GMP Manufacture of ATMPs in a Hospital Setting

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Karolinska Institutet

KAROLINSKA Universitetssjukhuset

GMP - Good Manufacturing Practice

- **Quality assurance system used in pharmaceutical industry**

- **FDA (US) published the first GMP regulations 1963 (28FR6385) partly in response to the Thalidomide (Neurosedyn in Sweden) disaster in Europe**

- **Patient safety - Ensure a high quality product**
  - Safe
  - Pure
  - Effective
  - Correct identity
  - Correct strength

- **GMP includes manufacturing and quality control**

GMP is More than a Facility

- **Buildings and Facilities**
  - Size, location, flow of materials and personnel, ventilation, building materials
- **Organization and staff**
  - Education, training, experience
  - Quality Assurance and manufacturing separate
- **Equipment**
  - Design, cleaning, maintenance, calibrations,
- **Production**
  - Standard Operating Procedures (SOPs), valida
- **Quality and controls**
  - Specifications, Testing, Sampling, Procedures,
- **Storage and distribution**
  - Quarantine/release, storage, distribution
- **Documentation**
  - Complete and well designed

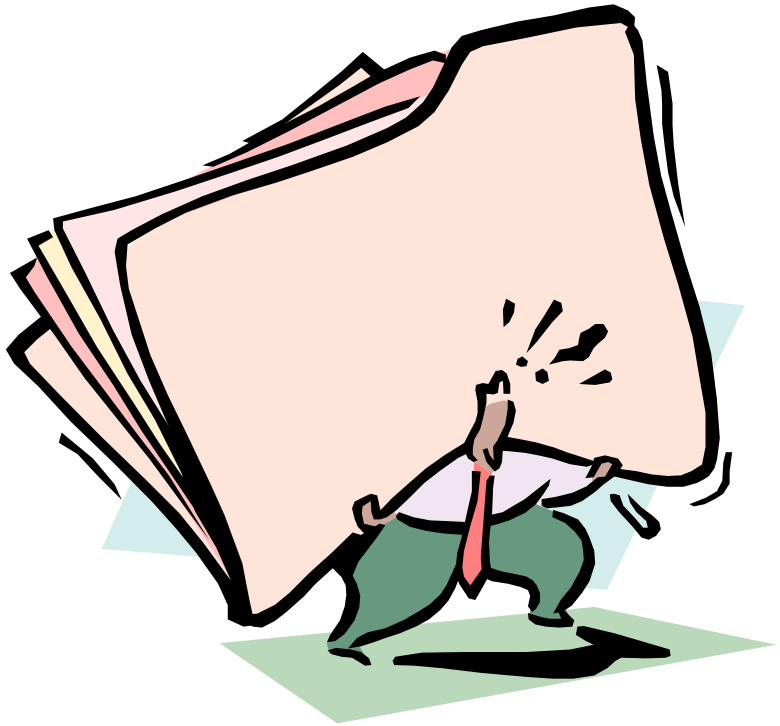
Outcome of Manufacture

Two products from manufacturing:

- Pharmaceutical Product
  - A characterized and consistent product
  - A validated and reproducible process
  - With pre-determined acceptance criteria and specifications

- Paper Product
  - Documented evidence to show that the product has been made to the correct standards

GMP – Generate More Papers



ATMP EU Regulation 1394/2007/EC

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)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the

Article 5

Good manufacturing practice

The Commission shall, after consulting the Agency, draw up guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

- *Defines and provides the legislative framework for ATMPs in the EU*

EU GMP Guideline for ATMP

EUROPEAN
COMMISSION

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

Document History	
Adoption by the European Commission	22 November 2017
Date for coming into operation	ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

- Guideline on GMP for ATMPs
- Into operation from 22 May 2018
- Authorised and investigational

  ATMPs

Brief History of Vecura GMP Facility and KCC

- **1996** Inauguration of Vecura GMP facility
- **1998** 1st Swedish gene therapy GMP product (cardiovascular disease) in trial
- **2003** Implementation of cell therapy
- **2007** Rebuilding/expansion of facility
- **2008** 1st Swedish cell-based GMP product (Alzheimers disease)
- **2012** Completion of clean room for scaled-out cell expansion
- **2014** First CAR-T product in clinical trial
- **2017** Establishment of Karolinska Cell Therapy Center (KCC)

Christer Sylvén, Jeffrey Isner and Gösta Gahrton at inauguration of Vecura, 1996

GMP manufacturing in bioreactor at Vecura

Karolinska Cell Therapy Center - KCC

In operation since January 1, 2017.

Mission

Provide support to researchers and clinicians developing therapies based on Advanced Therapy Medicinal Products (ATMP).

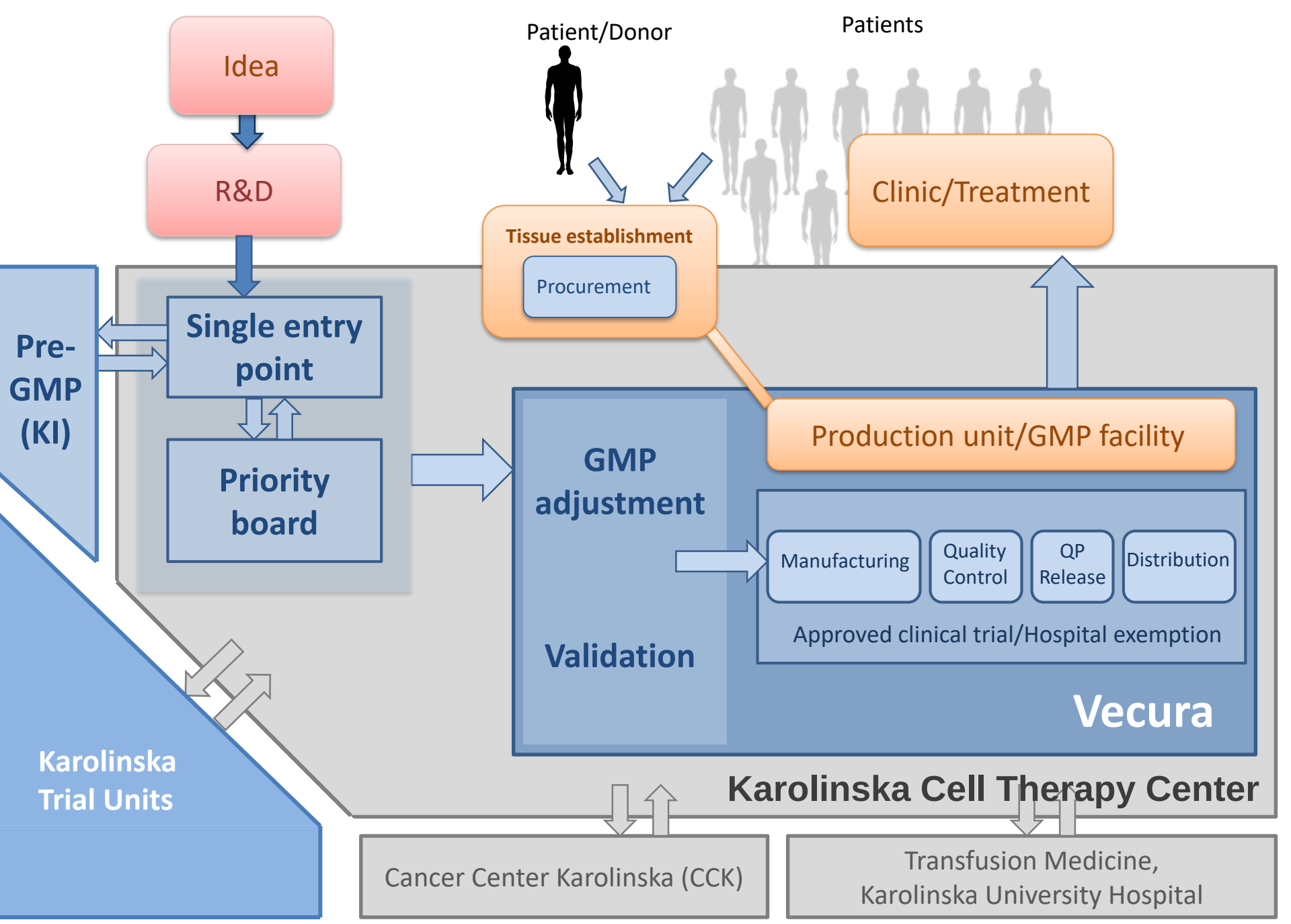
-GMP-manufacturing of ATMPs for clinical trials (Vecura)

-Regulatory advice/support

-Support to Pis and medical responsible individuals (Verksamhetschefer)

-Keep registry of ongoing ATMP-based studies and treatments at Karolinska

Budget of 15-20 MSEK. Supported by Vinnova/VR, Stiftelsen för Strategisk Forskning, KI/SLL Core facilitsupport, SFO, user fees and more.


Idea
R&D
Patient/Donor
Patients
Clinic/Treatment
Tissue establishment
Procurement
Pre-GMP (KI)
Single entry point
Priority board
GMP adjustment
Validation
Production unit/GMP facility
Manufacturing
Quality Control
QP Release
Distribution
Approved clinical trial/Hospital exemption
Vecura
Karolinska Trial Units
Karolinska Cell Therapy Center
Cancer Center Karolinska (CCK)
Transfusion Medicine, Karolinska University Hospital

Priority Board

Evaluates all new treatments and trials at Karolinska based on cells, tissues and ATMPs.

Chairman – Patrik Rossi

Patient safety – Torbjörn Söderström

Scientfic expertise – Matti Sällberg

Clinical expertise – Stephan Mielke

Pre-clinical expertise – Moustapha Hassan

Regulatory expertise – Marie Westman

Legal expertise – Helena Millstam

GMP/Manufacturing – Pontus Blomberg (adj.)

Project manager – Kristina Kannisto (adj.)

Convenes monthly

The statement made by the Priority Board is a recommendation.

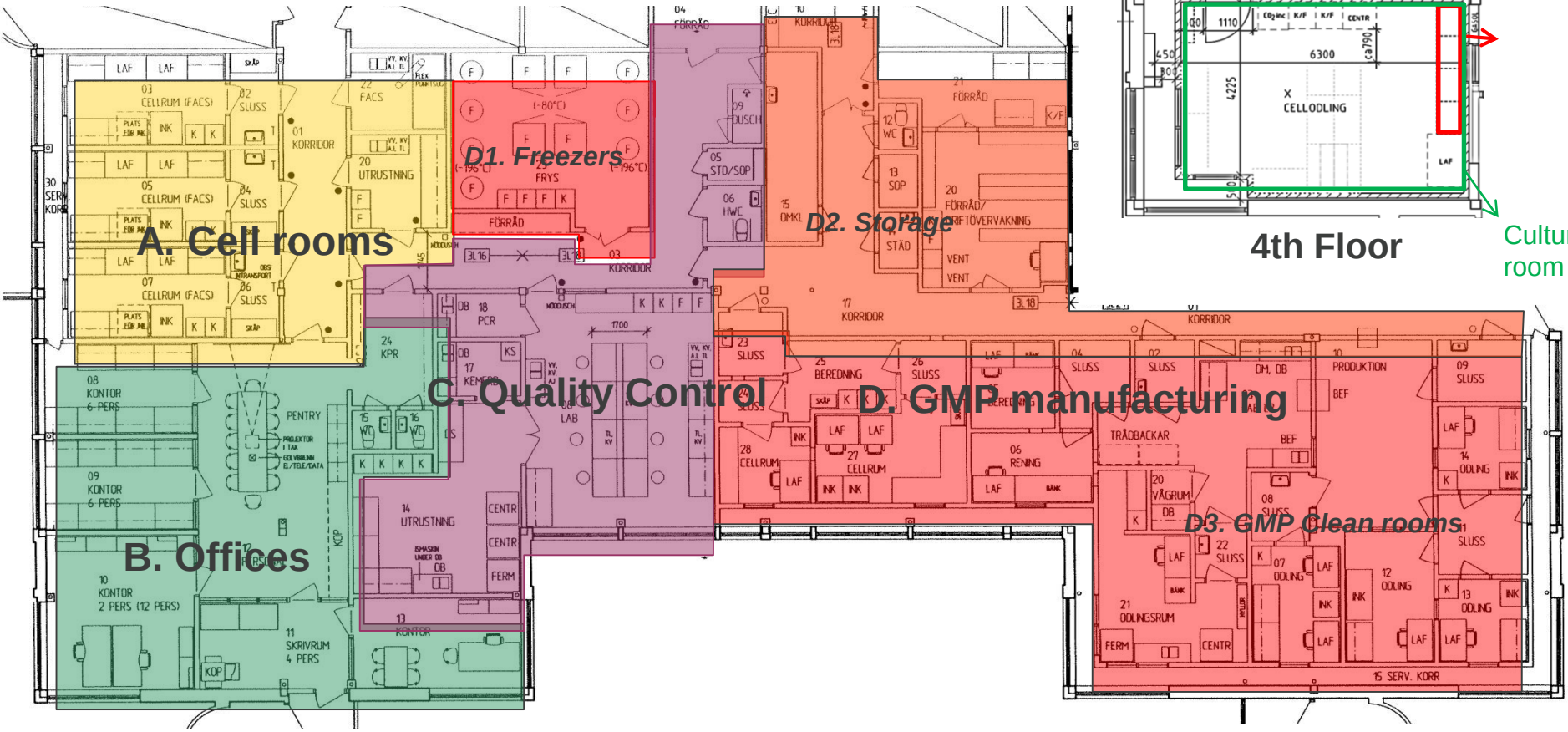
Decisions regarding treatment is made by the responsible VC

Vecura GMP Facility Facts

- **Provide researchers at Karolinska with ATMPs manufactured according to GMP**
- **Resource to other academic labs and biotech industry**
- **Permits issued by Swedish Medical Product Agency**
  - Manufacturing permit
  - Tissue Establishment
  - Hospital Exemption (product specific)
  - Wholesale distribution
- **Permits issued by County Council**
  - Hospital pharmacy function - may distribute ATIMP directly to the clinic
- **Passed inspection by the Swedish Medical Product Agency 2019-02-05/06 (manufacturing) and 2019-04-24/25 (tissue establishment)**

Karolinska University Hospital Huddinge

Floor Plan GMP Facility in Novum



3rd Floor

4th Floor

- Clean rooms
- Offices
- QC laboratory
- Freezer storage
- Total 810 m2

Clean rooms and their classification

- 9 Class B (ISO 5) (Class A in LAF) suites
- 1 Class B/BL2-BL3 suite
- 3 Class C (ISO 7) suite

KAROLINSKA University Hospital

ANNO 1810

Infrastructure

- **HVAC**
  - HEPA filtered air
  - 25 air changes per hour
  - Adjustable air pressure
- **Media**
  - Clean steam generator
  - Sterile filtered compressed air
  - CO_2 unit
- **Washing and sterilization**
  - Validated dish washer and autoclave
- **Cold storage** (-150, -80 , -20, +4^{o}C)
- **Facility Monitoring System**
  -air pressure, temperature, CO_2, O_2 etc

Provided Services

- Creation of GMP cell banks
- GMP production ATMPs
- Filling of product in dosage form
- Quality Control testing
- Stability testing program

Manufacturing Experience and Capabilities

- **Cell culture**
  - CellCube®
  - Cell factory
  - Wave® bioreactor
  - G-Rex
  - T-flasks

- **Cell separation and analysis**
  - CliniMACS®
  - Flow cytometry
  - ELISA

GMP Products and Clients

- Manufactured more than 50 different cell and gene therapy products for phase I/II clinical trials.
- Clients in Sweden, Denmark, Finland, The Netherlands, Great Britain, Italy, France, Austria and Poland.
- More than 700 patients have been treated with produced products.
- At present 15 ongoing projects

KCC/Vecura Staff

Director	Pontus Blomberg, Ph.D.
Production managers	Katrin Markland, M. Sci., Tek. Lic.
	Kristina Wikström, M. Sci., Dr. Med Sci. Lic.
	Kerstin Strömvall, Ph.D.
	Ulrika Eistrand, Ph.D.
QA/QC	Jenny Enger, M. Sci.
	Katrin Markland, M. Sci., Tek. Lic.
Lab. eng/BMA	Carin Mölleryd, M. Sci.
	Angelika Holm, Ph.D.
	Stephanie Boström, Ph.D.
	Nansi Essac, M. Sci.
	Mevlida Lalic, Chem. Engineer
Qualified person (QP)	Gudmund Hedenskog, M. Sci., Tekn. Dr
	Jenny Enger, M. Sci.
Single entry point	Kristina Kannisto, Ph.D.
R&D	Per-Henrik Holmqvist, Ph.D.
Medicinskt ansv. (VI)	Emma Watz, MD., PhD
Scientific adviser	Edvard Smith, MD., Ph.D.

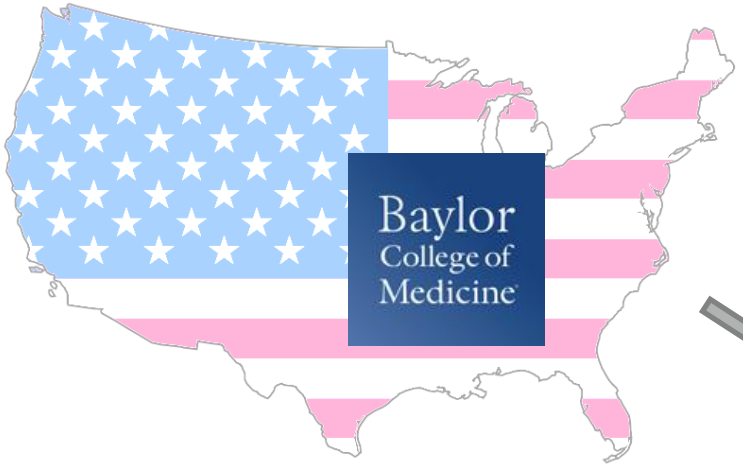
KCC Ongoing Projects

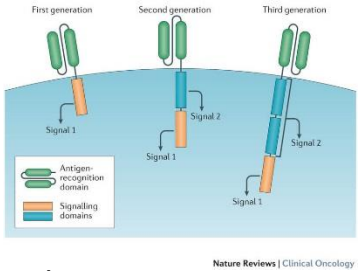
Product	Client	Status
Fetal mesenchymal stromal cells	Götherström, Karolinska	Ongoing clinical trial
Mesenchymal stromal cells	LeBlanc, Karolinska	Ongoing clinical trial
Human embryonic stem cells	Lanner, Karolinska	Manufacturing
Induced pluripotent stem cells	Falk, Karolinska/SME	Process development
T-reg	Ericzon, Karolinska	Process devolopment
NK-cells at AML	Malmberg/Björklund, Karolinska	Planning phase
Amniotic epithelial cells	Strom, Karolinska	Planning phase
NK-cells – Multiple myeloma	Karolinska/SME	Process validation
HIVIS DNA Vaccine	Penta Foundation, Italien	Application to ISS (Italy)
TILs - melanoma	Kiessling, Karolinska	Ongoing clinical trial
CD 19 CAR-T B-cell lymphoma	Essand/Enblad, Uppsala	Trial completed/Planning phase
Dendritic cells	SME	Distribution
Adenovirusvektor för tumörinjektion	LOKON (Loskog) Uppsala universitet/Akademiska Sjukhuset	Ongoing clinical trial
AdVince (Adenovirusvektor)	Essand, Uppsala universitet/ Akademiska Sjukhuset	Ongoing clinical trial

Treatment of B-cell Lymphoma with Genetically Modified Autologous T-lymphocytes (CD19 CAR-T)

Sponsor: Uppsala Universitet (M. Essand)

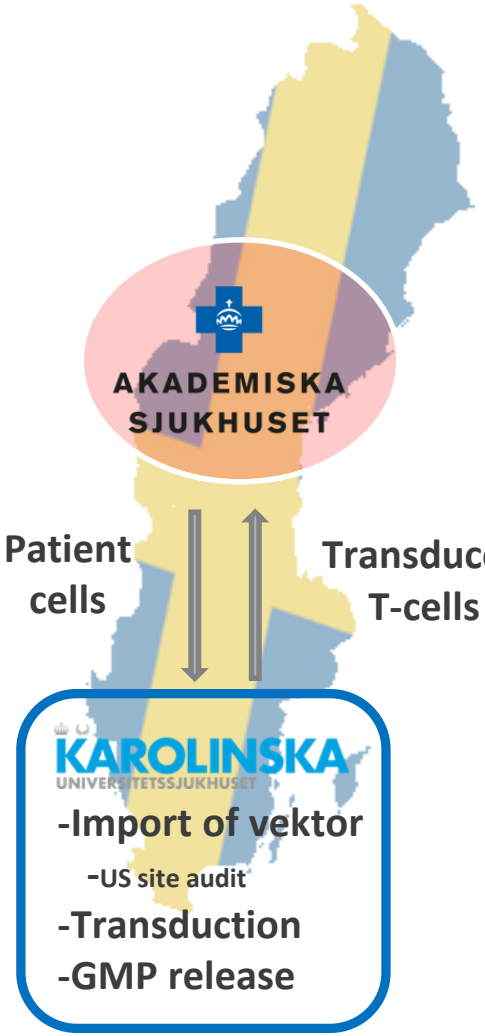
P.I.: G. Enblad, Uppsala universitet/Akademiska sjukhuset





3rd Generation CAR T CD19

Retroviral vector



-Production of CAR T CD19 for clinical trial 003:TCELL (2014-2019)

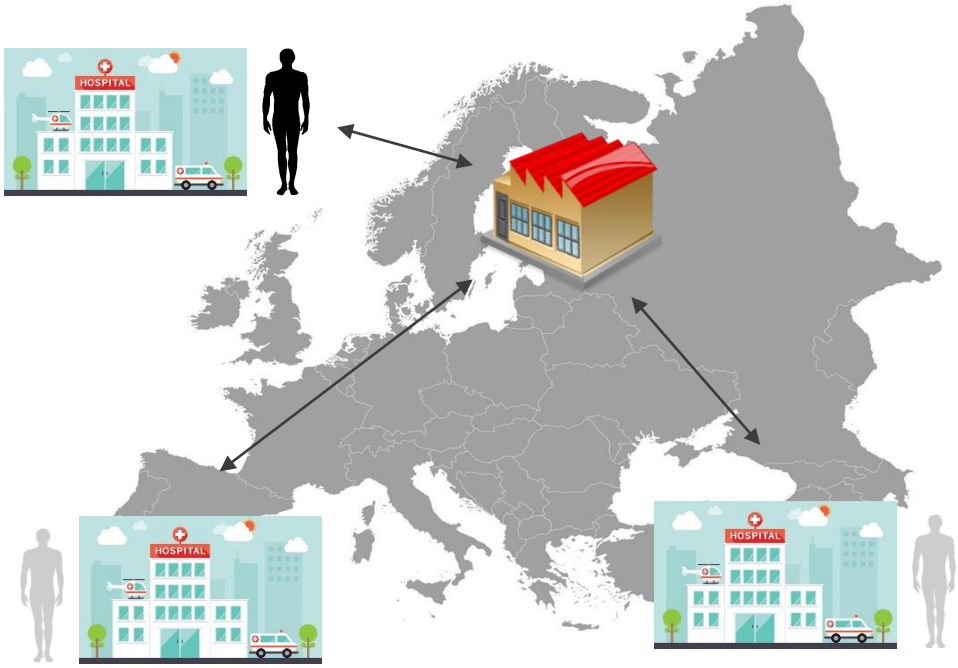
Timeline CAR T CD19 Programme

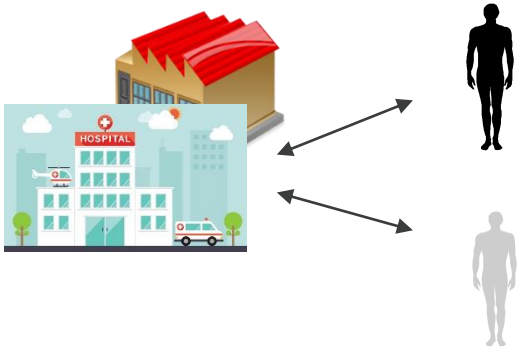
- **Initiation 2012**
- **2012-03 Audit at Baylor College of Medicine, Houston**
- **2012-08 – 2013-12 Technology transfer and validation of production protocols and analysis methods**
- **2014-04 Clinical trial approved by MPA**
- **2014-05 Initiation of Phase I/II clinical trial**
- **2016-04 15 patients treated (dose escalating study)**
- **2018 Publication - Enblad *et al* Clin Cancer Res; 24(24) 2018**
  - Treatment was generally safe with four patients requiring hospitalization due to adverse reactions
  - Six of the fifteen patients had CR (4/11 lymphoma and 2/4 ALL)
  - Three patients are still alive (>27-36 months)
- **2018 Initiation of repeated dosing regimen (25 patients)**
- **2019/2020 Completion of clinical trial (39 patients treated)**

ATMP - Manufacturing Challenges

- **Commonly products for first-in-man trials**
- **Starting material has very high intra-donor variability**
- **Limited availability of ”clinical grade” reagents for manufacturing**
- **Novel field so relevant equipment is lacking**
- **Regulations designed for batch processing rather than single product:single patient**
- **Release criteria/specification for the manufactured product difficult to define**
- **Scale-up/Scale-out**

Manufacturing Models for Cell Based ATMPs





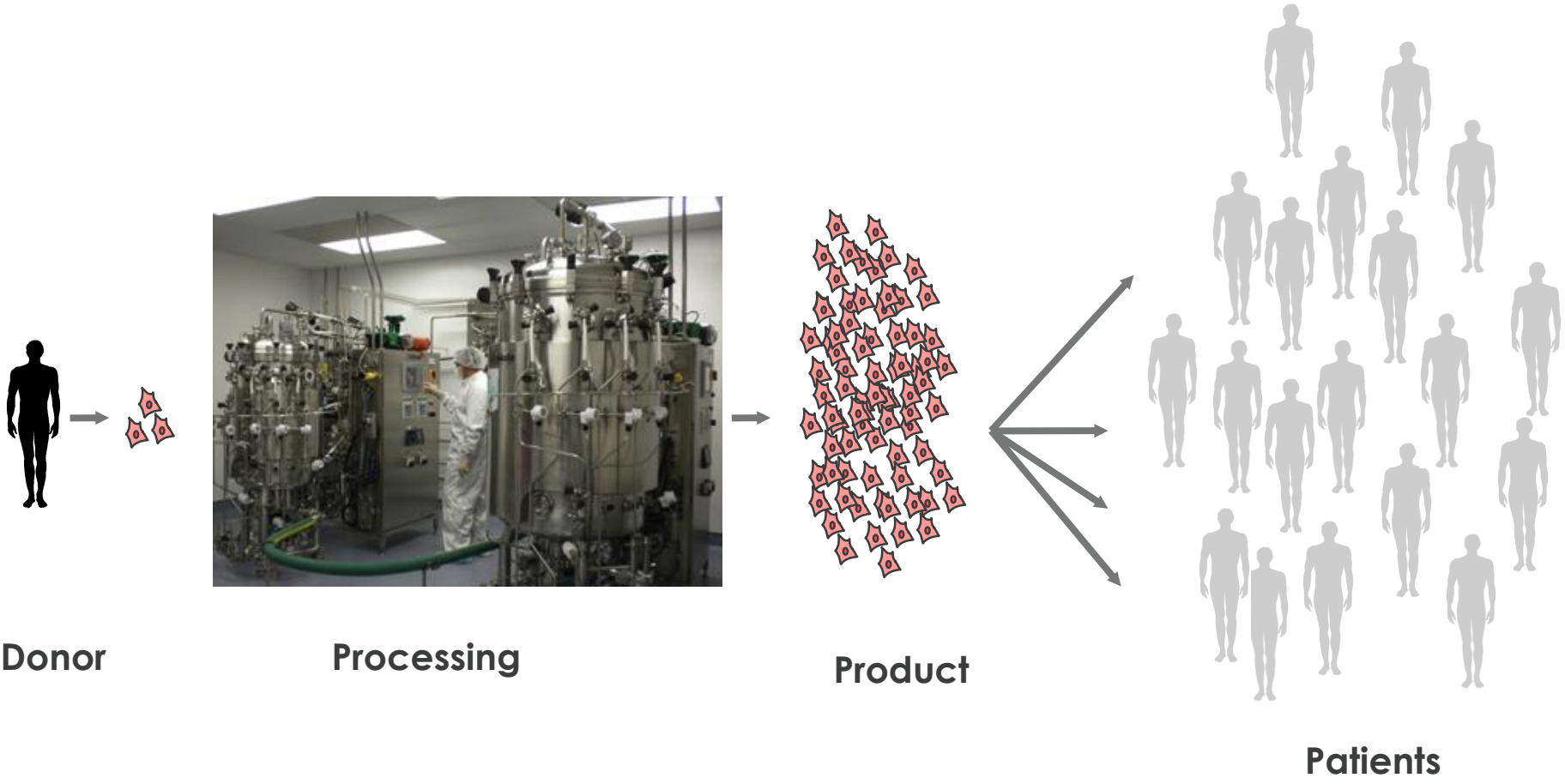
Centralised manufacturing

-Logistically challenging
-Saves resources
-Suitable for frozen products

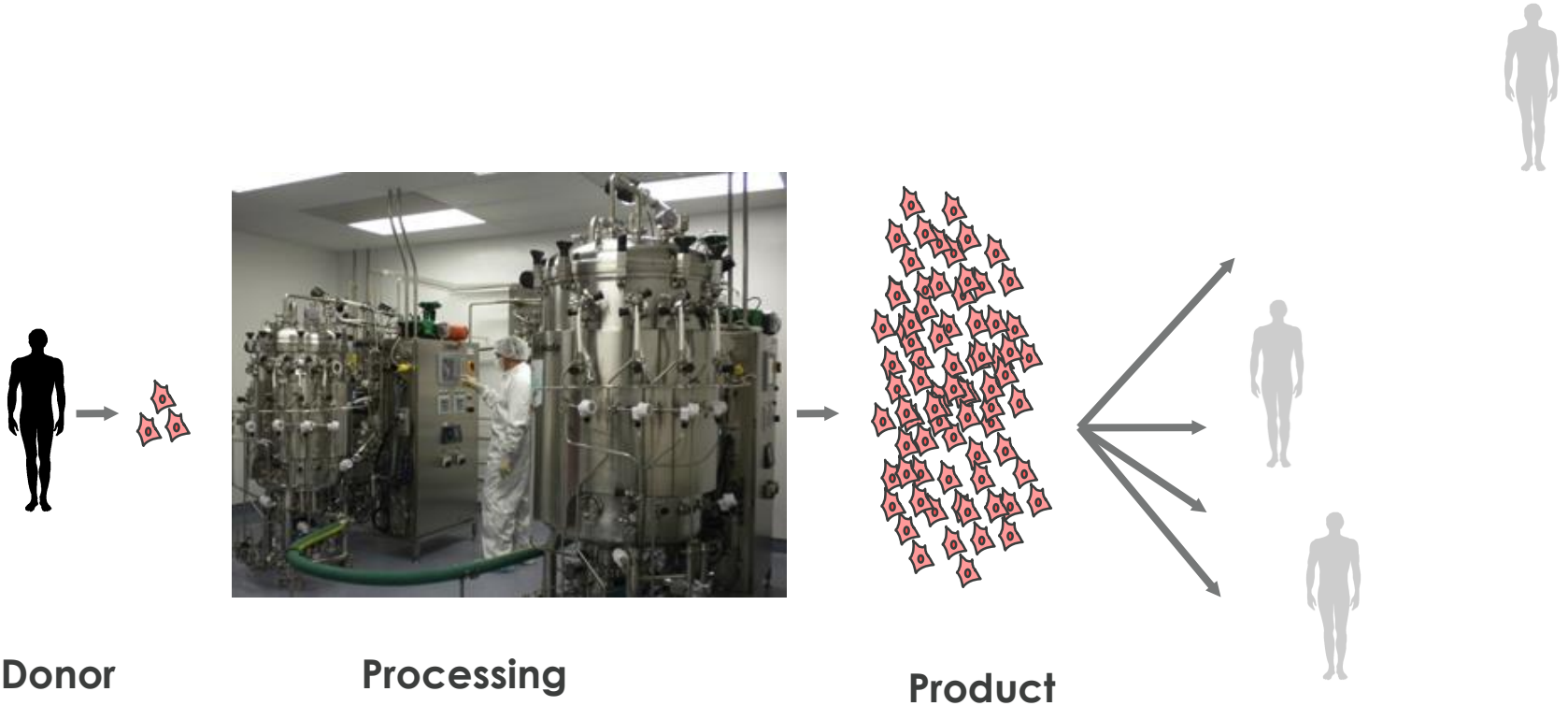
Point of care manufacturing

-Manufacturing at hospital or at facility in close proximity to the patient
-Suitable for instable products
-Hospital manufacturer of pharmaceuticals
-Require development of equipment technology to become routine

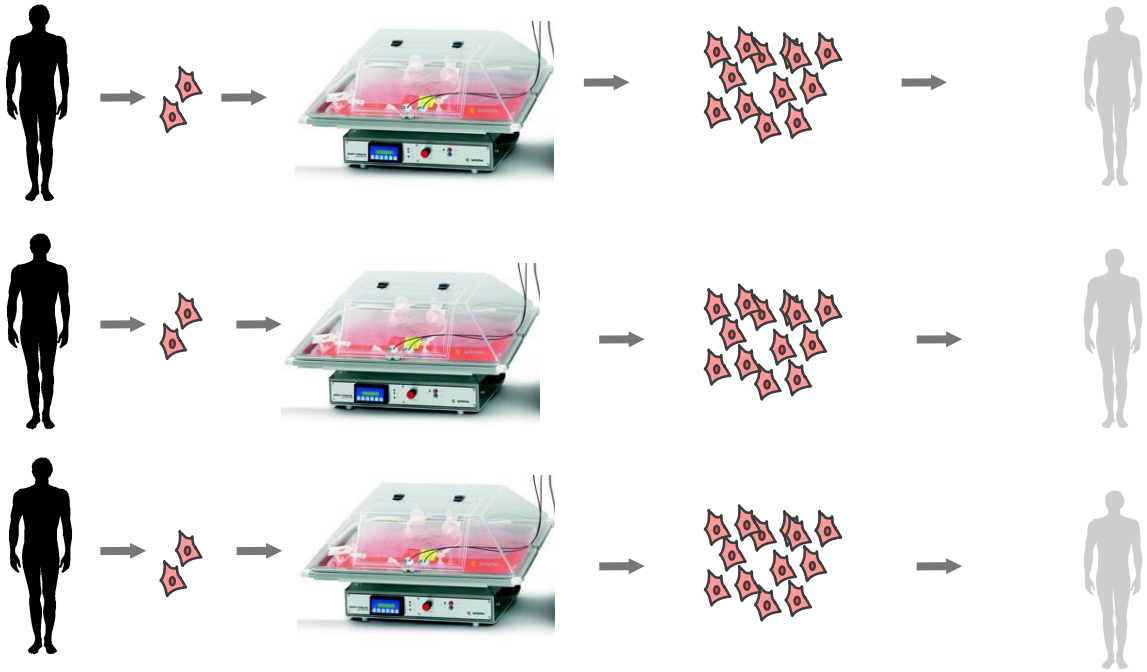
Large Scale Manufacturing of Cell Therapy Products



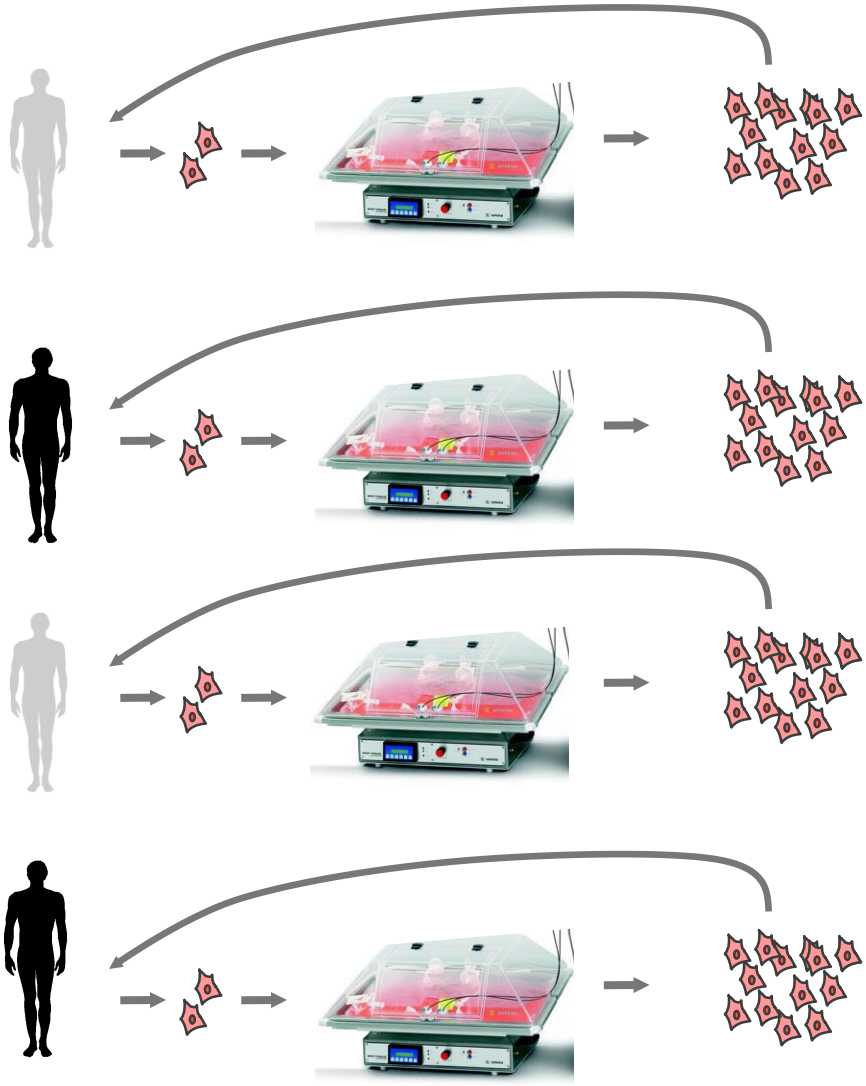
Large Scale Manufacturing of Cell Therapy Products



Scale-out of Cell Therapy Product



Manufacturing of Cell Therapy Products for Autologous Use



Process and Manufacturing Development Programmes

Up scaling - AdBIOPRO

Vinnova funded program for process development of cell therapy products (NK-cells) involving KCC, KTH and XNK AB.

Center for Advanced Medicinal Products – CAMP

VR/Vinnova support for a national center for the development of ATMP in Sweden.

CAMP
Guiding ATMPs to patients

Support of Pre-GMP-ANA Futura, Dep of Lab med

Facility for process and method development. In operation since 2019. Joint SLL/KI Core facility funding.

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Thank you!