Production and validation of CAR-T cells and T-cell receptors (TCRs) in an academic setting

Workshop on scientific and regulatory challenges of genetically modified cell-based cancer immunotherapy products

November 15/16, 2016

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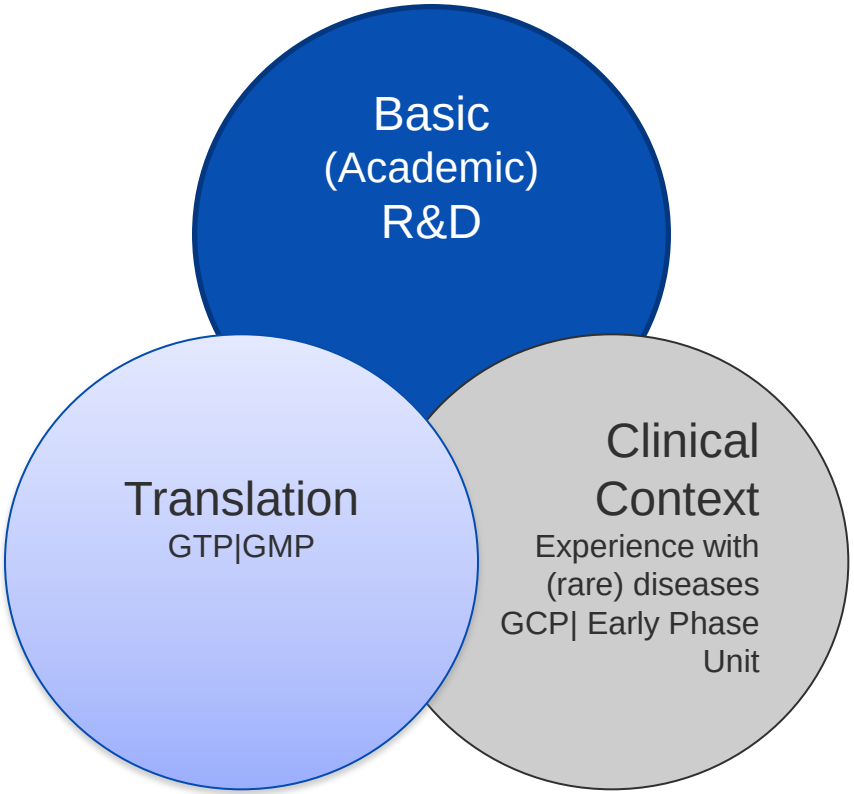
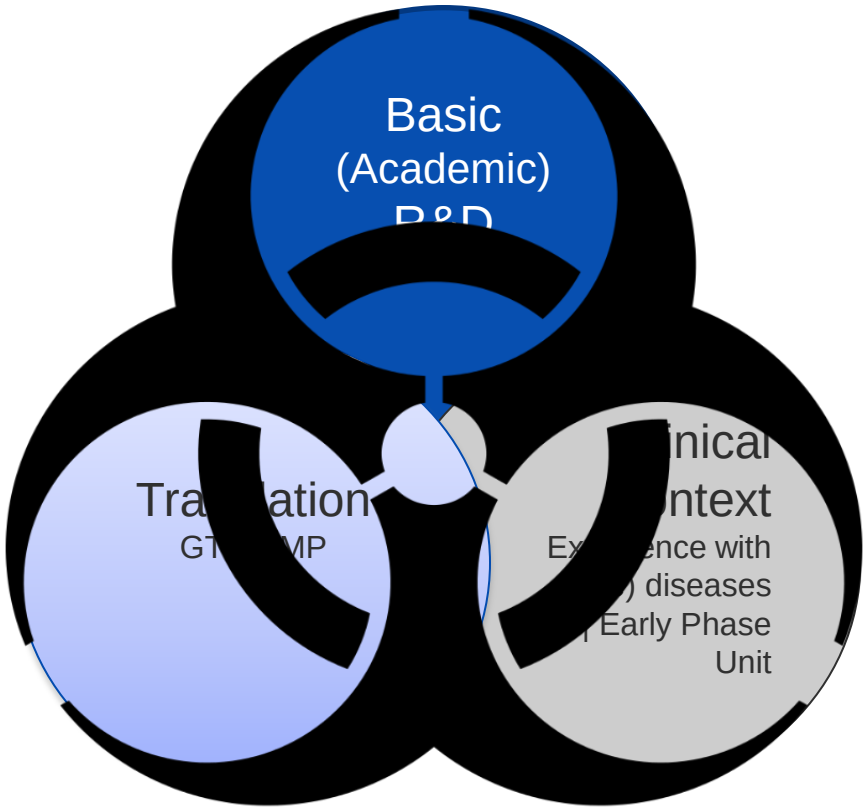
TUM School of Medicine

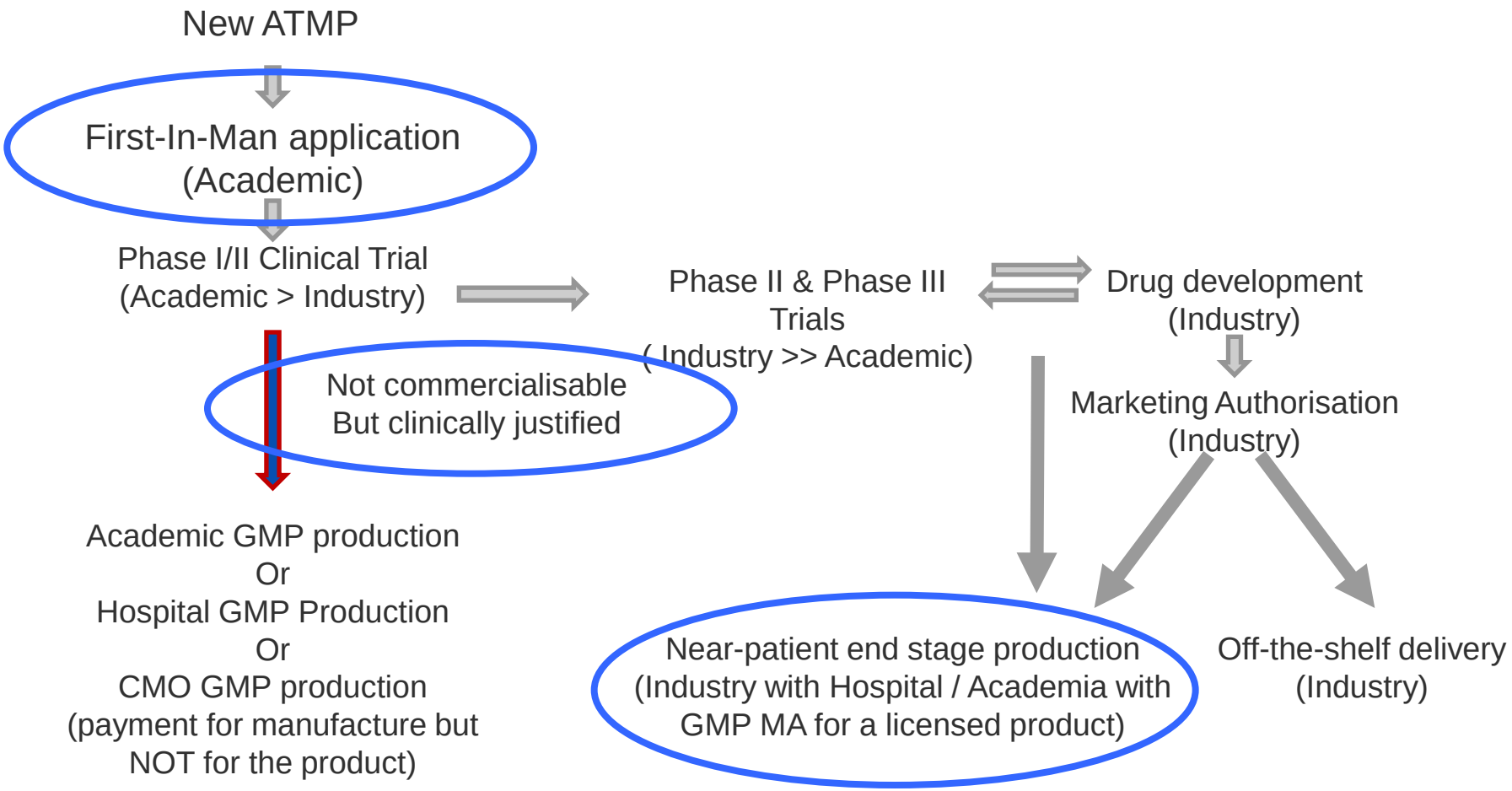
Academia: A Source of GTMP Development



Academia: A high-risk environment?



Academia in ATMP Development



CAR- and TCR-transduced T Cells in Academia: Strengths

- Access to human samples
- Access to human starting material
- Clinical trial enrollment
  - Cohorts of patients in rare diseases (registries, ultra-orphan diseases)
  - Connections to other academic centers (consortia, collaborations)
  - Active long-term follow-up

- Risk management: Clinical knowledge on site

De Wilde et al., Drug Discovery Today 2016

Example: Risk Assessment (Patient)

	Potential reason	Severity (S)	Probability (P)	Detectab. (D)	Risk priority (RPN)
Transmission of infectious agents to the patient	contamination	8 (critical)	4 (moderate)	2 (allm. certain)	**64 (low)**
Induction of autoimmunity or immunogenic reactions	contamination with unspecific T cells, TCR mispairing, off target reactivity	8 (critical)	6 (moderate)	3 (high)	**144 (moderate)**
Induction of anaphylactic reactions	immune response against allogeneic cells and proteins	6 (very important)	4 (moderate)	1 (allm. certain)	**24 (low)**
Impossibility of removing Ag-specific T cells	uncontrolled expansion of autoreactive cells	10 (catastrophic)	3 (low)	1 (allm. certain)	**30 (low)**
Potential of the vector for T cell tumor induction	integration into host DNA	10 (catastrophic)	2 (very low)	3 (high)	**60 (low)**
Integration of genetic material into host genome and germline	integration into host DNA	9 (critical)	1 (very low)	10 remote	**90 (low)**

Continous Risk Management

	Product		Patient	
	risk detection	action to take	risk detection	action to take
Transmission of infectious agents to the patient	microbiological testing	no administration of cells	body temperature, CRP monitoring	antibiotic treatment
Induction of auto- and alloimmunity	peptide library, number of CD3+	Cross-reactivity testing, lot release testing	GvH monitoring	Immuno-suppression, GvH therapy
Induction of immunogenic reactions	n.a.	n.a.	HAMA testing, clinical monitoring after application	steroids, prevention of further exposure
Impossibility of removing Ag-specific T cells	n.a.	n.a.	Ag-specific T cells	ATG, anti-CD52 mAbs
Potential of the vector for T cell tumor induction	number of viral insertions	PC testing	regular physical and radiological examination	chemoradio-therapy, mAbs
Integration of genetic material into host genome and germline	testing for replication competent particles	no administration of product	long-term follow up	contraception, antiviral therapy

CAR- and TCR-transduced T Cells in Academia: Outcompeted by Industry?

- Target Identification
- TCR Isolation and Sequencing/ CAR Construction
- Vector constructs
- Pre-clinical studies: „Proof of Efficacy“
- First clinical attempts

- Access to Biobanks

- Patent issues, faster development
- Access to vector suppliers
- GLP knowledge
- Product-driven decisional power

High-Risk environment:

- Clinical perspective
- Small customer for suppliers
- Limited time
- Limited funding resources
- In the face of unmet medical need and despair

CAR- and TCR-transduced T Cells in Academia: Validation

Heterogeneity:

- Extent of validation efforts
- Integration in the QA system
- Adherence to GMP annexes 15 and 16
- Definition of specifications
- Management of deviations and OOS

Specific issues not accounted for (or misinterpreted):

- Vector: Quality vs availability (state of the art, supplier)
- Pre-clinical data: Design modification, Comparability
- Selected Cell population, changes
- Safety and efficacy of transduction: mean copy number per cell, Insertion site
- Immunogenicity

CAR- and TCR-transduced T Cells in Academia: ATMPs

„Cultural Differences“:

- Cell-based Medicinal Products
  - Haematopoietic Progenitor Cells and DLIs
  - GMP Experience
- Tissue Engineering:
  - Plastic and Reconstructive Surgery, Transplantation Medicine
- Gene Transfer Medicinal Products:
  - Extensive basic research
  - pre-clinical knowledge

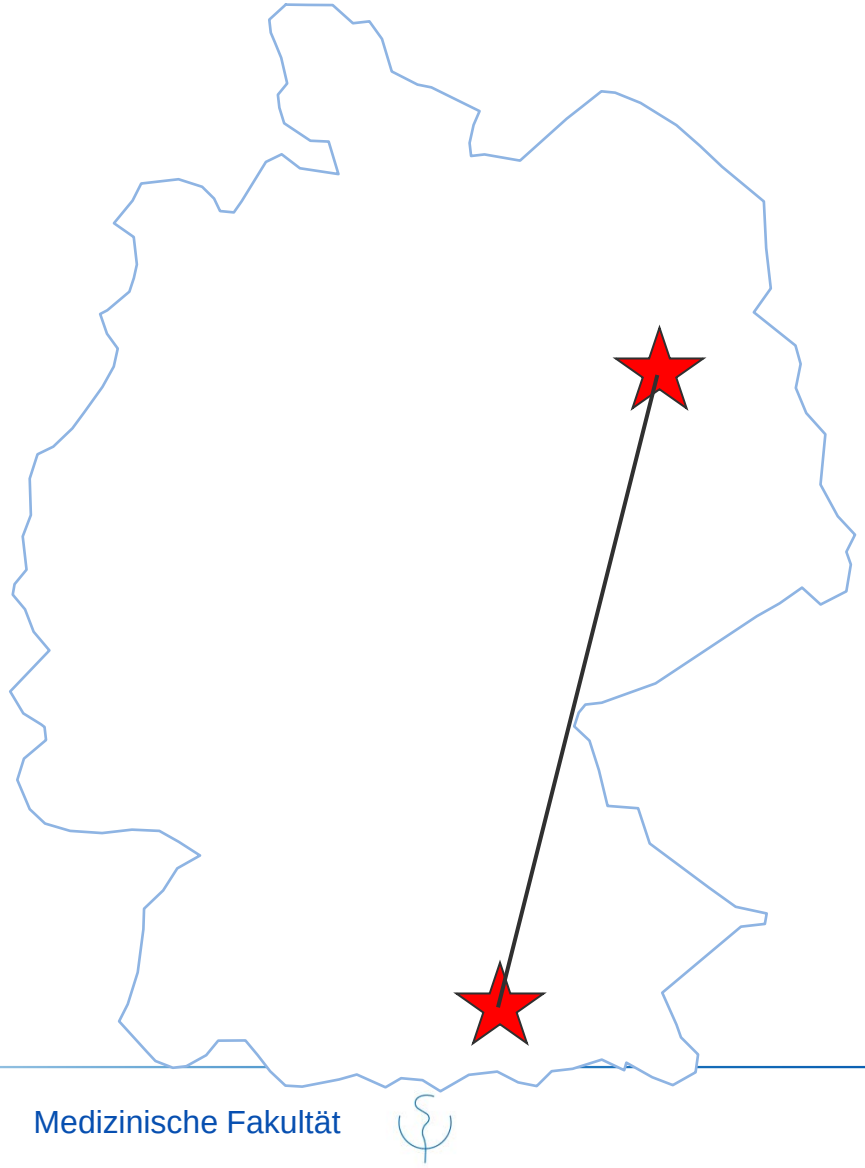
Similar Developments in bioprocessing:

- Reduced extent of clean room infrastructure
- High up-front costs
- Decentralised / re-distributed models of manufacturing

United we stand (separated we fall): Academic Manufacturing Networks

- Shared Auditing
- Joint user requirements
- vendor qualification, material qualification
- Backup in case of facility shutdown
- Close to (or: identical with) Apheresis site
- Common set of documents:
  - Risk analysis
  - Media fill protocols
  - Validation plans and protocols
  - ...
- Attractive for Sponsor-initiated trials: Network of Academic CMOs

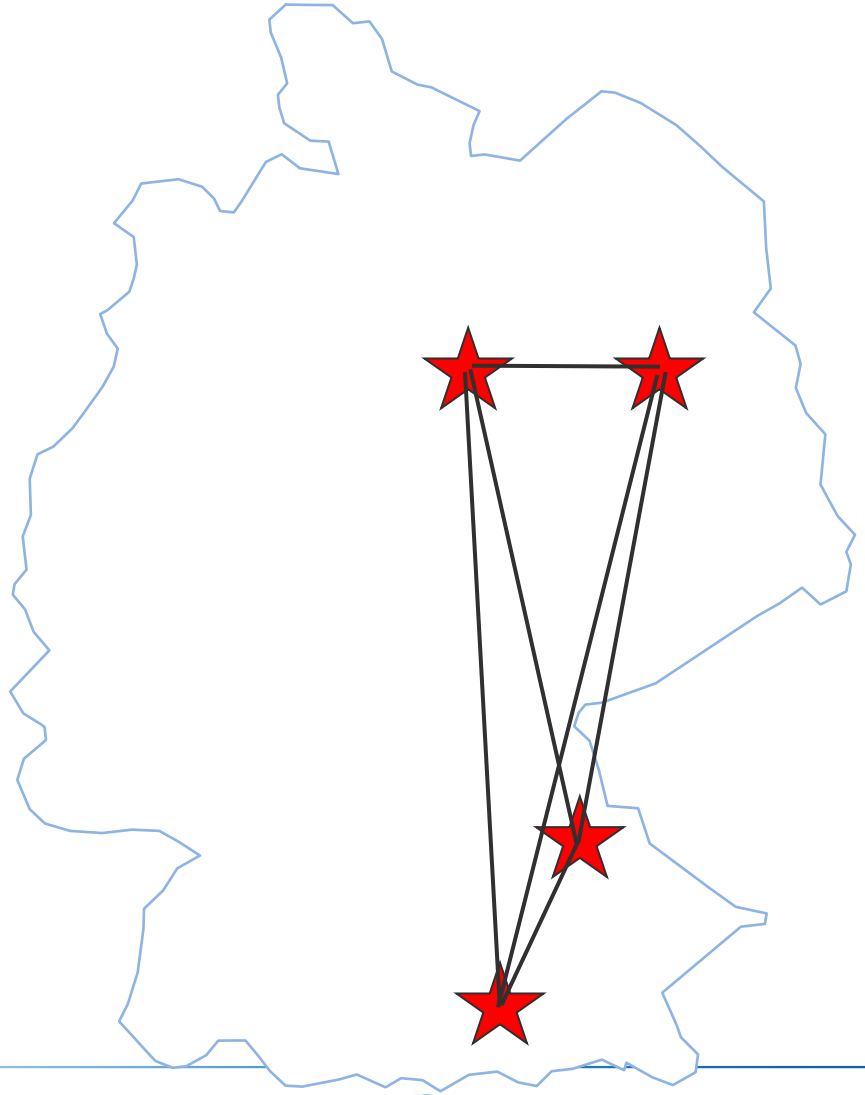
Networks of Quality Assurance



- Electronic QA System with Network option
- QA Workshops

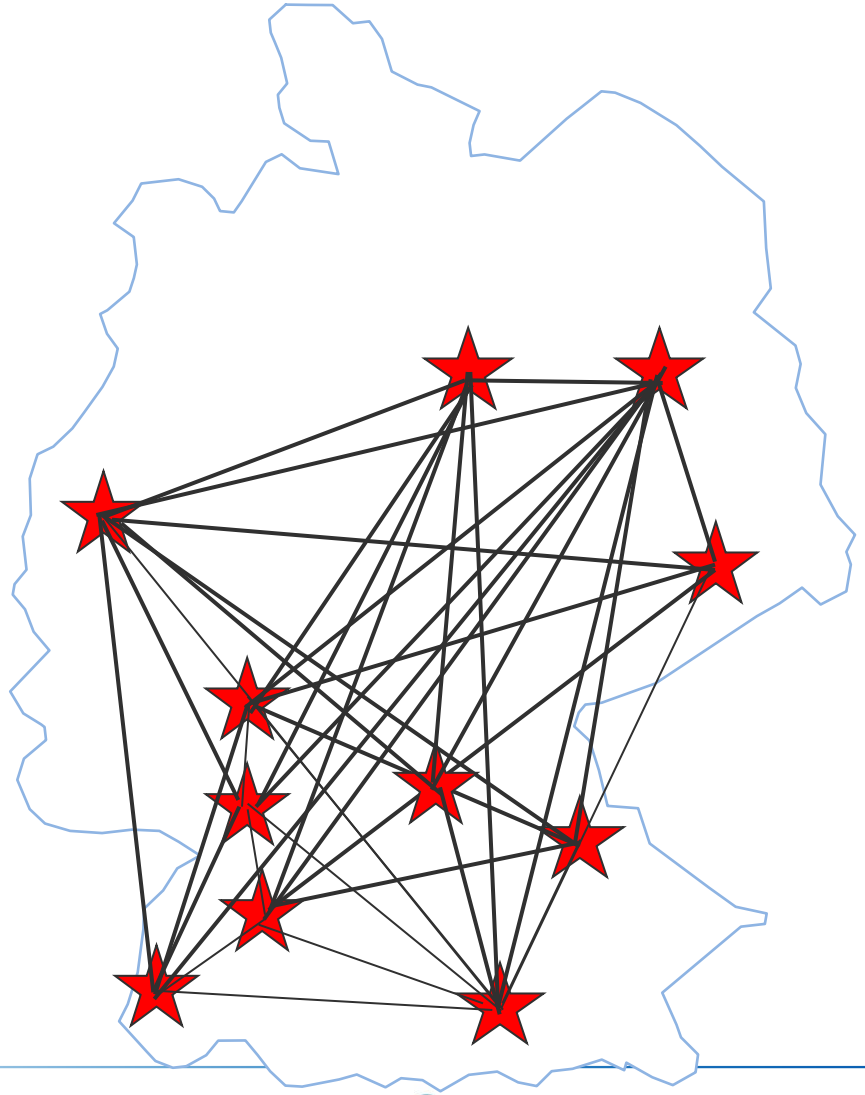
SFB – TR 36

Networks of Quality Assurance



- Electronic QA System with Network option
- QA Workshops
- Quality Circle

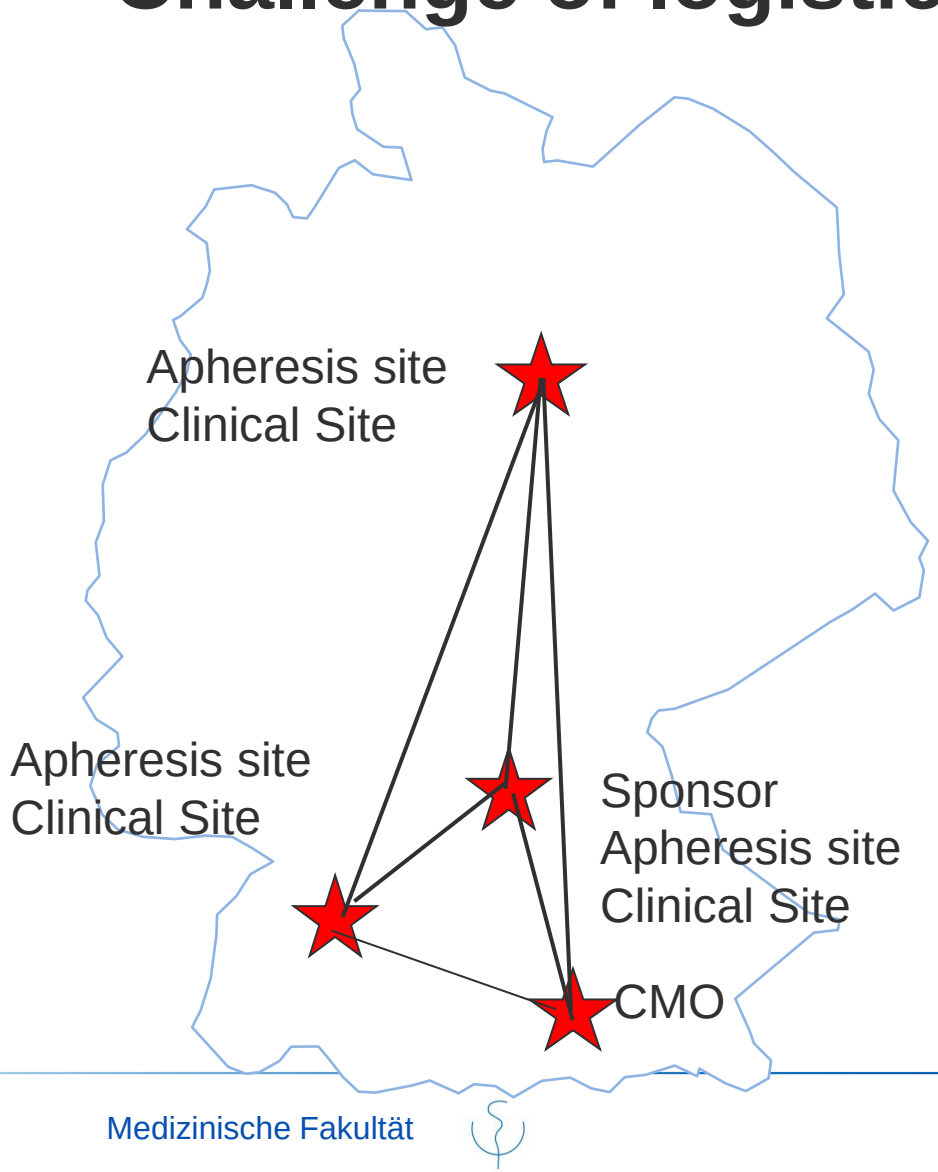
Networks of Quality Assurance



- Electronic QA System with Network option
- QA Workshops
- Quality Circle
- DKTK
- Future Academic GMP Networks

DKTK German Cancer Consortium

Challenge of logistics



- Clinical site enrols participant
- Sponsor orders manufacture
- CMO interacts with apheresis centers
- Dual release
- Transport of apheresis product
- Transport of IMP

Challenge of logistics: EU level

- Enrolment

Sponsor: Liverpool
CMOs: London, Munich
Clinical sites:
- Warsaw
- Brescia
- Vienna

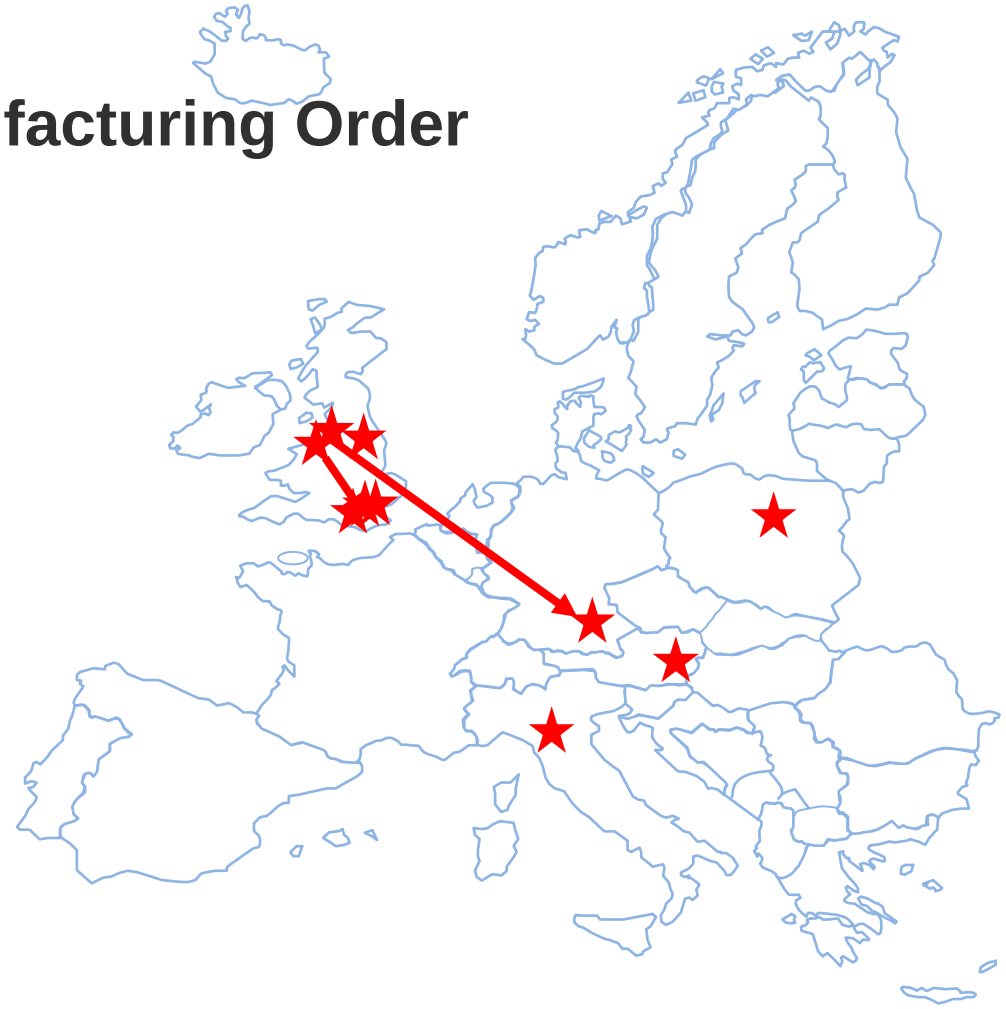
TETRA

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 681027.

TUMCells

Challenge of logistics: EU level

- Manufacturing Order



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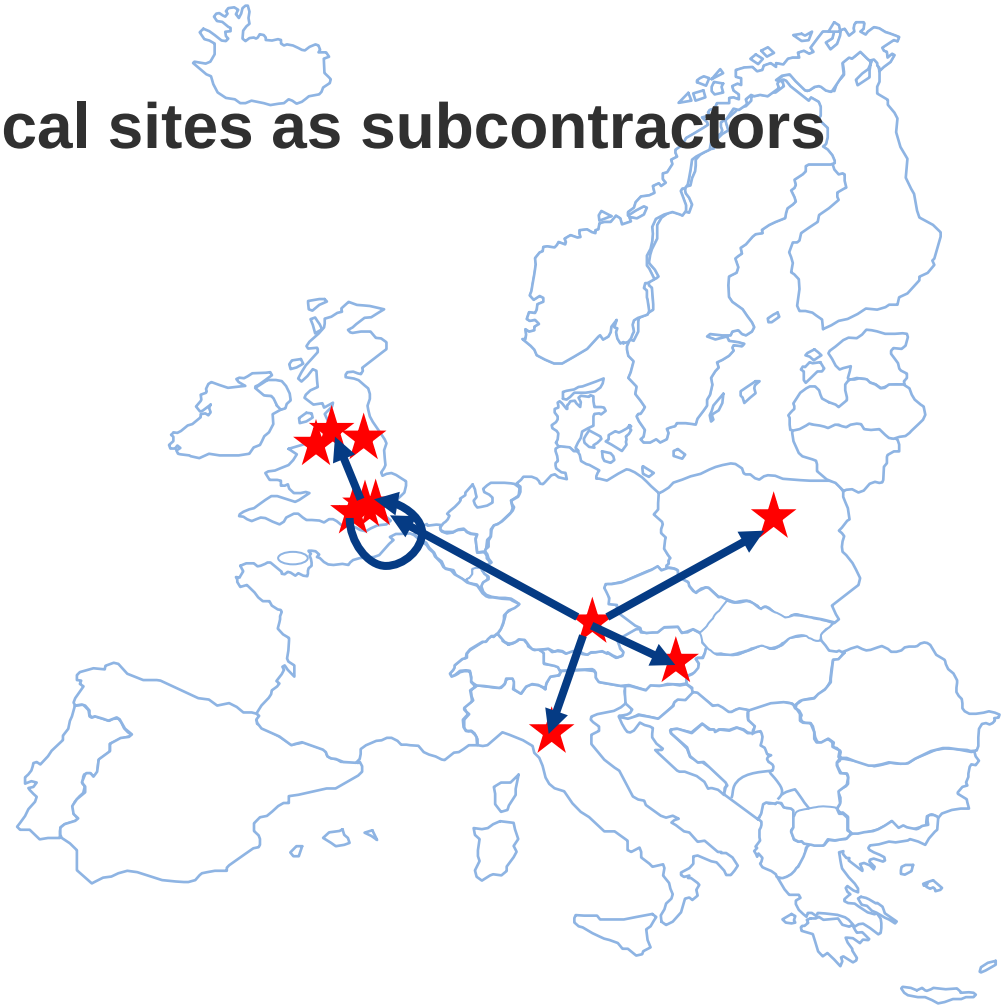
Challenge of logistics: EU level

- Clinical sites as subcontractors



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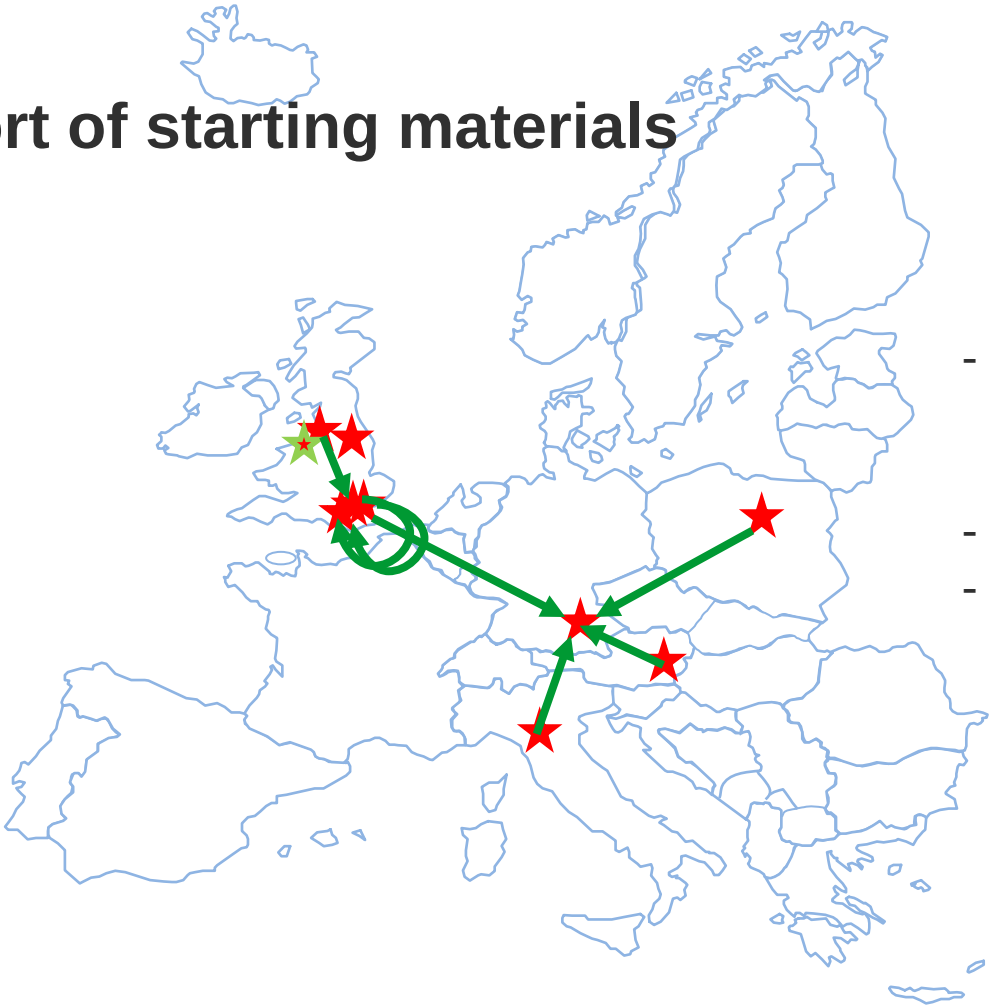
Challenge of logistics: EU level

- **Import of starting materials**



- Import licenses to DE:
  - Clinical Sites
  - NHSBT
- Contracts, Auditing
- Transport validation

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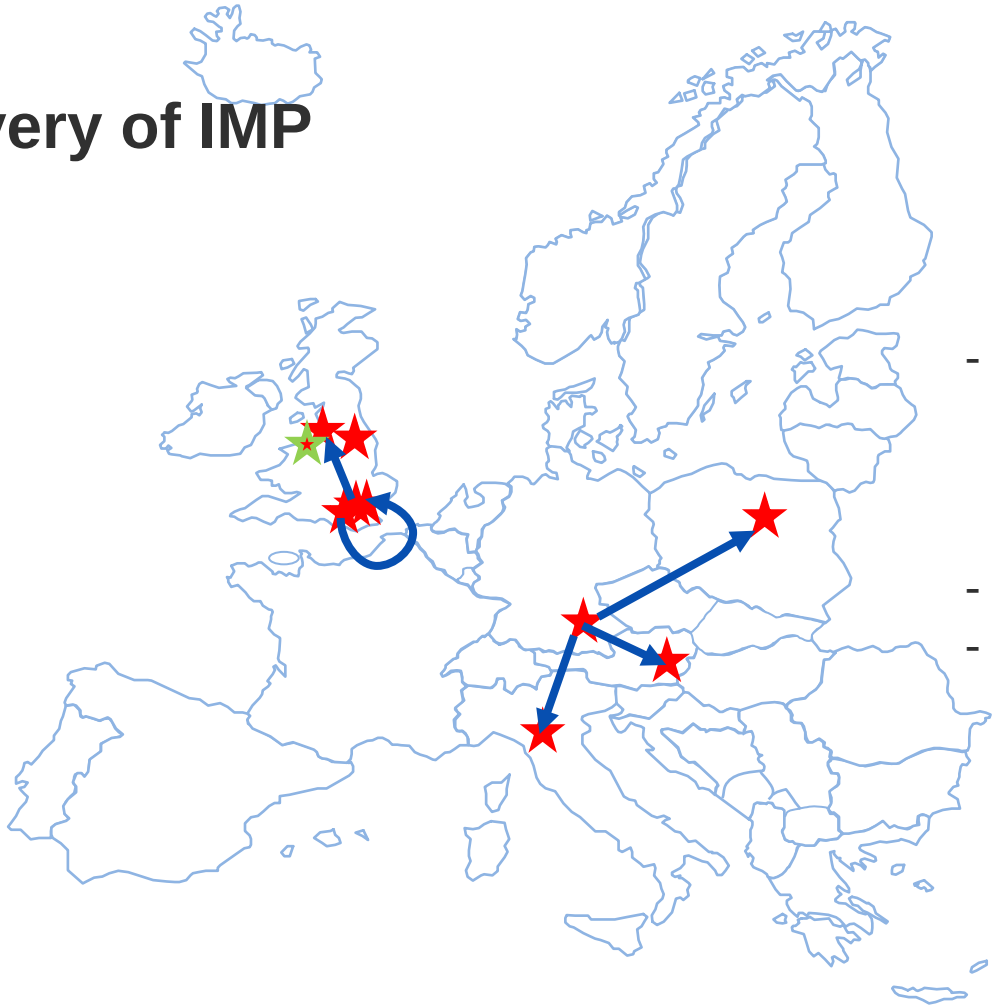
Challenge of logistics: EU level

- **Delivery of IMP**



- Import licenses from DE:
  - Warsaw
  - Vienna
  - Brescia
- Contracts, Auditing
- Transport validation

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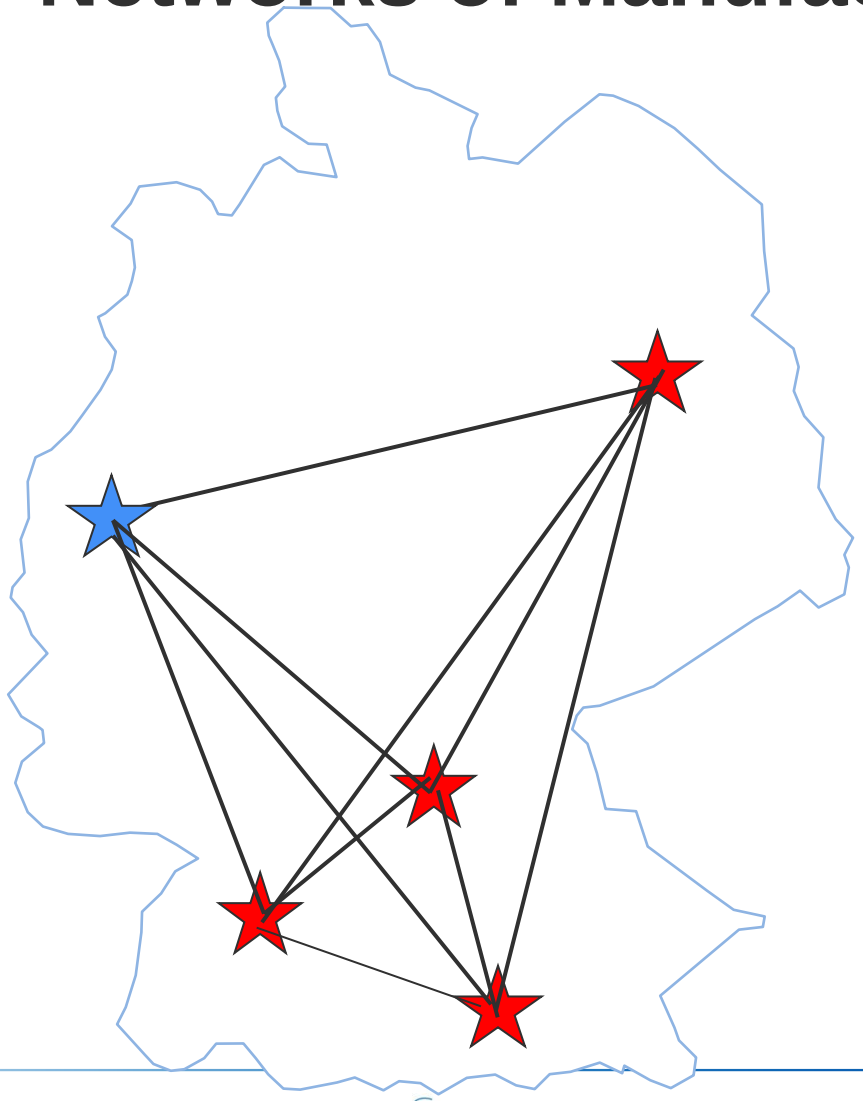
CAR- and TCR-transduced cells: Academia and Industry

- Competitive models for logistics
- Competitive Product Development
- Distance to Patient
- Diverging ideas of success

- Collaboration:
  - a window of opportunity offered by chance (καιροσ)
  - a missed opportunity when the winds change

Networks of Manufacture: with Industry



- Shared Auditing
- Joint user requirements
- vendor qualification, material qualification
- Backup in case of facility shutdown
- Close to (or: identical with) Apheresis site
- Common set of documents:
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  - Validation plans and protocols
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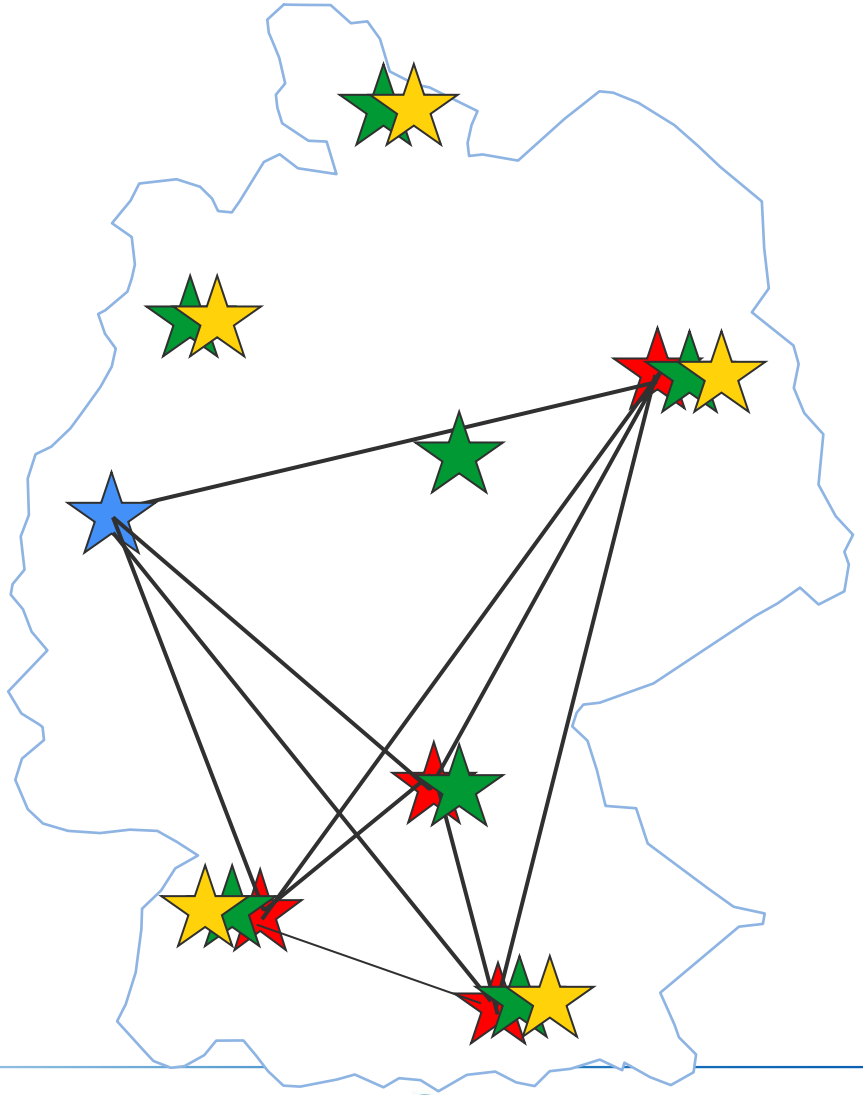
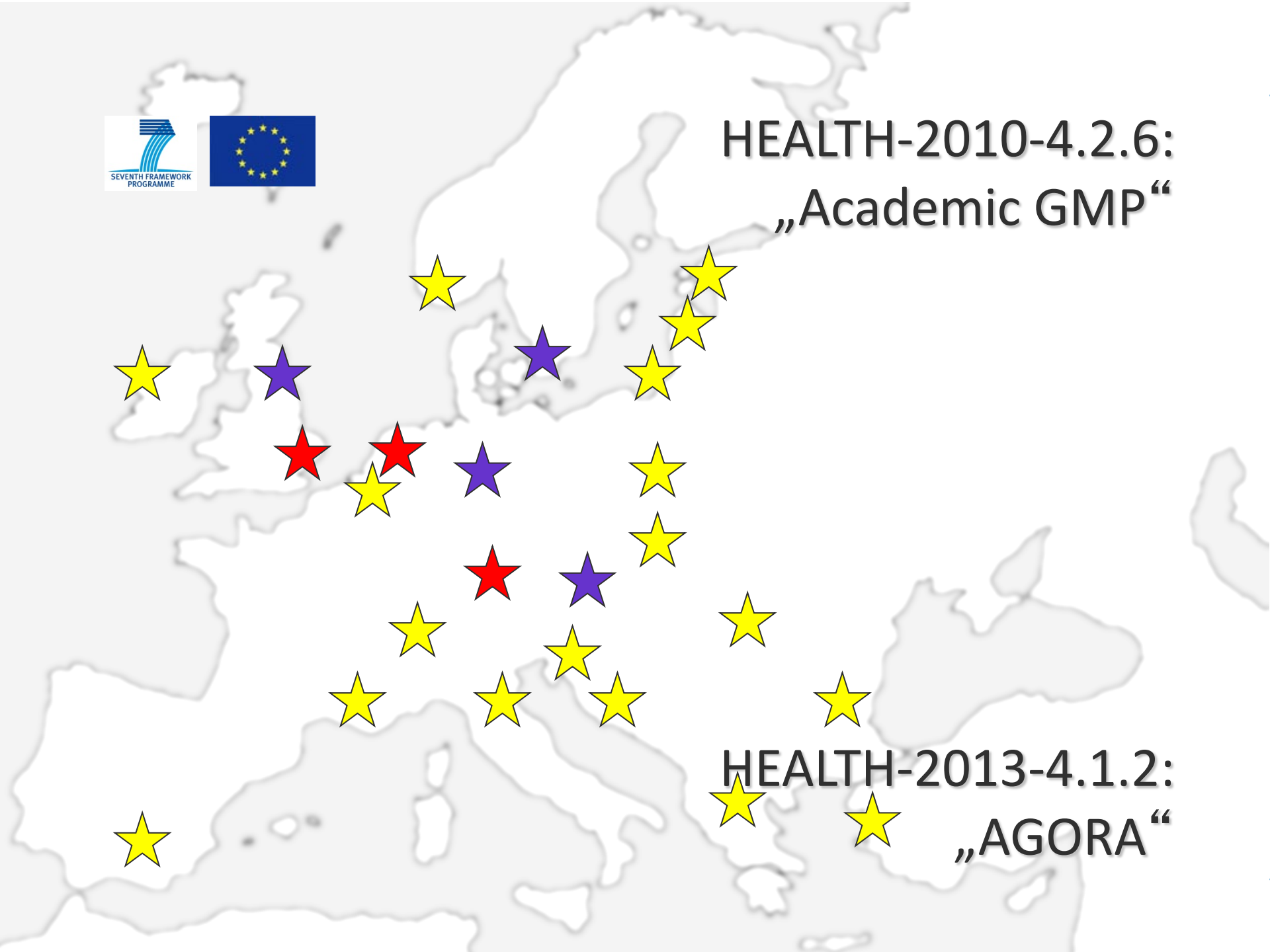
Clinical trial: CD19 CAR T cells in B cell leukemia



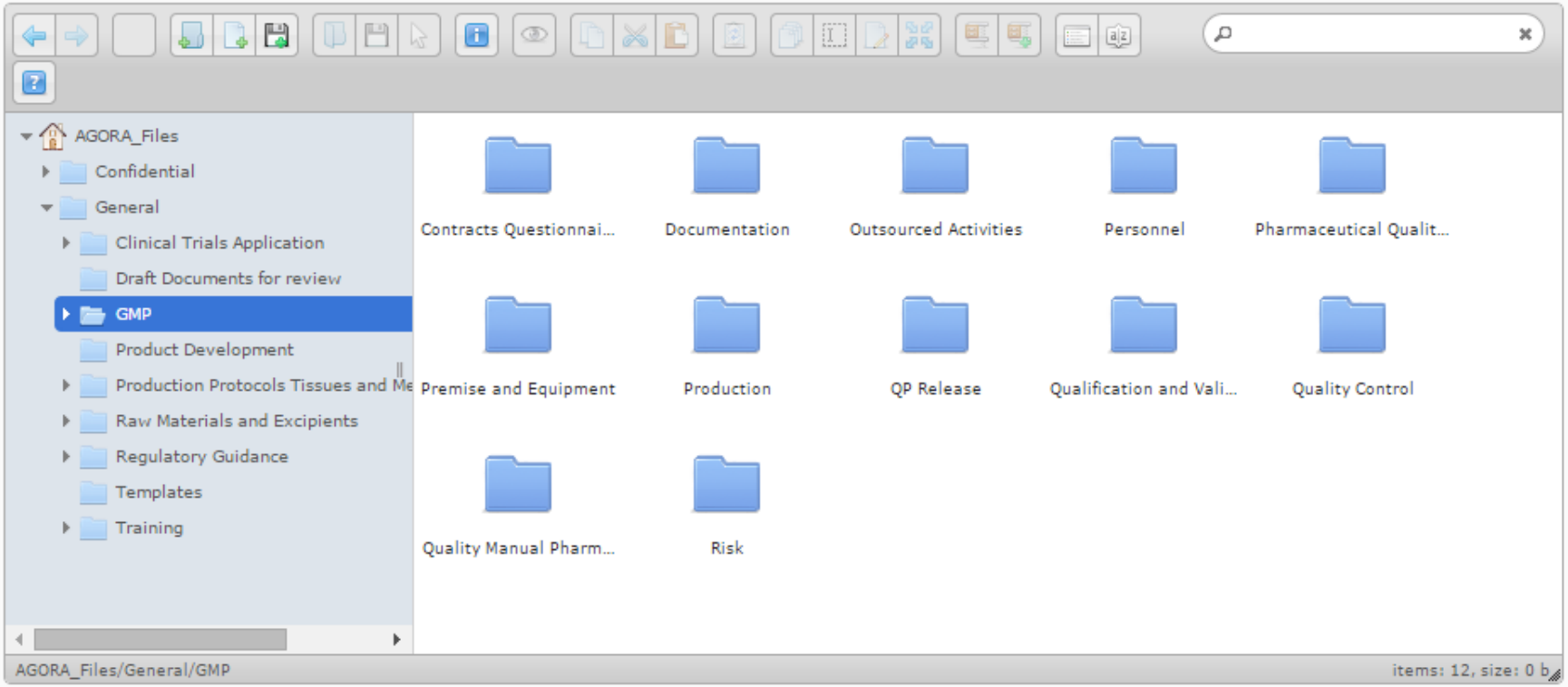
- Phase I/II trial in patients with r/r disease
- Sponsor: Miltenyi Biotec
- CD19 positive B cell malignancies (ALL, NHL incl. CLL)
- 7 trial sites, 12 departments (pediatric, adult)
- 4 IMP manufacturing centers


HEALTH-2010-4.2.6:
„Academic GMP“
HEALTH-2013-4.1.2:
„AGORA“

Examples:

- Consensus List of mandatory SOPs (minimum)
- Points to consider: Characterization of CAR constructs for usage in CAR-transgenic T cells
- Import supplier approval
- ...

For information about local authorities and GMP experts use the following link: http://agora-gmp.org/interactive-map/ .



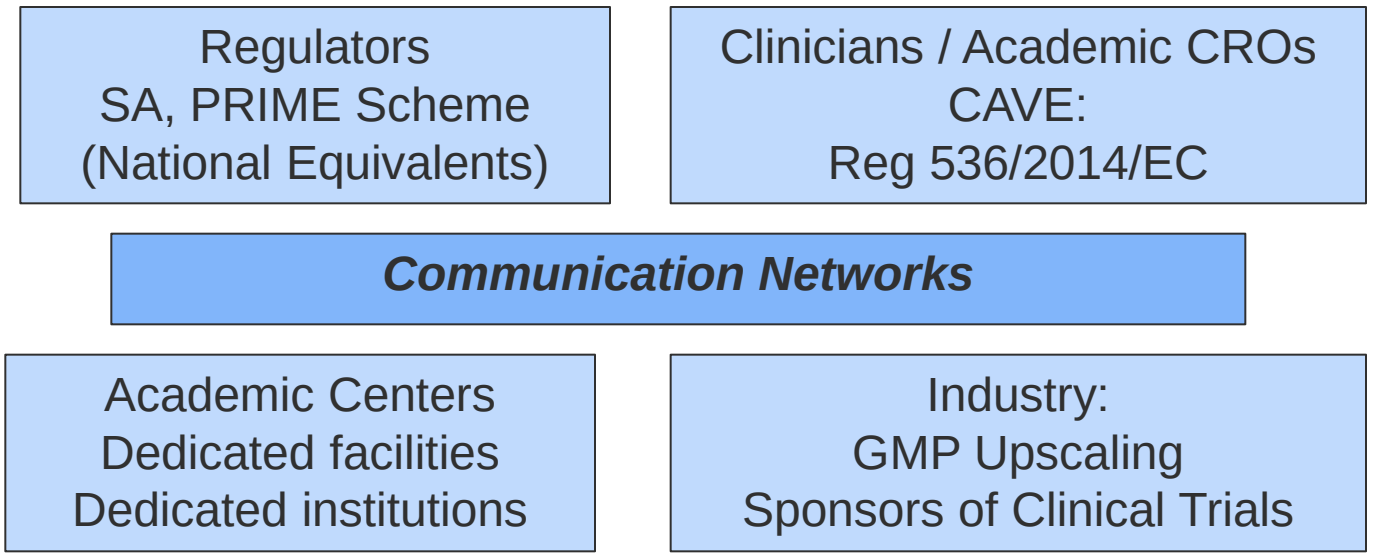
Proposals: GTMPs in Academia

- **Toolbox for GTMP Development**:
  - ACADEMIC GMP, AGORA EBMT, EQPA
- **European Hospital Exemption Registry**
  - Clinical Data
  - Safety Issues
  - Contact Points
  - Database close to the EU CT Database (cf.: Regulation 536/2014/EC)
- **Registry of „Common best practices“**
- **Pre-competitive Platforms** (Academia-Industry; cf.: IMI Consultation Process, http://www.imi.europa.eu/content/advanced-therapies-consultation)
- Joint Concepts of (realistic) **Pricing and Reimbursement**
- Curricula for **Training in Biosciences** (EuroTech Universities)

Vision: Academic CGT Competence Center

- **Existence within a well-defined framework**:
  - GMP-certified manufacturer
  - Quality and Risk Management
  - Qualification and Validation
- **Master processes** for Manufacture, QC and Release lead to
- **Individual products** (defined by the CAR/TCR to be included)
- **Accreditation** by local and national Competent Authorities:
  - Local CA: Quality of **Infrastructure and Processes**
  - National CA/ EMA: Quality of **Products**
- **Well connected with other centers**
- **New Concepts of Specificity Assessment** (CAR-T Cells): Access to Biobanks ?

CAR/ TCR transduced cells: From Project to Processes and Products



CAR/ TCR transduced cells: Platforms and Registries

hPSC^{reg} | ***ATMP Registry?***

Funding bodies
IMI, EC, National Public Funds, Charity

Regulators
SA, PRIME Scheme
(National Equivalents)

Clinicians / Academic CROs
CAVE:
Reg 536/2014/EC

Pre-Competitive Platforms

Academic Centers
Dedicated facilities
Dedicated institutions

Industry:
GMP Upscaling
Sponsors of Clinical Trials

Thank you!

- TUM School of Medicine
  - TUMCells Executive board:
    - D. Busch
    - G. Machens
    - C. Peschel
  - TUMCells Advisory Board
  - Angela Krackhardt
- Helmholtz Centrum München
- Munich Immunotherapy Consortium

- TUMCells Team:
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  - M. Neuenhahn
  - J. Pelzel
  - T. Roßmann-Bloeck
  - S. Schmalix
  - V. Segschneider
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- Project Partners at LMU:
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  - T. Käuferle

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