What does it take to translate?
Lessons learned in Regenerative Medicine

Duda GN. [1,2,4], Petersen A[1,2], Brauer E[1,2], Cipitria A[1,2,],Checa S[1,2], Soodmand E[1,2], Volk HD. [2,3], Schmidt-Bleek K.[1,2], Bucher CH.[1,2]

[1] Julius Wolff Institute and Center for Musculoskeletal Surgery

[2] Berlin Institute of Health Center for Regenerative Therapies

[3] Institute for Medical Immunology

[4] Wyss Institute for Biologically Inspired Engineering, Harvard

Charité - Universitätsmedizin Berlin

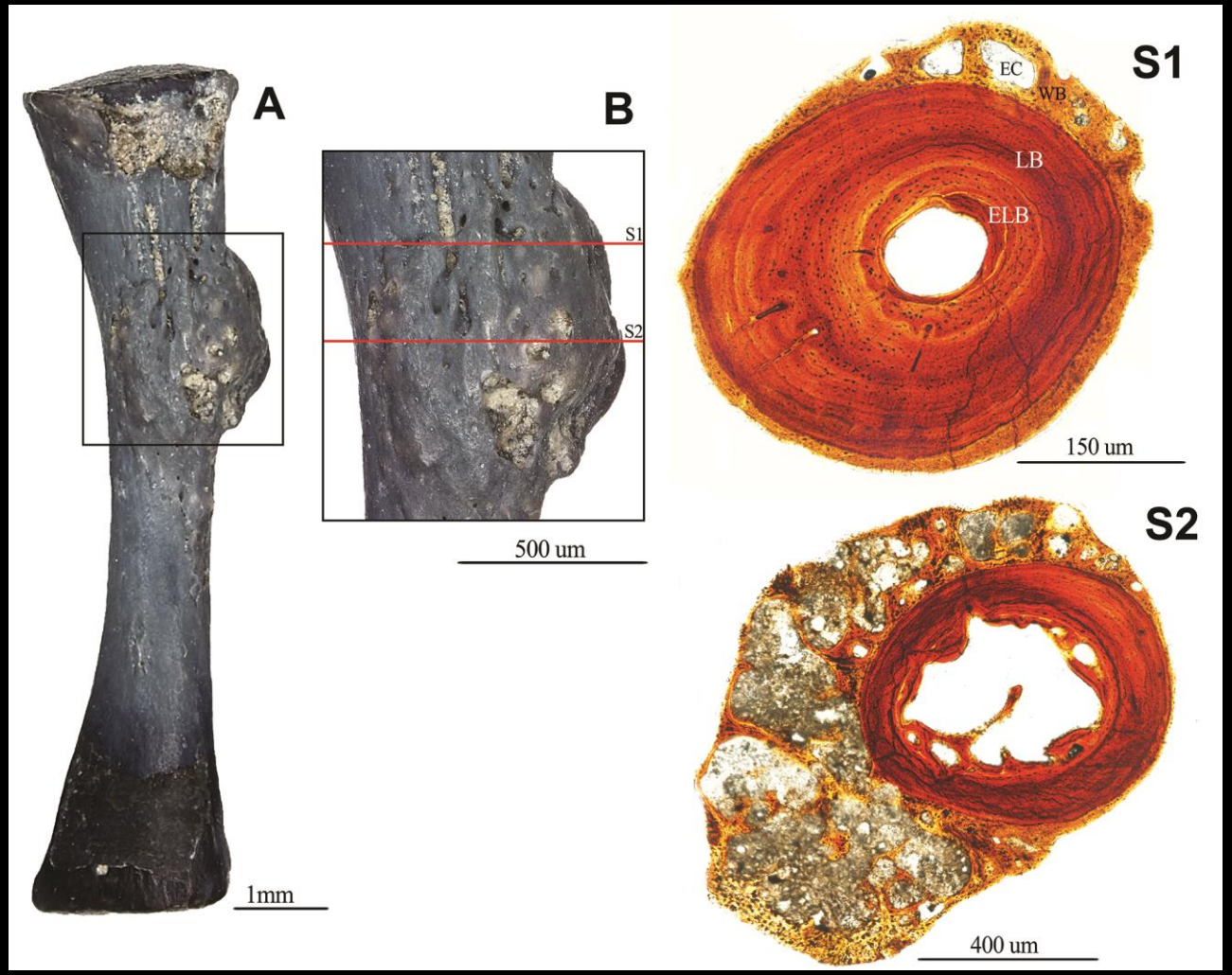
Charité

Julius Wolff (1836 – 1902)

1860	Medical training at the Charité
1890	Foundation 1st Clinic for Orthopaedic Surgery at the Charité
1892	Most relevant orthopaedic publication: "The Law of Transformation of Bone" („Das Gesetz der Transformation der Knochen")
1902	Initiation of the German Orthopaedic Society
2008	Foundation of the Julius Wollf Institute

Regeneration - complete

Regeneration - conserved



Clinical relevance of bone healing research

- Up to 10 % of fx patients experience delayed or non-union
- Real delayed healing ratio higher but unknown
- With aging population, fx numbers will increase
- In elderly patients, delayed or unsatisfactory fracture healing outcome is rising

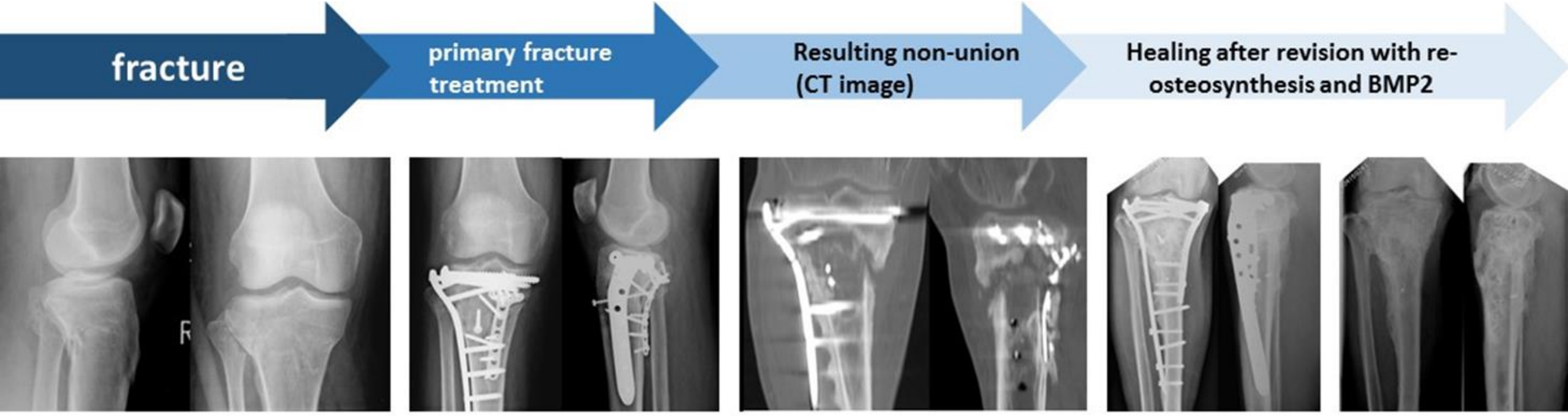
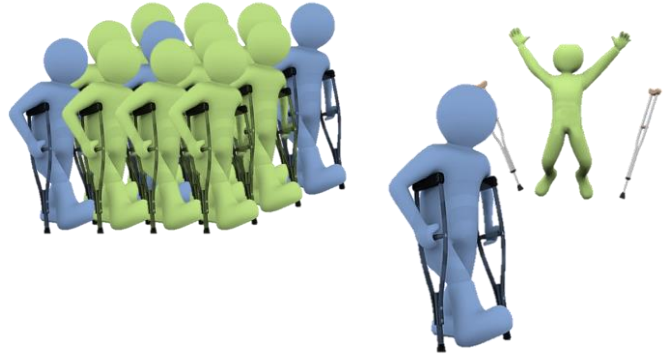


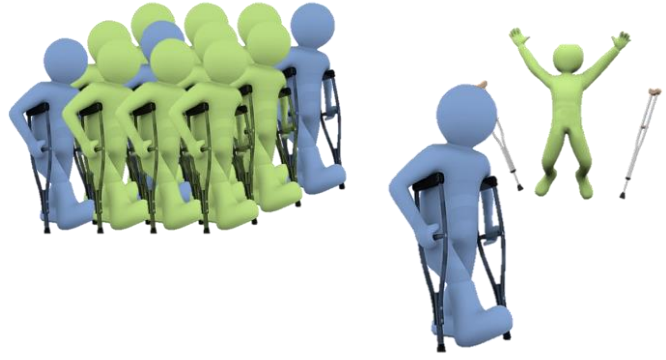
Image adapted from Schmidt-Bleek et al., 2015, CGFR

What are we known for…?



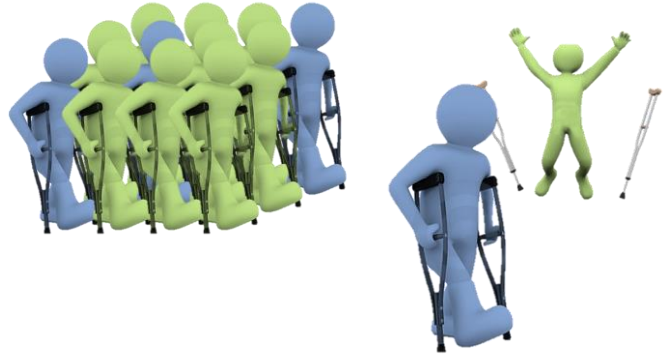
- **New, globally accepted treatment concepts**
  based on results from KFO 102, SFB 760, FOR 2165
- **Translation requires crossing borders**
  medical need – mechanistic knowledge – technology innovation – dissemination – acceptance
- **Translation is…**
  first in patient?

What are we known for…?



- **New, globally accepted treatment concepts**
  based on results from KFO 102, SFB 760, FOR 2165
- **Translation requires crossing borders**
  medical need – mechanistic knowledge – technology innovation – dissemination – acceptance
- **Translation is…**
  reimbursement established?

What are we known for…?



- **New, globally accepted treatment concepts**
  based on results from KFO 102, SFB 760, FOR 2165
- **Translation requires crossing borders**
  medical need – mechanistic knowledge – technology innovation – dissemination – acceptance
- **Translation is…**
  establish a new standard of care?

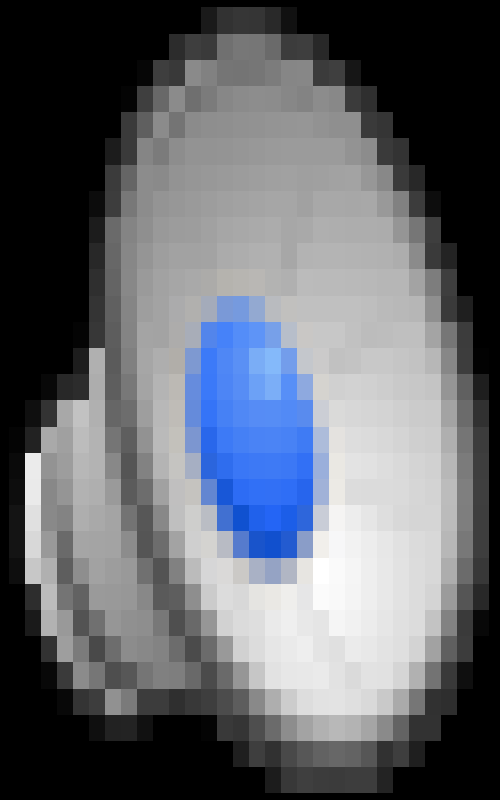
What are we known for…?

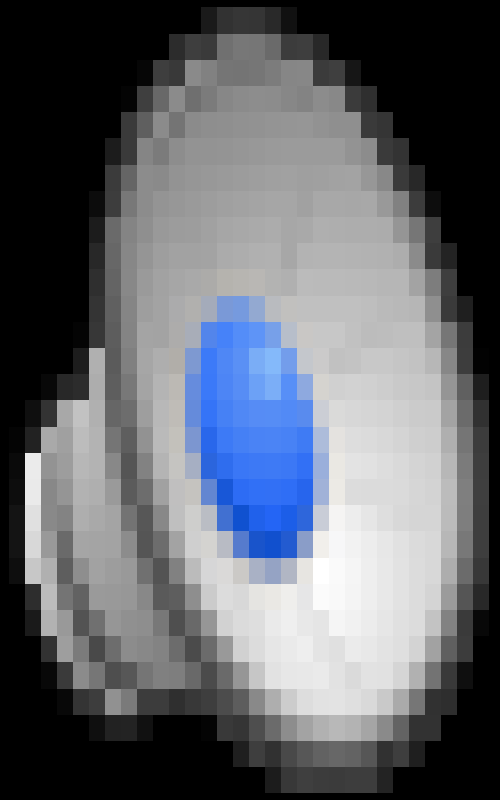
Hip Joint

10 patients (8m/2w) age: 50 - 68 years

Knee Joint

9 patients (6m/3w) age: 60 - 75 years





What are we known for…?

Globally used reference https://orthoload.com/

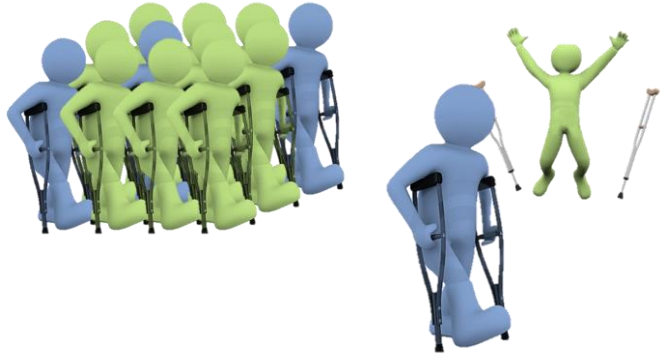
Basis for pre-clinical assessments of any new device (ASTM, ISO) and failure analyses

Lessons learned…

- Academy is thrilled by the new and unknown
- Industry is eager in novelty but with clear de-risking strategy
  - reliable information/knowledge/technology
  - that easily integrates into existing processes

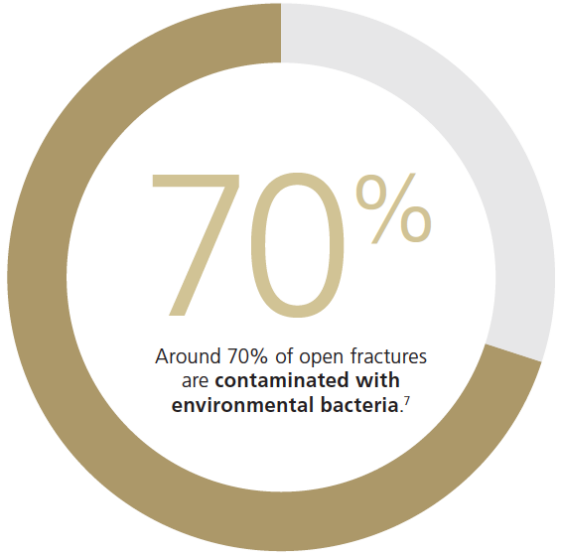
  - new knowledge: Helps to compensate or reduce existing risks
  - new product: Substantially progresses towards reduced risk

What are we known for…?



- **New, globally accepted treatment concepts**
  based on results from KFO 102, SFB 760, FOR 2165
- **Translation requires crossing borders**
  medical need – mechanistic knowledge – technology innovation – dissemination – acceptance
- **Translation is…**
  establish a new standard of care?

What are we known for…?



Expert Tibial Nail PROtect

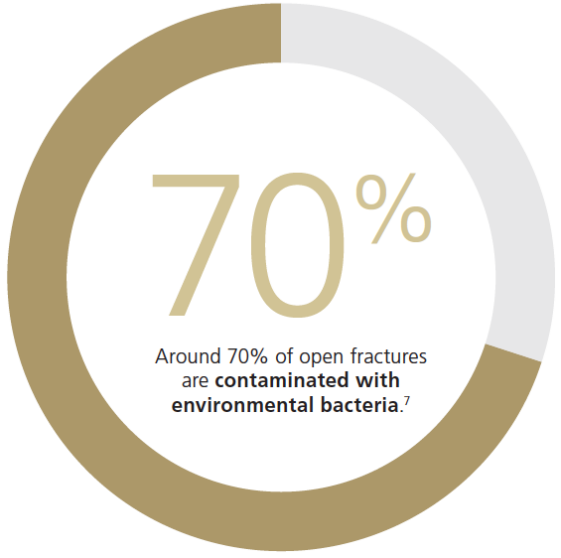
Enhance your first line of defense

DePuy Synthes
PART OF THE Johnson&Johnson FAMILY OF COMPANIES

What are we known for…?

- **Start 1998**
  adapting a concept established in stents
- **Preclinical studies** (DFG funded)
  - PoC in small and large animal models
- **Patent filed** (release of growth factors)
  - Company licenced
- **Initially: local release of proteins**
  - Freedom of operation?
  - BMP or TGF-ß/IGF-1 each $ 60 Mio
- **Hand over Charité to DePuySynthes**
  - Upscale production
  - FDA approval (20m^2, $20 Mio) each

What are we known for…?



Intended use*

The Expert Tibial Nail PROtect is intended to be used for the surgical treatment and stabilization of fractures of the tibia.

Expert Tibial Nail PROtect

Enhance your first line of defense

DePuy Synthes
PART OF THE Johnson&Johnson FAMILY OF COMPANIES

What are we known for…?

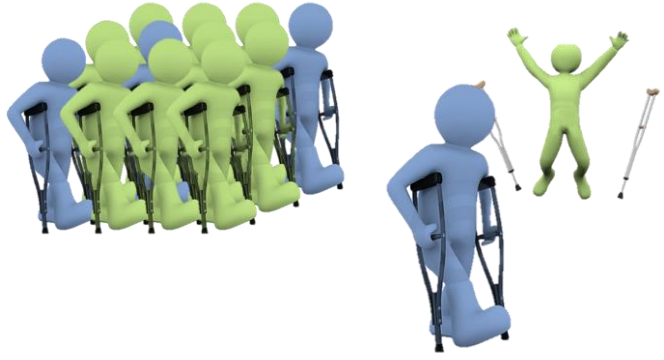
- **Start 1998**
  adapting a concept established in stents
- **Preclinical studies** (DFG funded)
  - PoC in small and large animal models
- **Patent filed** (release of growth factors)
  - Company licenced
- **Initially: local release of proteins**
  - Freedom of operation?
  - BMP or TGF-ß/IGF-1 each $ 60 Mio
- **Hand over Charité to DePuySynthes**
  - Upscale production
  - FDA approval (20m^2, $20 Mio) each
- **BUT: No prove for major claim possible**

Lessons learned…

- Definition of hypothesis is key

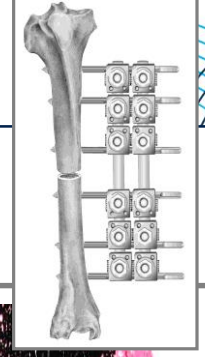
- Early on health economic assessment
- Opportunity check
  - definition of technologies (own IP)
  - “freedom to operate” (other IP)
  - identify stake holders
- Clinical approval pathway(s)

What are we known for…?



- **New, globally accepted treatment concepts**
  based on results from KFO 102, SFB 760, FOR 2165
- **Translation requires crossing borders**
  medical need – mechanistic knowledge – technology innovation – dissemination – acceptance
- **Translation is…**
  establish a new standard of care?

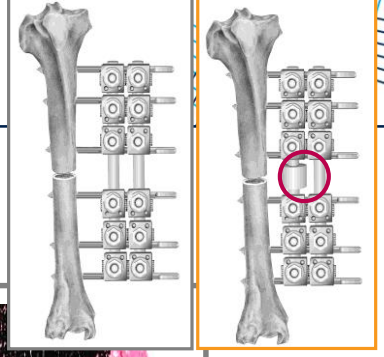
Clinical relevance of bone healing research



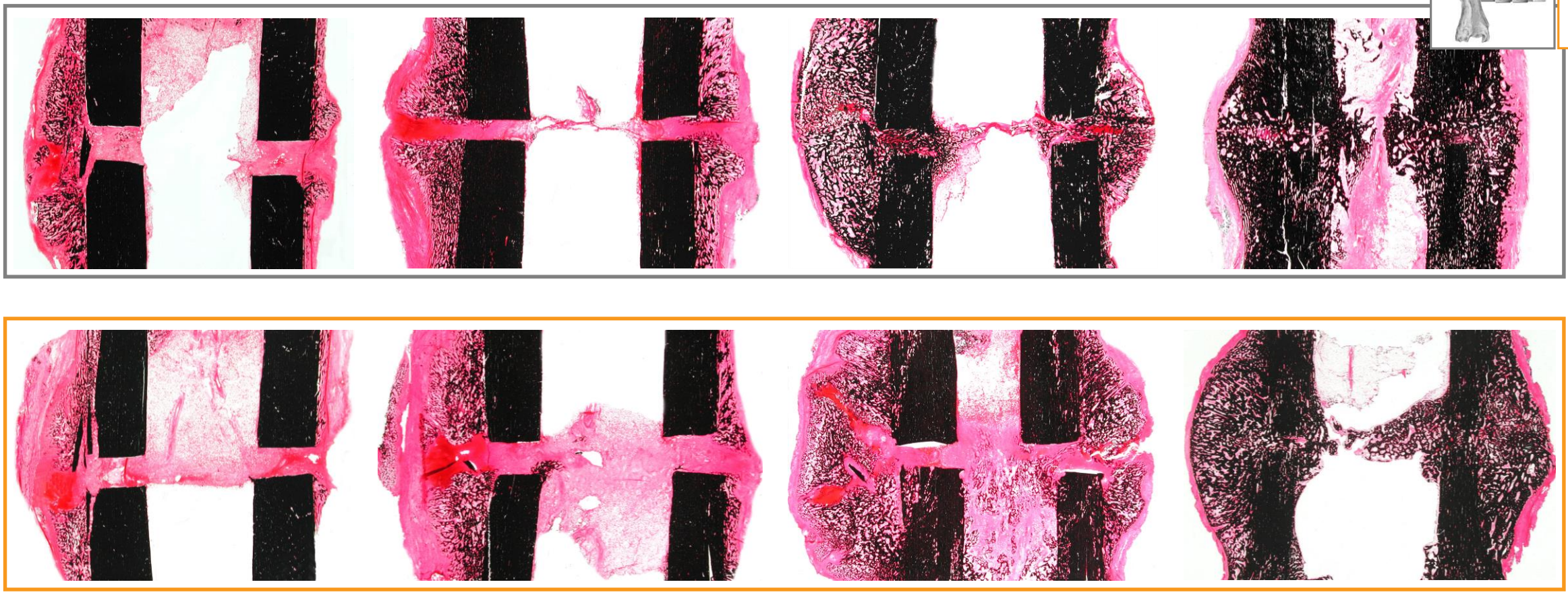
2 weeks | 3 weeks | 6 weeks | 9 weeks

(Schell et al. Bone 2006; Seebeck et al. Bone 2005; Schell et al. J Orthop Res 2005;
Klein et al. J Orthop Res 2004; Klein et al. Calc Tissue Int 2004; Klein et al. J Orthop Res 2003)

Clinical relevance of bone healing research



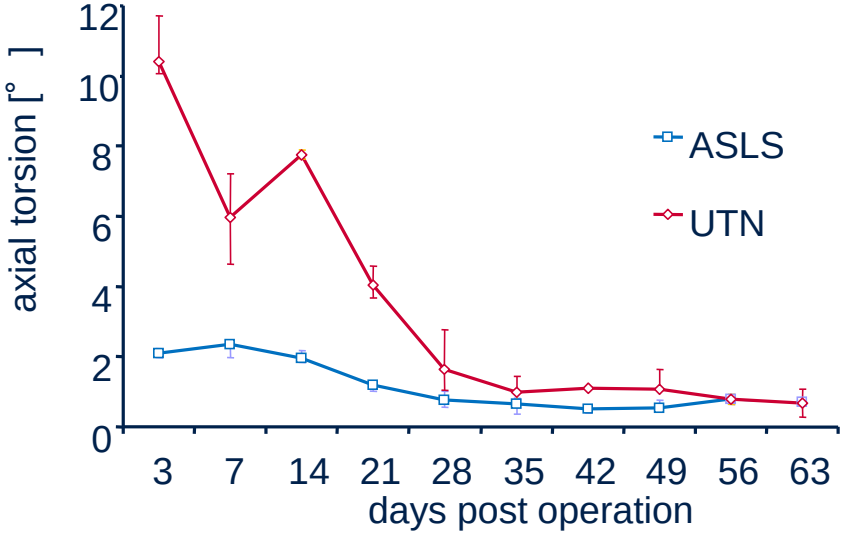
2 weeks | 3 weeks | 6 weeks | 9 weeks



(Schell et al. Bone 2006; Seebeck et al. Bone 2005; Schell et al. J Orthop Res 2005;
Klein et al. J Orthop Res 2004; Klein et al. Calc Tissue Int 2004; Klein et al. J Orthop Res 2003)

Clinical relevance of bone healing research

Lower torsion leads to improved bone healing

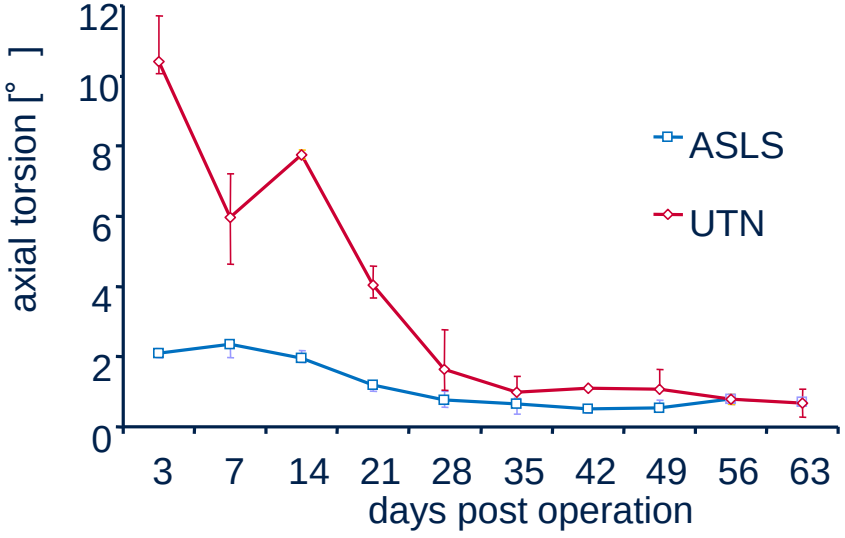


modified thread

standard

Clinical relevance of bone healing research

Lower torsion leads to improved bone healing



Angular Stable Locking System (ASLS). For angular stable locking of intra-medullary nails.

Clinical relevance of bone healing research

Randomized controlled trial (**LoE I**), **N = 142**, multi-center study (8 sites in 3 countries):

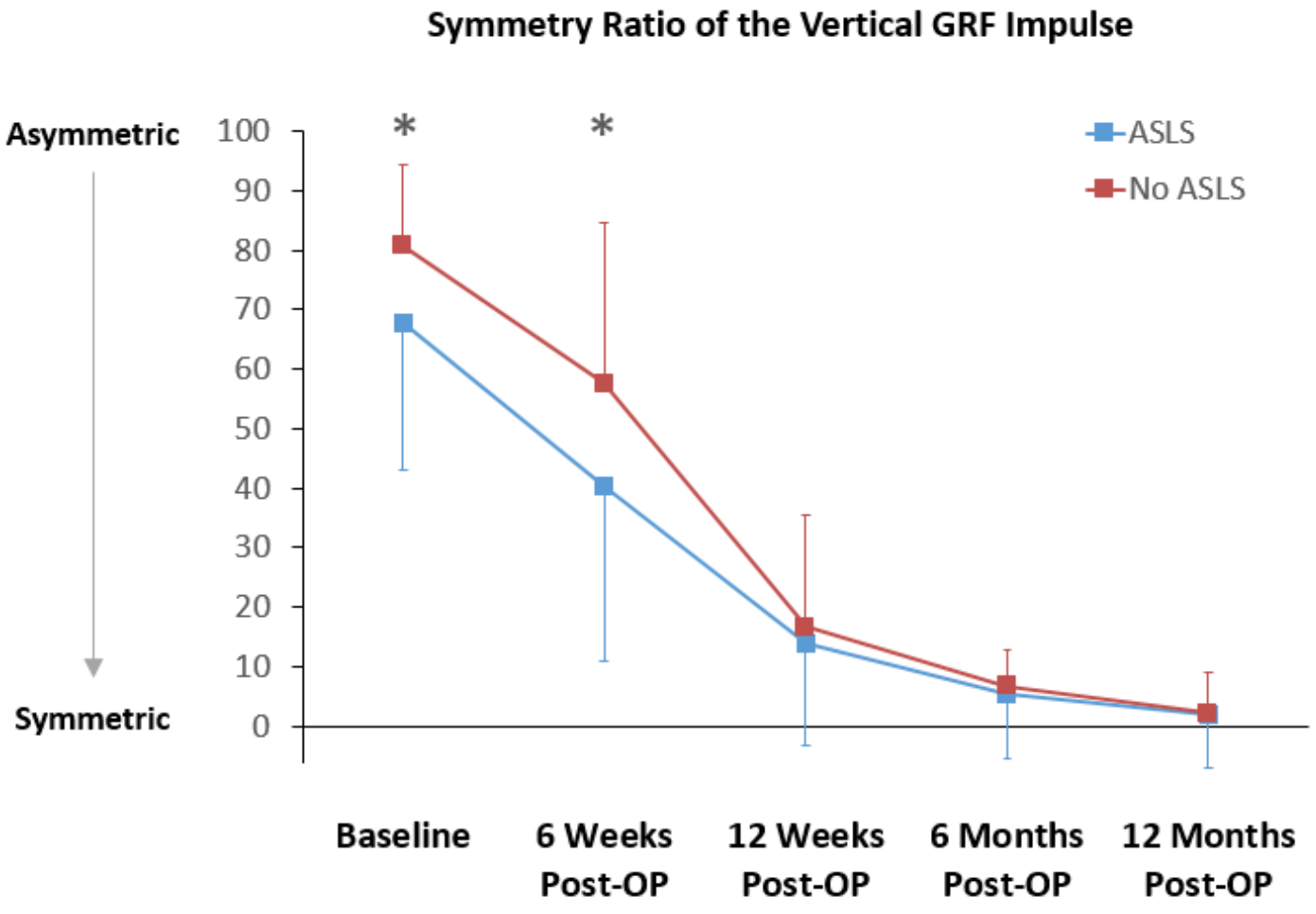
No difference in healing success

Angular Stable Locking System (ASLS). For angular stable locking of intra-medullary nails.

Clinical relevance of bone healing research

Randomized controlled trial (**LoE I**), **N = 142**, multi-center study (8 sites in 3 countries):

No difference in healing success … but …

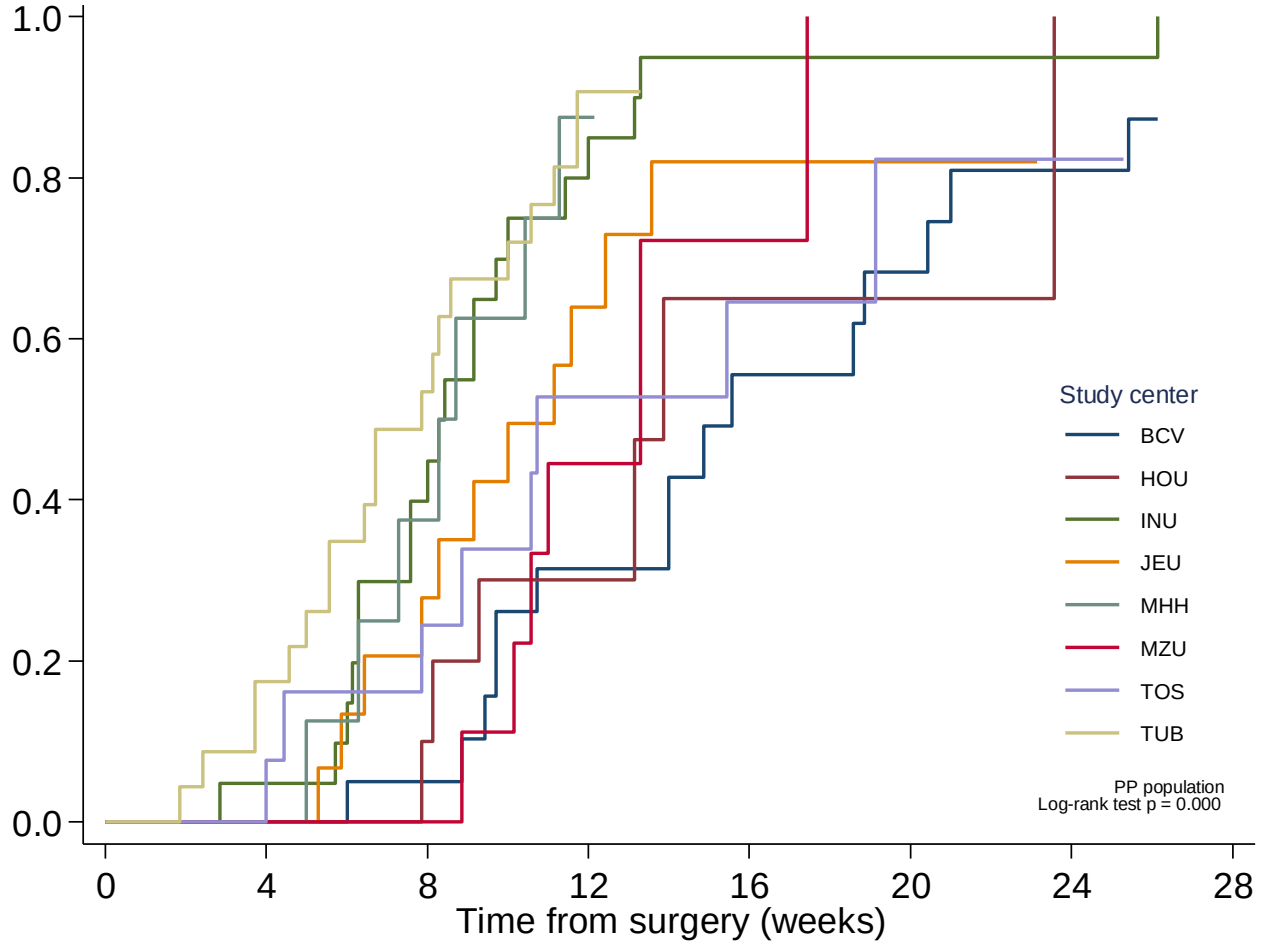


Angular Stable Locking System (ASLS). For angular stable locking of intra-medullary nails.

Clinical relevance of bone healing research

Randomized controlled trial (**LoE I**), **N = 142**, multi-center study (8 sites in 3 countries):

No difference in healing success



Angular Stable Locking System (ASLS). For angular stable locking of intra-medullary nails.

Lessons learned…

- Solid basic understanding

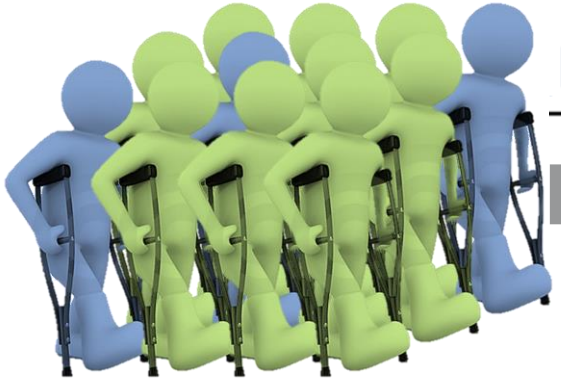
  bring novel solution based on novel concept/understanding

- Relevance of initial user group (clinical trials and beyond)
  - ensure endpoint definition and study design
  - engage potent multiplier
  - train the experts to novel concepts, ensure who is user
  - stay in the loop (ongoing learning curve)

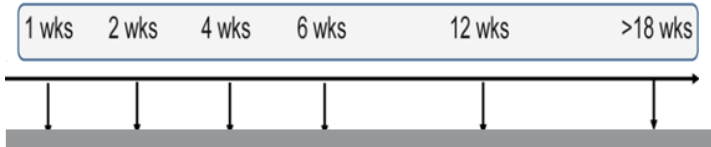
What are we known for…?

- **New, globally accepted treatment concepts**
  based on results from KFO 102, SFB 760, FOR 2165
- **Translation requires crossing borders**
  medical need – mechanistic knowledge – technology innovation – dissemination – acceptance
- **Translation is…**
  establish a new standard of care?

Phase I: Biomarker Development – Mechanism - PoC



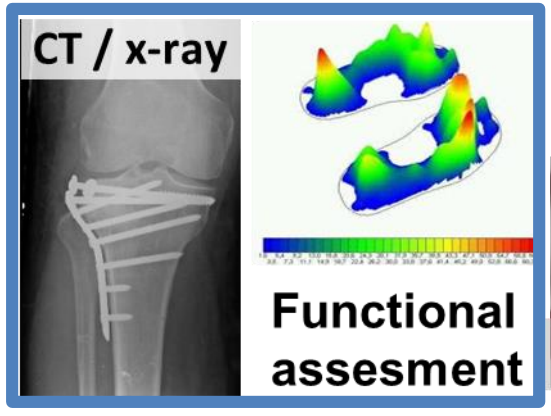
n=15



normal healing
n=8

delayed healing
n=7

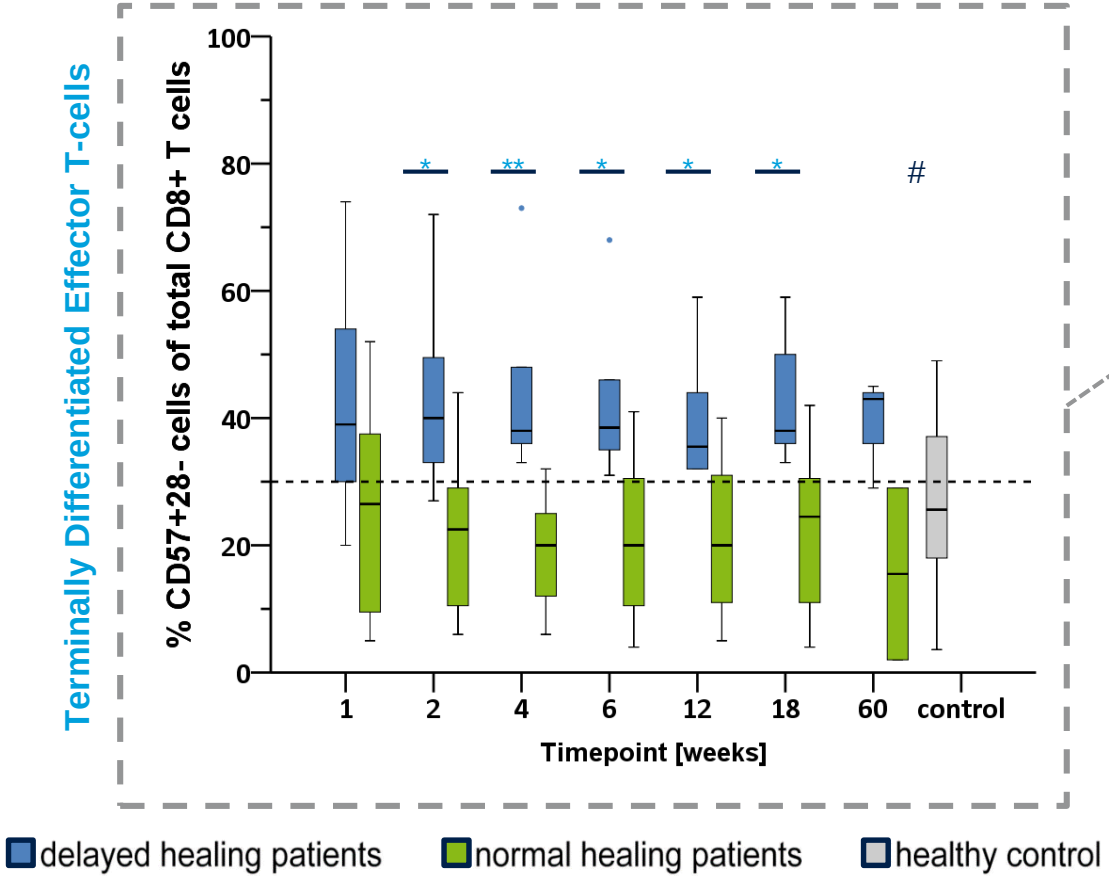
Pilot Study:

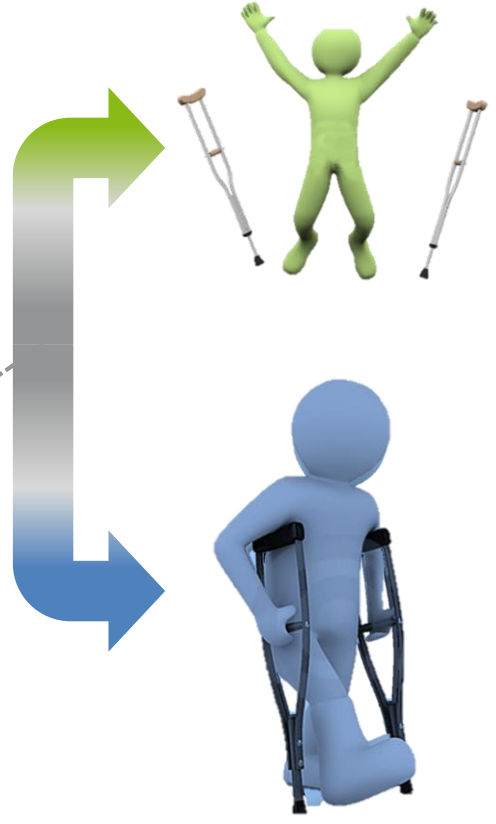


S. Reinke, et al., Sci Transl Med. 2013

Phase I: Biomarker Development – Mechanism - PoC

Persistent signature of CD8+ T_{EMRA} cells





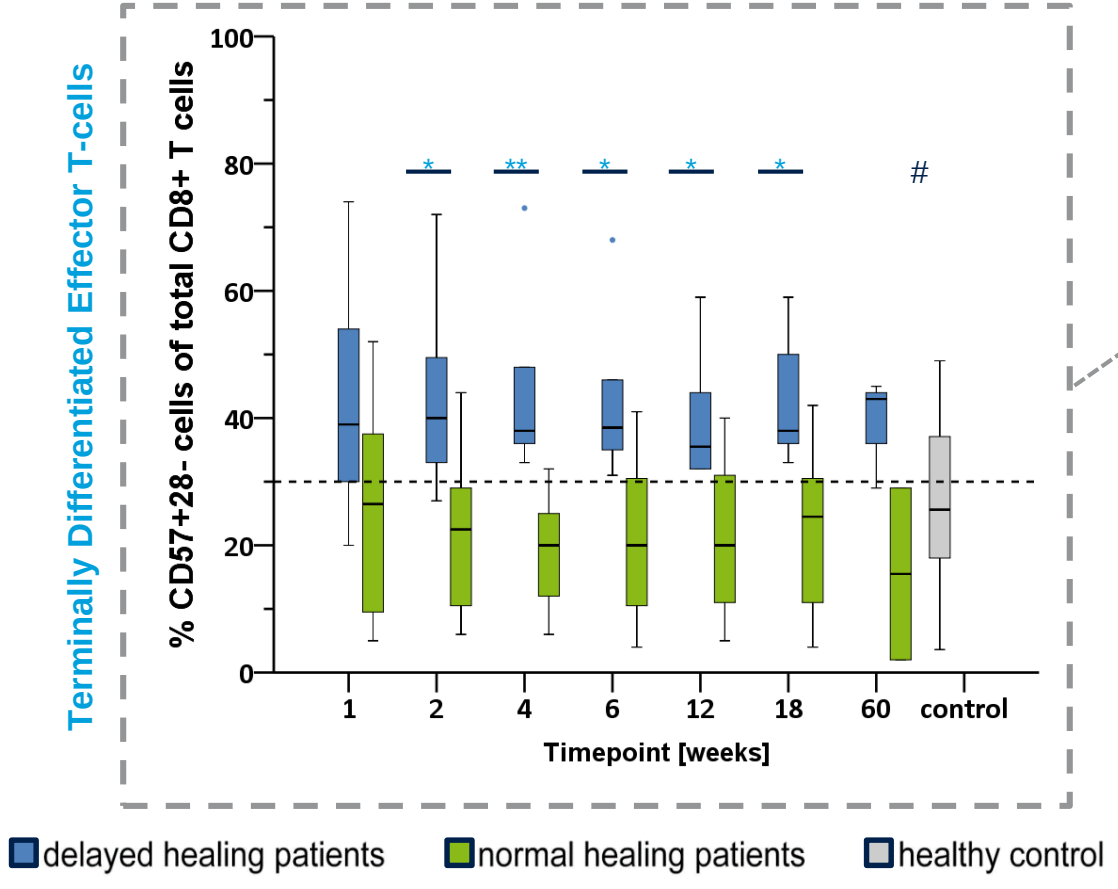
normal healing
n=8

delayed healing
n=7

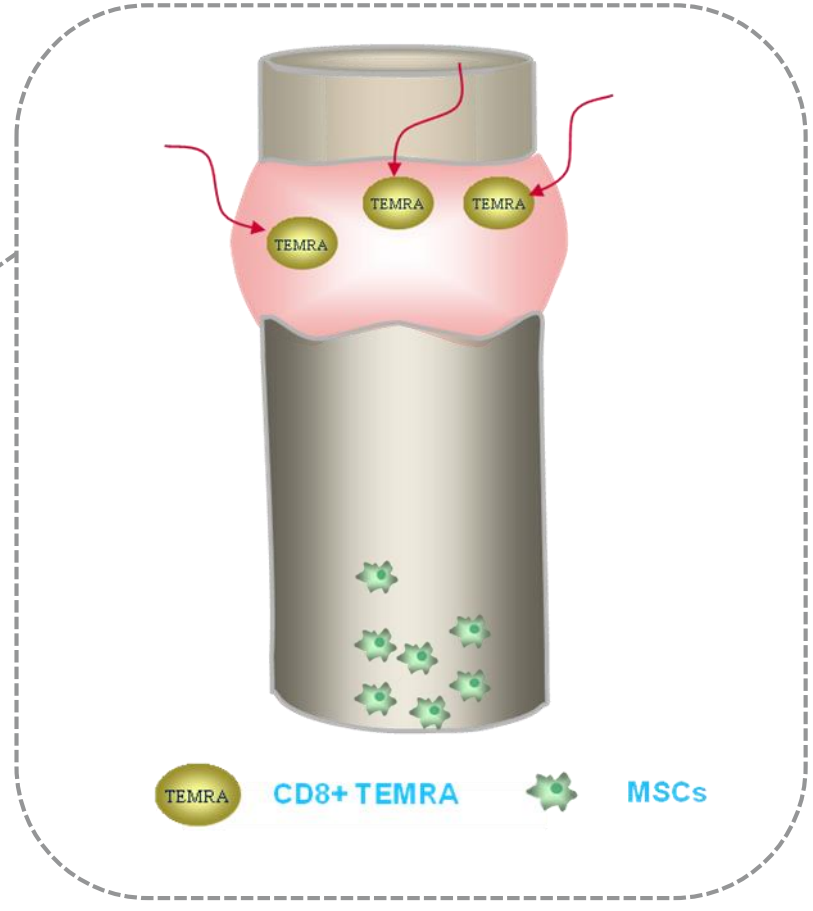
S. Reinke, et al., Sci Transl Med. 2013

Phase I: Biomarker Development – Mechanism - PoC

Persistent signature of CD8+ TEMRA cells

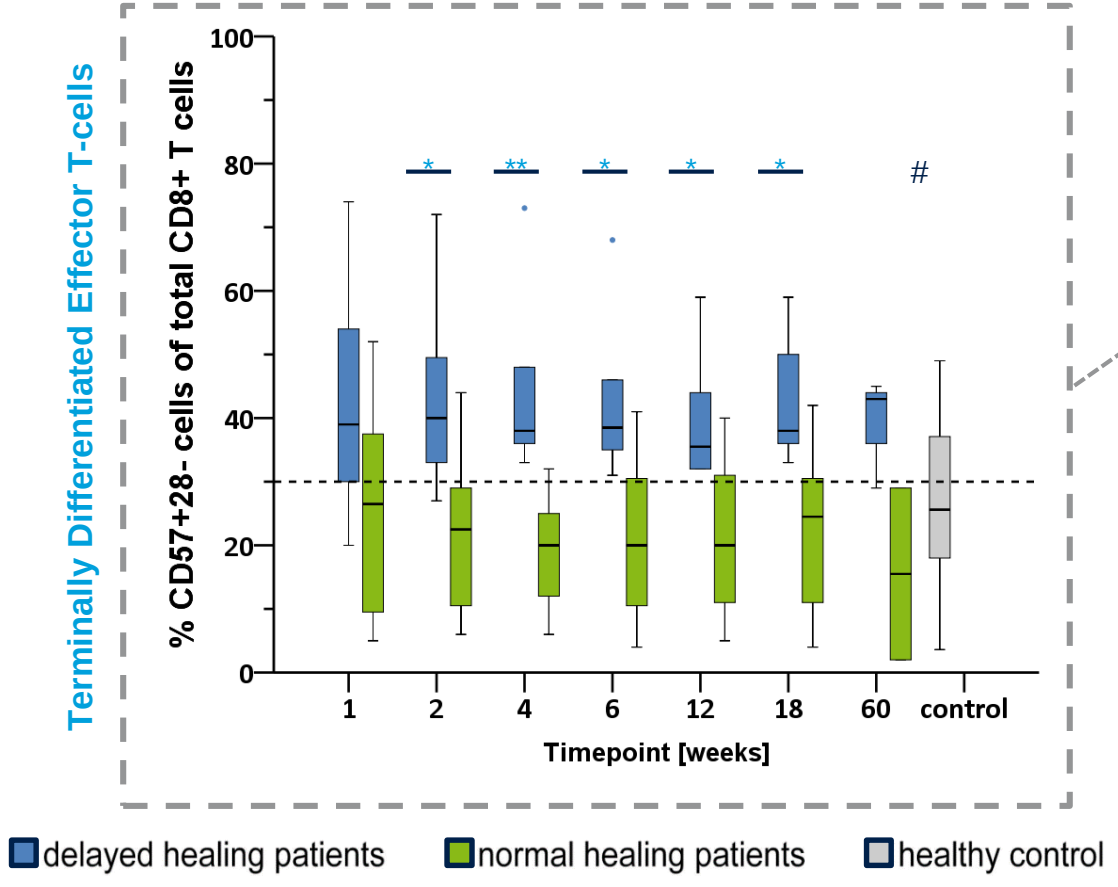


Accumulation:
3-fold at fracture site
compared to blood levels

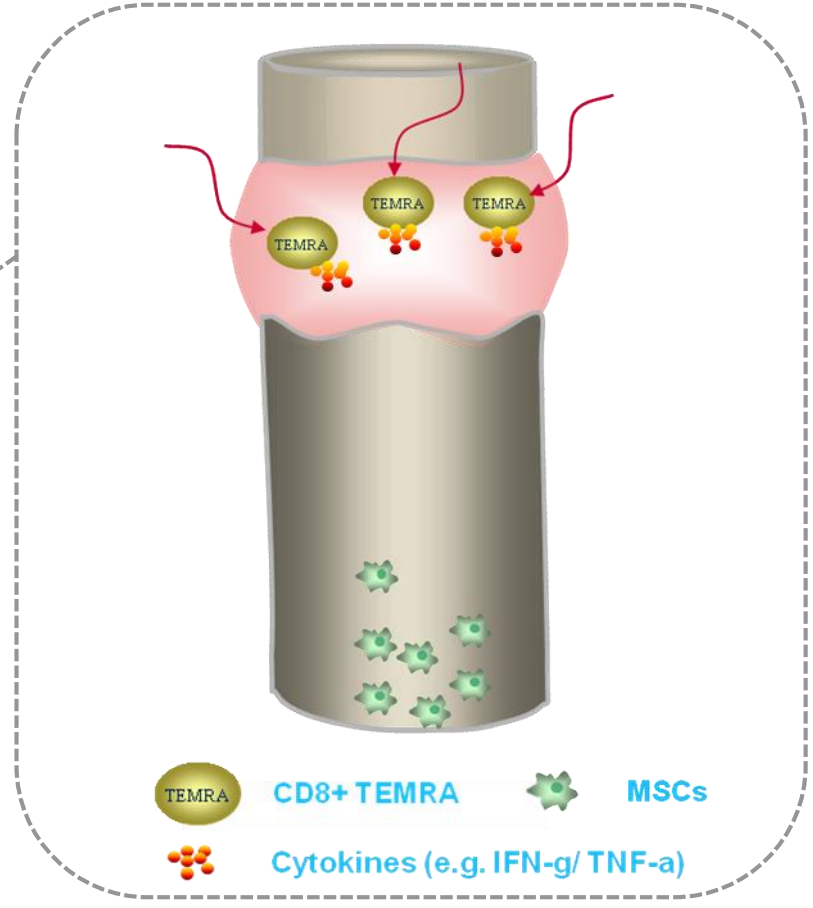


Phase I: Biomarker Development – Mechanism - PoC

Persistent signature of CD8+ T_{EMRA} cells

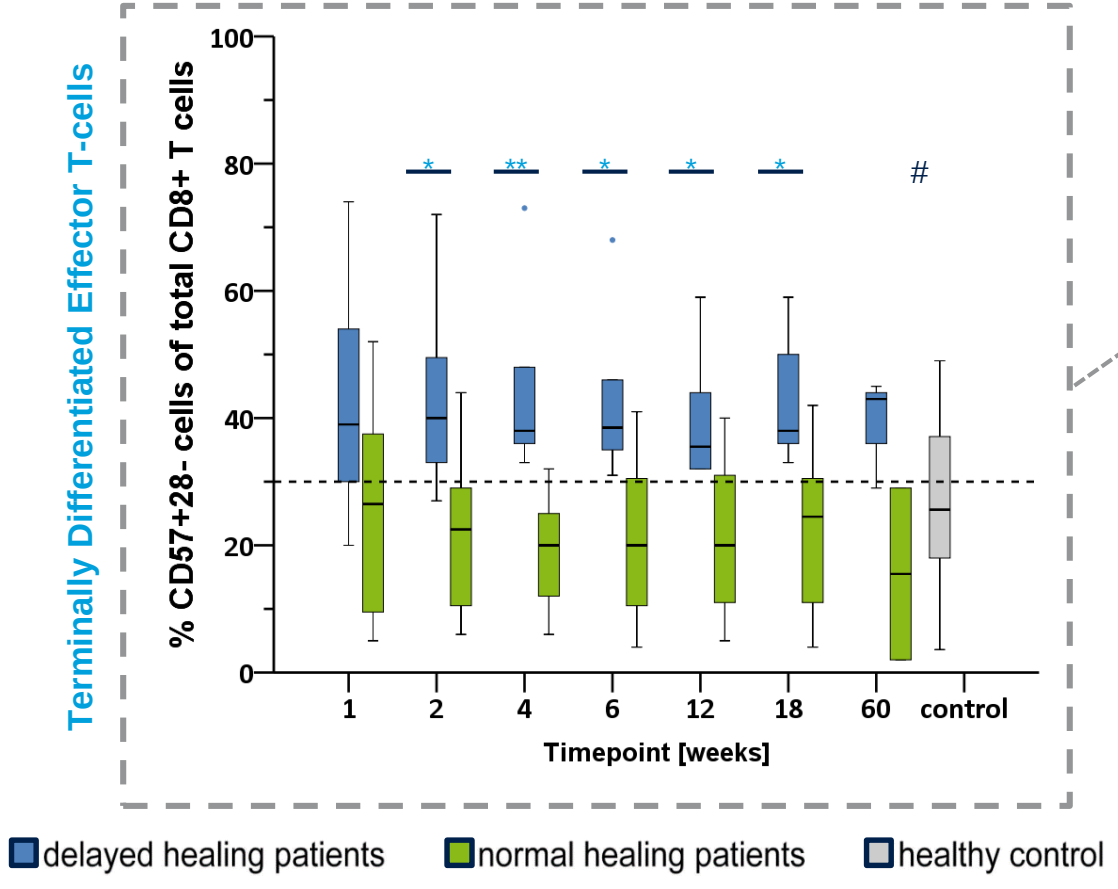


CD8+ T_{EMRA}: Strong **IFN-g + TNF-α** production & expression



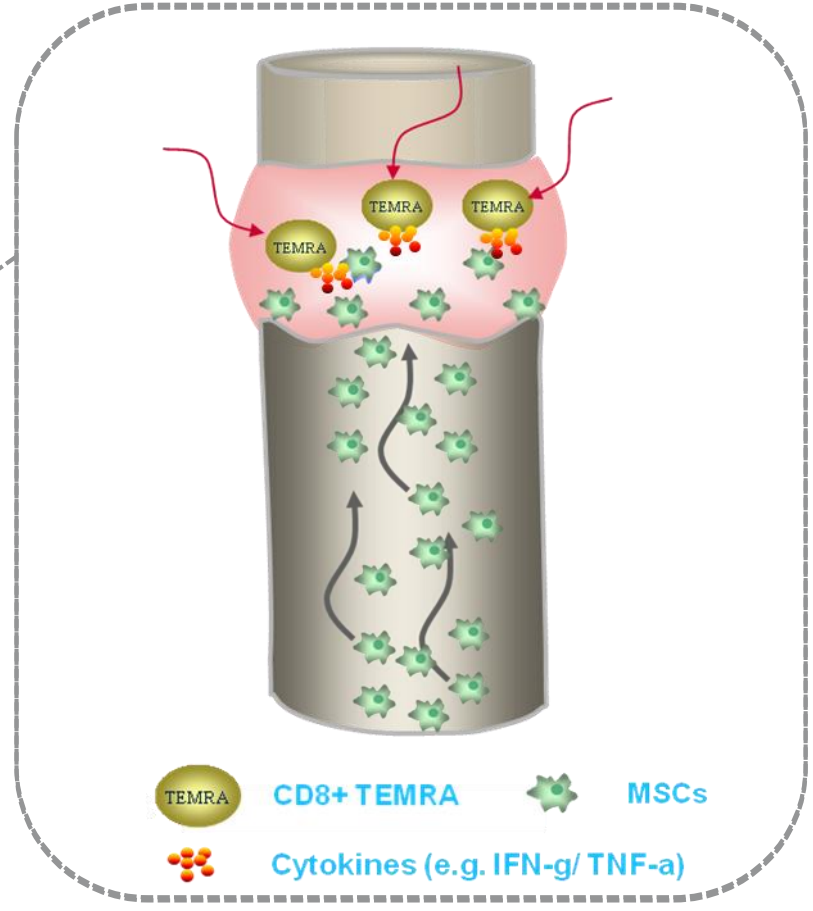
Phase I: Biomarker Development – Mechanism - PoC

Persistent signature of CD8+ T_{EMRA} cells



Inflammation:

- Apoptosis of progenitors
- Reduced osteogenesis

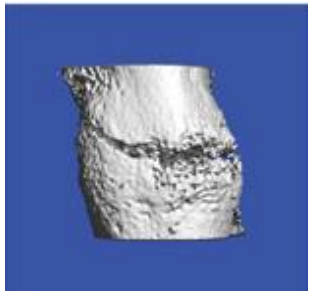


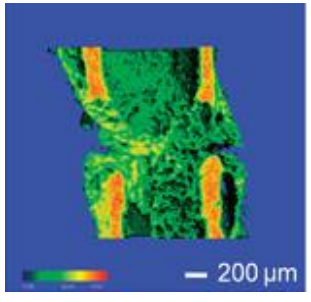
Phase I: Biomarker Development – Mechanism - PoC

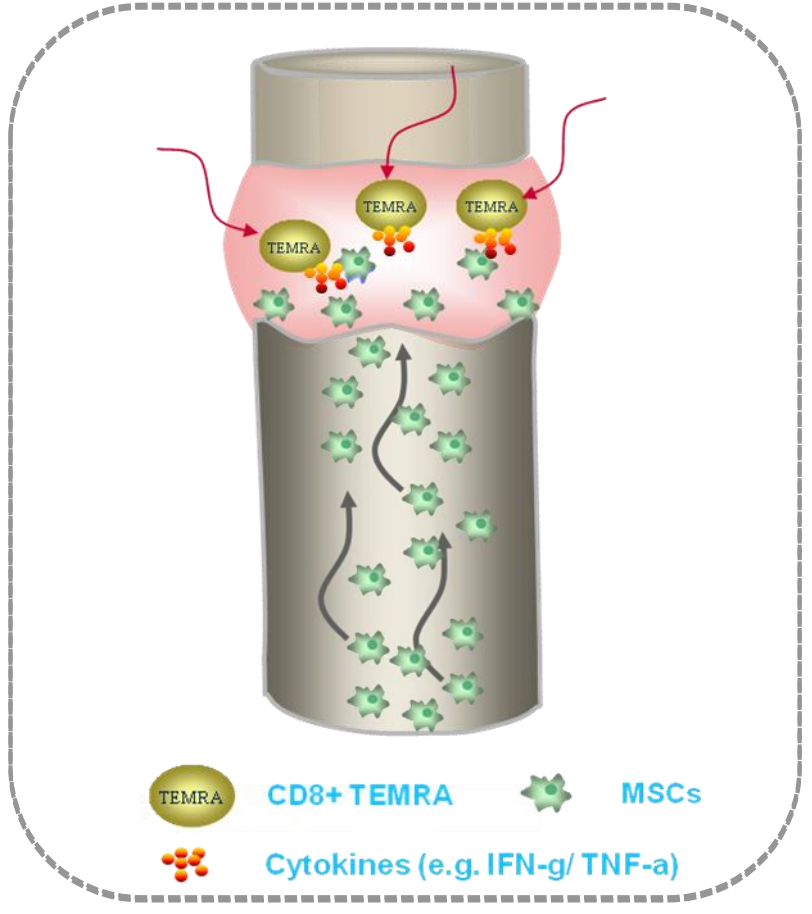
PoC in a clinically relevant mouse model

WTexp

WTexp group 21 days post-op

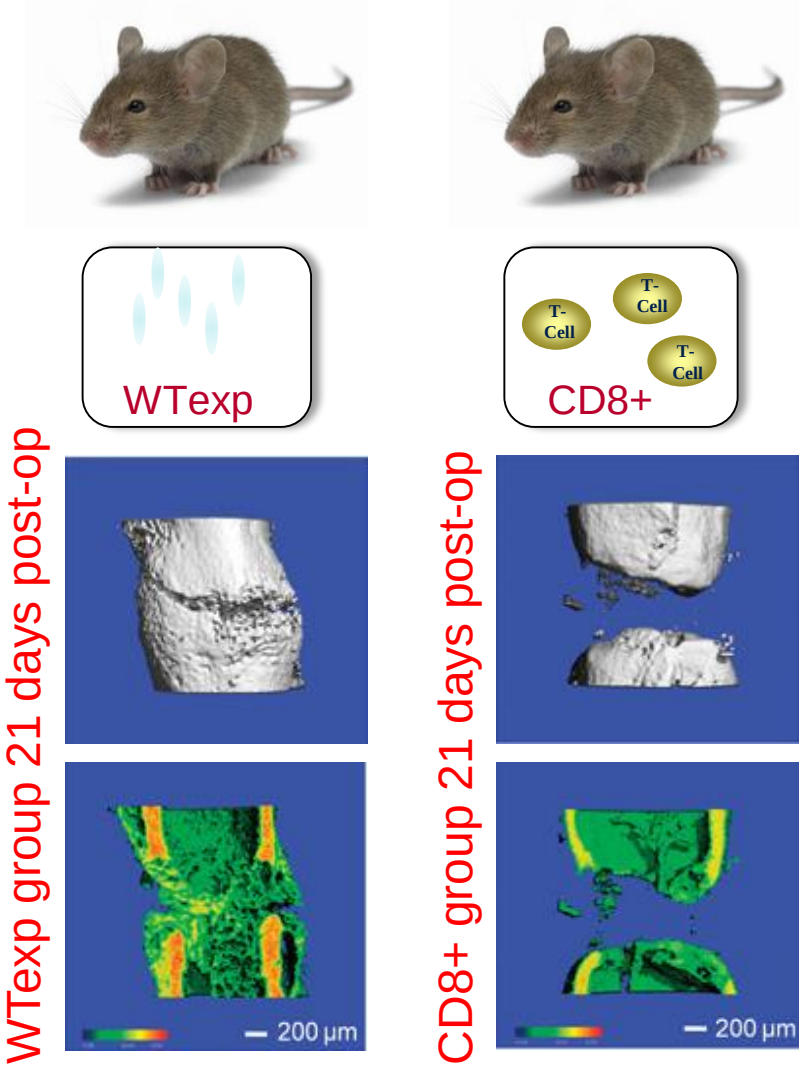


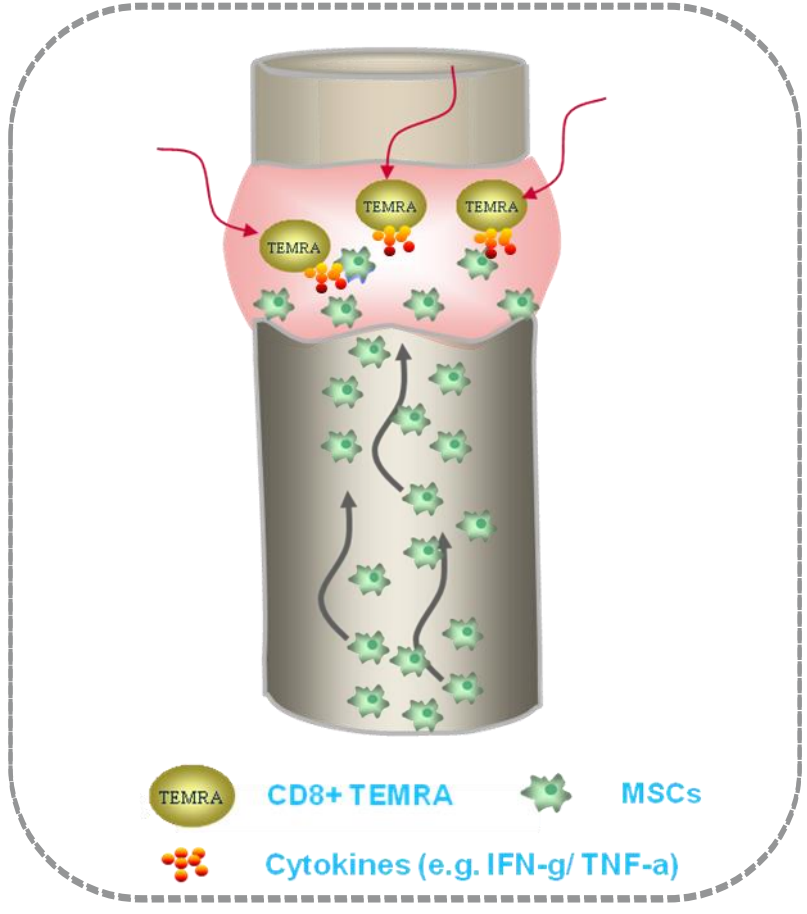




Phase I: Biomarker Development – Mechanism - PoC

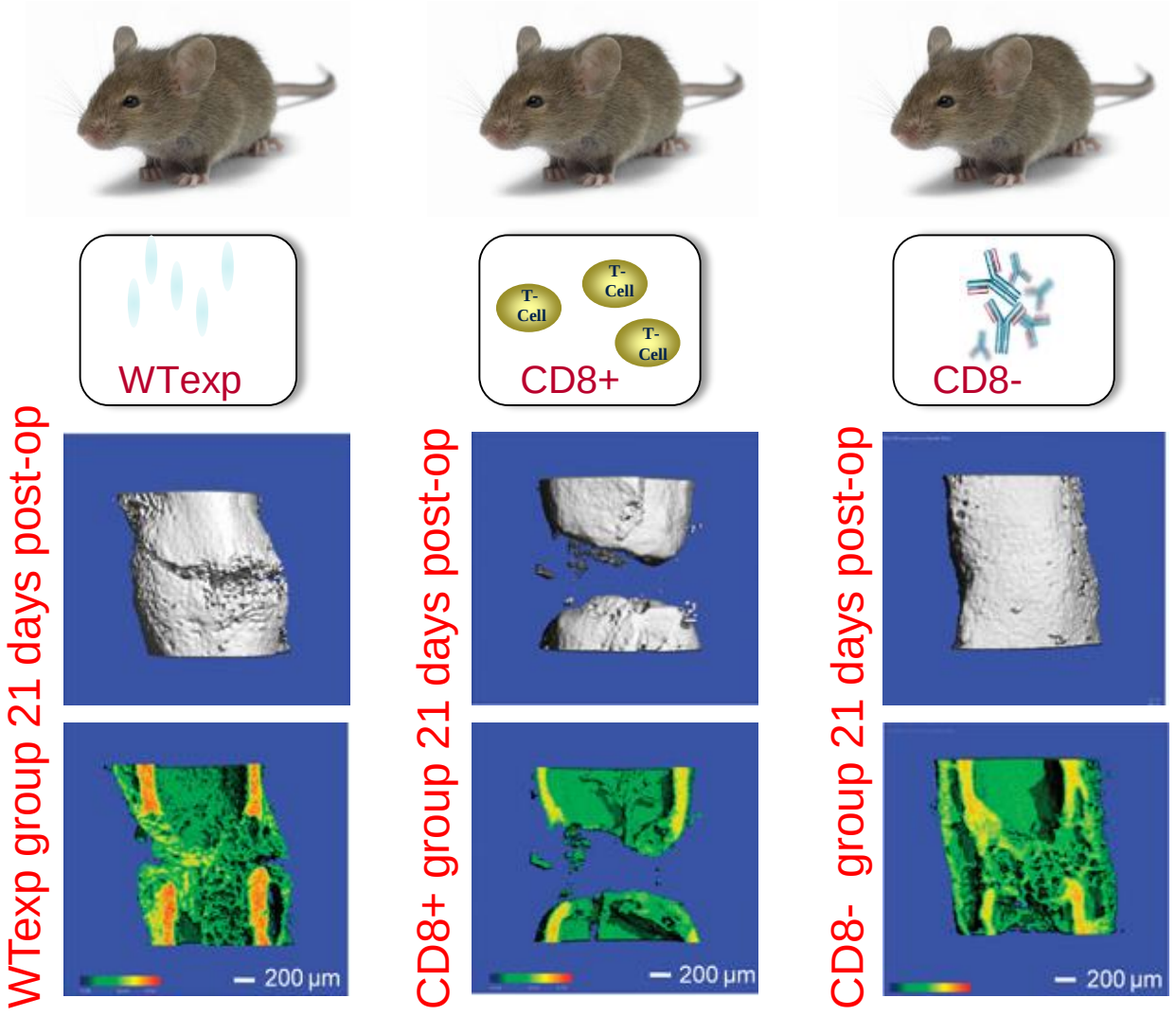
PoC in a clinically relevant mouse model

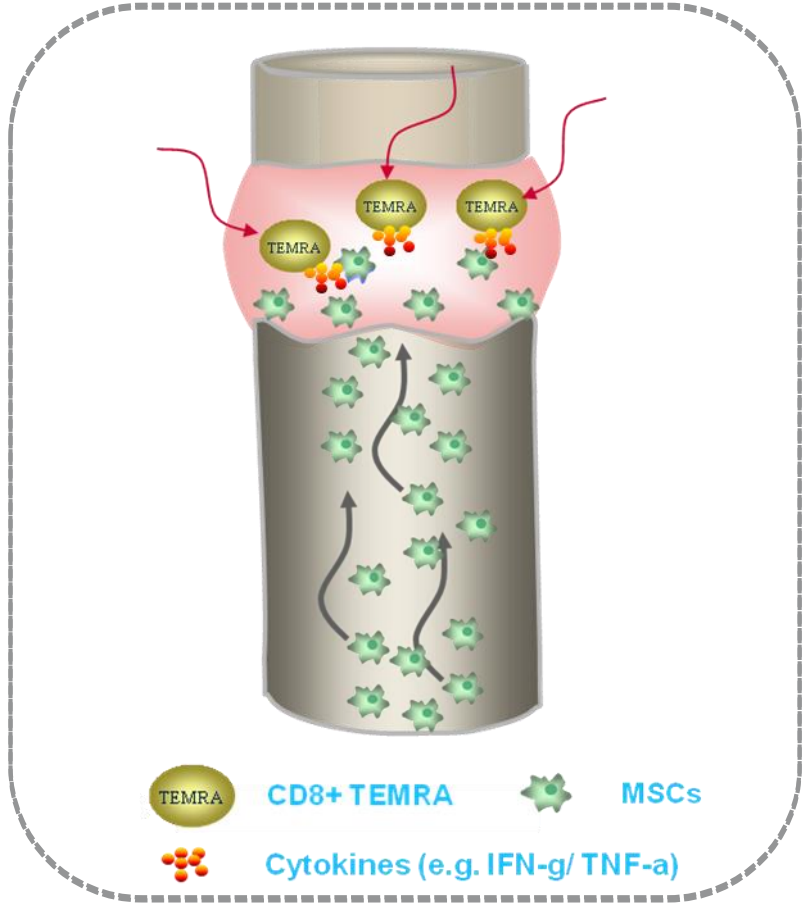




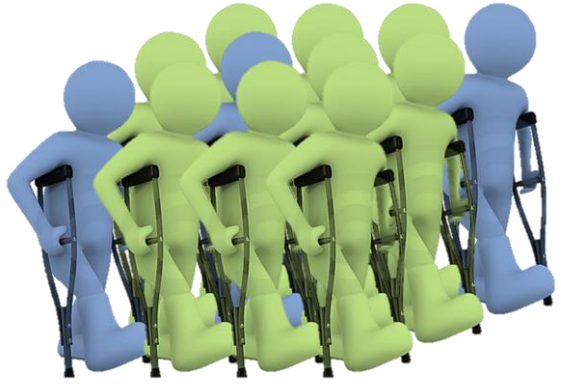
Phase I: Biomarker Development – Mechanism - PoC

PoC in a clinically relevant mouse model





Phase II: Biomarker Transfer Clinics – Confirmation



Pre-surgery

Biomarker

Blood level

Determine CD8+TEMRA levels

Predict healing outcome

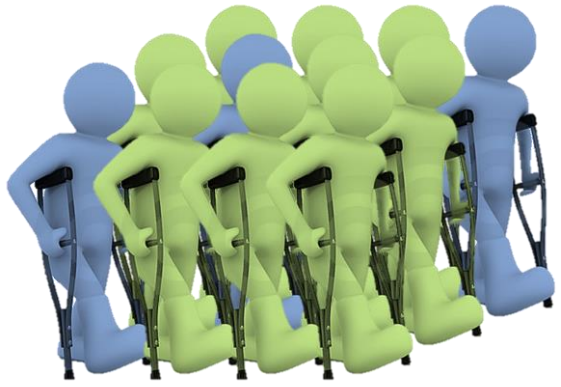
Standard

normal healing

early & targeted intervention

delayed healing

Phase II: Biomarker Transfer Clinics – Confirmation



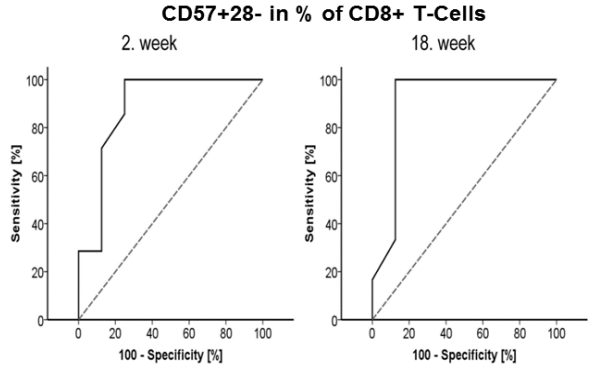
Pre-surgery

Biomarker

Blood level

Determine CD8+TEMRA levels

Predict healing outcome



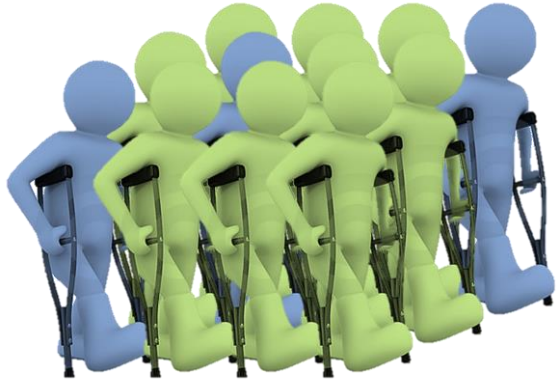
Cut-off	**30%**	**36%**
AUC	0.88	0.91
Sensitivity	**100%**	**100%**
Specificity	**75%**	**87.5%**

CD8+ T_{EMRA} cells at all study time points

High sensitivity and specificity for predicting the outcome of fracture healing

- ✓ Pre-analytics
- ✓ Method validation
- ✓ PoC Study

Phase III: Prospektive Biomarker Validation



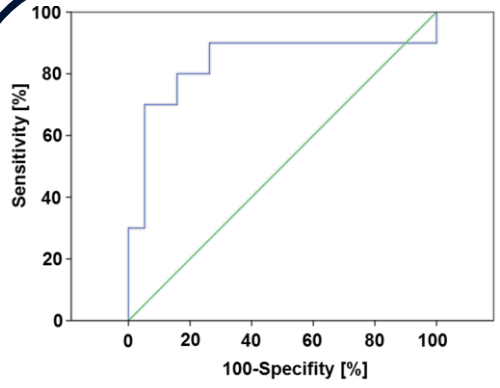
Pre-surgery

Biomarker

Blood level

Determine CD8+TEMRA levels

Predict healing outcome



Prospective Validation

N (total) = 68
Cut-off (preOP) 38%

AUC	**0.83**
Sensitivity	**70%**
Specificity	**95%**

- ✓ Pre-analytics
- ✓ Method validation
- ✓ PoC Study
- ✓ Confirmation pre-defined cut-off level
- ✓ Health economic analysis

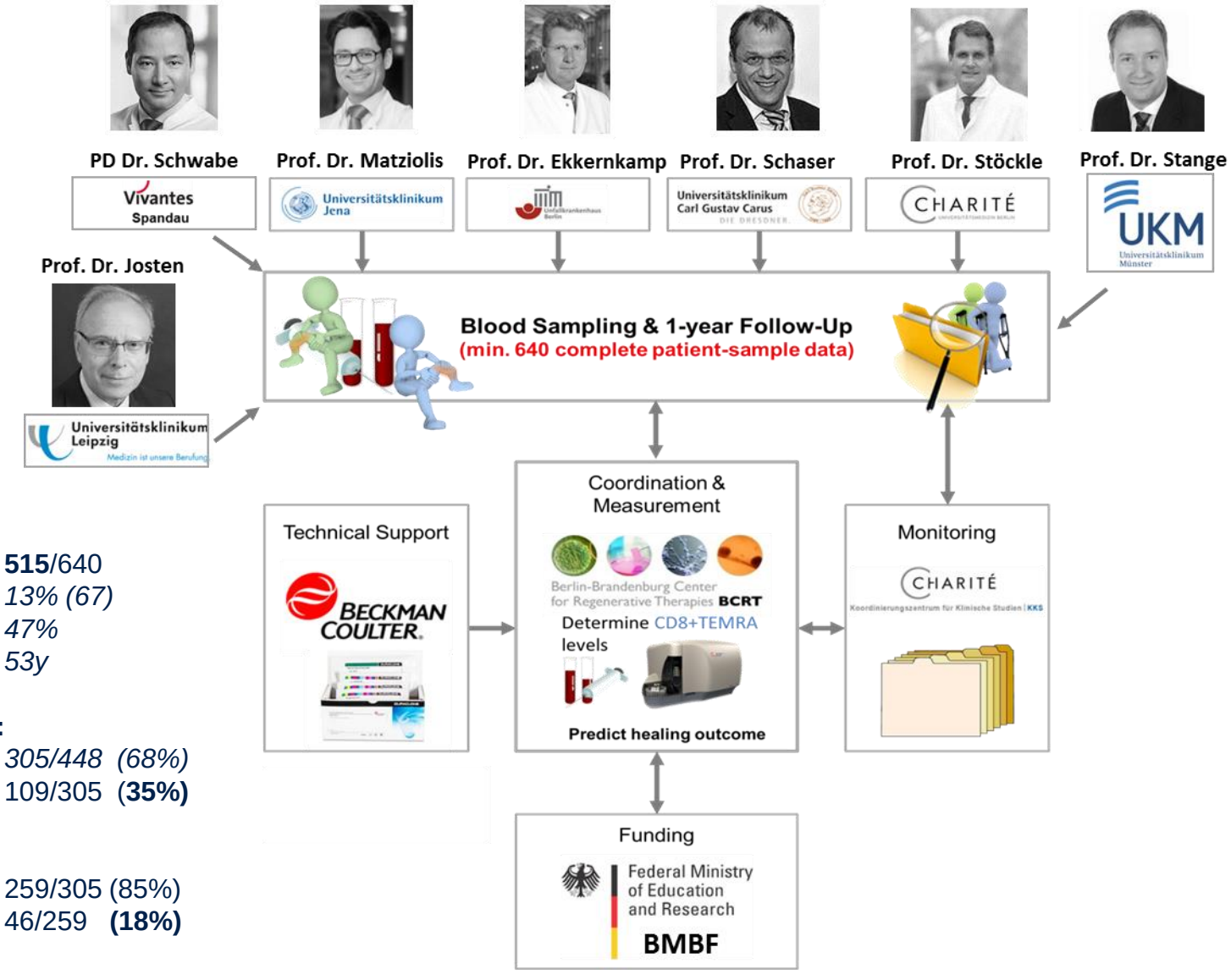
BeckmanCoulter

BioBone

Phase III: Prospektive Biomarker Validation

multicenter-prospective study

BioBone



Coordination:
Simon Reinke / Sven Geißler

Patients-in (03/2020):	**515**/640
drop out rate:	*13% (67)*
Women:	*47%*
Mean Age:	*53y*

1. Endpoint (4.5 months):

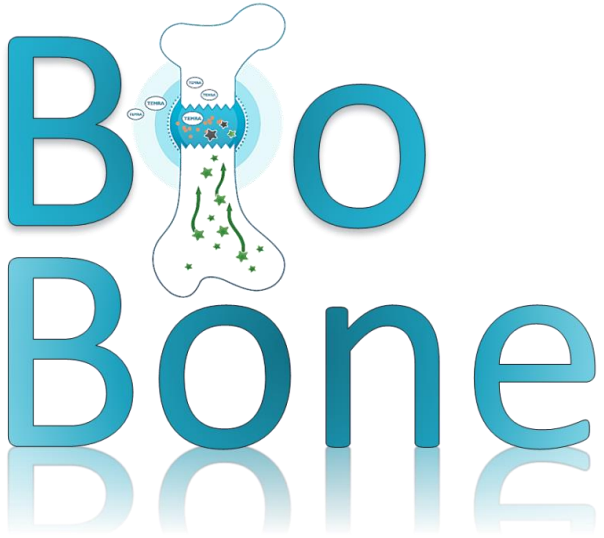
Patients (total):	*305/448 (68%)*
Non-Healed:	109/305 (**35%)**

2. Endpoint > 9 months:

Patients (total):	259/305 (85%)
Non-Healed:	46/259 **(18%)**

Phase III: Prospektive Biomarker Validation

multicenter-prospective study



Coordination:
Simon Reinke / Sven Geißler

Patients-in (03/2020):	**515**/640
drop out rate:	*13% (67)*
Women:	*47%*
Mean Age:	*53y*

1. Endpoint (4.5 months):

Patients (total):	*305/448 (68%)*
Non-Healed:	109/305 (**35%)**

2. Endpoint > 9 months:

Patients (total):	259/305 (85%)
Non-Healed:	46/259 **(18%)**

- Technology development
  but no market access

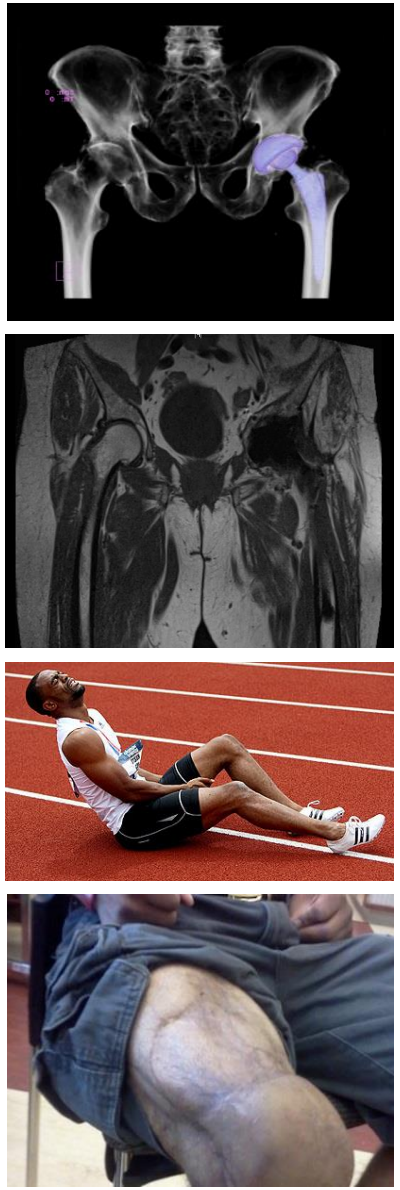
- Market access
  but no own techmology

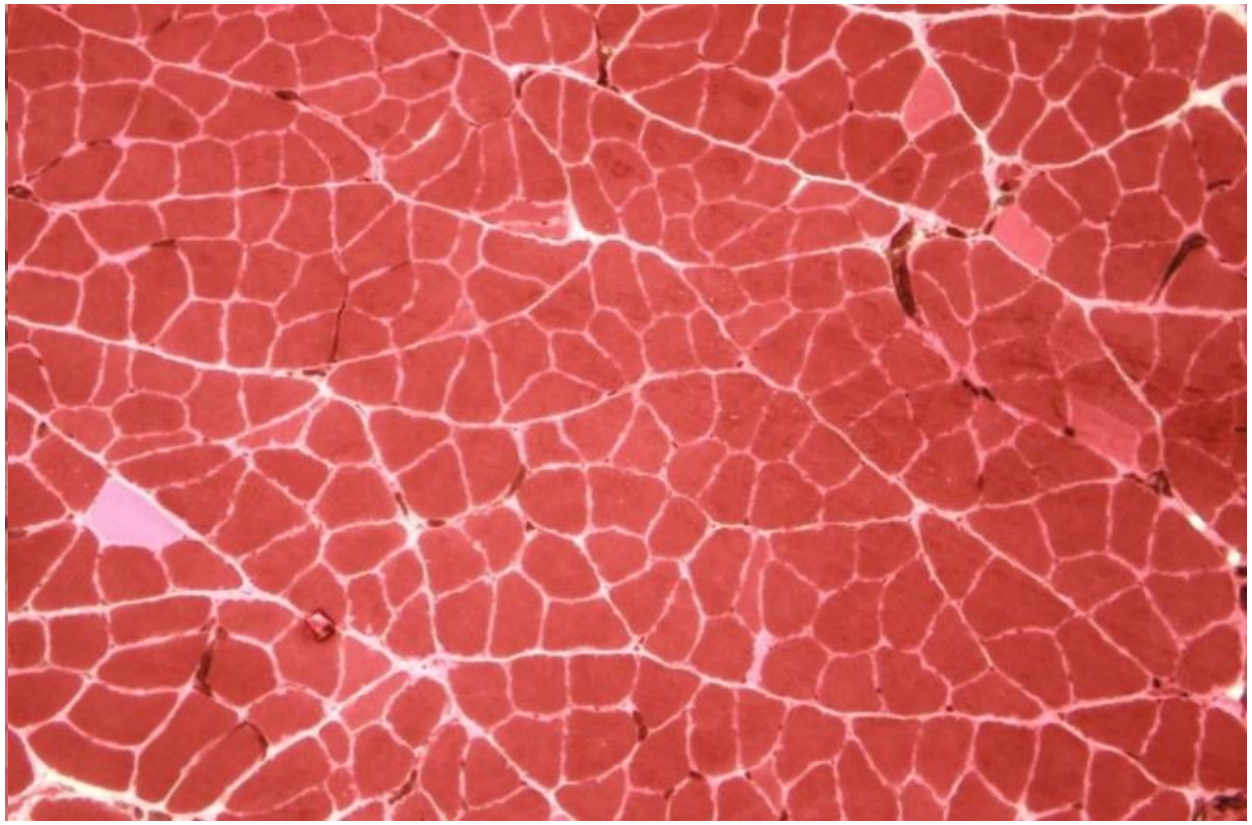
- Intended use:
  This reagent is used as an aid in the differential diagnosis of patients with long bone fractures having, or suspected of being at risk of having, a biologically compromised healing capacity resulting in delayed or permanent failure of bone healing (= non-union or pseudoarthrosis).

Lessons learned…

- Idea & concept (including basic science)
- Translational partners are real partners
  - people, role in organisation, trust, long standing partnership
- Diversity in stake holders
  - technology ownership vs. market access vs. sales capabilities
  - in companies: different languages, different (sales) strategies
  - tech transfer, own IP strategy, own business development

Learn from bone healing for muscle regeneration?





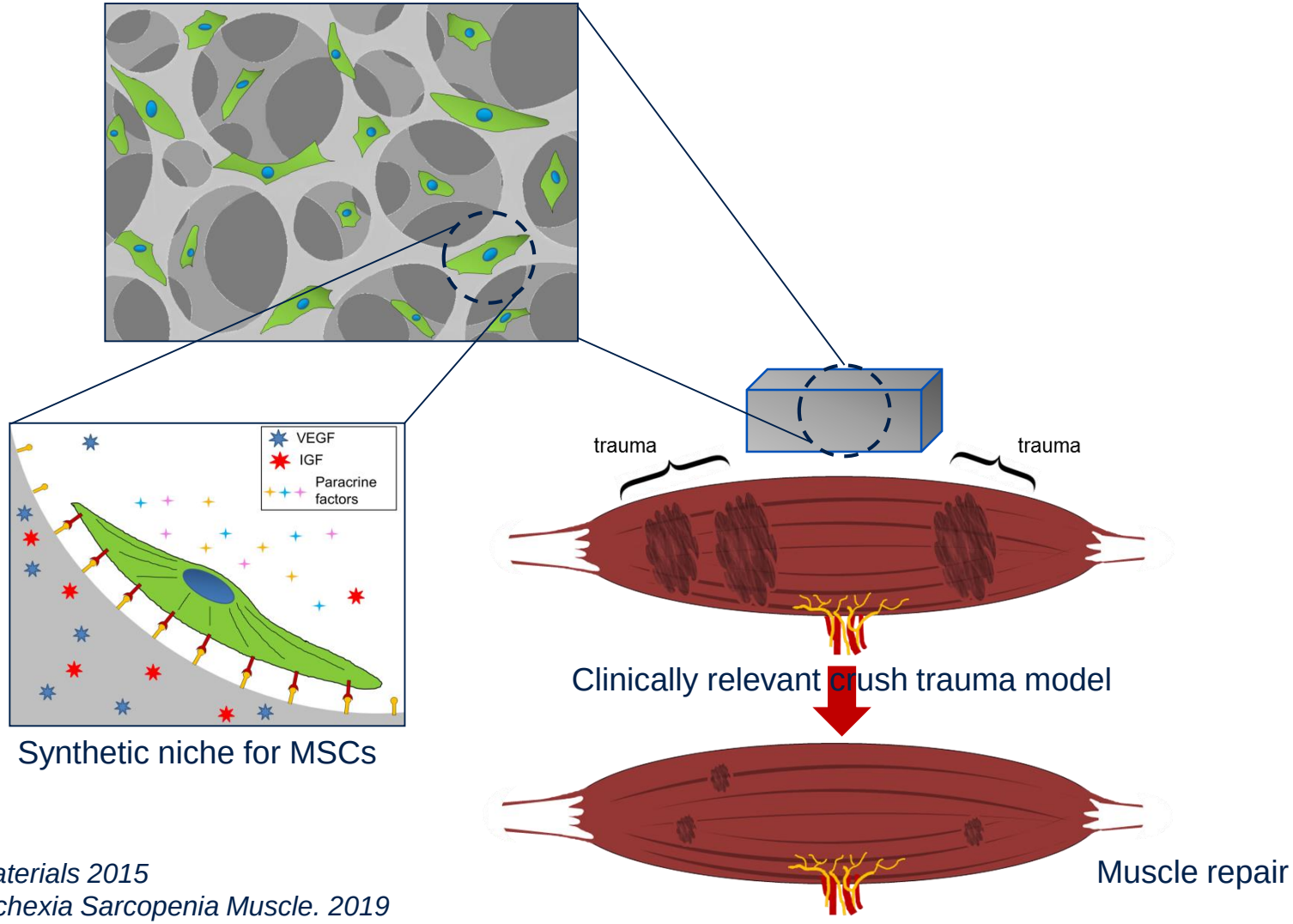
- Anti-inflammation to enable regeneration
- Avoid fatty degeneration

Damm et al, Clin Biomechanics, 2019, ESB Award

BIH Regeneration
BIH Center for Regenerative Therapies (BCRT)

CENTRUM FÜR MUSKULOSKELETALE CHIRURGIE

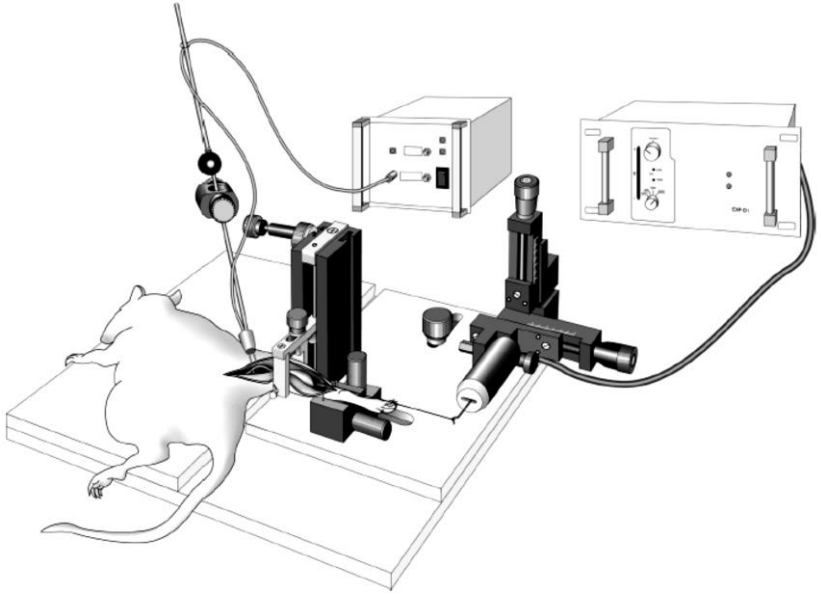
Learn from bone healing for muscle regeneration?



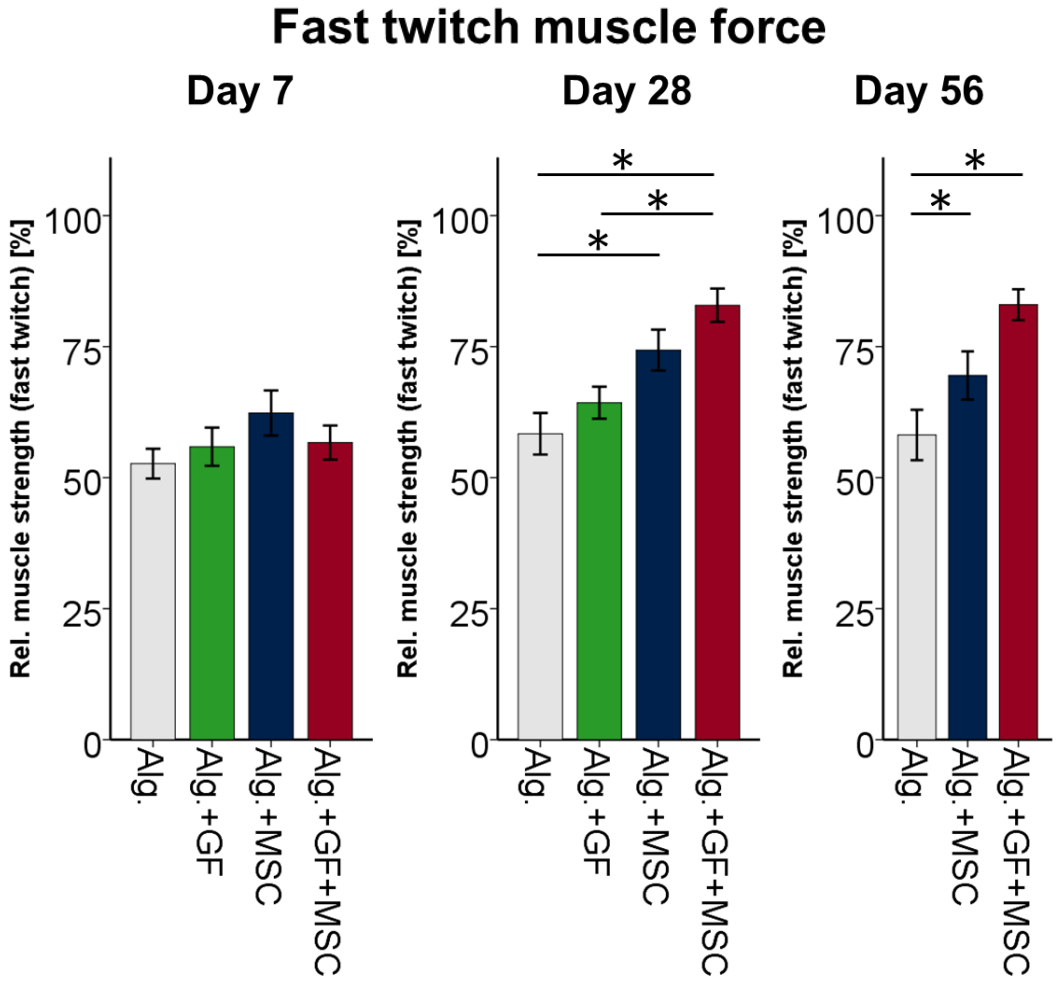
Qazi et al, Biomaterials 2015
Qazi et al., J Cachexia Sarcopenia Muscle. 2019

Learn from bone healing for muscle regeneration?

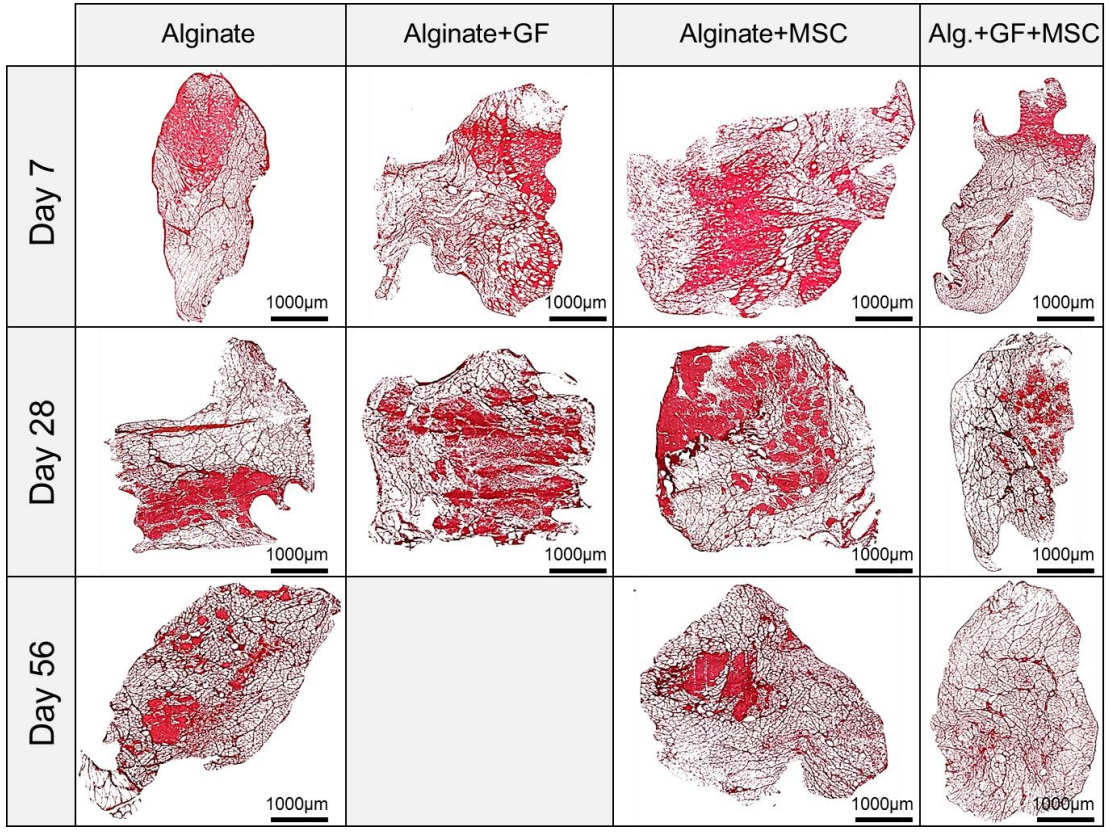
- MSC transplantation improve muscle strength.
- GF alone not beneficial,
  but can stimulate MSCs signaling.

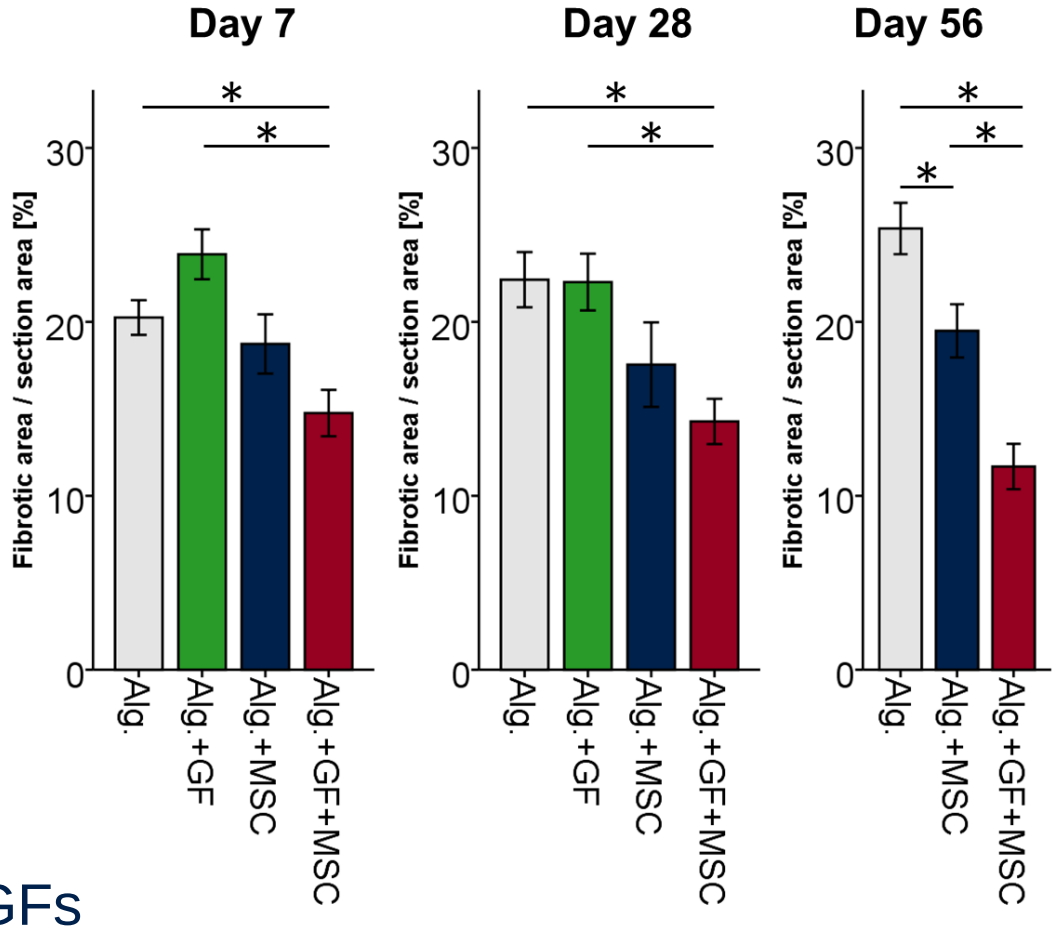


Pumberger et al, Biomaterials 2016
Qazi et al, Biomaterials 2017



Learn from bone healing for muscle regeneration – reduce scarring



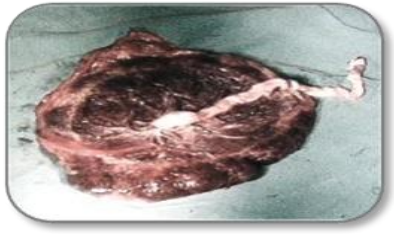


Significant reduction in scaring with MSCs & GFs

Pumberger et al, Biomaterials 2016
Qazi et al, Biomaterials 2017

Stem cells – off the shelf?

Placenta expanded stromal cells (PLX) for supporting endogeneous regeneration - from preclinical studies to phase III multicenter clinical trials



Placenta

Cell Expansion 2D

ICS Intermediate cell stock

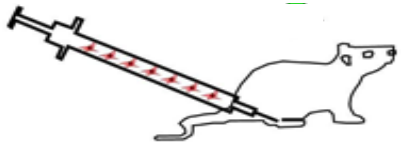
PLX products
Off the shelf products
(>20,000 therapeutic units/placenta)

Downstream Detachment, wash, formulation, freezing

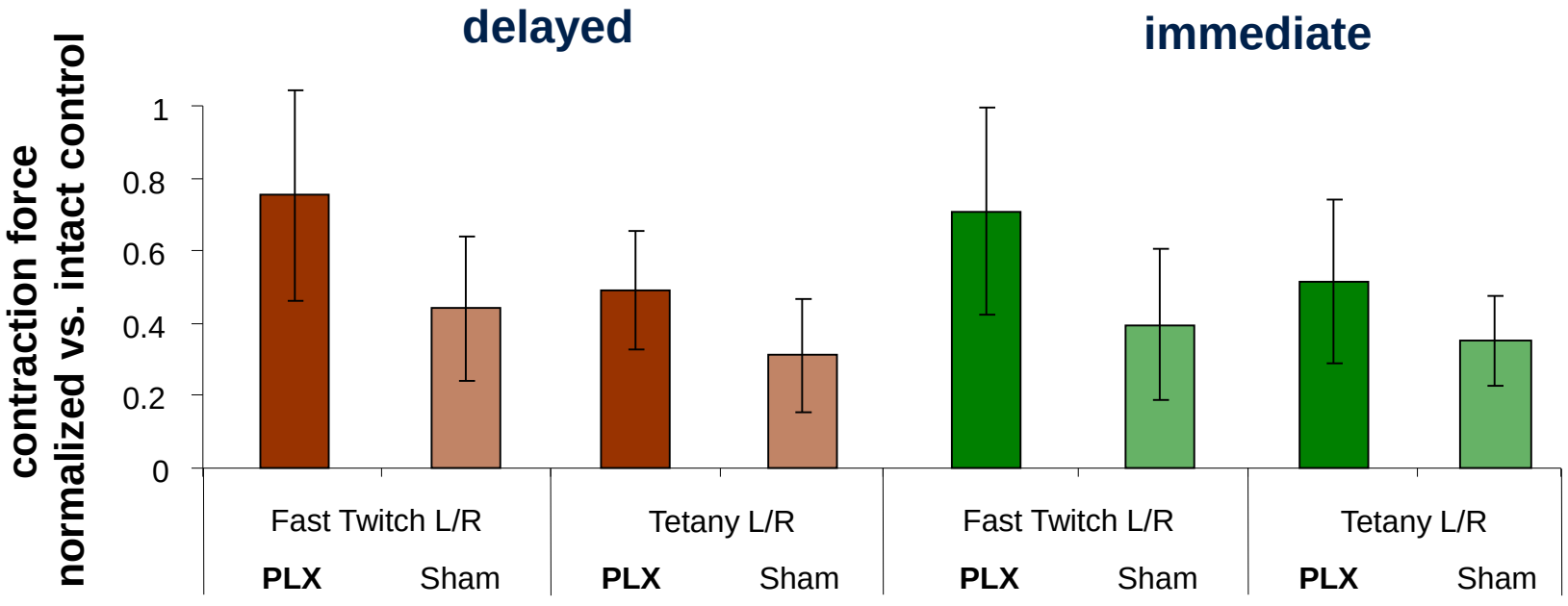
Cell Expansion 3D

Pluristem Therapeutics Inc.

Stem cells – off the shelf?

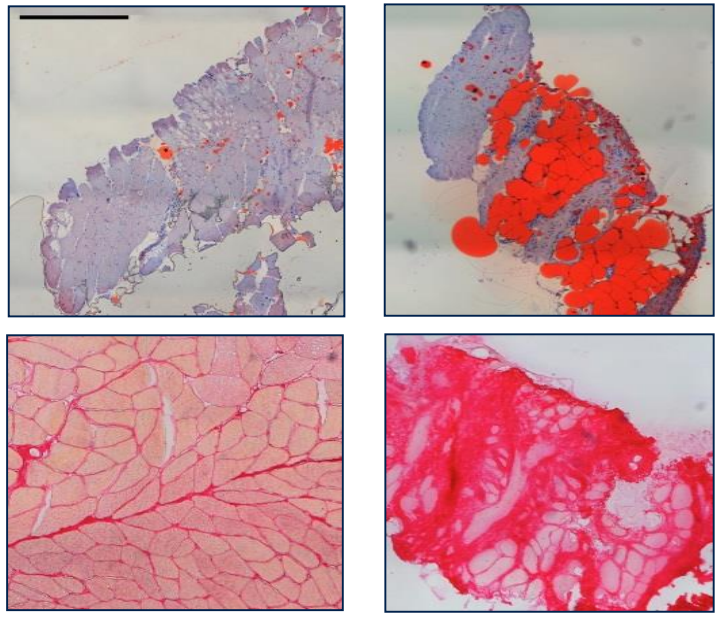


Day 0	Day 0/7	Day 28
Trauma	Transplantation of PLX	Force test and histologic analysis



Stem cells – off the shelf?

Aim at complex pathogenesis in muscle injury/ischemia: myopathy, ischemia, myofiber necrosis, inflammation

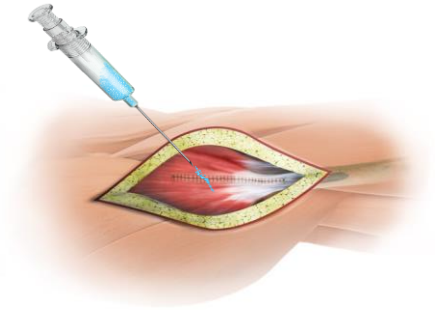


pre THA

6 months
post THA

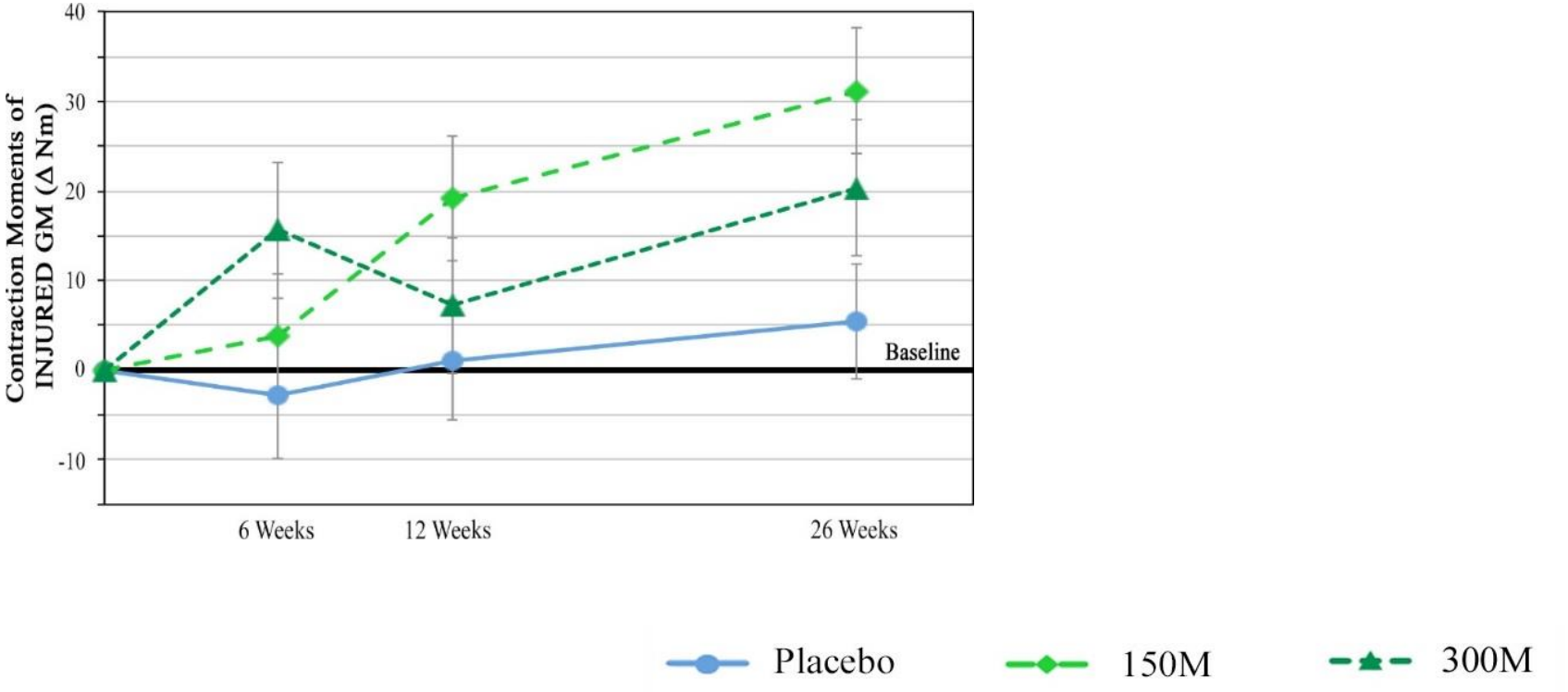
VEGF Angiogenin Angiopoetin 1 HGF	Angiogenesis ↑
Osteopontin SDF1, GDF15 MIF, TNF	Immunomodulation: Inflammation ↓
Decorin MMP1, HGF TGFß Galectin1	Muscle Regeneration ↑

EMA Phase I/IIa approval study



PLX-PAD was considered to be safe (n=20 patients)
Efficacy: placebo vs. intermediate dose vs. high dose

INCREASE IN GLUTEUS MEDIUS STRENGTH

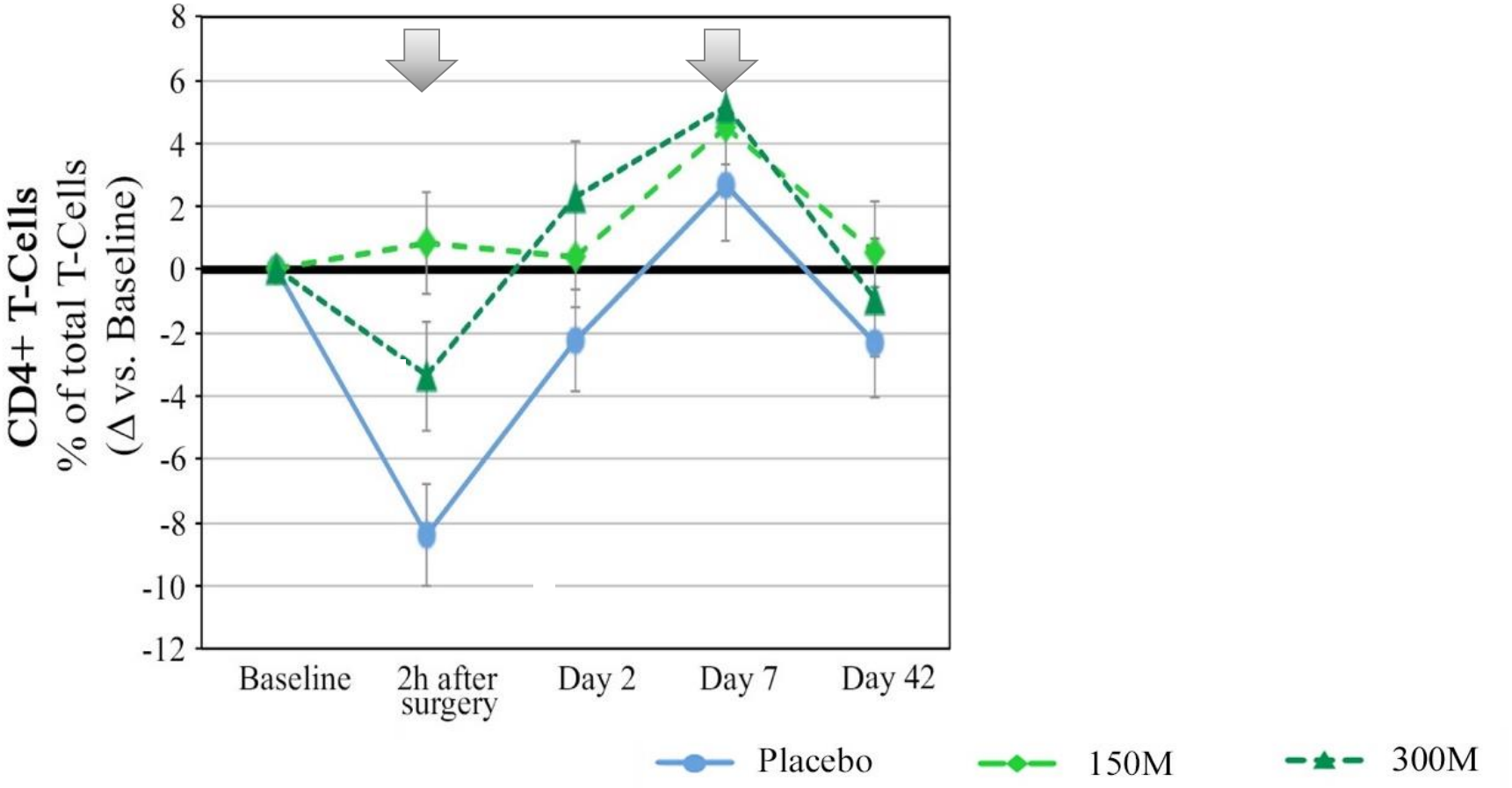


Winkler et al, J Cahexia Sarcopenia Muscle 2018

EMA Phase I/IIa approval study

PLX induces immune modulation

- „Good“ guys are kept (CD4+) if PLX present, but the high dose catches up…

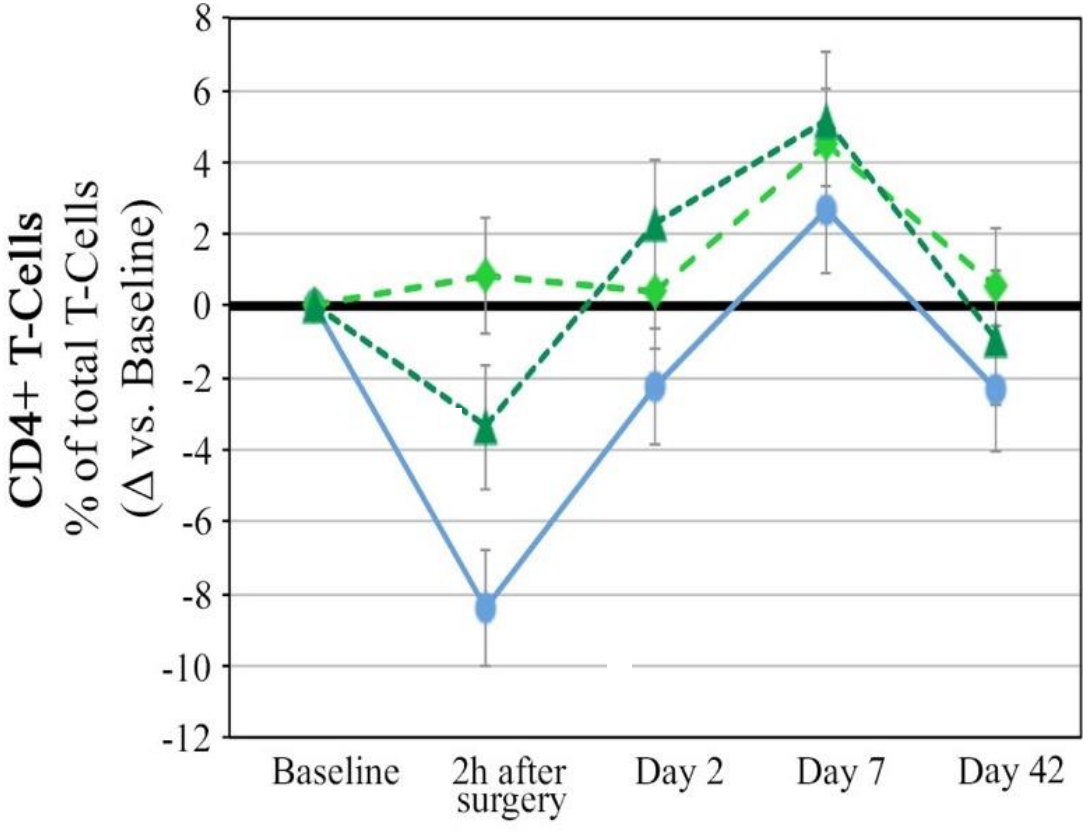


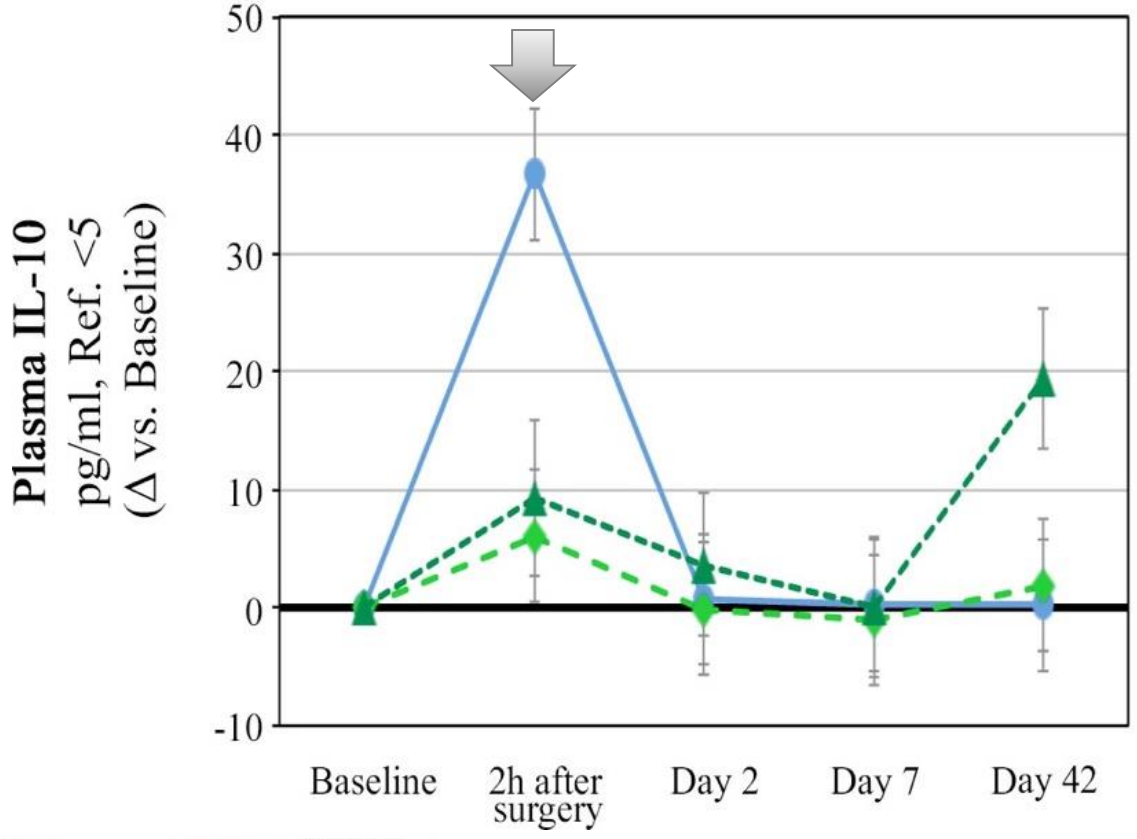
Winkler et al, J Cahexia Sarcopenia Muscle 2018

EMA Phase I/IIa approval study

PLX induces immune modulation

- But why is 300M less good than 150M?





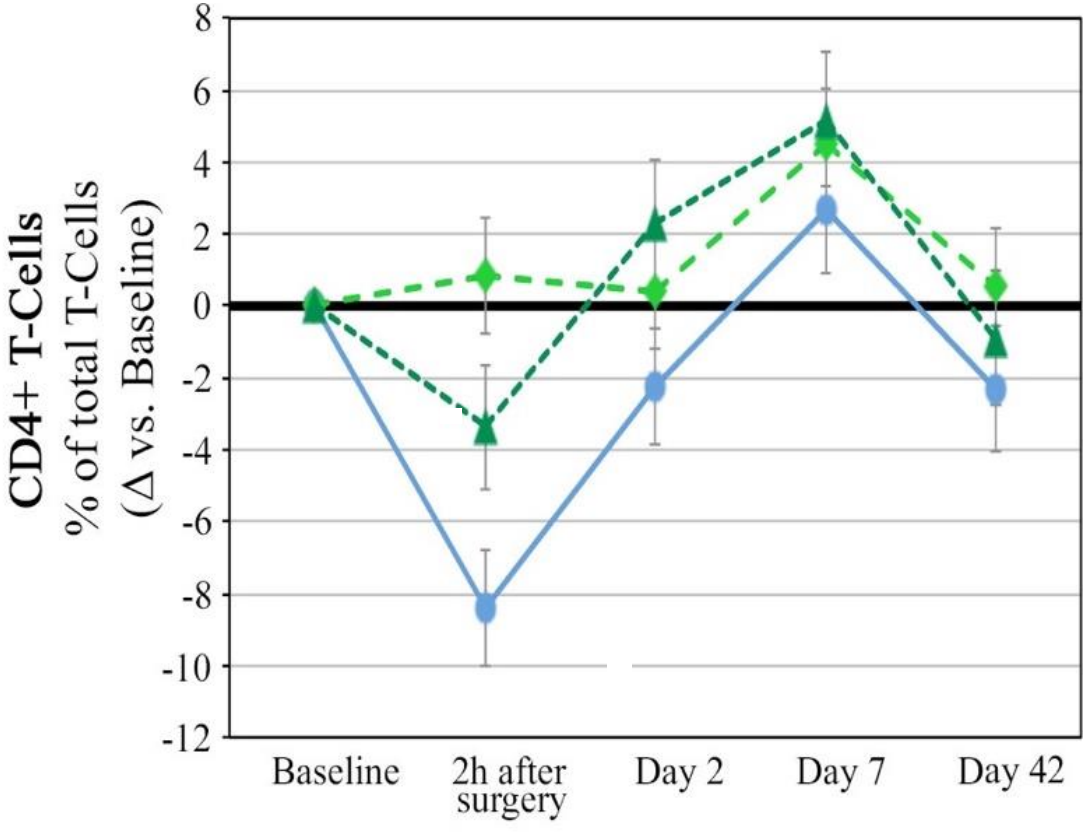
Placebo 150M 300M

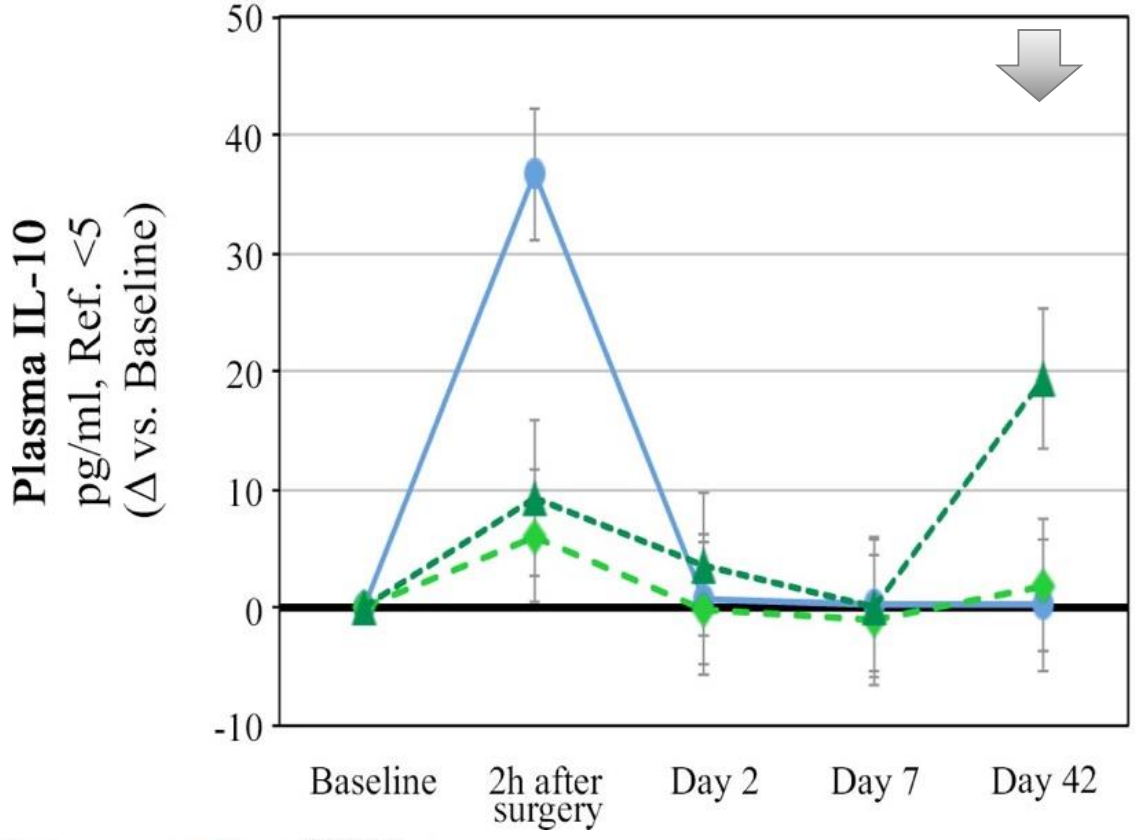
Winkler et al, J Cahexia Sarcopenia Muscle 2018

EMA Phase I/IIa approval study

PLX induces immune modulation

- But why is 300M less good than 150M? Reduced postOP stress related immunological changes





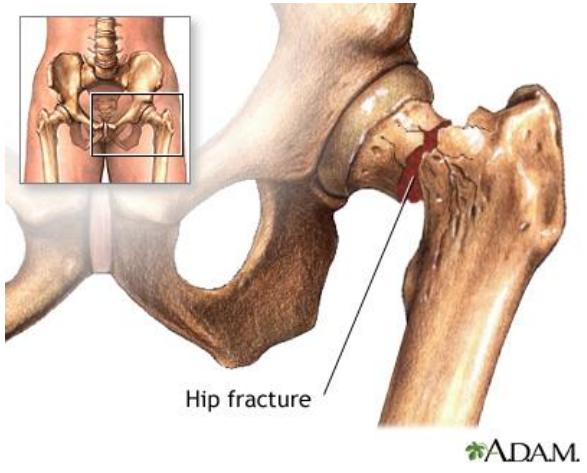
Placebo 150M 300M

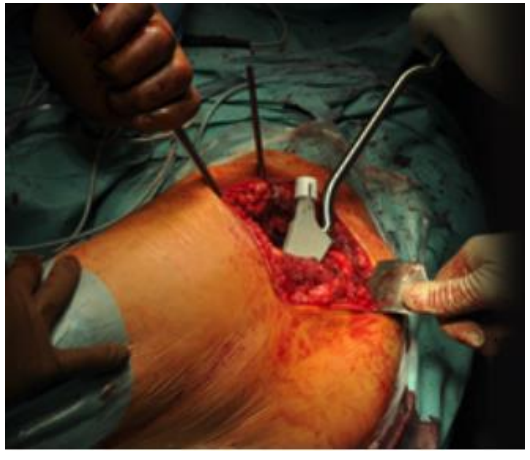
Winkler et al, J Cahexia Sarcopenia Muscle 2018

EMA Phase III approval study: Multicentre clinical trial

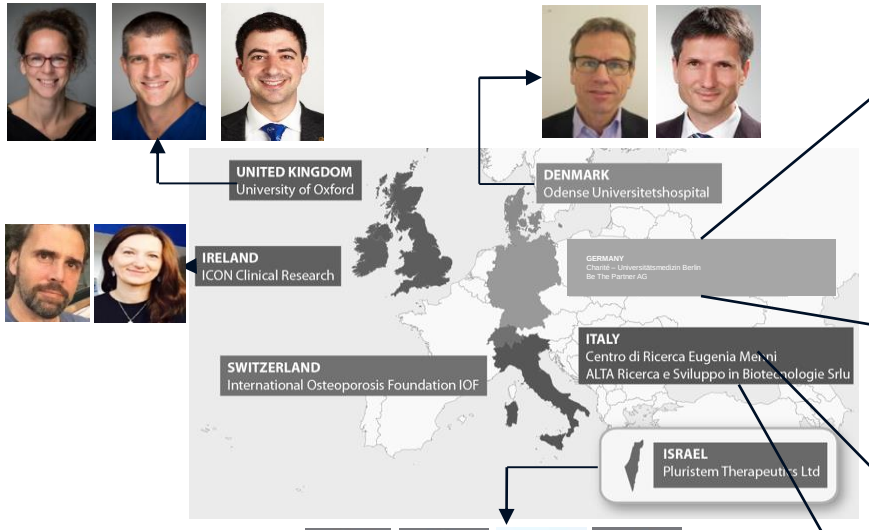
Unmet medical need: Femoral neck fractures

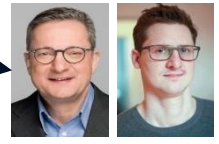
- Intraoperative muscle **trauma** on top Fx & **sarcopenia** in elderly patients
- impaired mobilization + **surgical stress** in frail
- high mortality





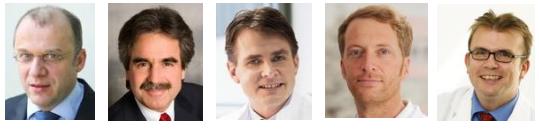
EMA Phase III approval study: Multicentre clinical trial





European Commission

External Advisory Board



hipgen

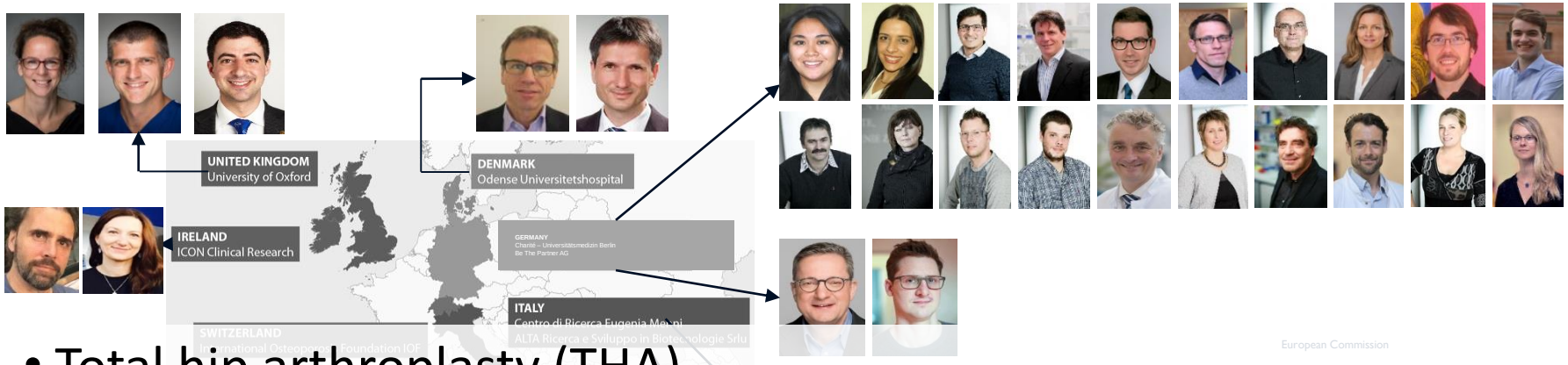
Pluristem Therapeutics Inc.

JULIUS WOLFF INSTITUT

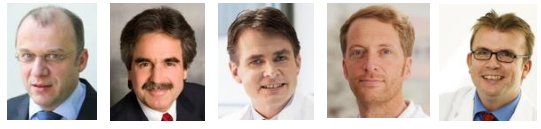
BIH Regeneration
BIH Center for Regenerative Therapies (BCRT)

CENTRUM FÜR MUSKULOSKELETALE CHIRURGIE

EMA Phase III approval study: Multicentre clinical trial



- Total hip arthroplasty (THA)
  or Hemiarthroplasty (HA) via lateral approach
- IP administration IM during surgery in 10 injections (1.5mL each)
- **240 patients total** *(09/2018 1st patient in, 11/2019 50% patients enrolled)*

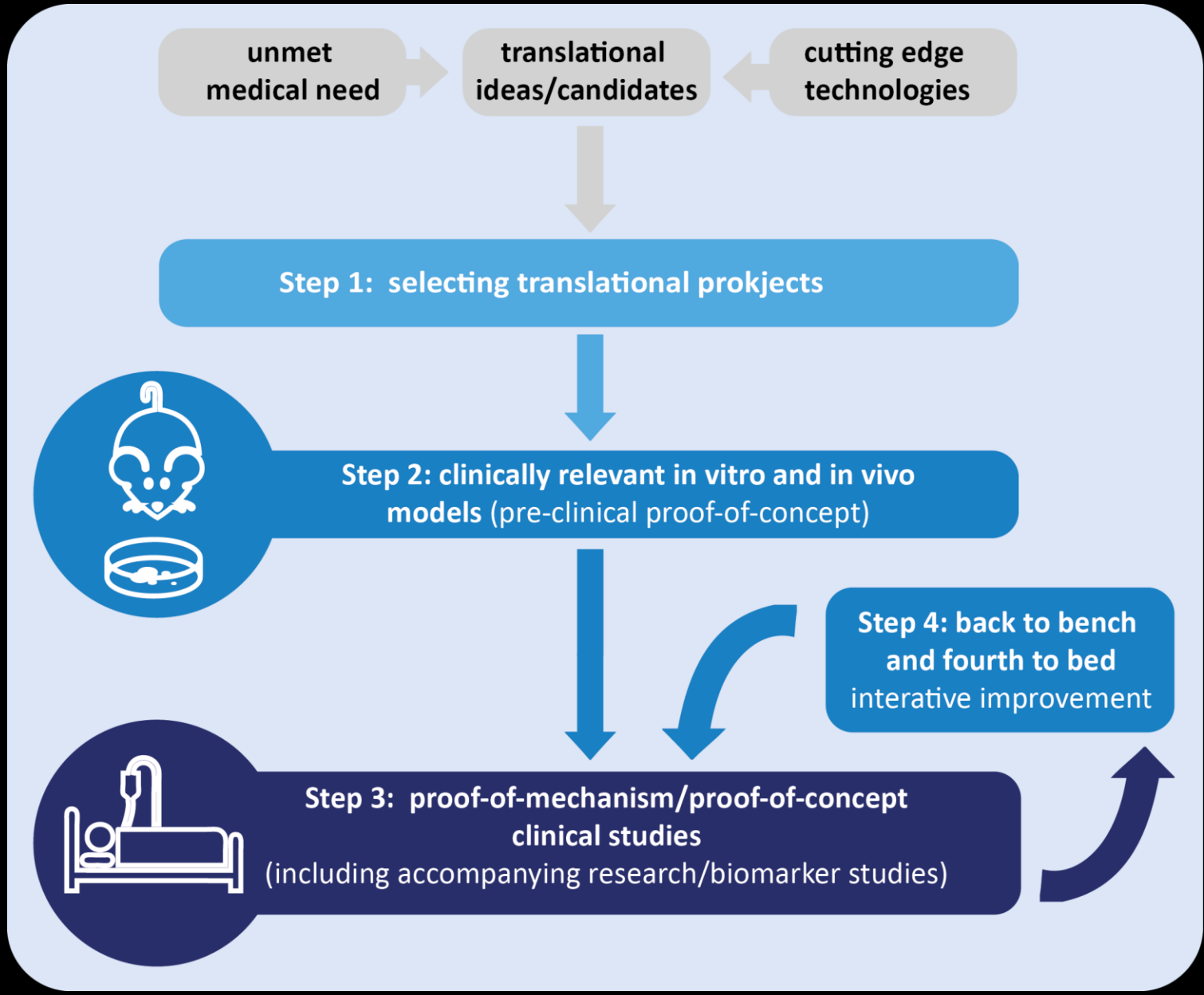


hipgen

Pluristem Therapeutics Inc.

Lessons learned…

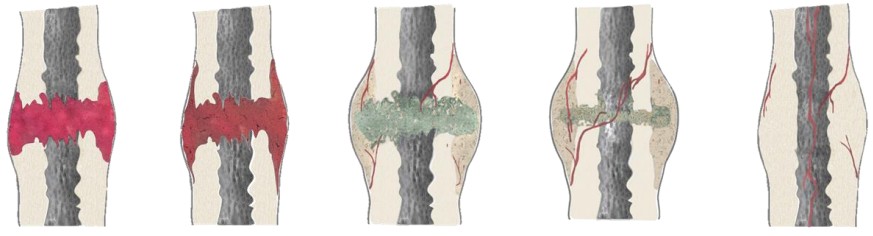
“refined translation”

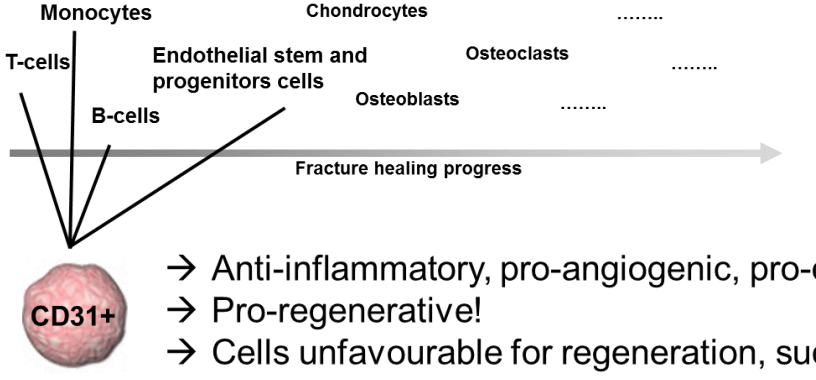


Volk HD et al., Sci Transl Med 2015
DFG Positionspapier “Translation“ Sept 2019

PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial

“prospective, mono-center, single-blinded, randomized, controlled study to assess the safety and efficacy of applying concentrated autologous CD31+ cells to promote bone healing in patients at risk with humeral head fracture”



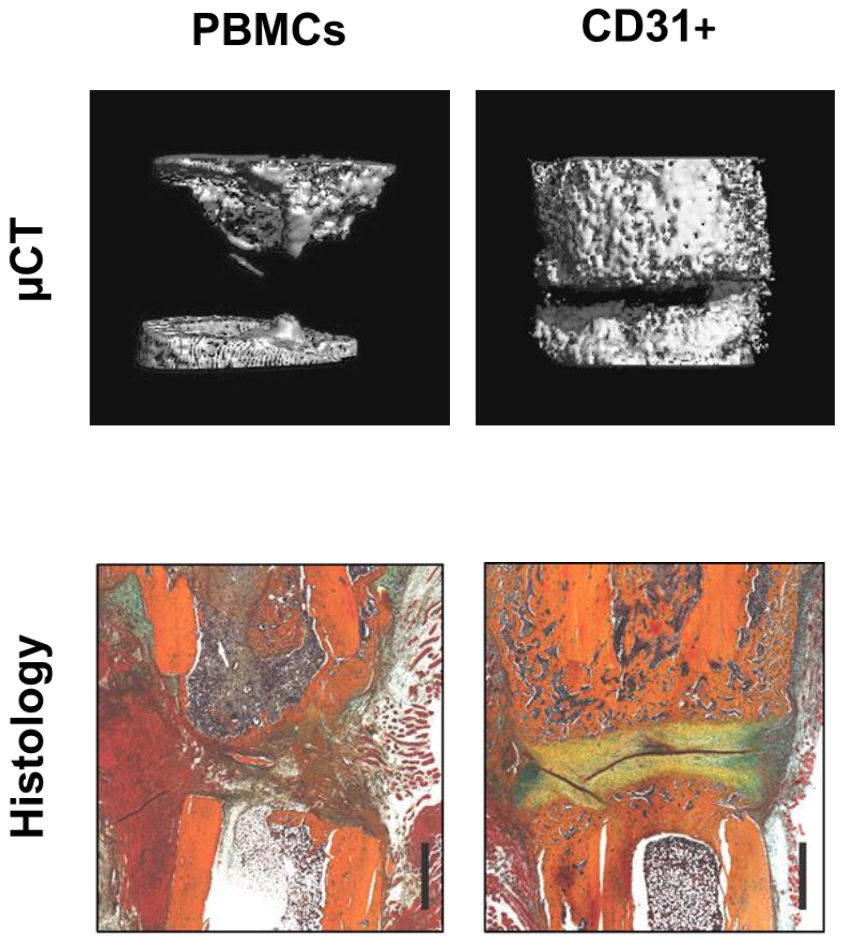


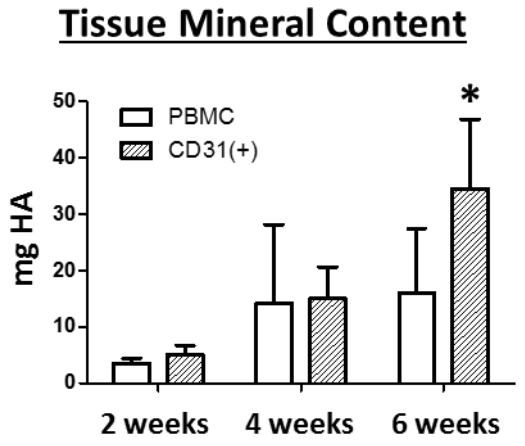
→ Anti-inflammatory, pro-angiogenic, pro-osteogenic
→ Pro-regenerative!
→ Cells unfavourable for regeneration, such as TEMRA cells, are CD31-

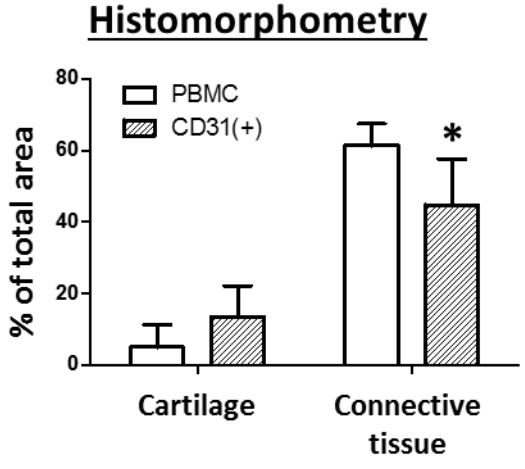
Hypothesis

Intra-operative CD31+ cell concentration improves biologically impaired bone healing

PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial



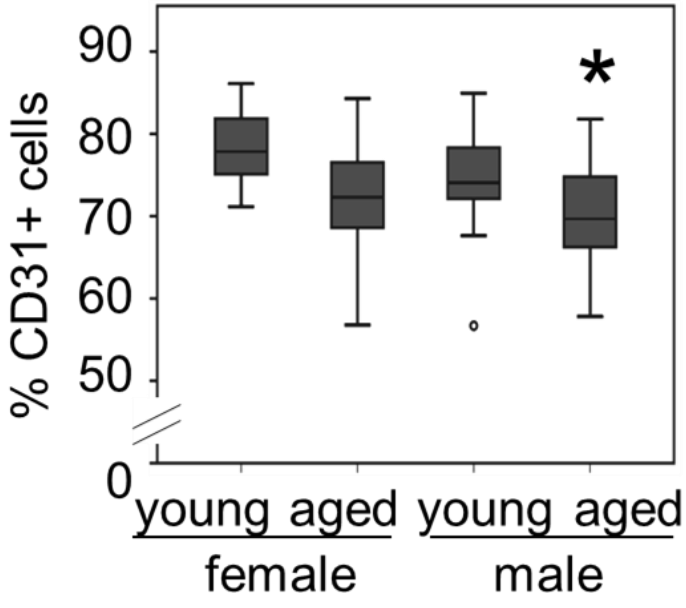




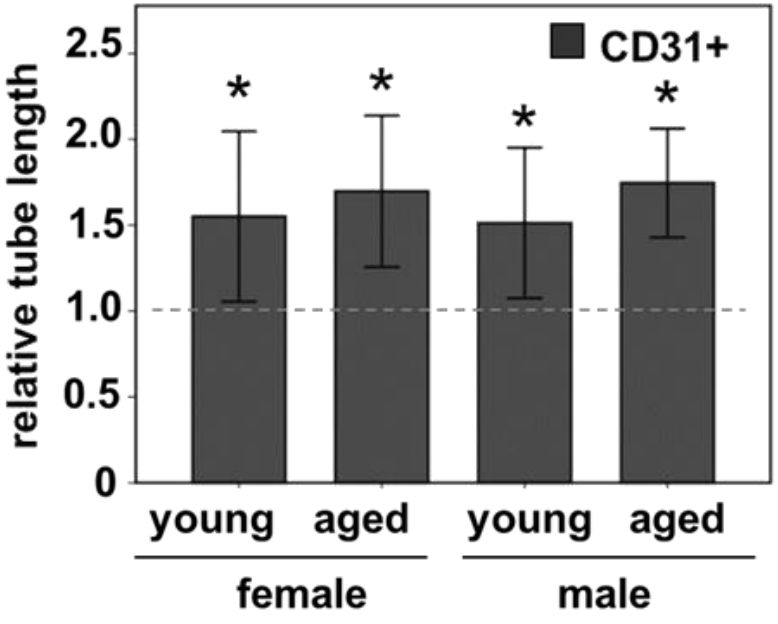
* Significant to control, p≤0.05, n≥5, bar = 1mm

PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial

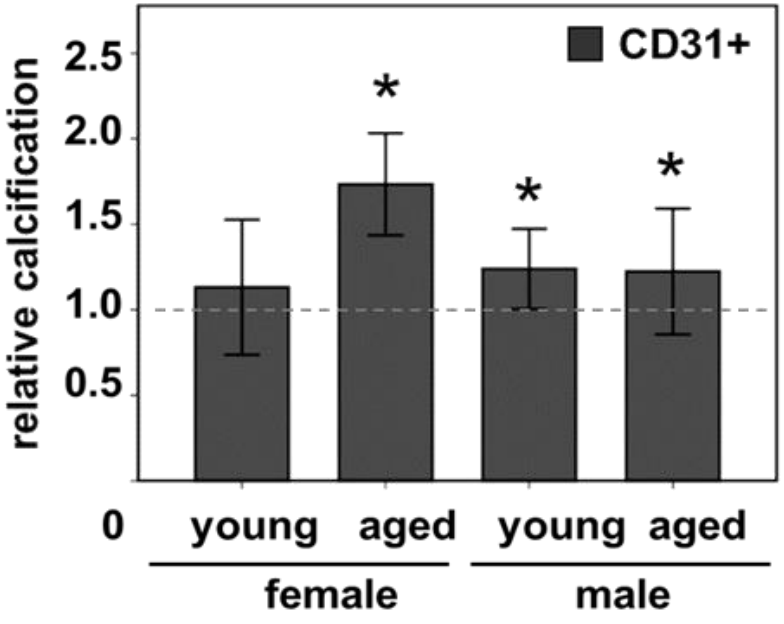
Availability



Angiogenic Potential

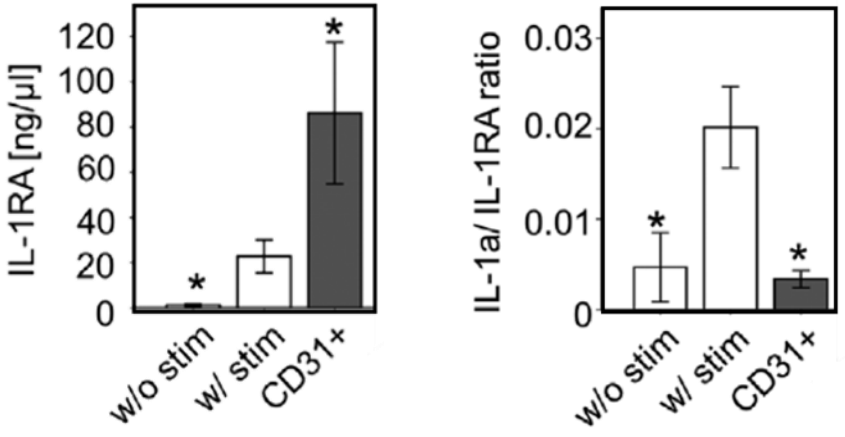


Osteogenic Potential

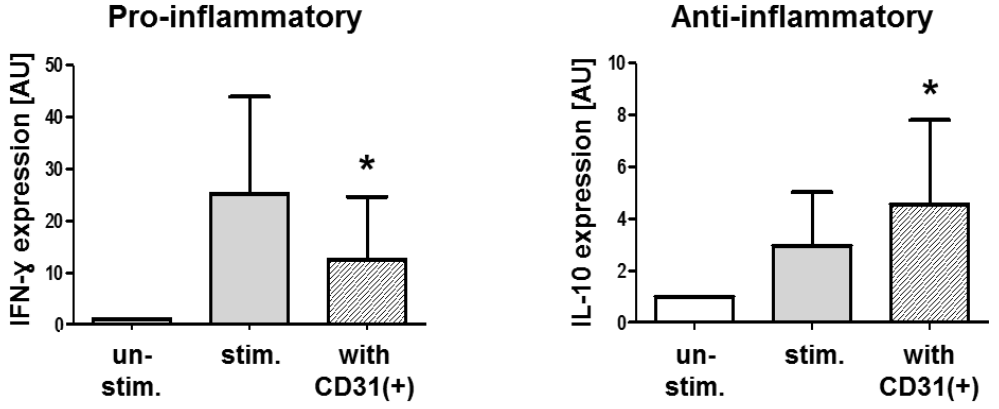


PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial

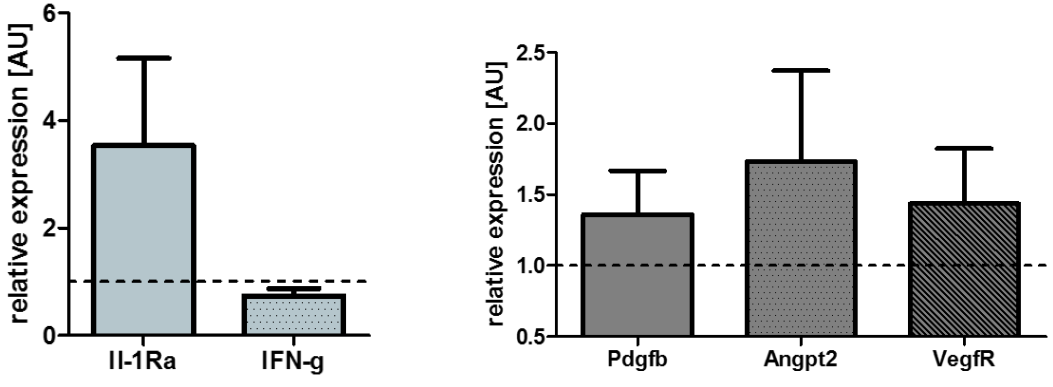
Innate Immune Response - CD14+ LPS Stimulation



Adaptive Immune Response - CD8+ TCR Stimulation



Molecular profile of hematoma of treated rats

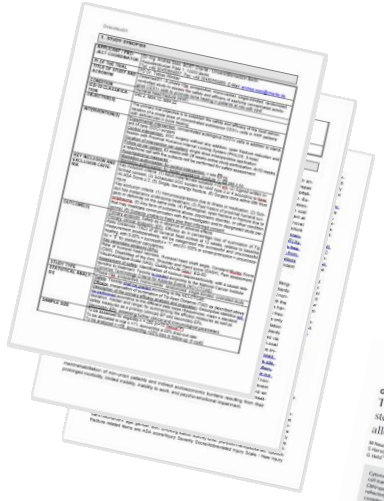


Sass et al., J Bone Miner Res. 2017
Loeffler et al Trends Endocrinol Metab. 2018
Loeffler, Sass et al., Front Immunol. 2019

PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial

- BMBF Call „Early clinical trial“ - OsteoHeal31

- PEI statement as minimally manipulating enrichment method
  Enrichment method in clincial study on CMV-specific T-cells (Neunhahn et.al, 2017)



- EMA-classification of OsteoHeal31 as non-ATMP (2018)

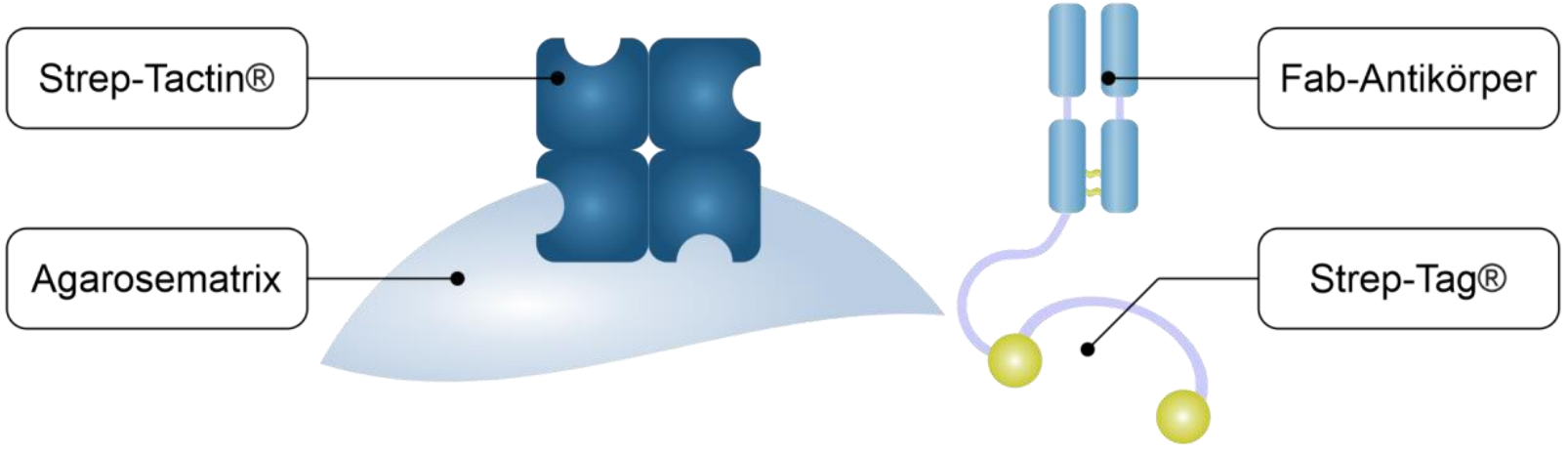
Subject: Osteoheal31 (product ref.: H0004981) - Scientific recommendation on classification of ATMP according to Article 17 of Regulation (EC) No. 1394/2007

Further to the submission dated 04 January 2018 of an application to determine whether the medicine you are developing is an advanced therapy medicinal product, I am pleased to inform you that the Committee for Advanced Therapies (CAT), following consultation with the European Commission, has adopted at its plenary of 16 March 2018 a scientific recommendation of the classification of Osteoheal31, according to according to Article 17 of Regulation (EC) No. 1394/2007.

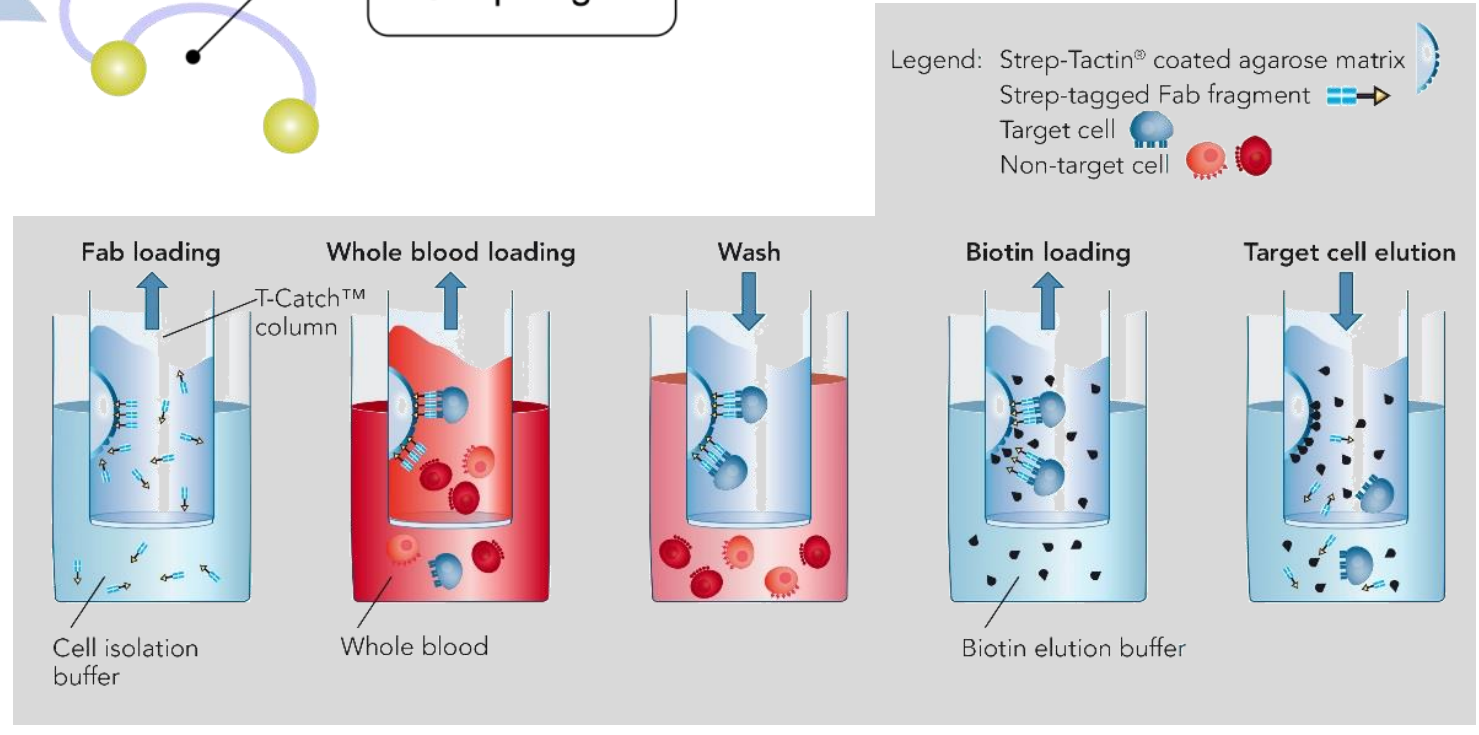
The EMA/CAT considers that product Osteoheal31, **does not fall within the definition of an advanced therapy medicinal product** as provided in Article 2 of Regulation (EC) No 1394/2007.

PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial

TACS-Technologie



ZIM
Zentrales Innovationsprogramm Mittelstand



CELLPEDIA
Experience Cell Selection

PEI Pre-Advice “Osteoheal31” as Phase I/IIa approval trial

Regulatory Requirements

Non-ATMP

- X gene therapy
- X tissue engineering
- X somatic cell therapy

No Investigational Medicinal Product

- √ Only administrating human blood cells

Regulatory Documents:

1. GMP-Manufacturing Allowance (LaGeSo)
2. Investigational Medicinal Product Dossiers (IMPD)
3. Information Brochure (IB)
4. Testing Schedule (research ethics committee)
5. Patient Information

6. Approval and Application for Clinical Study

Blood product according to transfusion law

Lessons learned…

- Sound idea & concept (including basic science)
- IP, identify a technology provider
- Seek advice early - with PEI/EMA or authorized bodies
  - definition of technology
  - definition of approval path
  - remaining gaps, what is really needed
  - eventually, definition of patient cohorts

@dfg_public
@berlinnovation
@ChariteBerlin
#Translation

Mind-Set (De-Risk)

Take a Risk
Deep dive into Prototyping, Visualization and Insight Sharing

Emotional and Subjective
Looking beyond the Field & Need Finding and Contemplation

Clinical Affairs
Verify medical needs and balance health economic opportunities (incl. health care provider)

„Opportunity Check“
Check freedom of operation while defining hypothesis

Infrastructure

Campus Regenerative Therapies

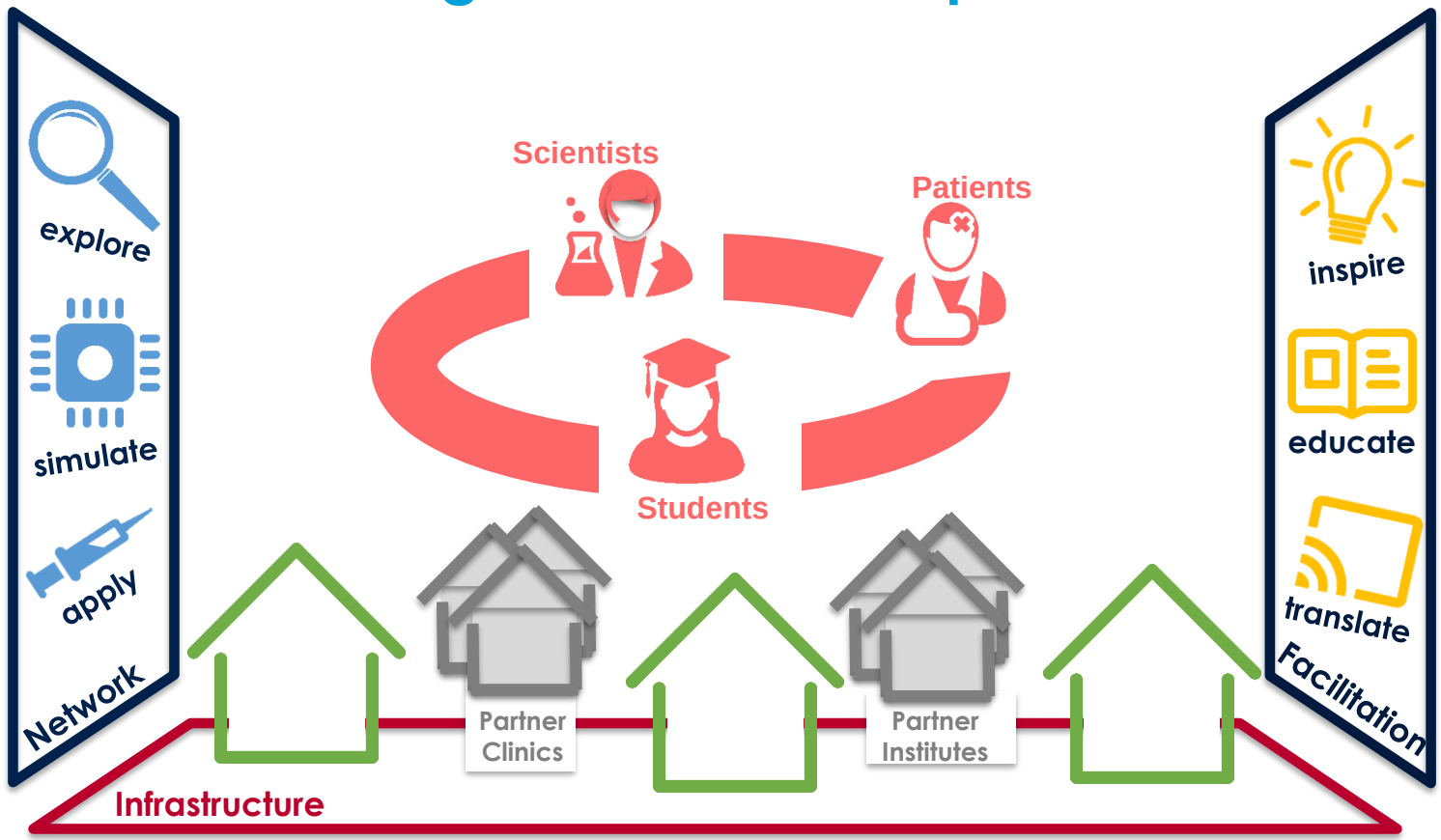
BeCAT

SIM

Cranach

Campus Regenerative Therapies

a **Campus** for People
for Research and Development of
Regenerative Therapies



R&D Network

BCRT - Exploration
by Clinical Driven Basic Research

SI-M - Simulation
employing Human Model Systems

BECAT – *Application*
of Advanced Therapies

Facilitation of R&D

ECRT – Inspiration
of New Ideas

BSRT – Education
of the Next Generations

BCRT – Translation
of Research into Diagnostics & Therapies

Acknowledgements

JWI & CMSC

- Katharina Schmidt-Bleek
- Annemarie Ploboth
- Ansgar Petersen
- Sven Geissler
- Simon Reinke
- Georg Bergmann
- Hendrik Schmidt
- Sara Checa
- Julia Löffler
- Claudia Schlundt
- Christian Bucher
- Sebastian Wendler
- Saeed Khomeijani Farahan
- Aline Lückgen

- Ulrich Stöckle
- Carsten Perka

Local

- Hans-Dieter Volk, Immunology & BCRT
- Petra Reinke, Nephrology & BCRT
- Andreas Radbruch, DRFZ
- Anja Hauser, DRFZ
- Raluca Niesner, DRFZ

- Peter Fratzl, MPI Colloids & Interfaces
- Richard Weinkammer, MPI Colloids
- Amaya Cipitria, MPI Colloids

- Stefan Mundlos, MPI Genetik & BCRT
- Uwe Kornak, MPI Genetik & BCRT

- Petra Knaus, FU Biochemistry
- Jessica Kopf, FU Biochemistry

- Andreas Lendlein, HZG Biomaterials
- Axel Neffe, HZG Biomaterials

National/International

- David Mooney, Harvard Wyss
- Viola Vogel, ETH
- Dave Grainger, U Utah

- Dietmar Hutmacher, QUT Brisbane
- Devakara Epari, QUT Brisbane

- Franz Jakob, Uni Würzburg

- Ralf Adams, MPI Münster

- Klaus-Dieter Schaser, Dresden
- Georg Matziolis, Jena

- William R Taylor, ETH Zurich
- Markus O. Heller, Southhampton
- Bettina Willie, McGill

Deutsche Forschungsgemeinschaft DFG

Bundesministerium für Bildung und Forschung

EINSTEIN CENTER Regenerative Therapies

www.orthoload.org

Berlin-Brandenburg School for Regenerative Therapies

FOR 2165 Regeneration in Aged Individuals

BERLIN-BRANDENBURG CENTER FOR REGENERATIVE THERAPIES