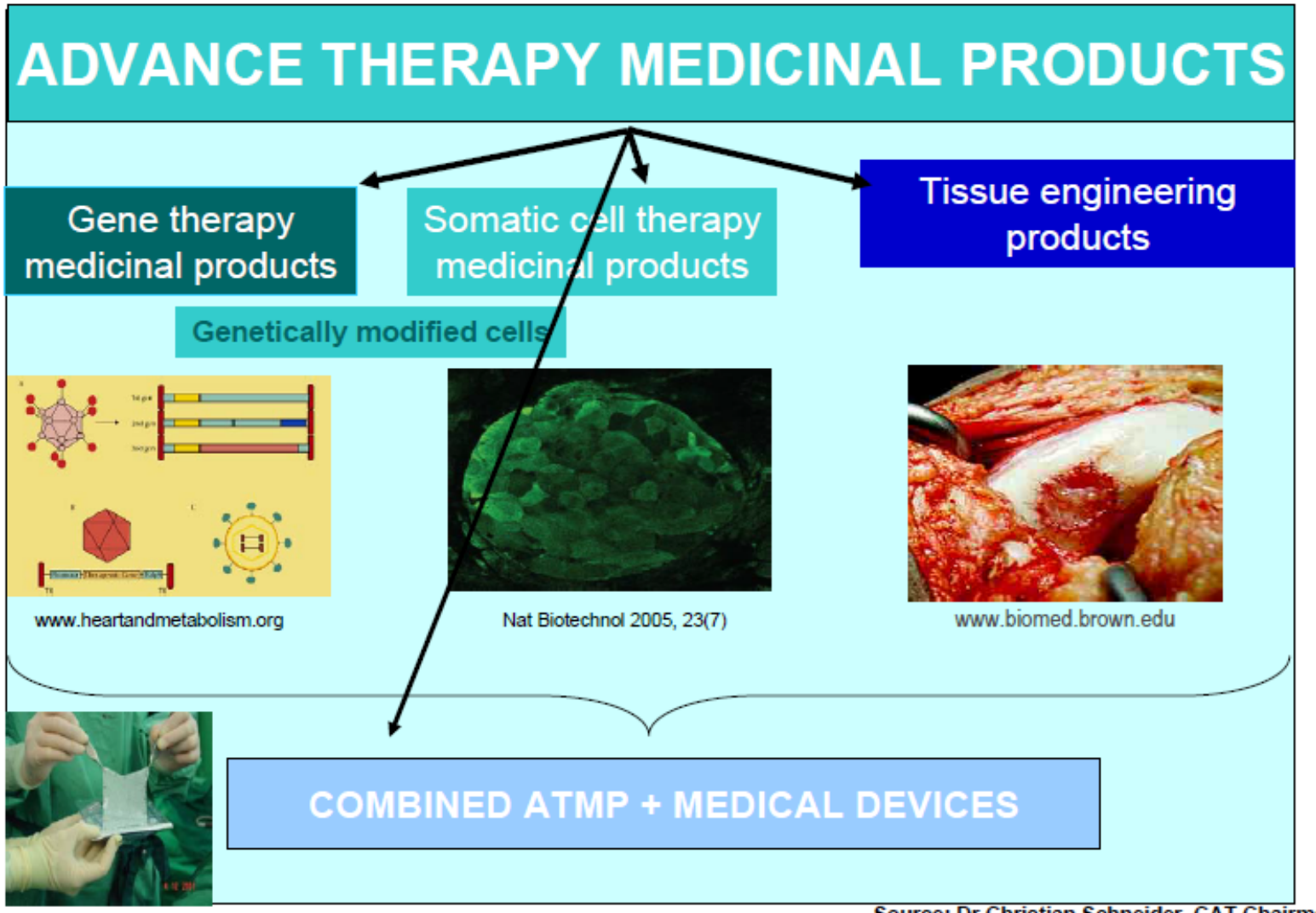
GlaxoSmithKline

Outline

- Introduction to ATMPs
- GSK's involvement in ATMPs
- CMC Challenges
- Opportunities for graduates



Source: Dr Christian Schneider, CAT Chairman

Excludes: Organ, bone marrow and blood transplants,

Criteria for being an 'ATMP':

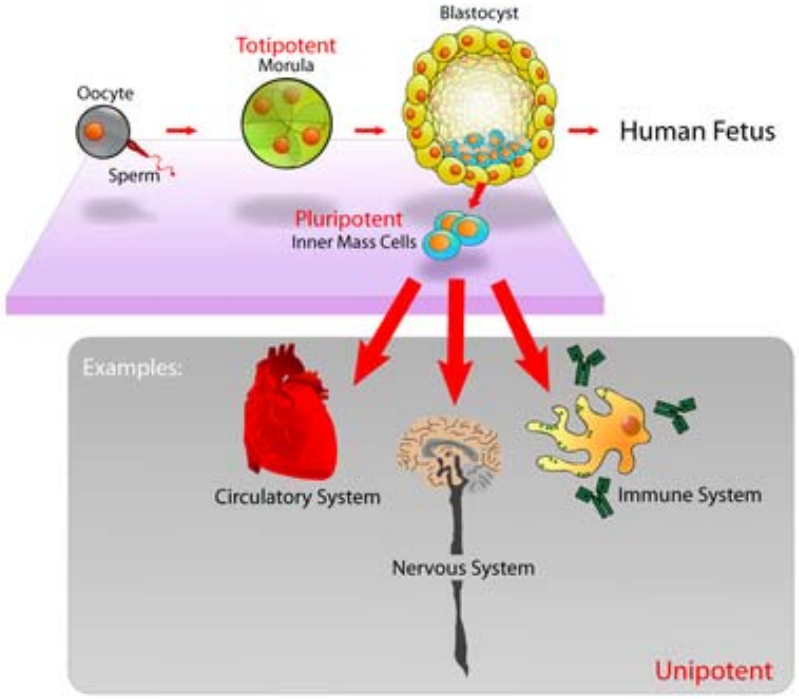
- The cells/tissue is either significantly manipulated/modified (purified, cultured, exposed to an antigen or treated in some way to alter its function) or
- Used for a purpose other than its original purpose

Tissue Engineered Product

- Engineered cells or tissue
- Used to regenerate, repair or replace human tissue
- This field is more mature than cell/gene therapies with some commercialised and routinely manufactured products

Stem Cells

- Embryonic Stem Cells
  - Undifferentiated ESCs are pluripotent– they have the ability to give rise to all the various cell types of the body and will expand in culture almost indefinitely
- Challenges
  - Ethical considerations– production of ESC lines requires the destruction of embryos
  - Implantation of undifferentiated cells may generate teratomas (benign tumors)
  - Implantation may elicit an immune response



Stem Cells

- Adult (or Somatic) Stem Cells
  - Undifferentiated cells found in tissues or organs (e.g. blood, bone marrow, fat tissue).
  - Normal function is to maintain and repair the tissue in which they're found.
- Challenges
  - More limited ability to differentiate– may yield some or all of the major specialized cell types of the tissue or organ
  - More limited ability to expand in culture

- Induced Pluripotent Stem Cells (iPSCs)
  - A pluripotent stem cell artificially derived from a non-pluripotent cell by inducing expression of specific genes
  - Typically iPSCs are derived by transfection of certain stem cell-associated genes into non-pluripotent cells using viral vectors
  - Many researchers are looking for alternative methods for inducing pluripotency
- Challenges
  - Inducing pluripotency may activate genes and cause cancer

Cell Therapy: Autologous Cell Therapy

- Patient's cells taken, manipulated and re-implanted
- 1 patient = 1 batch
- Personalized medicine—patient's cells are the starting material
- Lower immunogenicity risk
- Challenges
  - Very close integration of clinical-manufacture-commercial
  - Separation and control of batches (and samples)

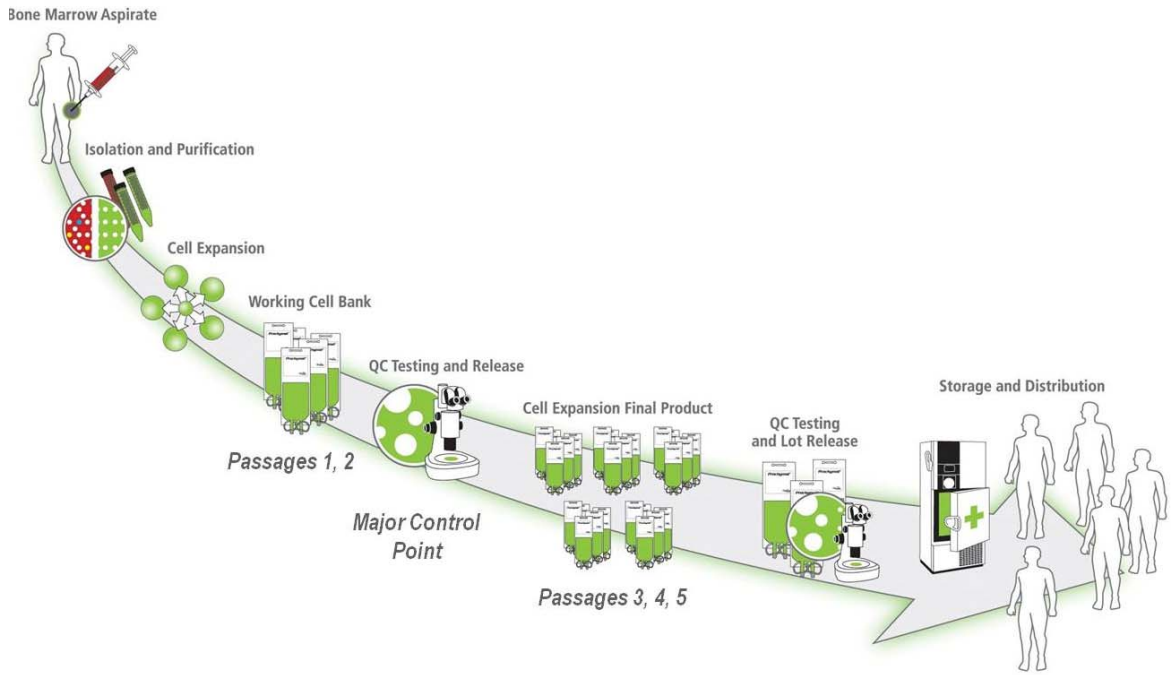
Autologous Cell Therapies

- **Provenge (Dendreon)**
  - Indication: Prostate Cancer
  - Mechanism of Action: Stimulate patient's immune system to attack cancer cells
  - FDA approved April 2010

- **ChrondroCelect (TiGenix)**
  - Indication: Cartilage defects
  - Mechanism of Action: Patient's expanded cartilage cells repair defects
  - Approved in 2009 and commercially available in Belgium, the Netherlands, Luxemburg, Germany, the UK, Finland and Spain.

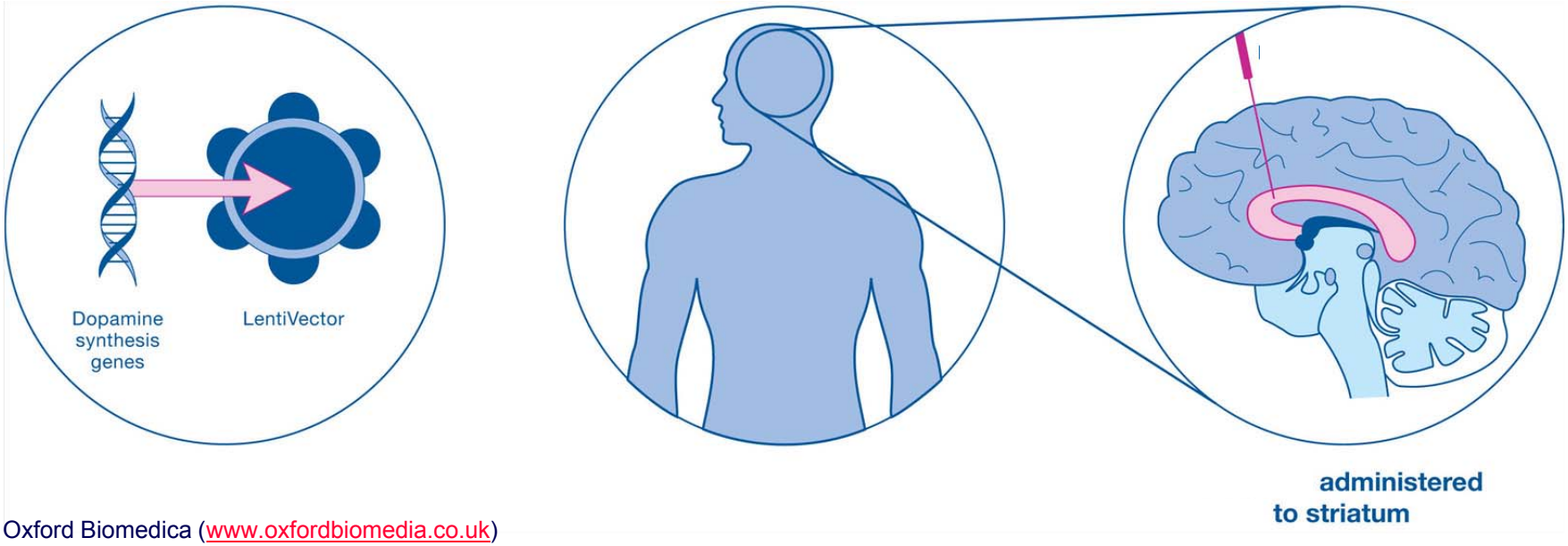
Cell Therapy: Allogeneic Therapies

- One donor sample used to treat many patients
- Better economies of scale– processes may use small reactor scale
- More normal supply chain
- Challenges
  - Greater immunogenicity risk



Gene Therapy

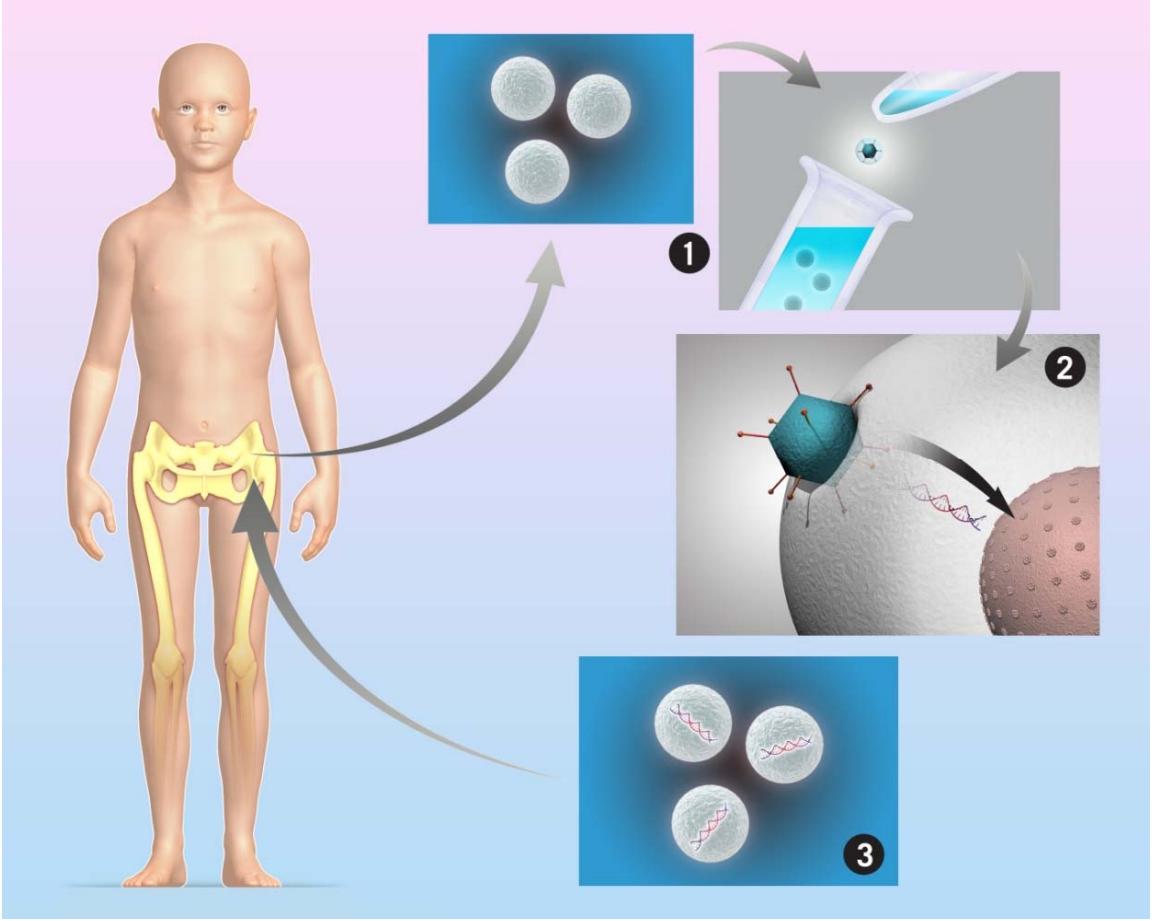
- Use of a vector to insert a missing gene, correct a faulty gene or disrupt an existing gene
- Direct (in vivo) Gene Therapy
  - Vector is dosed directly to the patient, which then transduced cells in vivo
  - Vectors are infectious organism based (e.g. virus) or DNA based
  - More challenging issues regarding safety and efficacy but much simpler supply chain



From Oxford Biomedica (www.oxfordbiomedia.co.uk)

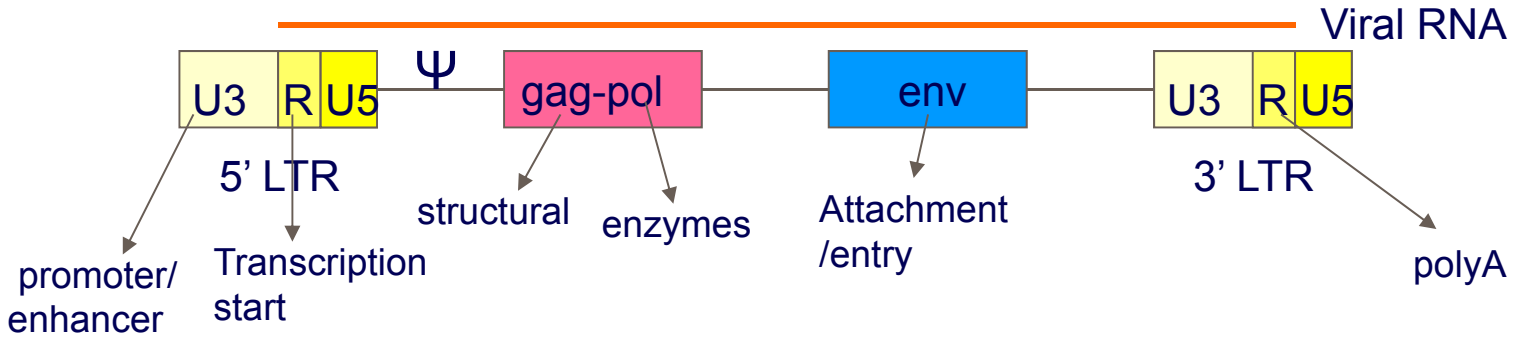
Gene Therapy

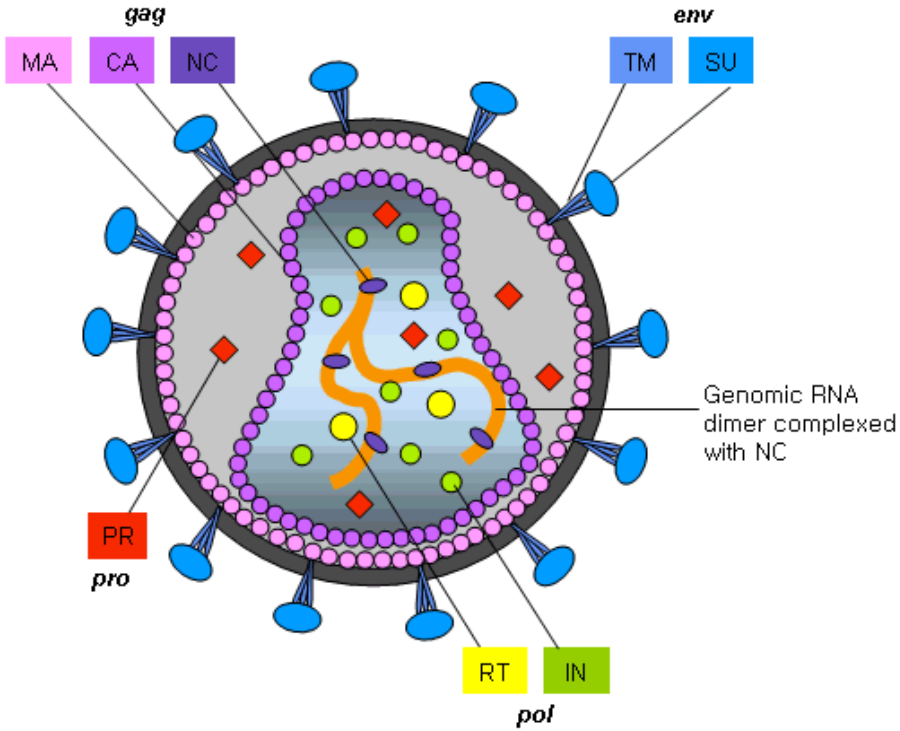
- Ex-vivo Autologous Gene Therapy
  - Patients own cells are harvested and purified, then transduced (gene modified) using a vector carrying the gene/insert of interest
  - Vector is previously made and stored frozen
  - Modified cells are returned to patient for infusion
- Currently most promising area of gene therapy



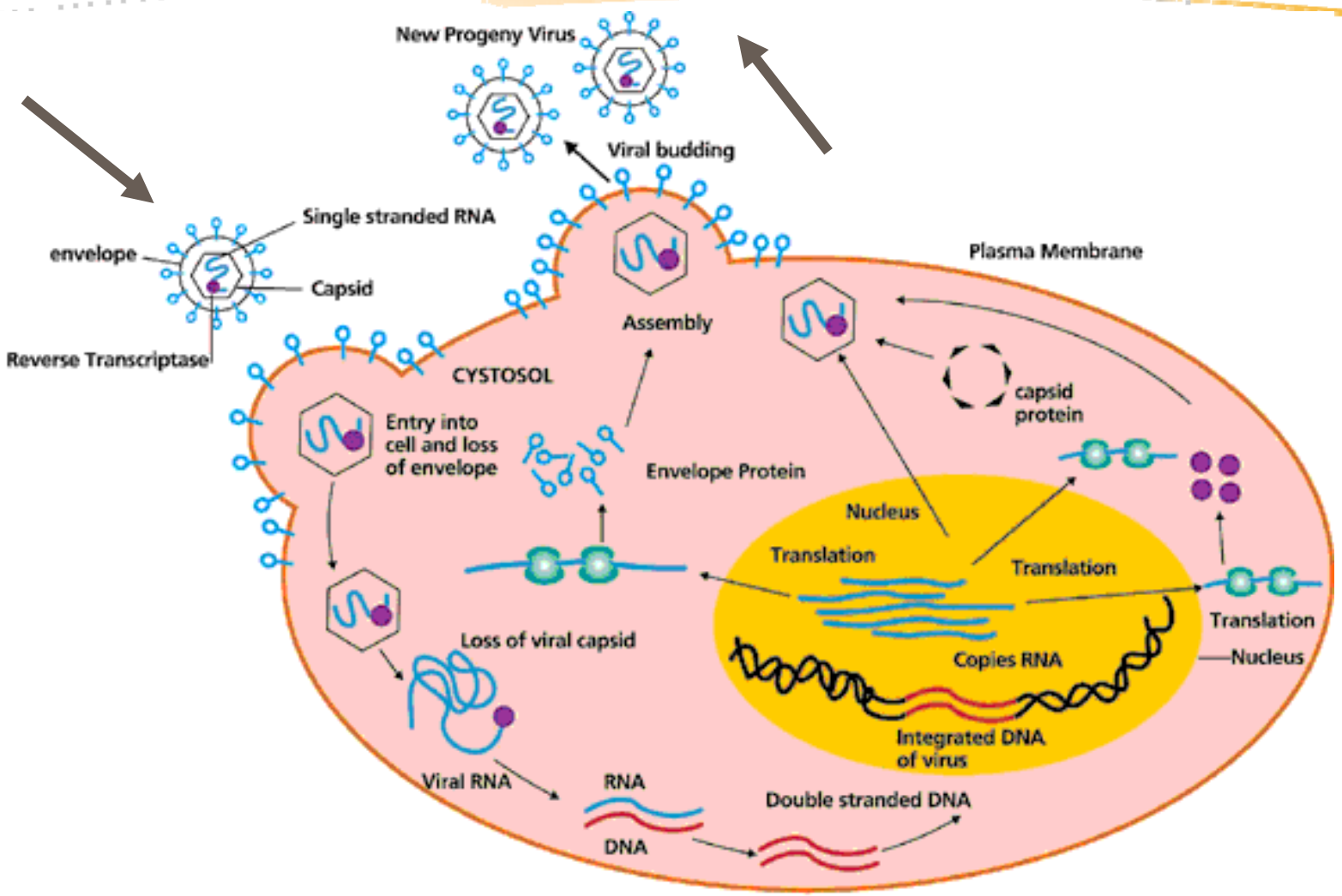
Technical Time Out

Retroviral genome / Virion structure

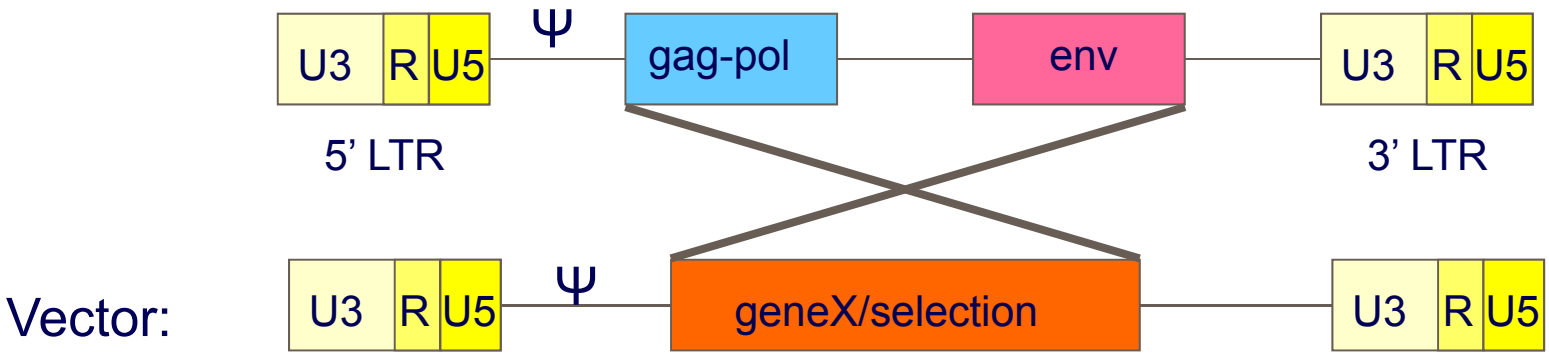




Retroviral Lifecycle

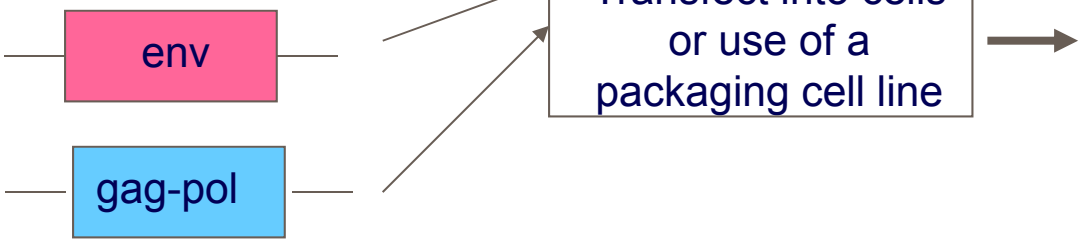


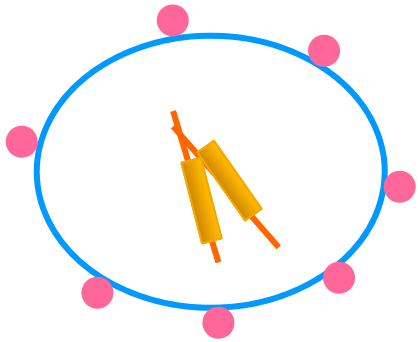
Replication-defective retroviral vectors



Virus production:

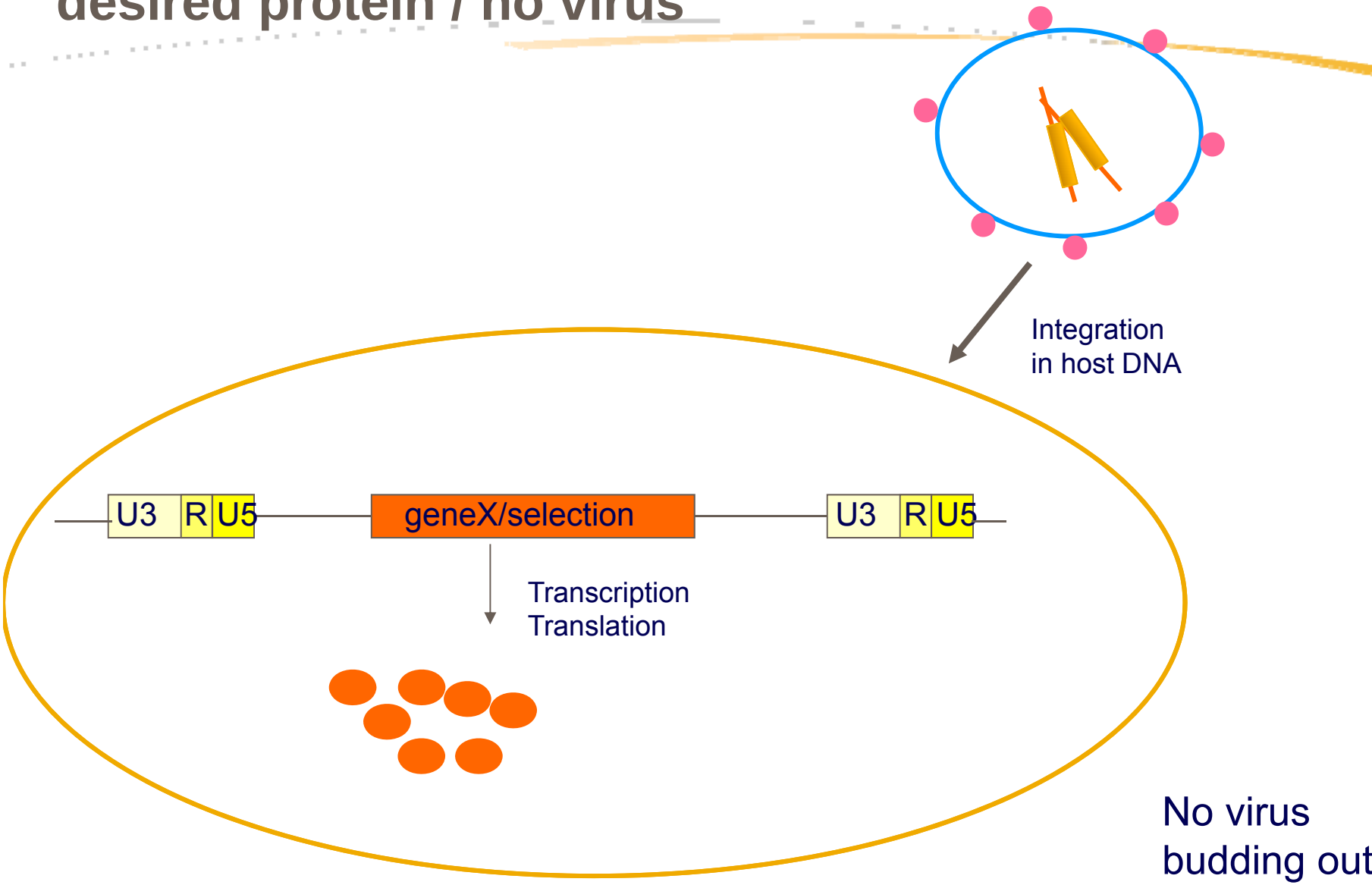
Viral proteins provided
in trans for virus production:





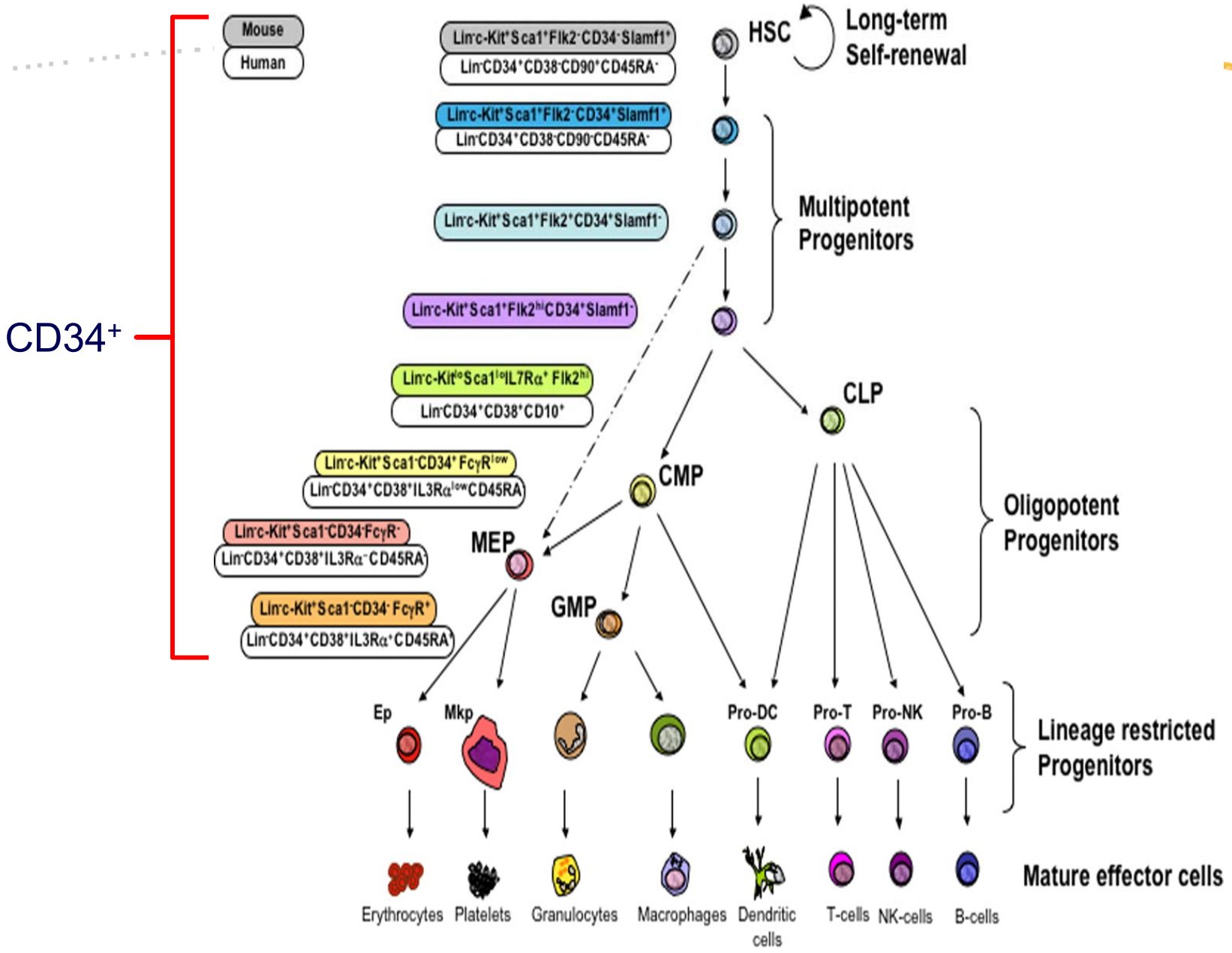
RNA does not contain
sequences for viral replication

Upon transduction (‘infection’): Production of desired protein / no virus



No virus budding out

Hematopoietic Hierarchy



GSK's Involvement in ATMPs

GSK Rare Diseases (established Feb 2010)

Our mission is to build and grow an integrated, world class capability in rare disease treatments from genomics through to commercialization, that leverages GSK's pipeline and expertise, accesses innovation from academia and public research and enables GSK to deliver more products of value to an underserved patient population.

GSK Rare Diseases: Pipeline of Differentiated Assets

RNA-based nucleotides for Duchene Muscular Dystrophy

- Progressive, disabling and fatal muscle wasting disease affecting boys and young men; no approved therapies to date
- **GSK in-licensed an antisense oligonucleotide ('968) from Prosensa BV (2009)**
- '968 addresses mutations amenable to an exon 51 skip (13% of patients)
- Ongoing pivotal study
- Exclusive option to license nucleotides addressing further mutations

Pharmacological chaperones for Fabry Disease

- X-linked lysosomal storage disease; wide range of systemic symptoms
- **GSK in-licensed migalastat from Amicus Therapeutics (2010)**
- Alternative to IV therapies with the potential for broader tissue distribution
- Ongoing pivotal study

Gene therapy for serious and life-threatening rare disorders

- **Alliance with the Telethon Institute of Gene Therapy (2010)**
- Lead program with retroviral ex-vivo gene therapy for ADA-SCID
- Follow-on programs with lentiviral ex-vivo gene therapy for other primary immune deficiencies, lysosomal storage disorders and blood disorders

Alliance with the Telethon Institute of Gene Therapy

- Strategic alliance to research and develop ex-vivo gene therapy for rare genetic disorders (Oct 2010)
- TIGET recognized as a leading research center on gene therapy worldwide
- First time a global pharmaceutical company has become directly involved in the area of gene therapies applied to rare diseases

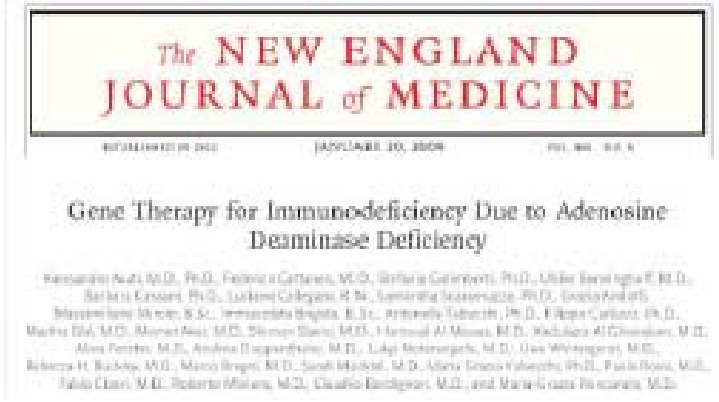
ADA-SCID: A Rare, Life-Threatening Disease

- Genetic, autosomal recessive condition caused by a deficiency in a crucial enzyme, adenosine deaminase
- Ultra rare: incidence estimates vary from 1 in 40,000 to 1 in 1 million births
- Deficiency in immune cells, including T-cells, B-cells and NK-cells
- Without treatment, children are at risk of death within months
- Treatment options
  - HLA-matched, related donor (available to only 10-20% of patients)
  - HLA-matched, unrelated donor
  - Mismatched related donor
  - Enzyme replacement therapy

  Target patient population for gene therapy
- Despite available treatment options, ADA-SCID remains life threatening

GSK/TIGET Retroviral Gene Therapy for ADA-SCID

- 18 patients treated with retroviral gene therapy as of June 2013
- All patients are alive after a median follow-up of 6.5 years*
- 2009 publication in the NEJM based on data in 10 children**
  - 2/10 patients (in the 2009 publication) required re-institution of long-term enzyme replacement therapy
  - 9/10 patients had immune reconstitution with increased T-cell counts and normalization of T-cell function
  - Overall favorable safety and AE profile
    - No evidence of insertional mutagenesis


The NEW ENGLAND JOURNAL of MEDICINE

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

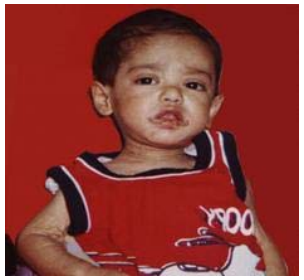
* As of June 2013, data is available for 18 patients, including 12 treated in the pivotal study, 3 treated in pilot studies and 3 treated under compassionate use.

** Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency (NEJM, 2009)

HSR-TIGET research

Follow-up programs

Wiskott-Aldrich Syndrome



- Prevalence: 0.015/10 000
- Symptoms: persistent thrombocytopenia, autoimmune disease and blood malignancies
- **Median survival age: 14 years old**

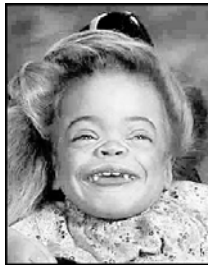
Metachromatic leukodystrophy

- Prevalence: 0.016/10 000
- Symptoms: rapid loss of brain and body functions
- **Median survival age: 5-10 years old** in most common form

Globoid leukodystrophy

- Prevalence: 0.075/10 000
- Symptoms: fever, limbs stiffness, seizures, feeding difficulties and slowing of mental and motor development
- **Median survival age: 2-3 years old** in most common form

Mucopolysaccharoidosis type I

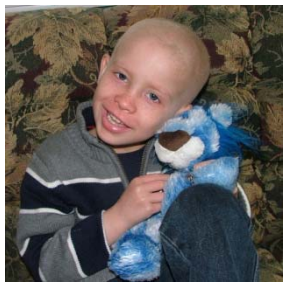


- Prevalence: 0.015/10 000
- Symptoms: skeletal and connective tissues irregularities leading to obstructive airway disease, respiratory infections, or cardiac complications
- **Median survival age: from 10 to early adulthood**

Beta-thalassemia

- Incidence: 100 000 per yr
- Symptoms: severe anaemia and related complications
- **Median survival age: 30-35 years old** in Western countries, **10-15** in countries with limited healthcare resources

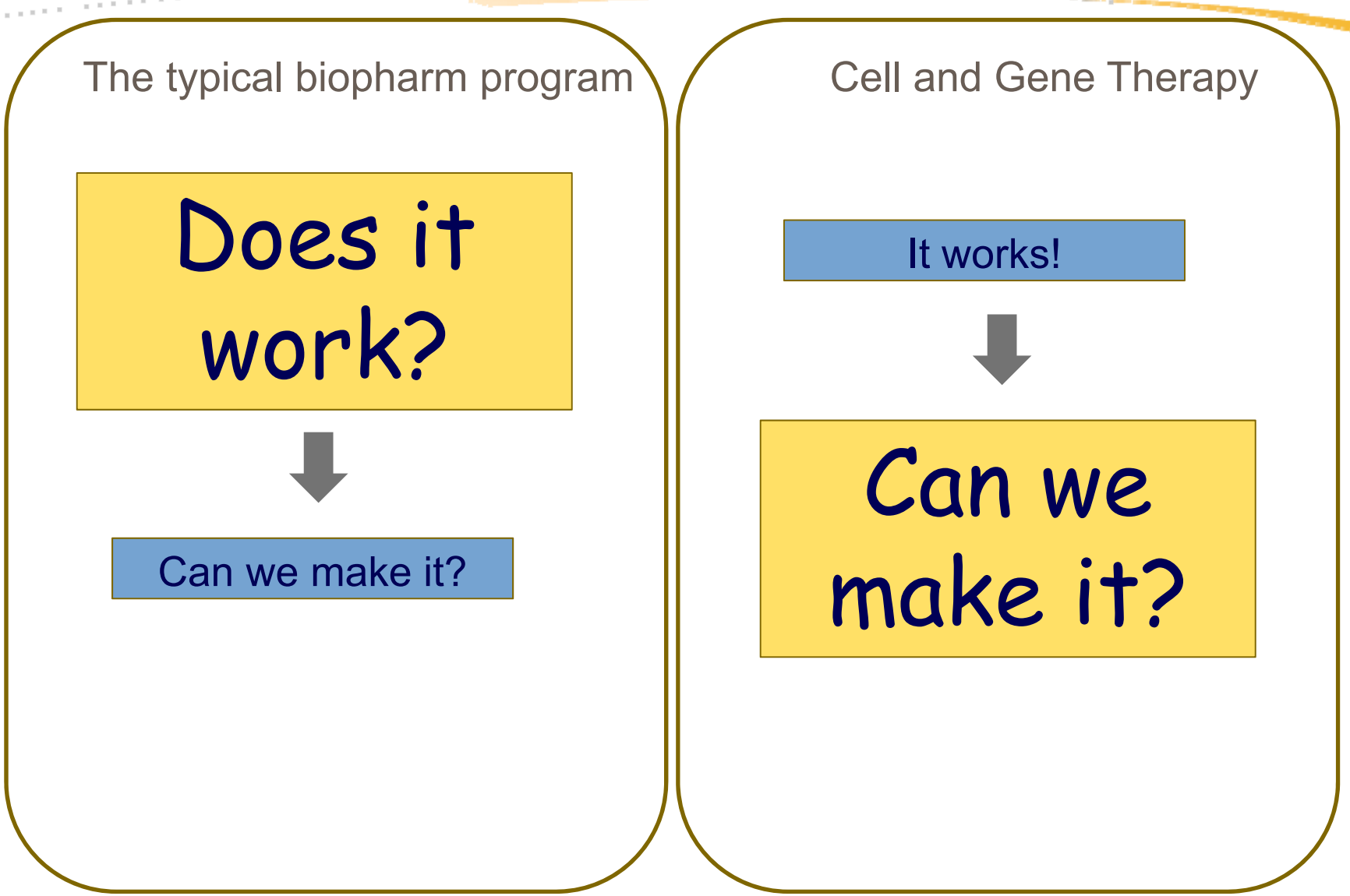
Chronic granulomatous disorder



- Prevalence: 0.02/10 000
- Symptoms: chronic fungi and bacterial infections and related complications
- **Median survival age: ~38 years old with successful BMT**

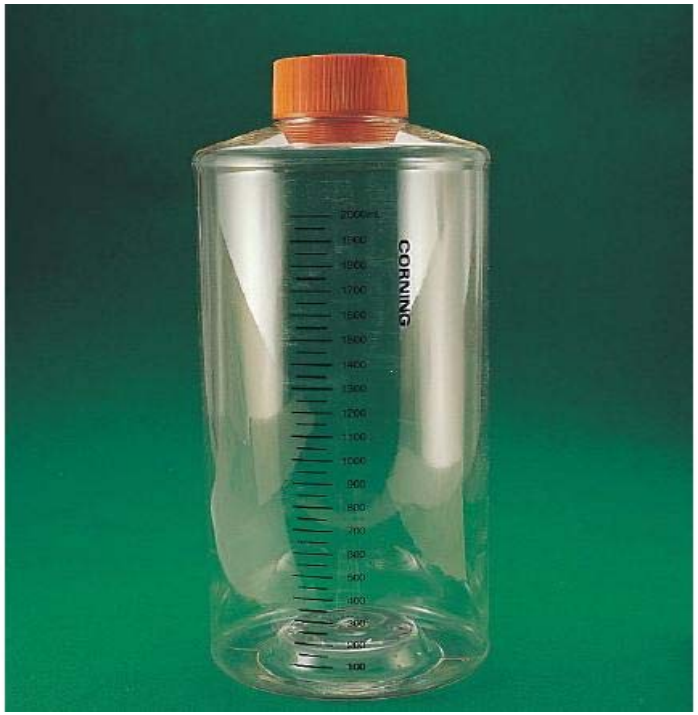
Unique CMC Challenges

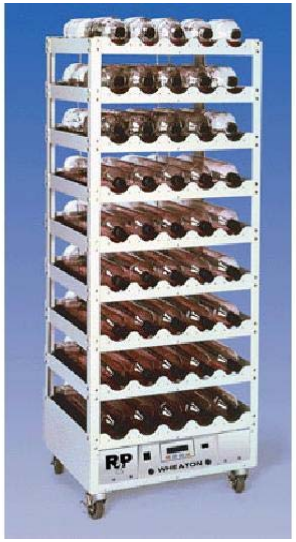
CMC on the Critical Path



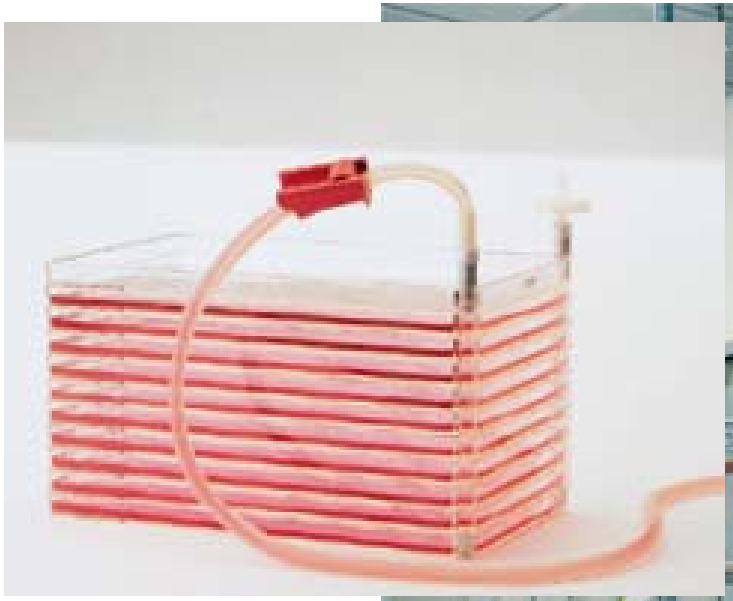
Large Scale Commercial Production

- There's an immaturity of production technologies
- Current processes primarily use lab scale/academic technology
- There's a need to move practice from "academic" to GMP industrialization





Growth of Virus in Cell Factories



Process will need to be scaled-up or scaled-out to supply large patient populations

Aseptic Processing Challenges

- There can be number of generic aseptic processing risks associated with these products
  - Typically small scale series of unit operations with a significant level of repeated operator interventions over protracted periods within open biosafety cabinet.
  - Autologous cell therapy can have processes requiring over 1000 individual open aseptic manipulations to be performed through purification and transduction

Aseptic Processing Challenges

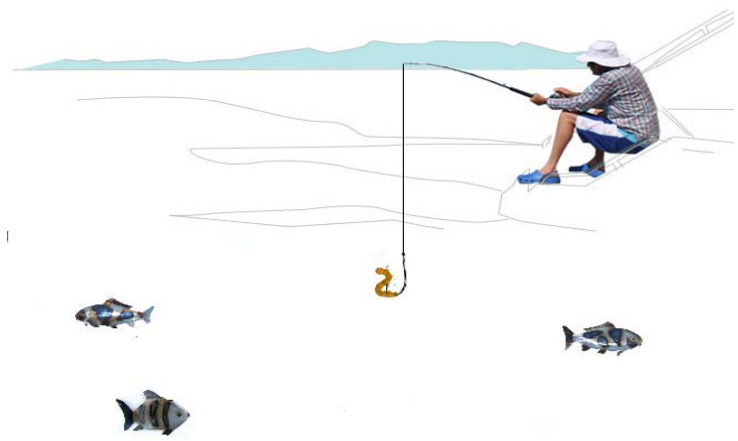
- Core aseptic processes require a lot of support equipment and materials which serves to challenge the aseptic core activities more than conventional commercialised processes.
- High number of transfer activities between the Grade B and Grade A zones

Aseptic Processing Challenges

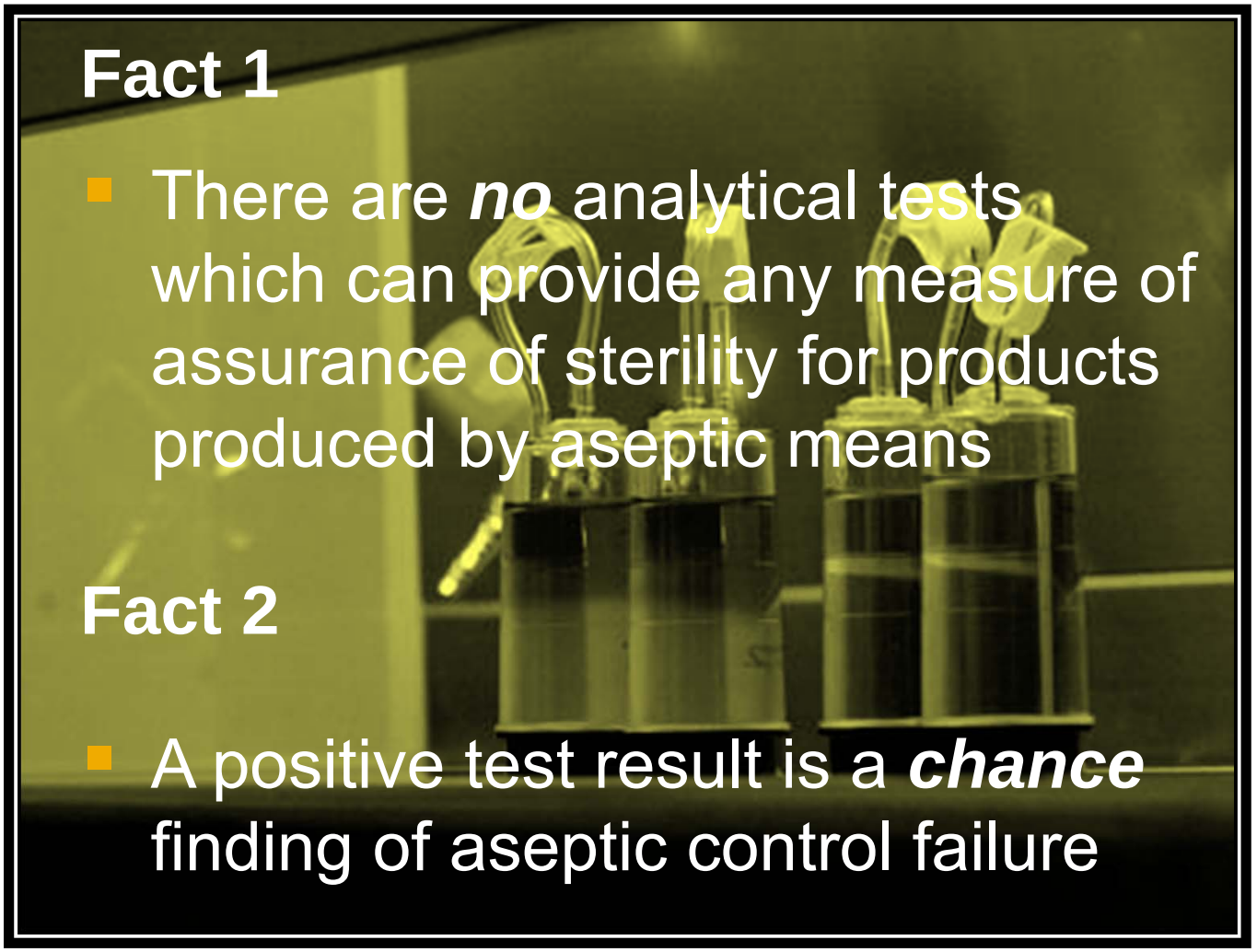
- Often operate under **conditional release** (shelf life may be on the order of hours) with limited assurance gained from environmental monitoring programmes and process simulation
- Conditional release systems not underpinned by comprehensive risk assessments

Environmental Monitoring

- Only a small fraction of the air and surfaces that can have an influence on product can be tested
- Monitoring techniques have low recovery efficiency
- A limited range of organisms can be isolated using common media and incubation conditions
- A positive isolate is a significant event
- A negative result may be misleading



Aseptic Challenges- Risk Assessment and Parametric Release



Fact 1

- There are ***no*** analytical tests which can provide any measure of assurance of sterility for products produced by aseptic means

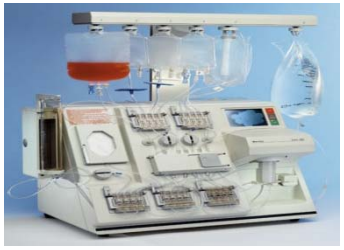
Fact 2

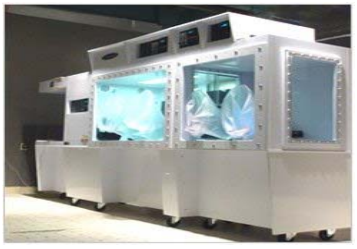
- A positive test result is a ***chance*** finding of aseptic control failure

How do we overcome the challenges and increase our confidence?

Aseptic improvement will occur in stages .....





Open Unit Operations Modular /Containment Integrated

Unlike conventional aseptically prepared products and presentations there is **no established integrated state of the art technology** for enclosing these autologous/allogenic cell based therapy processes at the moment **.**

Supply and Logistics of Autologous Cell/Gene Therapies: A New Paradigm—Supplying a Service as well as a Product

Scheduling

Cell Collection

Clinical setting

Cell Infusion

Ship to Manufacturing Facility

Limited Sample/Product Stability
Security of supply chain is Critical

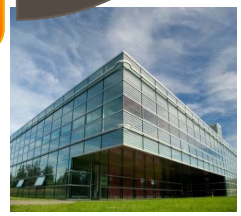
Ship to Clinic

Manufacture and clinical sites may need to be in close proximity

Patients may need to relocate to be near a production hub

Manufacture

Manufacturing Facility



Absolute requirement for an effective tracking system throughout the process to assure delivery of the right batch to the right patient

Evolving Regulatory Landscape

- EU: Regulated by EMA, CHMP, but with 'CAT' (Committee for Advanced Therapies) as the specialised technical committee supporting reviews and generation of policies
- US: Covered by CBER's Office of Cellular, Tissue and Gene Therapies (OCTGT) and HCT/Ps (Human cells, tissues and cellular and tissue-based products).
  - Required to follow GTPs (Good Tissue Practice) as well as GMPs. GTPs are primarily concerned with the spread of infectious disease.

- Industry Groups working with regulators to address major challenges
  - ISCT- International Society for Cellular Therapy
  - EBE- European Biopharmaceutical Enterprises
  - PDA- Parenteral Drug Association

Immaturity of Supply Base

- Raw materials and reagents used to supply these processes are typically avoided in pharmaceutical manufacturing (e.g. serum and other animal-derived components)
- Available reagents are typically research grade (e.g. growth factors used in cell culture and stem cell differentiation)
- Regulatory and Quality Assurance strategies using science- and risk-based approaches are required to enable commercial production

Process Validation - Three questions to ask:

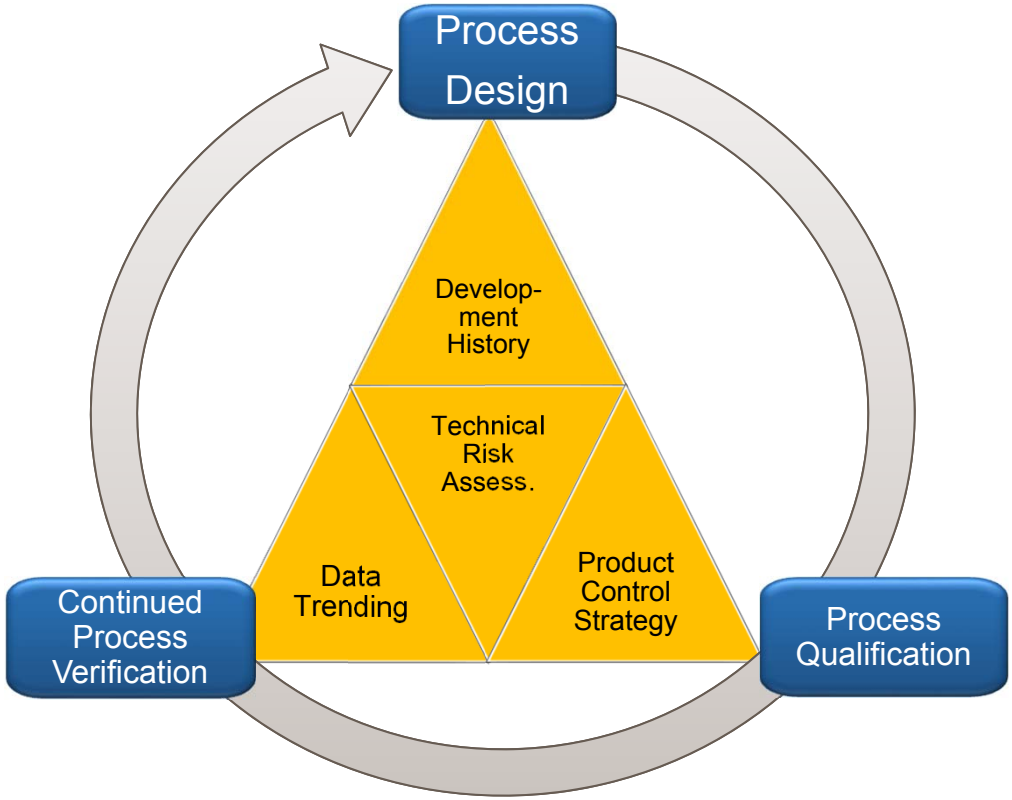
- Do I have confidence in my manufacturing process? Or, more specifically, what scientific evidence assures me that my process is capable of consistently delivering quality product?
- How do I demonstrate that my process works as intended?
- How do I know my process remains in control?

- **The challenges:**
  - How do we demonstrate consistency and control of the process when each batch is initiated with inconsistent starting material?
  - Starting materials (e.g. bone marrow) for autologous therapies are precious and there is very limited supply.

Inherent challenges AND Expectations for Process Validation are changing

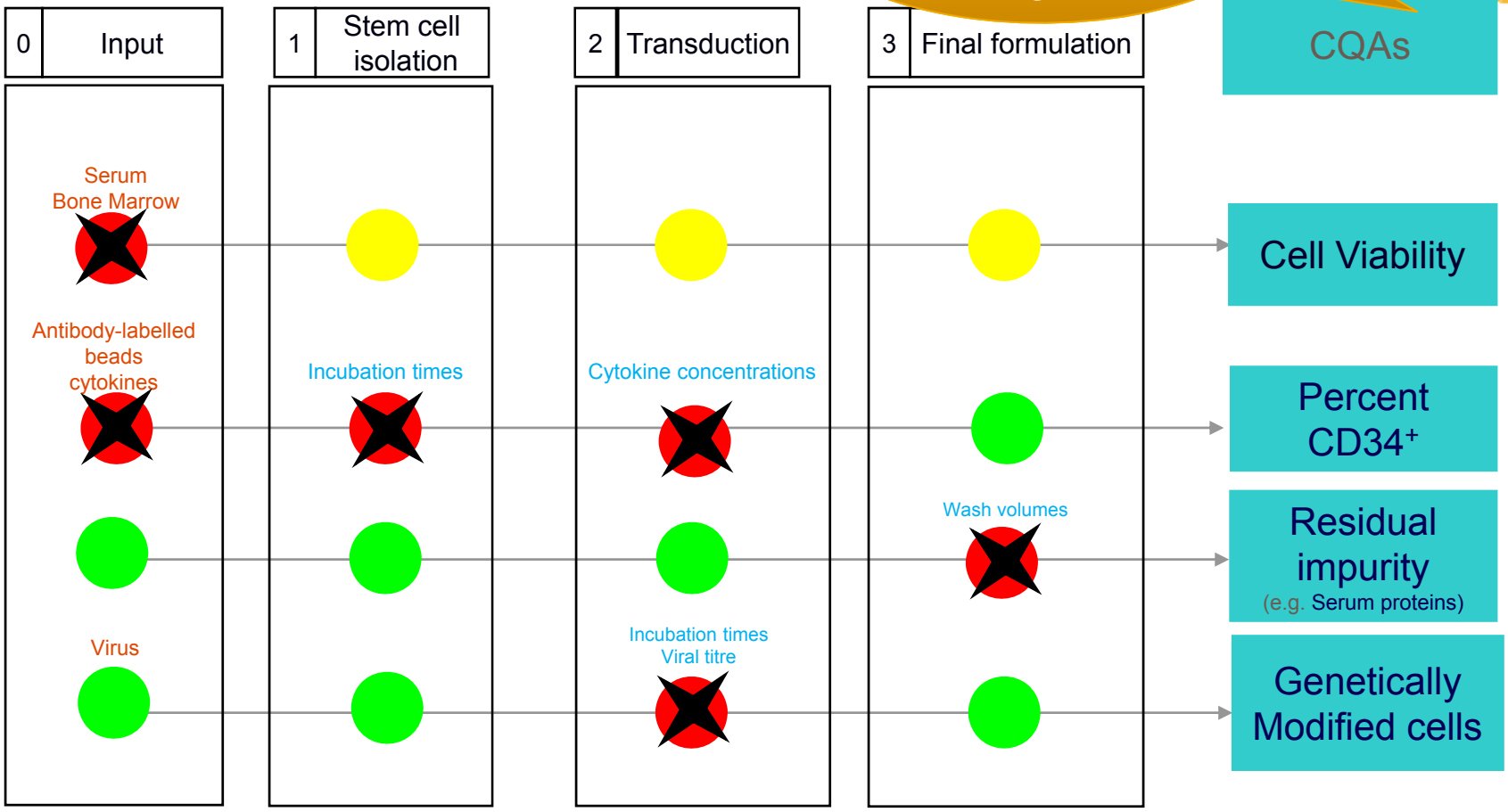
- Process Validation Lifecycle
  - Iterative
  - Not a one-off event
- Product Quality Lifecycle
  - Process understanding
  - Knowledge management

A new approach



What is a control strategy ?

Additional challenge may be understanding of MOA to define CQAs



Example Control Strategy for Gene Therapy

Development and Product Lifecycle

- Many of these products will require monitoring/testing of the patient on a regular basis post-treatment
- Very often these products will utilise Early Access Programs which allow for supply to patients prior to approval.
- Clinical development of ATMPs does not always follow the conventional Phase 1/2/3 route. In common with rare disease indications, clinical programs are often compressed into one or two studies, followed by conditional approval with post-marketing commitments
- Different commercial scenario (not a classic supply and demand scenario)
  - Products will more likely have a patient pull
- High cost of goods driven by
  - small scale of manufacture,
  - potential need for capital investment
  - high degree of testing required.
  - need for ongoing patient testing/monitoring

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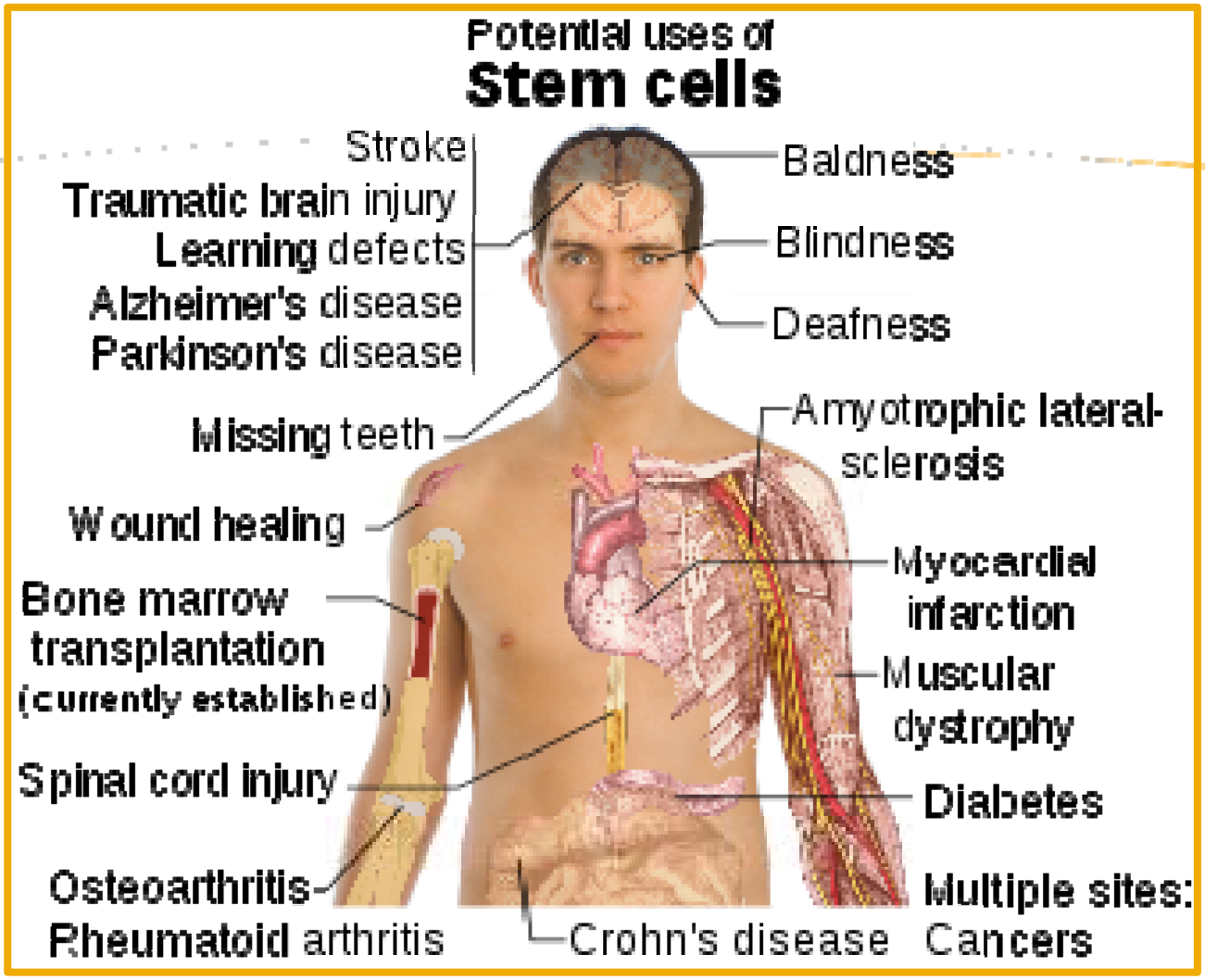
Opportunities



- Meet the otherwise unmet medical need
- Paradigm shift towards cure from disease management

ATMP Landscape

- While many products have shown proof of concept, very few products are yet commercially approved. Over the next 5 years the leading wave of products are expected to approach file and launch

  - The field is moving from a pure science focus led by small biotechs/universities, to a focus on how to commercialise these therapies

  - Over the next few years, the regulatory requirements, industry practices, expectations will be developed and become benchmarks

Why group ATMPs together and with Biopharms

- ATMPs constitute a diverse range of product types
  - Multiple therapeutic areas
  - Varied biology and MOA
- However, from a CMC and supply perspective, there are many commonalities in technology and approach:
  - Heavy focus on cell line development, virology, cell culture, characterisation
  - Controls and considerations for adventitious agents
  - Complex testing requirements
  - Need to consider early comparability / bioequivalence between development phases and balance with spend
- Significant overlap with Biopharm CMC skill-set but with a number of specific requirements too which we need to identify, address and build up

Integration of Research and Development Expertise

- The Challenge
  - Primary understanding of these processes and products lies with those working in academia, basic research or the practice of medicine
  - Staff with experience in good science but who have not had exposure to regulatory or Quality issues associated with product development
- The Opportunity
  - There is a need for folks with cell biology/virology background with an understanding of
    - Quality Risk Management
    - Control strategies
    - GMP
    - Regulatory guidance
    - Regulatory submission preparation
    - Supply chain logistics
    - Process engineering
    - Process validation

Key Take Aways

- ATMPs hold great promise in the treatment of diseases, especially those with an otherwise unmet medical need.
- There are tremendous challenges to commercialization of these products which require us to take new and innovative approaches to ensuring patient safety and efficacy of the products that is comparable to that of traditional pharma products.
- The success of ATMPs will be dependent on use of science- and risk-based approaches to their development and manufacture.
- Biopharmaceutical skill sets and technologies are a foundation on which to build for ATMPs but we need to be prepared to fundamentally look again at many of our paradigms around supply chain, process control etc. so a cross functional approach is critical.
- We need skilled, creative professionals with the right combination of experience to bring these products to market.

Acknowledgements

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