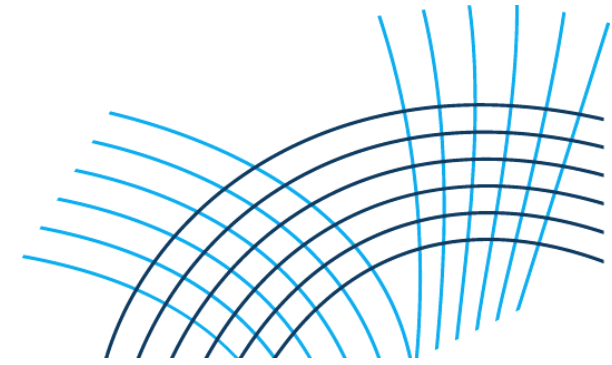


The regenerative face of the immune system for musculoskeletal healing

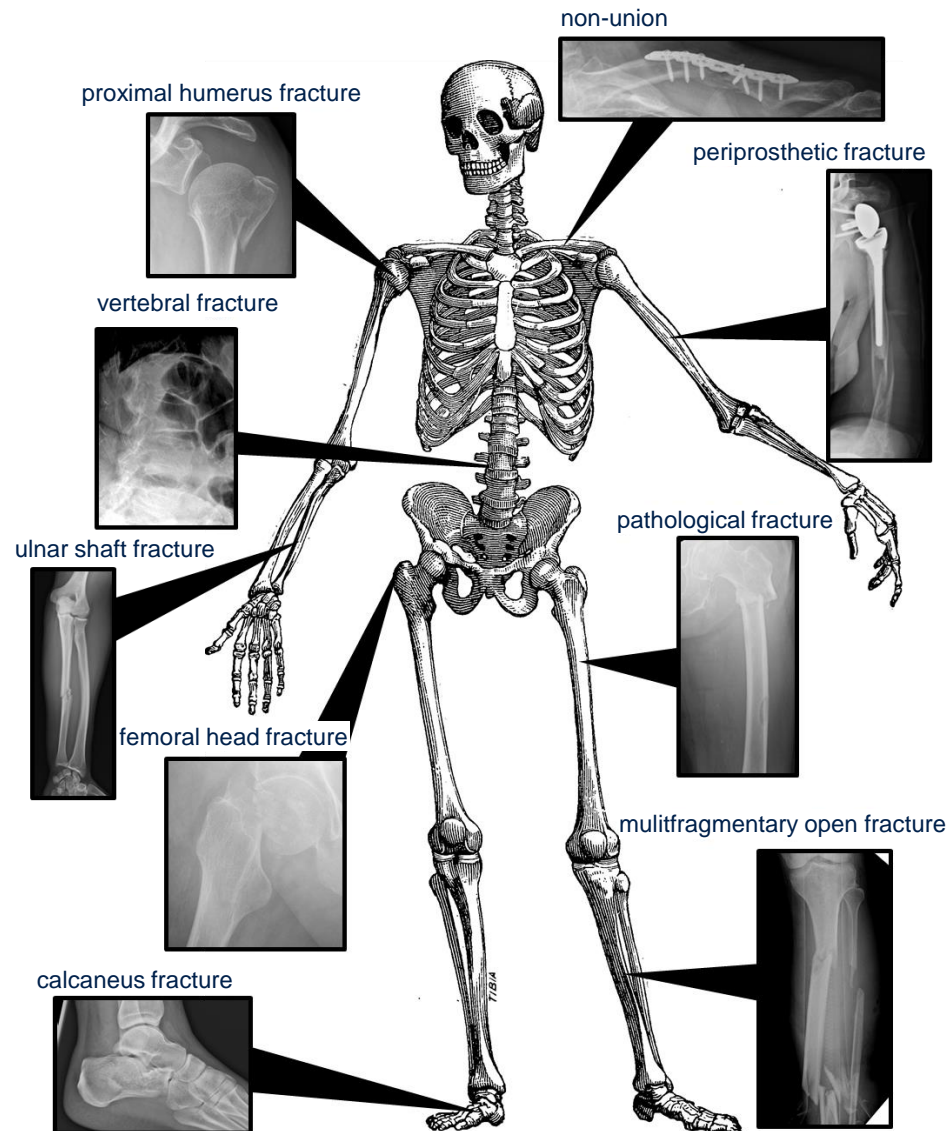
K. Schmidt-Bleek¹, CH Bucher², GN Duda^{1,2}

¹ Julius Wolff Institut

² Berlin Institute of Health Center for Regenerative Therapies
Berlin Institute of Health, Charité - Universitätsmedizin Berlin



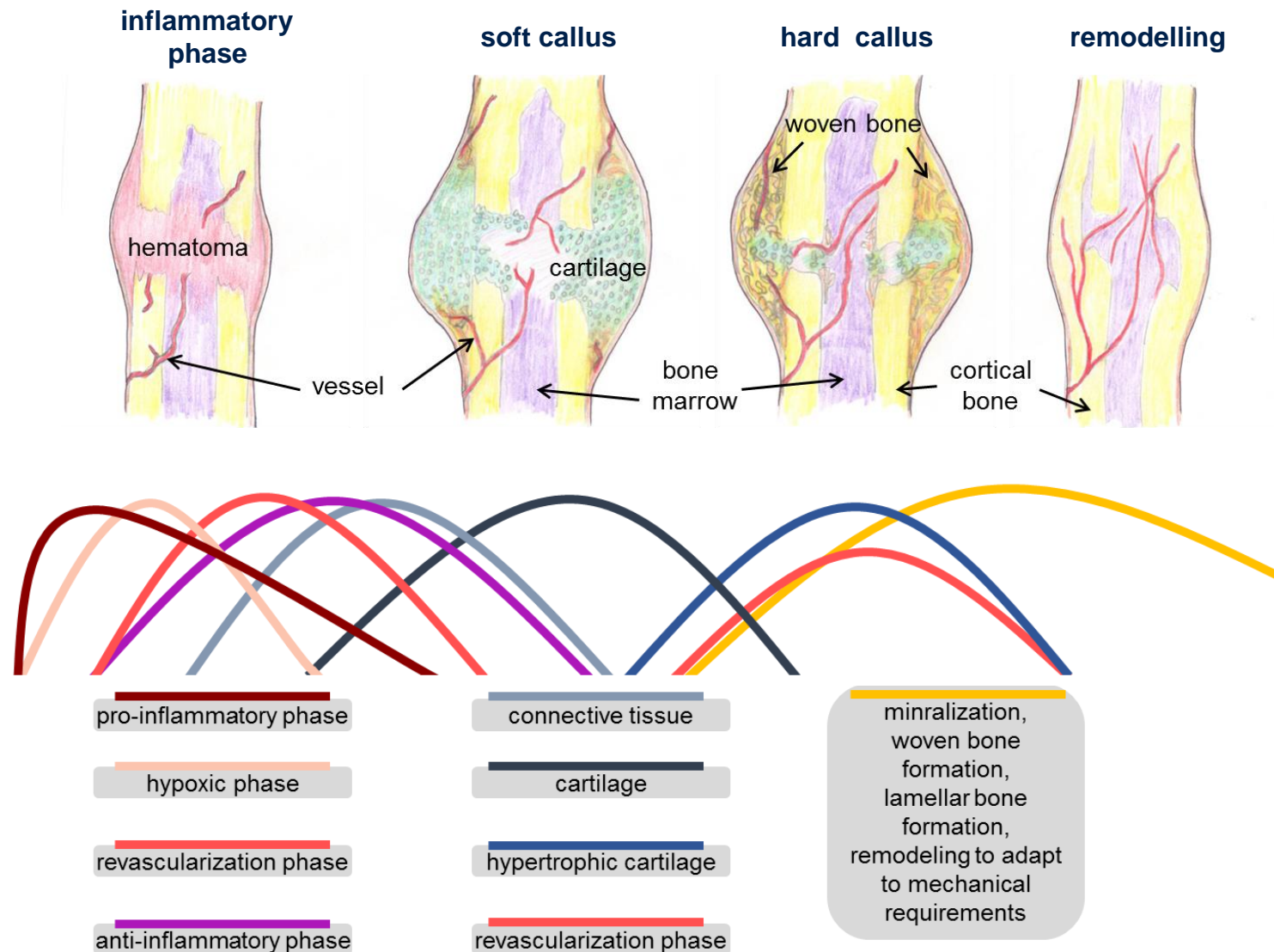
Delayed bone healing still is an unsolved clinical problem



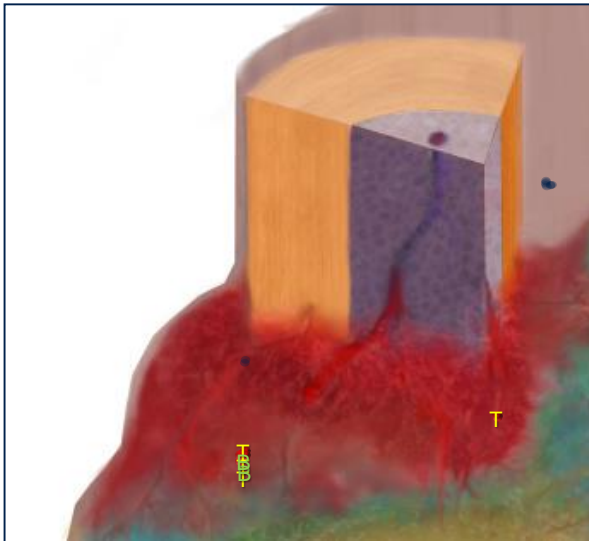
- Multi Centre Study - BioBone:
>600 patients included
- Healing outcome:
after 6 M 30%;
after 9 M 18% delayed healing
- ~160-190 million new bone fractures
occur each year, > 400 million patients
suffer consequences of such an injury
[doi:10.1016/S2666-7568\(21\)00172-0](https://doi.org/10.1016/S2666-7568(21)00172-0) (2021)



The fracture healing process

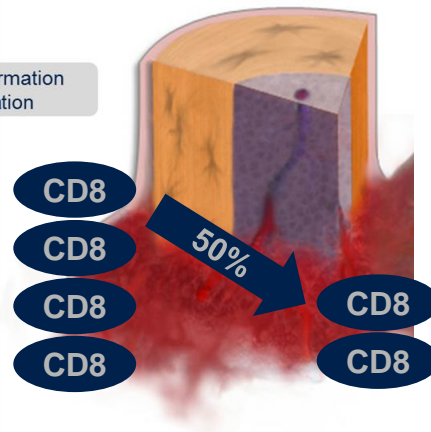


The initial healing phase



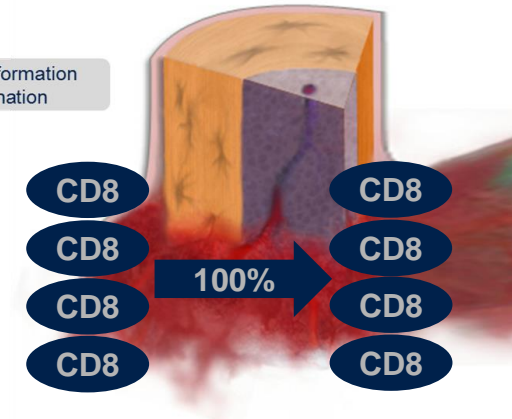
normal healing

hematoma formation
and inflammation



delayed healing

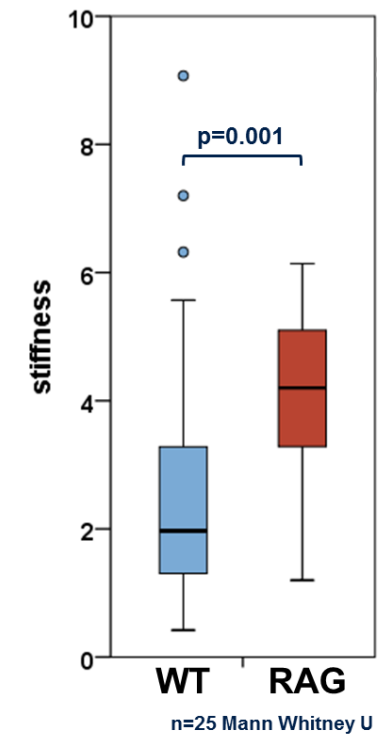
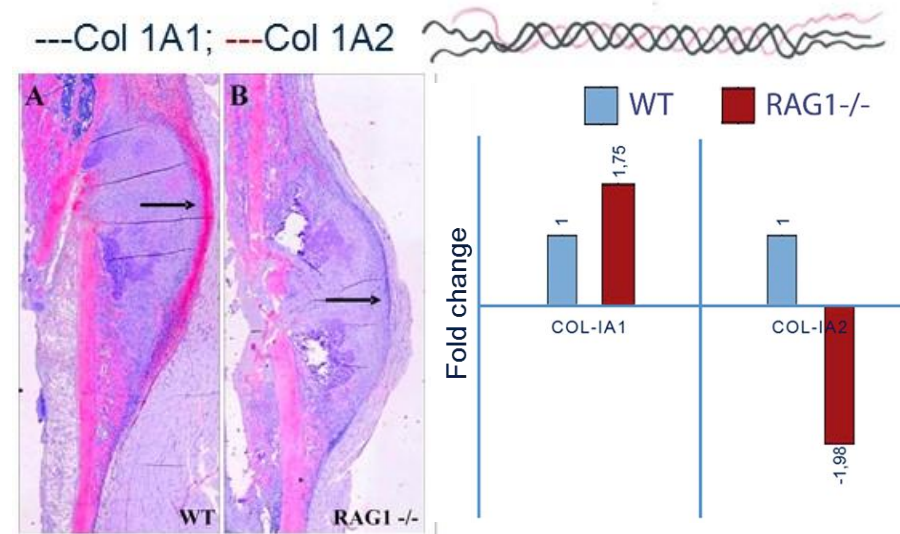
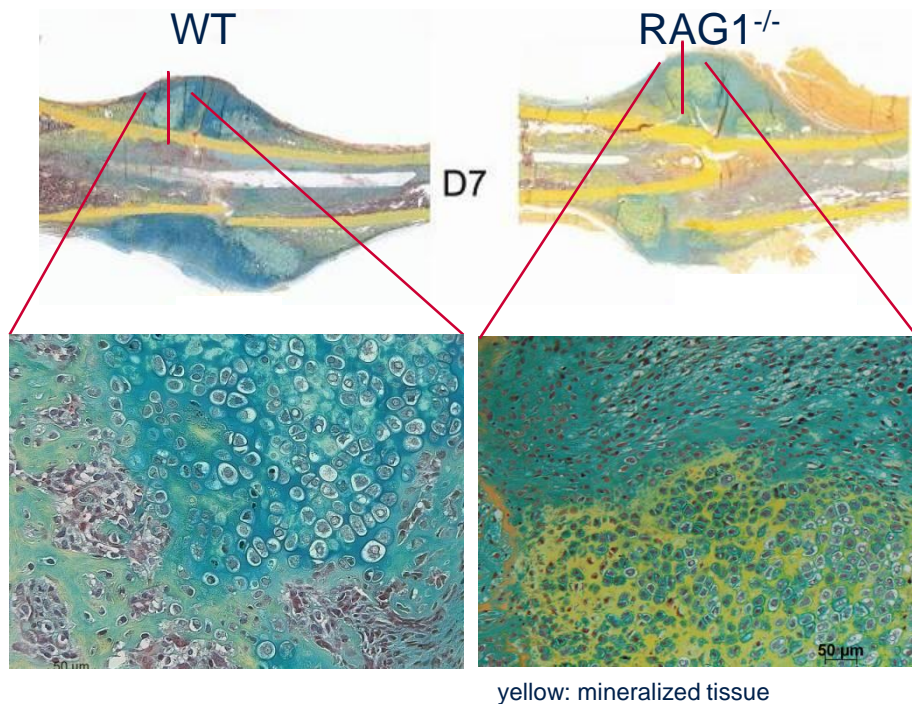
hematoma formation
and inflammation



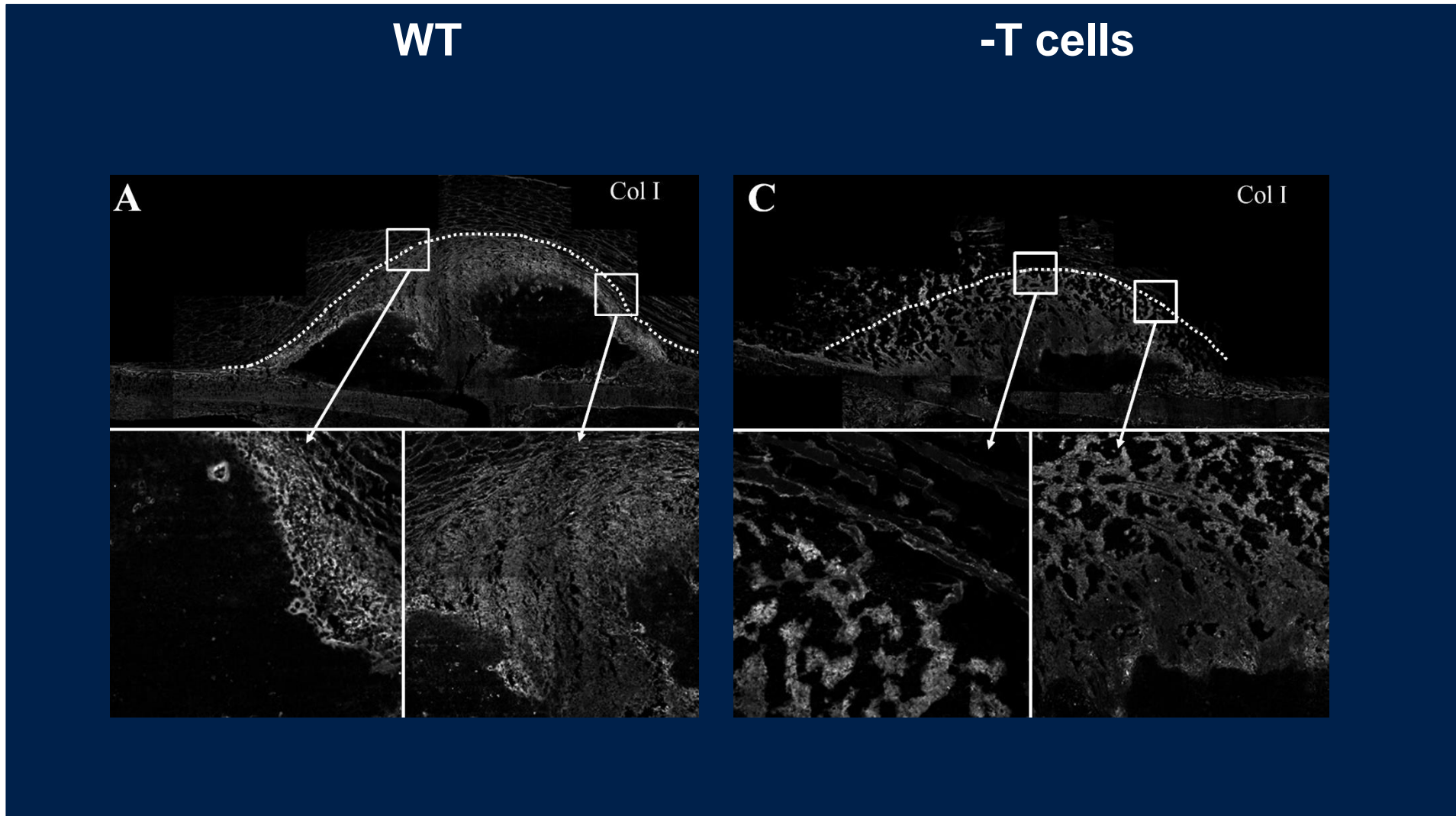
Regeneration and the adaptive immunity

Without B and T cells the bone is stiff = less elastic and thus prone to fracture

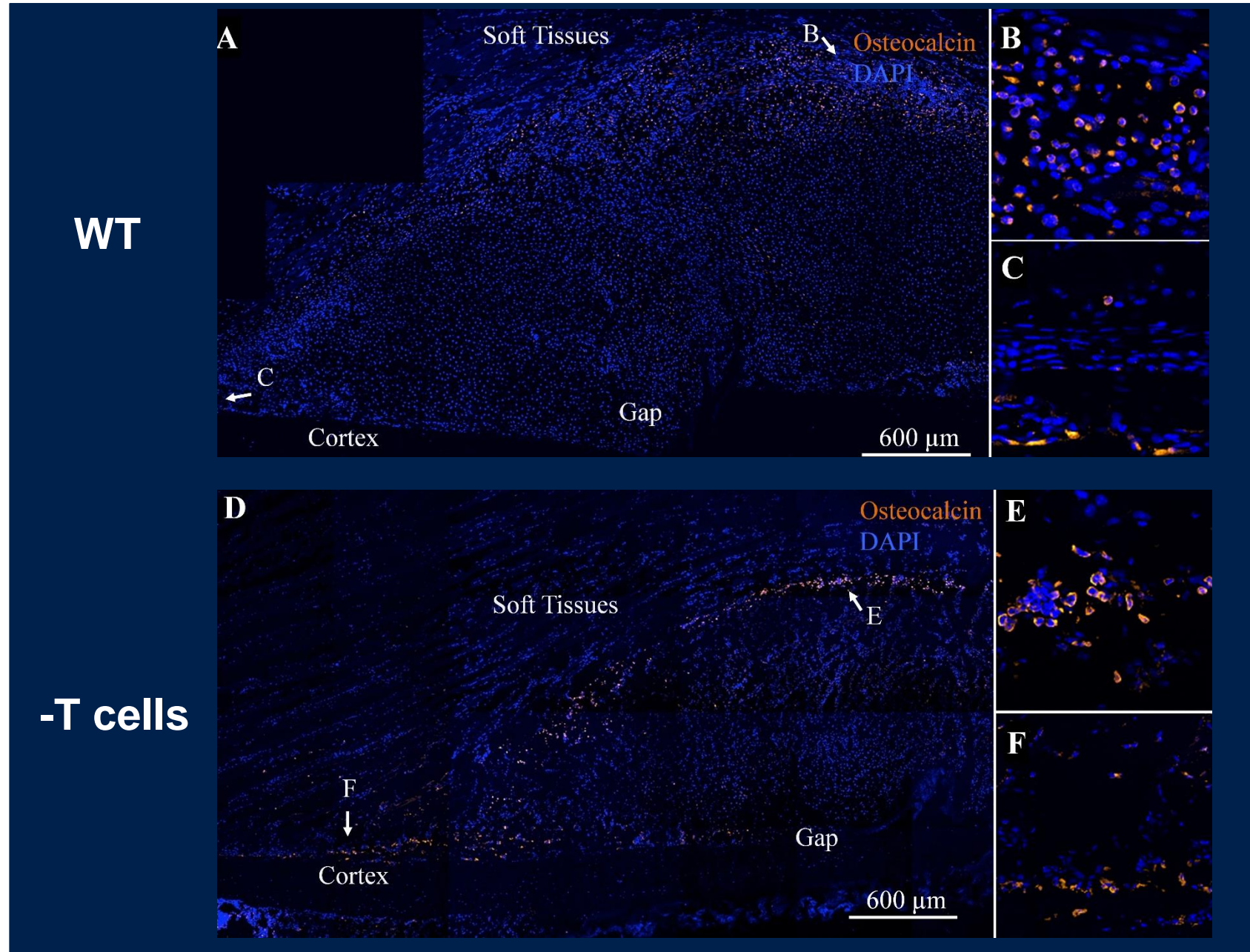
Bone healing without adaptive immune reaction \Rightarrow Fast mineralisation \Rightarrow Imbalance in collagen I formation



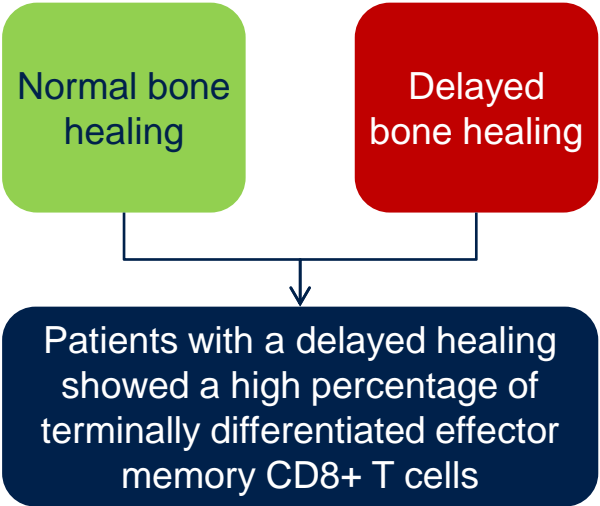
Collagen I formation is dependent on T cells



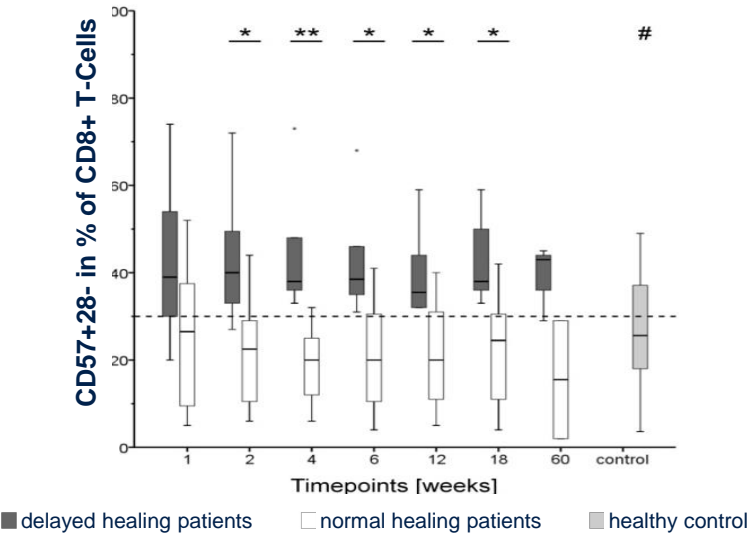
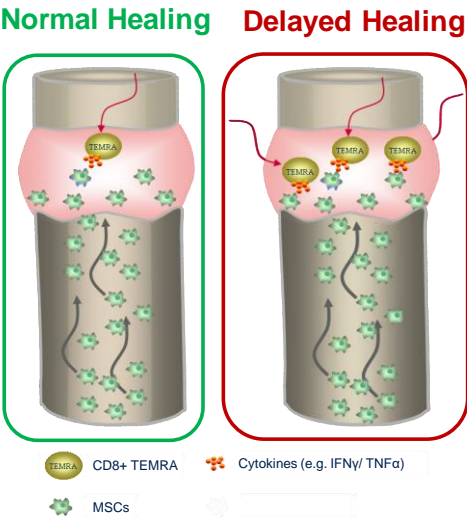
Osteoblast distribution is dependent of T cells



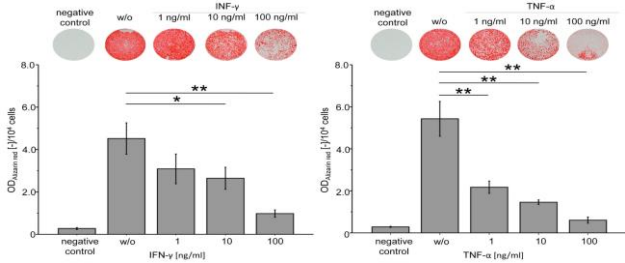
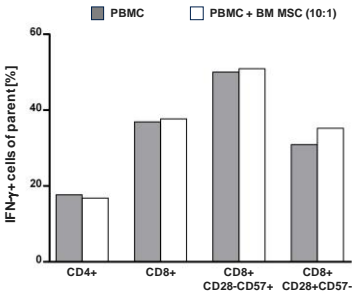
A clinical study to evaluate bone healing



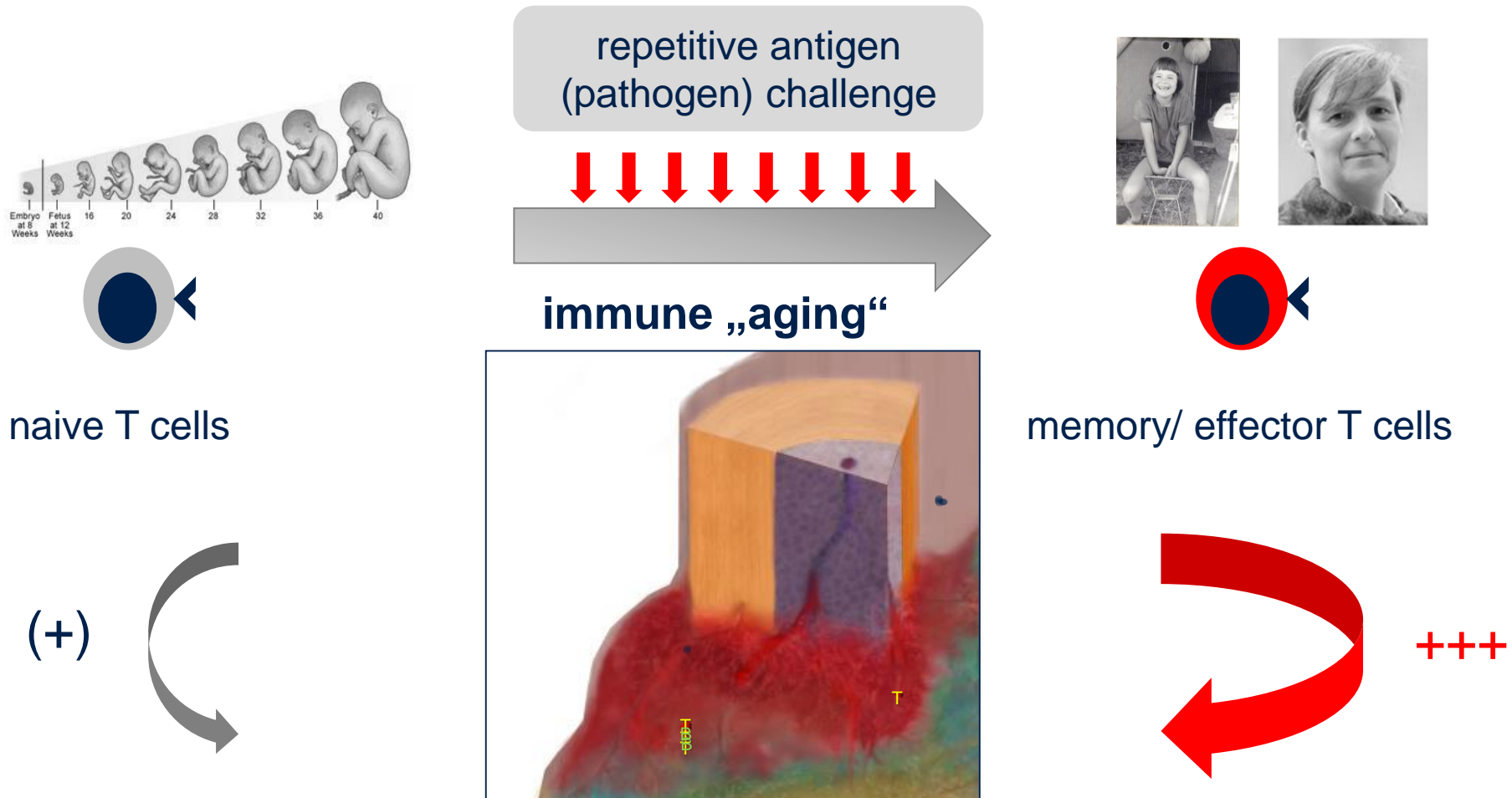
CD8+ effector T cells accumulate within the fracture hematoma



CD8+ effector T cells express high amounts of pro-inflammatory TNF α and IFN γ , cytokines that hinder osteogenic differentiation



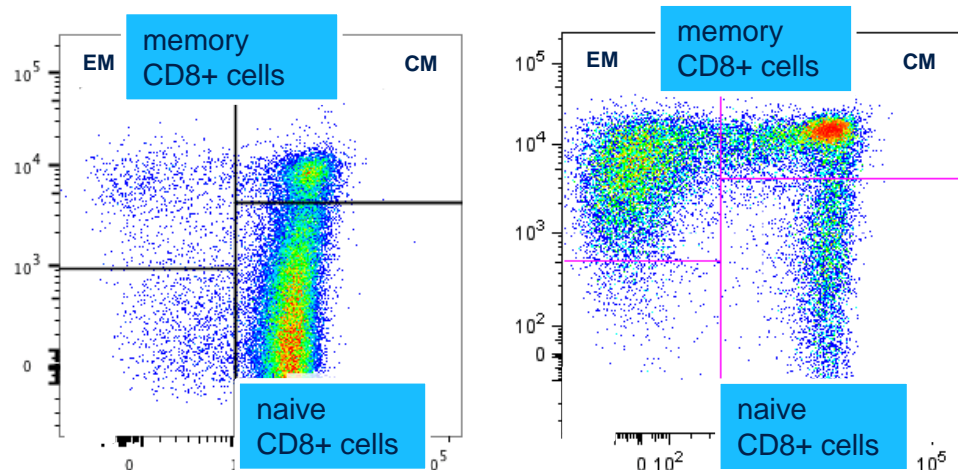
Memory and effector T cells that increase with the evolving immune memory increase the initial pro-inflammatory reaction upon injury



A pre-clinical model for immunological aging



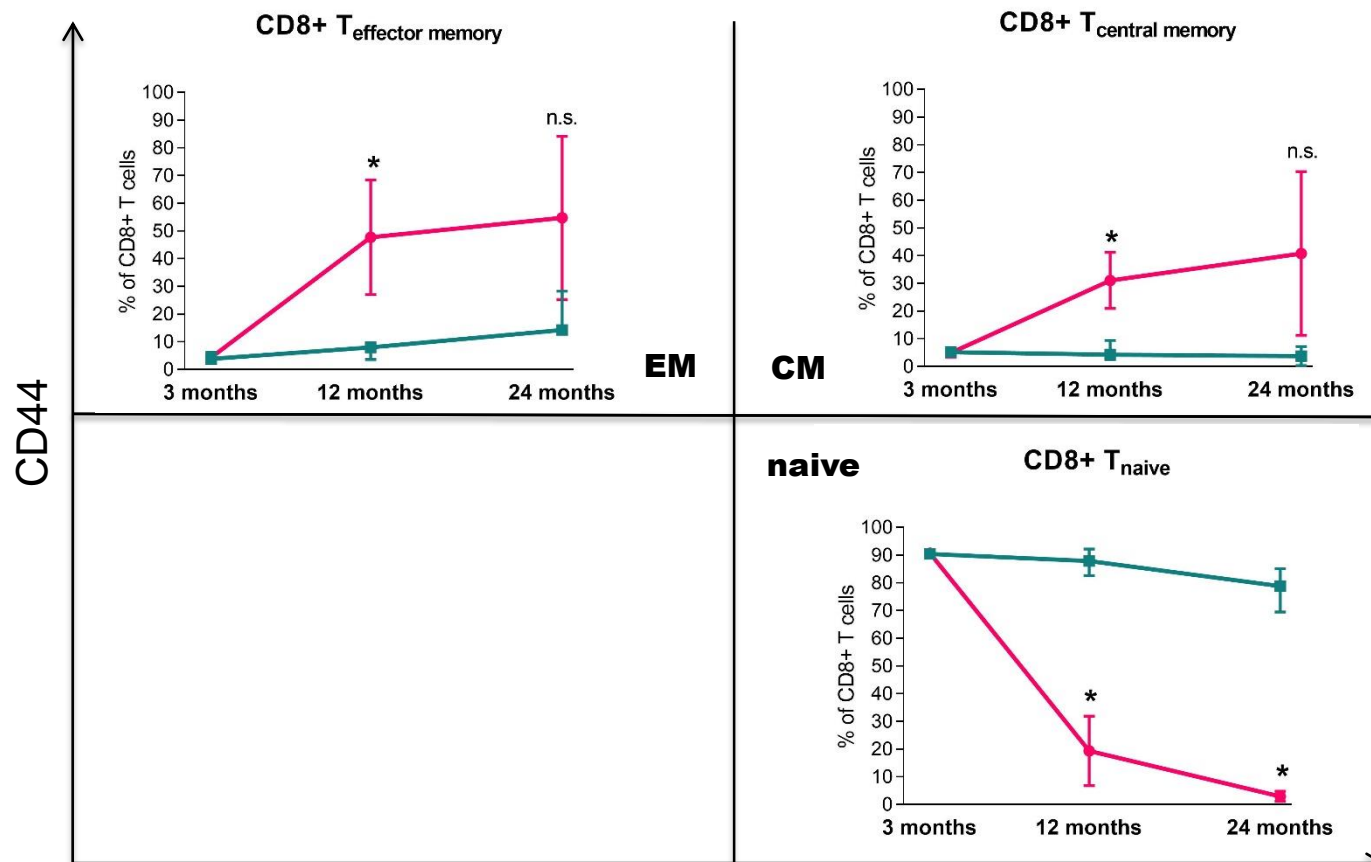
flow cytometry: CD8+ T cells



3 month old mouse (SPF)
Illustration by Gosia Herba

12 month old mouse with an
experienced immune system

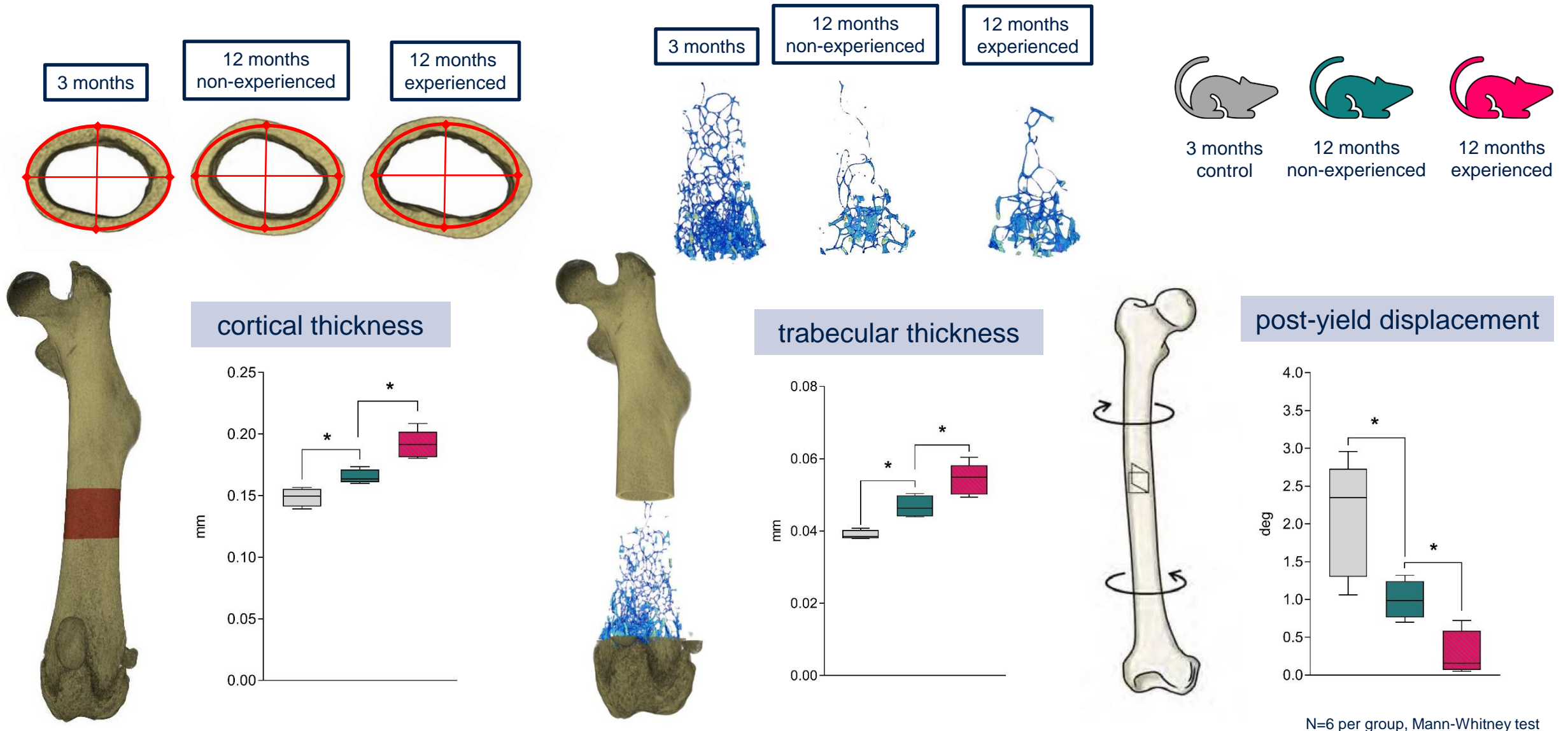
CD8+ T cell compartment and housing conditions



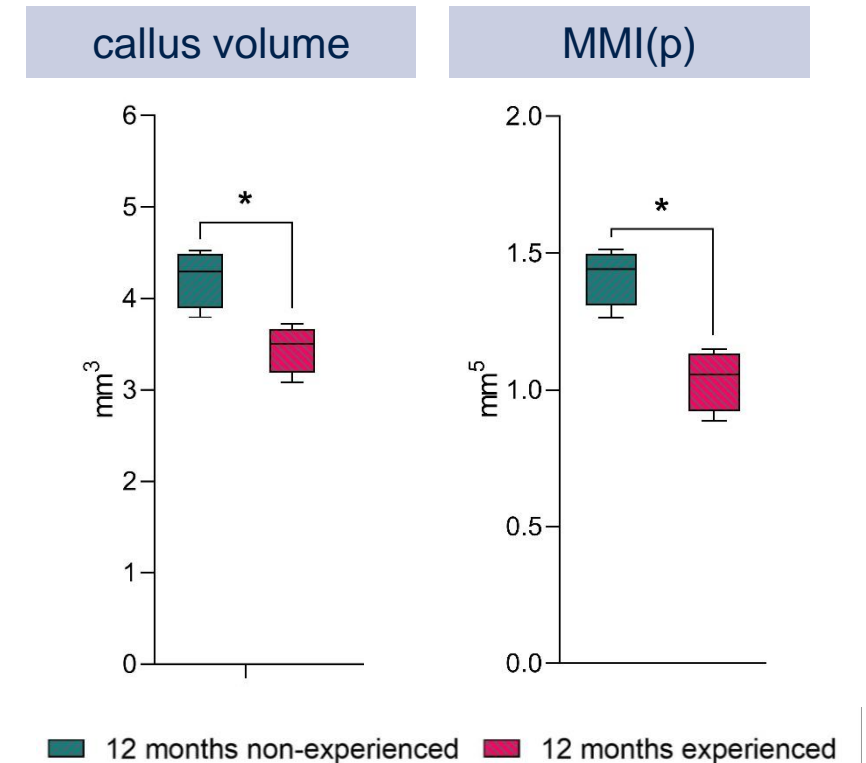
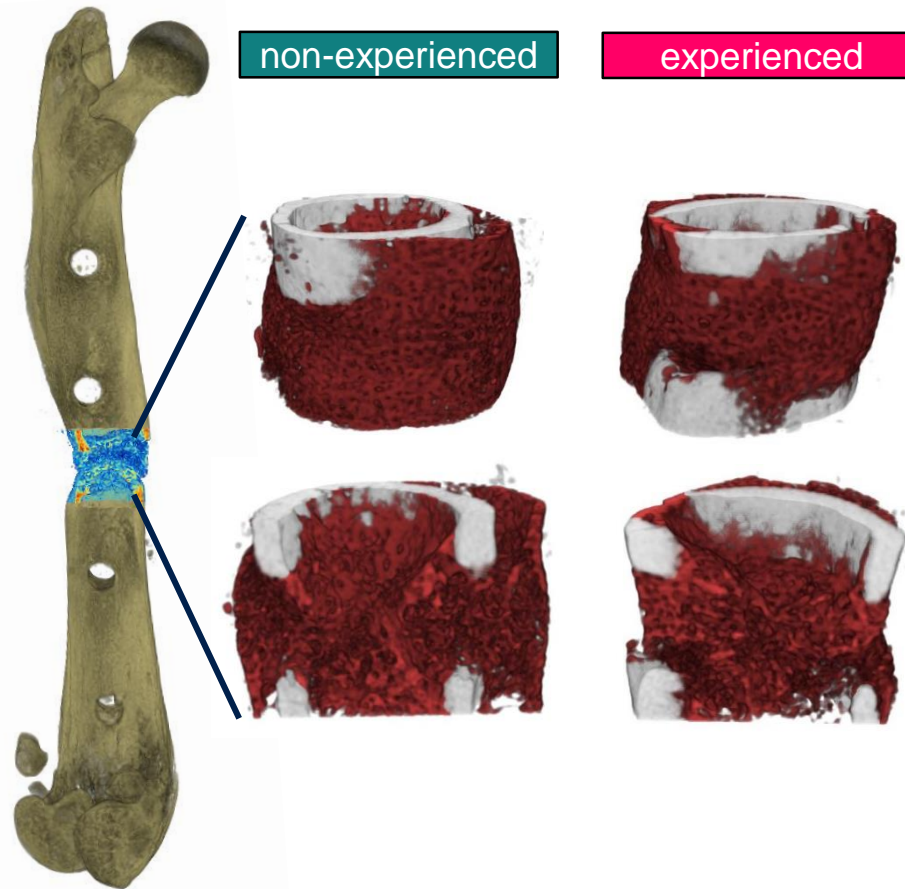
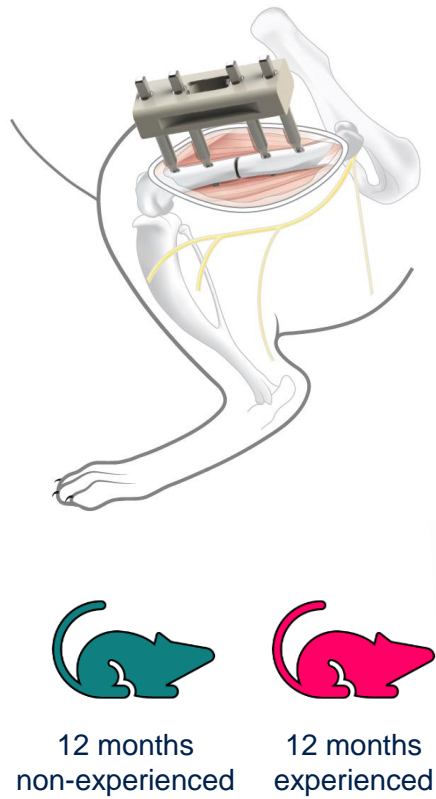
N=6 per group, Mann-Whitney test



Adaptive immunity affecting the bone phenotype



Influence of experience on fracture healing



N=6 per group, Mann-Whitney test

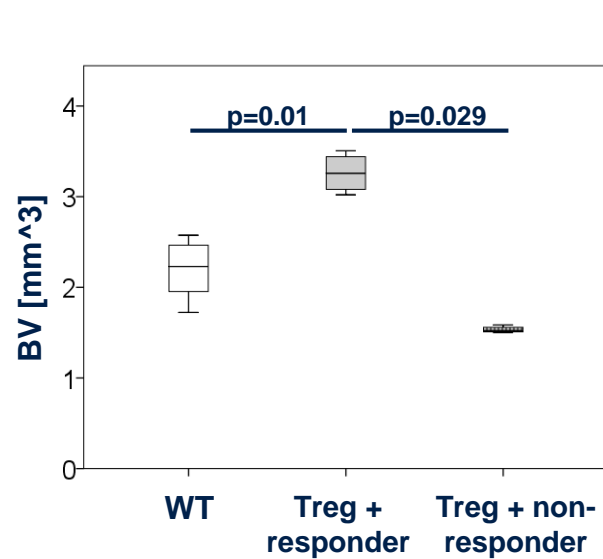
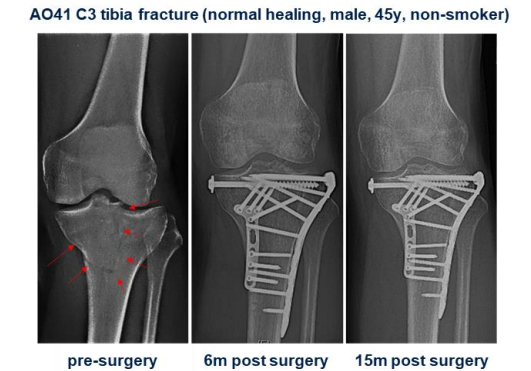
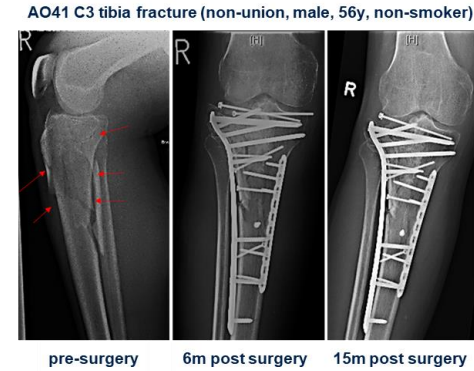
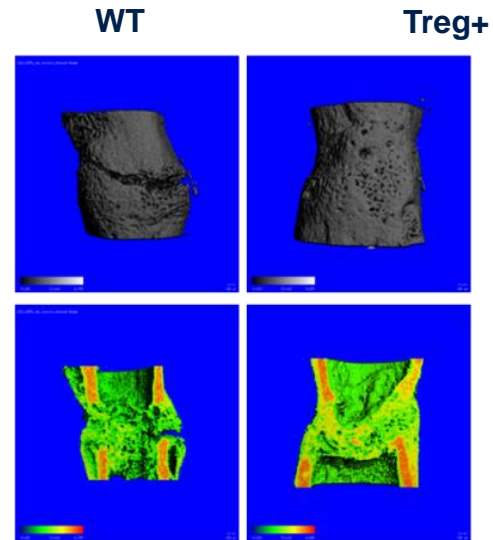
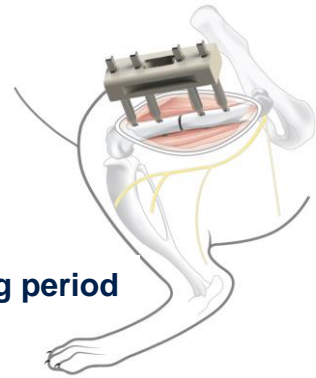


- Bone healing is a complex, very well orchestrated process
- The adaptive immune system does play an important role in bone regeneration
- Effector memory CD8+ T cells and their pro-inflammatory signalling do have a negative influence on the regenerative potential

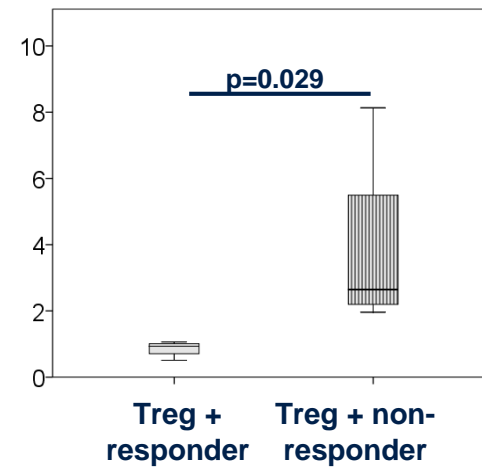
The question that keeps us busy right now is:
How to use this knowledge to enhance bone healing?
How to use this knowledge to develop new treatment approaches?

=> Our strategy is to downregulate the influence of the effector memory CD8+ T cells.

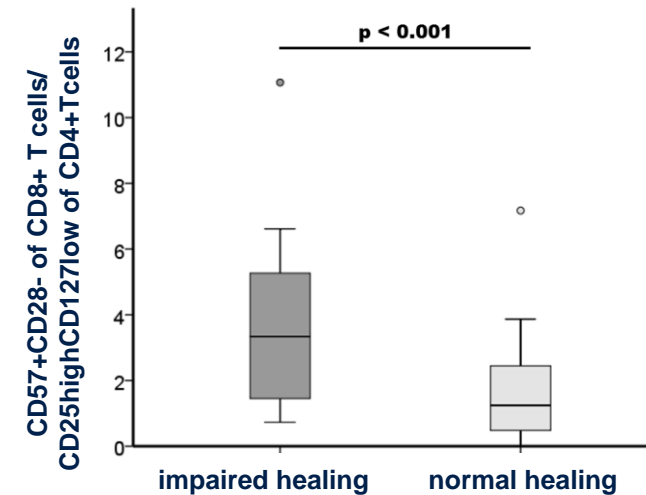
Targeting the natural counter balancer - Tregs



CD8+ effector T cells/
CD4+ Treg



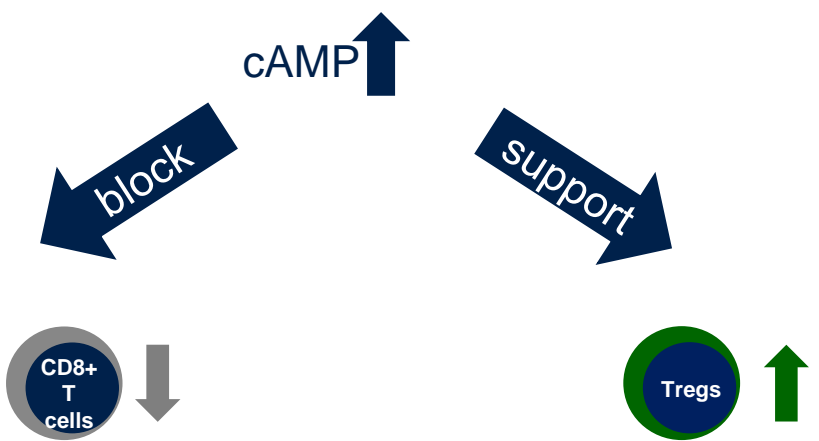
CD8 T_{EMRA} / CD4 Treg ratio
in peripheral blood of fx patients



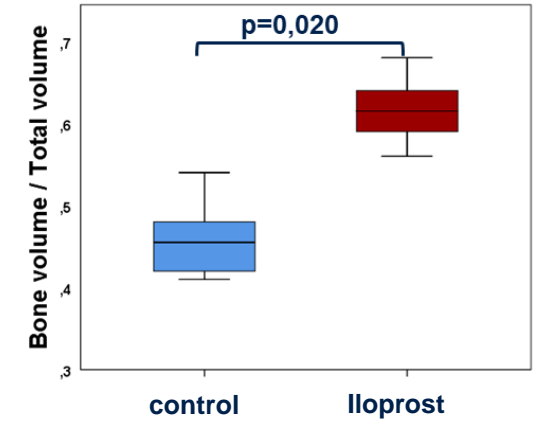
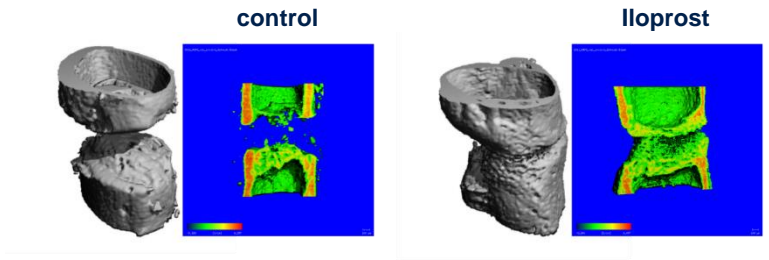
Reducing the activity of CD8+ T cells



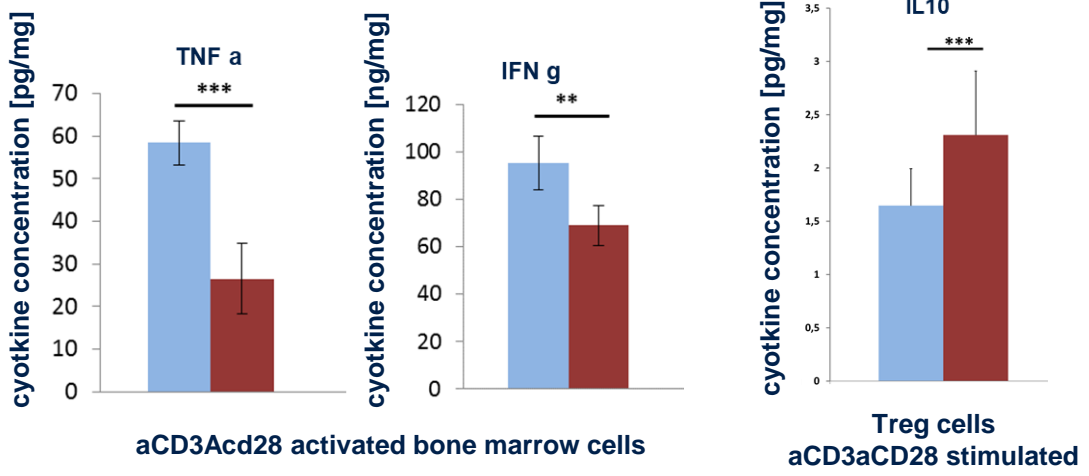
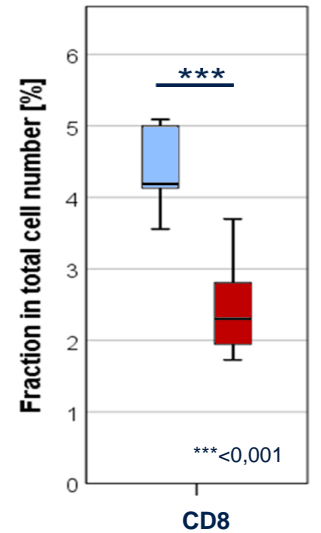
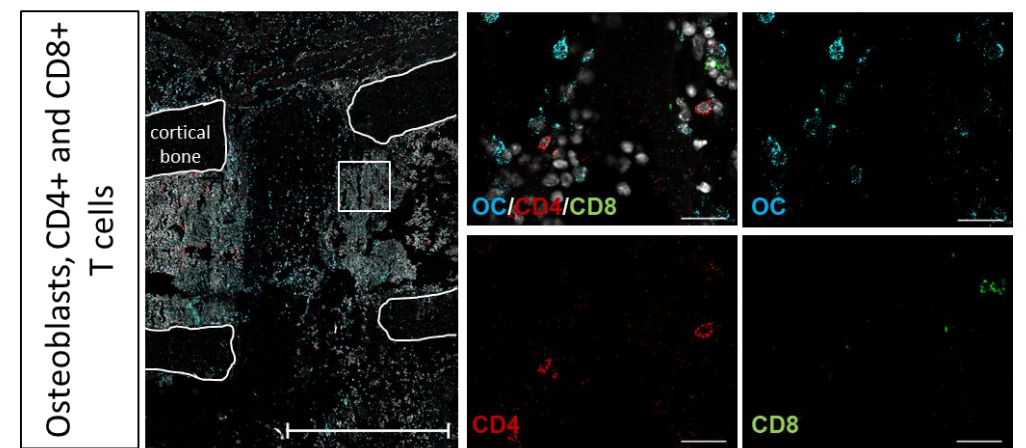
Prostacyclin (Iloprost)
(Adenylatcyclase)



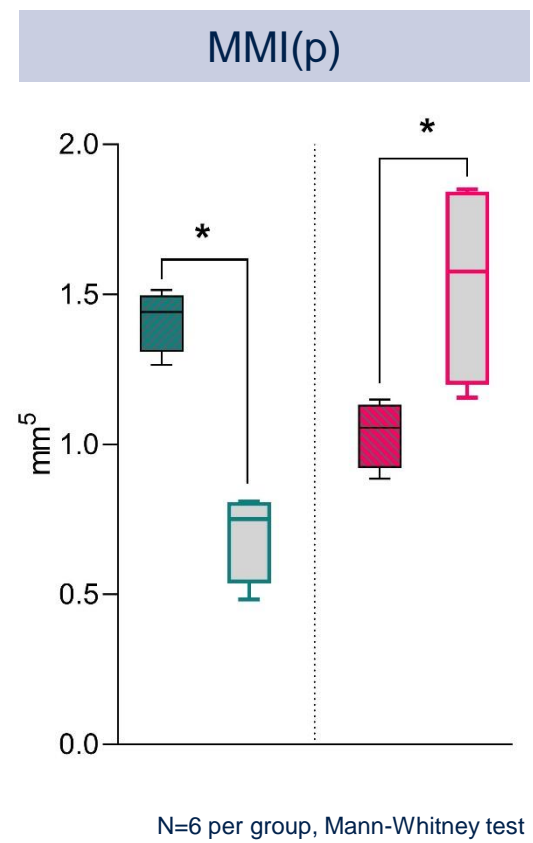
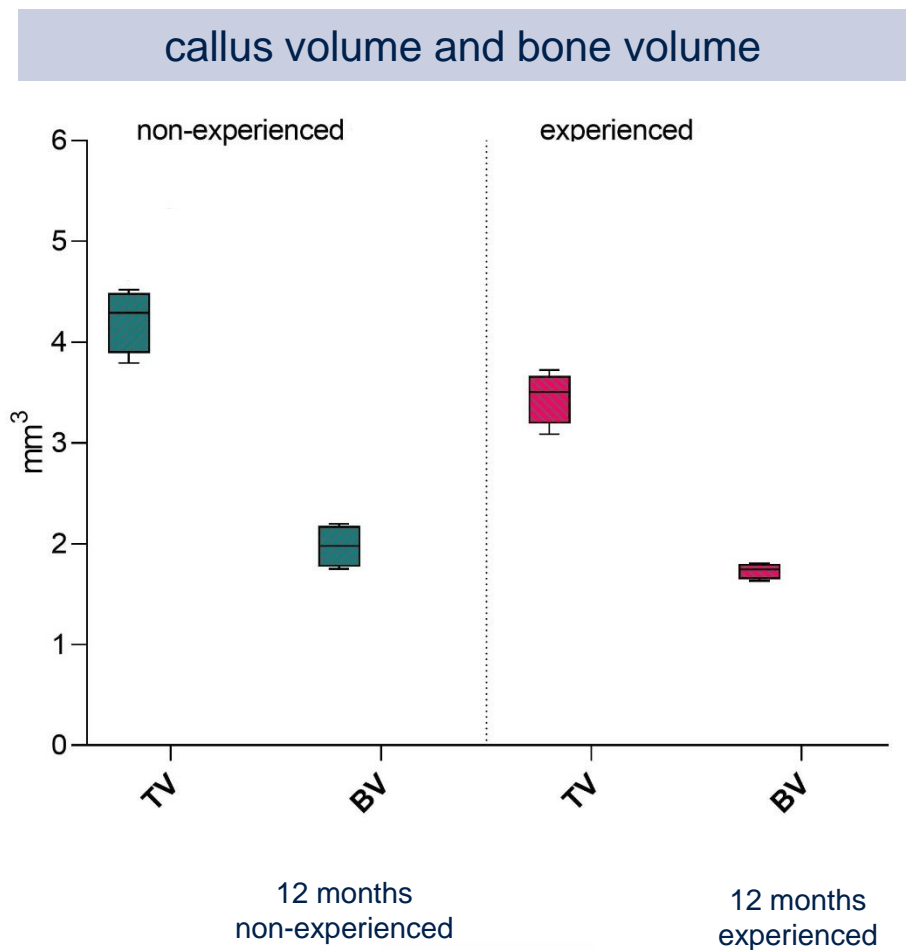
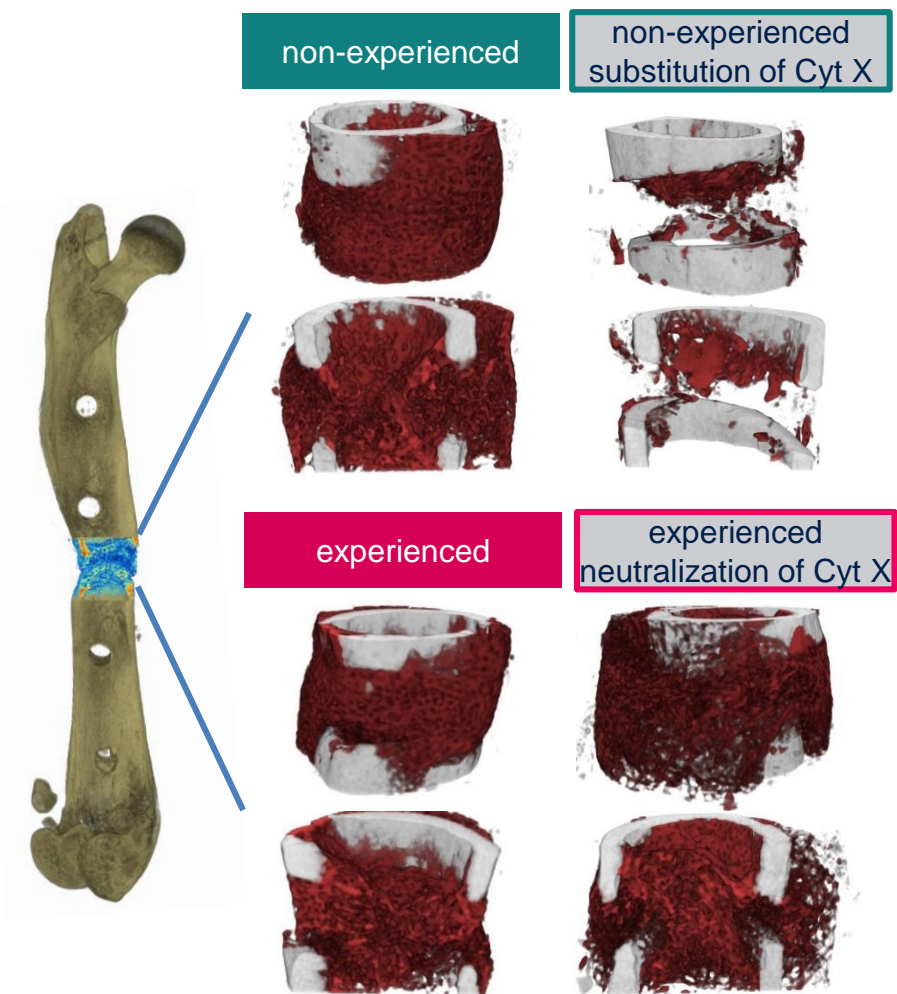
µCT healing outcome day 21:



Histology day 3:



Using cytokines as levers to rejuvenate the immune reaction



The regenerative face of the immune system for musculoskeletal healing



- Immune cells are important for successful bone regeneration
- Naive immune cells have positive effects on the bone quality
- Immune cell compositions can be harnessed for patient stratification to determine the healing potential early on
- Immune modulation could be a promising field for future new treatment approaches



- High percentages of effector memory CD8+ T cells delay bone regeneration
- Regulatory T cells can turn detrimental if the ratio of effector memory CD8+ T cells to regulatory T cells is too high
- Immune modulatory therapy approaches need to be tailored to the patient specific immune reaction
- Immune modulatory therapy approaches need to be correlated with the bone healing process



Facies systematis immune in regeneratione duo latera habent:
unam utilis et unam malum – cellae immunes habent lanus facem!



Thank you !

AG Biology of Bone Healing



Dr. S. Geissler



Dr. CH Bucher



JULIUS WOLFF INSTITUT



BERLINER
INSTITUT FÜR
GESUNDHEITS
FORSCHUNG
Charité & Max-Delbrück-Centrum



CENTRUM FÜR
MUSKULOSKELETALE
CHIRURGIE