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Welcome!

Cell and gene therapy in oncology - The development of academic innovations

6th of October

ARTIS Royal Zoo


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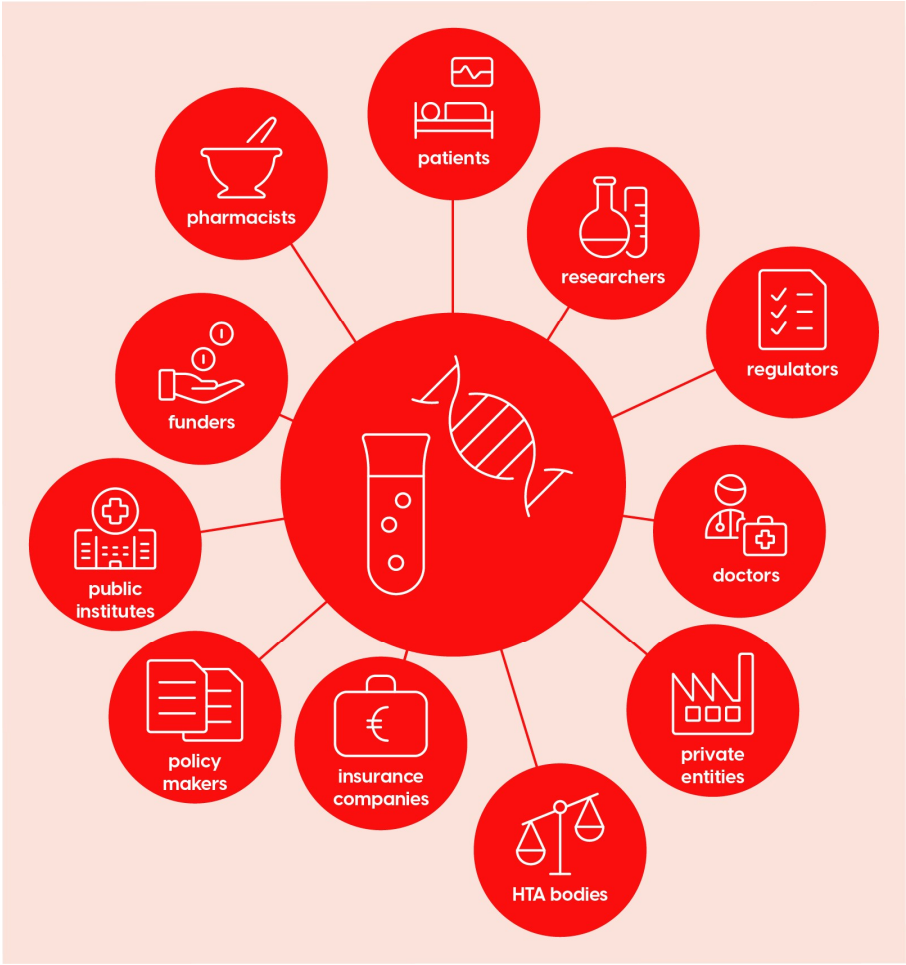
Speeding up developments by improving the innovation environment

Highlights of KWF report

Cell and gene therapy in oncology, 6 October 2021

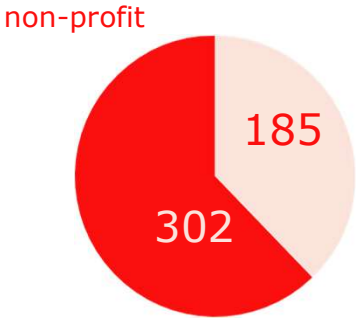
Delphi Coppens

Welcome

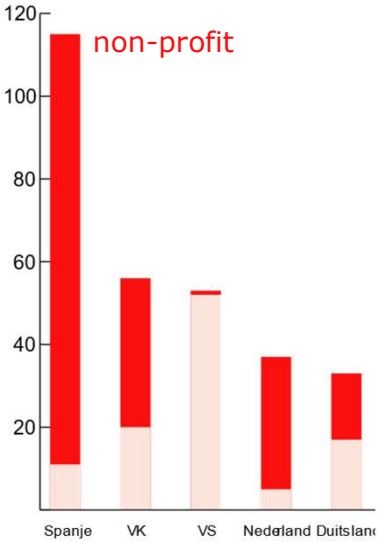

patients
pharmacists
researchers
regulators
funders
public institutes
doctors
policy makers
insurance companies
private entities
HTA bodies

Few products are reaching clinical practice

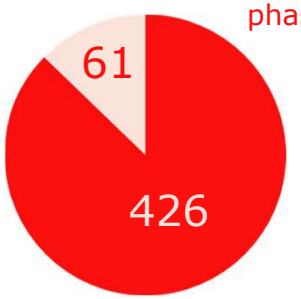
EU ATMP clinical pipeline (2010-2015)



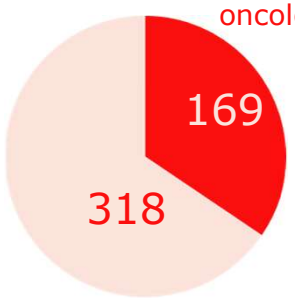
public/private sponsor:
mostly non-profit in EU



origin sponsor:
mostly non-profit in NL



research phase:
mostly explorative
(phase I/II trials)



target indication:
mostly oncology

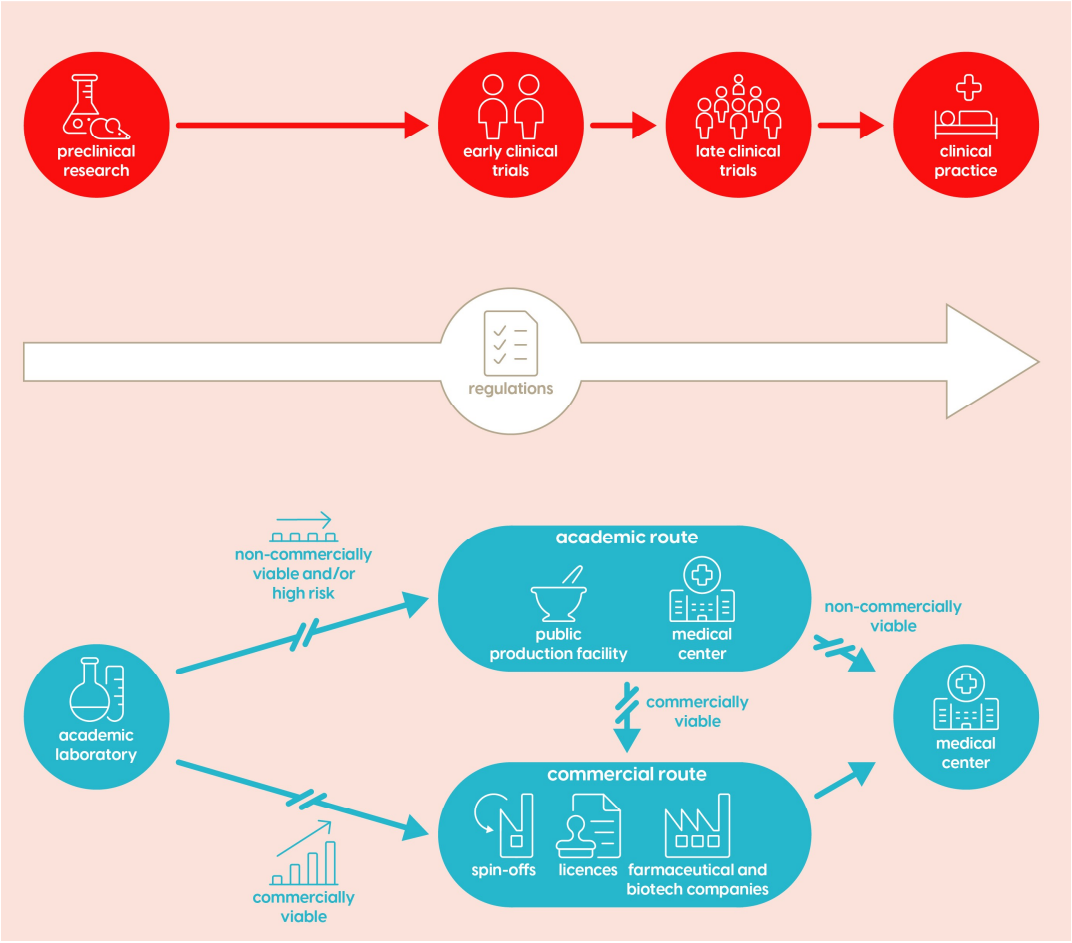
→ Few EU products from public early trials reach late stage development

Boráň et al (2017) Hum Gene Ther Clin Dev

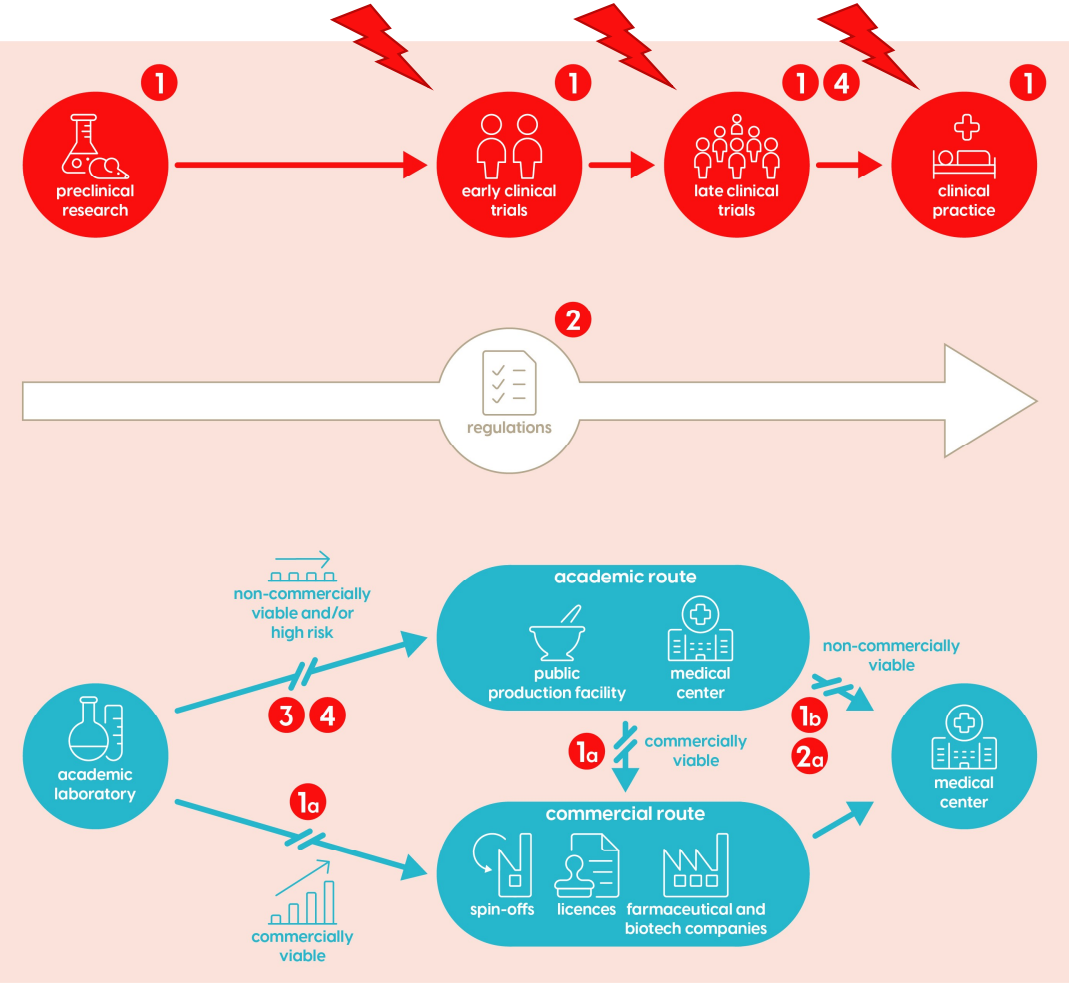
Speeding up developments – but how?

- Goal: provide insights in how to advance academic developments by improving the innovation system
- Inventory of academic development trajectories and perspectives:
  - T cell, NK cell, and dendritic cell products; translational research - clinical practice
  - Future perspectives and role of stakeholders

The innovation system for cell and gene therapy



Bottlenecks and recommendations



Recommendations

1. Coordination and support by a centralised body
2. Regulatory clarity and fit-for-purpose requirements
3. Platform for knowledge dissemination and collective production capacity
4. Financial support for product development and late stage trials

Schedule of the day

10.30-12.00

Manufacturing and quality

- GMP production in an academic institute
- DARE-NL
- UK Catapult
- Panel Discussion

13.00-14.30

Clinical development

- Late stage trial design
- From bench to bedside to commercialisation
- Totality of evidence
- Panel Discussion

15.00-16.30

Route to clinical practice

- Valorization strategy
- From phase 3 to clinical practice
- Patient perspectives
- Panel Discussion

16.30: Conclusions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Session 1: Manufacturing and Quality

Moderator: Pauline Meij

- GMP production in an academic institute - Harry Dolstra
- DARE-NL: Dutch platform for cancer-specific ATMP Research to ensure harmonized development, clinical testing and sustained patient access - Trudy Straetemans
- UK Catapult, an independent centre of excellence to advance the growth of CGT – David Sexton
- Panel Discussion

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DARE-NL

Dutch platform for cancer-specific **A**TMP **Re**search to ensure harmonized development, clinical testing and sustained patient access

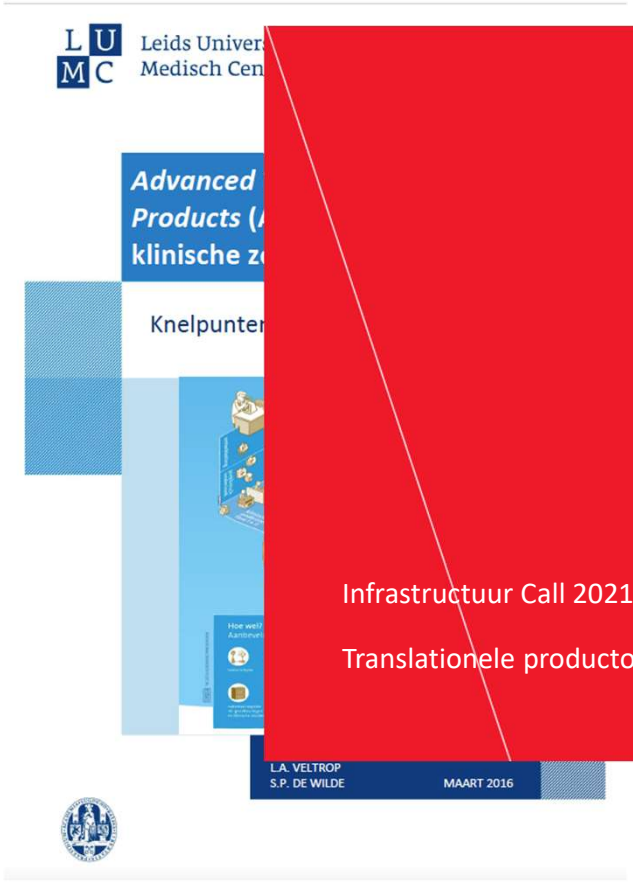
Proposal project number 13876
Infrastructure Call 2021-II

Center for
Translational Immunology

Cell and gene therapy innovation in NL

Advanced Therapy Medicinal Products (ATMPs)

Identification of the challenges for clinical implementation



2016

2019

What makes ATMPs unique from other drugs?

- ‘Living drugs’
- Often based on patients’ own immune cells
- Rapid developing field: new technologies evolving
- Gene engineering
- Very short shelf-live

NL joined forces in DARE-NL to tackle the hurdles

Collectively defined hurdles for cancer-specific cell and gene therapy in Academia

- Scattered knowledge in NL
- Regulatory challenges at level of (ATMP for GMP, CCMO, GMO) and EU level
- Limited supply of GMP ingredients like viral vector / plasmids etc
- Need of highly skilled staff at crossroad of disciplines: biology, pharmacy & engineering, regulatory and health economics
- IP, legal expertise & business development expertise
- Uncertain and unknown pathway to clinical implementation / market authorization / HE
- Uncertainty around reimbursement & affordability
- Limited insight in actual development costs & production costs (hidden costs)

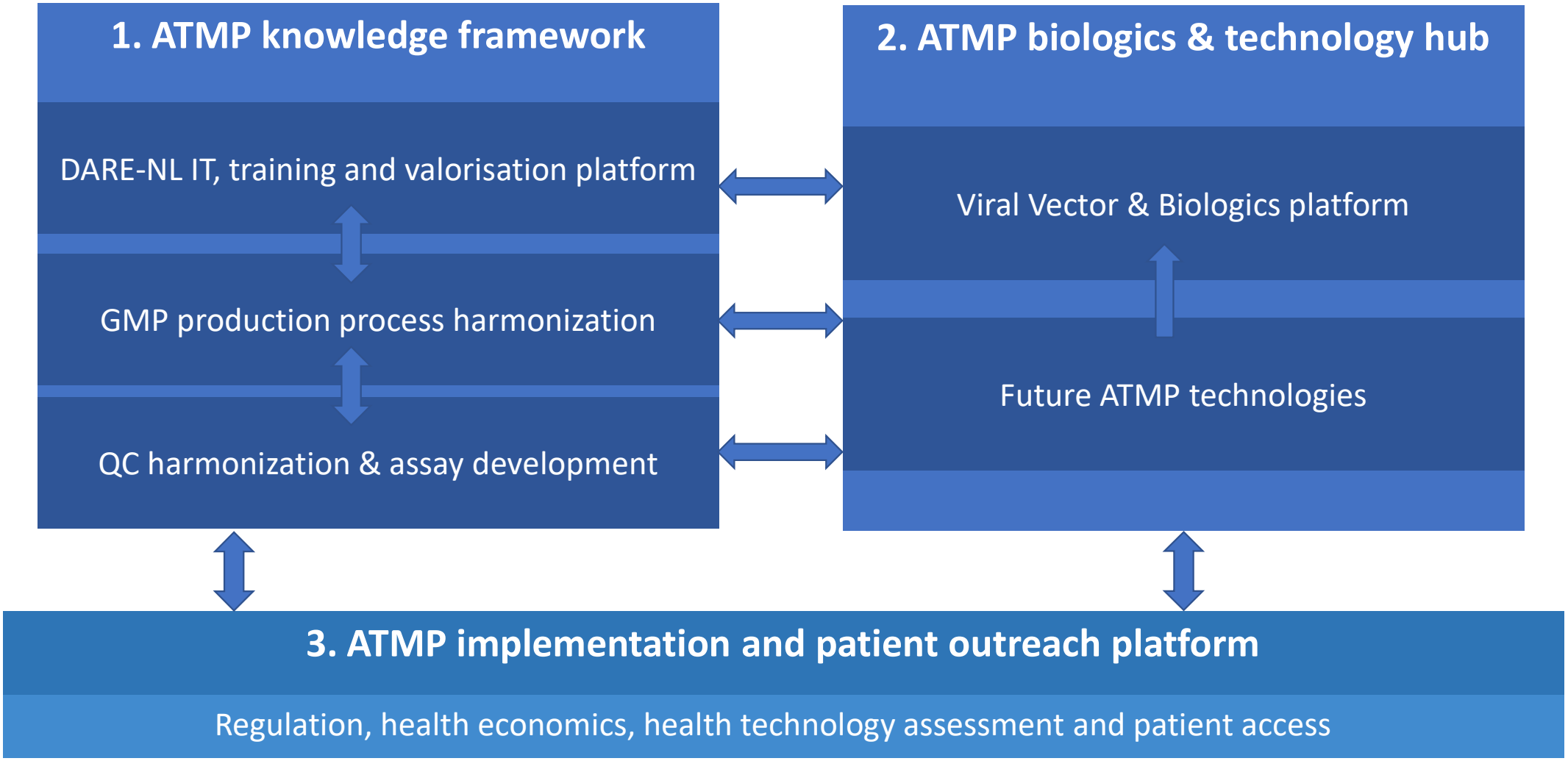
National transdisciplinary multi-stakeholder infrastructure

Keywords

- **Connecting** translational ATMP expertise in NL
- Enhance the **critical mass**
- **Harmonization and exchange** of procedures, protocols of quality control and processes under GMP
- Joint efforts and **dialogue towards policy makers** in NL and EU
- Availability of **key GMP ingredients** (i.e. viral vectors) for academic use
- Mapping needs for **innovative technologies** for their application in the clinic

- Strong project / program management
- Connection to existing structures in oncology / ATMP development national and international

Proposed key deliverables



1. ATMP knowledge framework

Setup of DARE-NL data, training and valorization platform

- Implementation of an IT infrastructure, document, data & knowledge exchange
- Establishment of a centralized educational program - tailor made - for each type of ATMP personnel
- Set up a centralized valorization framework for supporting:
  - Sharing data in context of IP generated by DARE-NL partners and valorization
  - Business plan for a sustainable DARE-NL infrastructure

GMP production process harmonization

- Harmonize risk assessments for raw materials, substances and disposables
- Central qualification procedures suppliers & QC laboratories
- Harmonize generic procedures and SOPs
- Shared registry for product specific validation and production data

QC harmonization & assay development

- Create and validate standardized assays for safety, appearance, purity, identity and potency
- Implement standardized assays in QC laboratories of DARE-NL partners
- Overviews of international requirements for QC & joined discussions with authorities

2. ATMP biologics & technology hub

Academic GMP viral vector manufacturing platform

- Setup of lentiviral vector production process
- Setup of retroviral vector production process
- Preclinical validation studies and QC testing
- Towards clinical-grade vector production
- Biologics Platform distribution system

Future ATMP technologies

- Mapping the landscape of new technologies
- Key non-viral engineering technologies
- CRISPR/Cas-9 reagents and transfection technologies
- GMP manufacturing roadmaps for key biologic ingredients

3. ATMP implementation and patient outreach platform

Regulation, health economics, health technology assessment and patient access

- Regulatory pathways, strategy, and evidence requirements
- HTA, reimbursement, and evidence requirements
- Map economic capabilities and business development
- Create an informal multi-stakeholder sandbox
- Stimulate expansion of timely patient access
  - Appoint a patient relations liaison
  - Voluntary HE & ATMP trials registry
  - Patients perspective on Dutch R&D strategy for ATMP development

Active support by
-Dutch Cancer patient organization
-Hematon
-Vereniging Kinderkanker Nederland

Workpackage distribution

1. ATMP knowledge framework

WP1: Setup of DARE-NL data, training and valorisation platform - EMC

WP2: GMP production process harmonization - UMCU

WP3: QC harmonization & assay development - NKI

2. ATMP biologics & technology hub

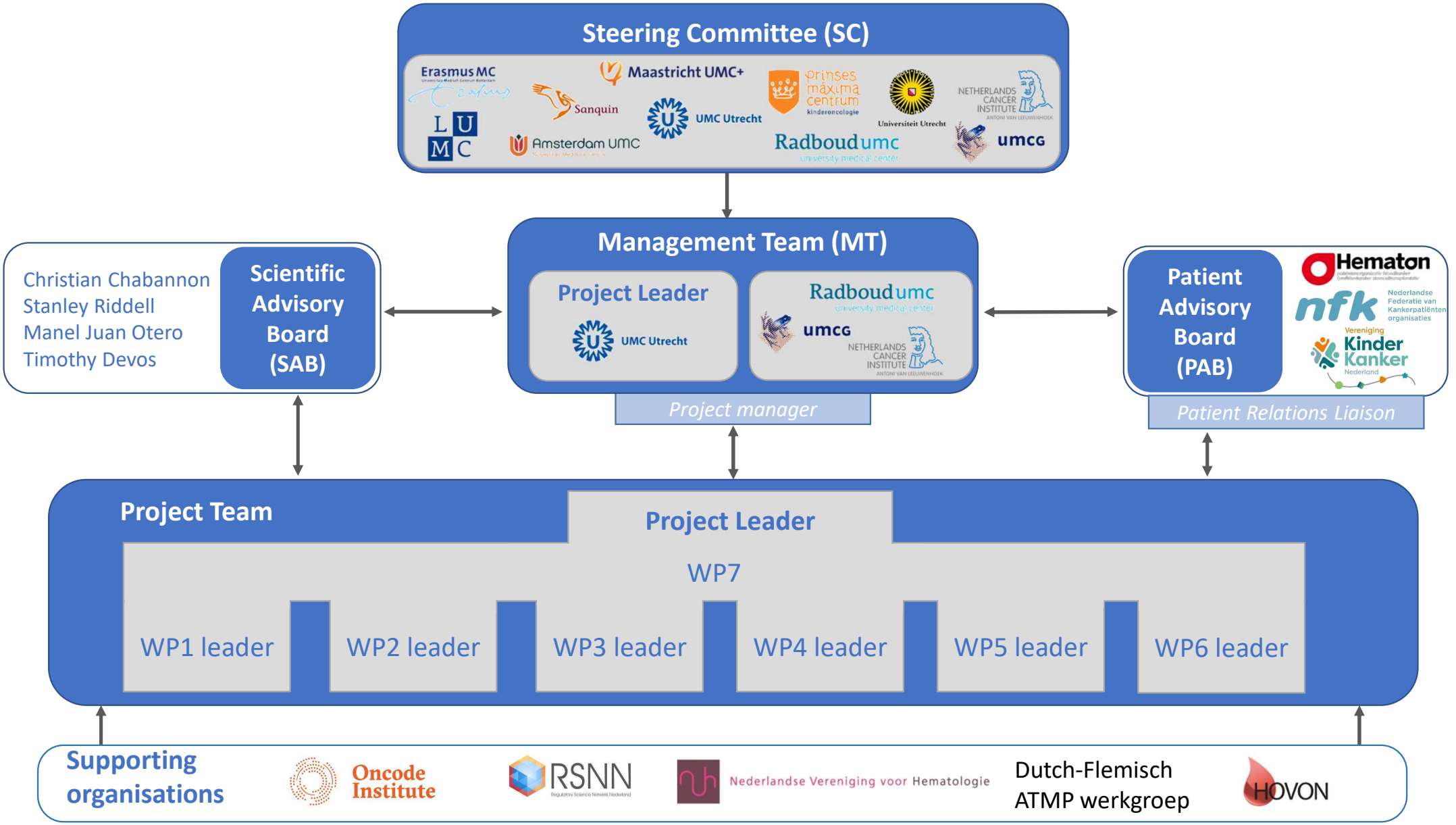
WP4: Viral Vector Platform - UMCG

WP5: Future ATMP technologies - Radboud UMC

3. ATMP implementation and patient outreach platform

WP6: Regulation, health economics, health technology assessment and patient access – LUMC

WP7: Project management - UMCU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Maastricht UMC+
Sanquin
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Project Leader
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Project manager
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Manel Juan Otero
Timothy Devos
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Patient Advisory Board (PAB)
Hematon
nfk
Nederlandse Federatie van Kankerpatiëntenorganisaties
Vereniging Kinder Kanker Nederland
Patient Relations Liaison
Project Team
Project Leader
WP7
WP1 leader
WP2 leader
WP3 leader
WP4 leader
WP5 leader
WP6 leader
Supporting organisations
Oncode Institute
RSNN
Regulatory Science Network Nederland
Nederlandse Vereniging voor Hematologie
Dutch-Flemisch ATMP werkgroep
HOVON

Prinses Máxima Centrum kinderoncologie

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Pim Mutsaers
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Pauline Evers

Vereniging Kinder Kanker Nederland

Willemijn Plieger

KWF

Session 2: Clinical Development

Moderator: Jürgen Kuball

- Late phase clinical trial design for personalized medicine and rare disease indications - Peter van de Ven
- How to succesfully develop a dendritic cell product from bench to bedside to commercialisation– Joachim Aerts
- Totality of evidence as a principle for rational early drug development - Joop van Gerven
- Panel Discussion

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Late phase clinical trial design for personalized medicine and rare disease indications

Peter van de Ven

Senior Clinical Trial Statistician
Department of Data Science and Biostatistics
Julius Center for Health Science and Primary Care
UMC Utrecht

'Cell and gene therapy in oncology - The development of academic innovations' conference
6 October 2021

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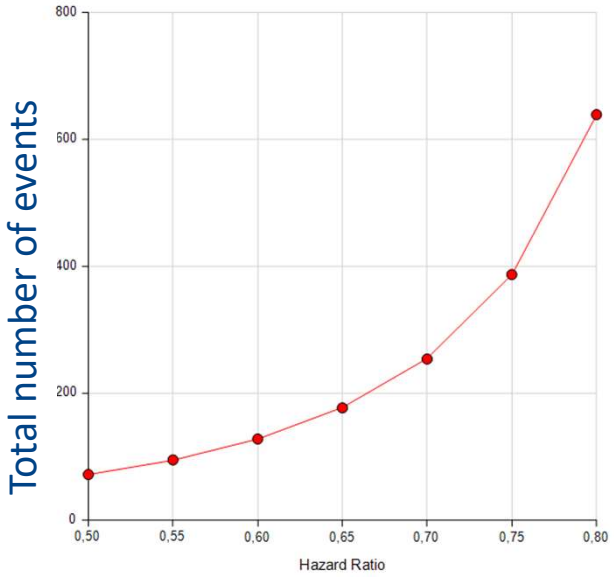
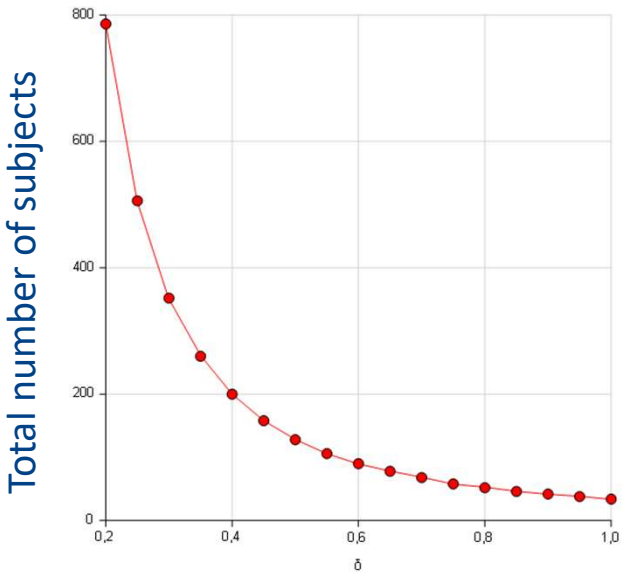
Outline

- Challenges for trials in heterogeneous and rare diseases
- Considerations for trials in heterogeneous diseases
- Examples of biomarker-driven and biomarker-based multi-arm trials
- Specific considerations for trials in rare diseases
- Conclusions

Challenges for trials in heterogeneous and rare diseases

Confirmatory trials generally require large numbers of subjects





δ: Standardized mean difference

δ = 0.2: small effect
δ = 0.5: medium effect
δ = 0.8: large effect

It may be simply not be possible to include the required number of subjects in (very) rare diseases

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Challenges for trials in heterogeneous and rare diseases

- Confirmatory phase III trials are generally run in unselected patients
- Success rates in unselected populations are generally low

Example: REMoDL-B trial in unselected DLBCL patients

3449 patients screened

918 patients randomized

RB(ortezomib)-CHOP vs. R-CHOP

Inclusion: 2011-2015

Publication: 2019

Outcome: **negative**

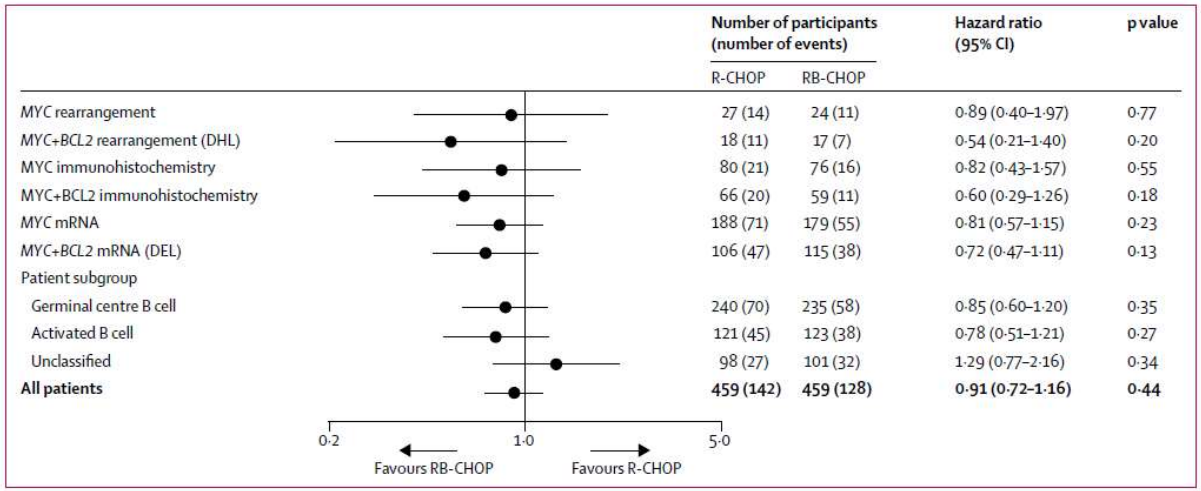

Figure 4: Forest plot of hazard ratios based on progression free survival for participants at high risk and with different molecular subtypes of disease, by treatment group

Data are for all randomised participants (ie, ITT population). Hazard ratios and p values are effect estimates from a multivariable model adjusted for IPI score. DEL=dual-expressor lymphoma. DHL=double-hit lymphoma. IPI=international prognostic index. ITT=intention-to-treat. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. RB-CHOP=rituximab, bortezomib, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

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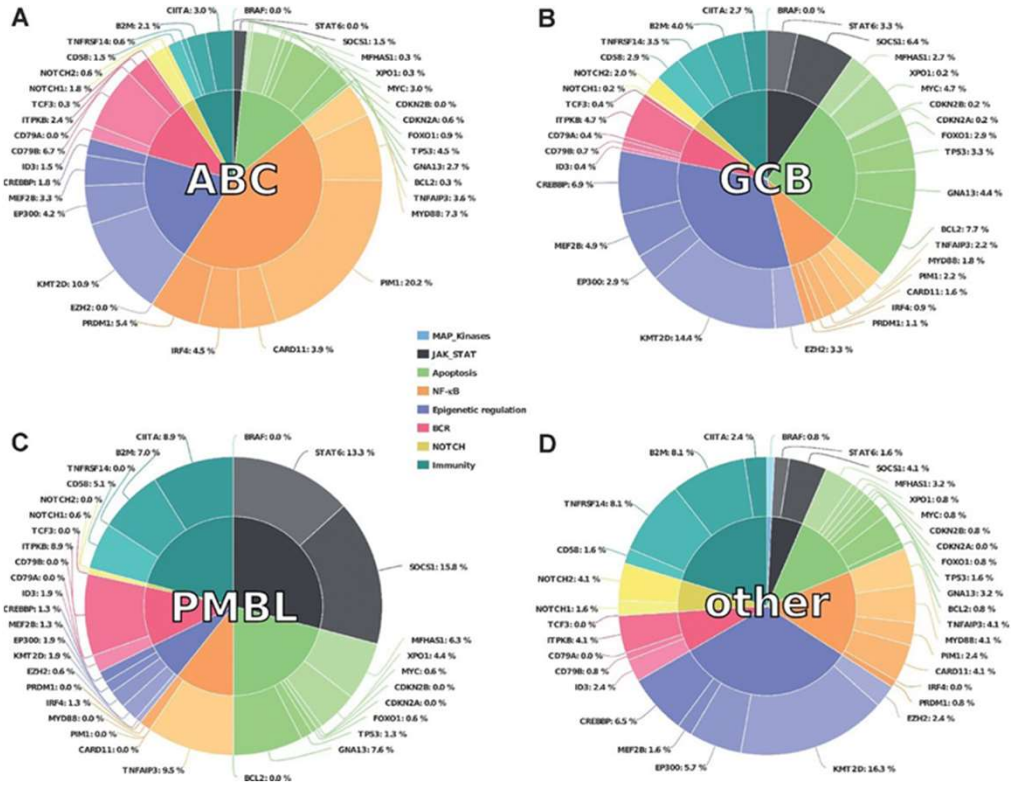
Challenges for trials in heterogeneous and rare diseases

- Heterogeneity **reduces treatment effect** in unselected trial populations

Illustration: Heterogeneity in mutation pathways in DLBCL patients

Dubois et al. Clin. Cancer Res (2016)



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Challenges for trials in heterogeneous and rare diseases

What about standard trials in **more selected** populations?

Randomized Phase II Study of R-CHOP With or Without Bortezomib in Previously Untreated Patients With Non–Germinal Center B-Cell–Like Diffuse Large B-Cell Lymphoma

John P. Leonard, Kathryn S. Kolibaba, James A. Reeves, Anil Tulpule, Ian W. Flinn, Tatjana Kolevska, Robert Robles, Christopher R. Flowers, Robert Collins, Nicholas J. DiBella, Steven W. Papish, Parameswaran Venugopal, Andrew Horodner, Amir Tabatabai, Julio Hajdenberg, Jaehong Park, Rachel Neuwirth, George Mulligan, Kaveri Suryanarayan, Dixie-Lee Esseltine, and Sven de Vos

Conclusion
Outcomes for newly diagnosed, prospectively enrolled patients with non-GCB DLBCL were more favorable than expected with R-CHOP and were not significantly improved by adding bortezomib.

Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non–Germinal Center B-Cell Diffuse Large B-Cell Lymphoma

Anas Younes, MD[1]; Laurie H. Sehn, MD[2]; Peter Johnson, MD[3]; Pier Luigi Zinzani, MD, PhD[4]; Xiaonan Hong, MD[5]; Jun Zhu, MD[6]; Caterina Patti, MD[7]; David Belada, MD, PhD[8,9]; Olga Samoilova, PhD[10]; Cheolwon Suh, MD, PhD[11]; Sirpa Leppä, MD[12,13]; Shinya Rai, MD, PhD[14]; Mehmet Turgut, MD, PhD[15]; Wojciech Jurczak, MD, PhD[16]; Matthew C. Cheung, MD[17]; Ronit Gurion, MD[18,19]; Su-Peng Yeh, MD[20]; Andres Lopez-Hernandez, MD[21]; Ulrich Dührsen, MD[22]; Catherine Thieblemont, MD, PhD[23,24]; Carlos Sergio Chiattone, MD, PhD[25]; Sriram Balasubramanian, PhD[26]; Jodi Carey, RN[27]; Grace Liu, PhD[28]; S. Martin Shreeve, MD, PhD[26]; Steven Sun, PhD[28]; Sen Hong Zhuang, MD, PhD[28]; Jessica Vermeulen, MD, PhD[29]; Louis M. Staudt, MD, PhD[30]; and Wyndham Wilson, MD, PhD[30]; on behalf of the PHOENIX investigators

CONCLUSION The study did not meet its primary end point in the ITT or ABC population.

Example: phase II and phase III trials in non-GCB subgroup of DLBCL patients **both negative**

More **flexible alternatives** to standard trials that combine showing of efficacy and subgroup selection are clearly needed

Considerations for trials in heterogeneous diseases

Focus on: **what works for which patients**, rather than what works on average

Consider **biomarker-driven** trials and **multi-arm** trials (for simultaneous investigation of multiple treatments)

Already during the trial, use the observed data for:

- **Adaptive randomisation**: allocate more patients to treatments with highest predicted probability of response
- **Adaptive enrichment**: identify within the trial the subpopulation in which detection of a treatment effect is most likely (e.g. whole population of biomarker-positive only)
- Included repeated interim assessments for:
  futility of subpopulation-treatment combinations
  efficacy to identify promising subpopulation-treatment combinations

Example of multi-arm trials: Platform trials

Oncology

The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer

What is I-SPY?

The I-SPY series of trials are changing the way new treatments are developed for breast cancer, helping make available new, better and more personalized treatments, faster. At the heart of the I-SPY program is the ground-breaking I-SPY 2 platform trial for neoadjuvant treatment of locally advanced breast cancer.

1400 patients enrolled

16 agents completed evaluation since 2010

3 agents received accelerated approval

GBM AGILE (**G**lioblastoma **A**daptive **G**lobal **I**nnovative **L**earning **E**nvironment) is a clinical trial to evaluate multiple investigational treatments for either newly diagnosed or recurrent glioblastoma to determine if any of these study treatment(s) improve overall survival as compared to standard treatments.

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COVID-19

REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

16,439	14,732	50
Patient randomisations	Patient randomisations with suspected or proven COVID-19	Current or completed interventions in 14 Domains
9,182	8,162	332
Total patients	Patients with suspected or proven COVID-19	Active Sites

RECOVERY

Randomised Evaluation of COVID-19 Therapy

GLOBAL CUMULATIVE TOTALS

43386 Participants

186 Active sites

Example of multi-arm trials: Biomarker-driven umbrella trials

Schematic of I-SPY II trial in breast cancer patients

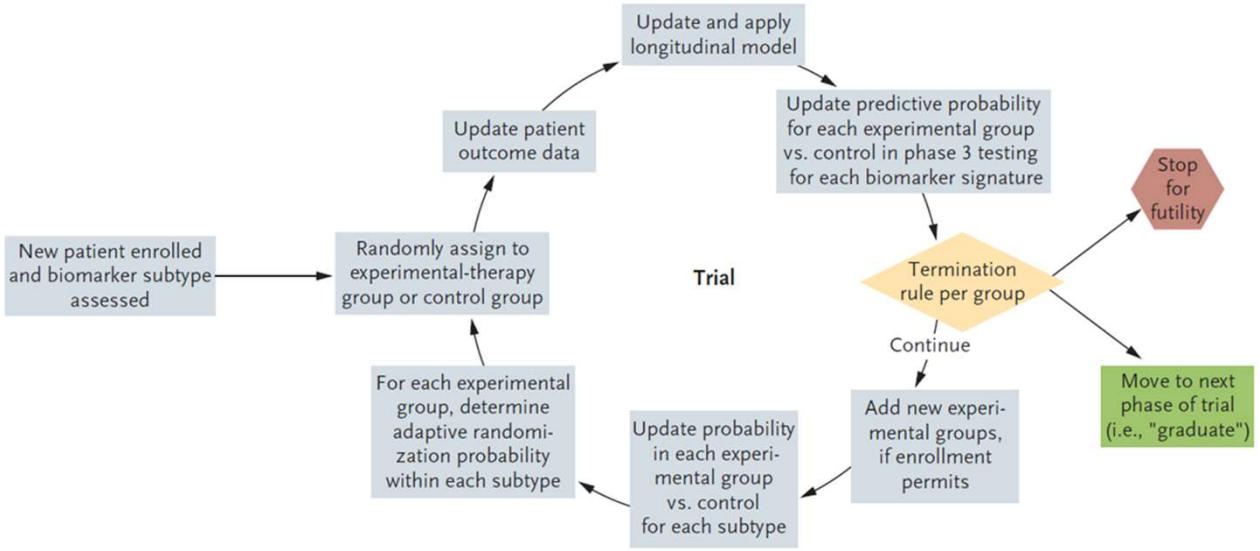

Figure from Park et al. (2016)/Rugo et al. (2016)

Innovative features:

- Succesful treatment-subgroup combinaties are identified within the trial
- Promoting of treatments to next phase is based on predicted probability of succes in a phase III study of moderate size
- Adaptive randomisation is used to increase the likelihood that patients are allocated to a treatment to which they will respond
- Use of longitudinal models to predict unobserved outcomes (pCR) for patients already included (using MRI)
- New treatments can be added to the trial at any time
- Ongoing control arm included

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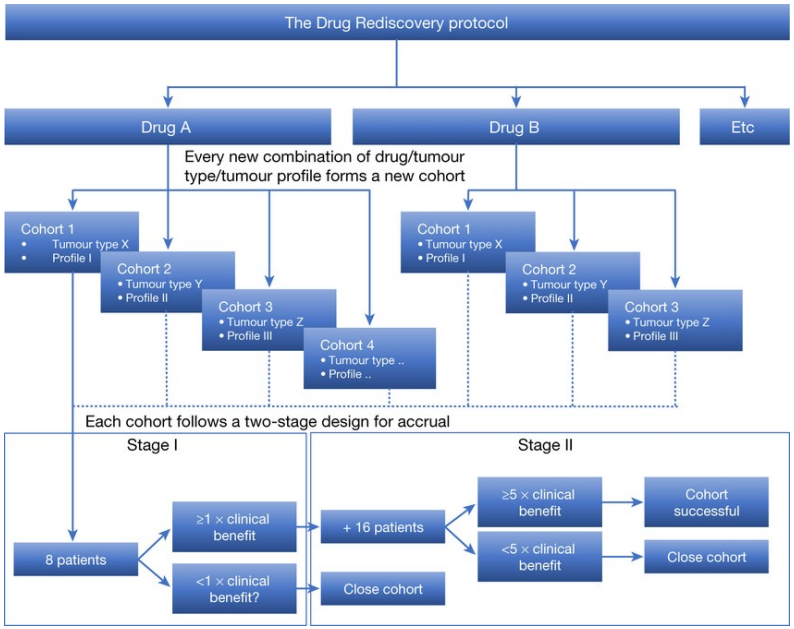
Example of multi-arm trials: Biomarker-based basket trials

Schematic of DRUP trial in patients with advanced cancers with potentially actionable variant



Innovative features:

- Patients receive treatments based on their tumour profile
- Many different tumour types considered in a single master protocol
- Large number of cohorts (drug/tumour type/tumour profile combination)

Figure from Van der Velden et al. (2019)

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Example of multi-arms trials: Comparison

	Biomarker-driven umbrella trial (I-SPY)	Biomarker-based basket trial (DRUP)
Pro's	Leaves room for unexpected efficacy in subgroup-treatment combinations	Multiple tumour types in a single trial Very efficient if belief in biomarker-treatment combination is correct
Con's	Early endpoint required, possibly in combination with early surrogate endpoints Highly complex protocol	Heterogeneity between tumor types ignored in some biomarker-based basket trials Basically, a collection of standard phase II trials

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Specific considerations for trials in rare diseases

Recommendations from small population clinical trial task force (Day et al. 2018): whenever feasible use an **RCT** with clinically relevant endpoint

Consider **multi-arm designs** for investigating **multiple treatments**

Advantages of multi-arm designs for rare disease settings:

- Sharing control arm, less patients on placebo, higher participation rate
- Comparison of experimental treatments
- Pooling data from experimental treatments with similar mechanism of action
- Sharing of resources, reducing overall trial costs

Specific considerations for trials rare diseases

Increase **power** and **efficiency** through

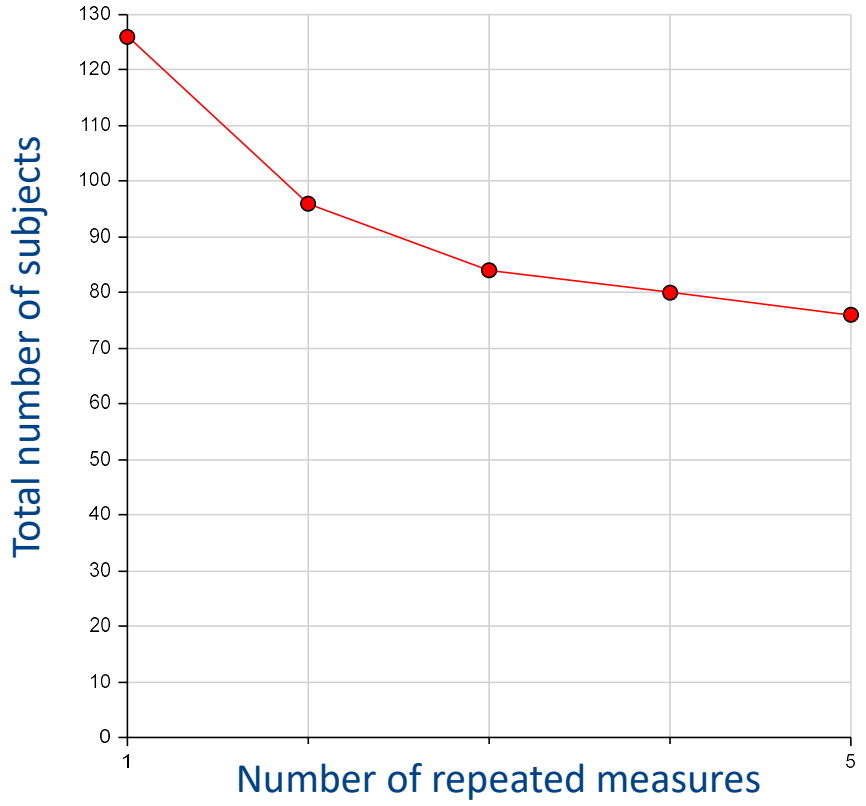
- Use of continuous endpoints and repeated measures when possible
- Use of composite endpoints and long-term follow-up (for time-to-event outcomes)
- Pooling over subgroups (also if formulation, dosing or outcome differs)
- Use of cross-over designs, group-sequential (multi-stage) designs or seamless adaptive phase II/III designs when feasible

Increase **information** and **evidence** collected in trials and beyond through

- Multiple endpoints (different objectives), stronger case if efficacy is shown on several clinically relevant endpoints
- Natural history and patient registry data, for primary outcome selection and potentially a extern control arm
- External sources for safety data (health records, post-marketing, extrapolation)

Specific considerations for trials rare diseases

Illustration: Potential reduction in sample size through use of repeated measurements



δ = 0.5: medium effect
correlation = 0.5

24% reduction through adding 2nd measurement

33% reduction through adding 2nd and 3rd measurement

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Concluding remarks

- Several examples of succesfull biomarker-driven/biomarker-based trials in oncology
- Multi-arm trials have clear advantages, but require more intensive collaboration between centers, cooperation of sponsors/industry and more preparation
- Clinical trials in rare diseases will remain challenging with implicitely small sample size
- In rare and heterogeneous diseases, there is no one-size-fits-all solution for trial design
- Important factors to be considerd when designing the trial include:
    - total number of patients available (prevalence of disease/subgroup)
    - heterogeneity of the disease
    - a-priori belief/evidence for efficacy of biomarker-treatment combinations
    - availability of a comparator treatment/justification for placebo arm
    - availability of early outcome measures and validated surrogate outcomes

Thank you

References

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- Rugo et al (2016). Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. *N Engl J Med. 2016 Jul 7;375(1):23-34*.
- Van der Velden et al (2019). The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. Nature. 2019 Oct;574(7776):127-131.
- Younes et al. (2019). Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2019 Mar 22

Additional: Trial designs used for approved stem cell and gene therapies

Tisagenlecleucel (Kymriah) approved for

- B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy

Axicabtagene ciloleucel (Yescarta) approved for

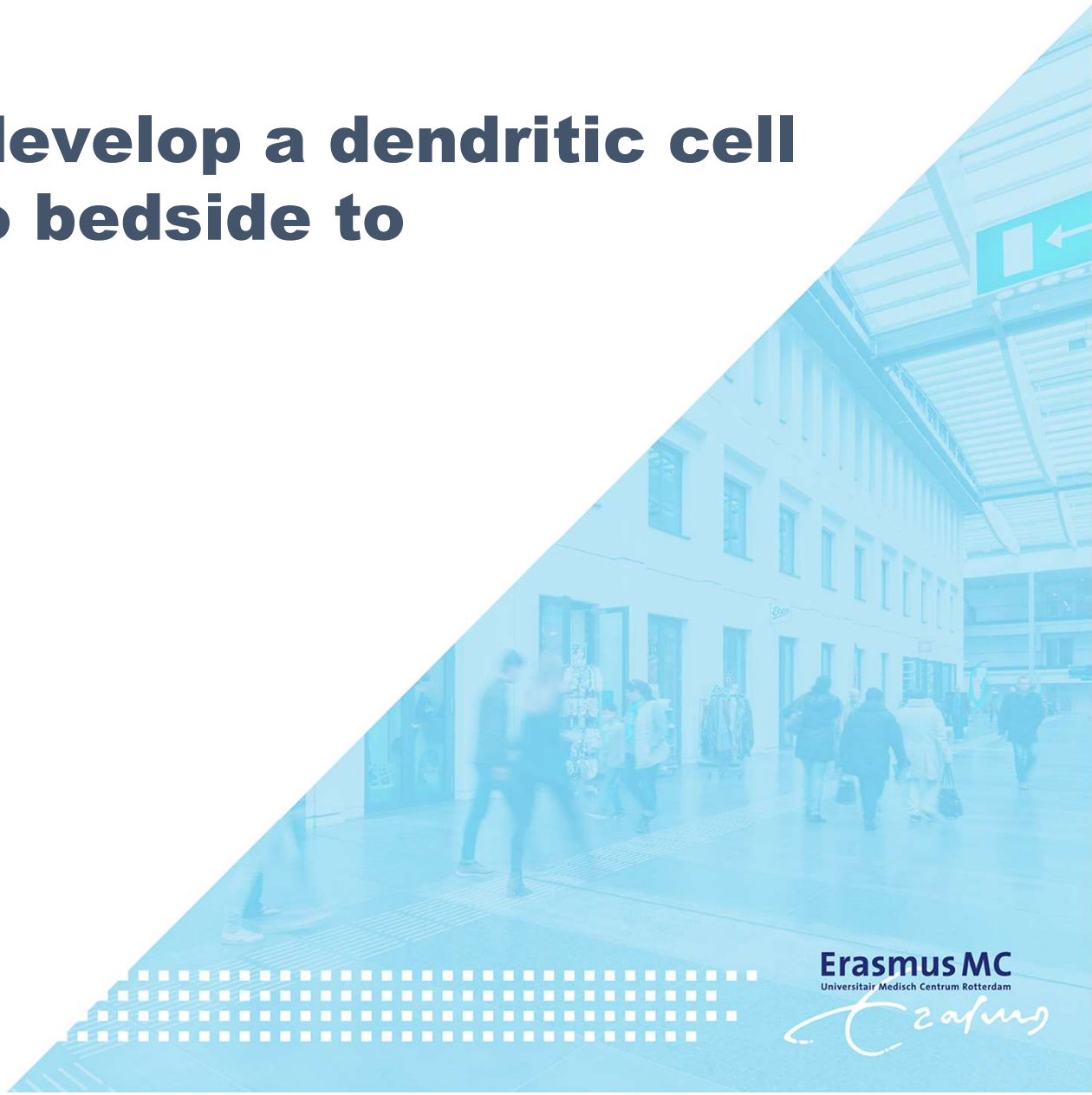
- relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

Approvals were based on **single arm phase II studies**, but in such exceptional circumstances evidence must be very convincing

KWF

How to successfully develop a dendritic cell therapy from bench to bedside to commercialisation

Prof Joachim G Aerts, MD PhD
Head of dept of Respiratory Medicine
Erasmus MC University
Rotterdam, the Netherlands
j.aerts@erasmusmc.nl



Presenter DISCLOSURES

Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**
MSD, BMS, Bayer, Amphera, Eli-Lilly	consultancy
Amphera	Stock owner
Erasmus MC	Patent on tumor cell lysate, combination IO

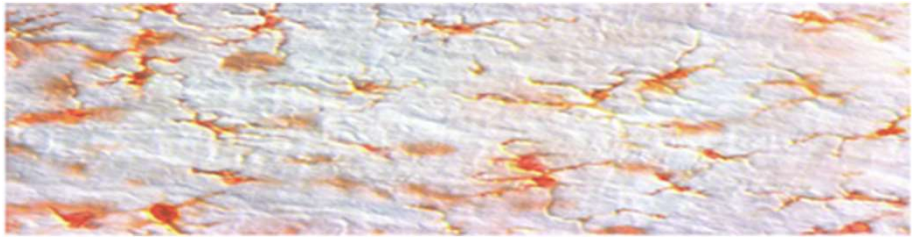
What are we talking about

Dendritic cells are the most potent antigen presenting cells

Activate innate and adaptive immune system

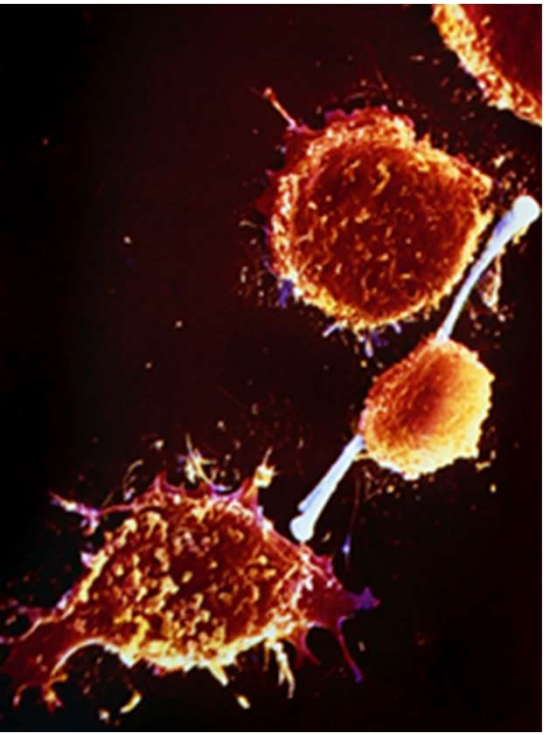
Can be loaded with different types of tumor antigens

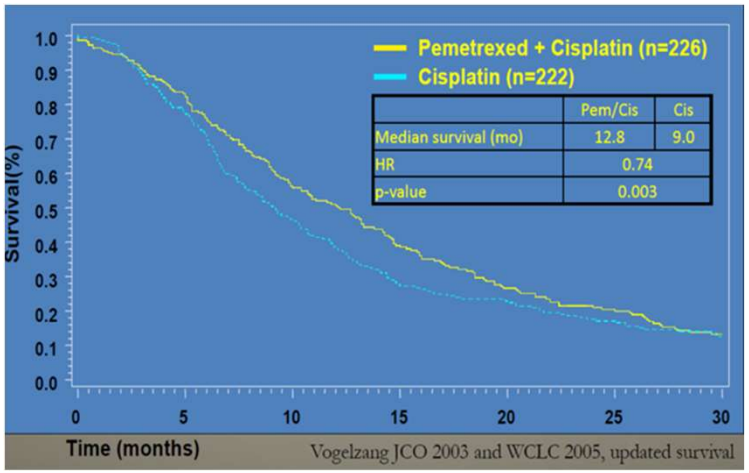
Can be cultured ex-vivo



Erasmus MC

The disease: Mesothelioma

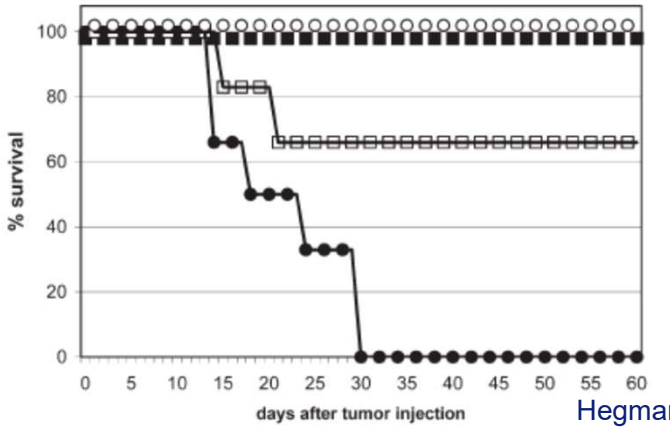




Courtesy: R Cornelissen MD PhD

Dendritic cell vaccination in mesothelioma

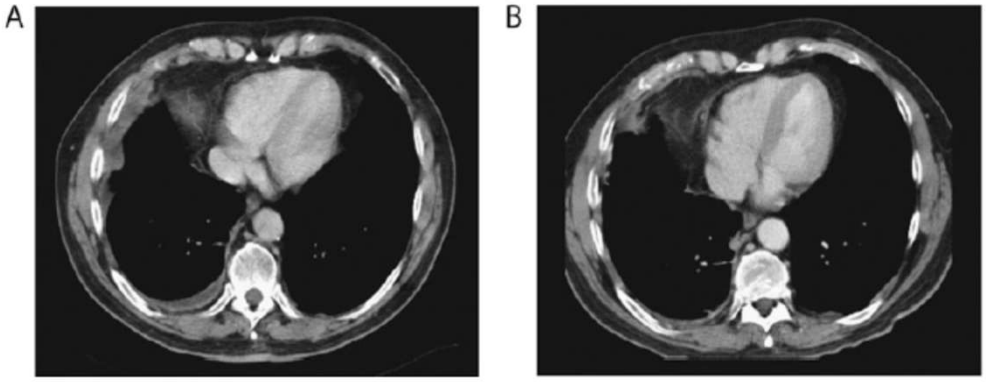
post-doc: Joost Hegmans PhD



Hegmans AJRCCM 2005

Collaboration with prof J de Vries and prof C. Figdor, Radboud UMC

Thanks to prof H Hoogsteden



Hegmans AJRCCM 2010

How to bring this further ?

100 patients screened to enter 10

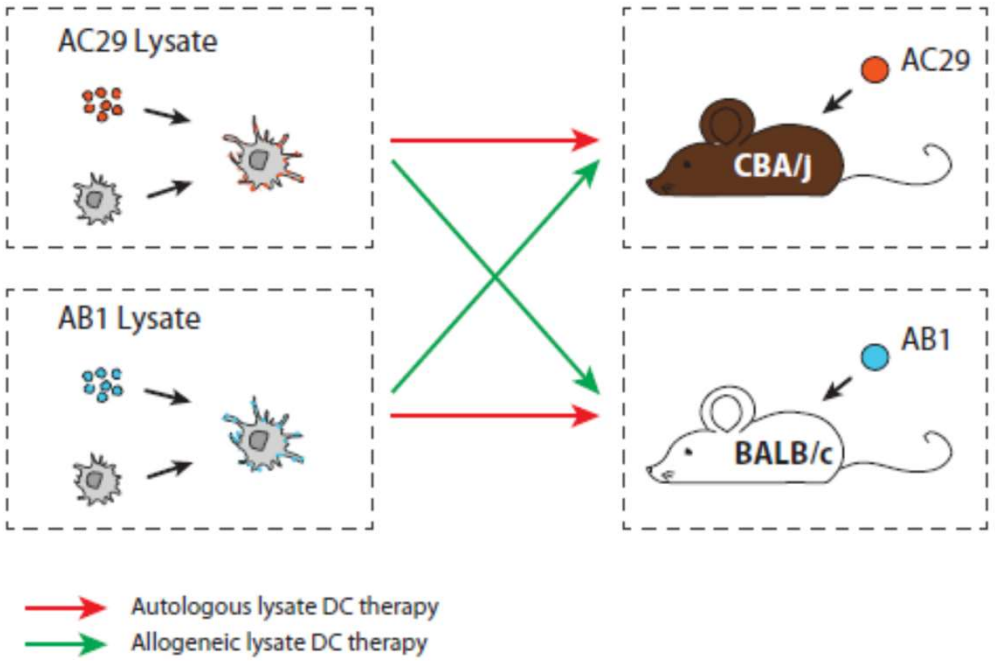
Funding for further studies

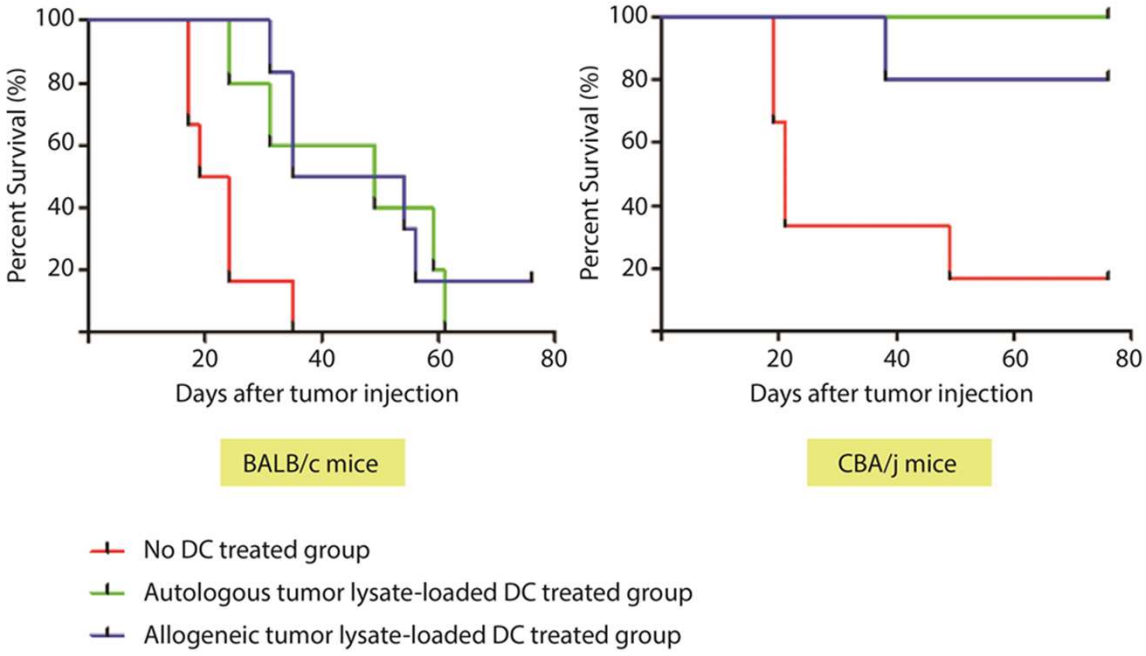
From autologous to allogenic?

- allogenic cells is not an option
- explore allogenic loading

Erasmus MC

Allogenic?
Back to the mouse





How to bring this further ?

From autologous to allogenic?

allogenic loading

Is this potentially open for patent filing?

different opinions

How to start the first trial?

funding voor cellular therapy

Erasmus MC

How to bring this further ?

From autologous to allogenic?

allogenic loading

Think where you want to go

Is this potentially open for patent filing?

different opinions

Work with the best people

How to start the first trial?

funding voor cellular therapy

how to develop your trial

Work with the best people

Erasmus MC

Our story

Allogenic lysate was optimally prepared.

Patent filing was supported by an experienced biotech investor.

A spin-off company was built by this investor in collaboration with TTO.

Erasmus MC

The Amphera story

Involvement of experienced team to the development of the product

- experienced business developer
- experienced manager in the field of biotech
- experienced financial expert
- experienced biotech investor

Involvement of a team of experts on the different fields of development

- patent lawyer
- regulatory affairs (orphan drug designation, FDA/EMA contact)
- quality assurance

Winner academic startup competition 2019

Erasmus MC

ATMP production

Production of product under GMP conditions.

Dedicated team of well educated technicians

AD NIEUWS REGIO SPORT SHOW VIDEO FUN

asbestkanker. © ANP

Experiment Erasmus MC met behandeling asbestkanker

Artsen van het Erasmus MC in Rotterdam hebben een nieuwe stap gezet in de strijd tegen asbestkanker. Voor het eerst wordt een veelbelovende behandeling getest op een kleine groep patiënten.

Door: Adrianne De Koning 09-06-15, 06:21 **Laatste update:** 04-03-16, 13:23

Longarts-oncoloog Joachim Aerts van het universitair medisch centrum is opgetogen dat zijn kliniek toestemming krijgt voor toepassing van de experimentele methode. Er bestaat nog geen medicijn tegen asbestkanker. ,,Daarom houden alle specialisten die met deze ernstige ziekte te maken hebben ons onderzoek de komende tijd nauwlettend in de gaten," zegt Aerts.

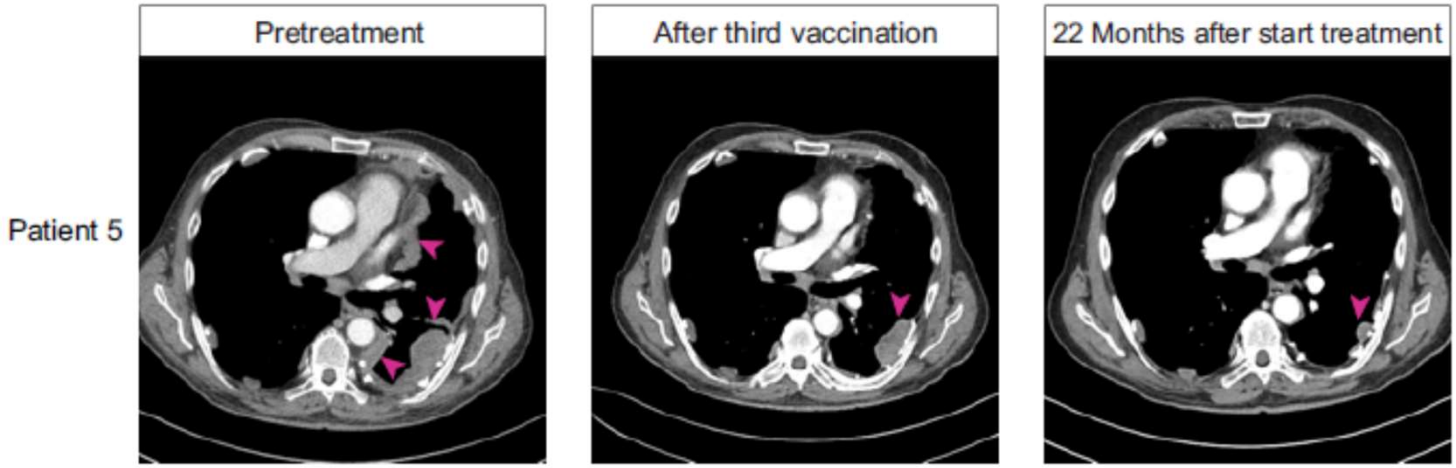
Witte bloedcellen

Bijzonder aan de aanpak is dat witte bloedcellen van de patiënt zo worden getraind dat het lichaam de kankercellen aanvalt. In eerdere fases van het onderzoek waren daarvoor tumorcellen van de patiënt zelf nodig. Dat gebeurde via een riskante ingreep in de longen die maar bij één op de tien patiënten mogelijk was. Die kankercellen kunnen na jaren onderzoek nu in het laboratorium van Erasmus MC worden gekweekt. De cellen worden vervolgens zo geprogrammeerd dat het afweersysteem van de patiënt een wapen wordt tegen tumoren. De nieuwe methode, die veel minder belastend is dan een chemokuur, wordt de komende maanden toegepast bij negen patiënten met asbestkanker. Als de behandeling zo succesvol is als de specialisten verwachten, komen volgend jaar meer patiënten in aanmerking.

The start

Funding by ZonMw/KWF and Amphera: first in human study of MesoPher

Study reached primary outcome of safety and immunogenicity and clinical activity



How to go from here

Amphera and Erasmus team developed a registration phase 3 study

which was discussed with EMA and FDA

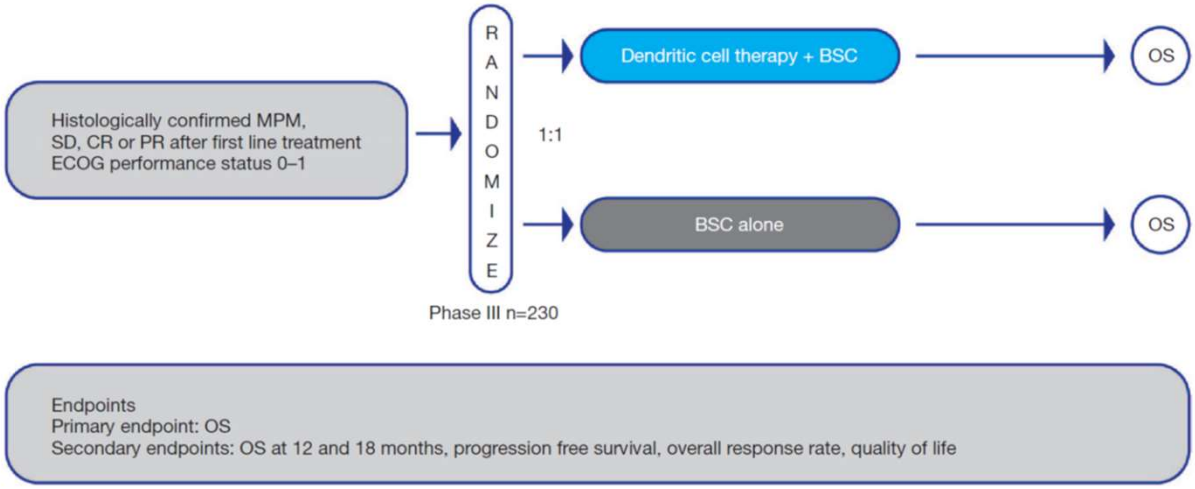
how to fund such a trial

- HORIZON subsidy
- Private investors
- Innovation credit (RVO)

Where to produced this ATMP

Where are we now

A phase III trial is ongoing and results are expected in 2022.



The Amphera team works on:

- regulatory
- registration
- product development
- upscaling
- IP
- finance
- etc
- etc

Erasmus MC

knowledge is power

Knowledge:

on the proof of principle/prinicple/product is in the department
from bench to bedside is an academic task

on the clinical development and registration is external
the path towards commercialisation is a specialised task

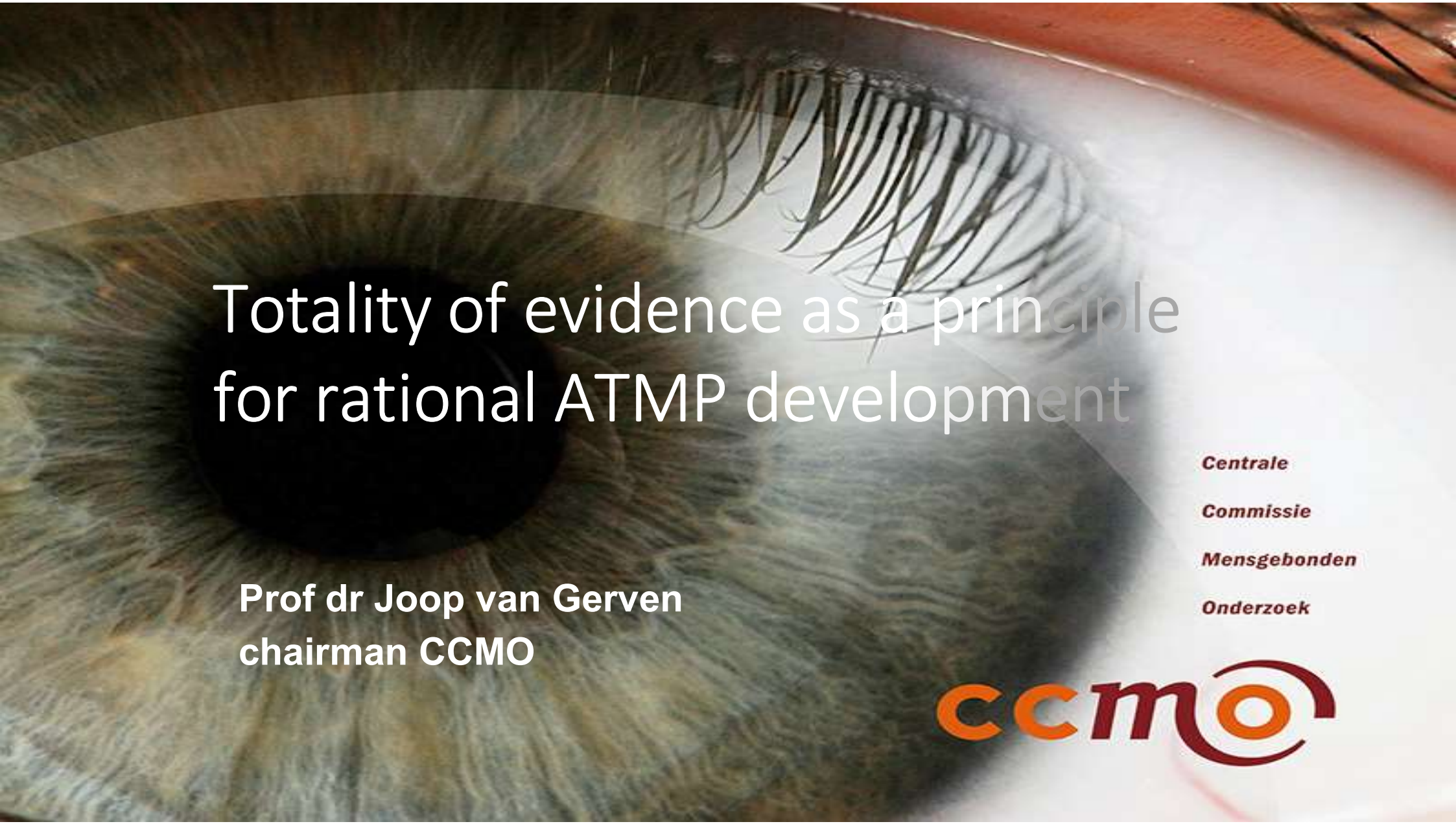
Erasmus MC

Thank you for your attention

j.aerts@erasmusmc.nl

Erasmus MC

KWF



Totality of evidence as a principle for rational ATMP development

Prof dr Joop van Gerven
chairman CCMO

Centrale
Commissie
Mensgebonden
Onderzoek

ccmo

Overview

- ATMPs *vs* non-ATMPs
- Development of ATMPs:
  - case building (scientific, mechanistic)
  - bridge building (investigators↔regulators)
- Towards ‘totality of evidence’: follow the compound

What are ATMPs?

- Advanced Therapy Medicinal Products (2020)

	Approved (Cancer)	
– cell therapies (*incl NK-cells*)	5	60%
– tissue engineered products	-	-
– gene therapies (*incl CAR-T*)	17	76%
– antisense oligonucleotides	10	0%
– small interference RNA	6	17%
– viruses (vaccines*)	8	25%

- CCMO is competent trial authority

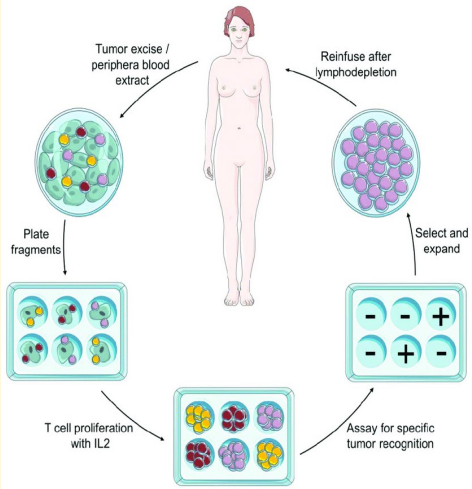
* CCMO is competent committee for new vaccines, which are not always ATMPs

- McBlade JW. Clinical trials: first in human applications - Biological products and ATMPs. EMA FIH Training, London, 30. March 2017

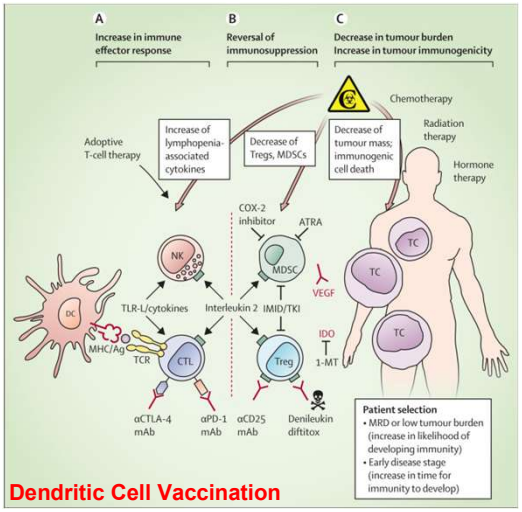
What are *not* ATMPs?

- certain cell products that are *not substantially manipulated*
  - regulated under cells and tissues directives
  - *eg* products for *homologous* use
- products used for *non-medical use*
  - cosmetic surgical applications: 'stem cell' facelifts …
- tissues/organs for transplant – heart / liver …..
  - no manufacturing process
  - no manipulation
- whole human blood
- devices that act by means other than pharmacological, immunological or metabolic
  - some protein products are proposed as devices as they lack pharmacodynamic action

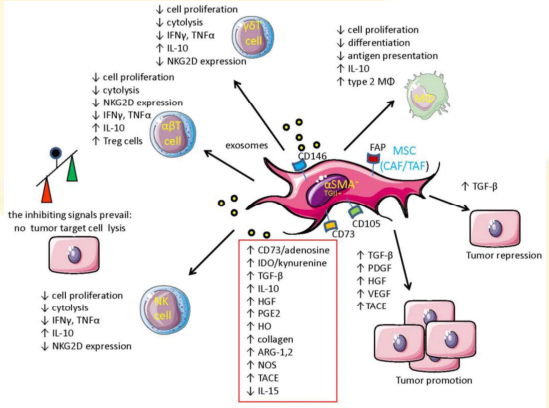
Cell Therapy Strategies



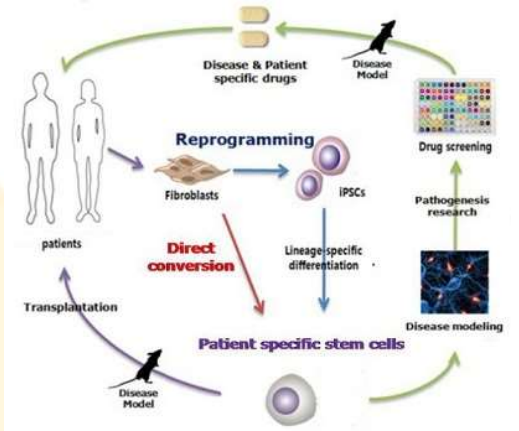
Adoptive T-Cell Therapies



Dendritic Cell Vaccination



(Mesenchymal) Stromal Cell Therapies



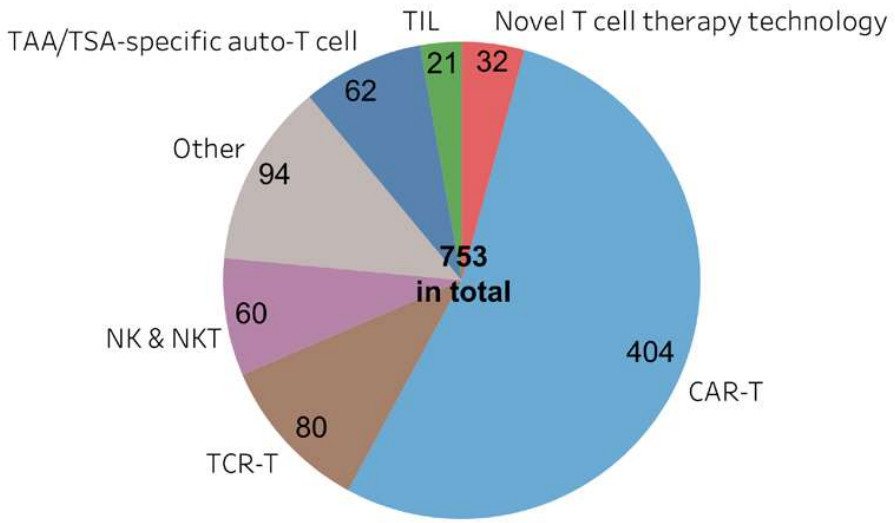
(Individualized) Stem Cell Therapies

Anguille S, Smits EL, Lion E, Van Tendeloo VF, Berneman ZN. Clinical use of dendritic cells for cancer therapy. Lancet Oncology 2014;15(7):e257-e267

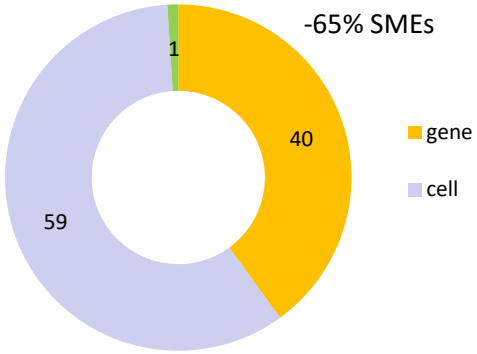
Poggi A, Giuliani M Mesenchymal Stromal Cells Can Regulate the Immune Response in the Tumor Microenvironment. Vaccines 2016;4(4),41; doi.org/10.3390/vaccines4040041

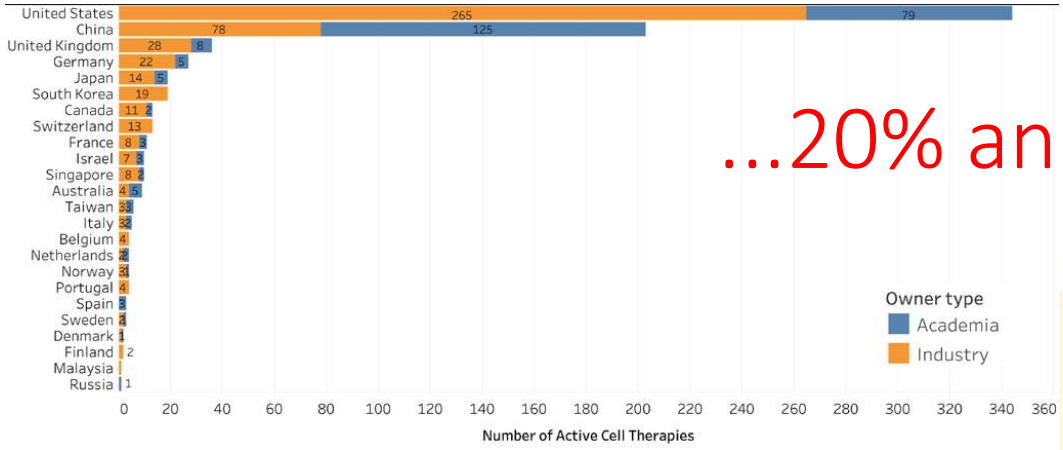
Soler M. Nanoplasmonic Biosensors for Clinical Diagnosis at the Point of Care. Thesis, UA Barcelona, Apr 2015

Cell Therapies in Development (2018)



ATMPs in development:
-271 EU developers
-65% SMEs



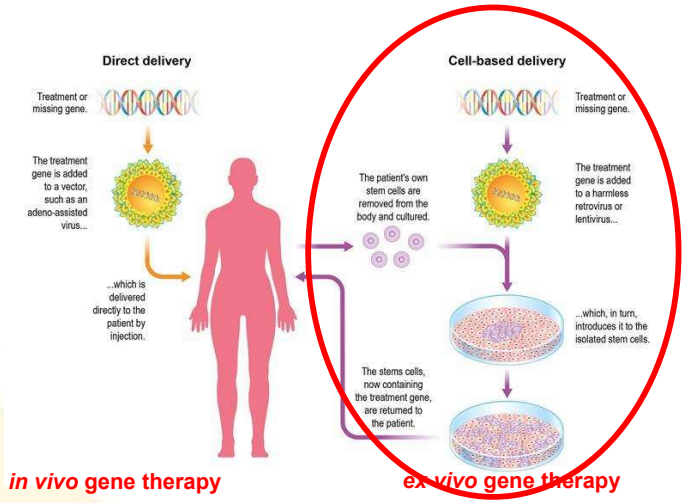


...20% annual increase...

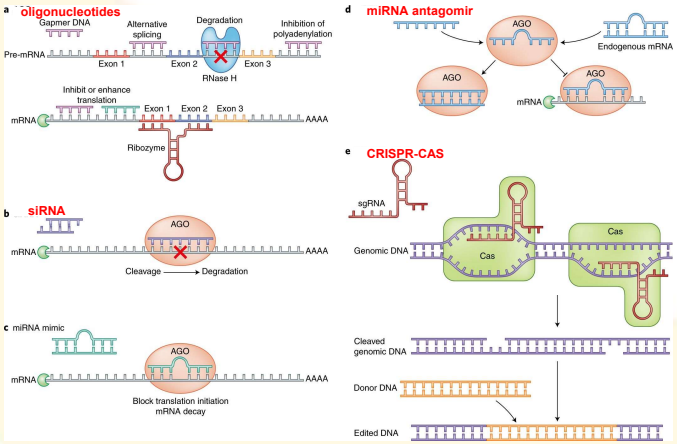
Tang J, Hubbard-Lucey VM, Pearce L, O'Donnell-Tormey J, Shalabi A. The global landscape of cancer cell therapy. Nat Rev Drug Disc 2018;17:465–466

Renske ten Ham. Challenges in commercial advanced therapy development in Europe. FIGON DMD Day 1. October 2018

Gene Delivery and Silencing Strategies



cancer
(CAR-T *etc*)



Lieberman J. Tapping the RNA world for therapeutics. Nature Struct Mol Biol 2018;25:357–364

Regulatory Guidelines for Cellular Therapies

- Cell-Therapy and Tissue Engineering
  - EMEA/CHMP/410869/2006: **overarching guideline** for human cell-based medicinal products
  - CHMP/BWP/271475/06: guideline on **potency testing** of cell based **cancer immunotherapy** medicinal products
  - EMEA/149995/2008: guideline on **safety and efficacy follow-up and risk management** of ATMPs
  - EMA/CAT/571134/2009: reflection paper on **stem cell**-based medicinal products
  - Others: cartilage repair (EMA/CAT/CPWP/568181/2009), xenogeneic (EMEA/CHMP/CPWP/83508/2009), tissue engineered products (EMA/CAT/573420/2009)

- Gene-Therapy-Derived Cell Therapies
  - CHMP/GTWP/671639/2008: **quality, non-clinical and clinical aspects** of medicinal products containing genetically modified cells
  - EMA/CAT/499821/2019: Q&A on **comparability** considerations for ATMPs

- Others
  - ICH Quality Guidelines
  - European Pharmacopoeia Quality Guidelines
  - EU2004/23/EC: European Tissues and Cells Directive
  - EMA Scientific and Quality Guidelines for specific indications
  - FDA ATMP Guidelines

https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products#celltherapy

https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

Regulatory Guidelines for Gene Therapies

- Gene-Therapy Medicinal Products (GTMPs)
  - EMA/CAT/80183/2014: **overarching guideline** on quality, non-clinical and clinical aspects
  - EMEA/CHMP/GTWP/125459/2006: guideline on non-clinical studies required before **first clinical use** of GTMPs
  - EMA/CHMP/ICH/318372/2021: **nonclinical biodistribution** of GTMPs
  - EMA/CAT/80183/2014: Q&A on gene therapy
  - CHMP/GTWP/125491/06: guideline on **environmental risk assessment** of gene therapy
  - EMA/CAT/GTWP/44236/2009: reflection paper on **design modifications** during development
  - CHMP/GTWP/587488/07: reflection paper on quality, non-clinical and clinical issues relating specifically to recombinant **adeno-associated viral vectors**
  - EMEA/CHMP/ICH/607698/2008: ICH considerations on **oncolytic viruses**
  - CAT/CHMP/GTWP/671639/2008: guideline on quality, non-clinical and clinical aspects of medicinal products containing **genetically modified cells**
  - EMEA/273974/2005: guideline on non-clinical testing for **germline transmission** of gene transfer vectors
  - CAT/190186/2012: reflection paper on clinical risks deriving from **insertional mutagenesis**

https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products#genetically

https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

ATMPs in Early Drug Development: obstructions to studies in healthy subjects

- mechanism of action may be intrinsically (too) toxic
  - *eg* immunostimulatory agents (*cf* cytokine release withTGN1412 or CAR-T-cells)
- (too) difficult route of administration
  - *eg* intracranial injection of cells for Parkinson's Disease
- product corrects a deficiency that is not 'wrong' in a healthy volunteer
  - *eg* gene therapy to insert protein missing in patients
- lifelong exposure may result / intended
  - 1st dose usually not in ideal 'target' population, but in patients who 'failed' standard T*x*
- product immunogenicity
  - antibodies to product/vector may prevent potential future / readministration
  - auto-immunity to similar endogenous proteins
  - may differentially affect duration of action in animals and humans

ATMPs:
(Somewhat) Beyond Clinical Pharmacology

- ATMP species differences:
  - animal kinetics poorly translatable to humans
  - mainly relevant for interpretation of species-specific PD and Tox

- usually no 'pharmacokinetics' like for small molecule
  - *eg* target-mediated drug disposition
  - *eg* T-cell proliferation after transplant

- cells → hours (stromal cells) to months (T-cells *etc*) to years (stem cells)
- proteins → amino acids → no toxic metabolites
- genes → years to months (immunogenicity, oncogenicity)

- gene editing (oligonucleotides, CRISPR-cas):
  - poor target cell penetration → target ligand conjugates
  - chemical backbones → nonspecific/toxic metabolites may occur
  - permanent off-target effects

G3

1-FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

2-McBlade JW. Clinical trials: first in human applications - Biological products and ATMPs. EMA FIH Training, London, 30. March 2017

G3

-phosphorothioates
-chimeric modifications
-2' sugar modification

GERVENJMA; 25-9-2018

Preclinical Study Considerations

- Objectives:
  - biological plausibility/mechanism of action
  - biologically active dose levels
  - starting dose level, dose-escalation schedule, dosing regimen for clinical trials
  - feasibility/safety of clinical route of administration
  - patient (/healthy) volunteer eligibility criteria.
  - biomarkers of safety and biological effect
  - potential for transmission (public health, next generation)

- Product characteristics:
  - stage-appropriate production methods acceptable
  - use same product throughout development or characterize differences
  - species-specific products may be required

FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

Preclinical Study Considerations (c'td)

- Animal Species Selection for Biological Effects:
  - detailed assessment of relevance!
  - comparability of physiology and anatomy to humans
    - may be non-standard laboratory animal
    - *eg* large, immunodeficient or genetically modified
  - permissiveness/susceptibility to infection by/replication of viral/microbial vectors for gene therapy
  - immune tolerance to human cell therapy product or transgene
  - feasibility of drug delivery system/procedure
    - *eg* CSF infusion in mouse
  - validation of biological effect biomarkers for human trials

- Animal Disease Models:
  - may also be (more!) appropriate to test biological effect
  - interactions with disease course/pathophysiology in animals/humans
  - strengths/weaknesses of disease model
    - *ie* limited variability/fidelity - technical/physiological/anatomical constraints

FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

Preclinical Study Considerations (c'td)

- Proof-of-Concept:
  - 'mechanistically' effective dose range (biopharmaceutical molecules)
    - PAD → ATD
  - optimization of route of administration
    - confirmation of target site penetration
  - optimization of timing of product administration *vs* onset of disease/injury
  - optimization of dosing schedule
    - half-life, interval *etc*
  - characterization of mechanism of action or biological activities
    - biomarkers
  - adequate study design
    - natural history cohorts, concurrent controls, randomization, blinding

FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

Preclinical Study Considerations (c'td)

- Bioassays and Toxicology:
  - stepwise, multifactorial approach to understand biological plausibility in disease
  - *in vitro* characterisation
    - useful but not sufficient
  - *in vivo* animal models
    - toxicology/safety only in animals/models where product is biologically active
    - adequate timing/duration

- Specific toxicity risks:
  - T-cells: cytokine release syndrome, neurotoxicity
  - dendritic cells: limited (auto-immunity?)
  - stem cells: unknown: long-term tumor risk?
  - adenovirus: insertional mutagenesis, replication-competent virus
  - adeno-associated virus: insertional mutagenesis, immunology to capsids
  - retro- and lentivirus: insertional mutagenesis, replication-competent virus, germline integration, altered host gene expression
  - CRISP-cas9 off-target gene editing
  * gene therapies local over-expression of gene product

FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

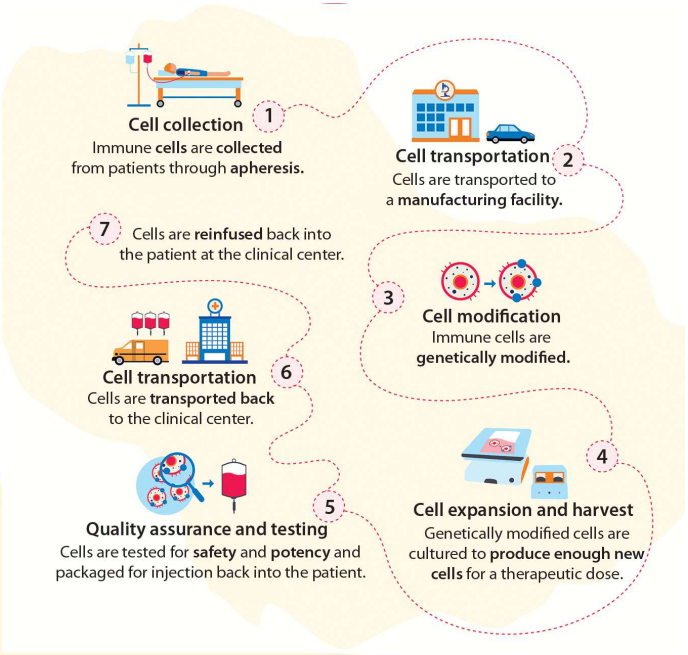
Early Clinical Study Considerations

- Integration of preclinical and clinical information:
  - mechanism of action *vs* pathogenesis
  - dose and route of administration
  - timing and duration of action *vs* pathophysiology and disease course
  - biomarkers of biological effects related to adverse/therapeutic effects
- Population selection:
  - integration of phase I- and phase II in same patients?
  - healthy volunteers??
  - end-stage (?) adult patients
  - pre- (?) symptomatic patients
  - adolescents → younger (?) children

FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

Principles of ATMP Development

- 'general scientific principles within the fields of pharmacology and toxicology apply '[1]
- 'flexible, science-driven review process' → combined CBG/CCMO/ZiN pre-advice
- integration of preclinical – early clinical – clinical stages of development during phase I-II-III
- aimed at (stepwise) validation of quality of entire process chain:
  - **potency assays**: '**specific ability** … **of the product** … **to effect a given result**.'[1]
    - study phase dependent ('risk-based')
    - discuss options/feasibility with CCMO/CBG
  - product (class) specific test(s)
    - may require multiple *in vivo/in vitro* assays
  - quantification of biological activity
    - validated well-correlating physical assay acceptable
    - available for product-release
  - supportive release specifications:
    - viability: usually >70%
    - cell number: minimum acceptable dose
  - predefined acceptance/rejection criteria
    - 'system suitability'
    - 'out-of-specs' policy
  - quality system requirements
    - references, positive, negative controls
    - accuracy, sensitivity, specificity, precision, robustness
    - stability, consistency



1-FDA Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013)

2-FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (2011)

Conclusions

- ATMPs create exciting new ways to treat wide range of diseases
- Complexity is challenging for development and production
  - flexible approach, communication between sponsors, investigators, authorities
  - need for academic input in development of best practices and standard approaches
- In the end, development should be built on rigorous scientific standards, aiming for integrated ('total') mechanistic evidence of clinical benefit
  - product → biological effect → pathophysiological effect → clinical benefit
    on-/off-target undesirable effect → adverse effect/risk
  - characterization → activity → disease biomarker → surrogate endpoint
    biomarker risk biomarker → side effect follow-up
  - potency assay release criteria → effect biomarkers → clinical/cost benefit

ccmo@ccmo.nl

www.ccmo.nl

KWF

Session 3: Route to clinical practice

Moderator: Anke Hövels

- Oncode – considerations for developing your valorization strategy – Ian Bell
- Tumor-infiltrating lymphocytes (TIL) for the treatment of metastatic melanoma: how to translate results from phase 3 to clinical practice – Inge Jedema
- Hematon – opportunities and challenges for new therapies through the perspectives of patients - Bregje Verhoeven
- Panel Discussion

KWF

Oncode Institute

Outsmarting cancer
Impacting lives

Route to Clinical Practice

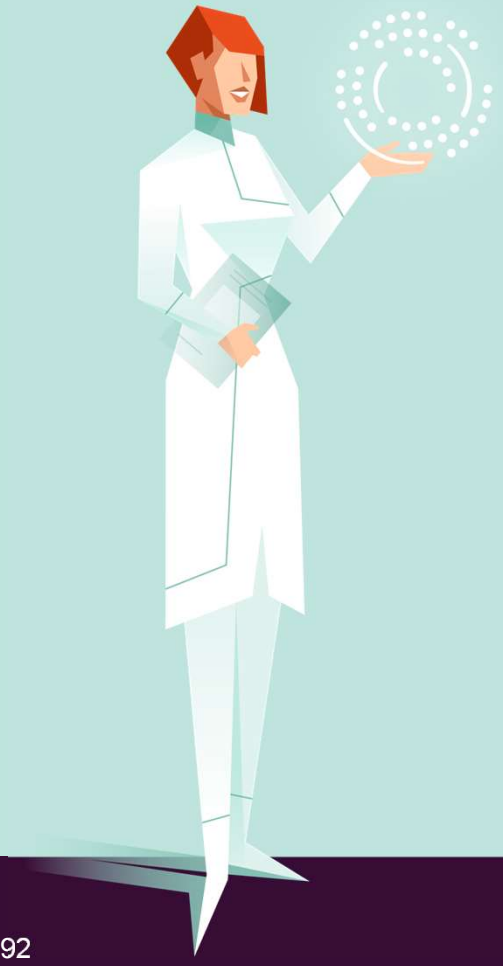
Considerations for Developing your Valorization Strategy

Ian Bell
Business Development
E: ian.bell@oncode.nl
P: +31 6 28 37 4976

- **Goal: Considerations for successfully moving your IP from the lab to the clinic:**
  - **IP Strategy**
  - **The Science**
  - **The Pitch**

IMPORTANT:

- **Work with your TTO**
- **Work with organizations like KWF and Oncode who can support you**
- **Seek out experts, advisors and colleagues who have done this before – they can help**



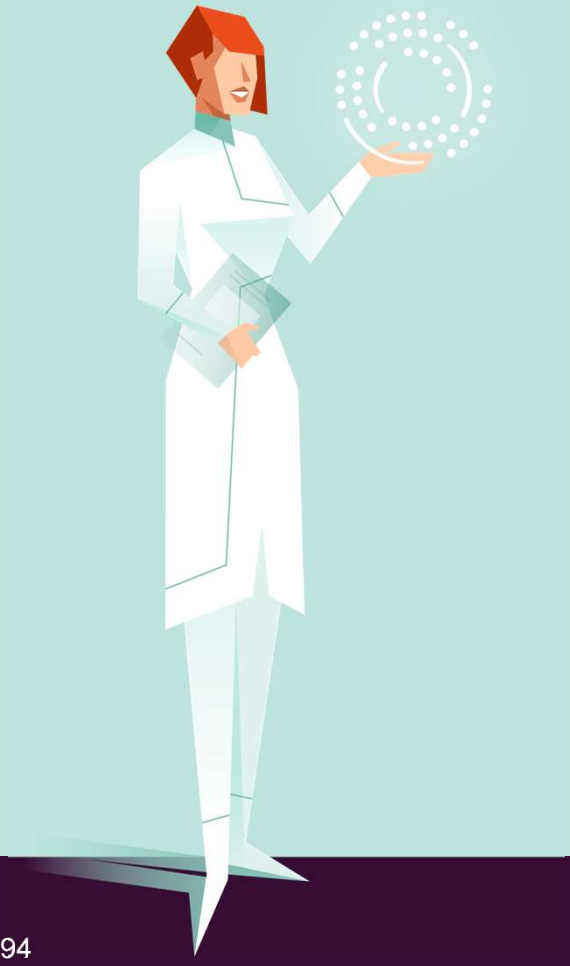
Intellectual Property Strategy

IP Strategy

- 3rd party restrictions:
  - who funded your work?
  - Material - AAV, lenti, CRISPR, etc.
- Leverage 3rd party data where you can (clinical trial set-up, manufacturing reagents, DMF/ASMF, etc.)
- Develop your TPP and business plan (business canvas)
- Licensing v. company creation:
  - Beware internal institution issues! - admin approval, OPA, COI, etc.
  - Run virtual if you can – CRA back to lab, space rental, etc.
  - Leverage non-dilutive grants
  - Have funding in place to support development and IP activities

- What is your intent (open science, license, company creation, other?)
- Plan your strategy (research results, publication and IP protection timelines)
- *Public Disclosure Implications – thesis defence, presentations, manuscripts, blogs, etc.

- Forms of IP protection (patent, trademark, copyright, trade secret)
- Use your resources (free databases for searching: USPTO, USPTO PAIR Portal, Espacenet, WIPO Patentscope, Google patents)
- Prior art searching (white space, competition, partners)



The Science

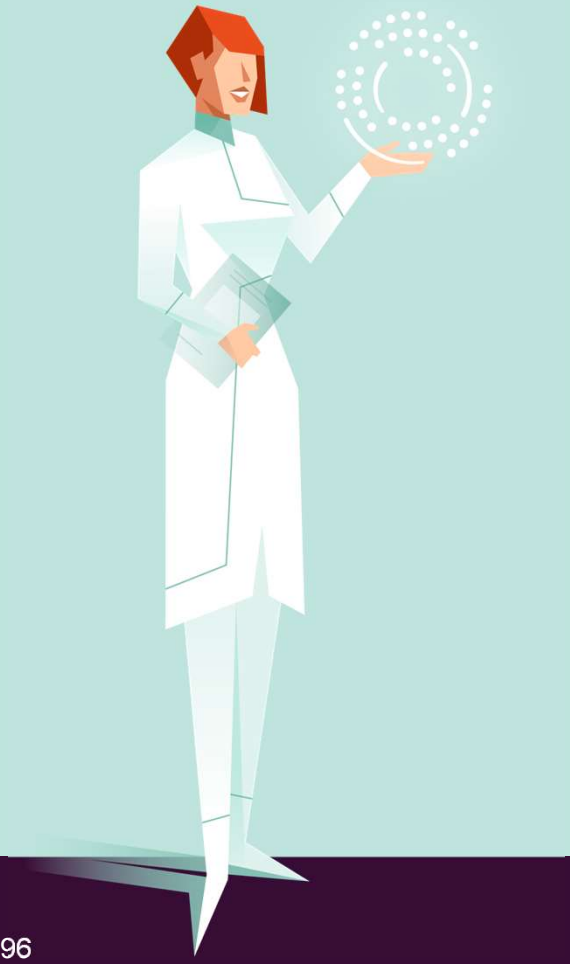
- Develop your TPP – what is your indication/properties versus gold standard equivalency?
- What is the addressable market and is there a sufficient patient population to support trials?
- FDA has issued guidance and guidance on TPPs for CGT.
- Work with the regulator:
  - FDA CBER guidance
  - FDA Office of Tissues and Advanced Therapies (OTAT) – see approved products and regulatory review documents
  - EMA Advanced Therapy and Medicinal Products (ATMP) – support and assistance available (PRIME scheme), EMA guidelines for ATMPs

Variable	Minimum essential	Ideal
Indication	Treatment of HIV-negative children aged 6–24 months and adults with diarrhea due to *Cryptosporidium hominis* or *Cryptosporidium parvum* infection	Treatment of children ≥ 1 month old and adults, including HIV-positive patients, with diarrhea due to cryptosporidiosis. Curative for additional diarrheal pathogens, and safe for use in syndromic treatment of diarrhea.
Product	Single agent or combination drug regimen	Single agent therapy
	Note that the risk of resistance is unknown and may require combination therapy.	
Target populations	Children ages 6–24 months with diarrhea due to cryptosporidiosis	Children ages 1–24 months with diarrhea due to cryptosporidiosis
	Immunocompetent adults with diarrhea due to cryptosporidiosis	Immunocompromised patients with diarrhea due to cryptosporidiosis
		Note that immunocompetent and immunocompromised patient populations may require distinct therapies.
Target countries	Countries that have been shown to have significant endemic cryptosporidiosis or that contribute heavily to the diarrhea burden in children	Countries accounting for 90% of morbidity and mortality due to diarrhea.
Clinical efficacy	Superiority to nitazoxanide in malnourished children	Cessation of diarrhea within 2 days in well nourished, HIV-negative children
	Equivalent to nitazoxanide in immunocompetent adults	≥90% efficacy in all patient populations
		Elimination of the effects of *Cryptosporidium* infection on malnutrition
Microbiologic efficacy	Superiority to nitazoxanide in malnourished children	Elimination of fecal parasite shedding within 2 days of starting therapy for all patient populations
	Equivalent to nitazoxanide in immunocompetent adults	
	Active against both *C. hominis* and *C. parvum*	
Safety/drug-drug interactions	Safe in patients ≥6 months old	Safe for syndromic treatment of diarrhea in patients ≥1 month old
	SAE rate ≤5% by Common Terminology Criteria for AEs; AEs ≥ Grade 2 no more than 30%	No drug-related SAEs by Common Terminology Criteria; minimal drug-related AEs
	No unmanageable drug–drug interactions	No CYP3A4 inhibition; no interactions with antiretroviral drugs
Formulations and dosage	Oral; maximum 3x/day for 14 days; liquid formulation or compatible with hydrodispersible tablet or granules appropriate for children available	Oral liquid or hydrodispersible tablet or granules given as a single dose
		Minimal or no food effect
Stability	≥2 years in Zone IVb (30°C 75% humidity)	≥3 years in Zone IV
Total cost per patient	$US2.00	≤$US0.50 (approximate total cost of nitazoxanide 100 mg/5 ml liquid formulation in India)

AE, adverse event; SAE, severe adverse event

doi:10.1371/journal.pntd.0003987.t001

- https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003987

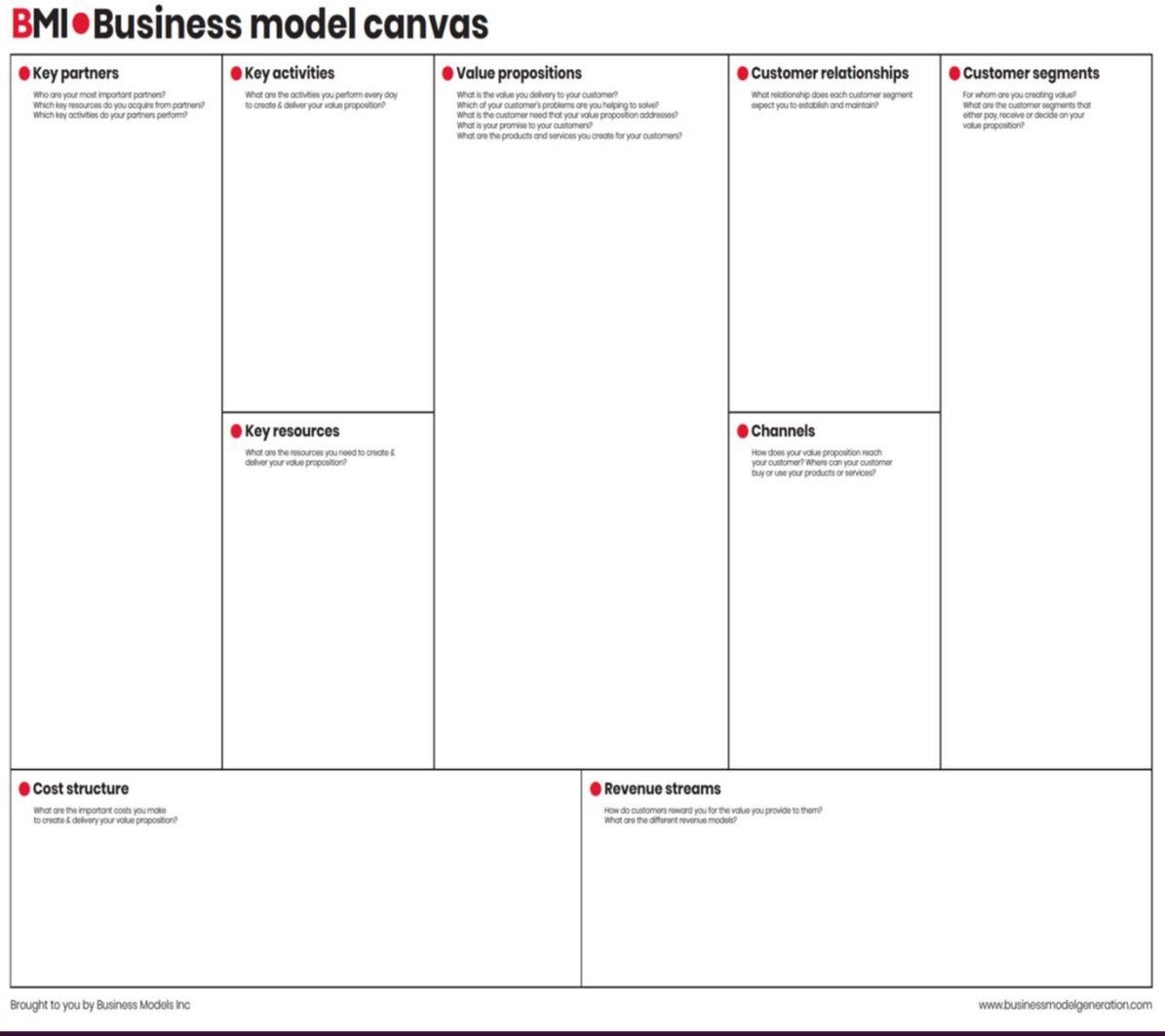


The Pitch

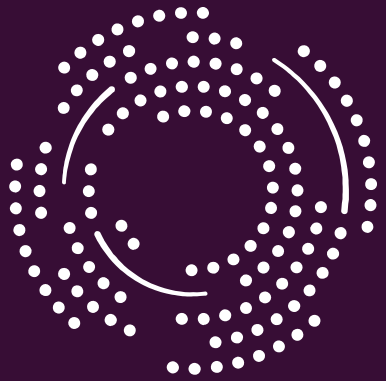
- Prepare your business plan (Business Model Canvas)
- Leverage bootcamps and local support (HIHR, Holland BIO, NWO's Venture Challenge
- Regional funds
- Build your network, engage with investors early - It's a courtship!

Final Thoughts:

- Do your due diligence on your partner – it is a marriage.
- Be careful when it sounds too good.
- Above all, be realistic!



Oncode Institute



Oncode Institute

Outsmarting cancer
Impacting lives

Trials and Tribulations: Glybera (gene therapy for LPLD)

- 1986 Dr. Michael Hayden (UBC) and Dr. John Kastelein (A'dam) search for gene responsible for LPLD. Kastelein returns to NL in 1998.
- ~2000 Dr. Colin Ross joins Hayden lab. In 2002 pivotal experiment succeeds. Cover of Nature in September 2004.
- Collaboration to demonstrate in feline model (Boyce Jones, Florence Italy)
- Kastelein founded Amsterdam Molecular Therapeutics (AMT) in 1998; Hayden lab providing scientific support.
- 2005 enrolled 8 NL patients in a clinical trial – success!
- Regulatory issues; 2.5 years for EMA approval – AMT liquidated in 2012
- Assets licensed to uniQure; struggle to obtain EMA approval; partnered with Chiesi Farmaceutici – Chiesi acquires EU rights, uniQure retained US/CA rights.
- EU sale in 2015 - €1M per treatment. Difficult to obtain reimbursement from insurers.
- Only ever 1 paying patient from Germany.
- In 2017 (2 years after going on market, Chiesi abandoned it, allowed EU marketing license to expire. Rights returned to Uniqure.
- Remaining lots (3 doses) given away. Only ever given to 31 patients worldwide (most treated for free in trials).
- https://newsinteractives.cbc.ca/longform/glybera?webview=true&appname=news-android-app

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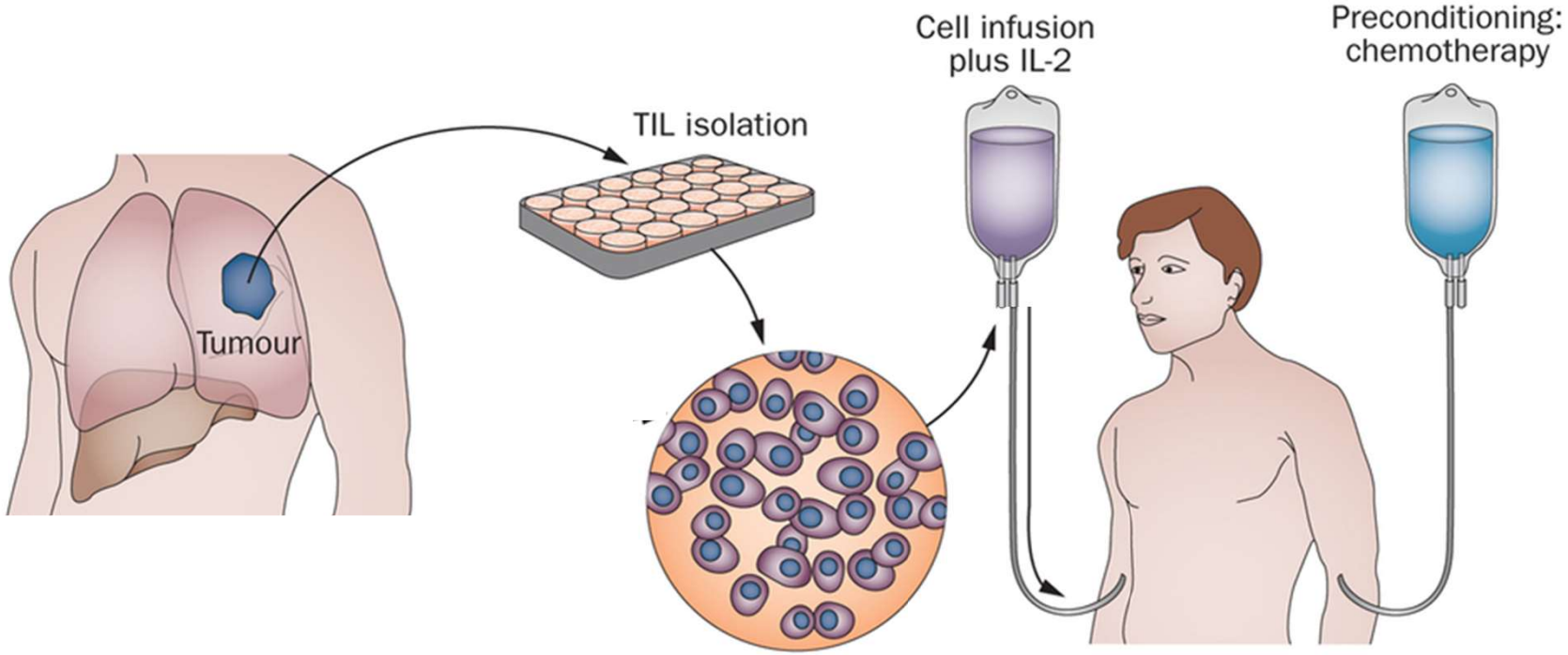
Tumor-infiltrating Lymphocytes (TIL) for the treatment of metastatic melanoma

How to translate results from phase 3 to clinical practice

Inge Jedema, head translational cellular therapy

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

Treatment with tumor-infiltrating lymphocytes (TIL)



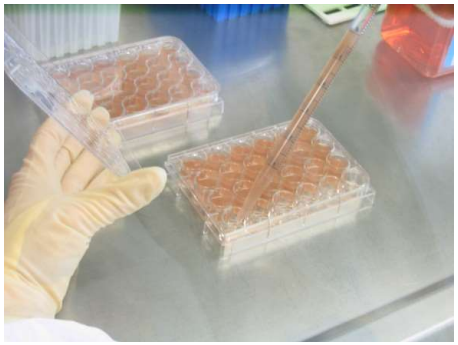
Rosenberg Nat Rev Clin Oncol., 2014

BioTherapeutics Unit (BTU) – Pharmacy AVL

- 1 cleanroom in the old Slotervaart Hospital
- 3 cleanrooms in the new complex of the AVL
- Production of ‘Advanced Therapy Medicinal Products’ (ATMPs) under ‘Good Manufacturing Practice’ (GMP) conditions

Preparation of tumor to cell suspension & initial culture

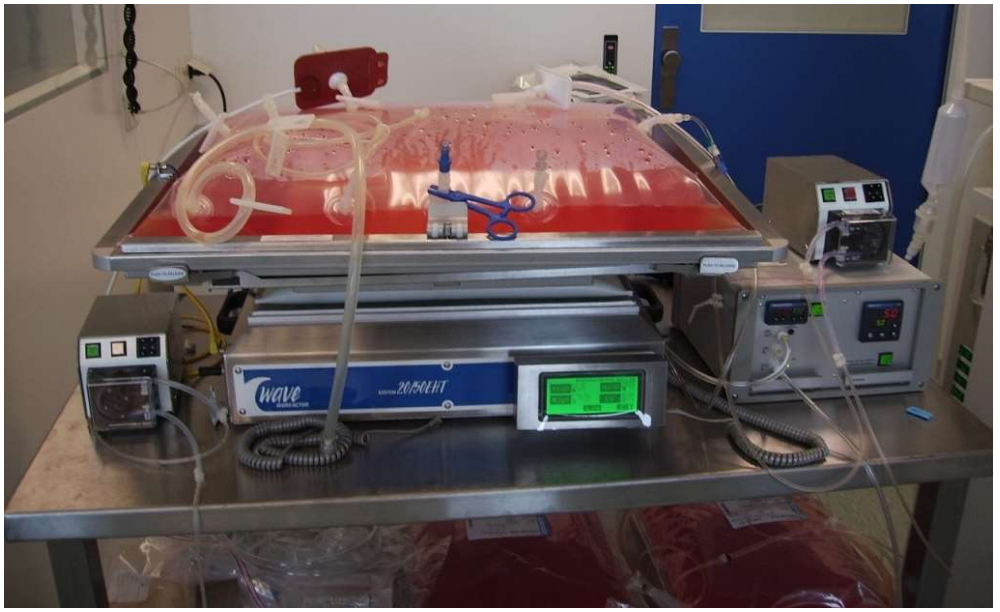
- Mincing
- Enzymatic digestion
- Culture with 6,000 IU/mL IL-2



Suspension with:
- Tumor cells
- T cells (TIL)

vd Berg et al, Journal for Immunotherapy of Cancer 2020

Rapid expansion phase of TIL culture



Xuri bioreactor

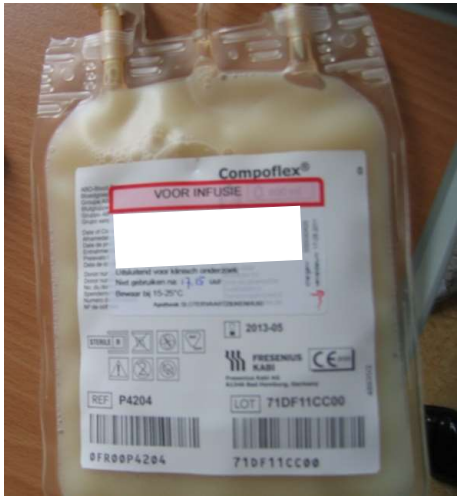
- 3,000 IU/mL IL-2
- αCD3 (OKT3)
- Irradiated feeder cells

- logistically challenging
- success rate 90%

vd Berg et al, Journal for Immunotherapy of Cancer 2020

Harvest and infusion of TIL product

- Washing and preparation of TIL product in 200 ml infusion fluid (fresh product)



Quality Controls (QC)	Specification
QC(1) Microbiological contamination	negative (day -2 before infusion)
QC(3) Total cell number	>$5x10^9$ TIL and < $2x10^{11}$
QC(4) Viability	>70% viable cells

Randomized phase 3 clinical trial to assess the effectivity of TIL treatment in patients with metastatic melanoma

- Feasibility and safety: phase 1 study in 10 patients (vd Berg et al, Journal for Immunotherapy of Cancer 2020)
- Ongoing randomized phase 3 study:
  - Patients with irresectable stage IIIc/IV melanoma
  - 1:1 randomization between:
    A. Ipilimumab (αCTLA4 checkpoint inhibitor)
    B. TIL treatment (+ lymphodepleting chemotherapy & IL-2 600,000 IU/kg/dose)
  - 168 patients
  - Study sites: AVL and CCIT, Herlev hospital (DK)
  - TIL production: AVL, Sanquin and CCIT, Herlev hospital (DK)
  - *Temporary reimbursement from the Dutch and Danish health insurance*

Eudract no. 2013-005406-54
Rohaan et al, unpublished (trial ongoing until Q1 2022)

Future:
TIL treatment for patients with metastatic melanoma

- Analysis of study results

- Hospital exemption (IGJ)
  - Limited number of patients
  - Risk of being challenged when other (commercial) party enters the market with a registered TIL product for same indication

Future:
TIL treatment for patients with metastatic melanoma

- Analysis of study results
- Hospital exemption (IGJ)

if study is successful

Future:
TIL treatment for patients with metastatic melanoma

- Analysis of study results
- Hospital exemption (IGJ)
- Market authorization: registration via European Medicines Agency (EMA)
  - As NKI/AVL(support VWS or other stakeholders?)
  - With commercial partner (pharma)?
  - Production capacity?

→ Keep TIL treatment available for patients at a reasonable price

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The Danish Cancer Society and Capital Region of Denmark Research Foundation

Patients and their families

KWF

Hematon
patiëntenorganisatie bloedkanker
lymfklierkanker stamceltransplantatie

Are new therapies developed with patients in mind?

Bregje Verhoeven
Patient Advocate

KWF Cell and Gene Therapy Congress, Amsterdam, October 6 '21

www.hematon.nl

Disclosures

Honoraria for participation Patient Advisory Boards, consultation and educational activities;

AbbVie, Amgen, Janssen, Pfizer, Takeda

Hematon receives from various industrial partners unrestricted grants to organize Hematon Webinars for patients on hemato-oncological diseases or specific treatments and their side effects.

New therapies – like CAR T - give hope to patients who have no further treatment options

Is progress being made with the needs of patients - as defined by patients - in mind?

Dutch CAR T-Cell landscape

3 Commercial CAR T-Cell therapies approved by EMA

2 CAR T-Cell therapies reimbursed in NL

Part of SOC for

Indications: R/R DLBCL, R/R ALL <25 yrs

≥ 2 lines of therapy

More is on its way

Multiple Myeloma, Mantle Cell lymphoma

Access for all?

- In- and exclusion criteria
  - *Efficacy & Safety*
  - *Multi centre trials/ adaptive designs?*
  - *Excluding ptnts who need treatment*
- Long supply chain
- Costs : price and reimbursement
- Compassionate use differs per country; Sluis period in NL

Solution: off the shelf therapies

the academic route/ HE

The promise of the academic route

- Alternative to or additional to commercial products we know? Other indications?
- Rare diseases, small patient groups -> multicenter trials
- Shorter supply chain. No need for shipping or freezing cells
- It's said to reduce the costs of CAR-T product

  Spain: 50.000 vs 350.000 Euro
- Broader in- and exclusion criteria?

➢ hope for treatment for more patients

Let’s talk about…

Regulatory hurdles

HTA

Evidence generation

Regulatory hurdles

- Academic medical centers miss knowledge, time and finances to build a dossier needed for EMA
- Regulation for Hospital Exemptions do not work in favor for academic medical centers nor patients

Regulatory adjustments are urgently needed

➢ Pilot

CAR-T: Challenges to HTA

- Are the models adapted to look beyond the immediate upfront cost and take into account longer-term savings?

- Value-based approaches to care must *not only* be evidence based but also incorporate quality-of-life considerations

Evidence generation

- Knowledge on Manufacturing & Regulation
- Clinical data

A uniform way of collecting (same) data needs to be part of the Dutch infrastructure

in a shared database related to academic products

Data is KEY to get the products sustainable in NL

We need REAL WORLD DATA to evaluate CAR-T for healthcare system and patients

- How will the treatment be used in clinical practice?
- Move towards outpatient treatment settings?
- What will be the time from apheresis to infusion in clinical practice in HE compared to CP
- Cost-effectiveness HE compared to CP?

What will be the QoL?

Long-term implications?

What else (do we need)?

- Moving therapy to earlier lines of treatment

- Patient information and education
- Harmonised trial protocols to be widely implemented

Patient involvement

In early phase of R&D of new therapies

Design clinical trial

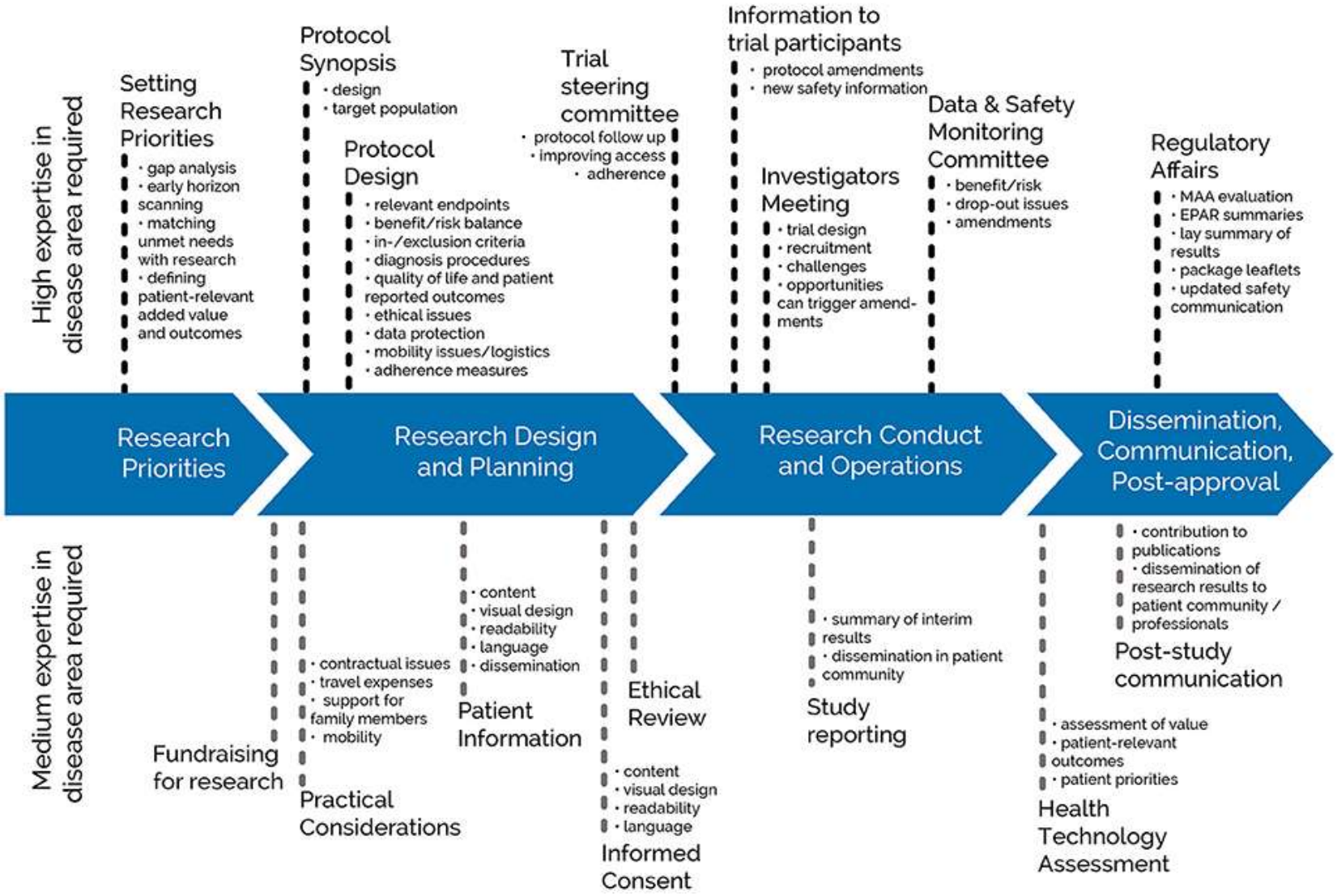
Ethical review of Clinical Trials – Ethic Committees*

Regulatory authorities

Health Technology Assessments

Klingmann I, Heckenberg A, Warner K, Haerry D, Hunter A, May M and See W (2018) EUPATI and Patients in Medicines Research and Development: Guidance for Patient Involvement in Ethical Review of Clinical Trials. Front. Med. 5:251. doi: 10.3389/fmed.2018.00251

Patient involvement in medicines R&D



Take home messages

Adjustment in regulation

Structured & uniform data incl PROM QoL& RWD

Integrate this from the beginning of new therapy development to increase the possibility that new therapies will reach clinical practice and save patients' lives

Hematon
patiëntenorganisatie bloedkanker
lymfklierkanker stamceltransplantatie

Hematon maakt deel uit van de Nederlandse Federatie van Kankerpatiëntenorganisaties en wordt gesubsidieerd door KWF Kankerbestrijding

Thank you for your attention

@bregjeverhoeven
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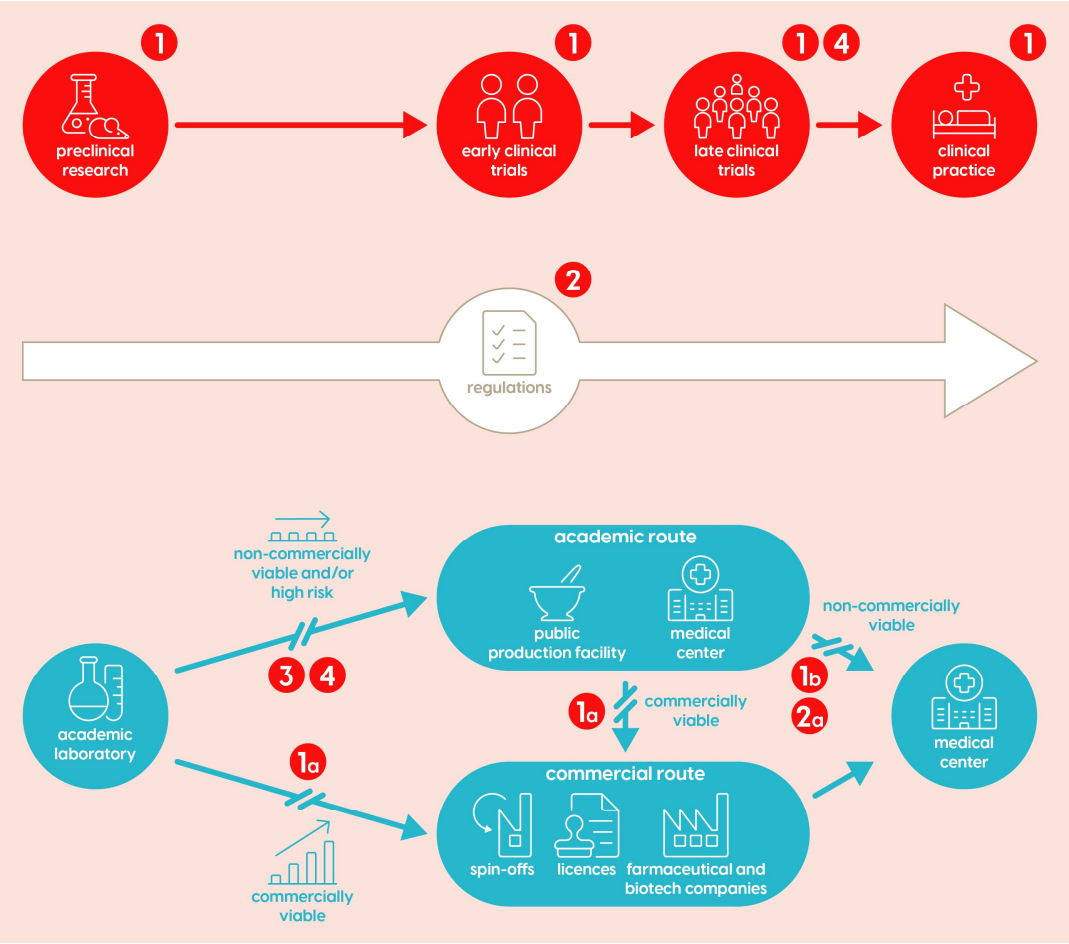
KWF

Conclusions

Carla van Gils

Take away of the day



Recommendations

1. Coordination and support by a centralised body
2. Regulatory clarity and fit-for-purpose requirements
3. Platform for knowledge dissemination and collective production capacity
4. Financial support for product development and late stage trials

Our commitment

KWF commits to the acceleration and stimulation of developments in the CGT field. We aim to act now and contribute to this goal by:

1. Financial support to enhance infrastructure for CGT manufacturing according to GMP.

2. Organizing a congress to enhance public collaboration and interaction and knowledge dissemination with organizations for valorization and regulatory bodies.

3. Lobbying for the development of clear, fit for purpose regulatory and HTA requirements, and more interaction among academics and regulatory bodies.

Let’s get started!!