Immunological Challenges of Regenerative Therapies – What, Why, How ?

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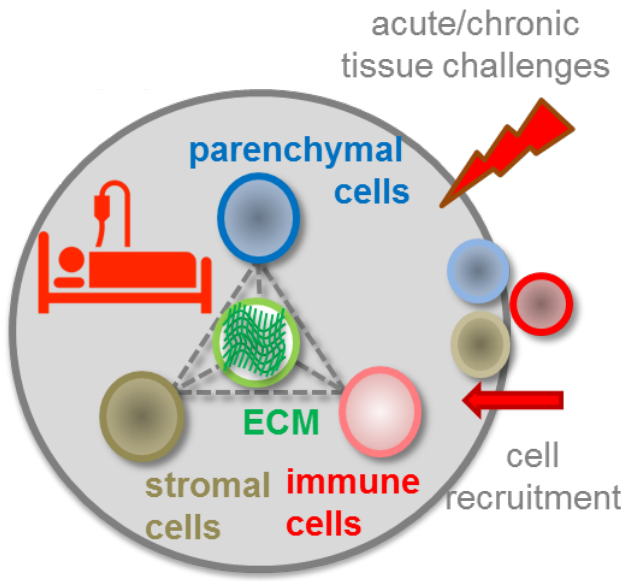
Charité – Universitätsmedizin Berlin and Berlin Institute of Health

Regenerative Therapies are more than Stem Cell therapies

Challenged Tissue Homeostasis following injury, chronic degeneration, cancer, autoimmunity…



Dynamic Tissue Homeostasis

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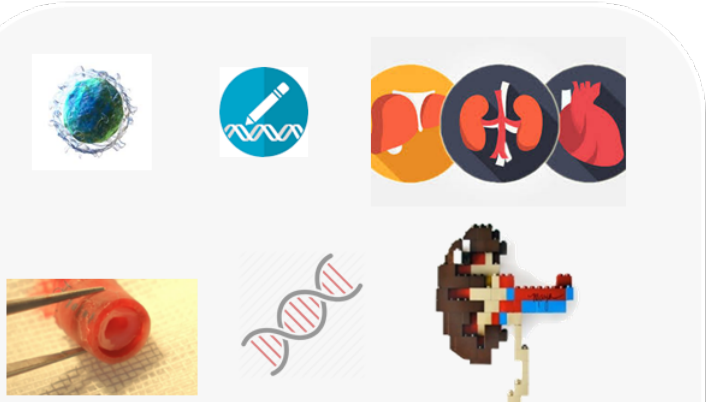
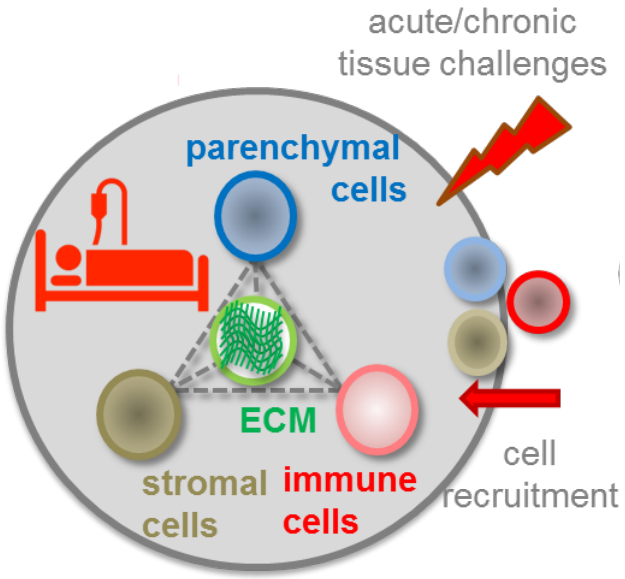
Replacement of non-functional cells/tissues
from organ transplantation to biological replacement approaches by *ex vivo* generated ATMP or bio-MD



in vitro manipulation to prepare *biological replacement products*



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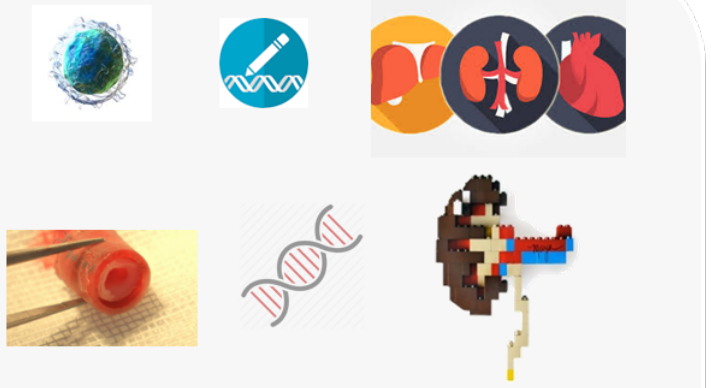
Support of **endogenous regeneration**
„*in situ* tissue engineering“ by cells, factors, biomaterials to restore dynamic tissue homeostasis



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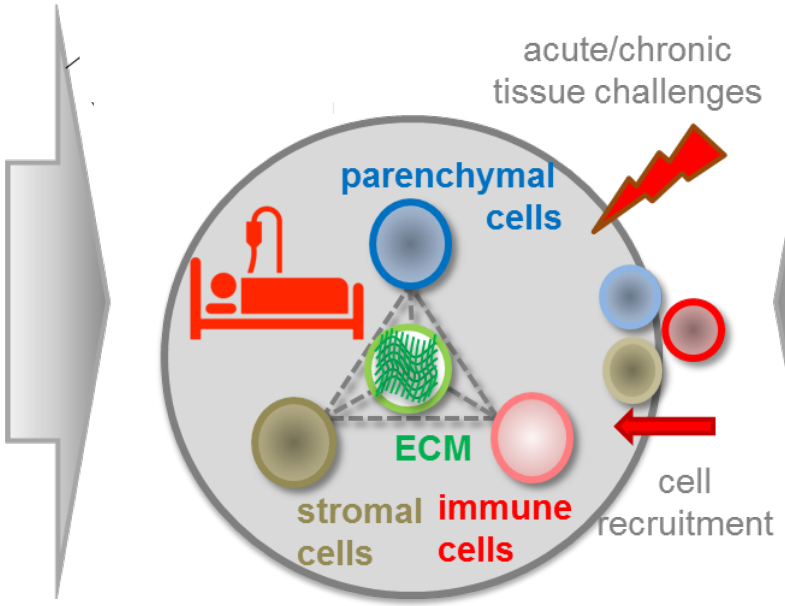

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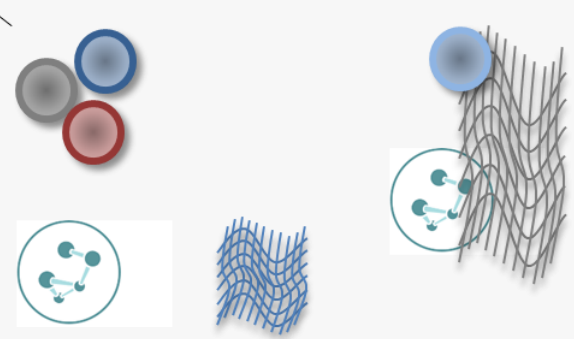

in vitro generation of therapeutics *supporting endogenous regeneration in vivo*

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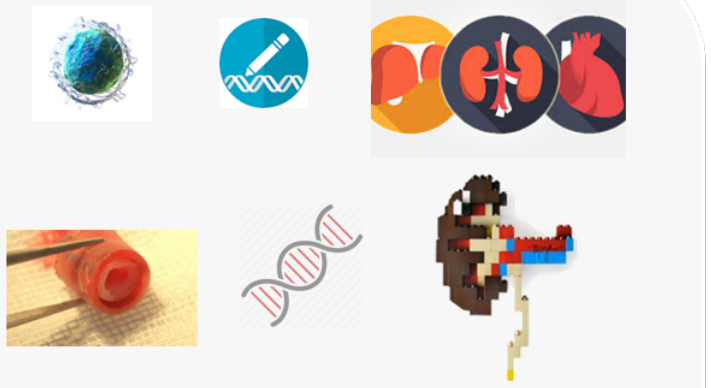

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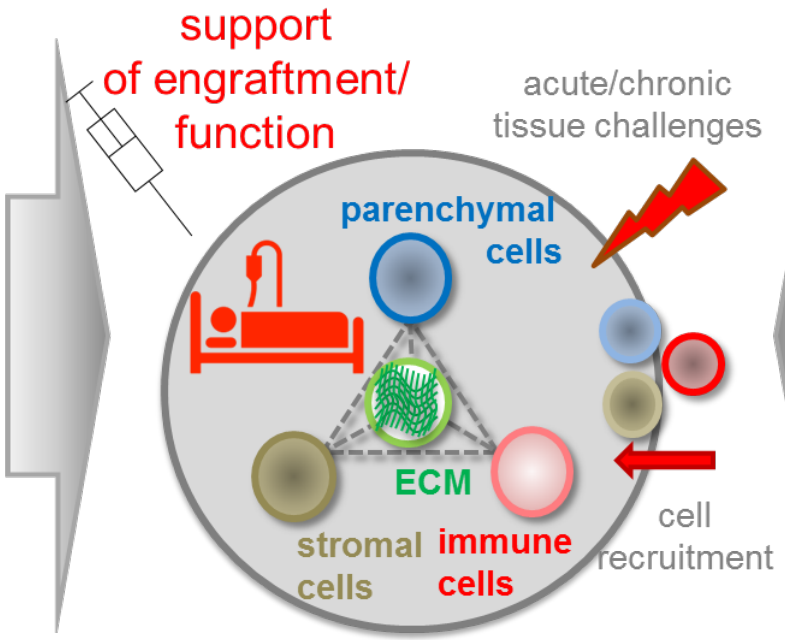

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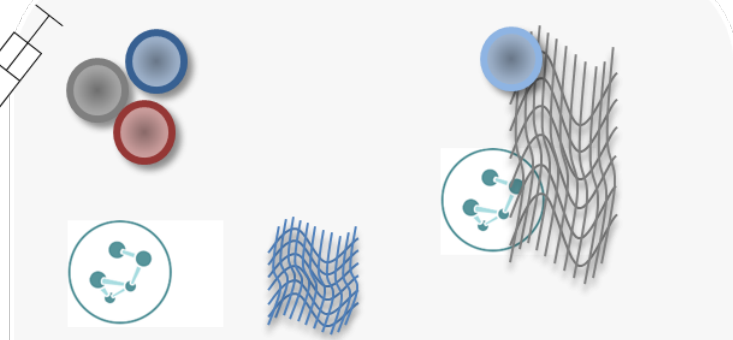

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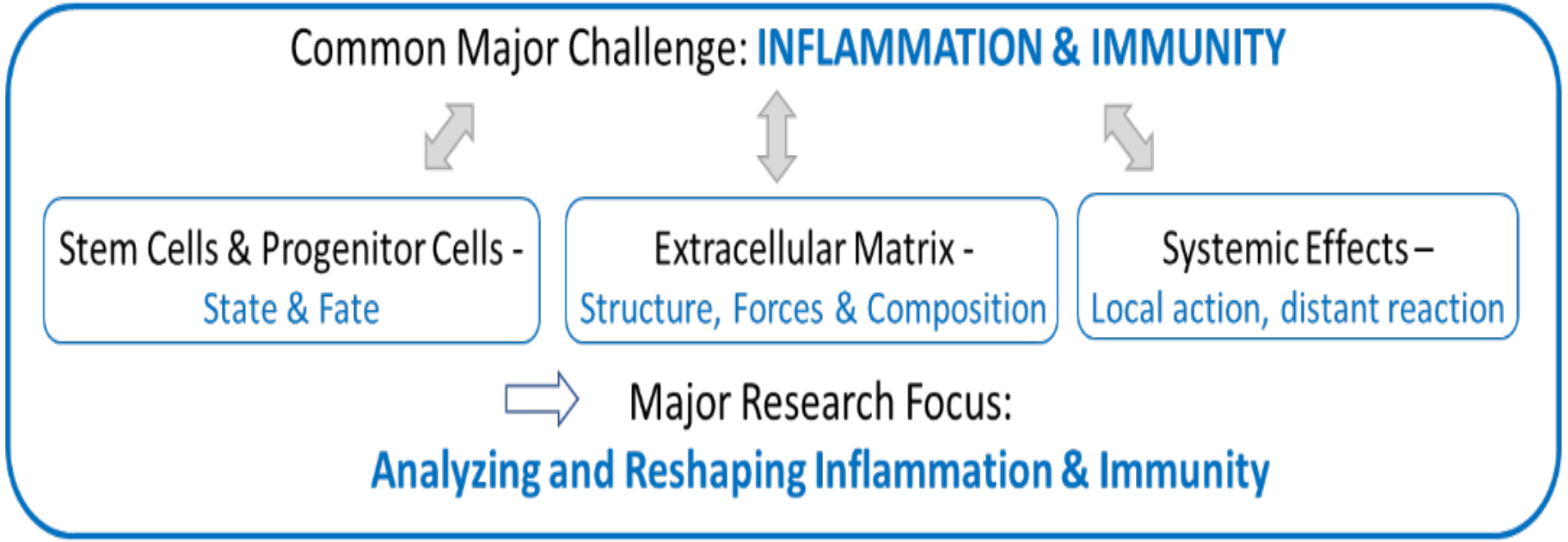
Inflammation/Immunity – a major common challenge



Goal:

to support endogenous regeneration and
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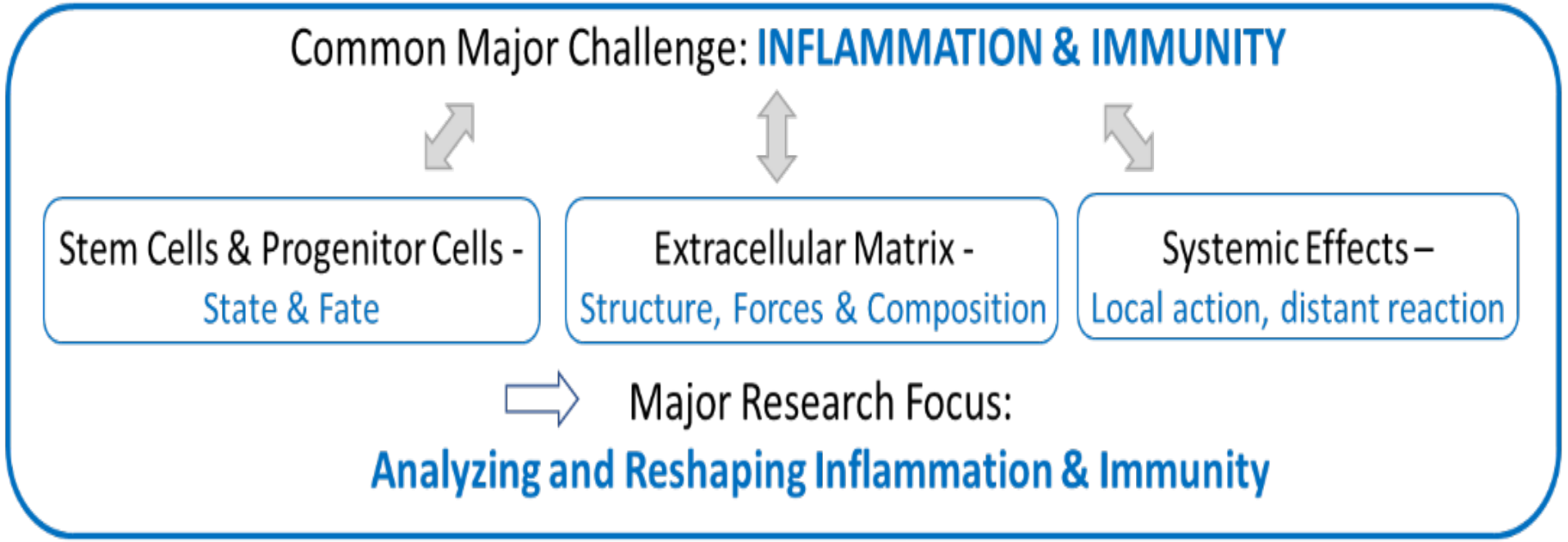

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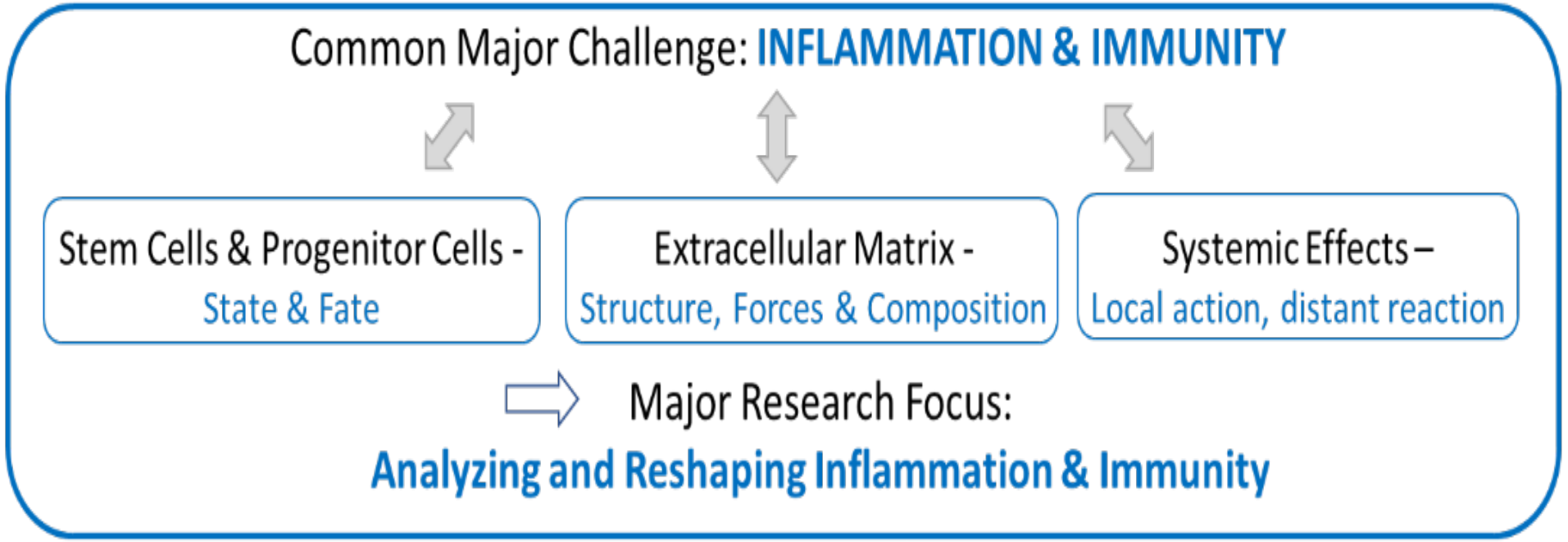

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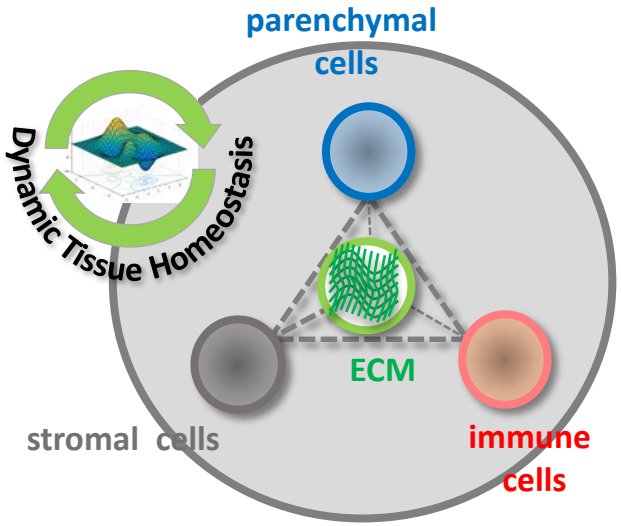
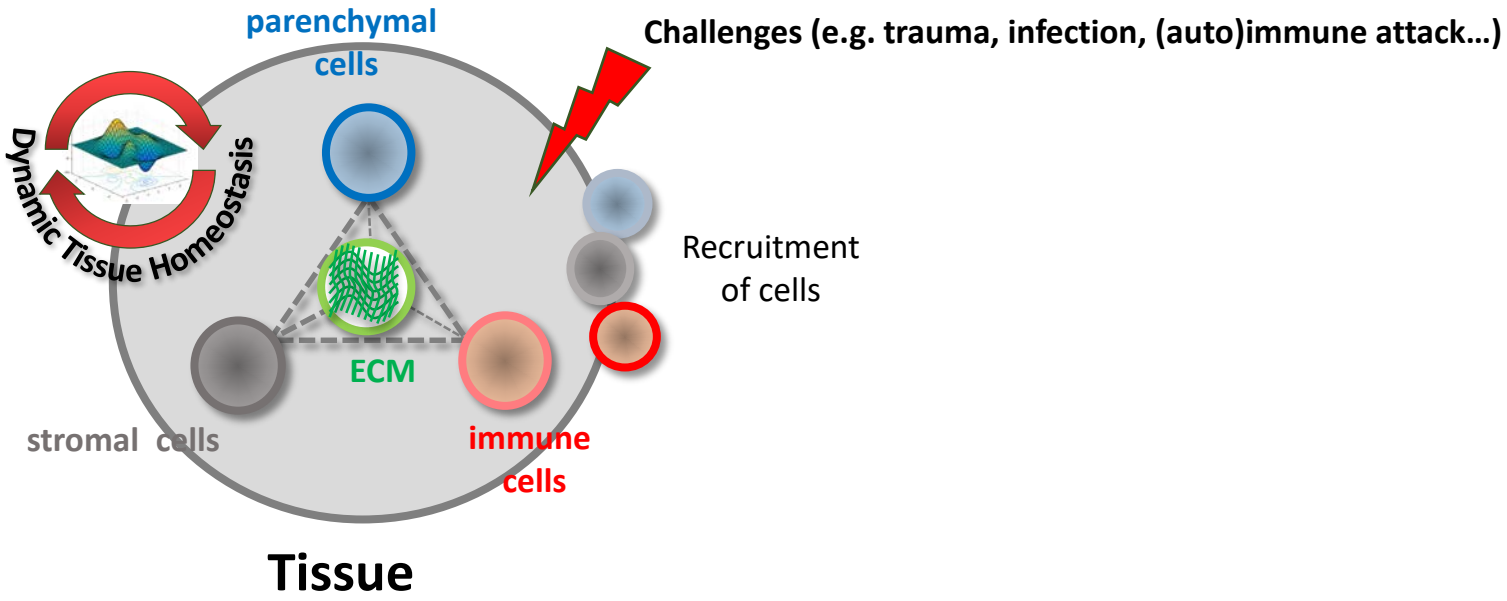
Intratissue immunity = part of dynamic tissue homeostasis



Tissue

Challenged tissue homeostasis triggers recruitment of cells



Enhanced tissue infiltration / inflammation by effector T cells

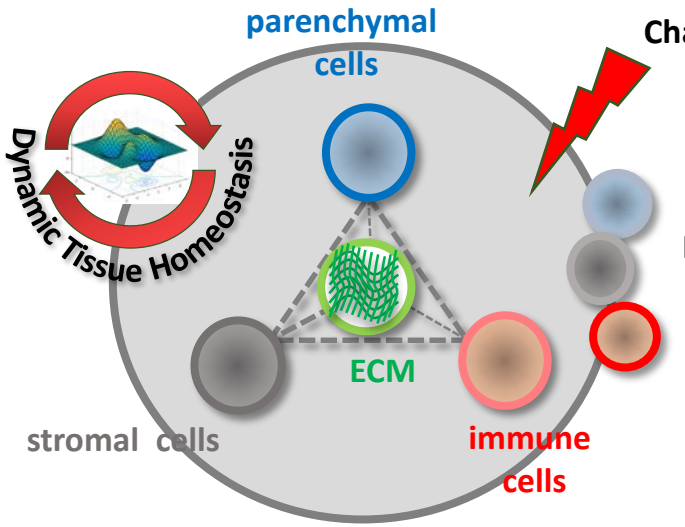
Repetitive antigen (pathogen) challenge

Naive / early memory T cells

Immune „Aging“

Effector T cells

infiltration/inflammation (+)

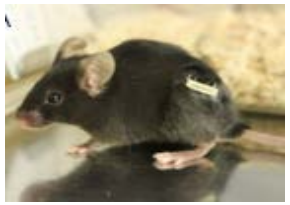


Tissue

infiltration/inflammation +++

SPF housing preserves naive immune system despite aging

SPF housing



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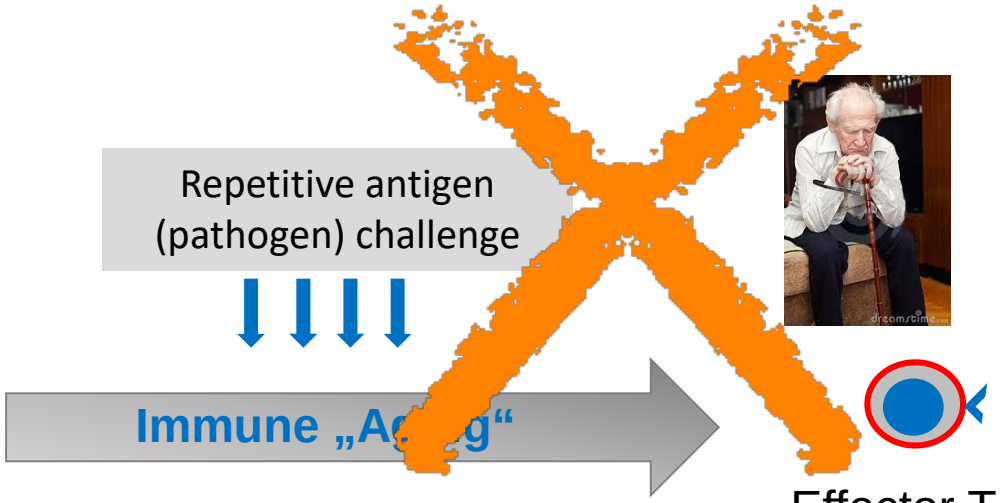

Immune „Ag[illegible]g“

Naive / early memory T cells

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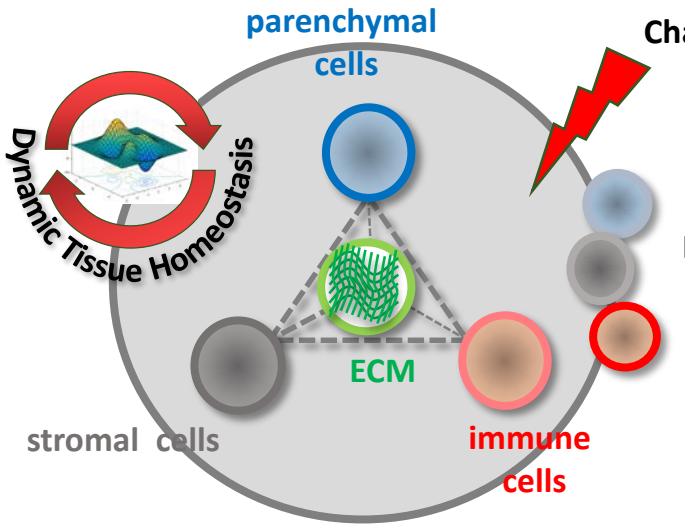

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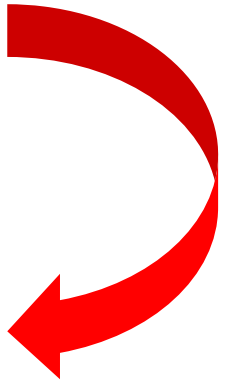

infiltration/inflammation

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Non-SPF housing brings murine system close to human ones

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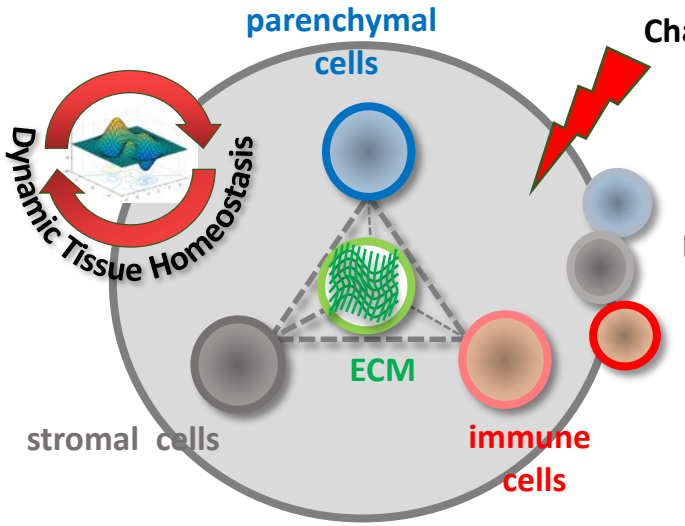

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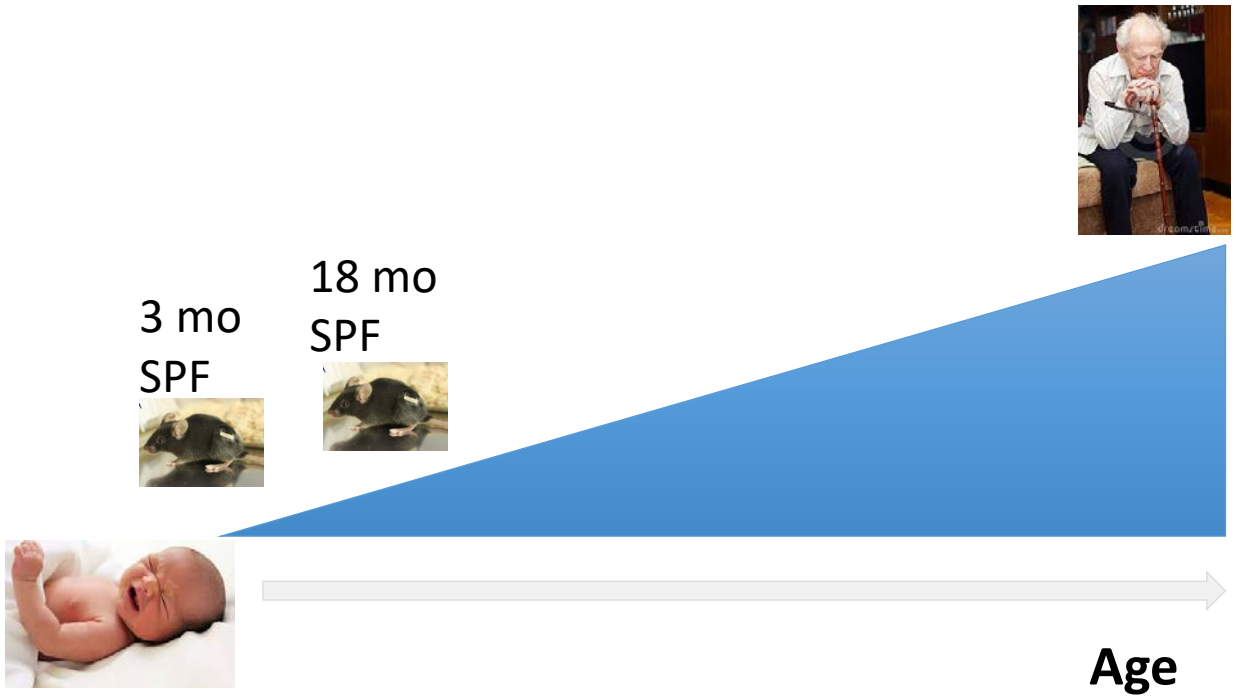
Frequency of effector T cells in spleen / blood



Japp A Cytometry 2017, Reinke S Sci Transl Med 2013, Schmidt-Bleek et al. Front Immunol 2017, Sbierski-Kind et al. Front Immunol 2018, Schlundt Front Immunol 2019

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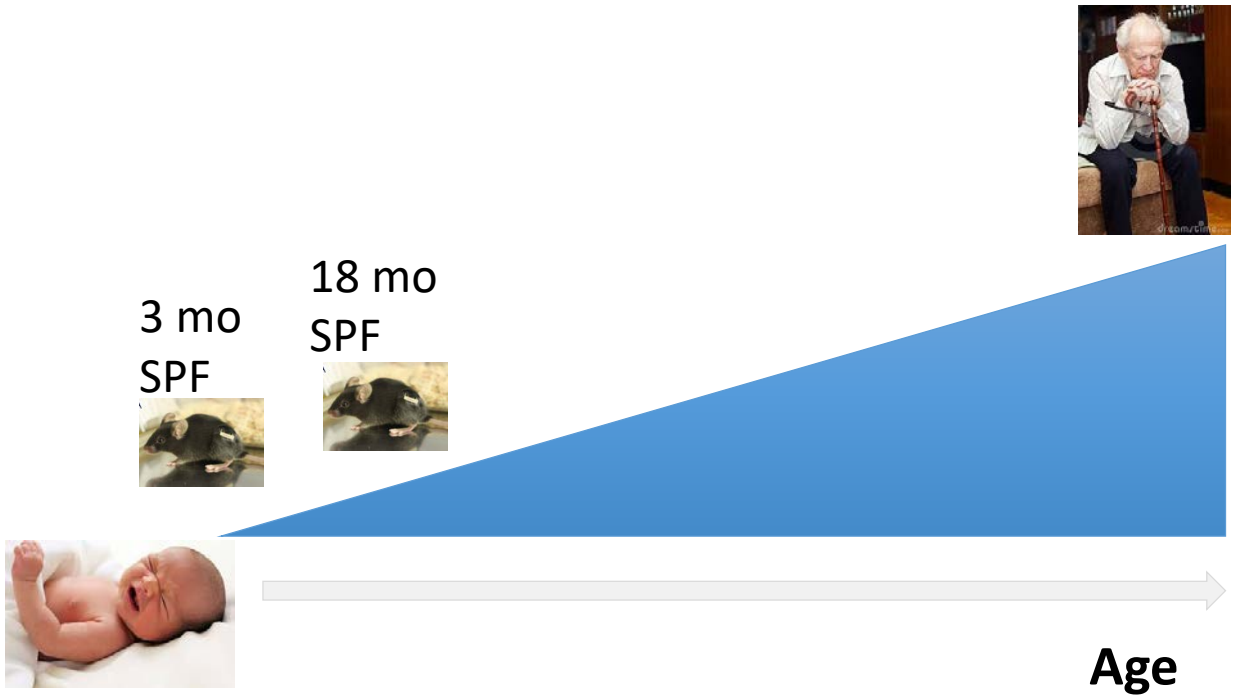
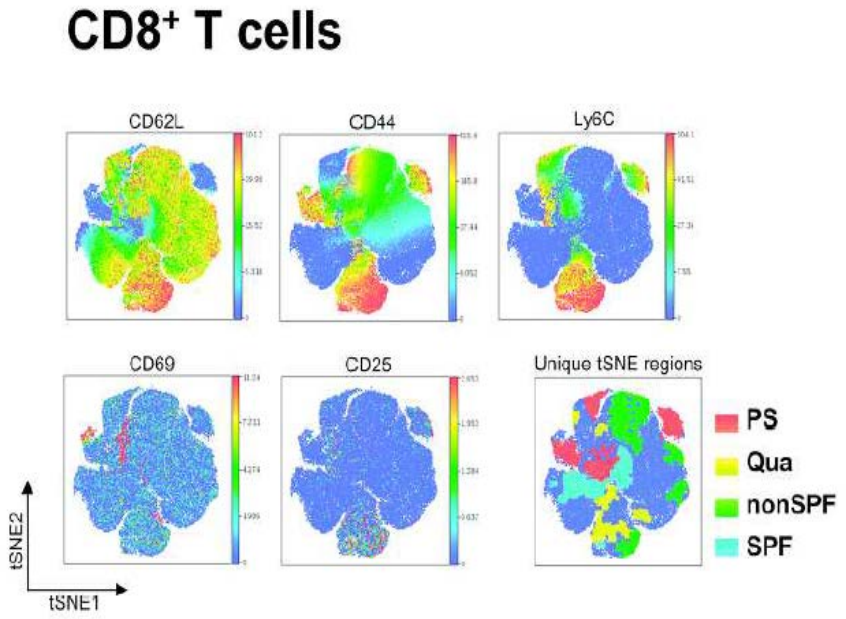


Multiparameter (40) CyTOF analysis



Enhanced and decreased level of Teff and Tnaive CD8+ (similar for CD4+, B-Ly, myeloid), respectively, in mice from pet shop (PS) vs. quarantine (Qua) vs. non-SPF vs. SPF housing.

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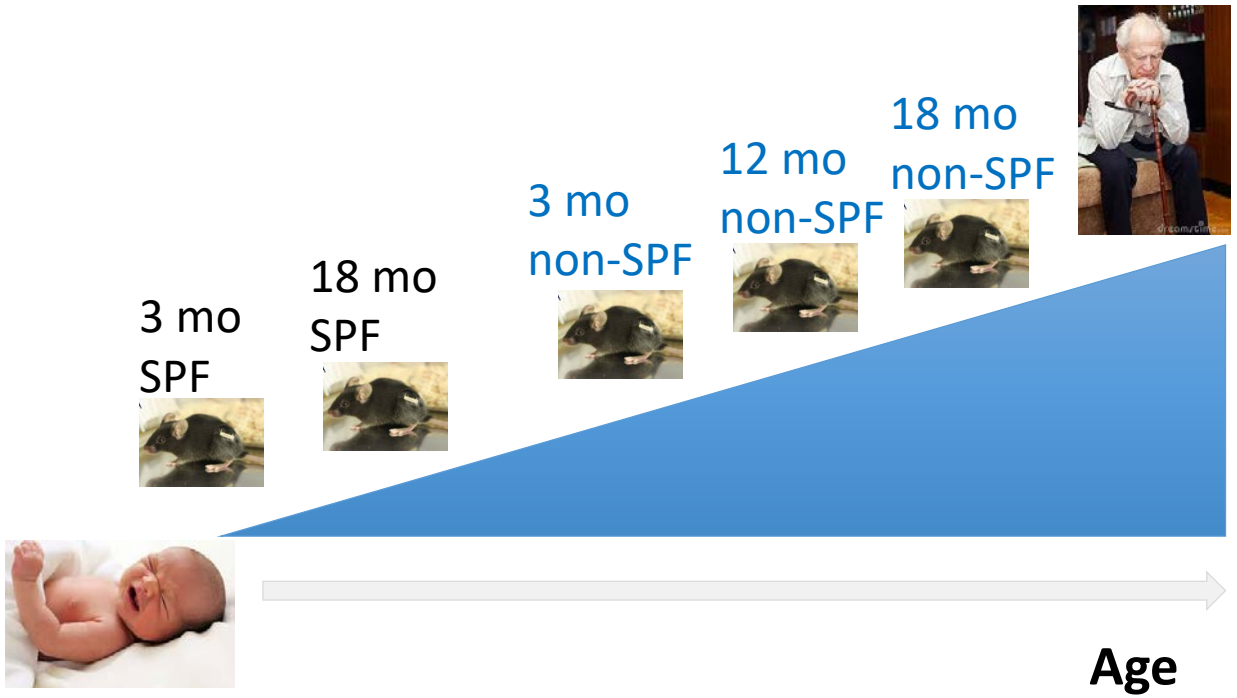

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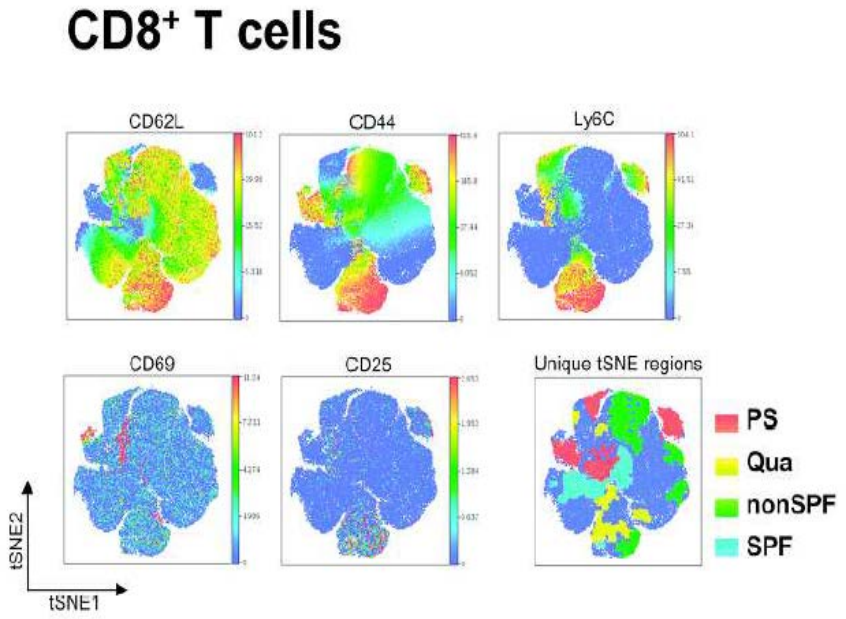

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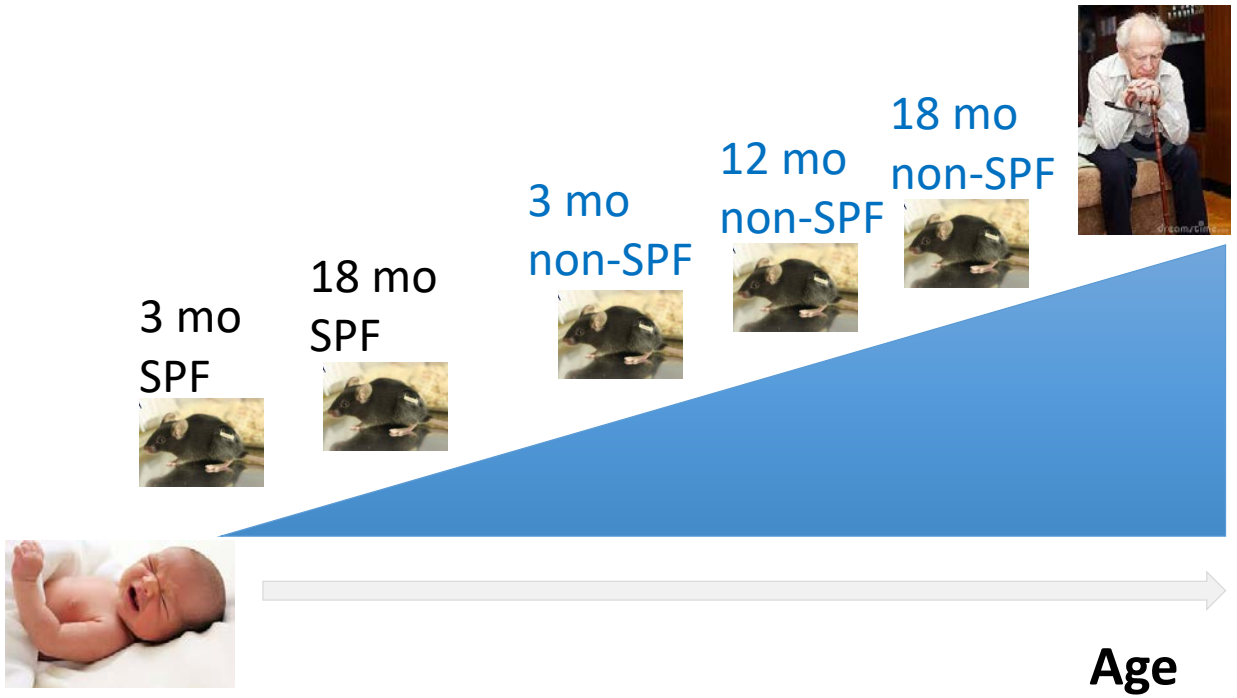
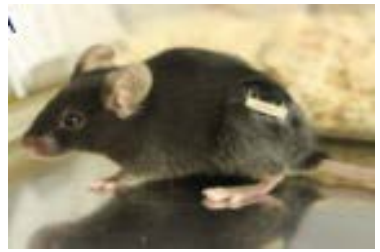
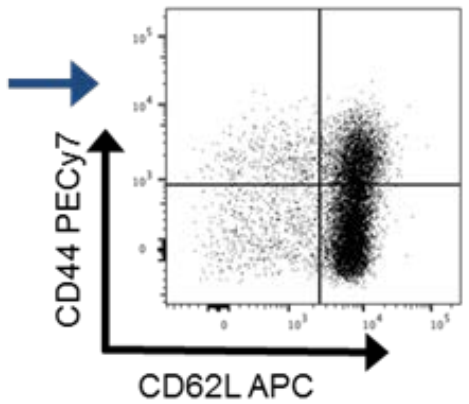


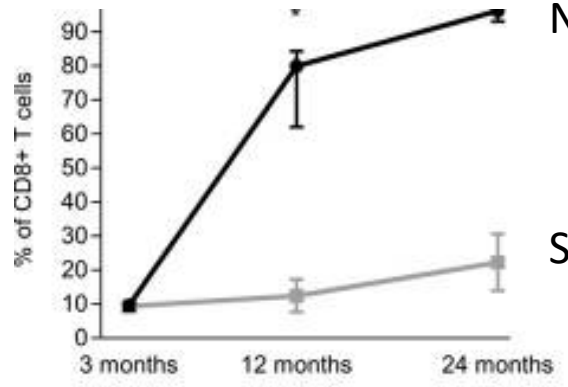
Fast Test of ImmunoAge - Flowcytometry

20-50 µl



Tnaive and Tmemory/effector cell counts





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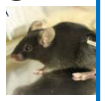
Freque

3 mo
SPF



ImmunoAging has a strong impact on the course of distinct disease models:

- Organ Transplantation
- Spontaneous abortions

- Bone fracture healing
- Acute muscle injury
- Type 2 Diabetes
- Acute Ischemia/Reperfusion Injury
- …

- Gene therapy

Katharina Schmidt-Bleek

Simon Reinke

Sven Geissler

Christian Bucher

Julia Sbierski-Kind

Andreas Thiel

Japp A Cytometry 2017, Reinke S Sci Transl Med 2013, Schmidt-Bleek et al. Front Immunol 2017, Sbierski-Kind et al. Front Immunol 2018, Schlundt Front Immunol 2019

Advanced Preclinical *in vitro & in vivo* Models

Conventional preclinical models
using mice kept under
SPF housing conditions and
biosamples from healthy donors

Limited predictive value for diseases

Advanced Models
Clinically relevant models

Large aimals

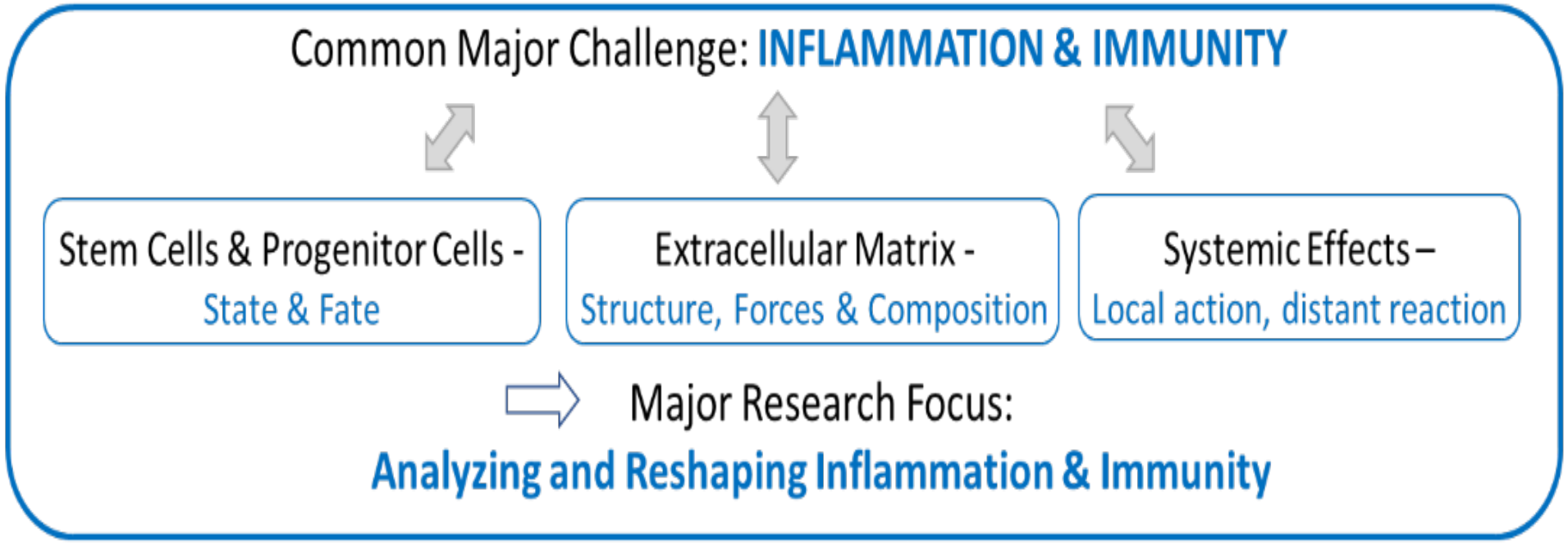
Humanized NSG mice
& ImmunoAged mice

Biosamples from
disease-specific
patient population

Multiorgan 3D-chips
„Patient-on-the-Chip“

Higher predictive value for diseases

Inflammation/Immunity – a major common challenge



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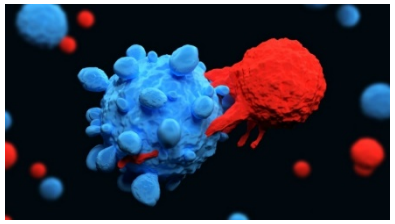
ImmunoTherapies – innovation drivers in medicine

Restorating Protective Immune Response

Fighting cancer and severe infections



e.g. checkpoint inhibitors

Reshaping Undesired Immune Response

Preventing Self-destruction or Transplant rejection

Biologics

e.g. anti-IL-17 mAb

„Living Drugs“ (ATMP)

e.g. CAR-T cells

e.g. Treg cells

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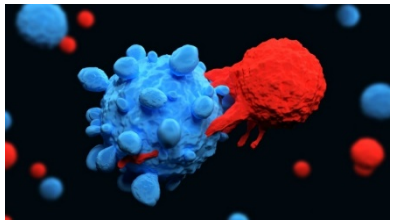

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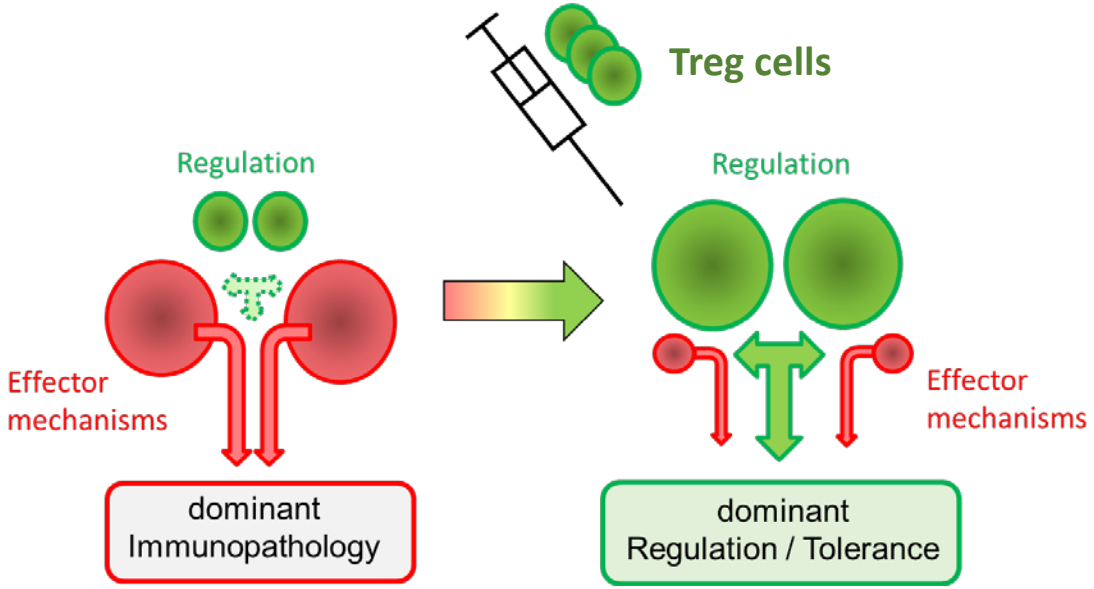
ReSHAPING undesired immune reactions by regulatory T cells (Treg)

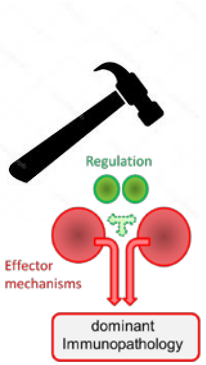
Problem:

Increasing prevalence of immune diseases (>10% of chronic diseases), Burden: >100 bn €/a EU[1]

Solution:

Reshape immune balance by Regulatory T cells (Treg)





Current strategy:
Control of dominant immunopathology by chronic multi-drug treatment

Aim:
ReSHAPE immune balance

[1]DG INTERNAL POLICIES
Workshop 2017
Autoimmune Diseases

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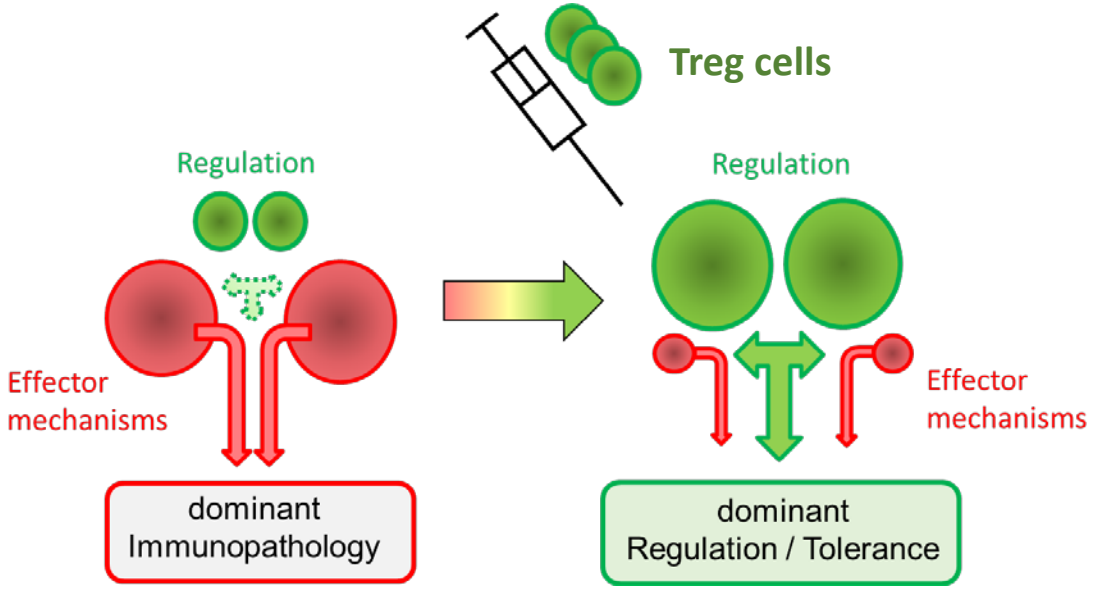
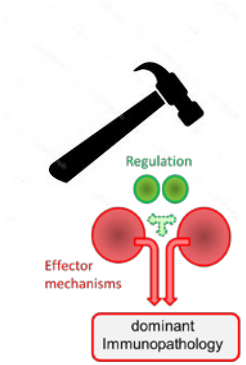


⇒ Transplantat Rejection
⇒ Autoimmunity
⇒ Autoinflammation
⇒ Regenerative Medicine incl. Gene Therapy

One Master Cell Product – Many Applications



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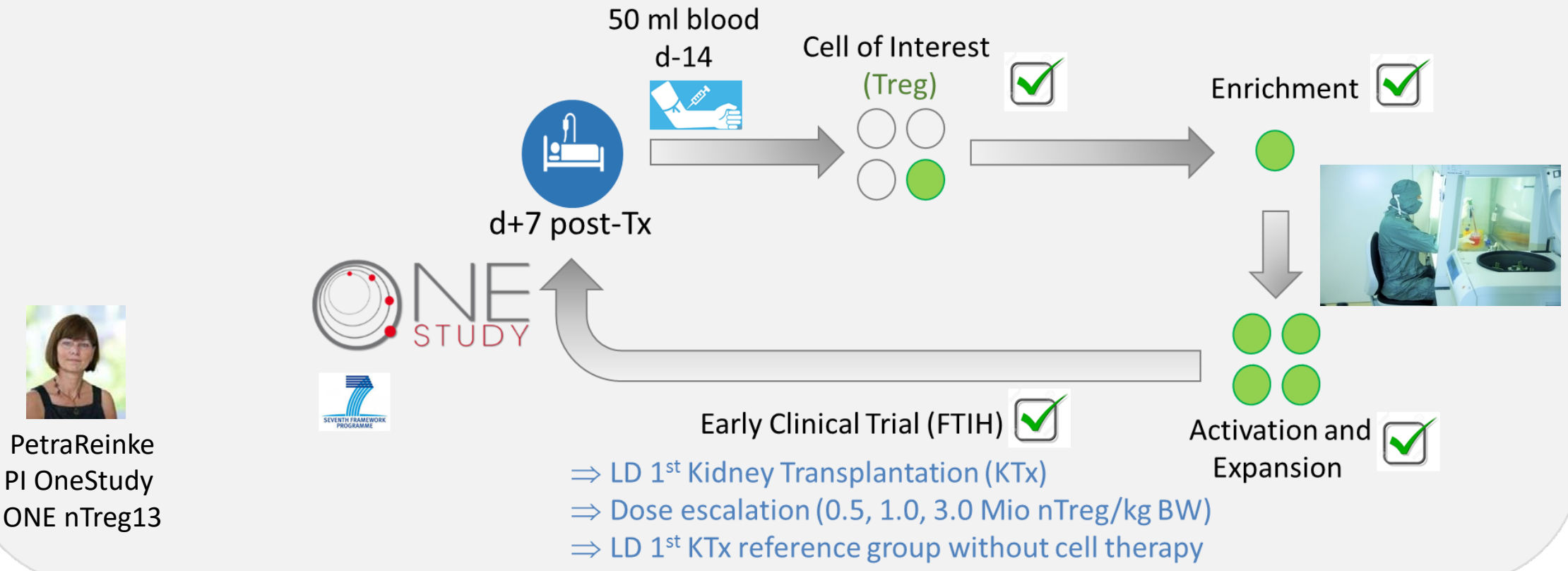
[1]DG INTERNAL POLICIES Workshop 2017 Autoimmune Diseases

ReSHAPING undesired immune reactions by regulatory T cells (Treg)

First-Time-In Human: our 1st generation regulatory T cell product

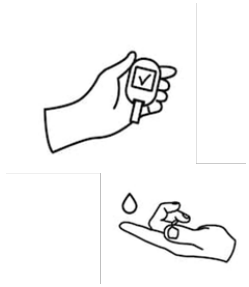
(Polyclonal CD25++FoxP3+CD4+ Treg)



PetraReinke
PI OneStudy
ONE nTreg13

Exemplary Case: My life is better by reshaping immune system

Kidney Transplan-tation



T1 Diabetes

Cardio-myopathy

Chronic Kidney Failure

Dialysis

1995 2015 03 / 2015 04/2015 10/2015 2019

Standard of Care

Lifelong Multidrug Therapy
(>30 pills/day)
adverse effects, costs, quality of life

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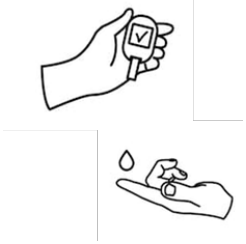
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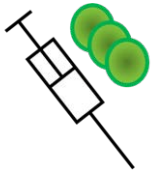

Regulatory T cell Therapy

1995 — 2015 — 03 / 2015 — 04/2015 — 10/2015 — 2019

ONE STUDY

SEVENTH FRAMEWORK PROGRAMME

Minimizing Immunosuppression

⇒ 3 pills/d instead >30 pills/d

⇒ safe (no infection, no cancer)

⇒ excellent graft function (creatinine 1.1)

Standard of Care

Lifelong Multidrug Therapy

(>30 pills/day)

adverse effects, costs, quality of life

Switch to FK monotherapy in the Treg therapy group is feasible (FIH phase I/IIa study)

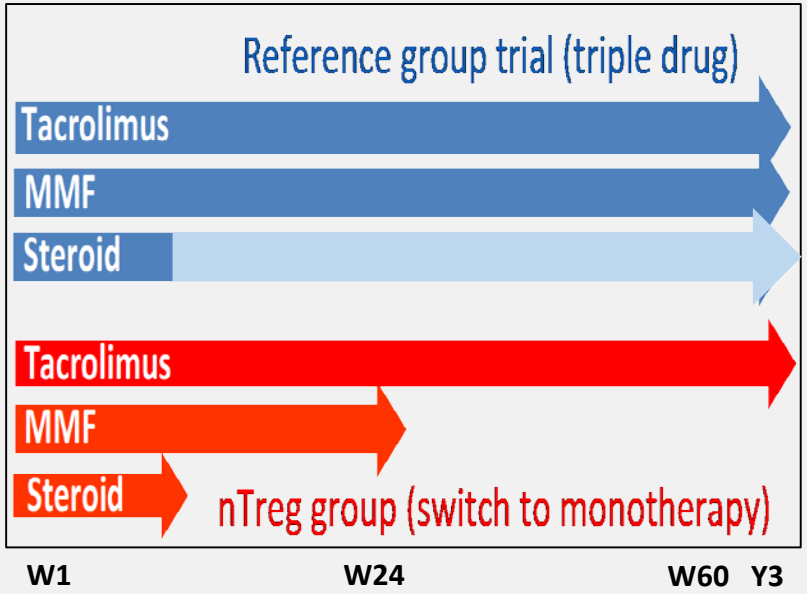
Promising clinical results in LD kidney transplant patients

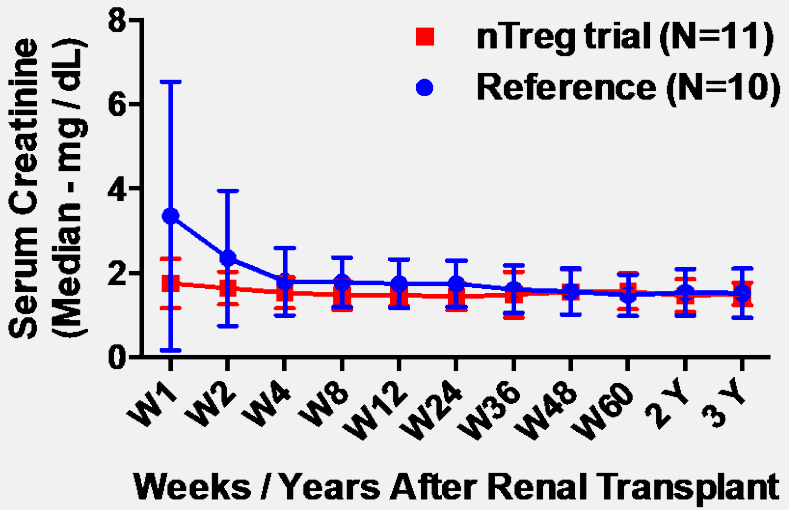
⇒ Safe

⇒ hints of efficacy

triple immunosuppression

=> FK monotherapy





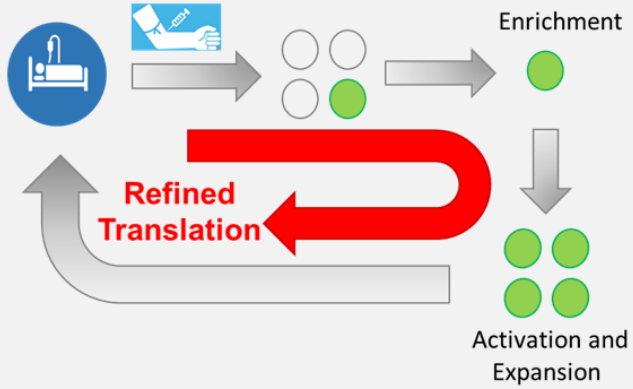
Refined Translation – from bed to bench and back to bed
next generation regulatory T cell (Treg) approaches

ONE STUDY

1st generation Treg is promising but there is space for improvement
=> Refined Translation

Promising clinical results in LD kidney transplant patients
⇒ Safe
⇒ hints of efficacy
triple immunosuppression
=> FK monotherapy

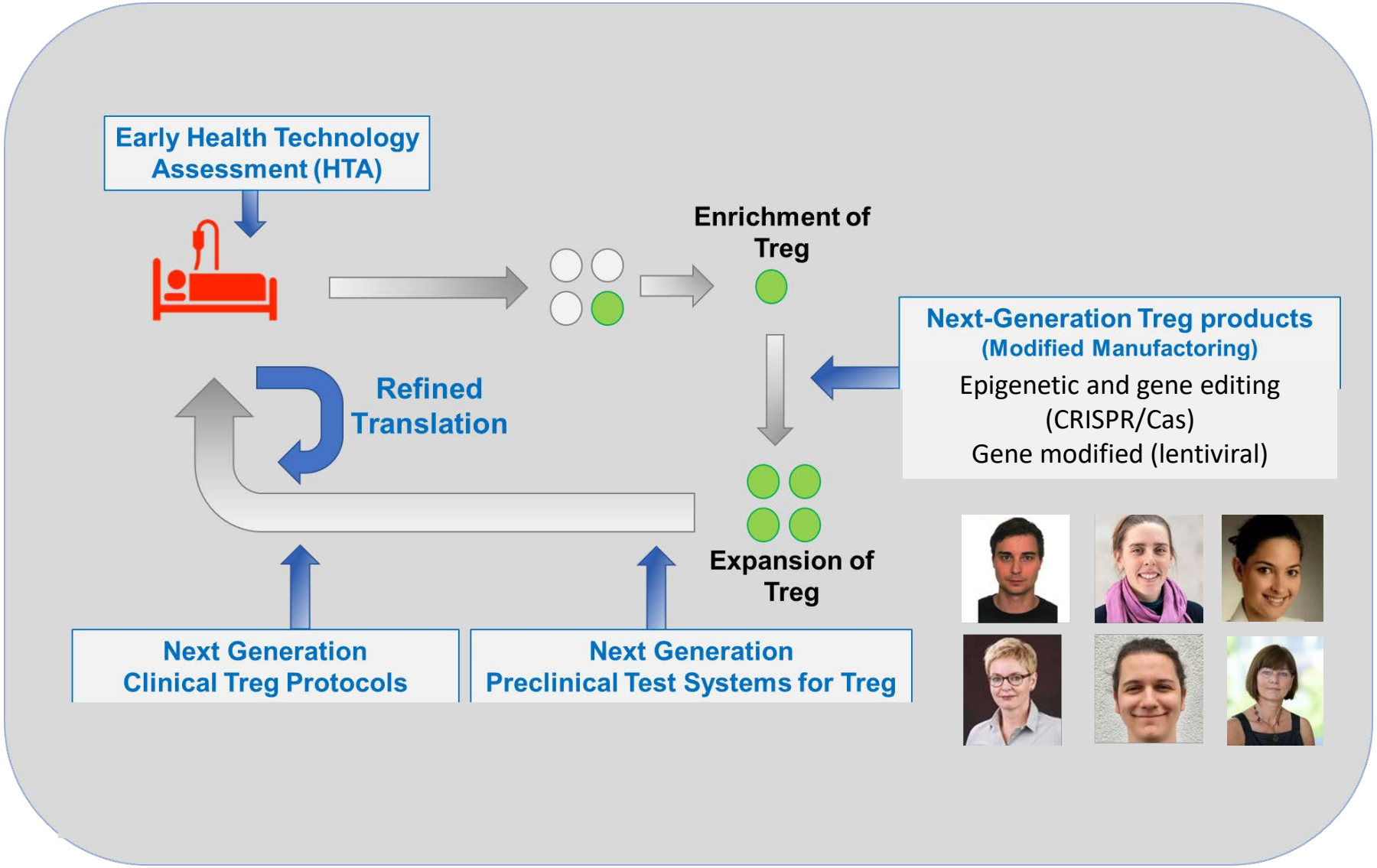
In-depth analysis of product and patient response:
⇒ 3/11 clinical non-responders who required switch back to standard immunosuppression
⇒ temporary expansion of Treg cells only
⇒ No dose-relationship of effects
⇒ No hints for tolerance (Tac monotherapy is required)



ReSHAPE

Horizon 2020 EU project
Coordinator: P Reinke

Refined Translation – from bed to bench and back to bed
next generation regulatory T cell (Treg) approaches



H2020

Next-generation CRISPR/Cas modified CNI - resistant Treg

Next generation T cell products:

(M. Schmück-Henneresse / D. Wagner / L. Amini)

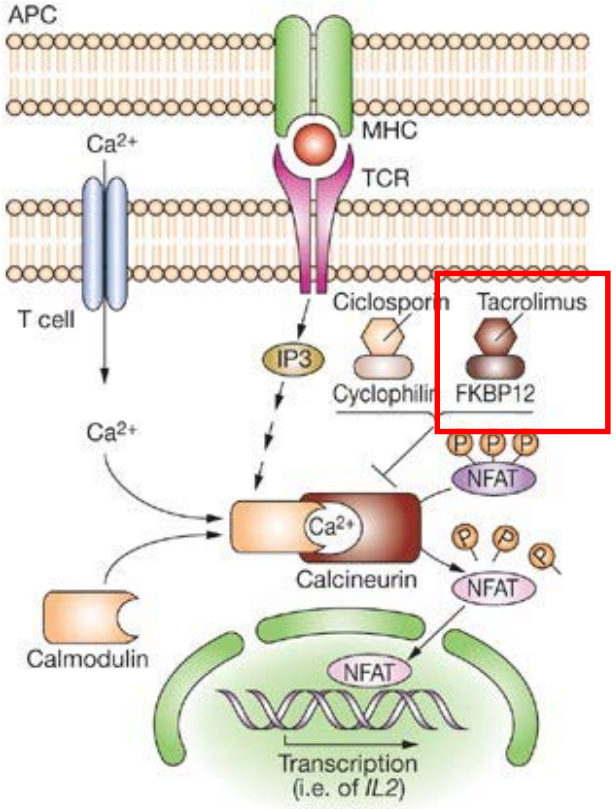
Michael Schmück-Henneresse
Junior Group Leader

Leila Amini

Ghazaleh Zarrinrad

Dimitrios L Wagner

Desiree J. Wendering



Problem:
Basal immunosuppression (tacrolimus) inhibits also Treg

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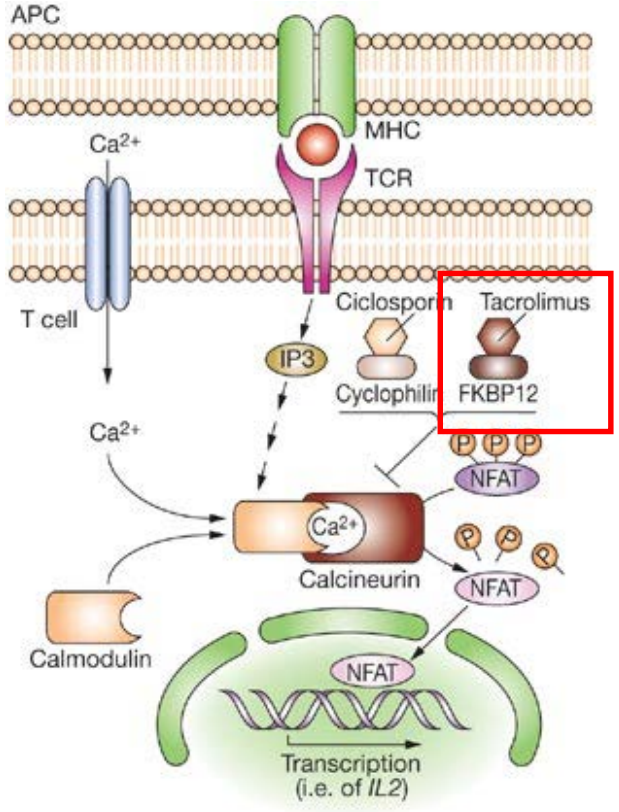


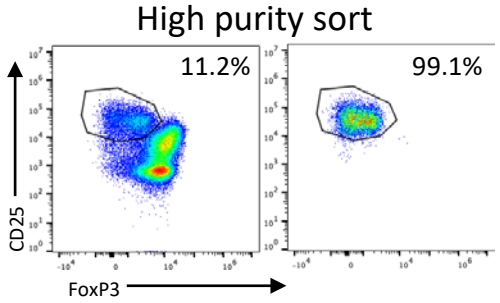
Problem:
Basal immunosuppression (tacrolimus) inhibits also Treg

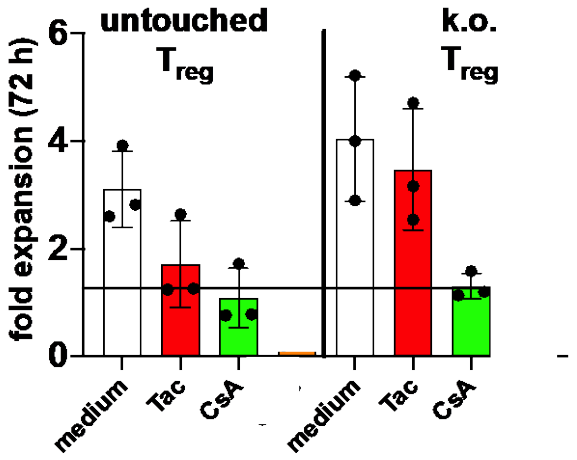
Tacrolimus-resistant FKBP12$^{-/-}$ T_{REG}

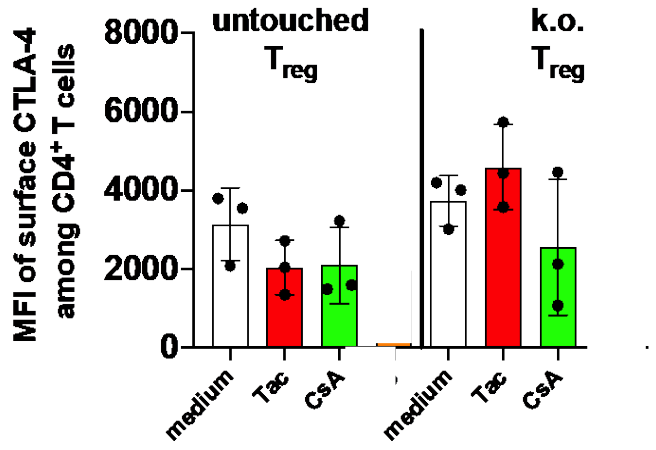
d7 of T_{REG} culture
Vector-free
CRISPR/Cas9-mediated
FKBP12-KO

Gundry MC et al. Cell Report 2016

High purity sort







Effective *in vitro* expansion and CTLA4 Expression of KO-T_{REG} under Tacrolimus but inhibition by CSA (safety switch)

Next-generation CRISPR/Cas modified CNI - resistant Treg

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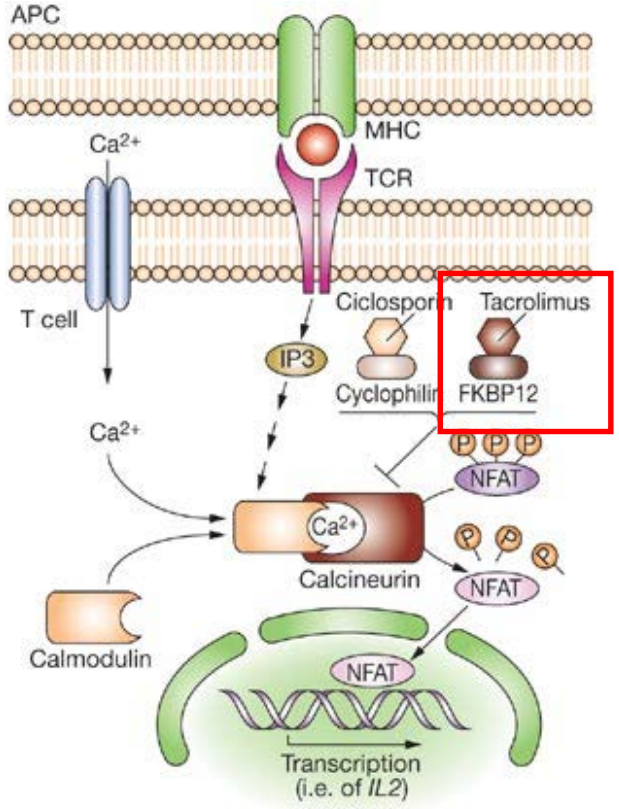

Problem:
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Tacrolimus-resistant FKBP12$^{-/-}$ T_{REG}

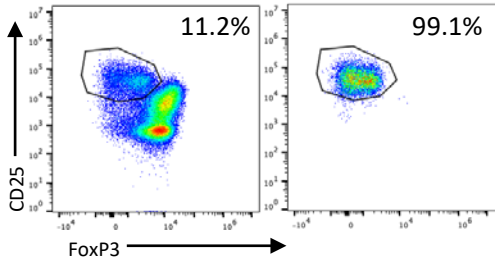
CRISP

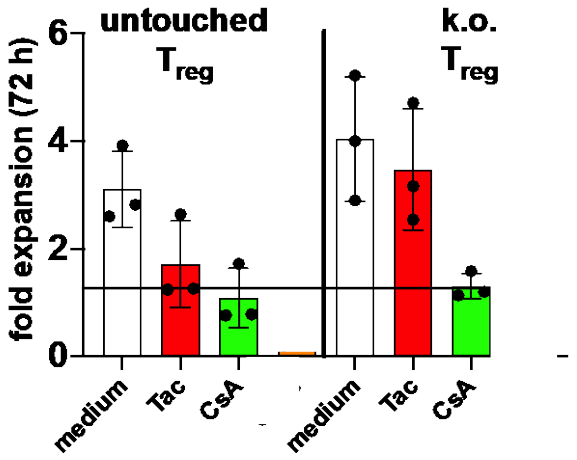
d7

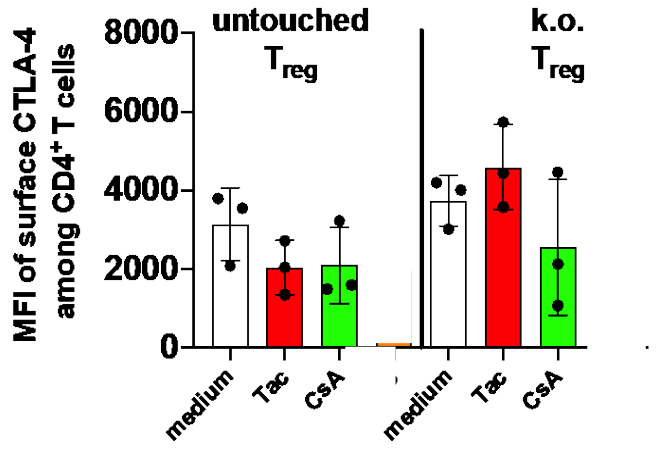
ProTac
FIH-Trial
2020/1

Cell Report 2016

High purity sort

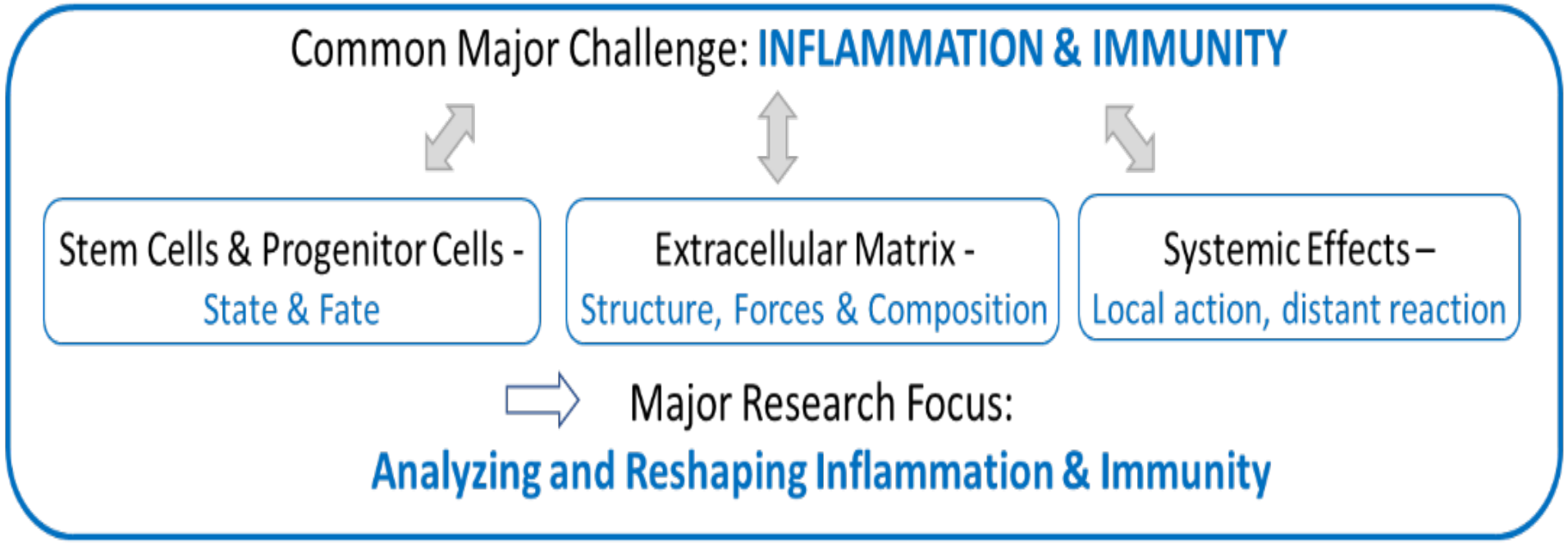






Effective *in vitro* expansion and CTLA4 Expression of KO-T_{REG} under Tacrolimus but inhibition by CSA (safety switch)

Inflammation/Immunity – a major common challenge



Goal:

to support endogenous regeneration and
to improve engraftment and function of biological replacement strategies

Challenges:

"Aged" immune system, **Immunogenicity of Therapeutics**, Reshaping Immune Response

Problem: Pre-immunity to SpCas9

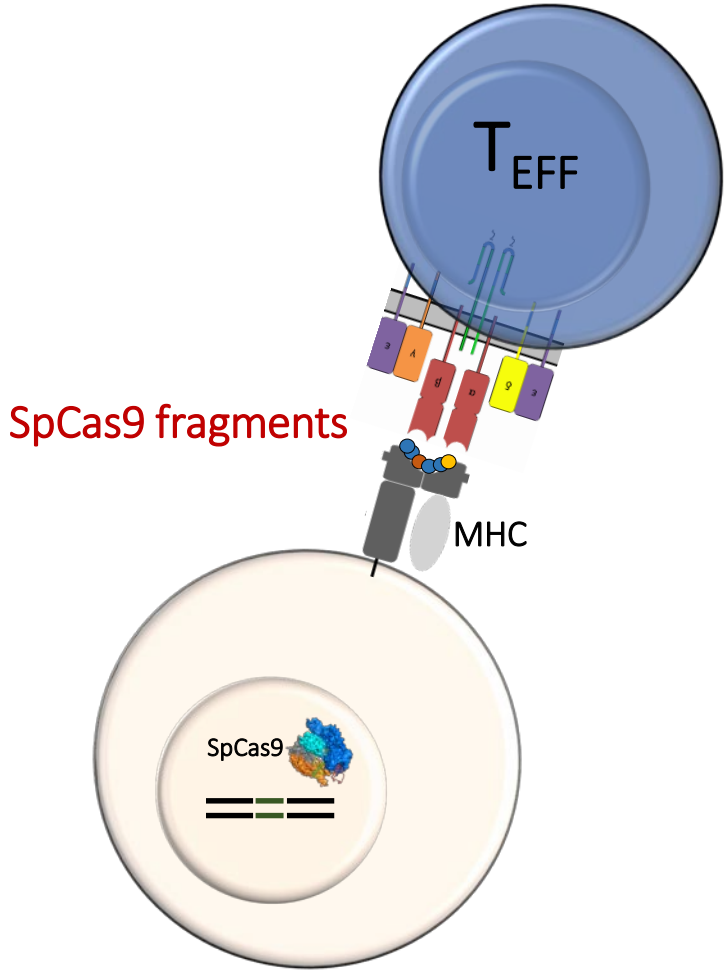
Michael Schmück-Henneresse
Junior Group Leader

Leila Amini

Ghazaleh Zarrinrad

Dimitrios L Wagner

Desiree J. Wendering



Gene-edited Cell
SpCas9-peptide presentation

nature medicine
LETTERS
https://doi.org/10.1038/s41591-018-0204-6

High prevalence of *Streptococcus pyogenes* Cas9-reactive T cells within the adult human population

Dimitrios L. Wagner[1,2,3], Leila Amini[1,2], Desiree J. Wendering[1,2], Lisa-Marie Burkhardt[1], Levent Akyüz[1], Petra Reinke[2,4], Hans-Dieter Volk[1,2,4,5] and Michael Schmueck-Henneresse[1,2,4,5*]

Pre-formed SpCas9-reactive Teff cells regonize CRISPR/Cas edited cell products

⇒ Release of inflammatory cytokines
⇒ Killing of gene-edited cells

Problem: Pre-immunity to SpCas9

Michael Schmück-Henneresse
Junior Group Leader

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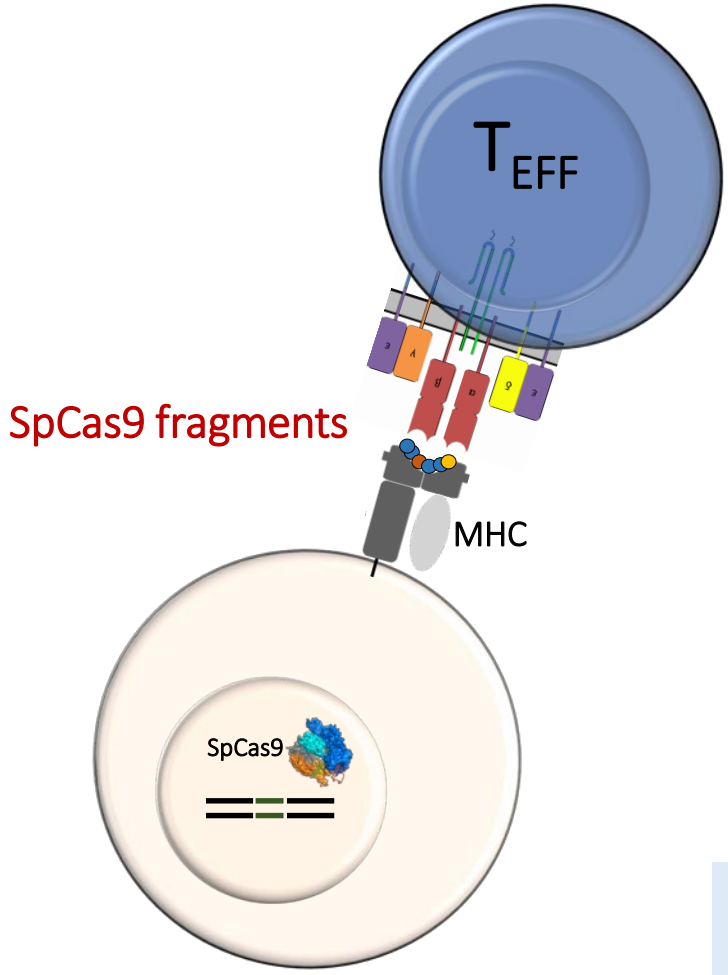

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Pre-formed SpCas9-reactive Teff cells regonize CRISPR/Cas edited cell products

⇒ Release of inflammatory cytokines
⇒ Killing of gene-edited cells

Problem solutions

Test for detecting „fading-out“ Cas peptides

Cas-specifc Treg

Problem: Pre-immunity to SpCas9

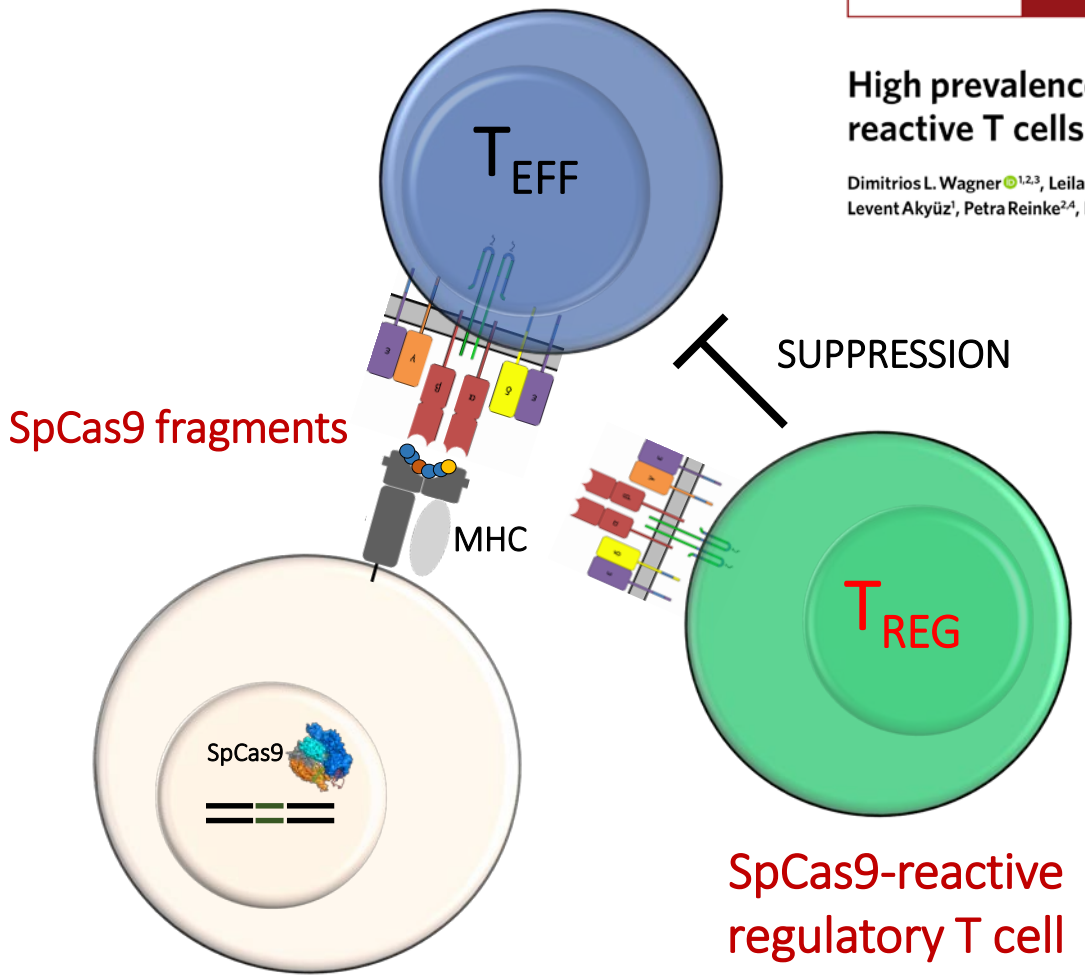
Michael Schmück-Henneresse
Junior Group Leader

Leila Amini

Ghazaleh Zarrinrad

Dimitrios L Wagner

Desiree J. Wendering



Gene-edited Cell
SpCas9-peptide presentation

SpCas9-reactive regulatory T cell

nature medicine
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SpCas9-specific **Treg cells** regonize CRISPR/Cas edited cell products and **inhibit**

⇒ release of inflammatory cytokines
⇒ killing of gene-edited cells

Conclusions for BIH/Charité Translation Strategy

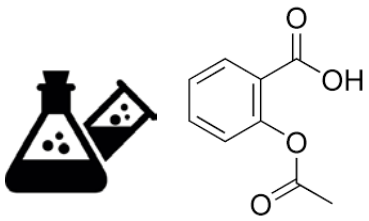
1. SPF housing limits the value of many experimental models as predictive disease models
   ⇒ Need for controlled „dirty“ housing at Charité/BIH

2. Reshaping immune responsiveness is a key element to support endogenous regeneration as well as engraftment of tissue replacement approaches that requires *in-depth* immune biomarker analyses
   ⇒ Need for high-end immune biomarker unit *(spin-off CheckImmune)*

3. Immune (cell) therapy is one of the most dynamic fields in medicine with high translational potency at academic centers
   ⇒ Need for developing a Hub (Be*CAT* + spin-off incubator + biotech/pharma) on Advanced Therapies at Charité/BIH

The Novel Class of „Living“ Drugs (Advanced Therapies) – a Game Changer

since >120 years

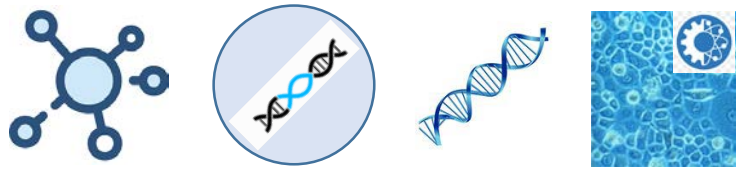


Defined, chemically produced
Small Molecules

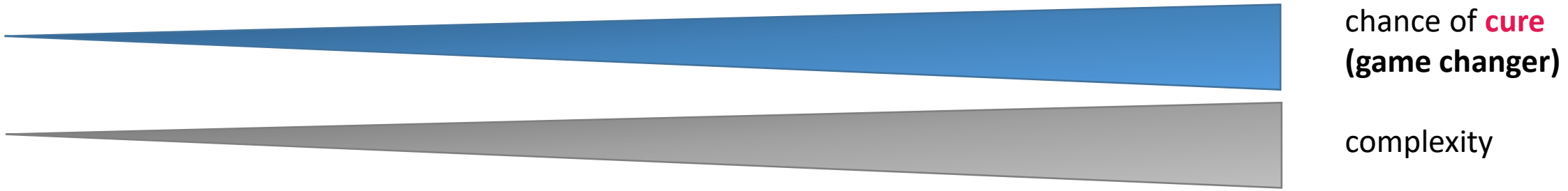
since >30 years

Protein-based drugs
produced in living cells
Biologics

since >10 years



“Living” drugs
(somatic cells, gene modified cells, in vivo gene therapy, engineered tissues)
Advanced Therapies (ATMP)



Complexity of chronic diseases requires complex therapeutic approaches

Advanced Therapies – not just a dream, it is already "reality"

1,069
Clinical Trials
underway worldwide
by end of Q2 2019

Phase I: 358
Phase II: 617
Phase III: 94

Gene Therapy

366

Gene–modified Cell Therapy

410

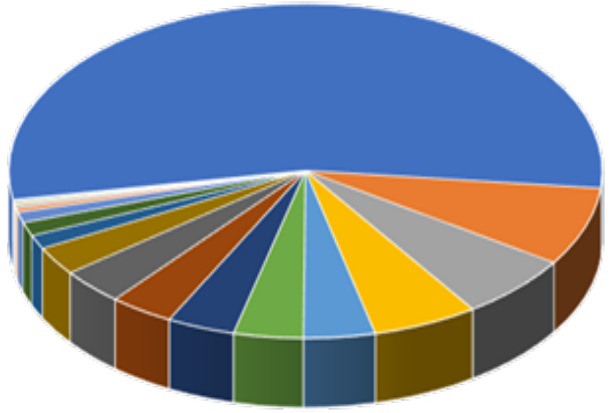
Somatic Cell Therapy

249

Tissue Engineering

44

Clinical Trials by Indication



- 1 Oncology
- 2 Cardiovascular
- 3 Musculuskleletal
- 4 Central Nervous System
- 5 Endocrine, Metabolic & Genetic Disorders
- 6 Dermatology
- 7 Hematology
- 8 Immunology & Inflammation
- 9 Ophthalmology
- 10 Infectious Diseases
- 11 Genitourinary Disorders
- 12 Gastroenterology
- 13 Respiratory Diseases
- 14 Surgery
- 15 Lymphatic Diseases
- 16 Ear Diseases
- 17 Geriatric Diseases
- 18 Radiation Diseases

2019: about a dozen products approved in Europe
(marketing authorization)

Alliance Regenerative Medicine Report Q2 2019

„Living“ Drugs (AT) – a **disruptive innovation** shattering current paradigms

drug discovery

drugs raw material

manufacturing

preclinical models

clinical trial design

pharmacokinetics pharmacodynamics

mode-of-action multiple effects

scaling-up

supply chain

ethics

complex data at all TRLs

health economy/ reimbursement

business models

Spin-off of BCRT: Berlin Center for Advanced Therapies (BeCAT)

CHARITÉ BeCAT BIH Regeneration
BIH Center for Regenerative Therapies (BCRT)

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN
BERLIN INSTITUTE OF HEALTH Charité & Max Delbrück Center

Peclinical Research on new Advanced Therapies

Research Areas:
RegMed & ImmunOnco

Research Module: **Cell products for supporting endogenous regeneration**

Research Module: **Tissue Engineering / combinatory products (bio-MD)**

Research Module: **Cell-based Gene Editing**

Research Module: **Targeted tumor therapy by immune cells**

BeCAT BERLIN CENTER FOR ADVANCED THERAPIES

Research Platform: **Manufacturing – Development & Quality Control**

Research Platform: **Biomarker – Development & Application**

Research Platform: **Clinical Development & Regulatory Affairs & Health Economics**

Regulatory Authorities (PEI/EMA, LaGeSo)

Refined Translation

Clinical Research Early Clinical Trials

First-in-Human, Phase I/IIa, Proof-of-Concept studies

Industry Partnership
Pharma & Biotech
& Technology Providers

Late Clinical Research and Marketing Authorization

§ 91b
Wissenschaftsrat 2017

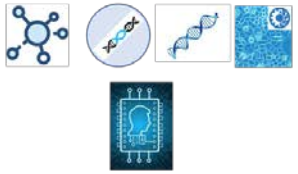
Concept ranked as 1st

30 Mio €
for the „hardware“
GMP-Research Building

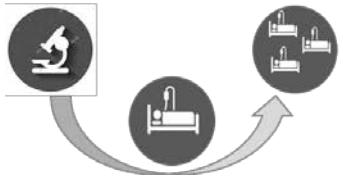
Prof. Dr.med. Petra Reinke

High need for targeted efforts and a sustainable **large-scale research initiative** in Europe

Transdisciplinarity



Technology

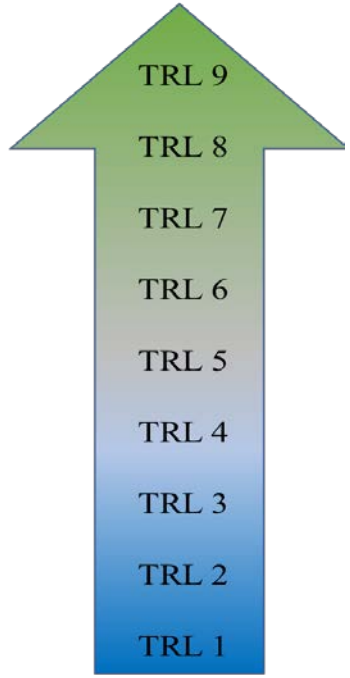


Translation

Academia-Industry **Partnership**

Alliances with **Patients,** Patient Advocates and General Practitioners

outgrowing commercial infancy



More
Faster
Successful
Affordable
Accessible

REBOOTS

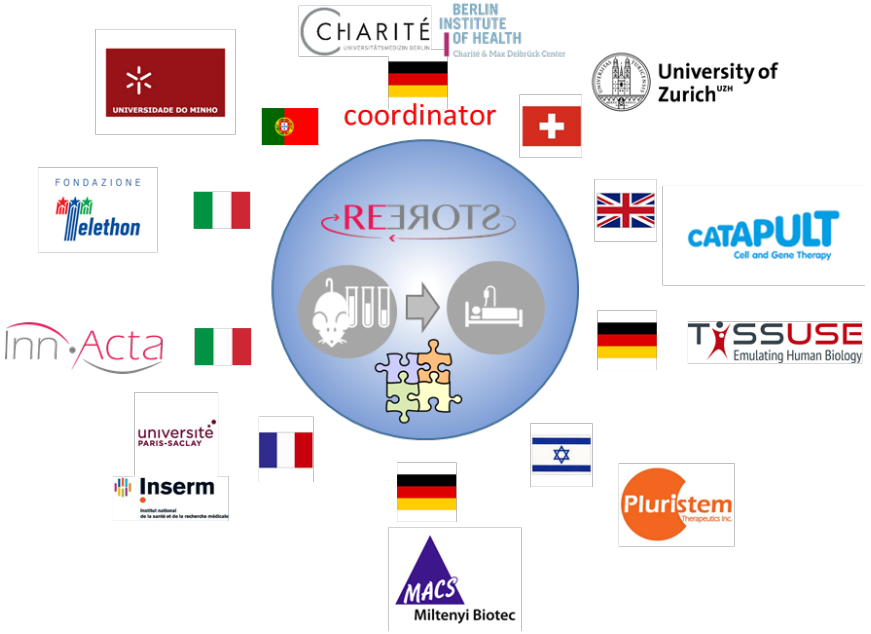
Mission:
Building-up an ecosystem to

Overcome the technological and regulatory roadblocks for Advanced Therapies in Europe and Deliver a pipeline of dozens of revolutionary Advanced Therapy products by 2030

Who is behind the RESTORE community ?

Core Team

(Academic Centers & Biotech/Non-for-profit org.)



Supporters

>300 from 21 countries

(EU-MS, EU-AC, USA, Canada, Singapur)

61% Academia, 22% Industry, 10% Networks, 7% Non-profit organizations

Active contribution of the whole RESTORE community
to the tasks of the 17 Working Groups in refining the roadmap
(256 involved; range 26-118 contributors / working group)

Key Elements to support Advanced Therapies in a new way

Bilateral interaction with Regulatory Bodies at national/EU level

Coordination & Support Action (CSA)

transparent and dynamic governance

Academic, Industry, Patient and Public Society

Structured Research and Innovation Actions (RIAs)

Infrastructure (Translational Hub´s)

Technology Research & Innovation Platforms

Private Public Partnership and innovative SMEs

Suitable Horizon Europe Programme Elements for RESTORE:

- European Regional Development Fund
- European Innovation Ecosystems & EIT Health
- European Innovation Council (EIC)
- RIA´s within Cluster Health
- Partnership Innovative Health Initiative
- Mission Cancer

RESTORE - Health by Advanced Therapies

https://restore-horizon.eu

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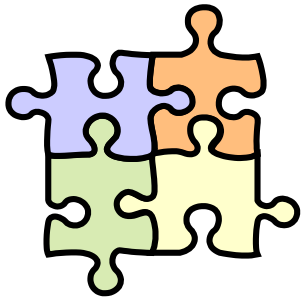
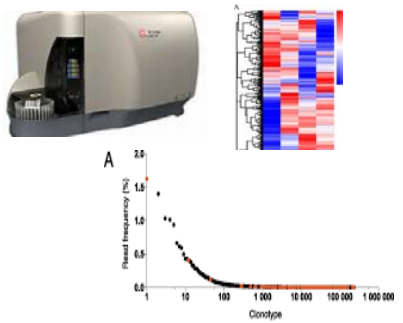
   ⇒ Need for developing a Hub (Be*CAT* + spin-off incubator + biotech/pharma) on Advanced Therapies at Charité/BIH

4. Immunology is a major common challenge for Regenerative Therapies and a research focus at the BCRT with internationally recognized USP
   ⇒ Need for adequate appointment policy

Acknowledgement





GMP

Petra Reinke
Sybill Landwehr Kenzel
Daniel Kaiser
Andy Roemhild
Carola Beier
Henrike Führer
Anne Forke
Insa Lehmann
…

Biomarker & Preclinics

Birgit Sawitzki
Nina Babel
Michael Schmueck-Henneresse
Dimitrios Wagner
Leila Amini, Ghazaleh Zarrinrad
Desiree Jaqueline Wendering
Mathias Streitz, Kerstin Jülke,
Gerald Grütz, Levent Akyüz
Christian Meisel + LB Immunology Team

Clinical Trial(s)

Petra Reinke
Mohamed Abou El-Enein
Sybill Landwehr-Kenzel
Anett Sefrin
Cordula Giesler
…

Physicians & Nurses

Funding (big elephant in the room)

Federal Ministry for Education & Research (BMBF)
European Union FP7 and H2020 projects
German Council of Science and Humanities §91b

Patients