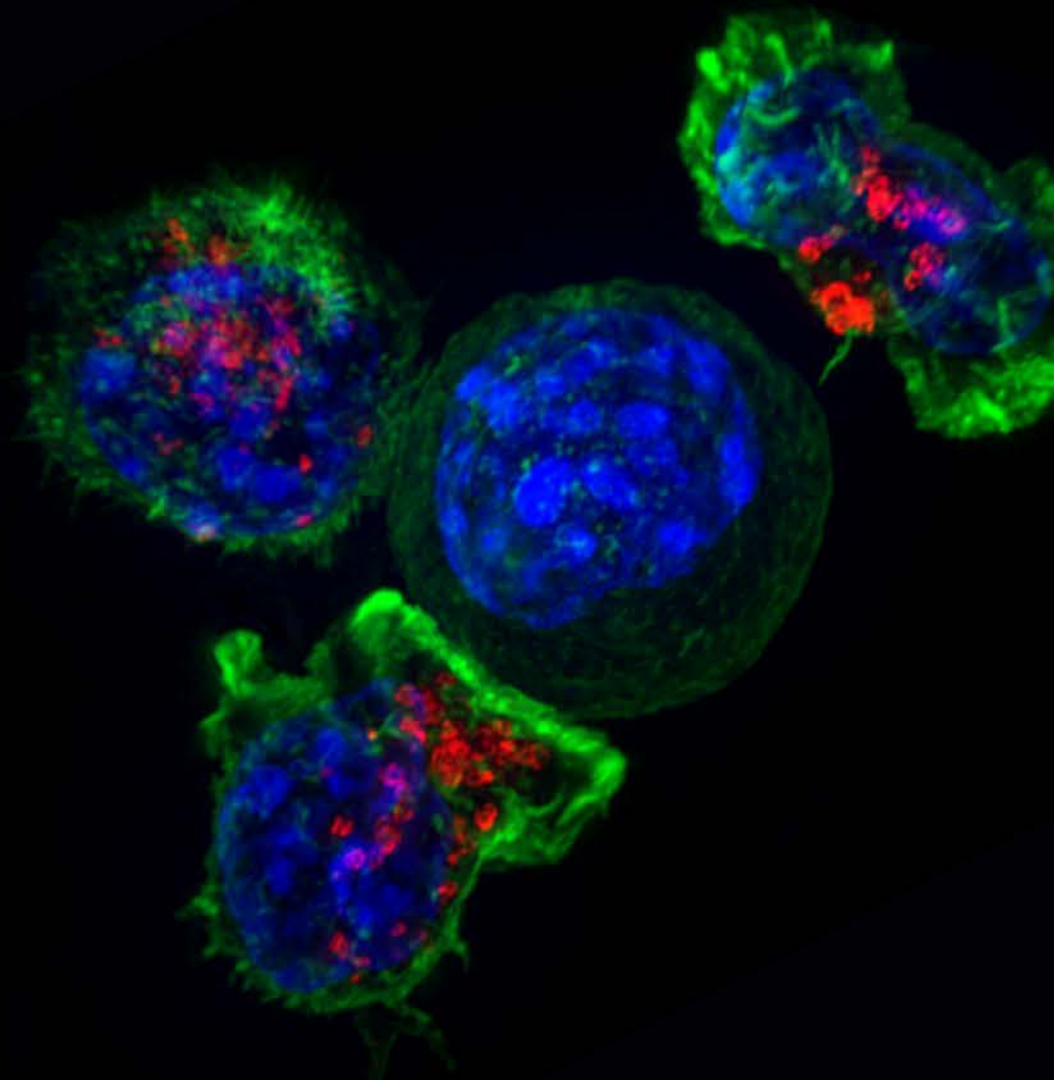
Modulating the Therapeutic Microenvironment Using Nanostructured Materials



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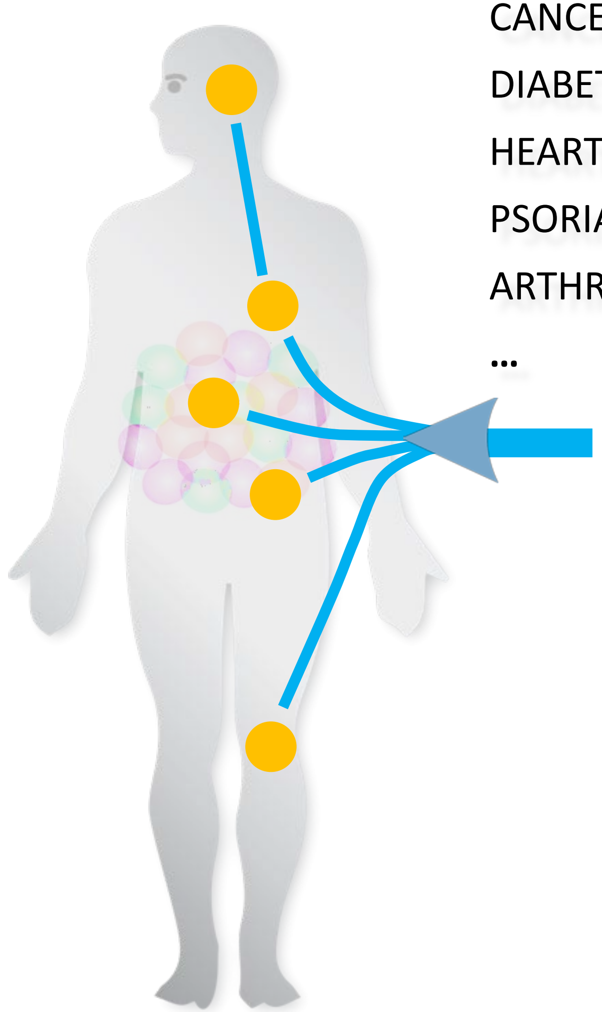
Advanced biomaterials for therapeutic delivery



CANCER

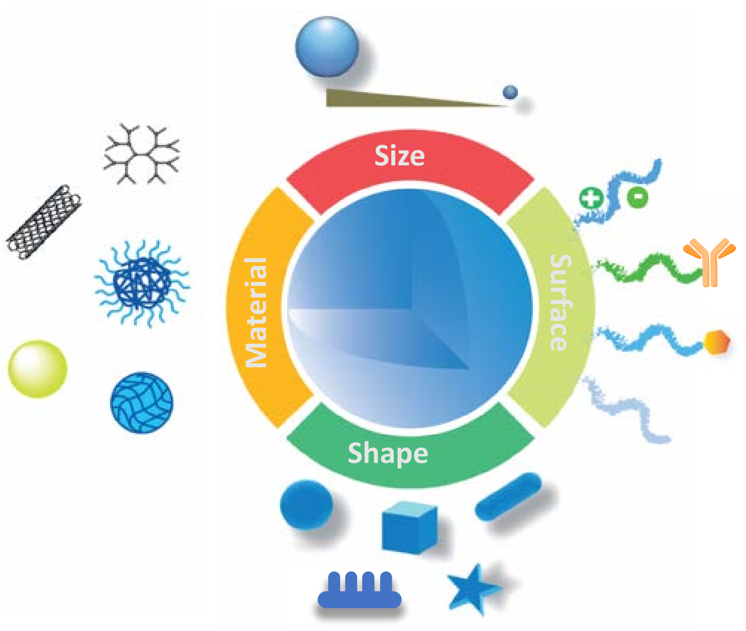
DIABETES

HEART DISEASE

PSORIASIS

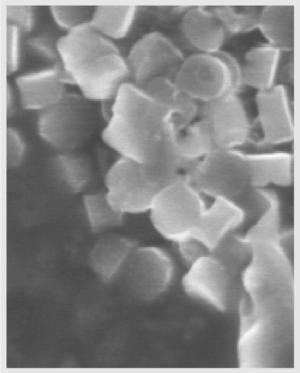
ARTHRITIS

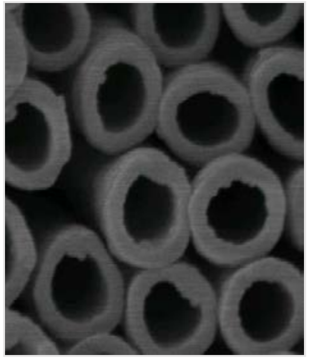
...

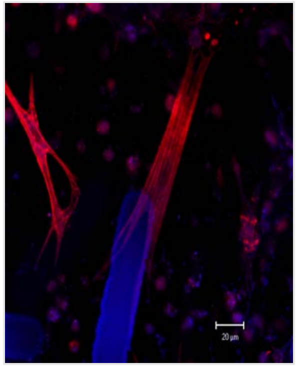


- Direct biophysical stimulation
- Biomolecule carrier/presenter

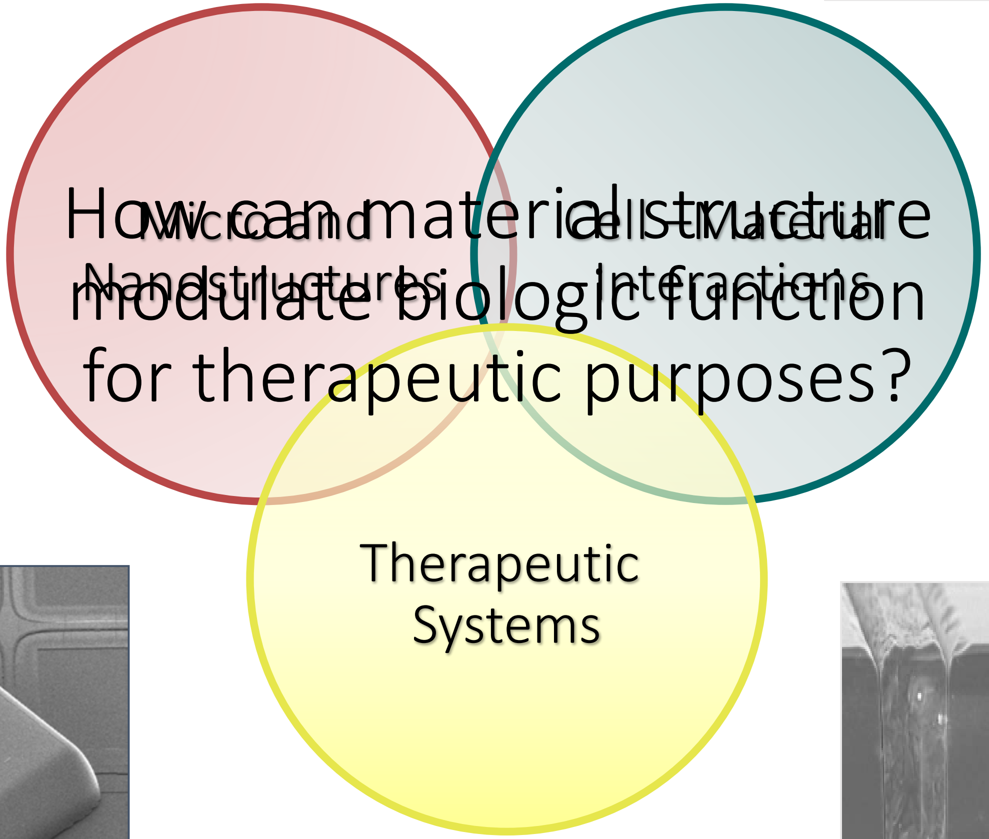
Picture credit: Zhang, Drug Discovery Today

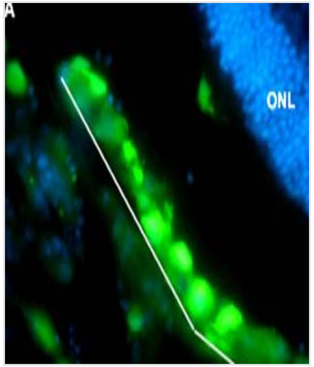


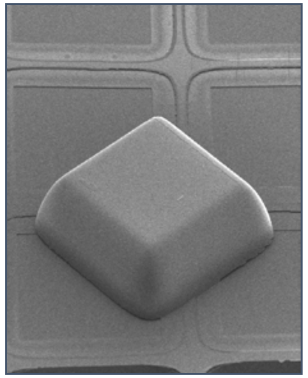


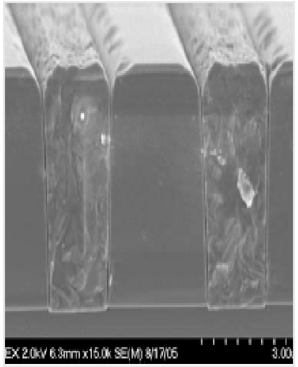


How can material structure modulate biologic function for therapeutic purposes?









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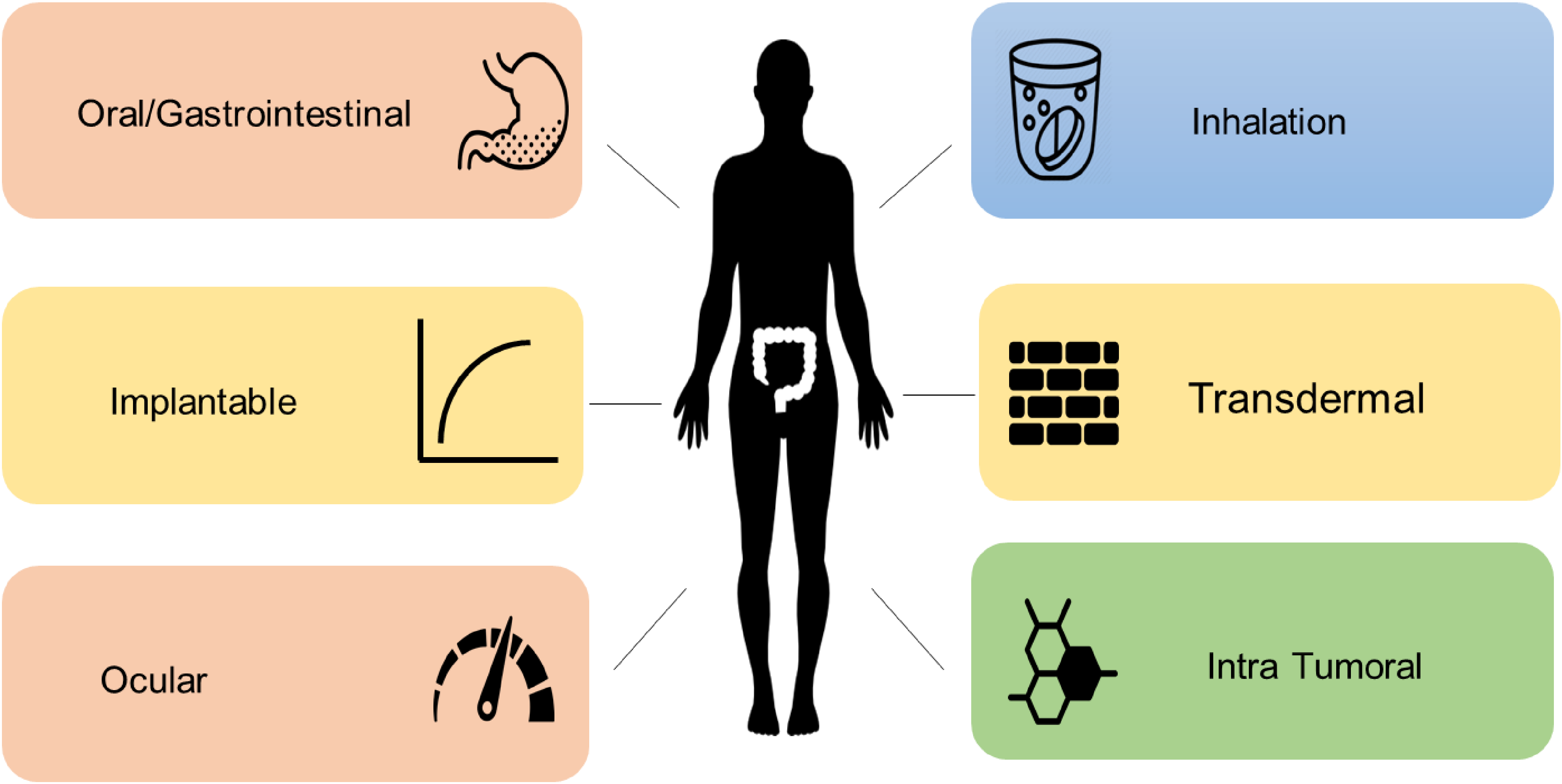
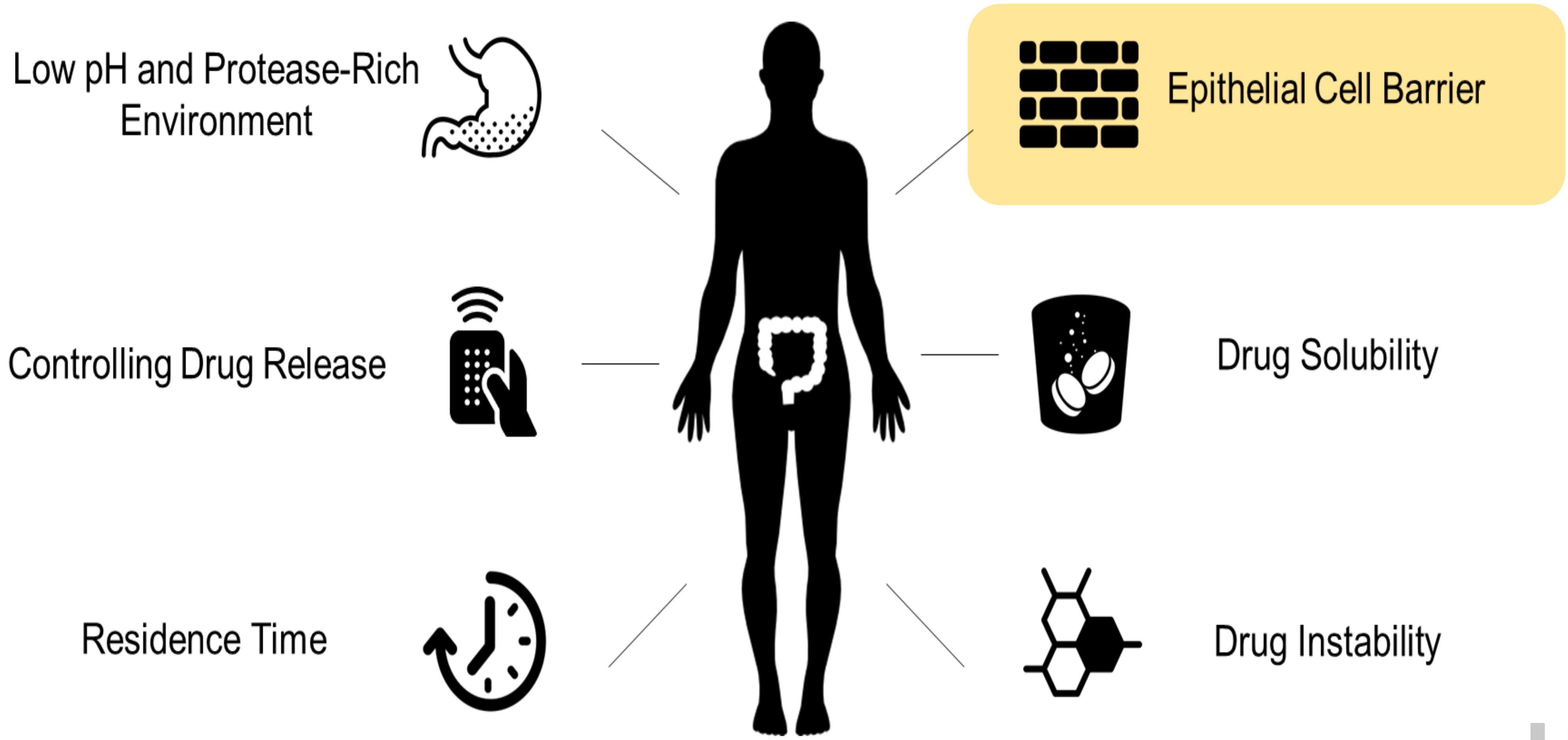
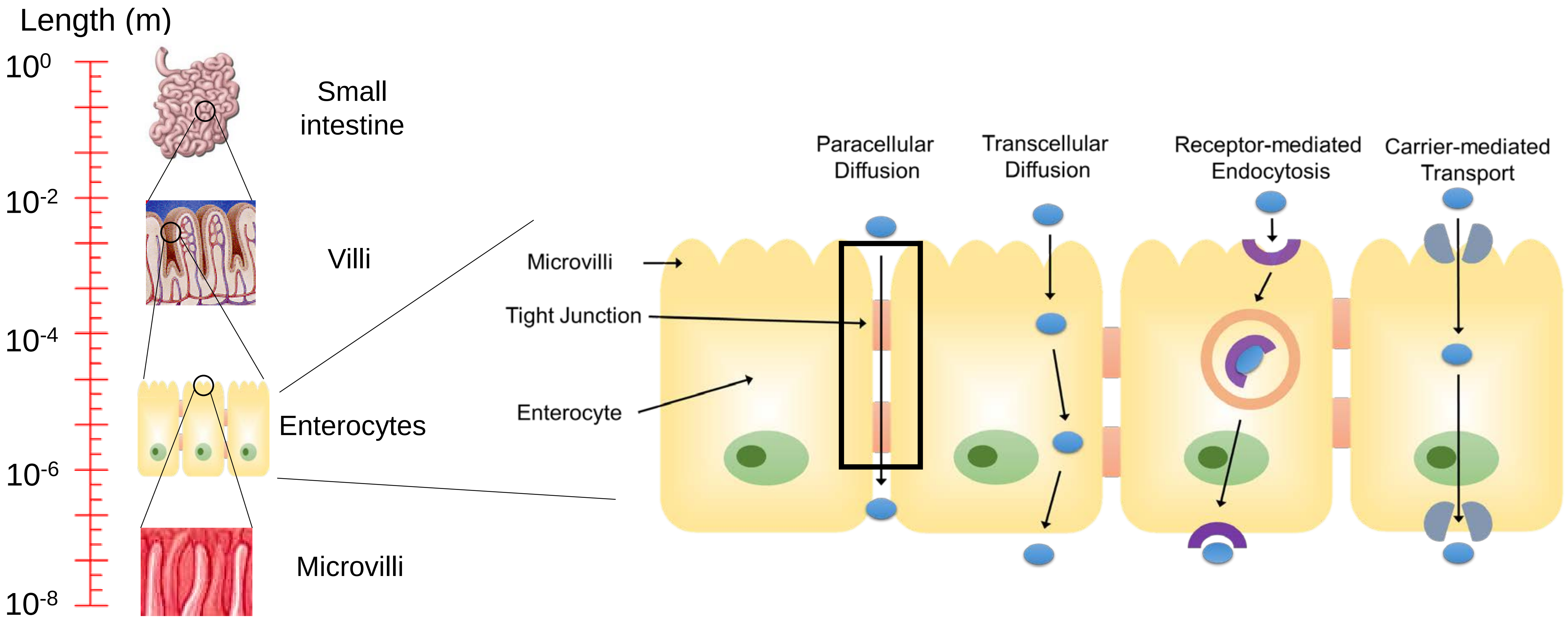
Desired Routes of Drug Delivery



Challenges to epithelial drug delivery



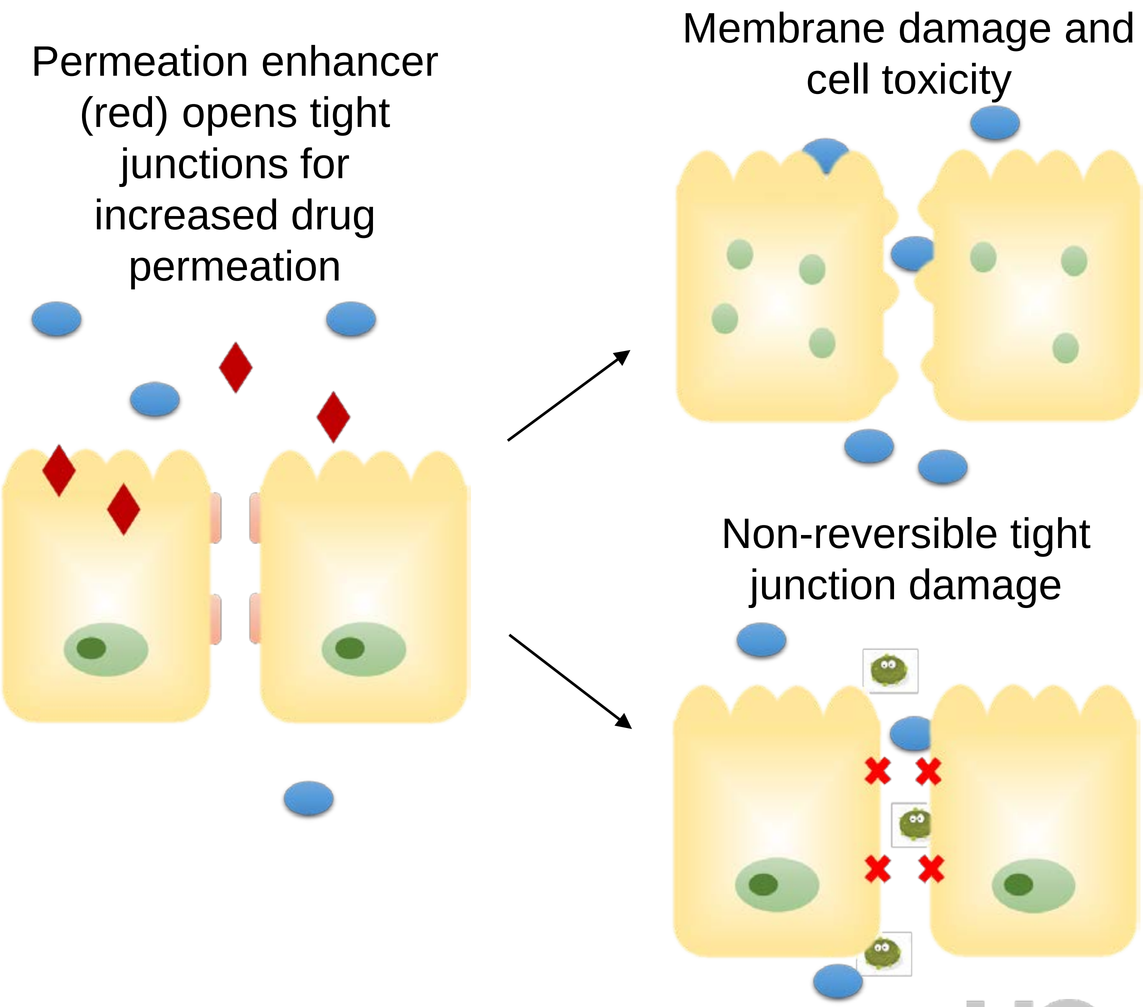
Revisiting the small intestine



Fox C et al., Journal of Controlled Release, 2015

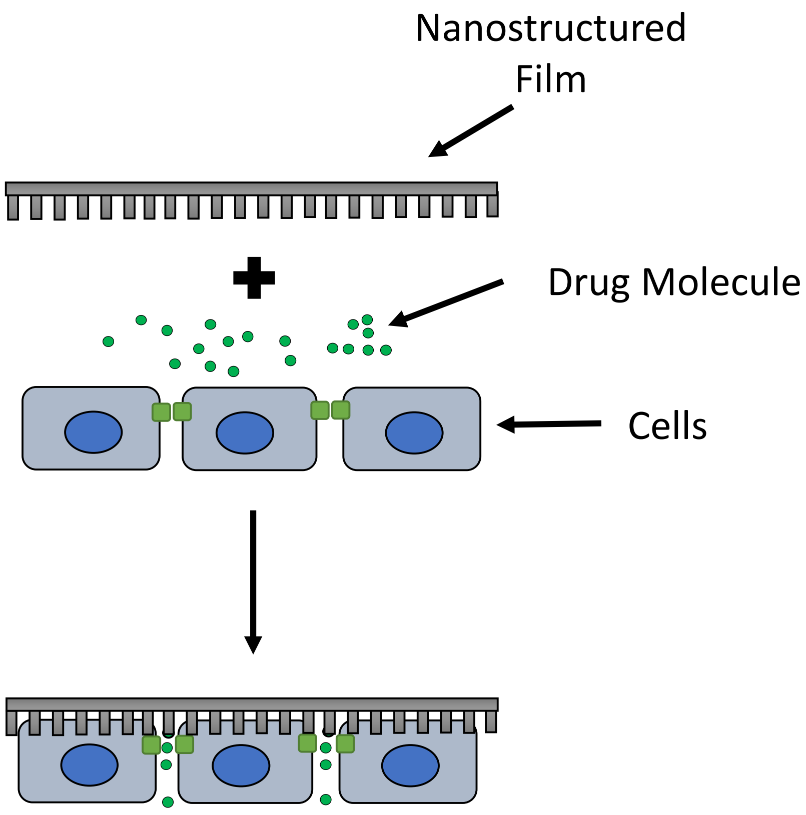
Drawbacks of paracellular permeation enhancers

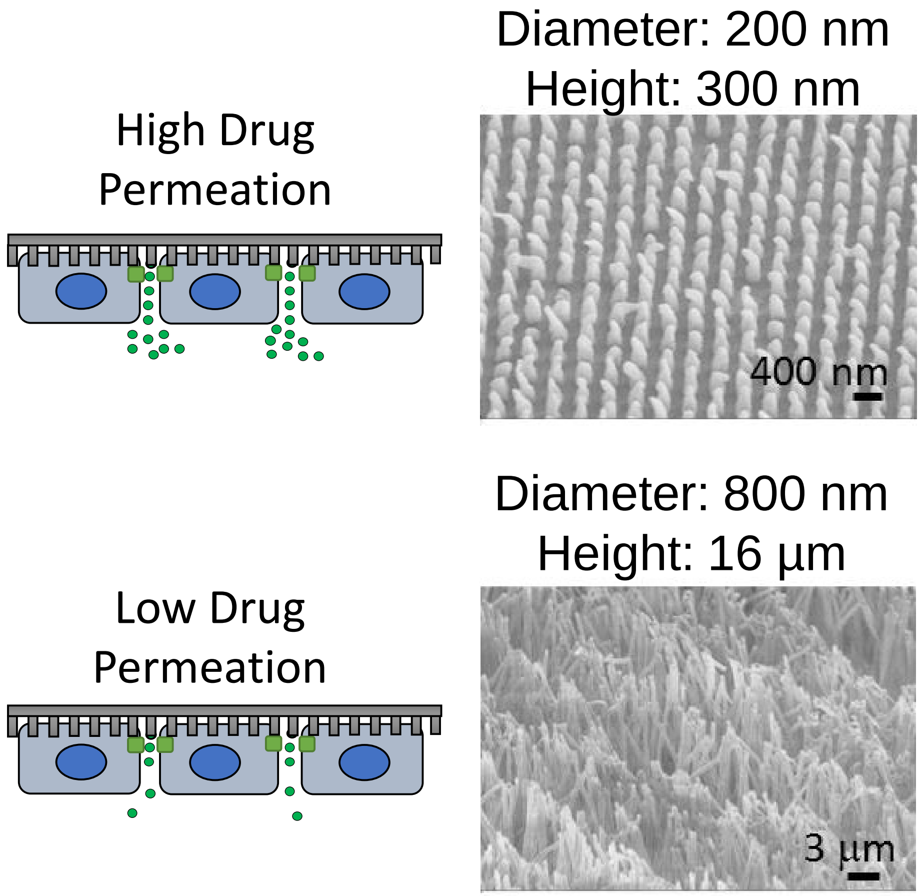
- Chemical permeation agents induce opening of tight junctions
  - Examples: Surfactants, chelators, and toxins
  - Toxicity to cells
  - Non-reversible tight junction opening



Opening Epithelial Barriers

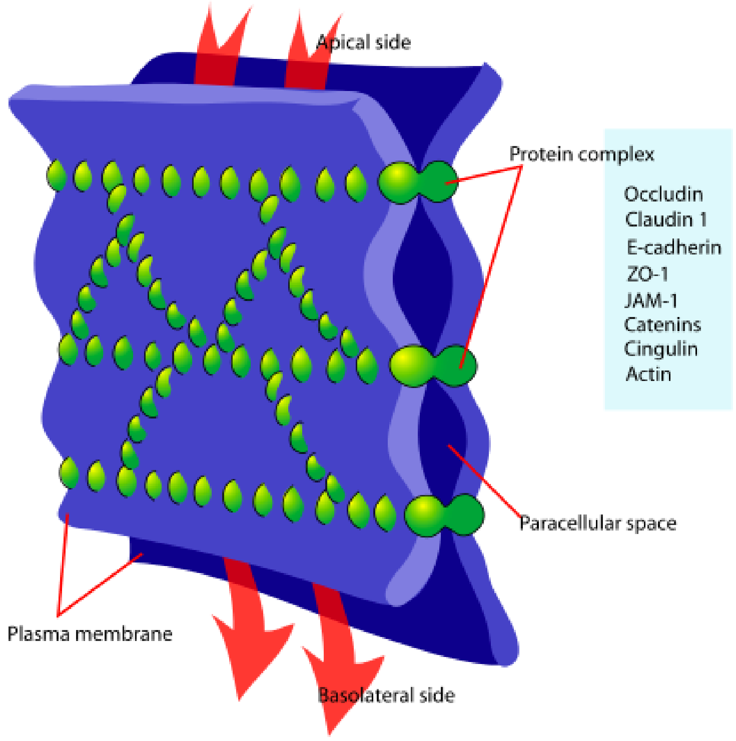
Topographical cues can enhance permeation of drug between tight junctions

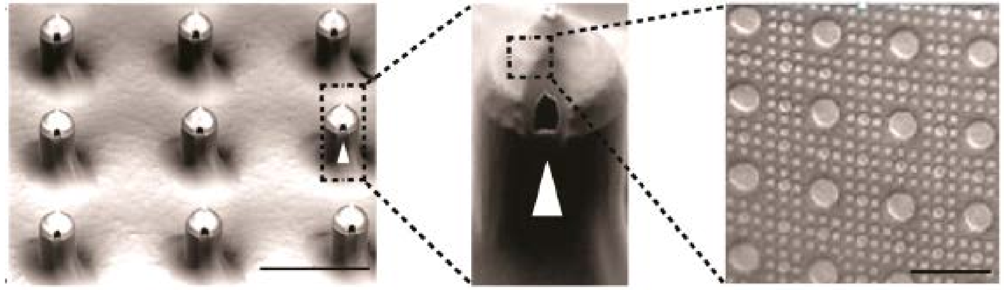


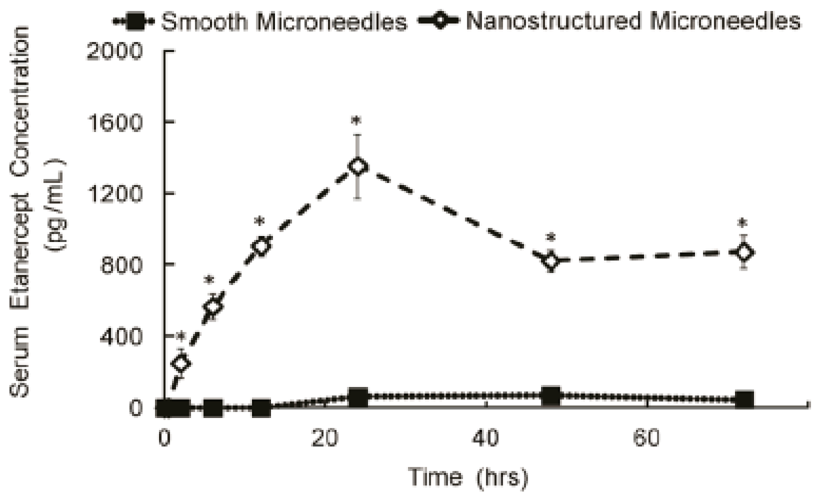


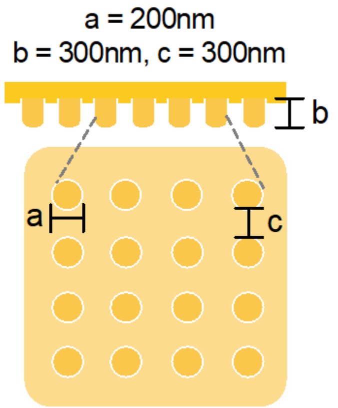
Kam et al., Nanoletters, 2014;
Stewart et al., Exp. Cell Res, 2017

Nanostructured microneedles enhance transdermal drug delivery



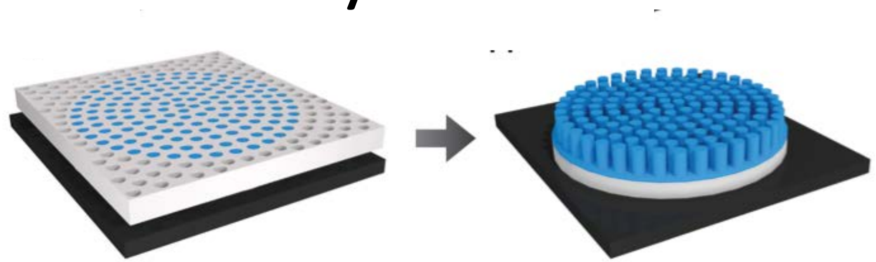


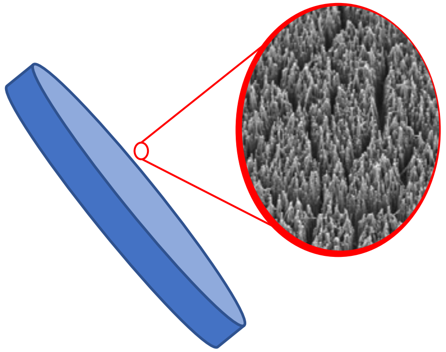




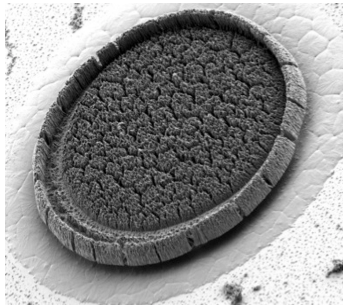
Sun, et al. Physiological Reviews, 2017
Walsh, et al. Nano Lett, 2015

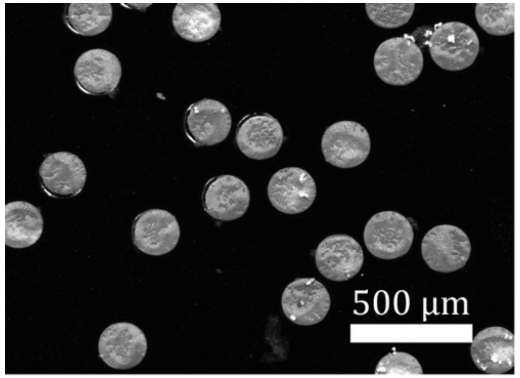
Nanostructured planar particles for enhanced oral delivery

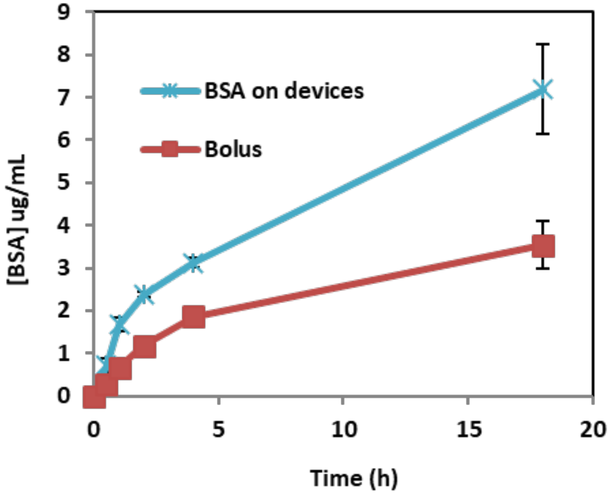


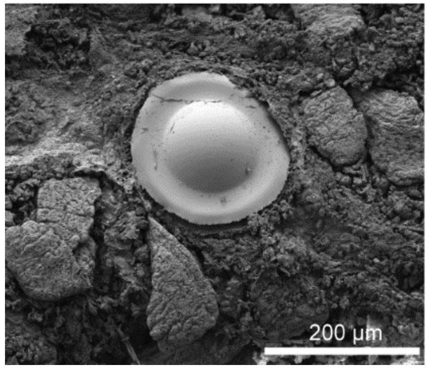


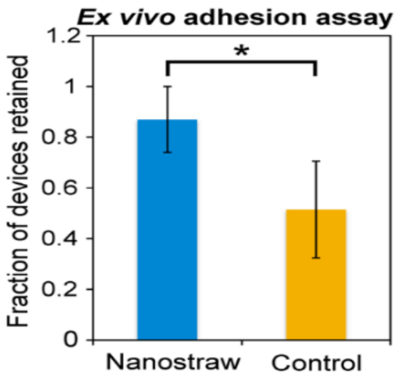
200 nm diameter

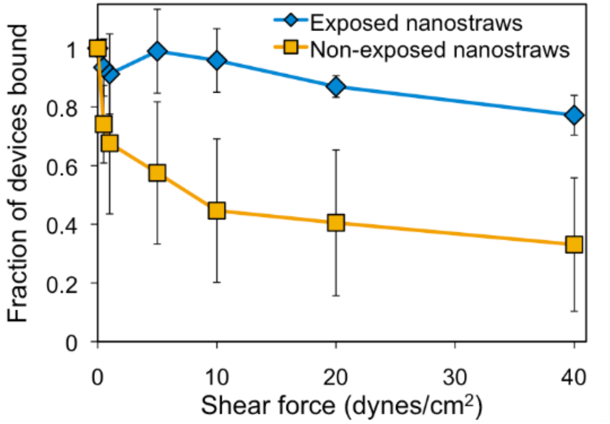








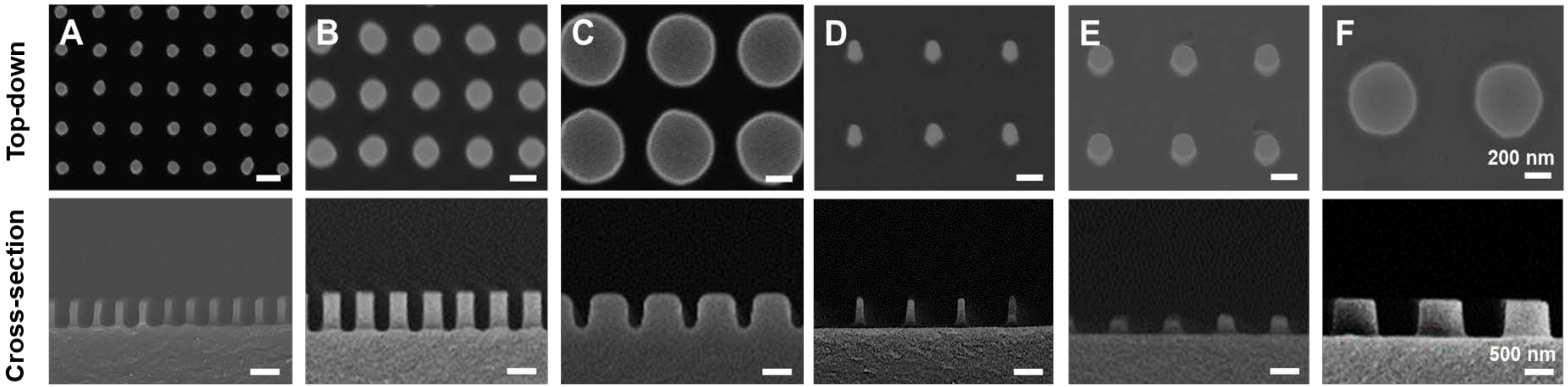


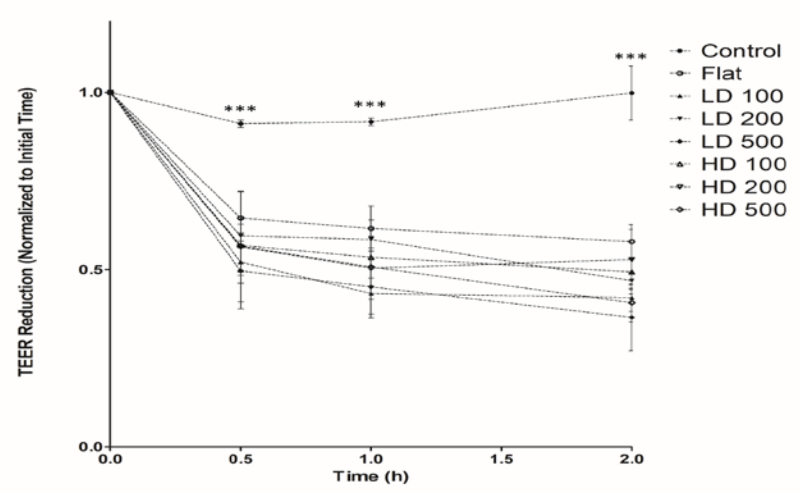


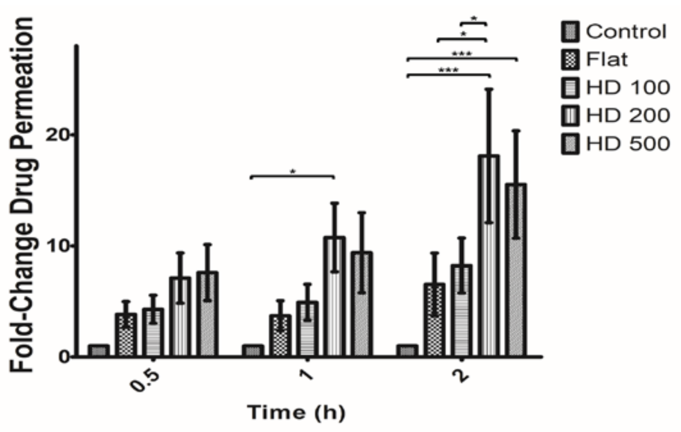
Fox et al., JCR 2015
Fox et al. ACS Nano 2016

Nanostructures can be tuned to facilitate permeation

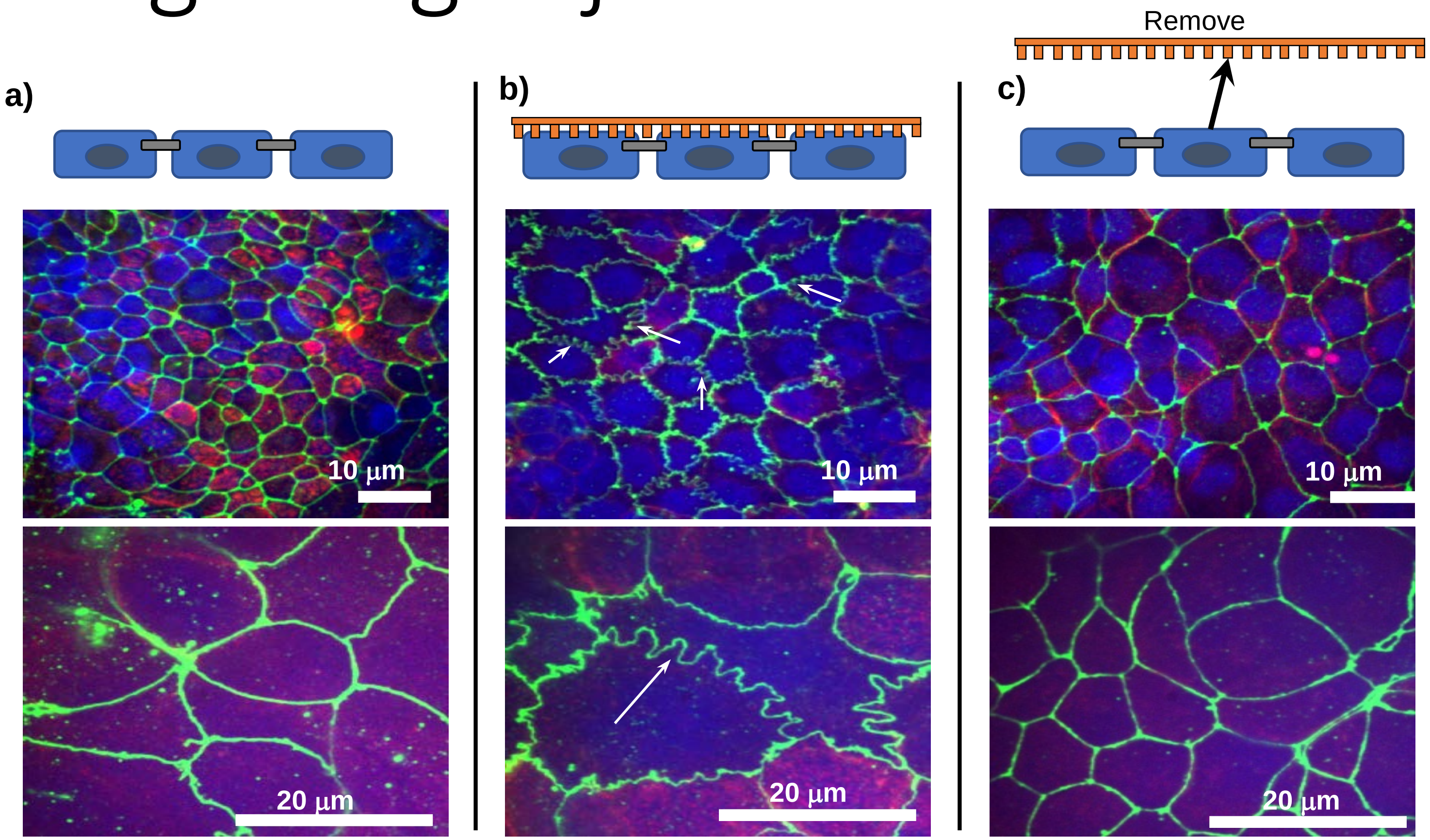
HD100 HD200 HD500 LD100 LD200 LD500





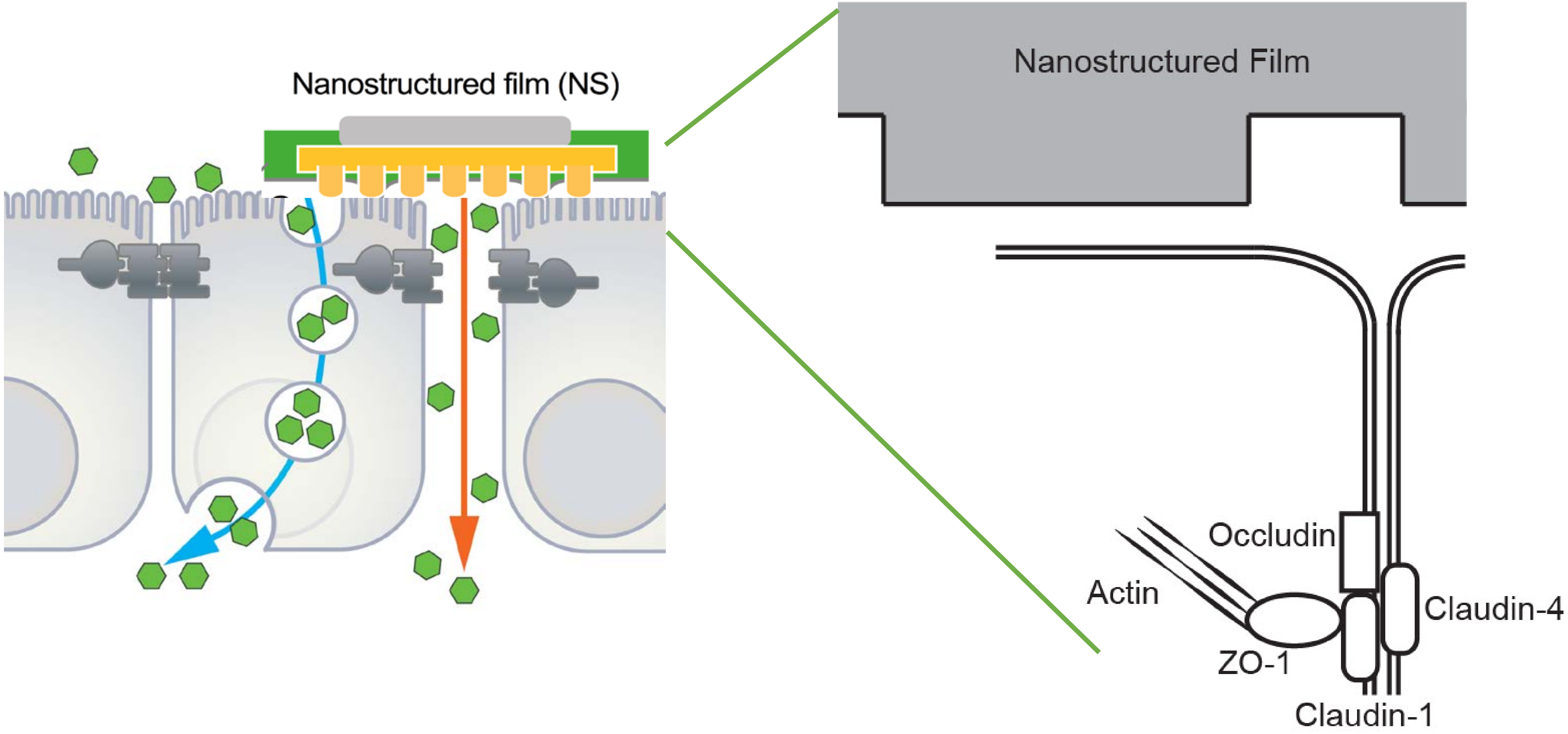


The process is reversible and involves remodeling of tight junctions



ZO-1 (tight junction protein), Caco-2 nuclei, F-Actin

Paracellular or transcellular? Mechanism?



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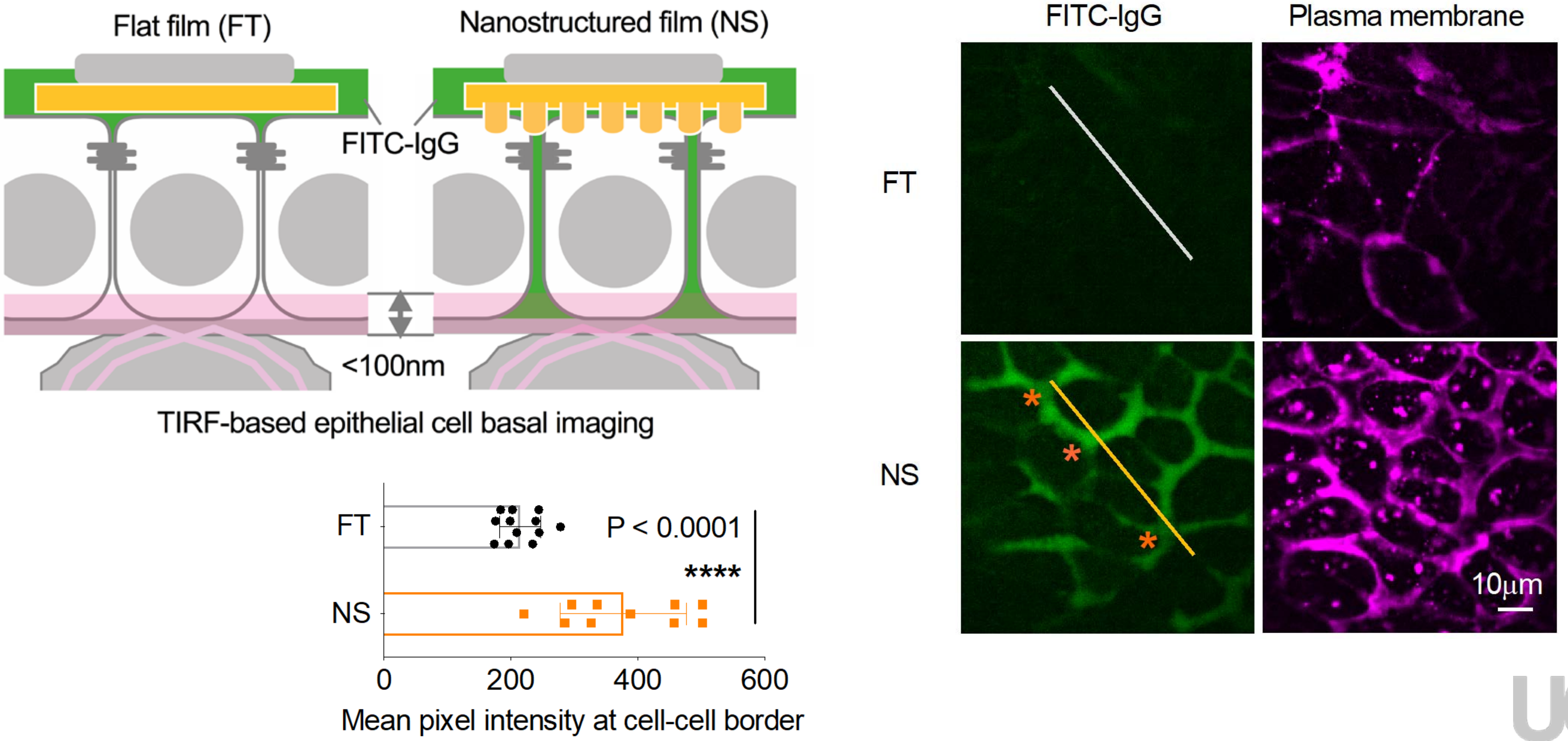
FITC-IgG present at apical cell-cell borders



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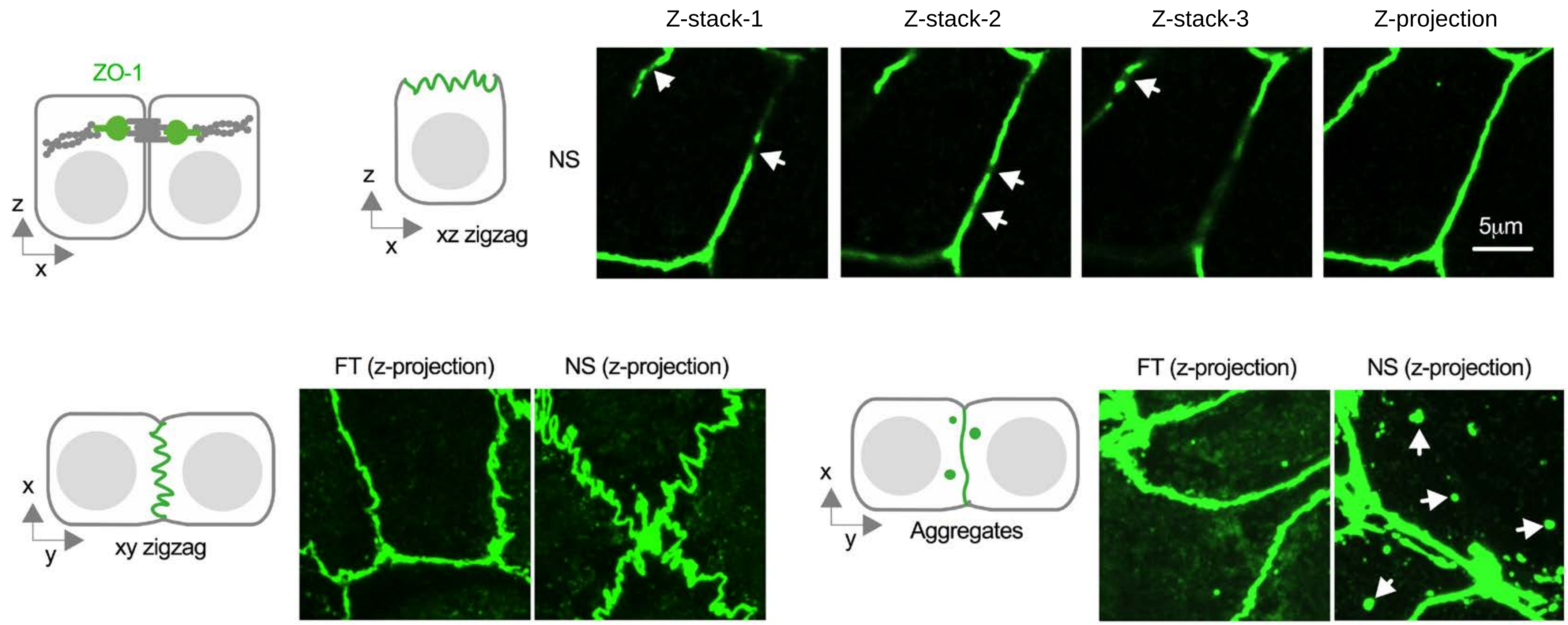
TJ scaffolding protein ZO-1 shows altered morphologies upon NS film treatment



Total level keep the same → reversible

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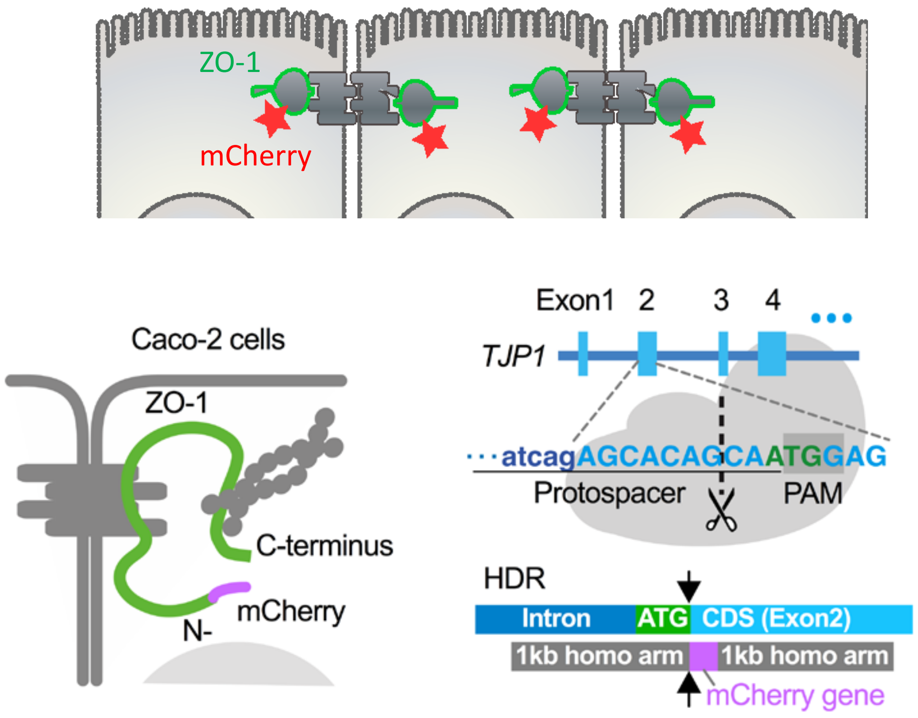
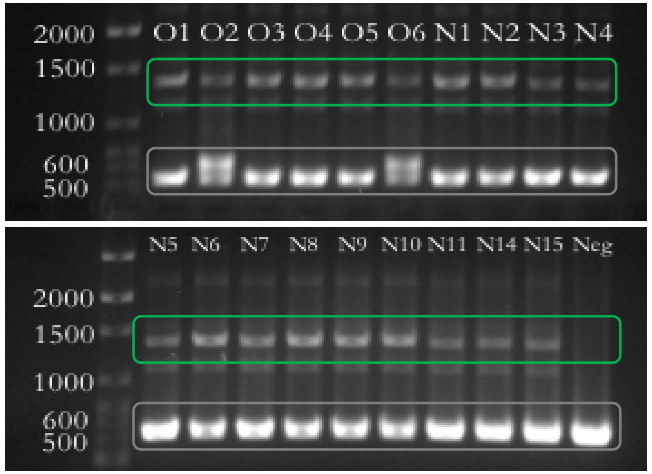
CRISPR-based gene editing to visualize tight junctions

Fluorescent protein fusion of TJP-ZO-1



ZO-1 proteins fused with mCherry-reporter at N-terminus through CRISPR

Clone isolation



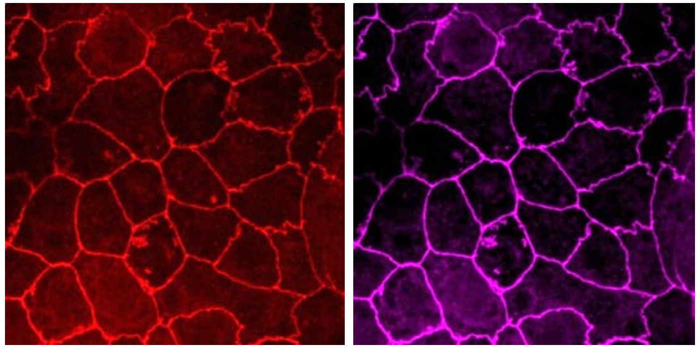
Inserted allele

Original allele

Inserted allele

Original allele

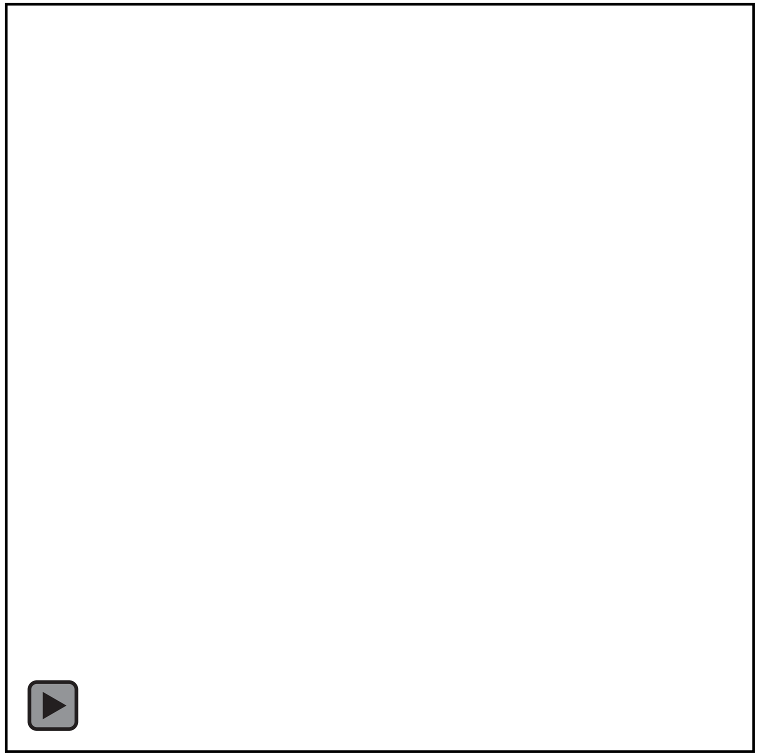
After *In Vitro* barrier model screening

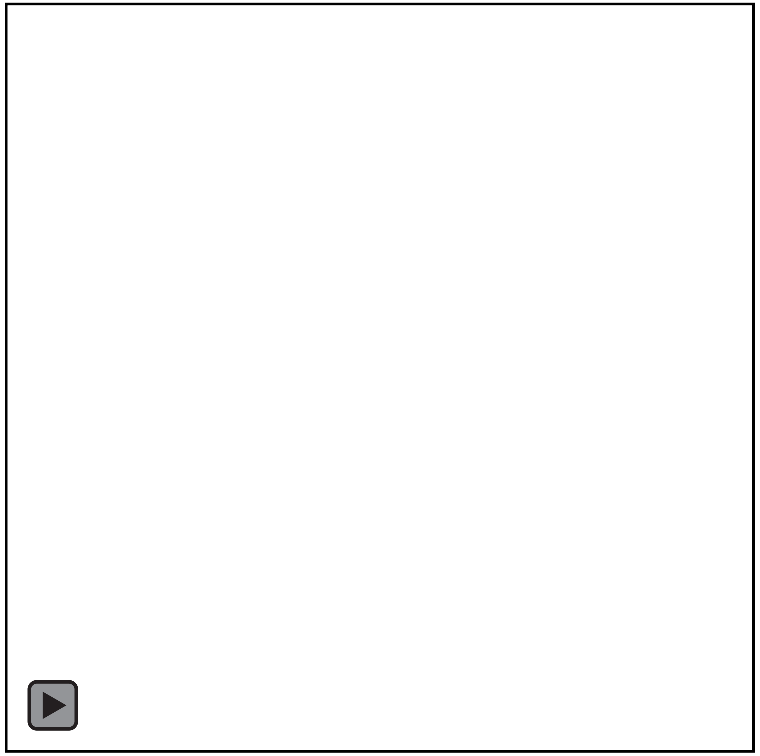


Endogenous mCherry-ZO1

ZO-1 ICC

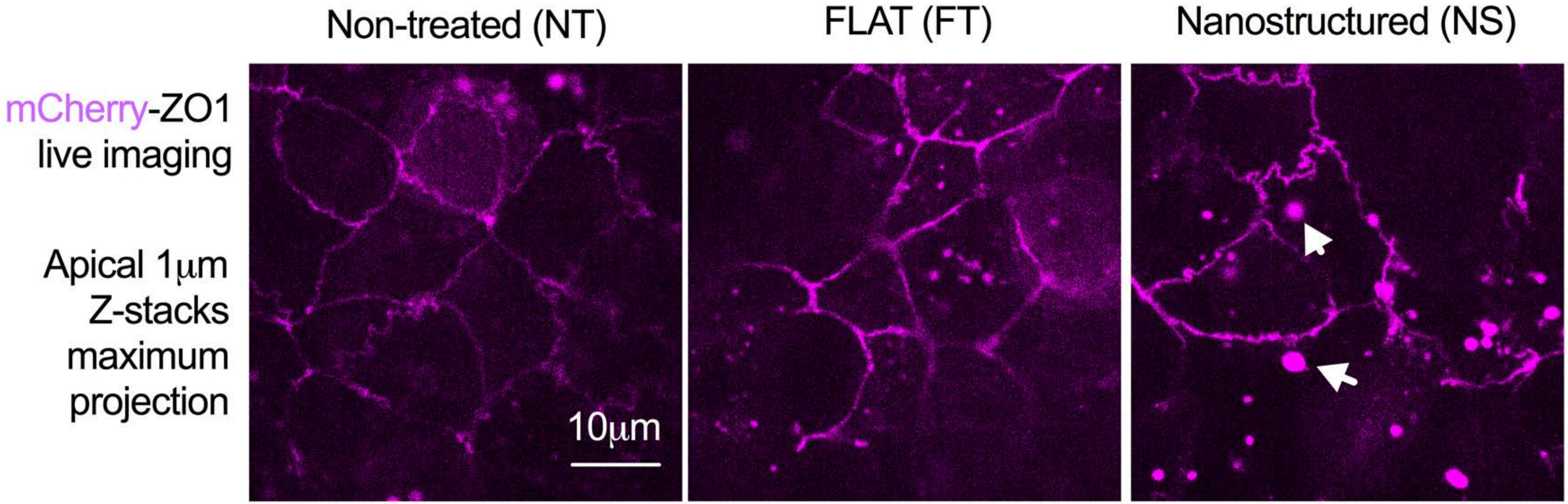
Dynamic changes in TJs with nanostructure contact



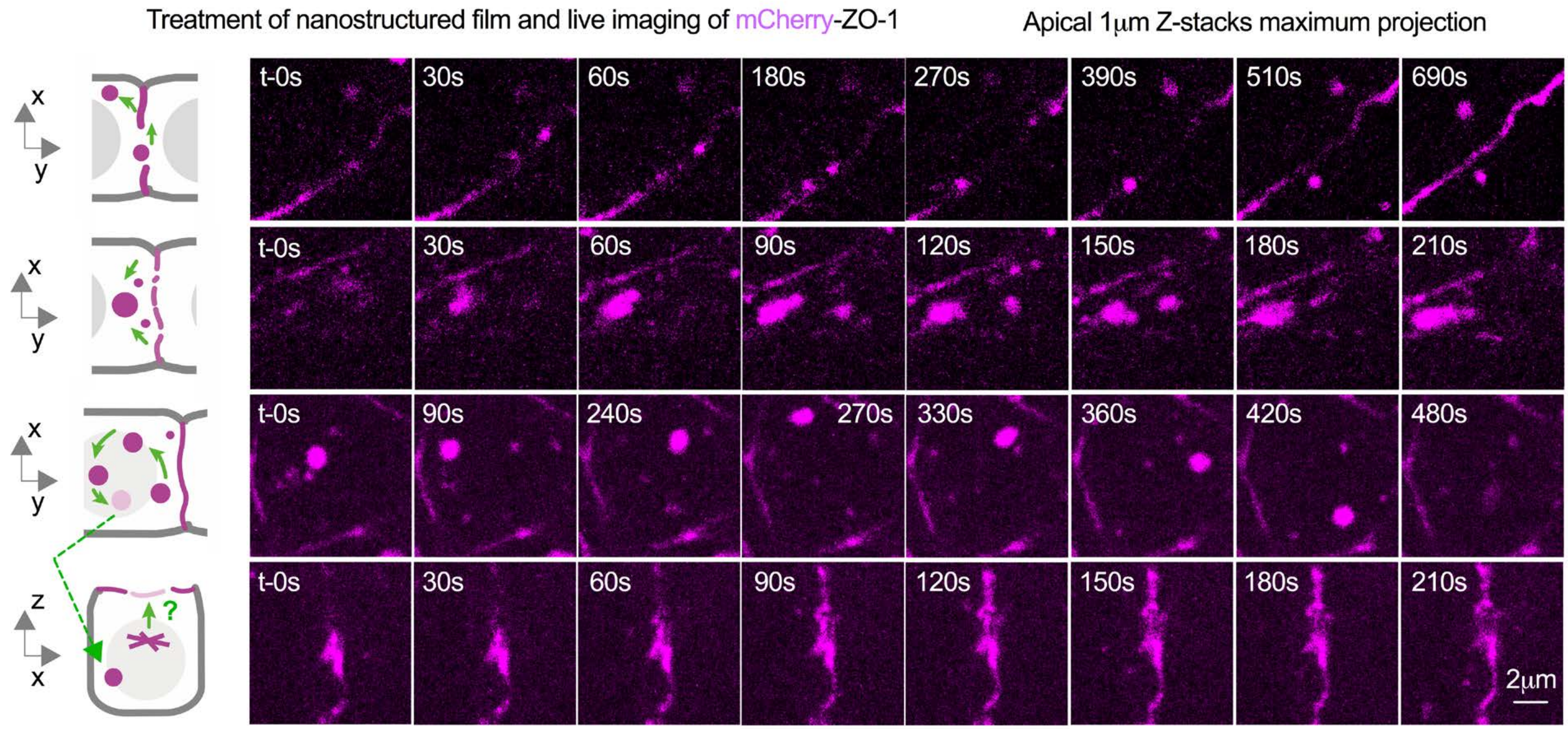


Time-Lapse Video of ZO-1 during Nanostructure Treatment
(MAX Z-projection, 2 locations 1s=5mins) TEER>>1800

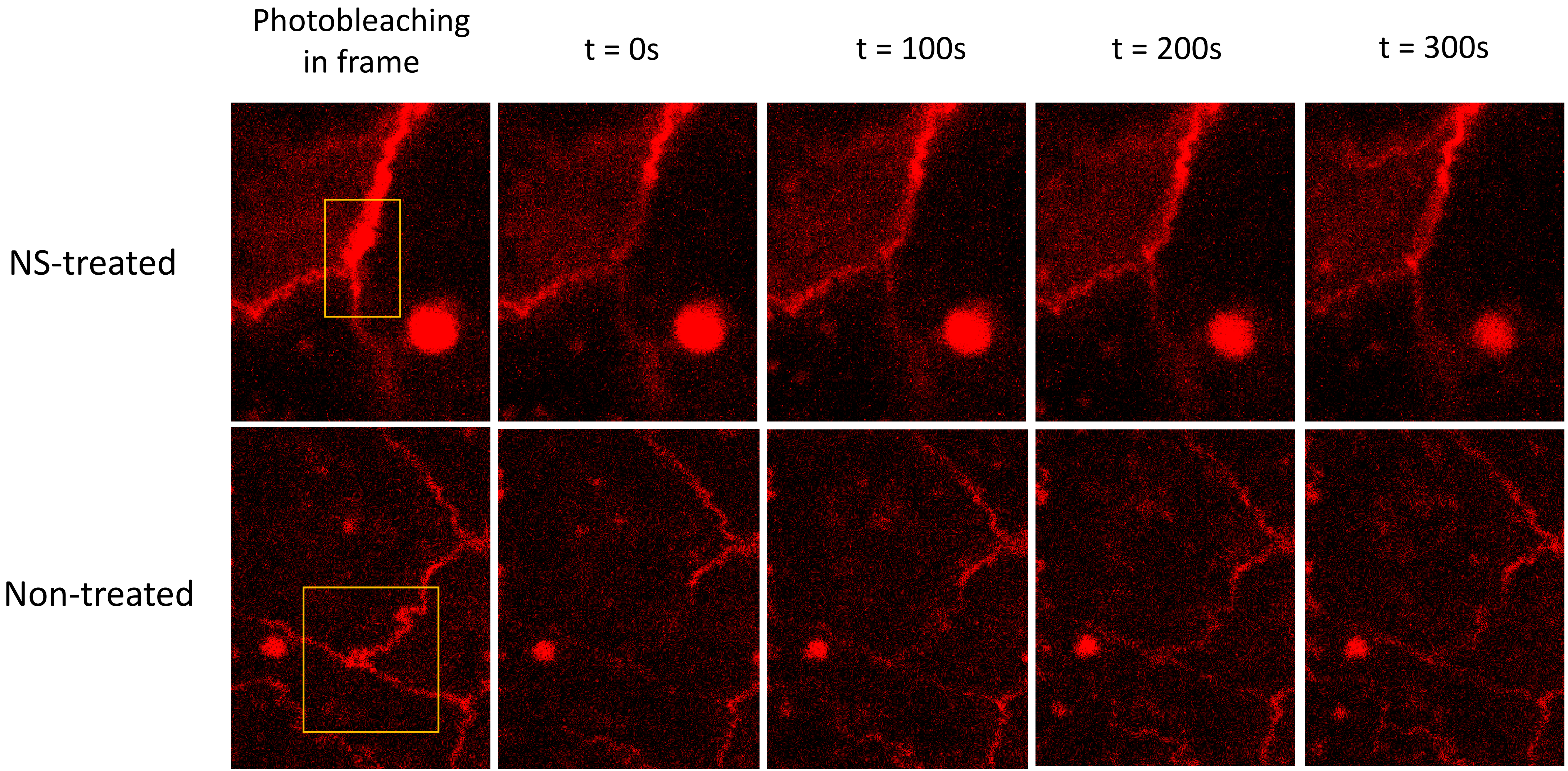
Large aggregates of ZO-1protein are formed on apical side when treated with NS film



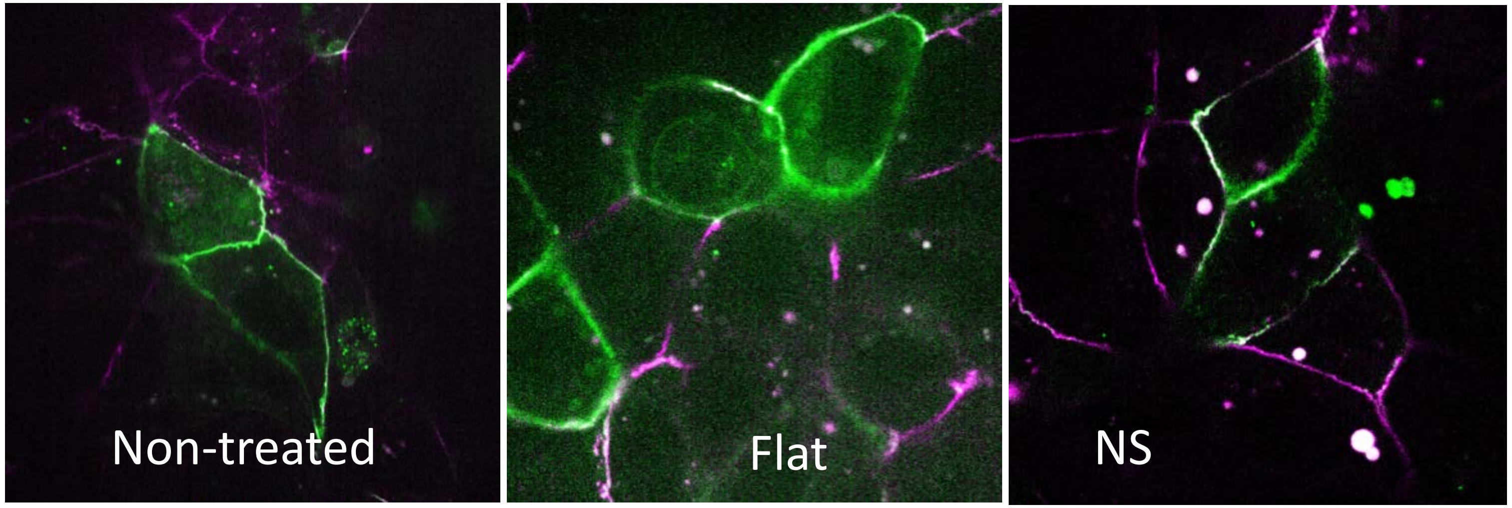
Active interaction between aggregates and border ZO-1



NS-film treated cells have faster recovery from FRAP



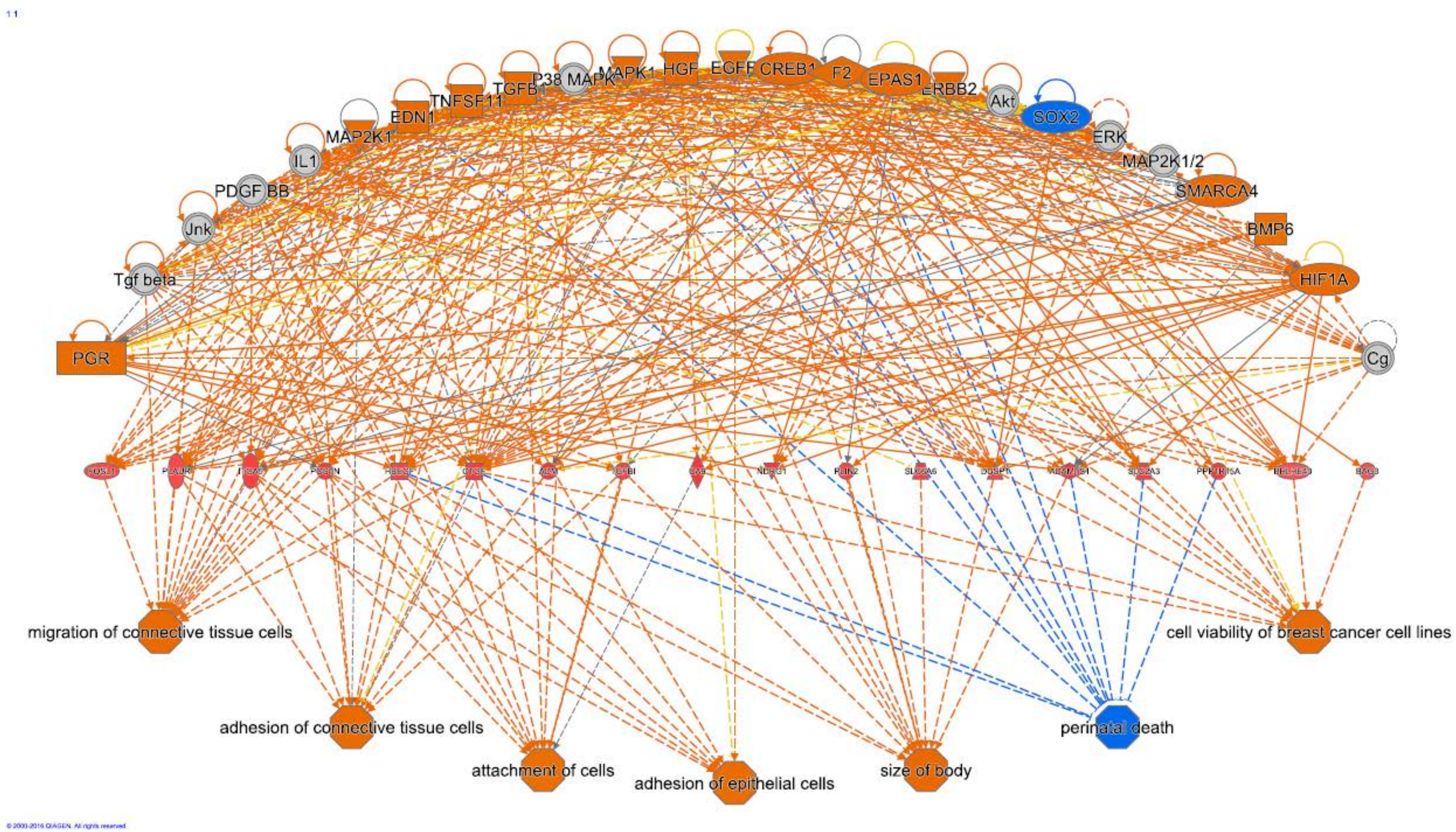
Junctional protein Claudin-4 colocalizes with ZO-1 aggregates



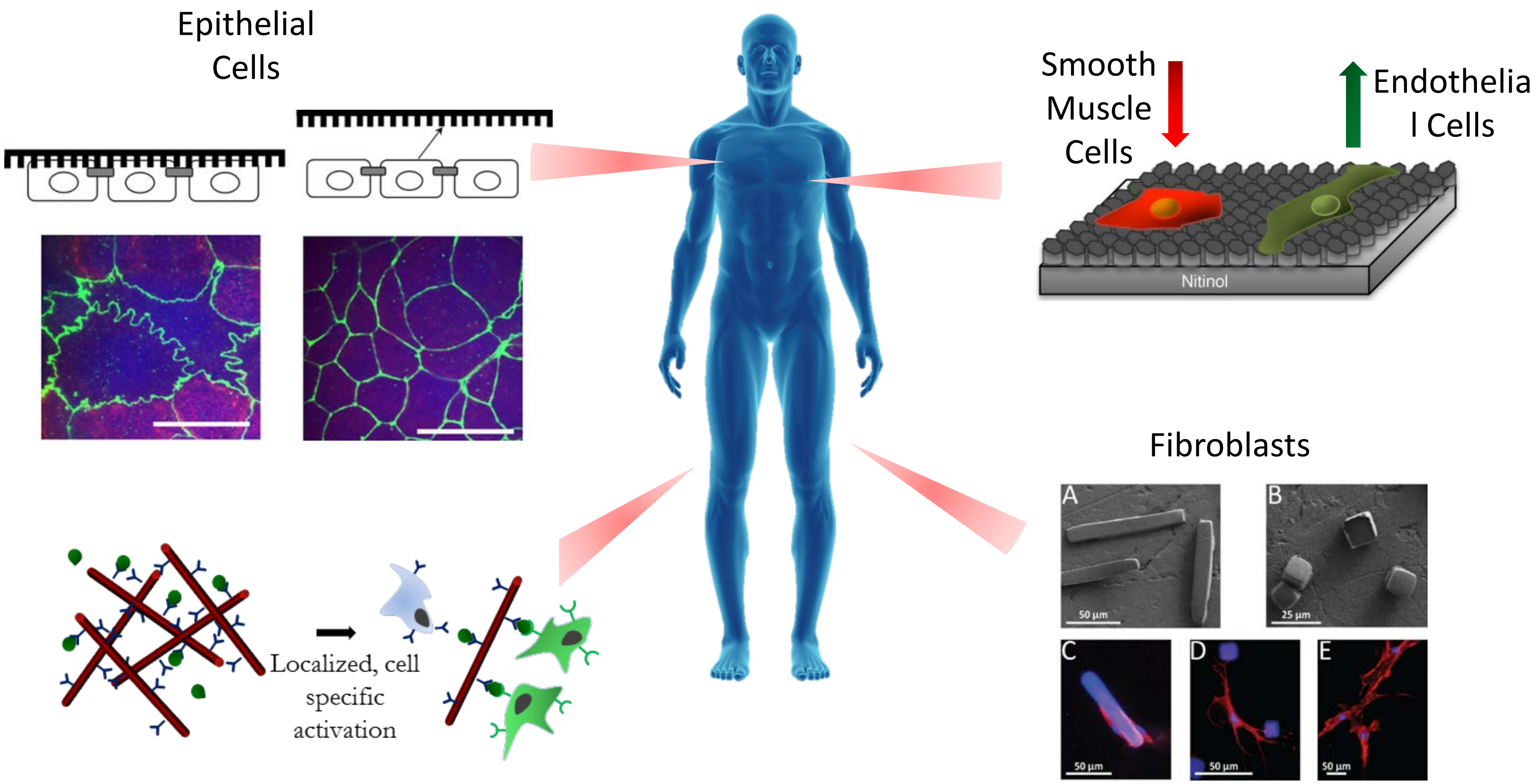
Video

endogenous mCherry-ZO-1 + AAV exogenous YFP-Cldn3,   Z projection of ~1um

Using physical cues to alter tight junction permeability: implications for delivery



Harnessing nanotopographical cues for therapy



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- Mike Koval, Emory
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- Bo Huang, UCSF

- NIH
- NSF
- Kimberly Clarke
- Zambone Ltd
- SPARC
- Eli Lilly