

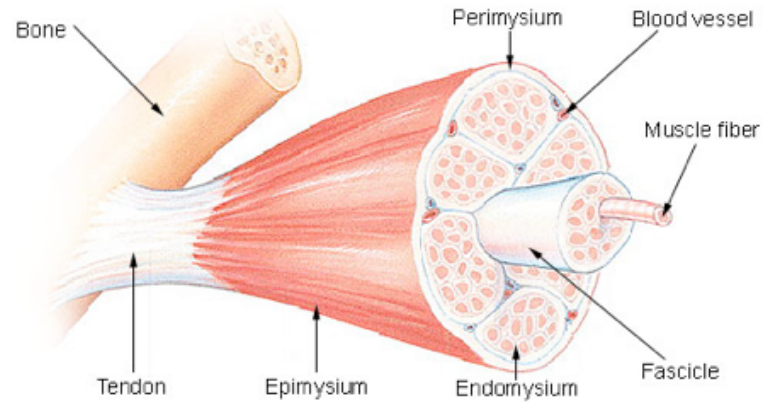


Gianni Cesareni

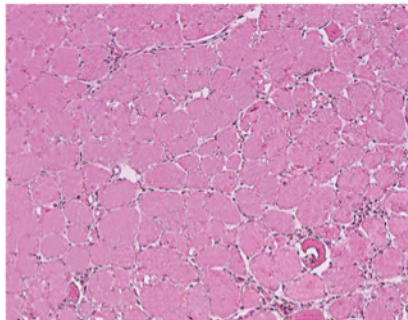
Why fat does not accumulate in the muscle of a healthy vertebrate?
A systems biology approach

Muscle regeneration

Structure of a Skeletal Muscle



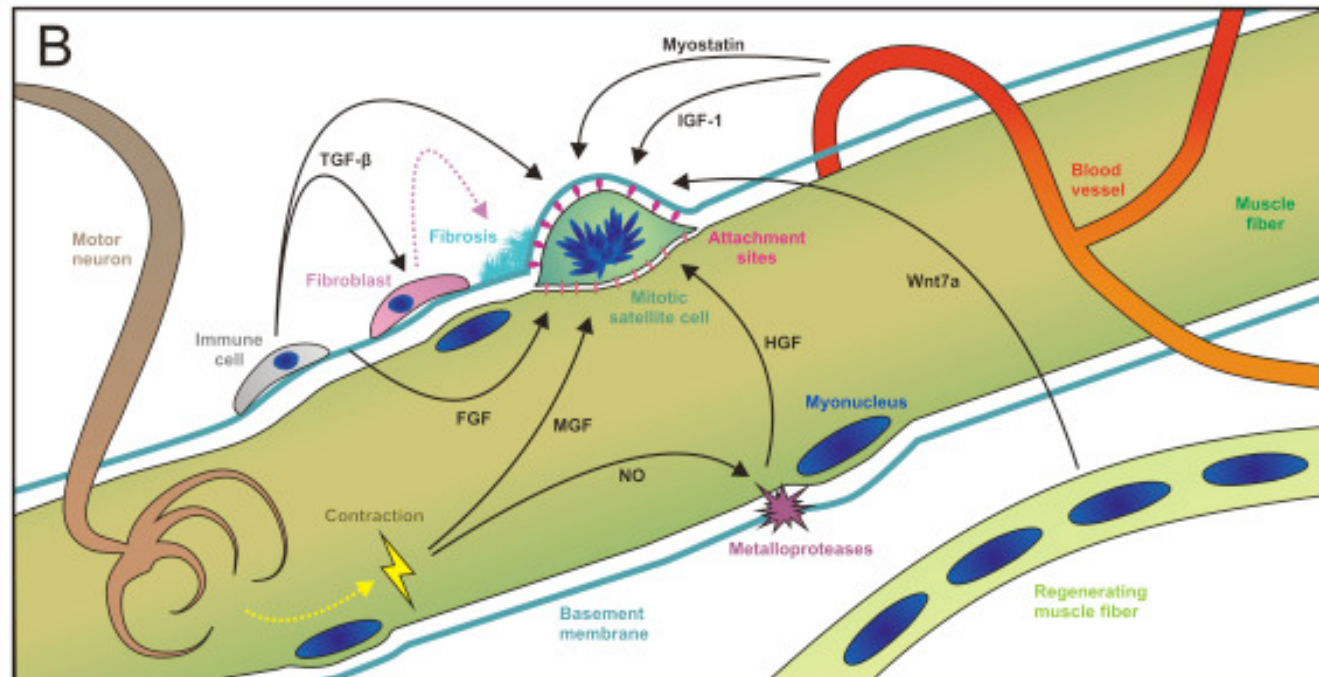
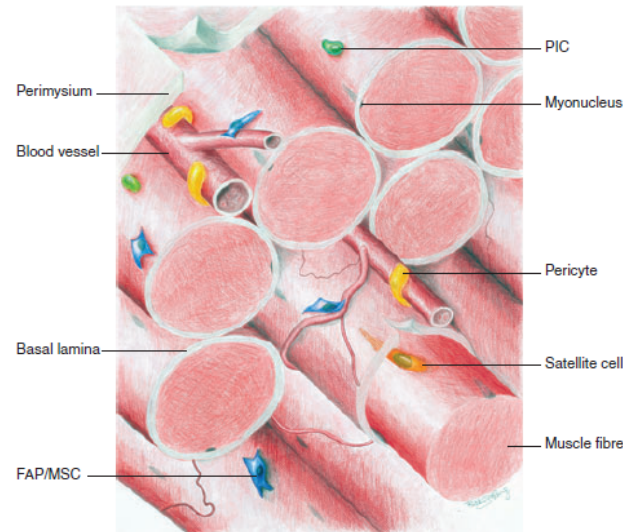
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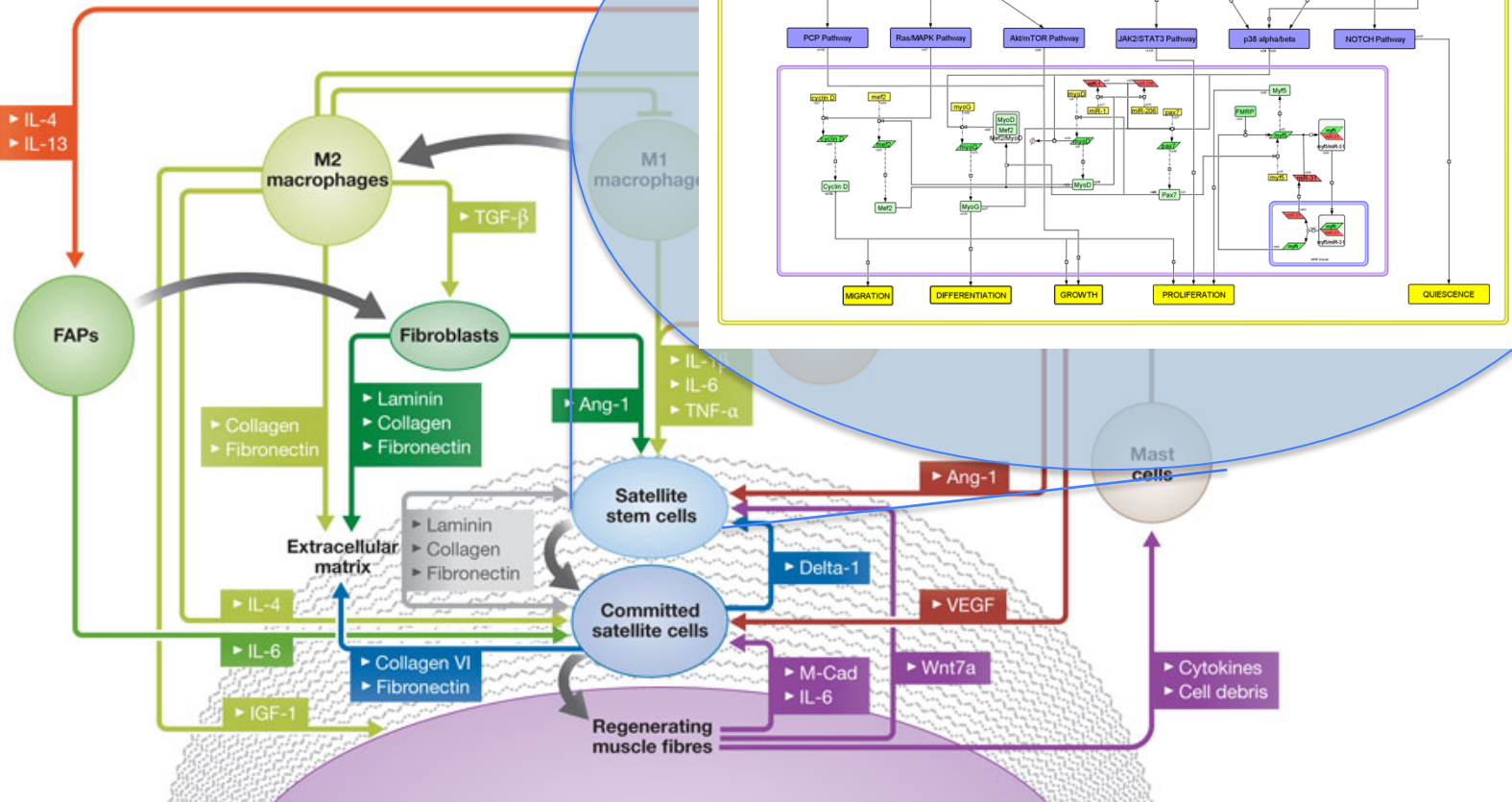
uninjured



A complex crosstalk between different cell-types

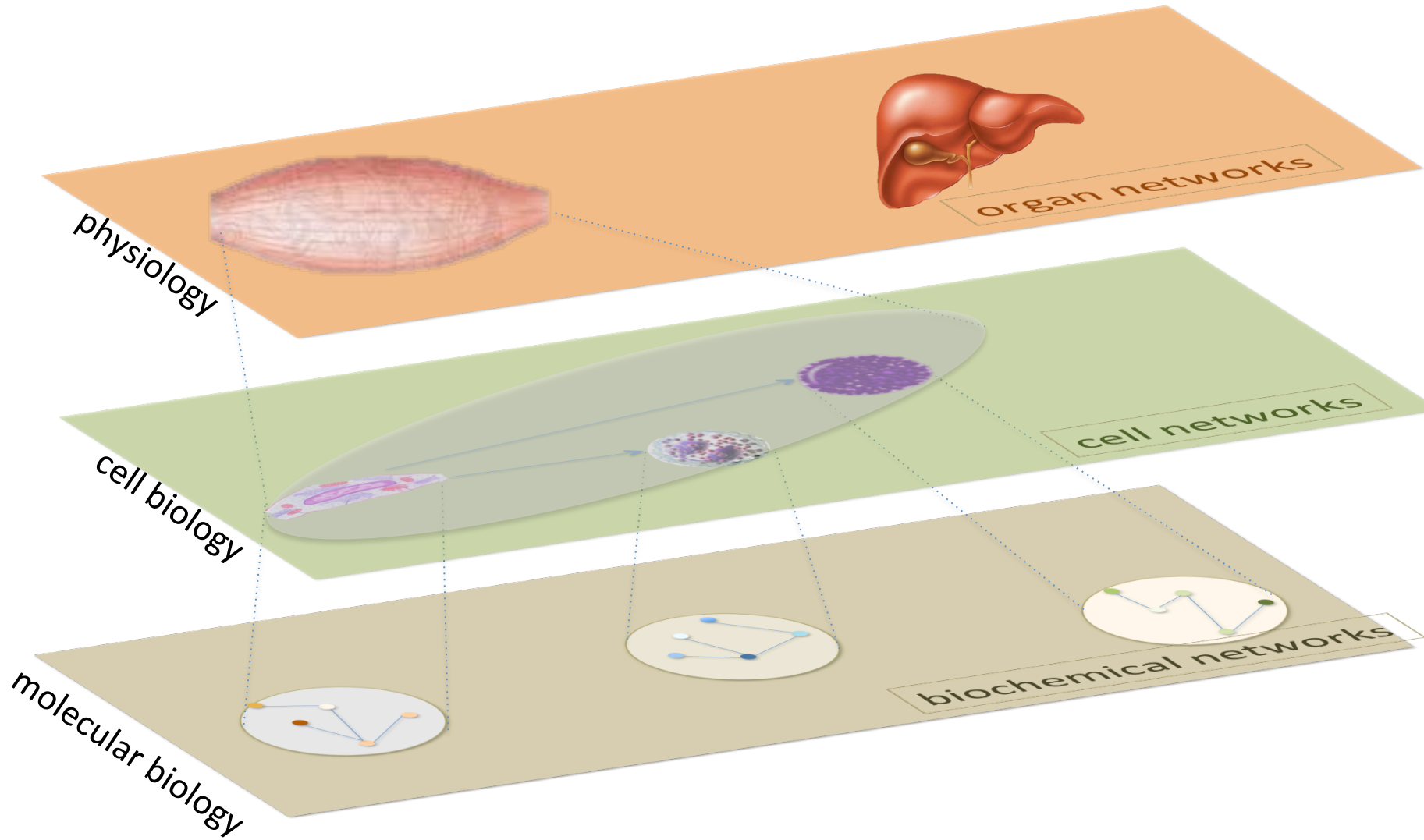


A cell interaction network

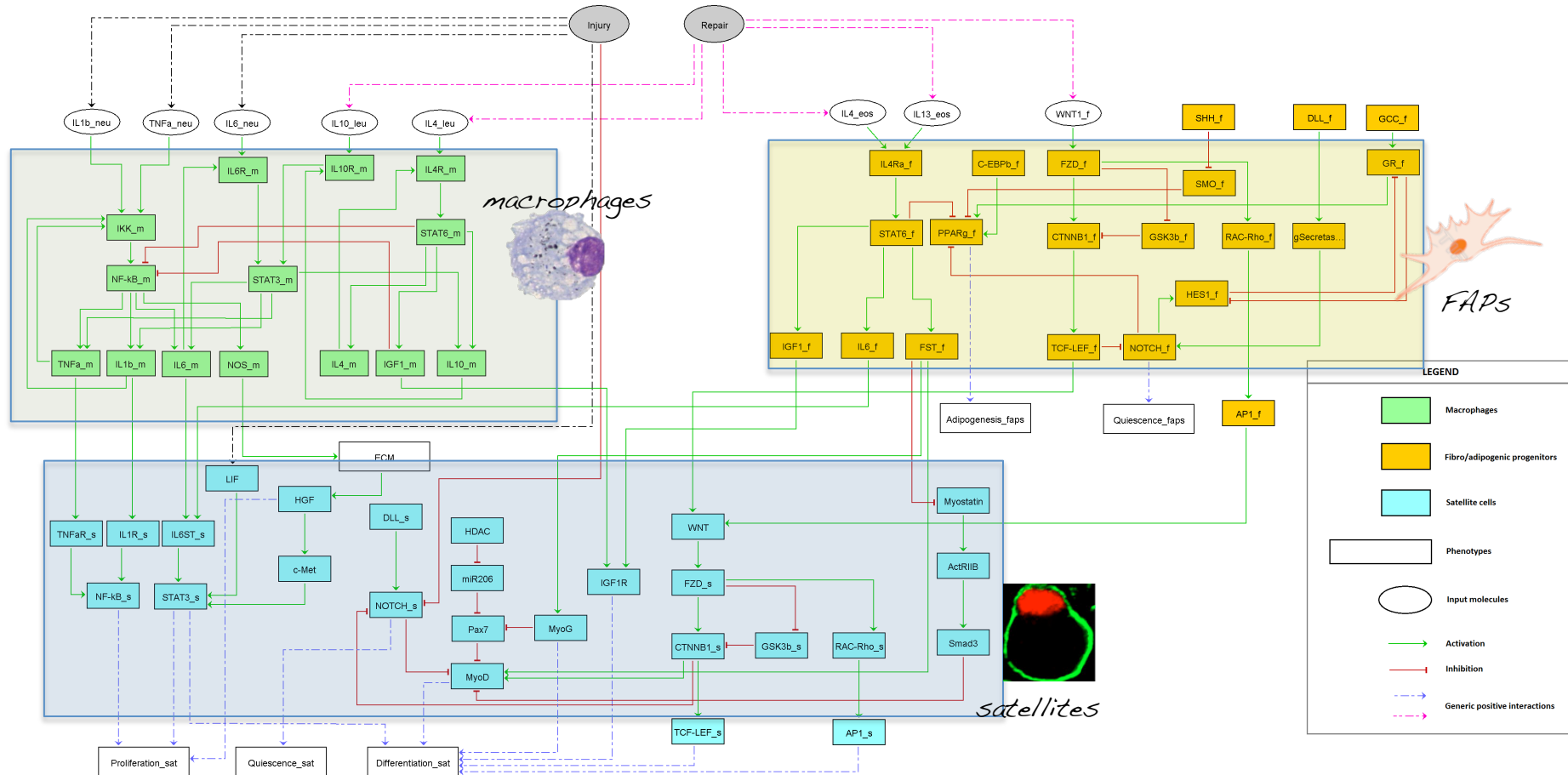


Betzinger et al

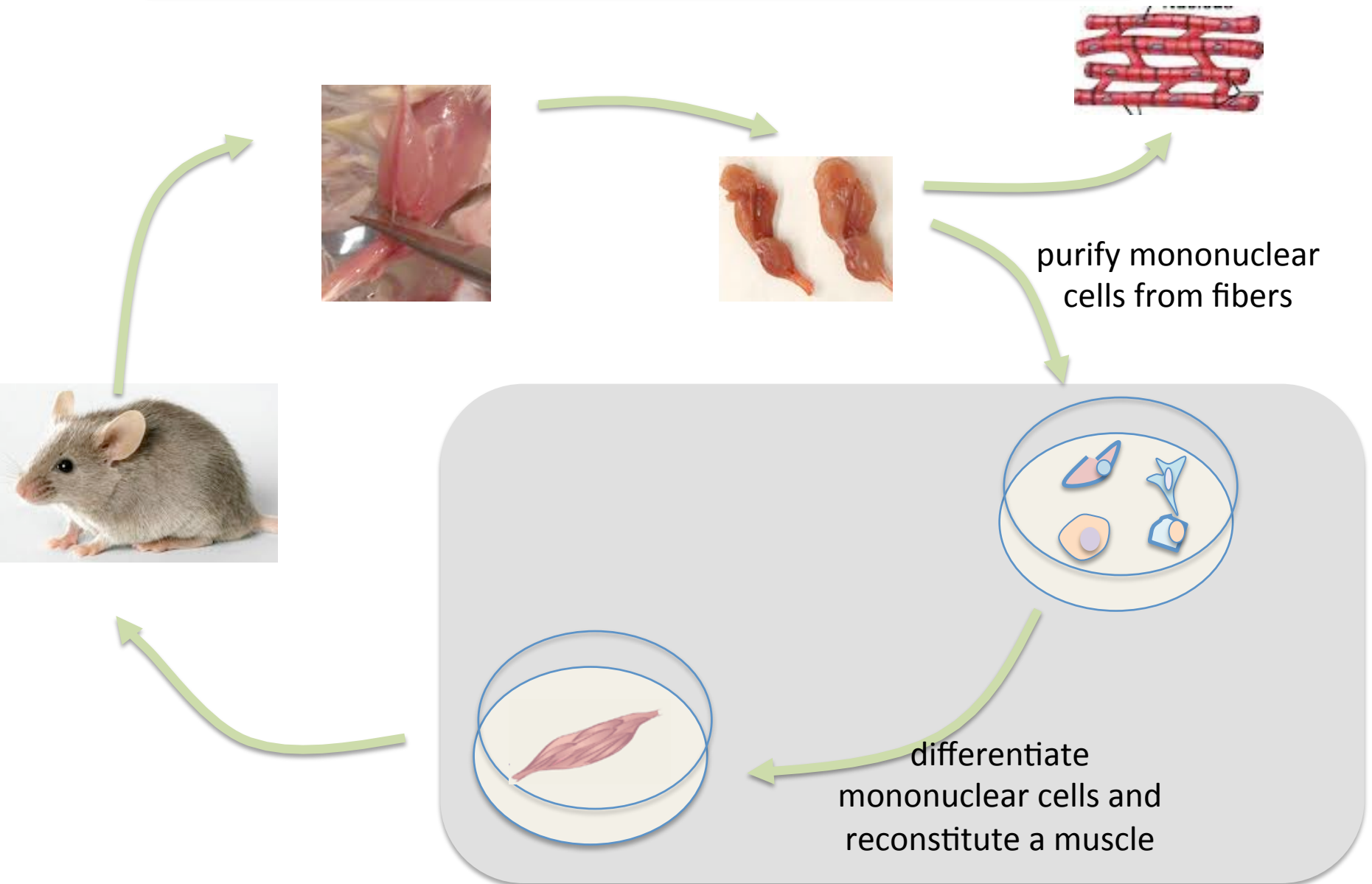
Multilevel modeling



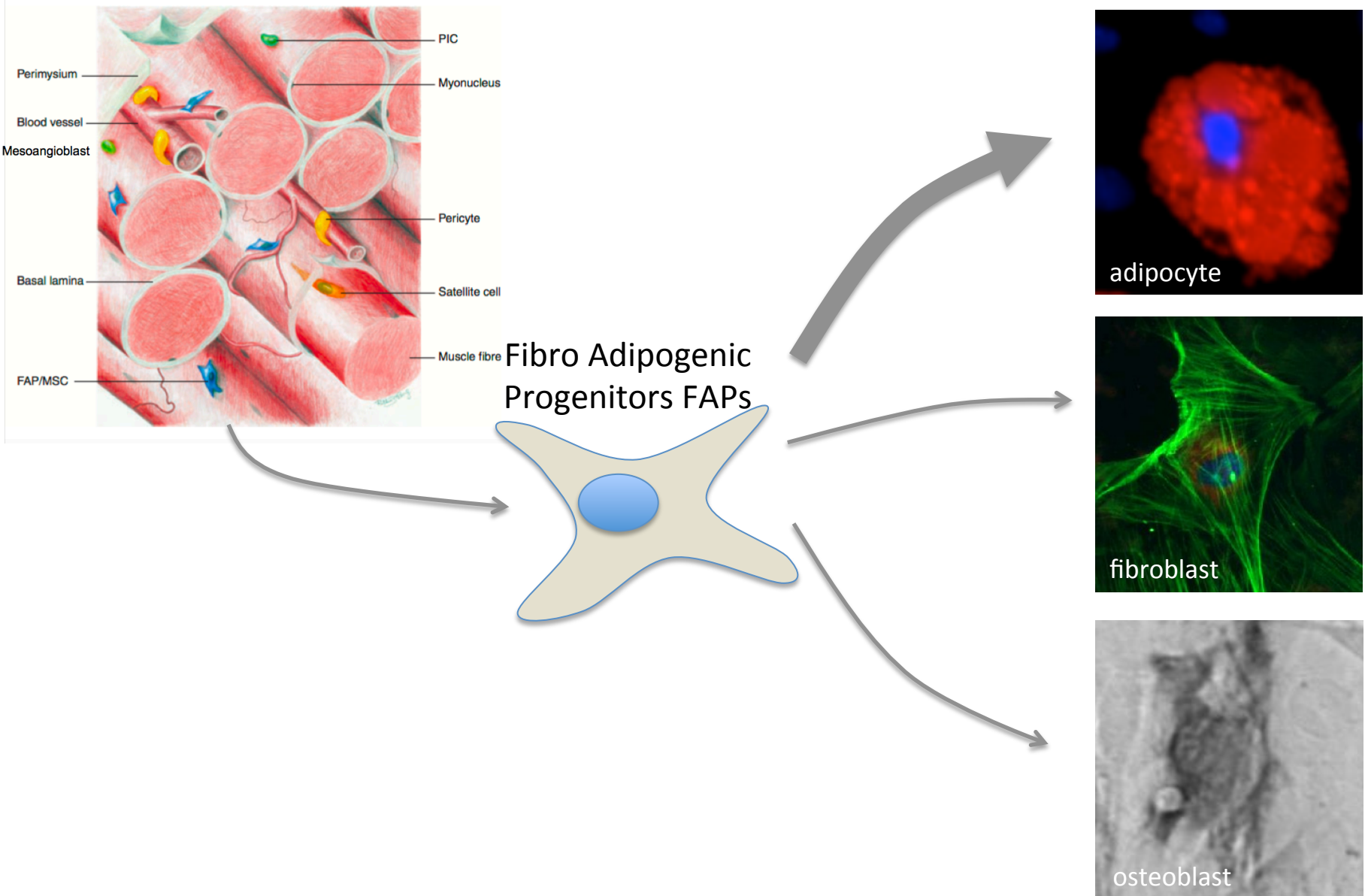
A simplified model of cell-cell interaction in the muscle



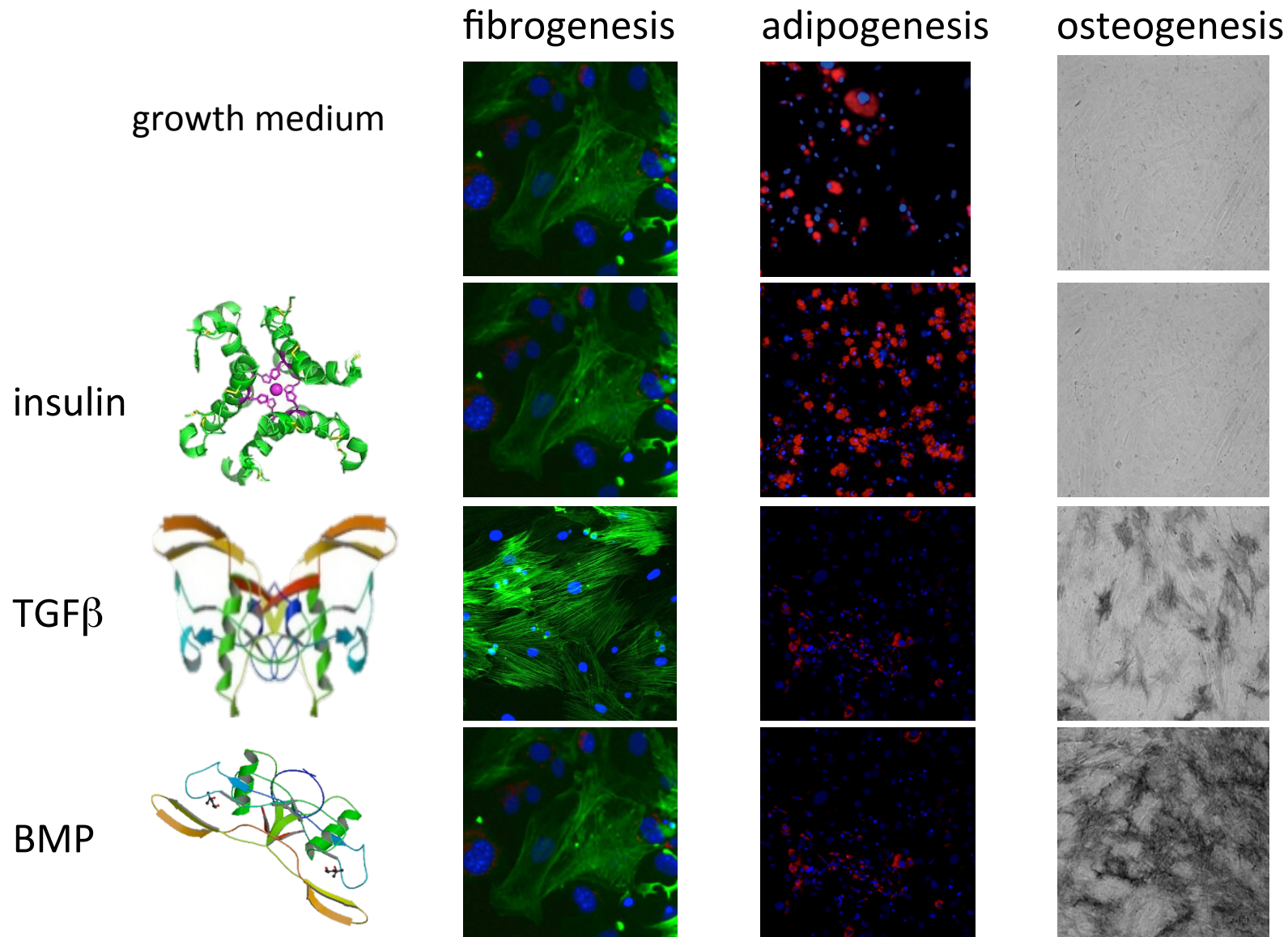
The experimental system



Each mononuclear cell types senses the environment and makes differentiation decision



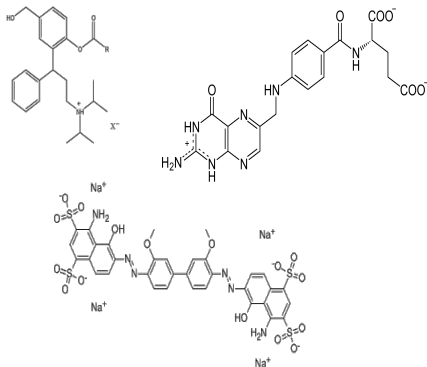
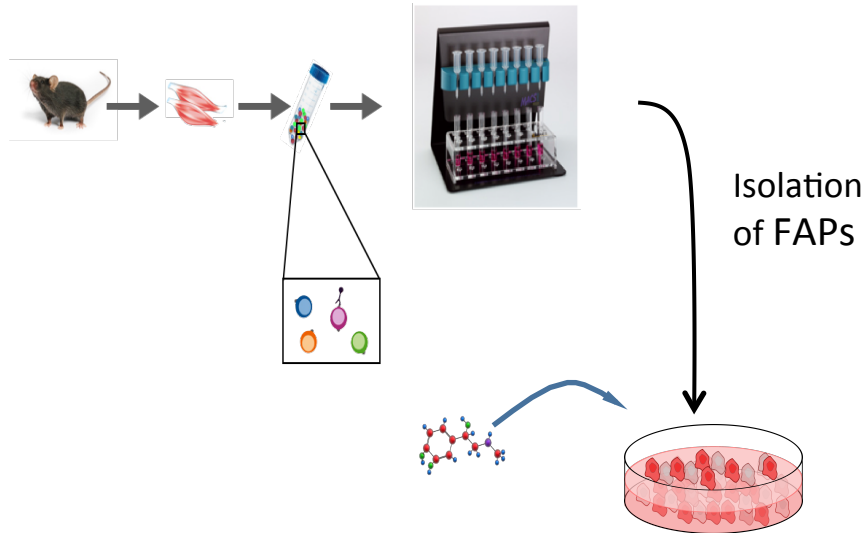
Modulation of FAP differentiation by growth factors



screening of small molecules that affect adipogenesis

5358 compounds:

- Prestwick
- Kinase Inhibitor (PKIS)
- Safe in man
- Post-translational mod. Inhibitors
- Cell active



active
compounds

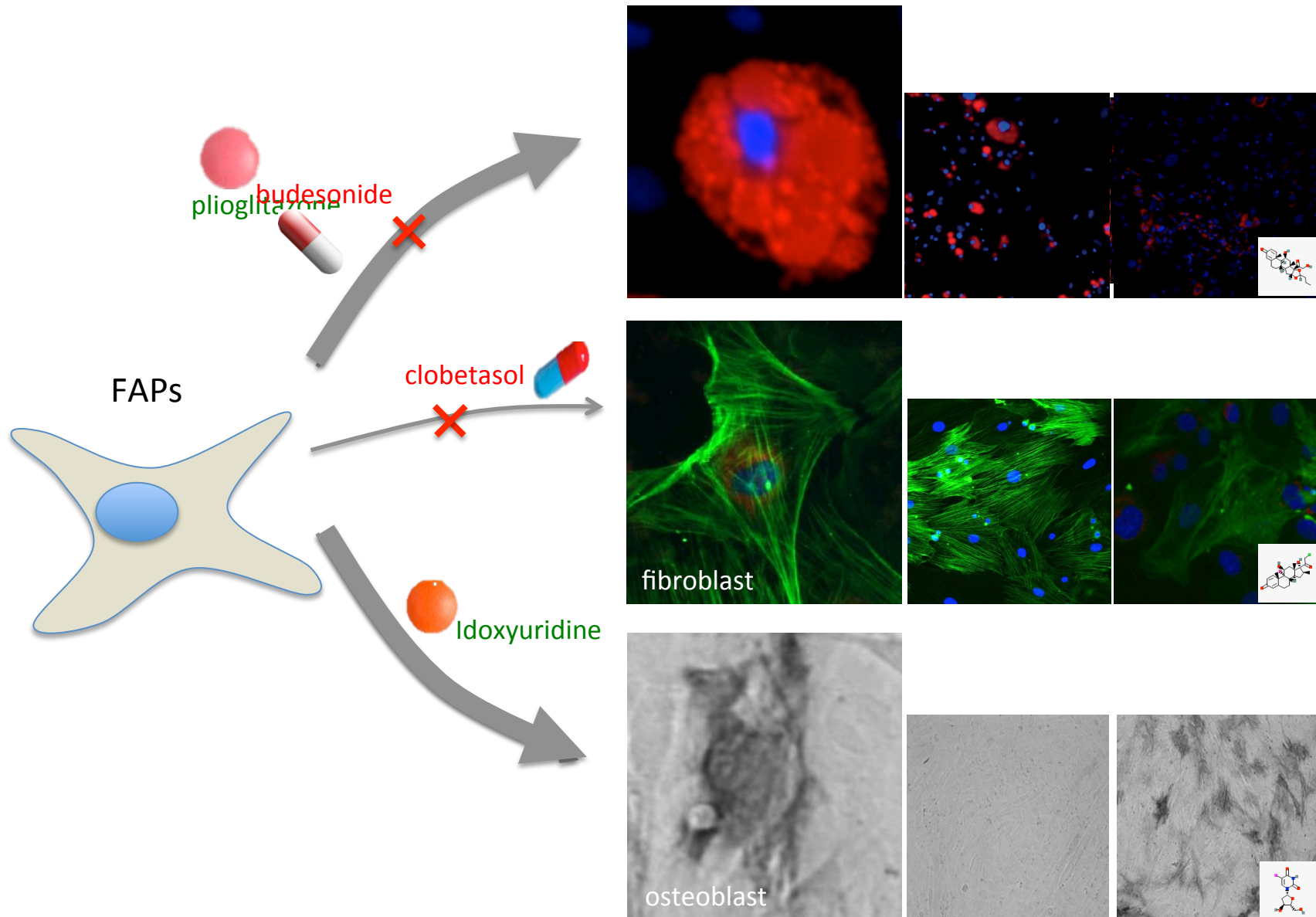


automated
image analysis

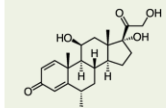
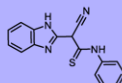
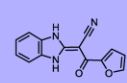
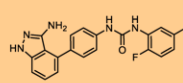
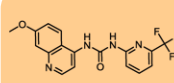
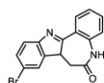
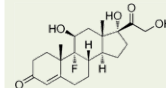
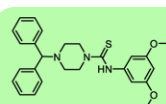
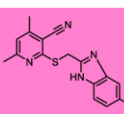
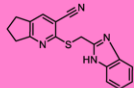
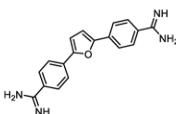
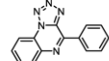
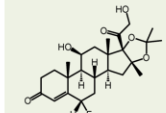
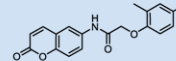
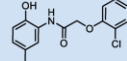
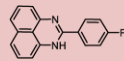
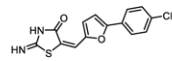
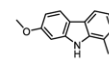
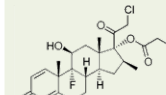
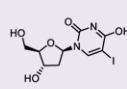
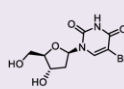
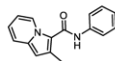
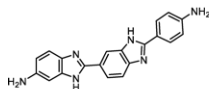
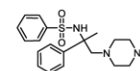
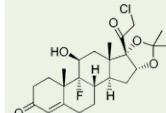
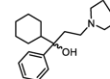
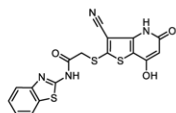
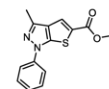
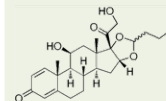
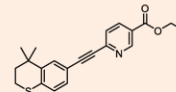
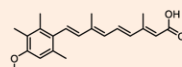
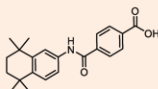
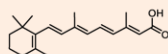
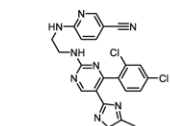


automated image
acquisition

small molecules that affect FAP differentiation

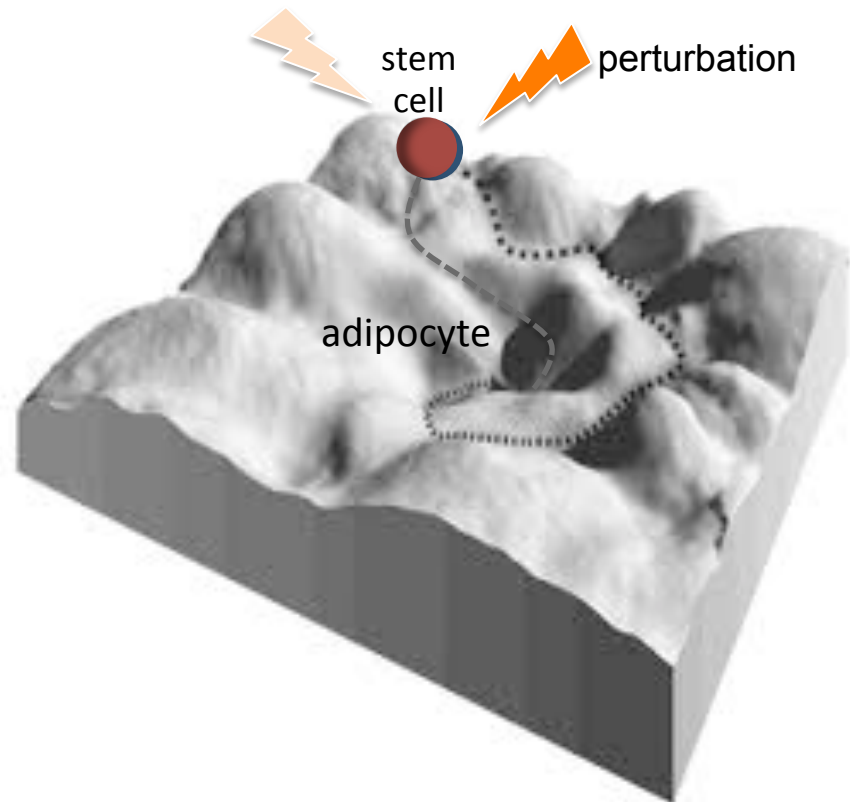


40 small molecules that affect adipogenesis



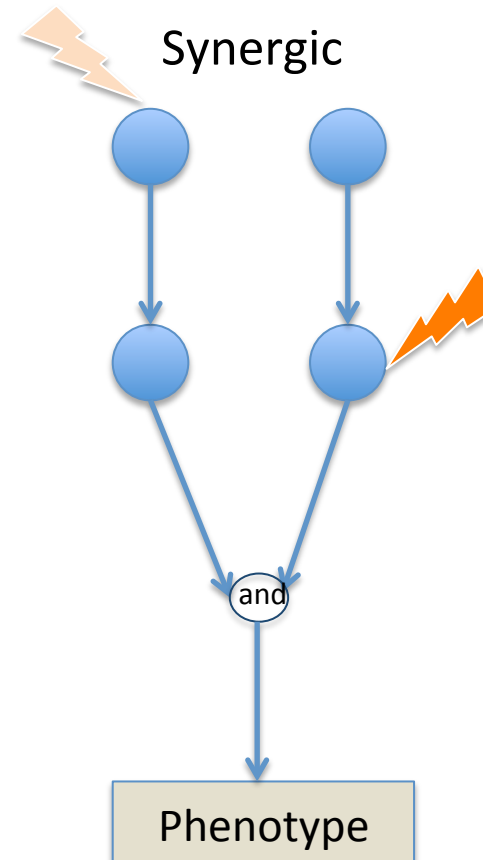
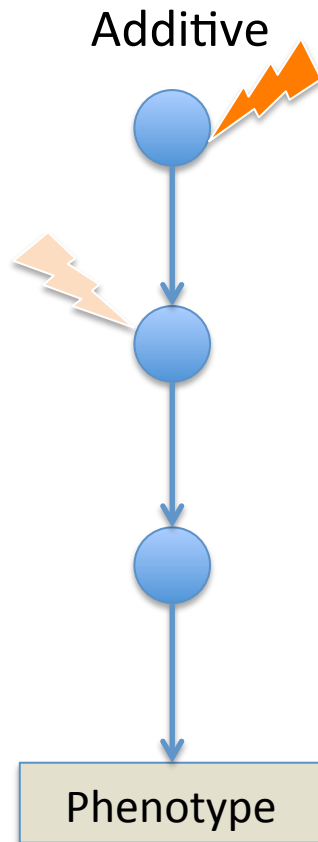
do all these molecules affect differentiation by the same mechanism

Paths in the
differentiation
hyperspace

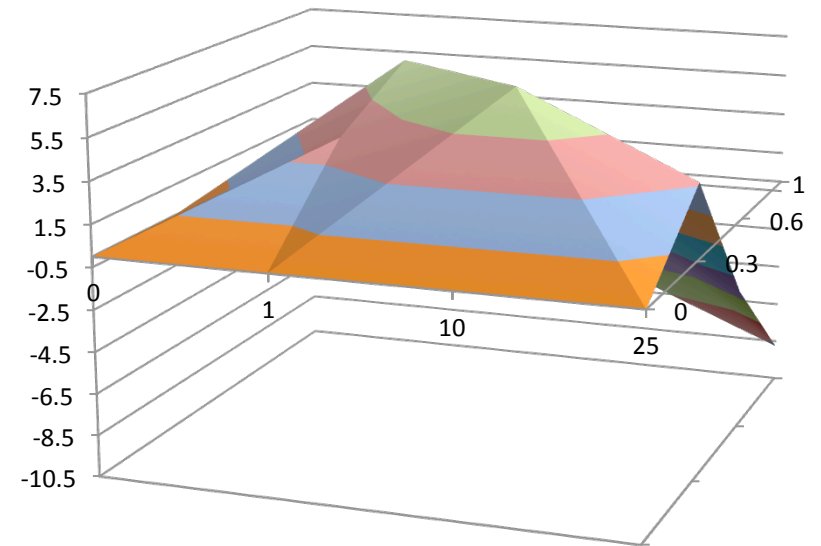
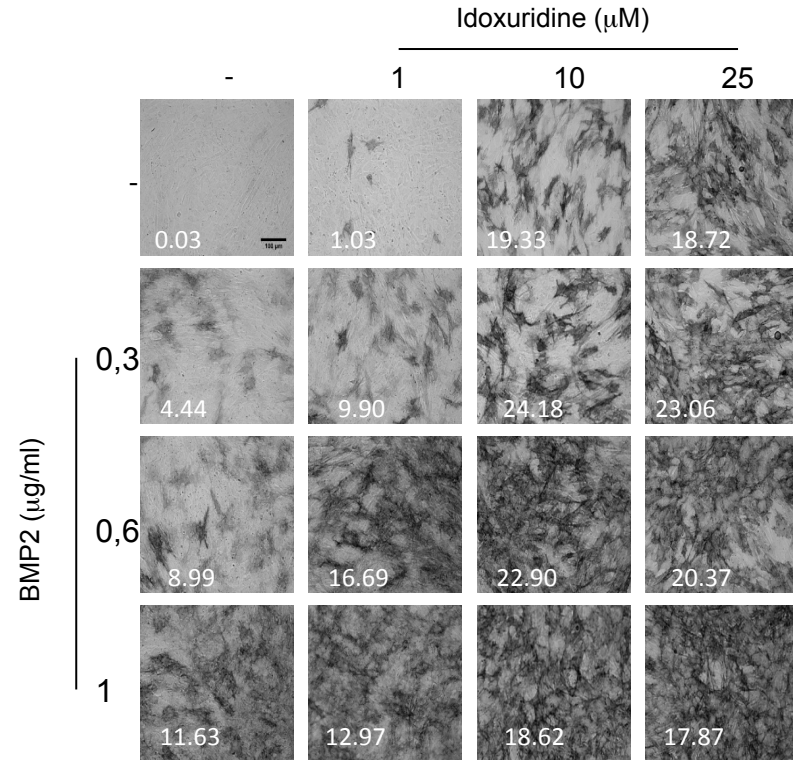


Is there a single path from an undifferentiated stem-like state to a terminally differentiated state?

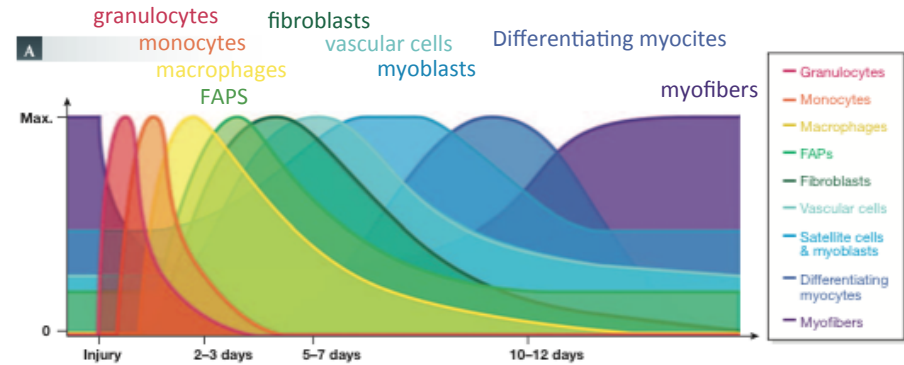
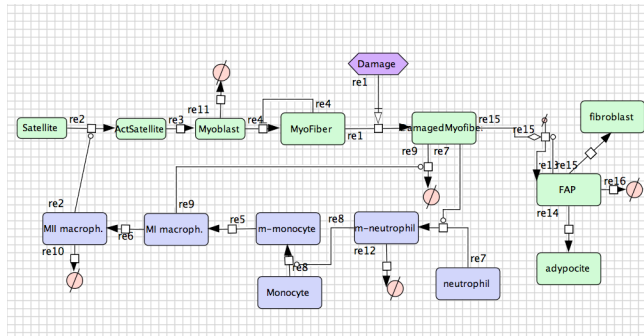
additive and synergistic interactions



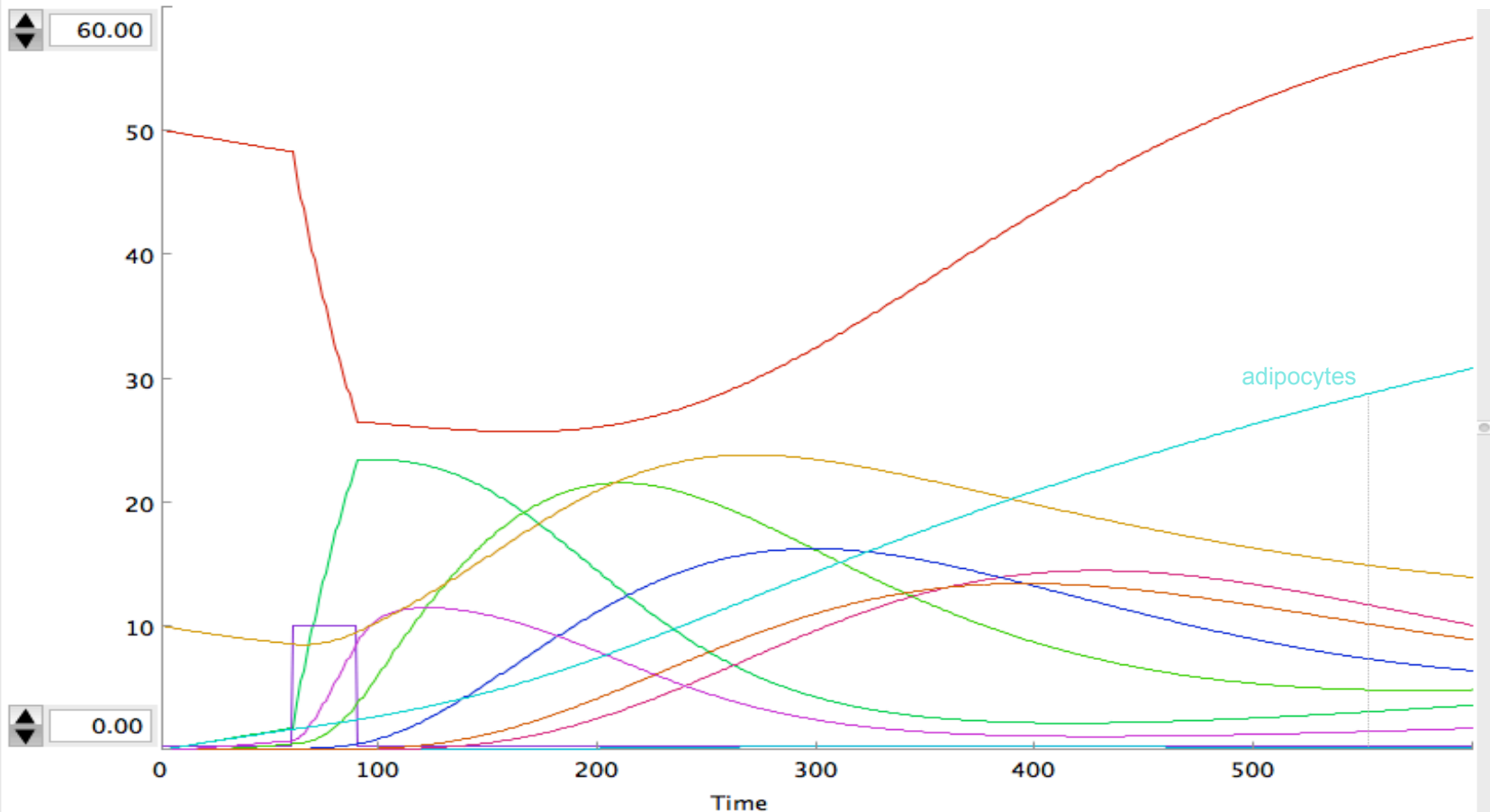
Idoxiuridine is synergic with BMP in inducing FAP osteogenesis



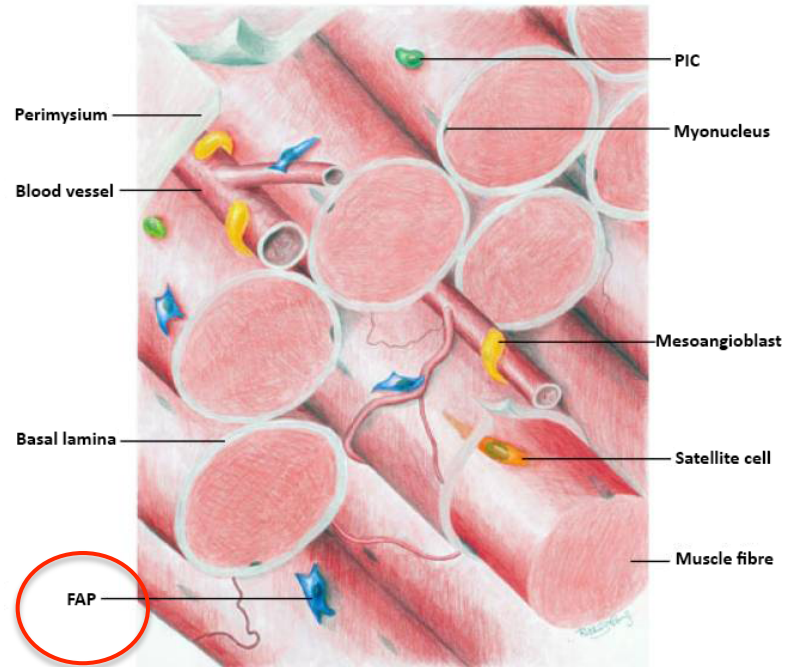
Does the model reproduces the dynamics of cell populations following muscle damage



Concentration raw ☒ Species ☐ Fluxes



Why are muscles from healthy young individuals essentially fat free ?



Purified FAPs, when cultivated in vitro, readily differentiate into adipocytes



Adipocytes do not infiltrate healthy muscles

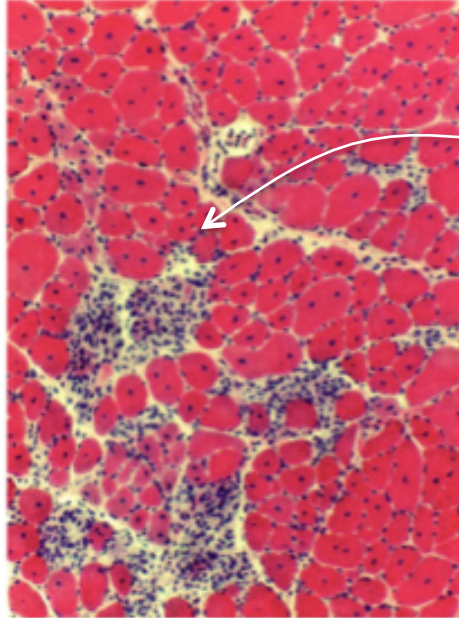
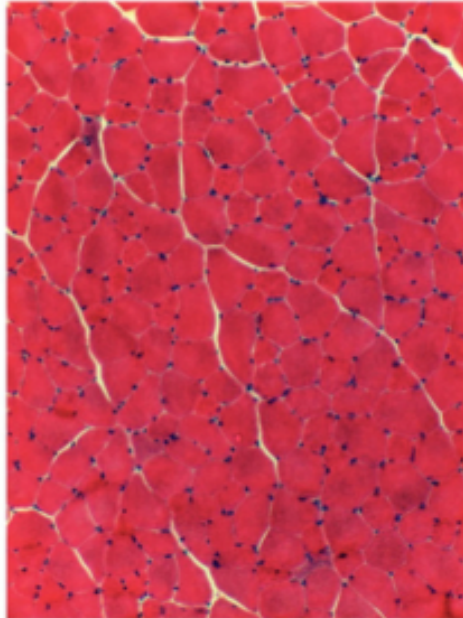


Wild type



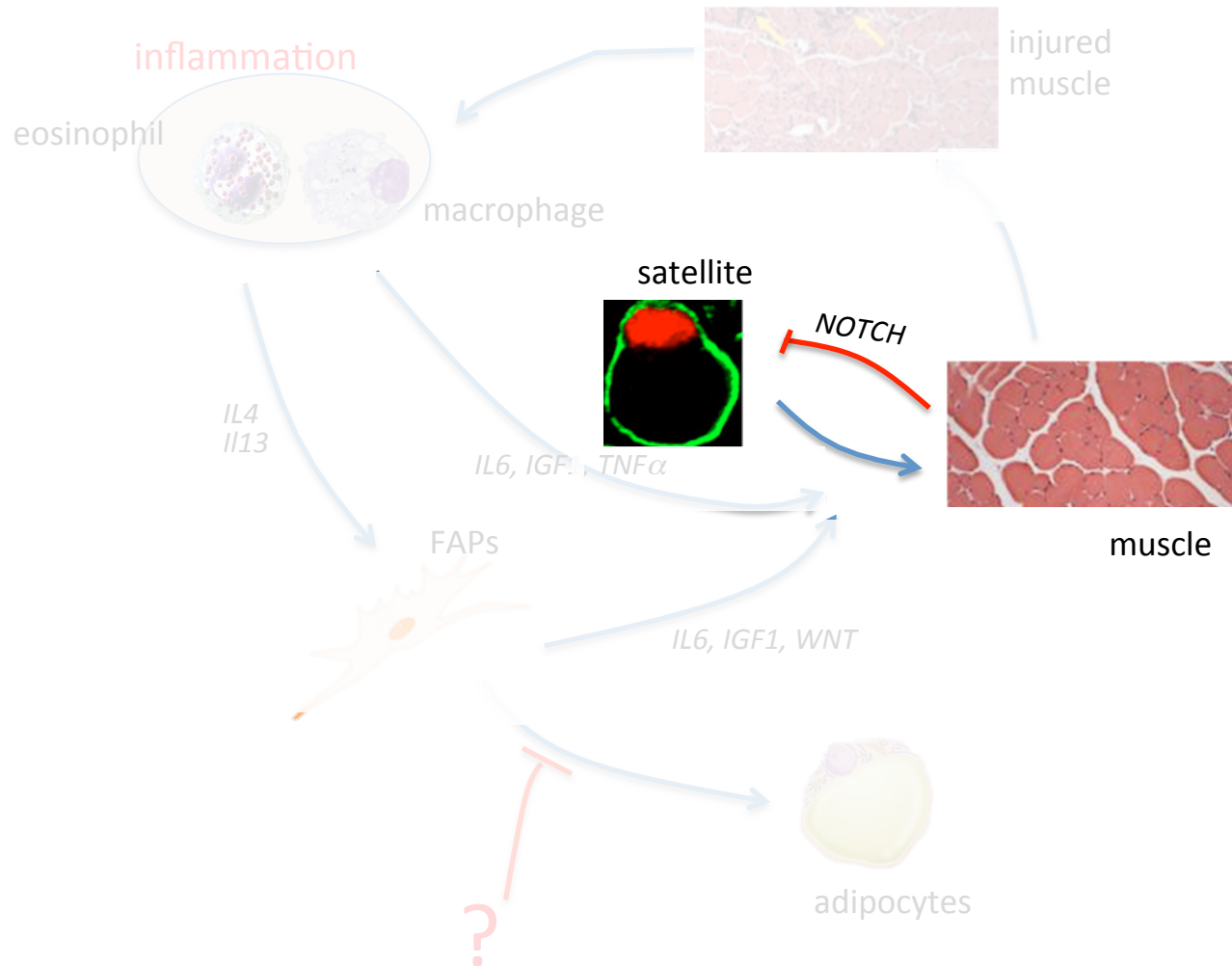
DMD⁻

H&E stain



adipocyte
infiltrates

The function of fibro adipogenic progenitors (FAPs)



Questions

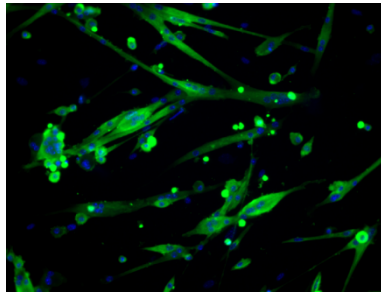
What are the signals that negatively control adipocyte differentiation of FAPs in healthy muscles *in vivo*?

Why do FAPs from dystrophic individuals lose sensitivity to this control mechanism?

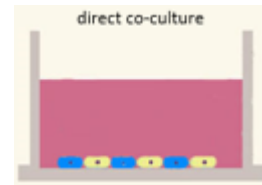
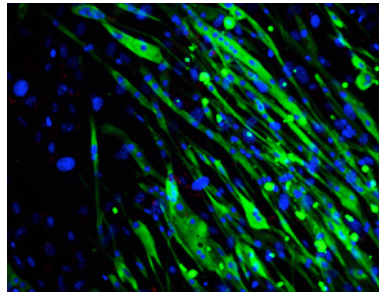
Interaction between satellite cells and fibroadipogenic progenitors (FAPs)

Satellite cells inhibits FAP adipogenesis by direct cell cell contact

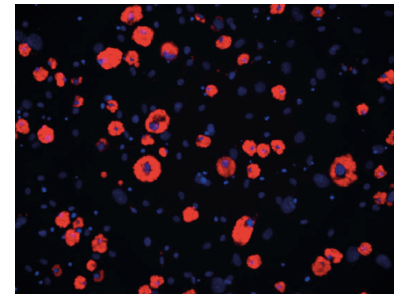
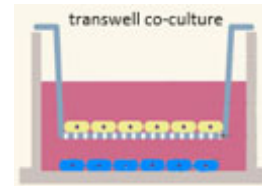
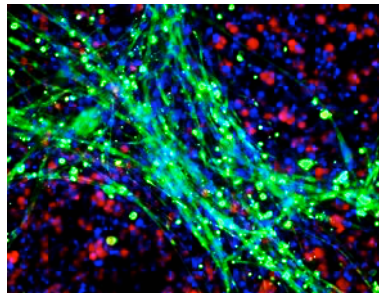
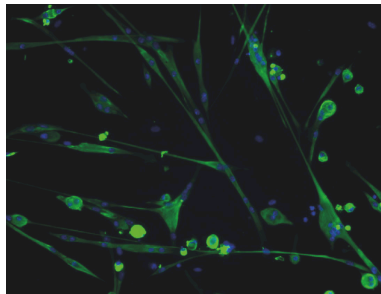
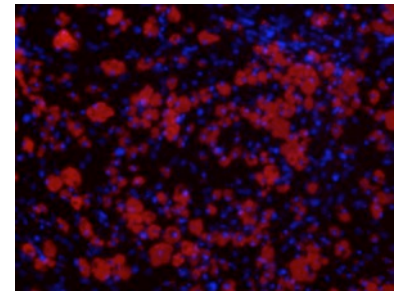
Satellite cells



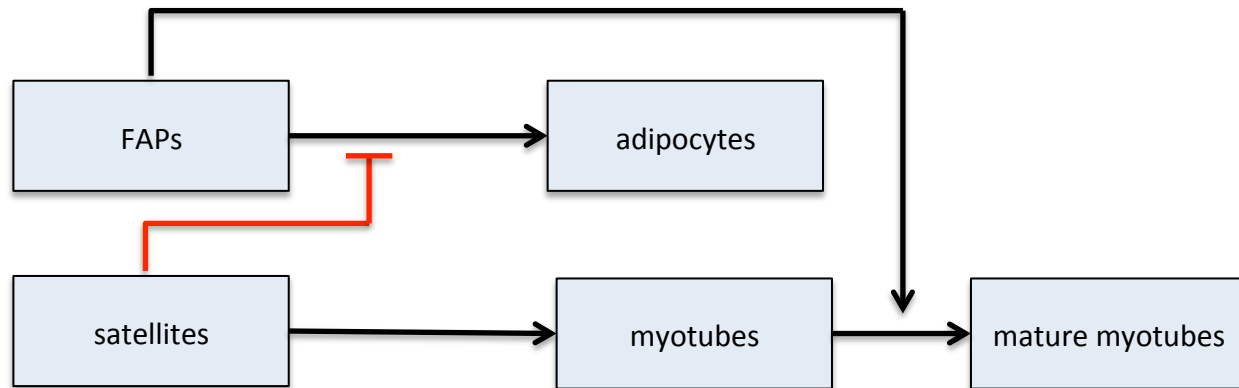
Satellite cells + FAPs



FAPs



FAPs and satellites form a stabilizing regulatory module



Conclusions

- A fine tuned interaction between satellite cells and fibro adipogenic progenitors promotes muscle regeneration and prevents fat infiltrations.
- Activation of NOTCH limits FAPs adipogenesis
- FAPs purified from mice that are defective in the dystrophin gene are insensitive to NOTCH inhibition and cause fat and fibrotic infiltration in the muscle.
- A decrease in the concentration of Ca pumps may render FAPs insensitive to NOTCH signals.

perspectives

- Investigate whether any of the modulators of FAP adipogenesis that we have identified in the screening modulate the satellite FAP interaction and revert the FAP mdx phenotype.
- Identify more cell cell interactions and the pathways/signals that are responsible for this cell crosstalk and implement them into an executable model of muscle regeneration.

Gianni Cesareni & Luisa Castagnoli

Current and former collaborators

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