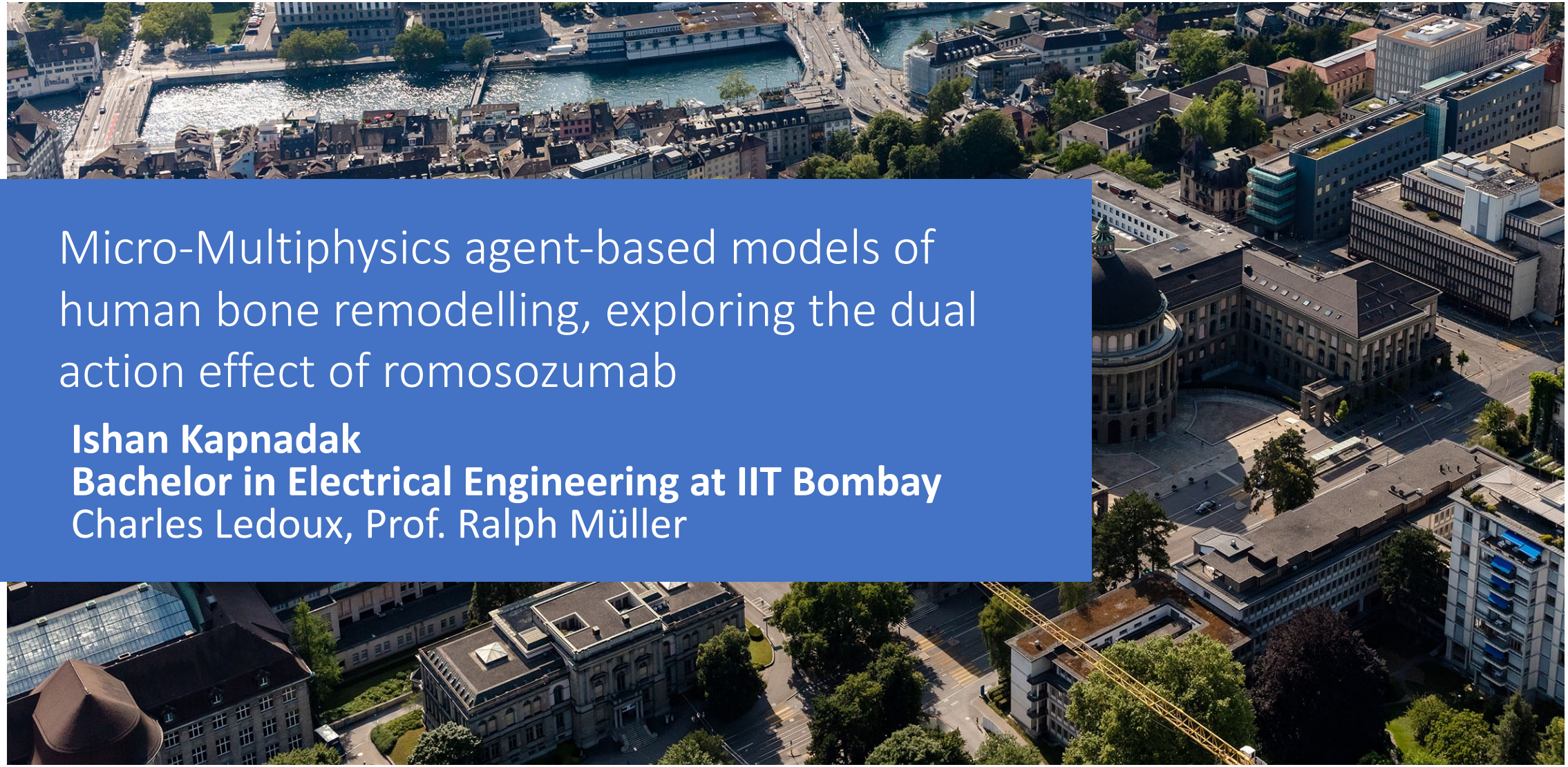
ETH zürich

Institute for Biomechanics



Micro-Multiphysics agent-based models of human bone remodelling, exploring the dual action effect of romosozumab

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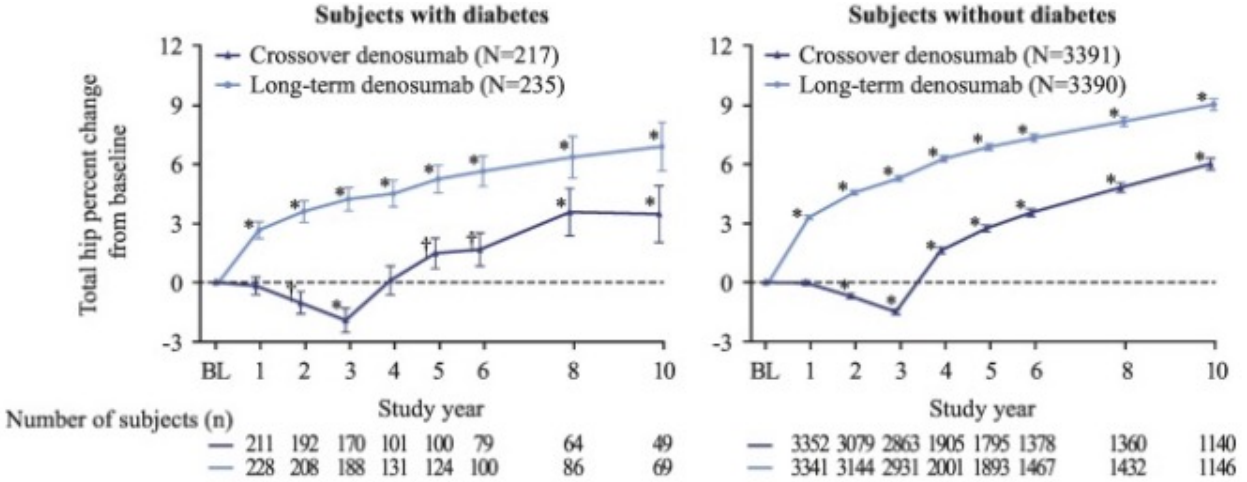
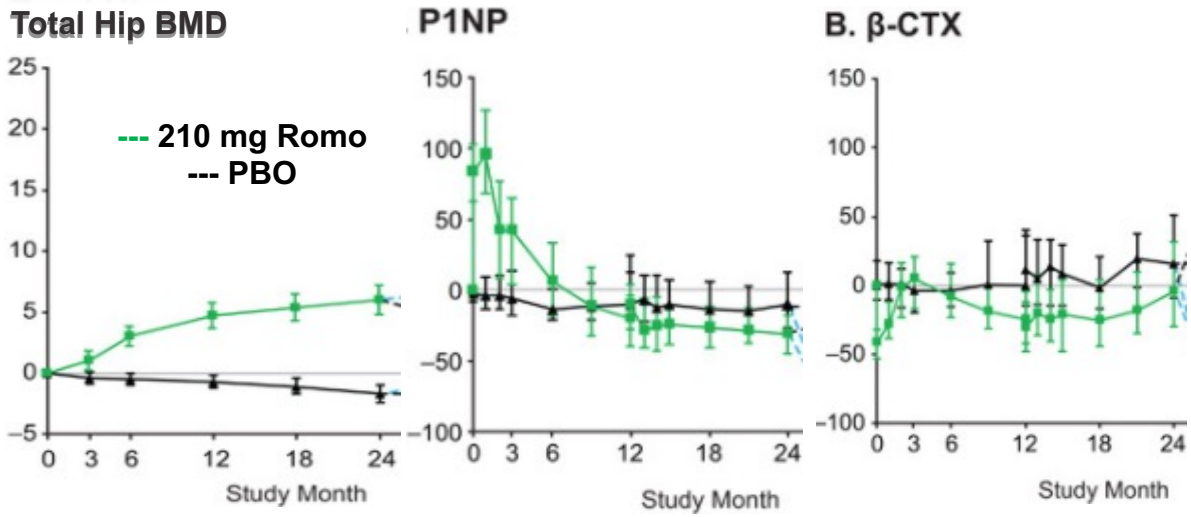
Treatment with romosozumab

- Pharmacological therapies commonly prescribed to high fracture risk patients may be divided into :
  - Anti-resorptive: bisphosphonates, denosumab...
  - Anabolic or dual-action: PTH & romosozumab
- Anti-resorptive medications decrease turnover
  - Less effective in diabetic patients where turnover is low anyways
- No data on anabolic treatment for patients with diabetes (e.g. anti-sclerostin antibody romosozumab)

Diabetic subgroup of FREEDOM trial had less effective response to denosumab



The sclerostin antibody romosozumab increases formation and reduces resorption instead of reducing both

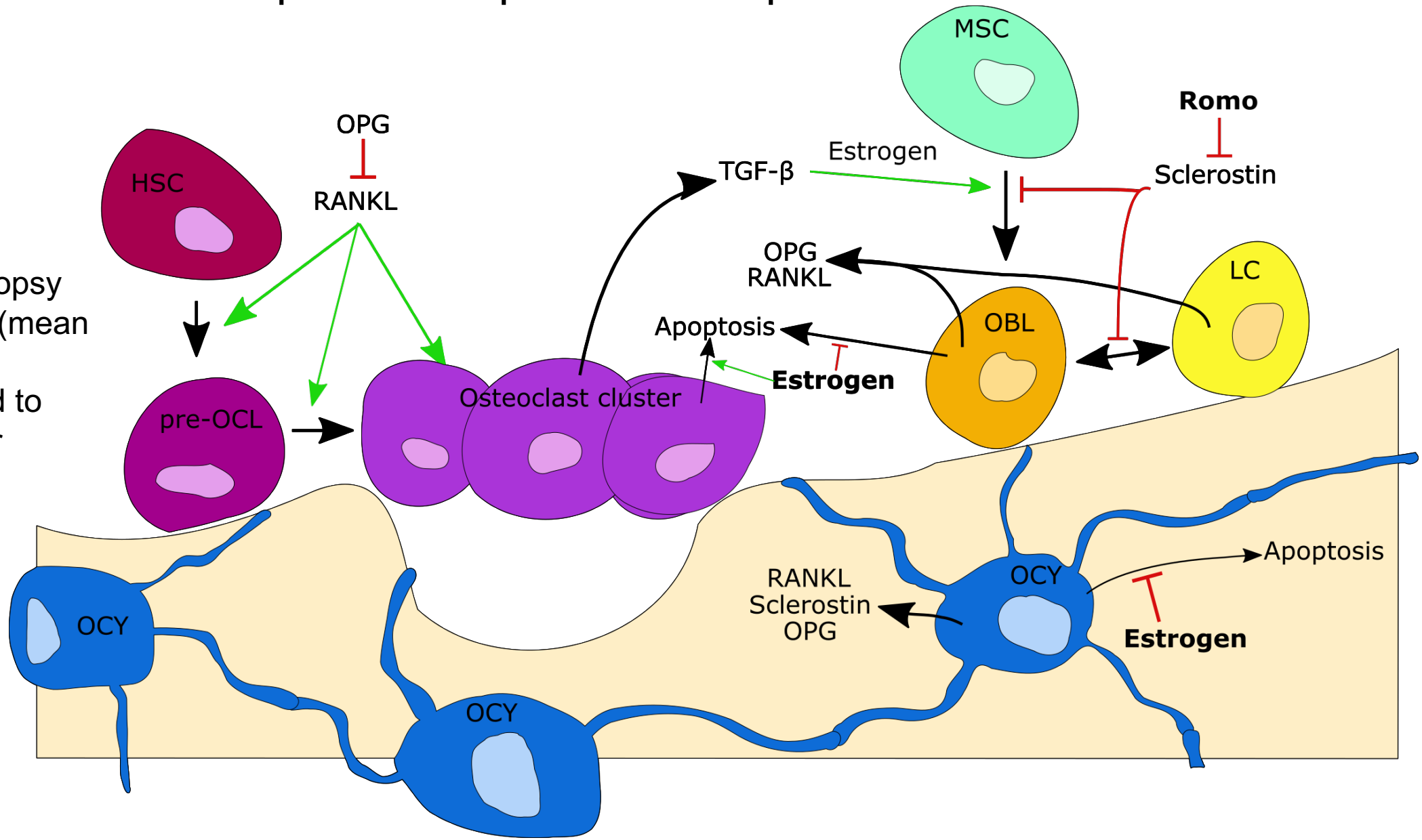


McClung et al. (2018), doi: 10.1002/jbmr.3452

Agent-based model of post-menopausal osteoporosis

Model input:

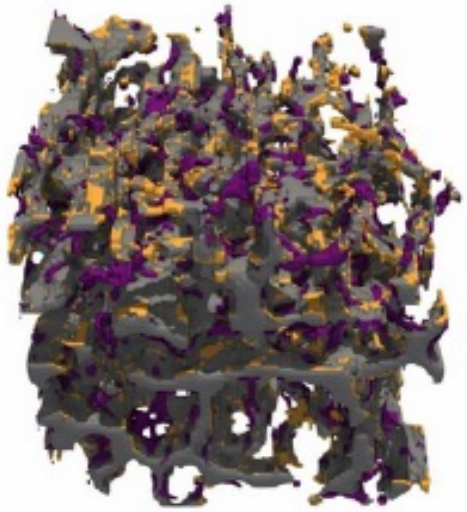
7 µ-CT iliac crest biopsy scans from women (mean age 72y), BV/TV distribution matched to FREEDOM trials for denosumab



Higher fracture risk in type 2 diabetes despite equivalent BMD

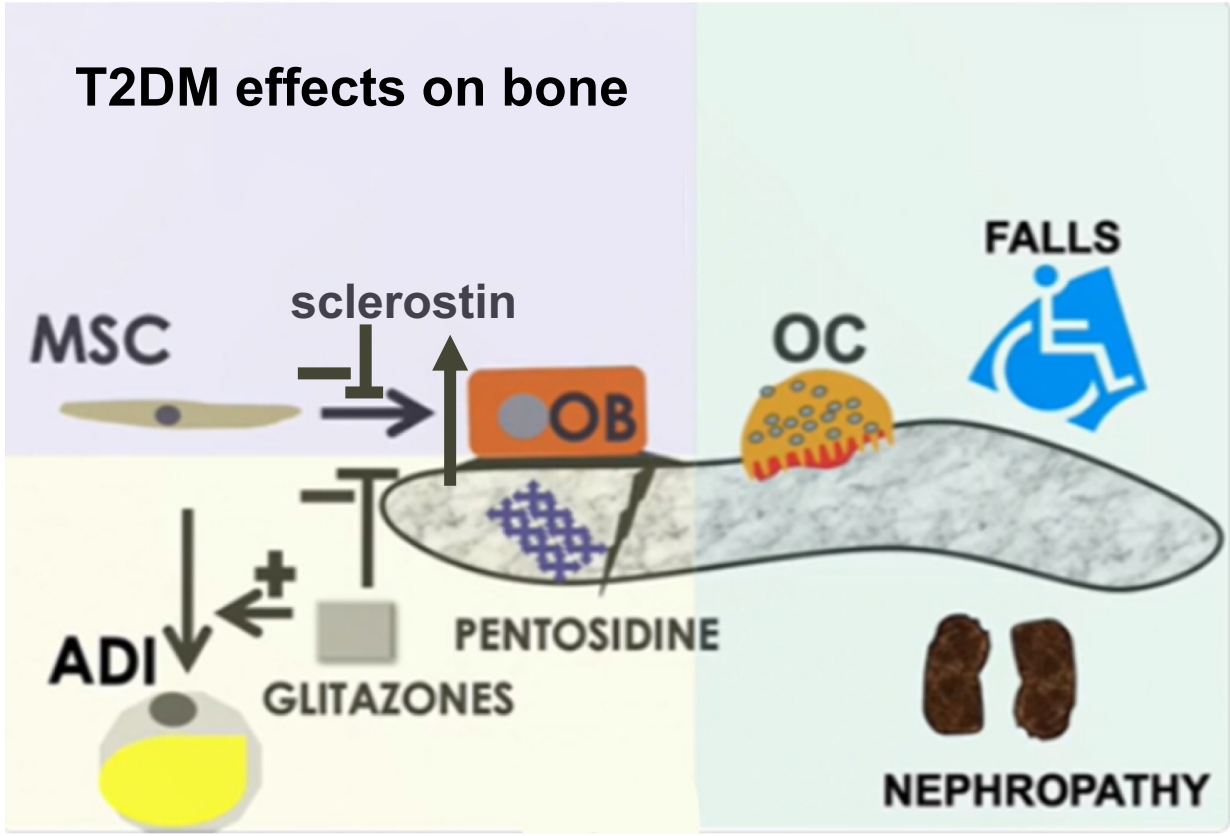
Mary's osteoporotic bone

Bone density is low and both resorption and formation are high, with resorption even higher than formation



Matthias' diabetic bone

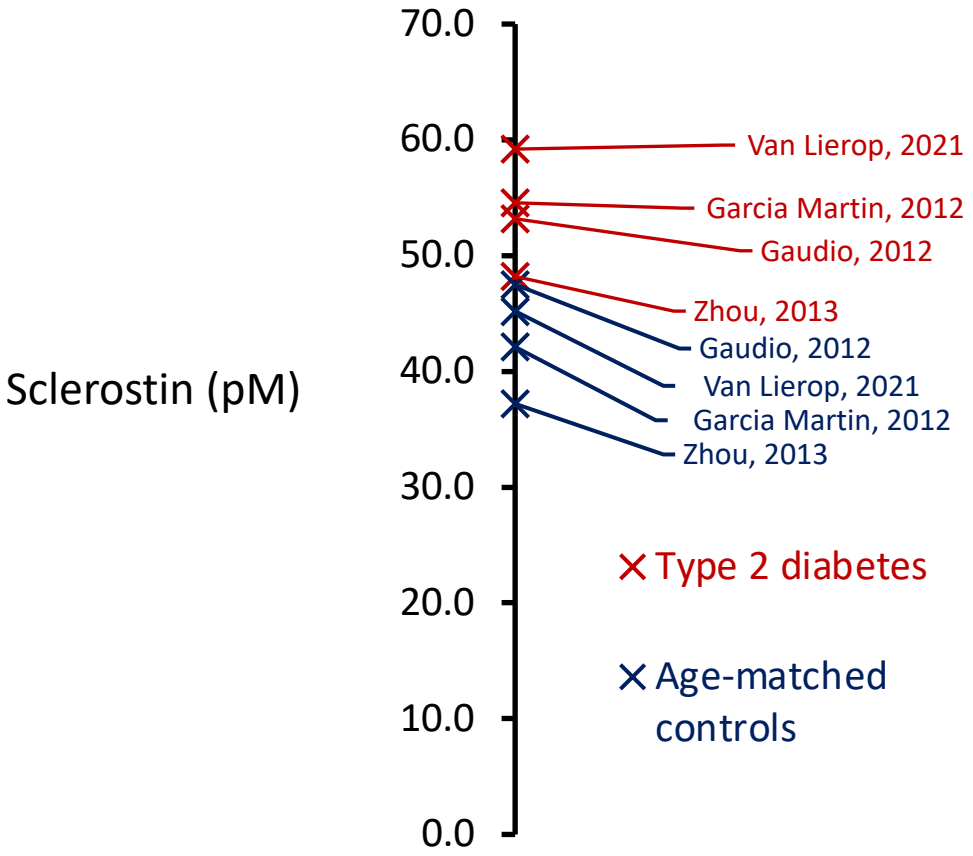
Bone density is high but the microstructure is weak and bone resorption and formation are both low.



[1]

Characterizing normal vs diabetic patients

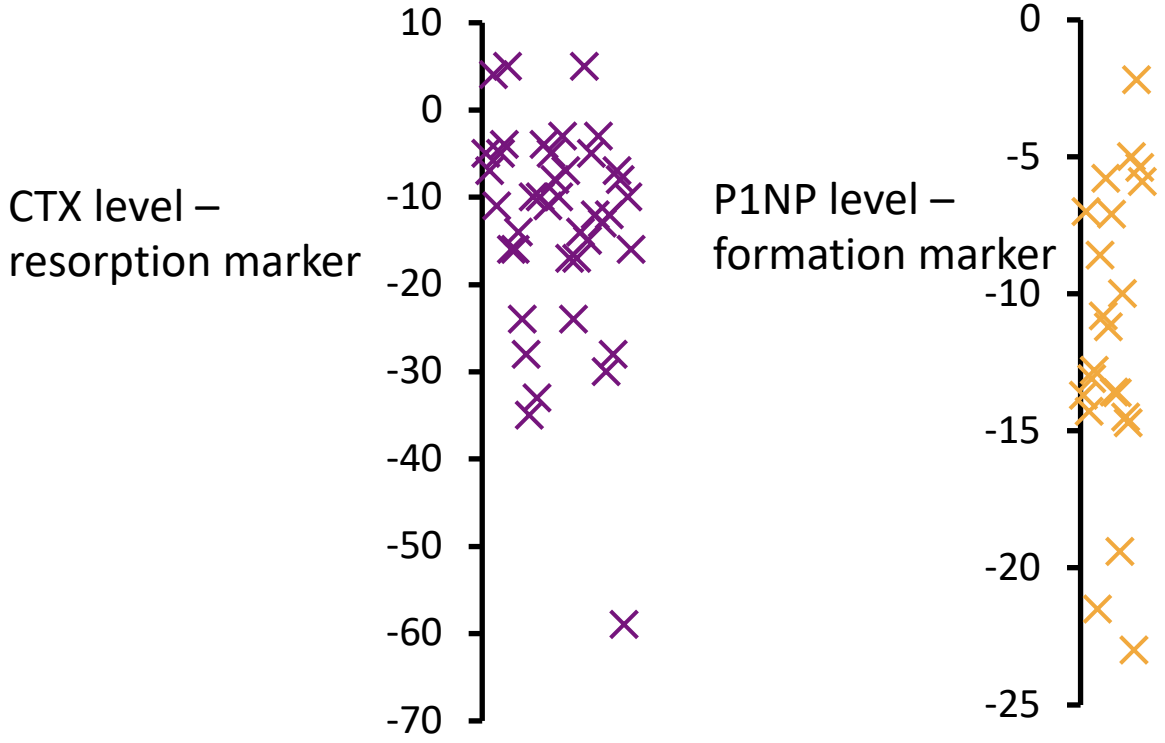
Cytokines



Elevated sclerostin

Bone Turnover

(% difference)



Reduced Bone Turnover

Adapt micro-multiphysics agent-based model to achieve 3 aims:

- **Aim 1**: Propose and implement mechanism to adapt existing model to obtain changes in formation and resorption post romo injection that match bone turnover marker (BTM) measurements in clinical trials.

- **Aim 2**: Generate 6-month pbo and romo in silico clinical trial results on 7 biopsies with new PMO model settings and compare BMD trends to previous results.

- **Aim 3**: Analyze effect of initial conditions on response to romo treatment.

Pharmacodynamics of romo: verifying diffusion and binding

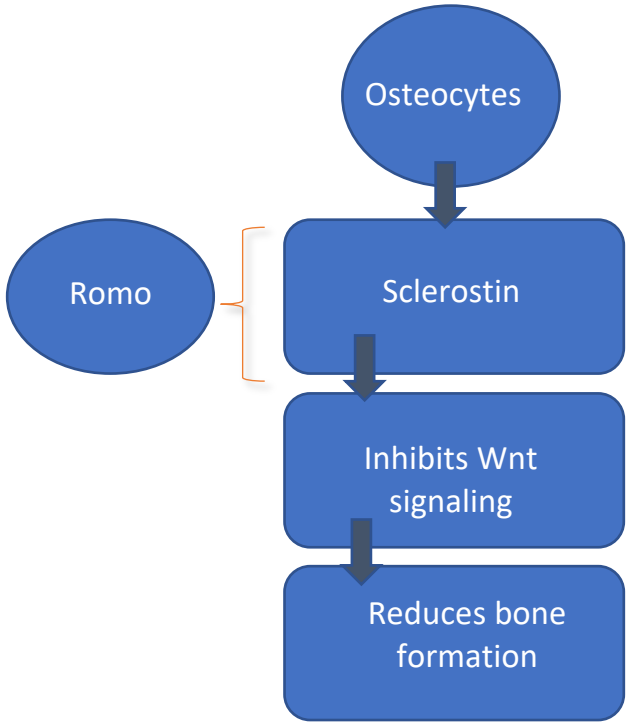
Match pharmacokinetics (210 mg/month sub.c.) from phase 1 clinical trials

SCL should drop post injection as it is bound

Verify cell and cytokine behaviour

Match BMD and BTM changes to phase 3&4 clinical trials

Mechanism of action

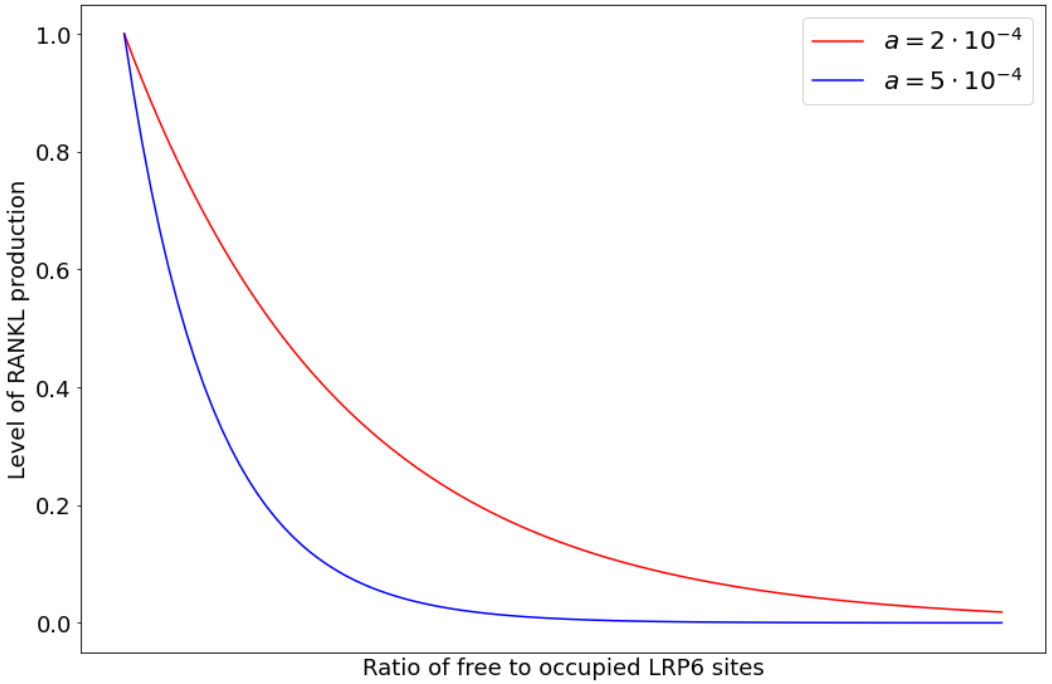


Sclerostin-dependent RANKL production

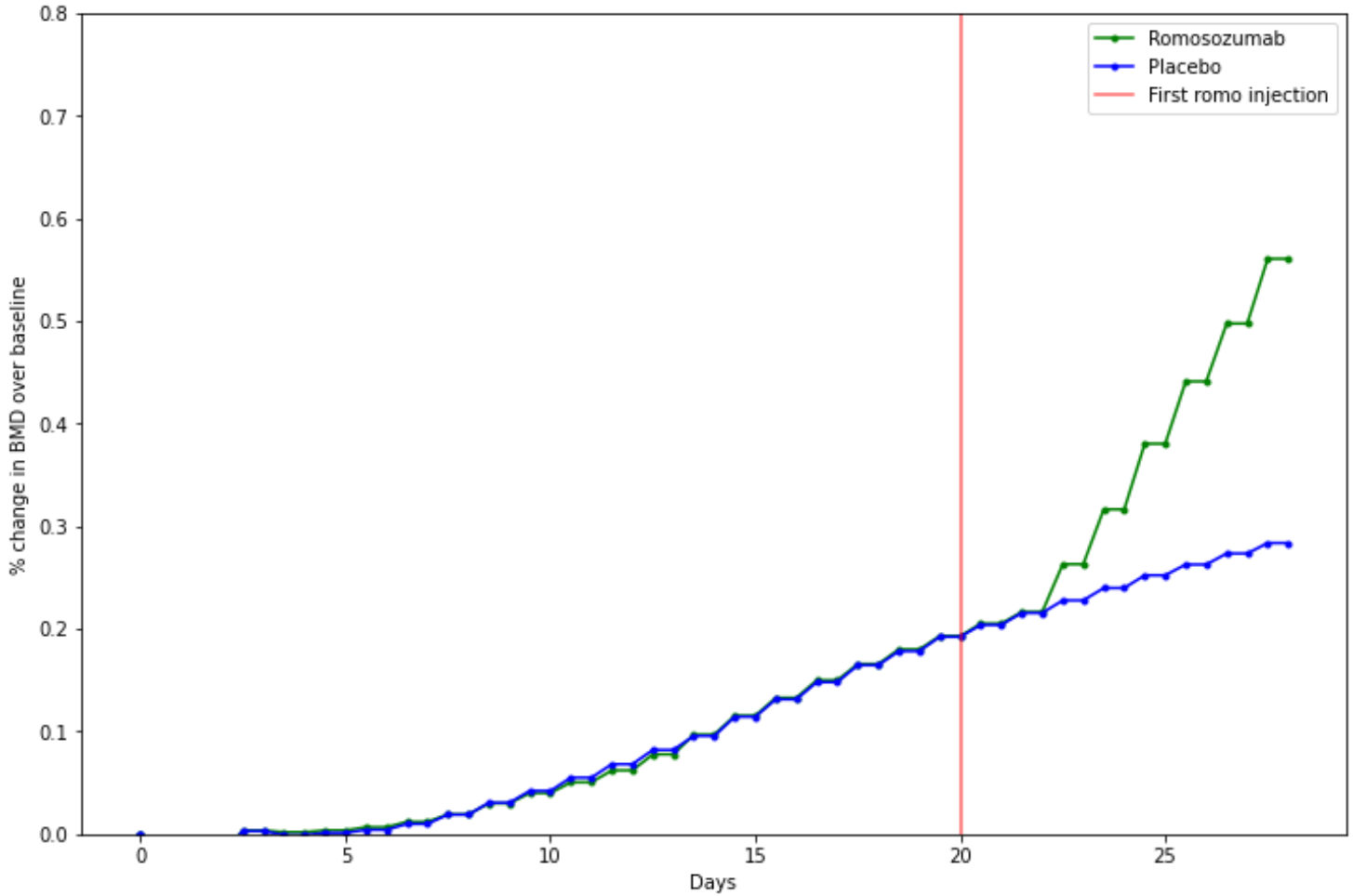
- Production of RANKL by osteoblasts and osteoclasts is sclerostin-binding dependent
  - Low RANKL production when sclerostin is low and LRP6 free sites are high
- Can characterize rate of RANKL production in terms of ratio of free and occupied LRP6 sites
  - One idea was to use an activation function that maps $(0, \infty)$ to $(0,1)$
- Hyperparameter *a* controls how quickly the rate decays as sclerostin drops
  - After trying out different values, an exponential activation function with $a = 2 * 10^{-4}$ seemed to give good results

$$\text{Rate of RANKL production} = e^{-ax}$$

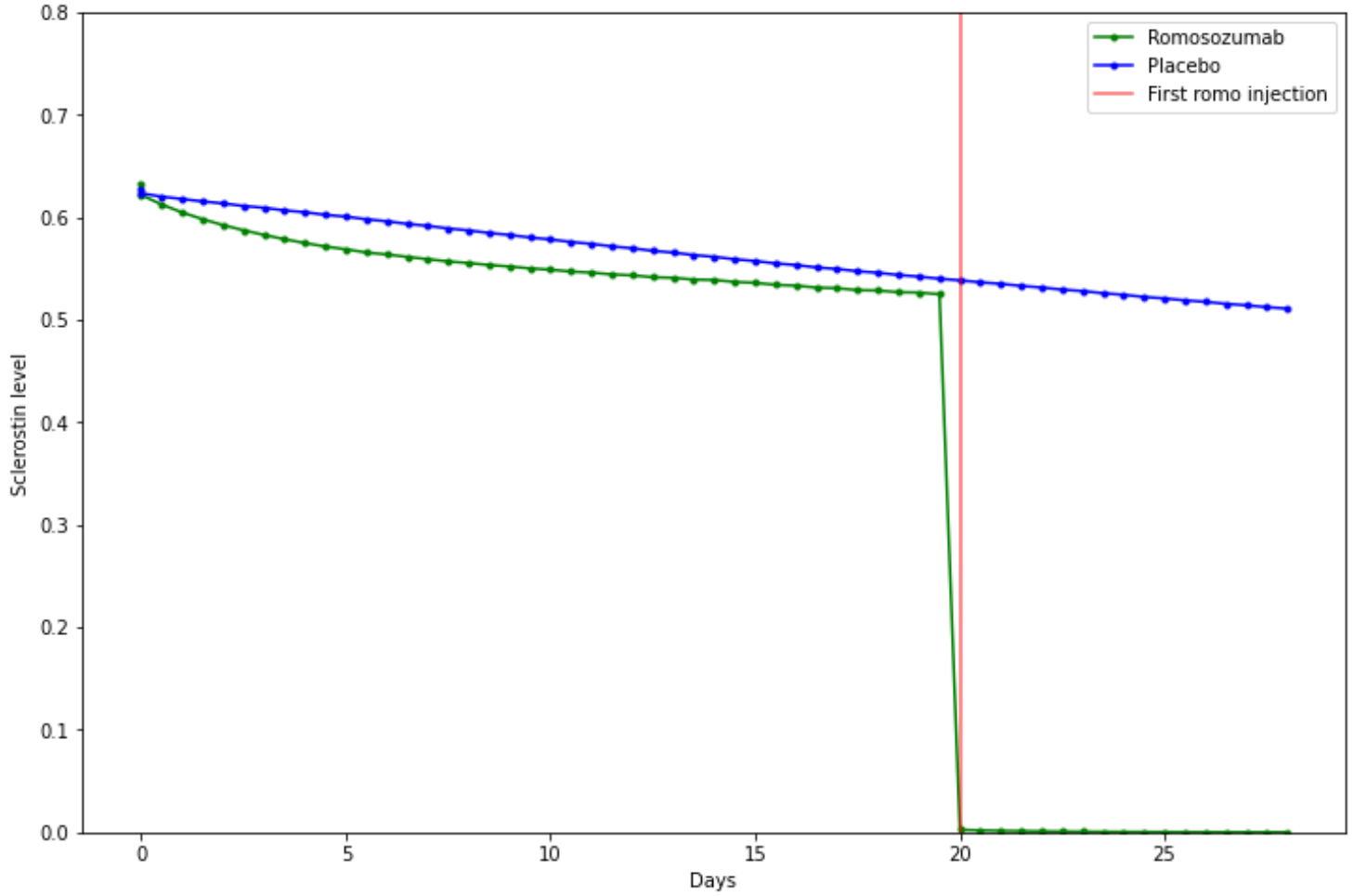
where x is the ratio of free to occupied LRP6 sites



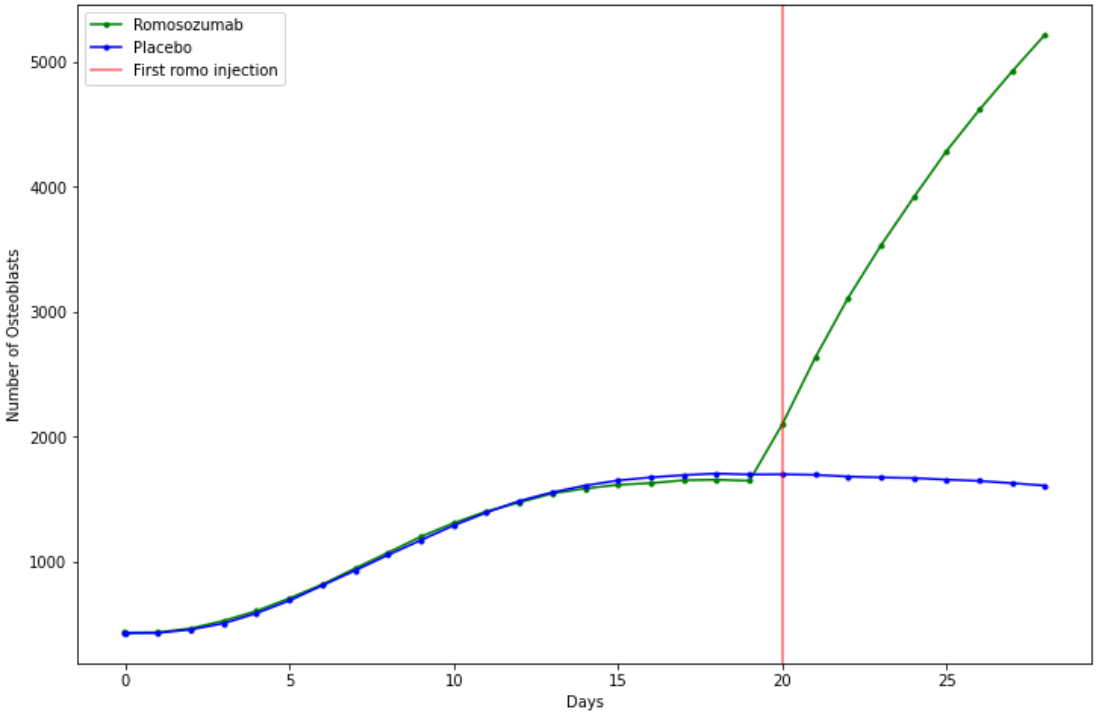
BMD starts to increase sharply post romo injection

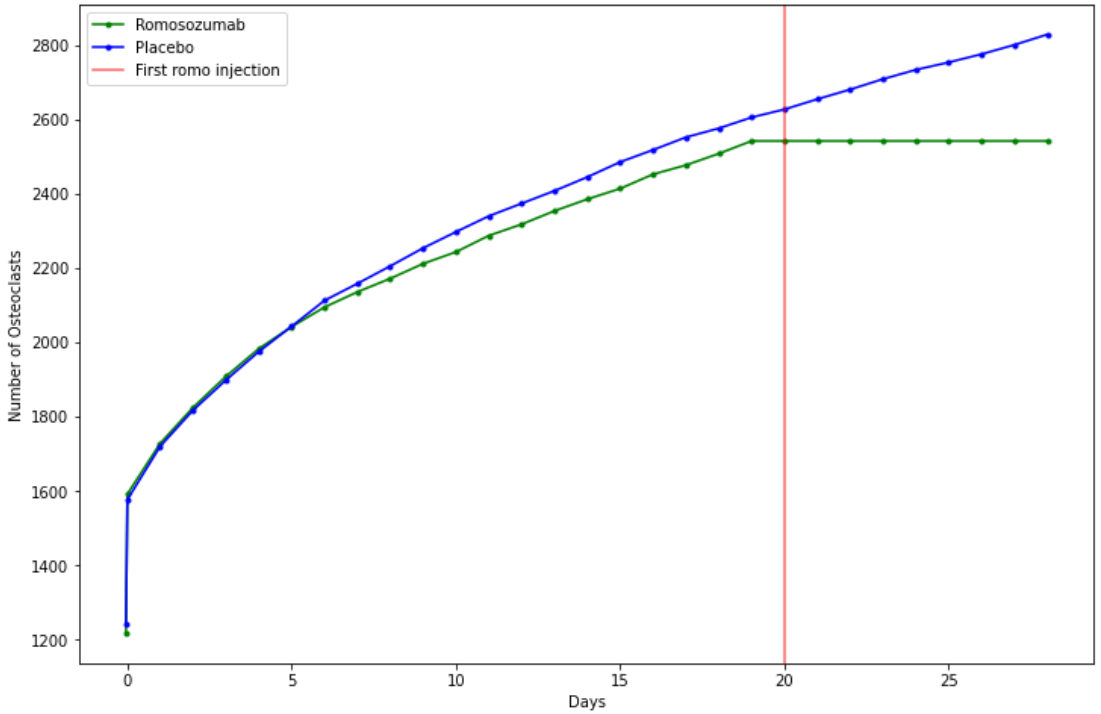


Sclerostin drops sharply post romo injection



Cell behaviour matches clinical trials





- Osteoblasts increase post romo injection
- Osteoclasts stop increasing post romo (with a slight drop)

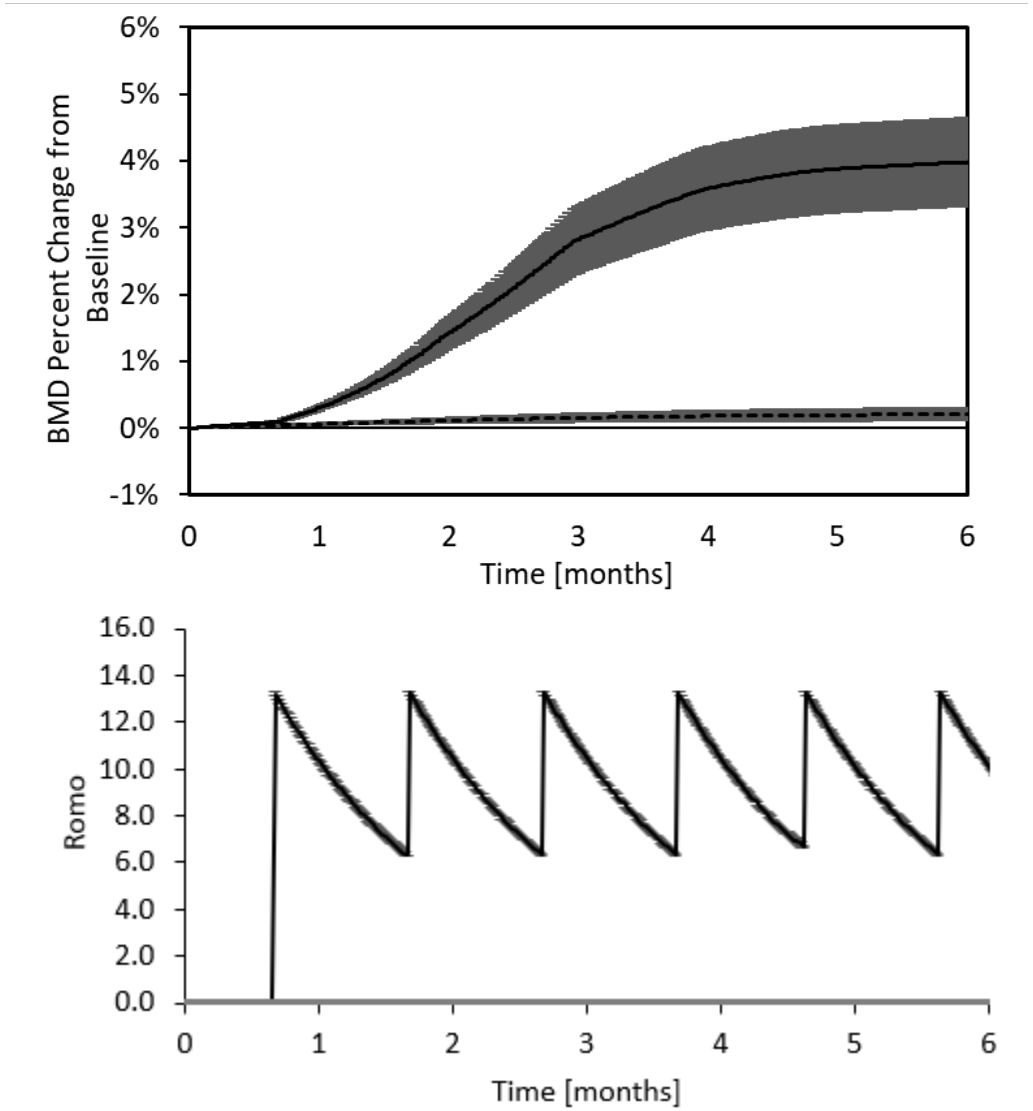
Discussion and limitations of aim 1

✓ Behaviour of cells and cytokines immediately post romo injection matches clinical trials

↓ Small sample size (N=7) with large interpatient variability

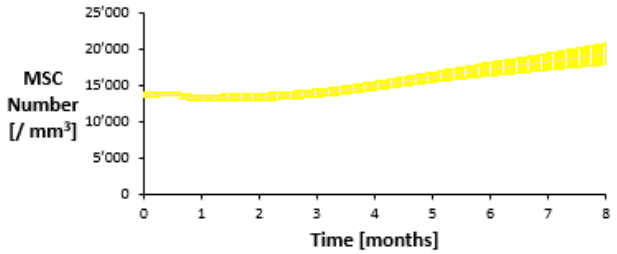
↓ Other pathways are thought to play essential roles in bone remodelling in diabetes (e.g. inflammatory pathways via interleukins)

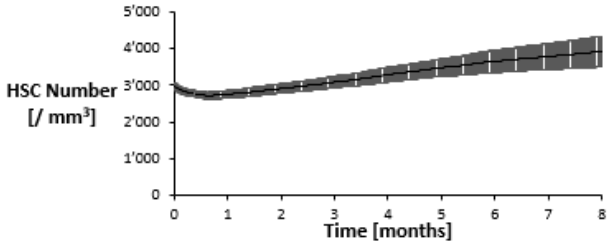
Romo and placebo simulations: Trends in bone mineral density

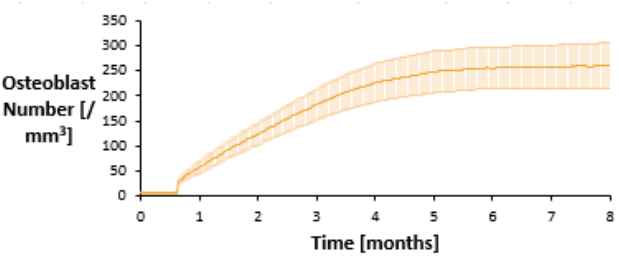


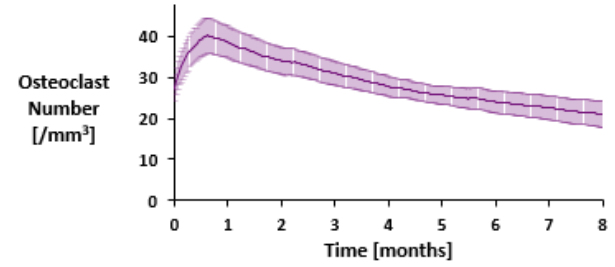
1 year romo and placebo simulations: Trends in cell numbers

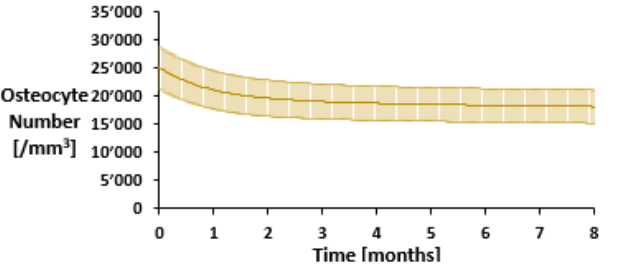
Romo

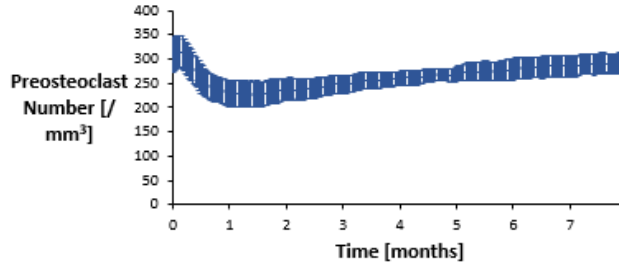




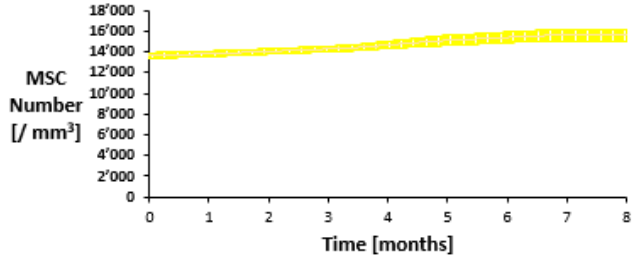


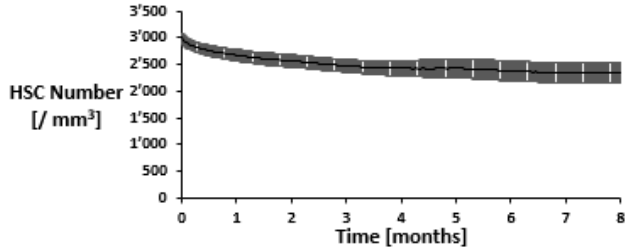


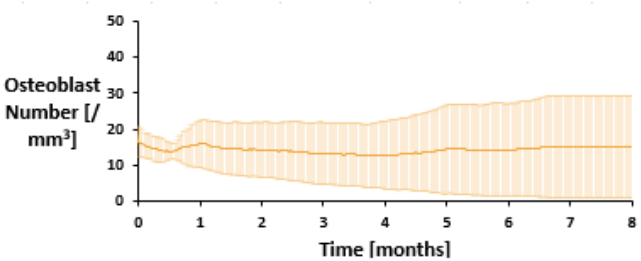


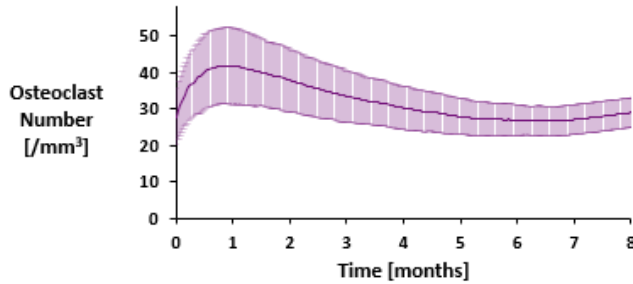


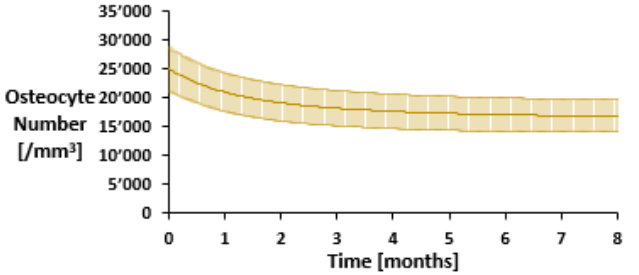
Placebo

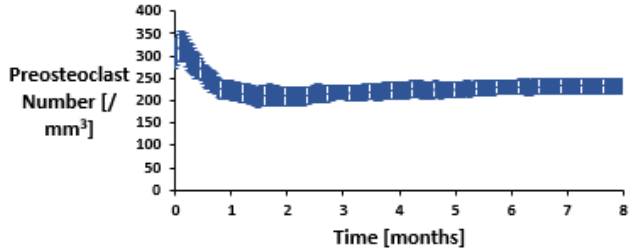












Discussion and limitations of aim 2

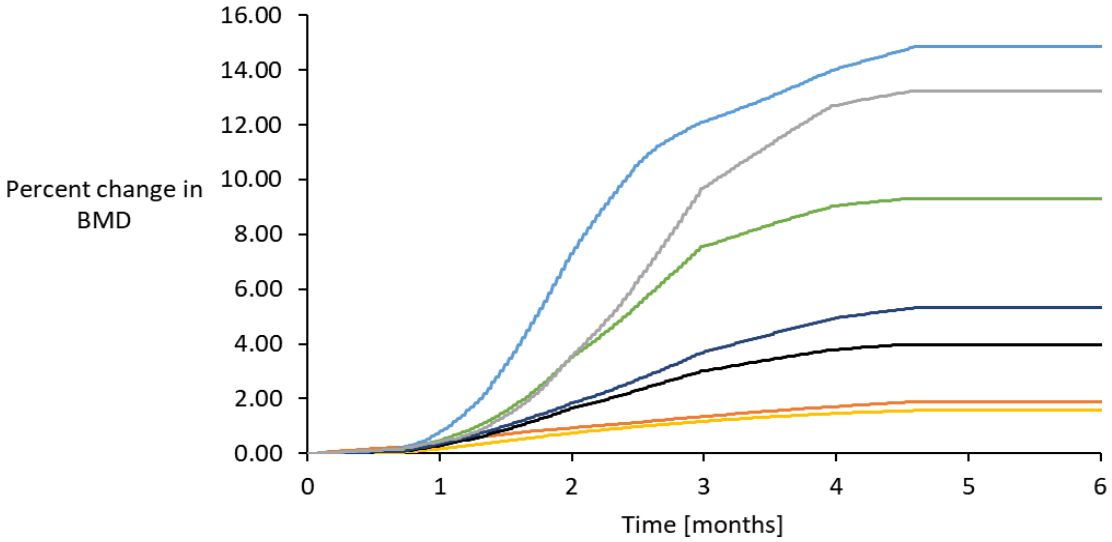
✓ Strong rise in BMD and levelling off as expected

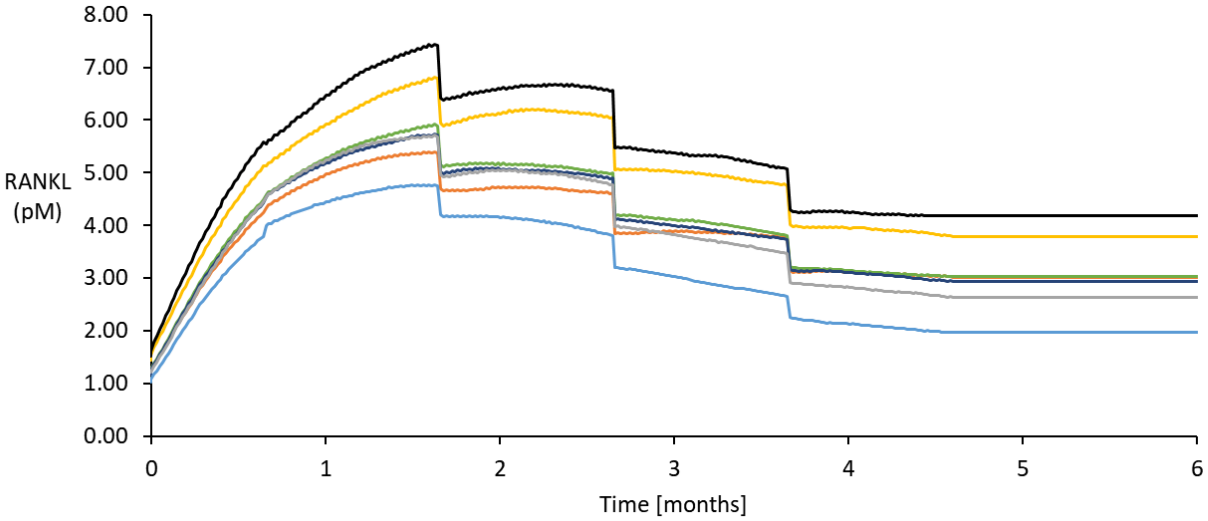
↓ Small sample size (N=7) with large interpatient variability

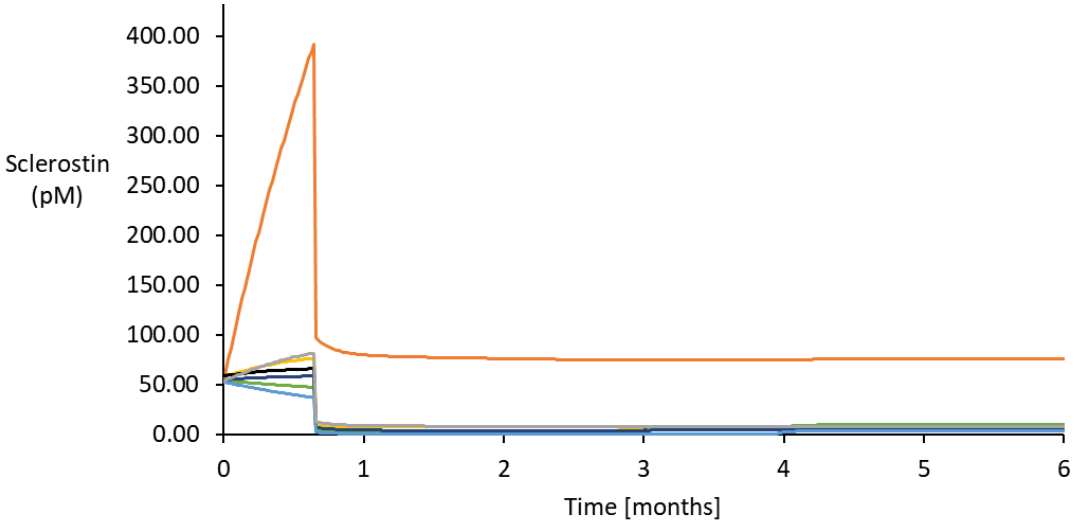
↓ Levelling off occurs earlier than expected

↓ Lack of info in literature about cell numbers to compare to.

Effect of initial conditions on response to treatment







BV/TV=21.4%
BV/TV= 15.7%
BV/TV= 13.0%
BV/TV= 11.4%
BV/TV= 9.6%
BV/TV= 6.8%
BV/TV= 7.8%

Discussion and limitations of aim 3

✓ Expected effects of romo injections on RANKL and sclerostin concentrations

↓ Small sample size (N=7) with large interpatient variability especially in BMD trends

↓ Future work: quantify effect of initial static morphometrics on response to treatment, looking especially at SMI and surface gradient as was done for denosumab treatment

Conclusion

✓ The adapted micro-MPA model closely matched trends in romosozumab clinical trials.

✓ Simulated the effect of romosozumab on a previously untested patient demographic, suggesting significant potential of anabolic treatment using romosozumab in patients with diabetes mellitus.

- Validation by future clinical trials needed, especially considering increased risk of adverse cardiovascular events in diabetic patients.

Thank you!