From nature to nanoparticles:
Advancing oral delivery through permeation enhancement

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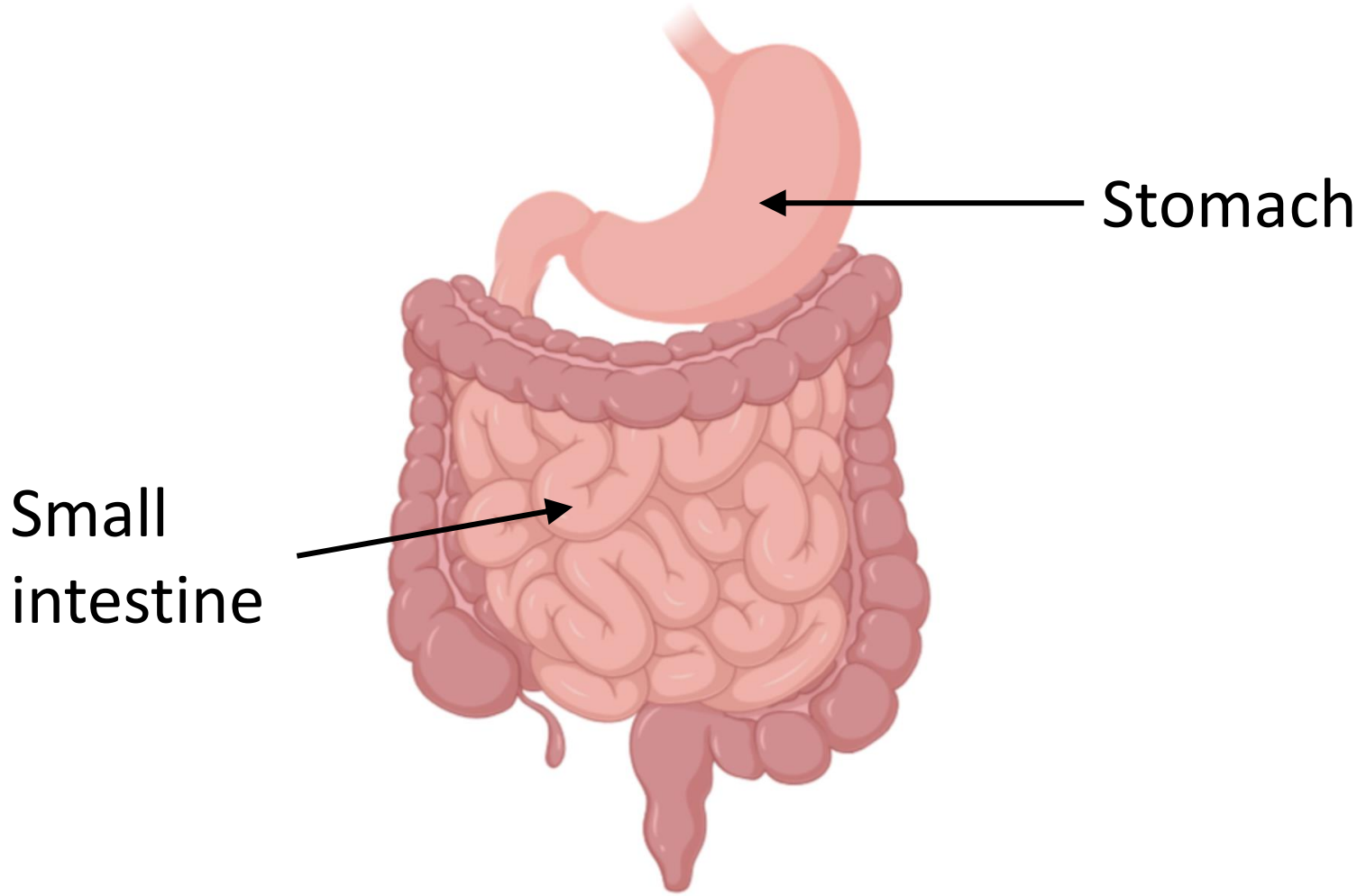
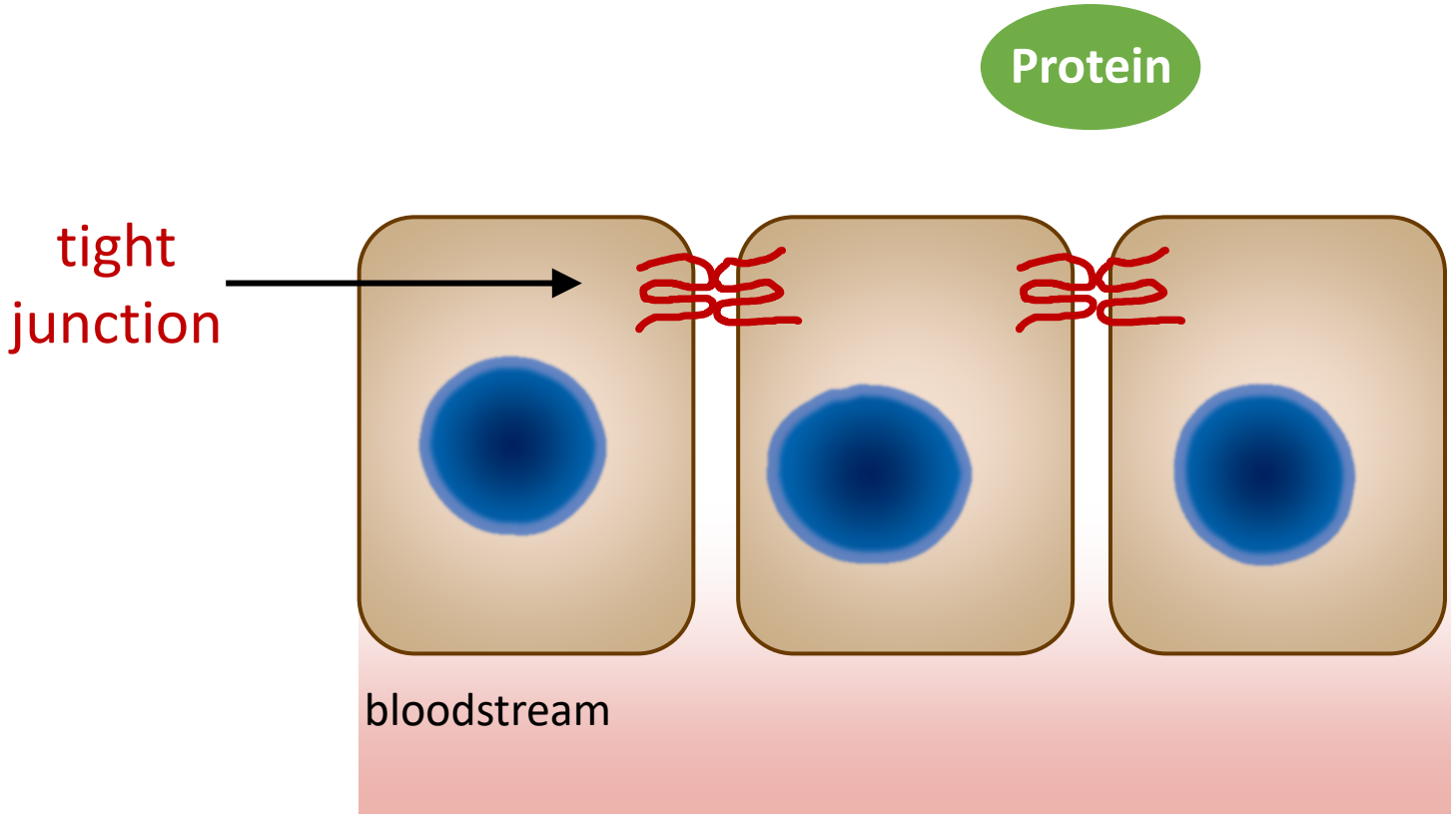
Carnegie Mellon University

Protein therapeutics are amazing, but the need for injection limits impact.

Oral delivery is patient-friendly, but not protein-friendly.



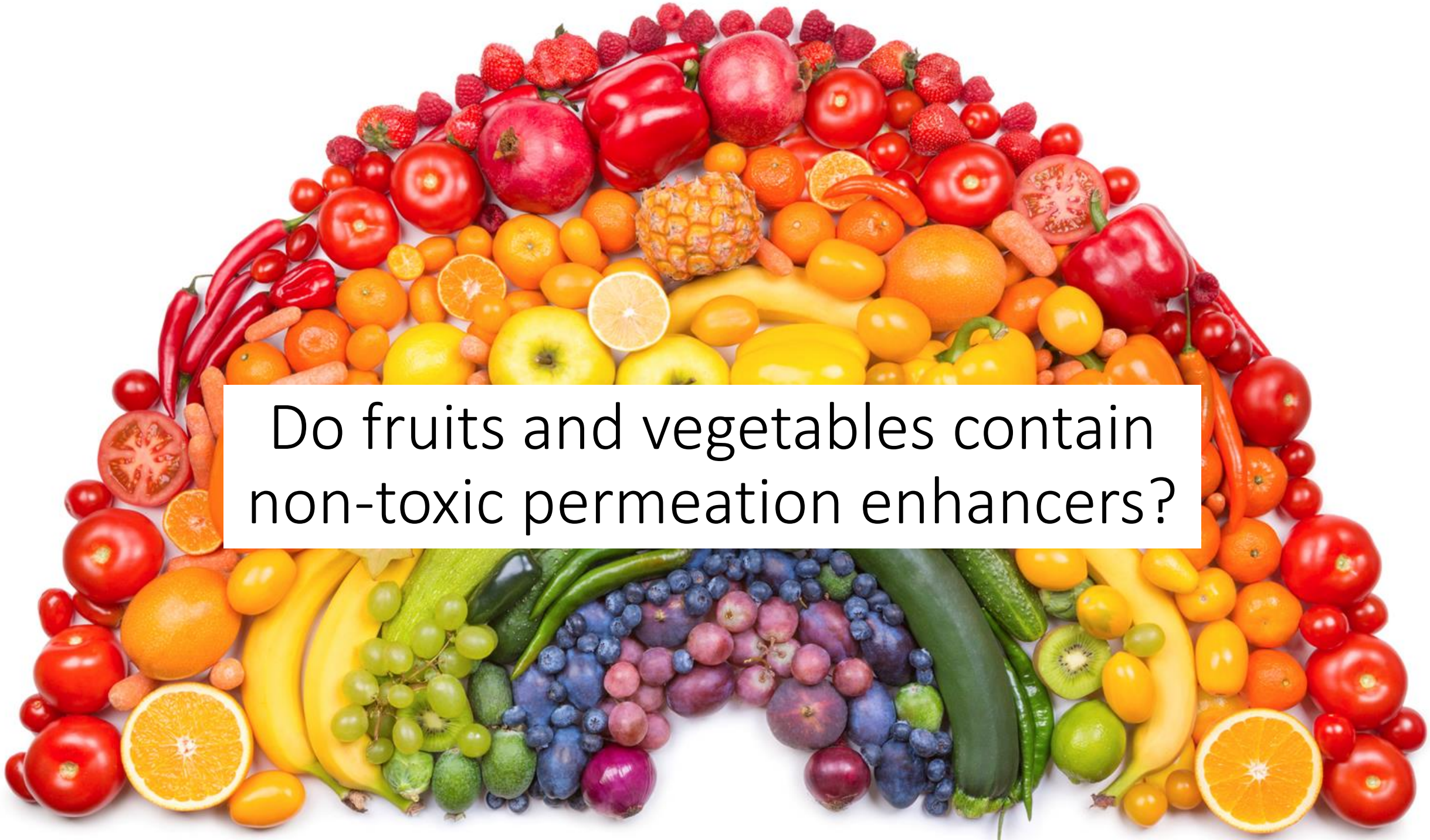
Tight junctions between cells are the major barrier preventing protein transport.



Can we identify a potent, non-toxic permeation enhancer?

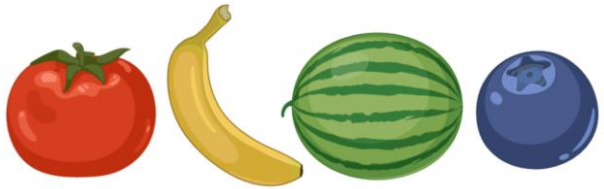
I love the garden.


Peron
Black Pineapple
Gold Medal
Dad's Sunset
Thornburn's Terra Cotta
Costoluto Genovese
Carbon
Golden King of Siberia
Aunt Ruby's German Green



Do fruits and vegetables contain non-toxic permeation enhancers?

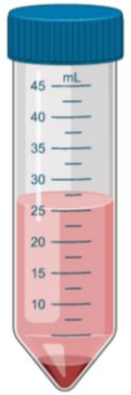
Fruits and vegetables were processed for cell culture.



blend

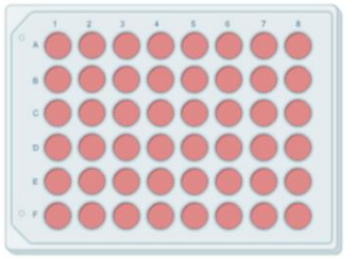
smoothie

centrifuge

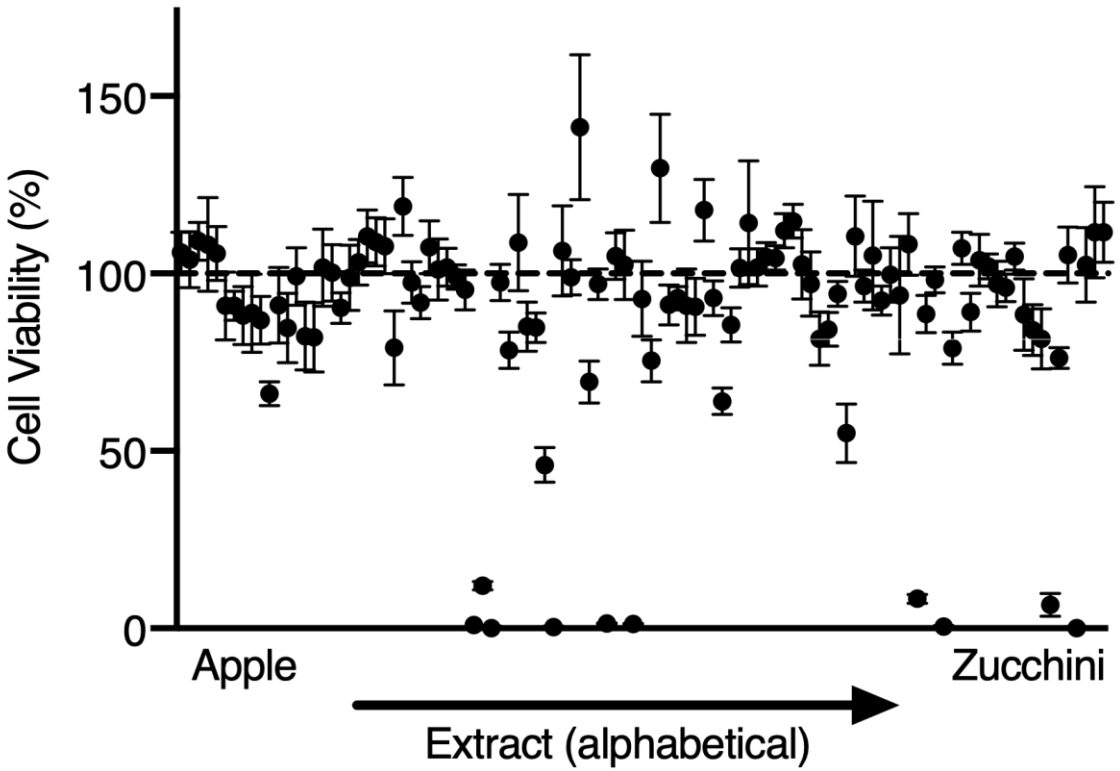


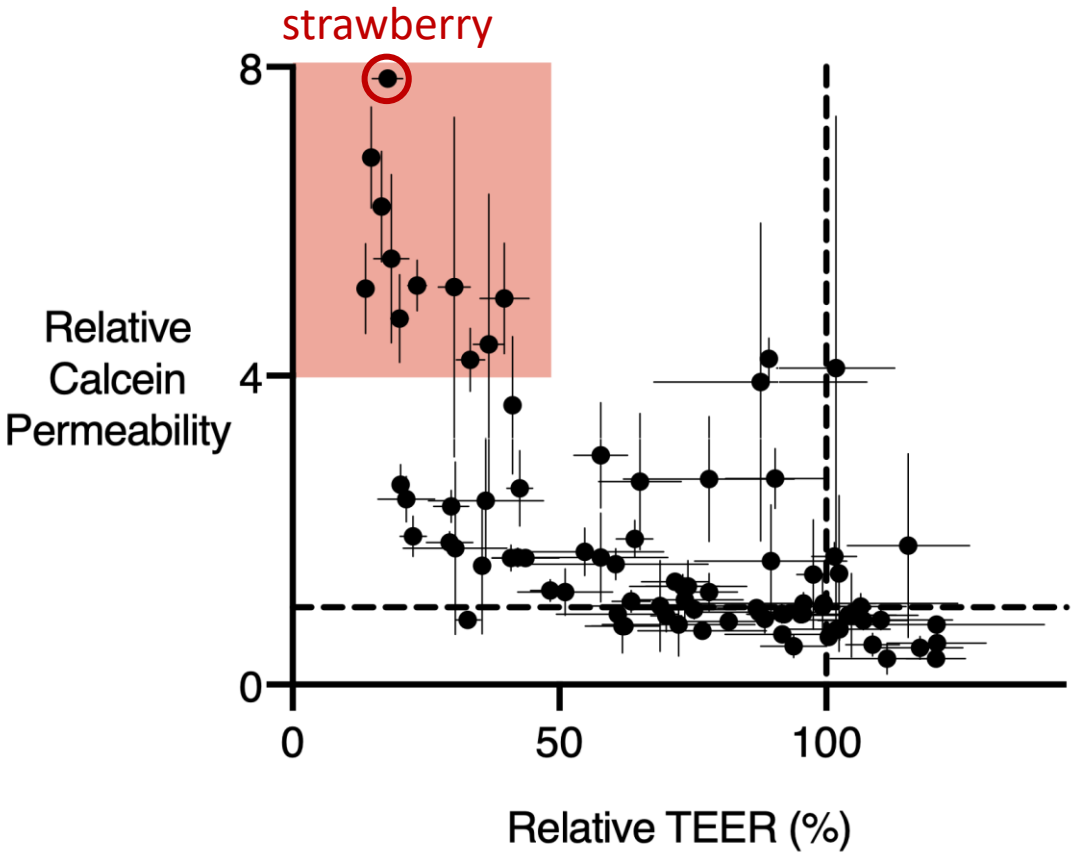
H_2O-soluble fraction

intestinal cells



Most fruits & vegetables were non-toxic, and some enhanced intestinal permeability.

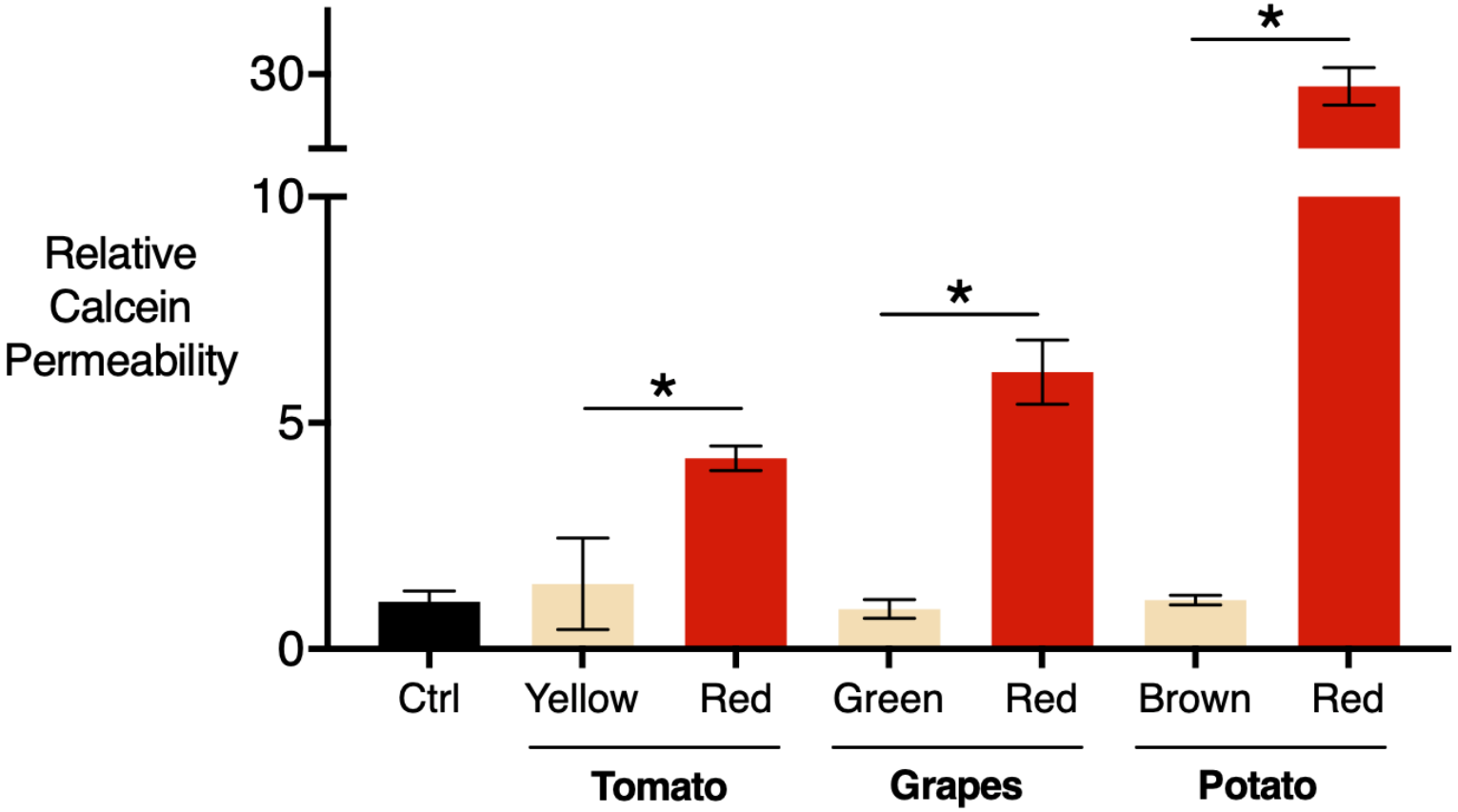




Lamson et al., *PNAS* 2022

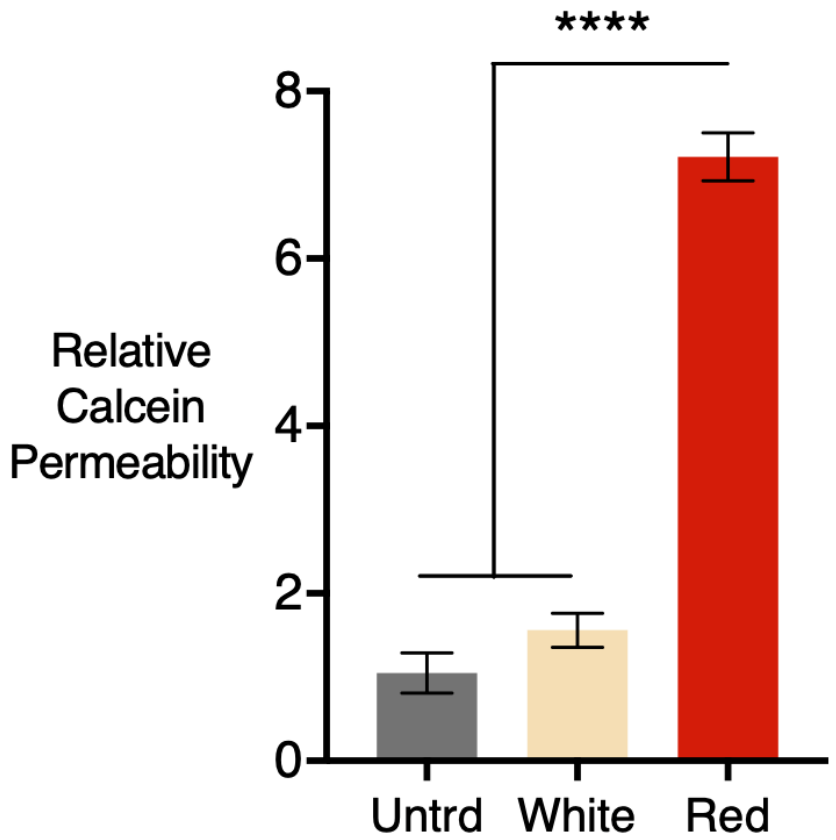
What compound in strawberry is responsible for permeation enhancement?

Red fruits and vegetables preferentially enhanced permeability.



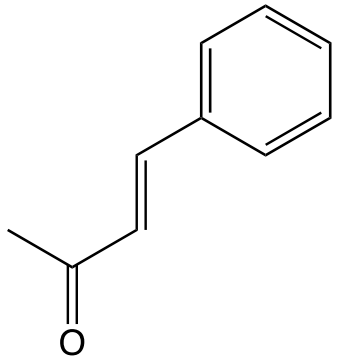
Lamson et al., *PNAS* 2022

Red, but not white, strawberries improved intestinal permeability.

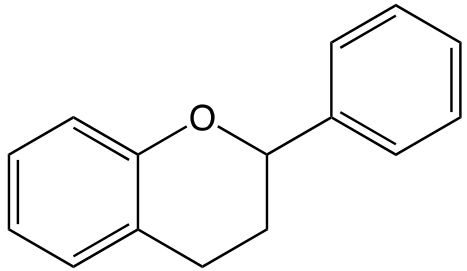


Lamson et al., *PNAS* 2022

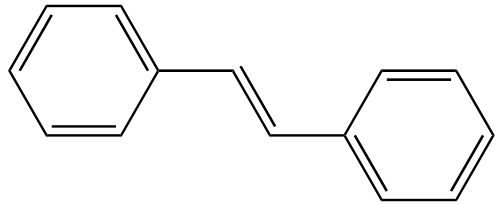
Red color in fruits and vegetables comes from polyphenols.



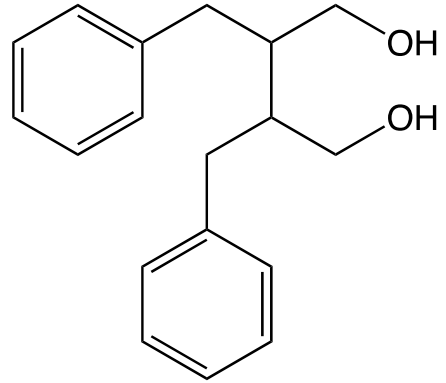
phenolic acids



flavonoids

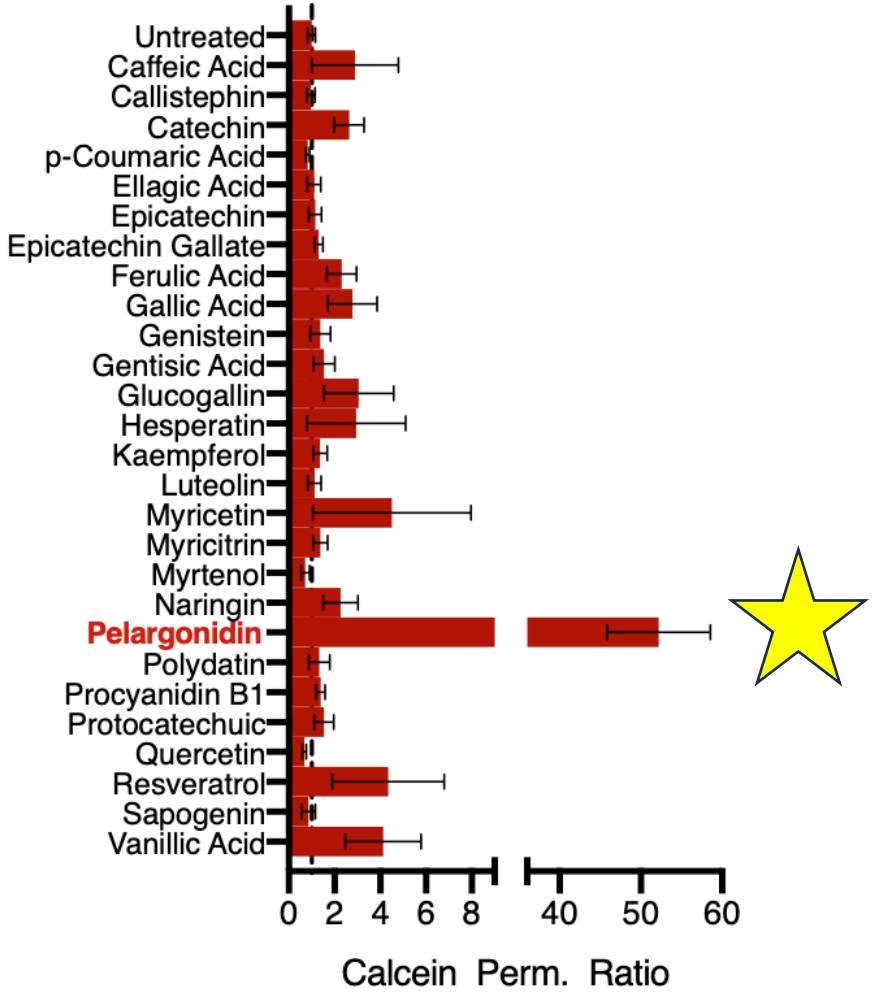


stilbenes



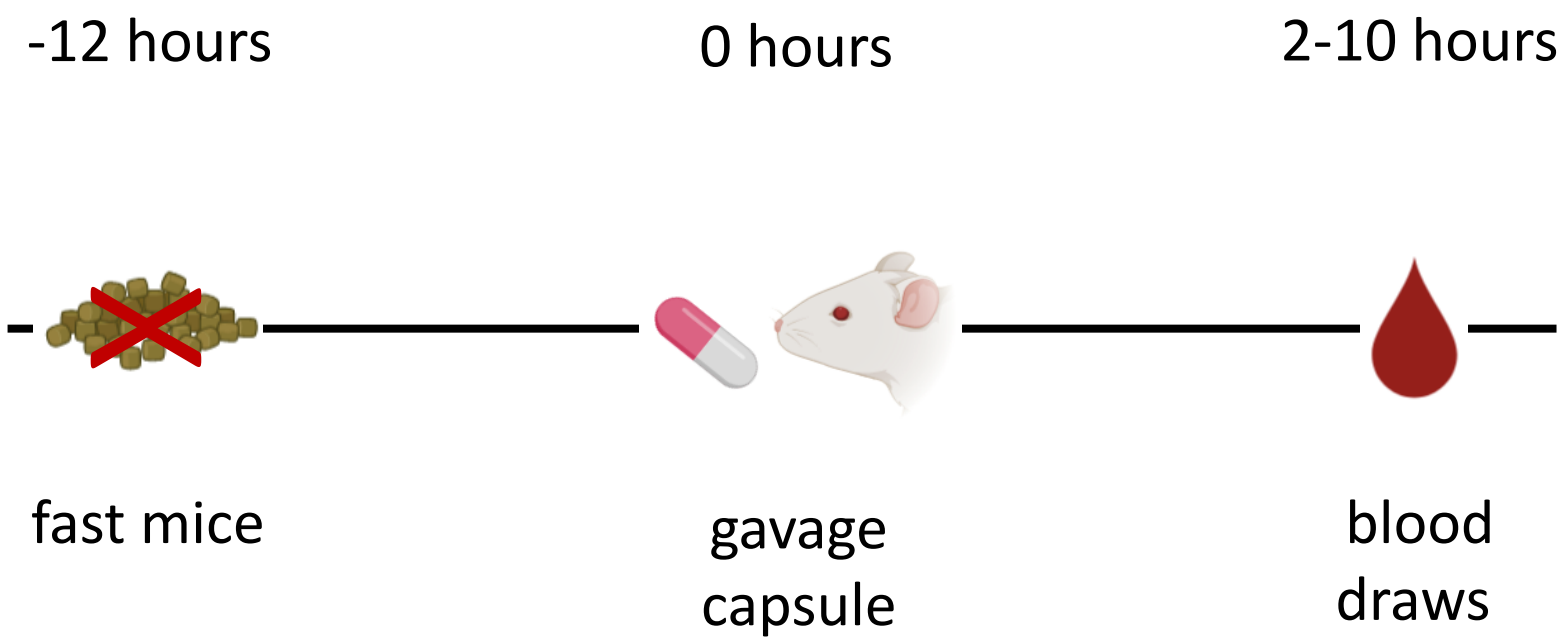
lignans

The active component in strawberry is the anthocyanidin molecule, pelargonidin.

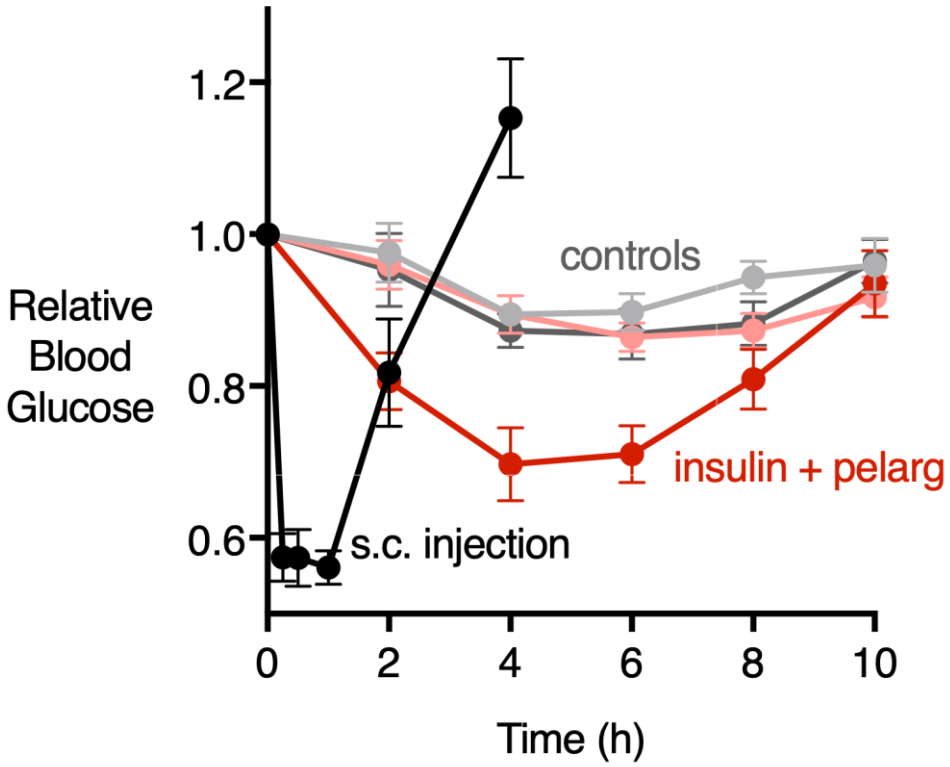


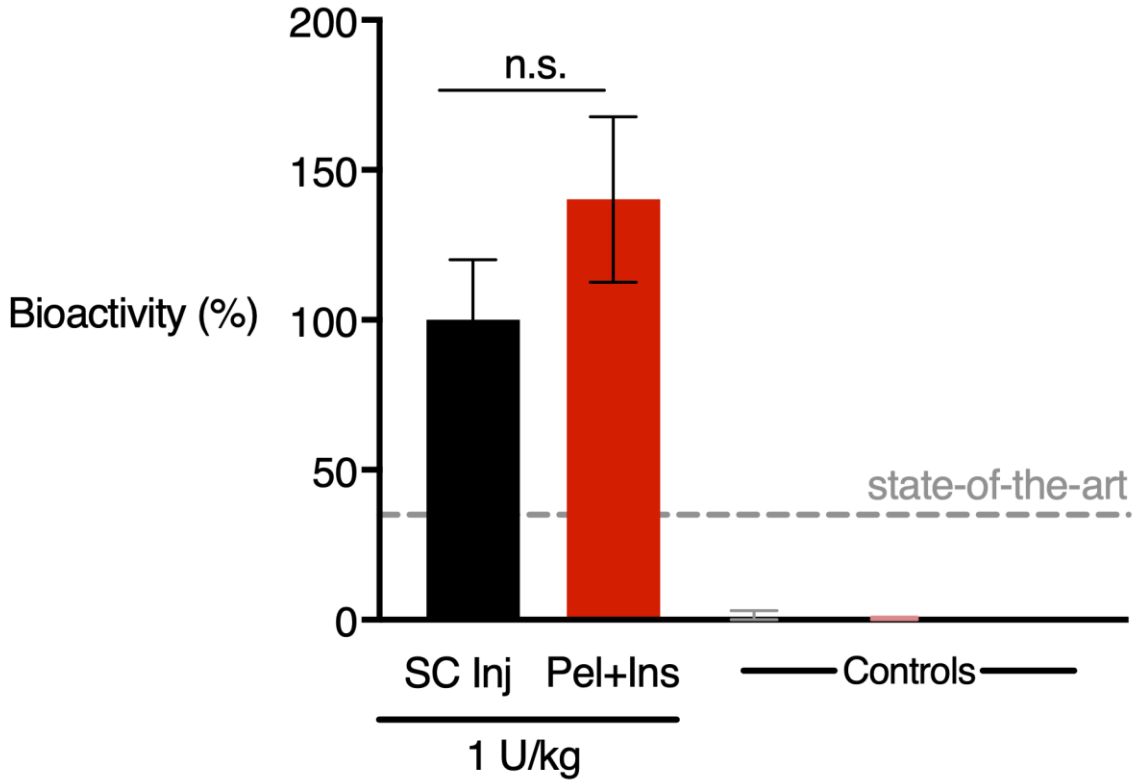
Does pelargonidin enhance protein delivery in vivo?

We delivered capsules containing pelargonidin and insulin to mice.



Oral pelargonidin-insulin outperforms subcutaneous injection.



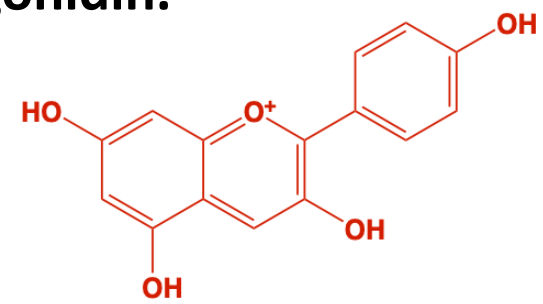


Lamson et al., *PNAS* 2022

Fruity summary

1. Fruits contain permeation enhancers.

2. The active component of strawberry is pelargonidin.

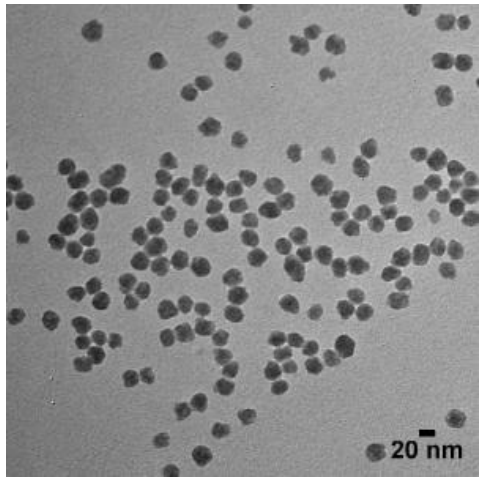


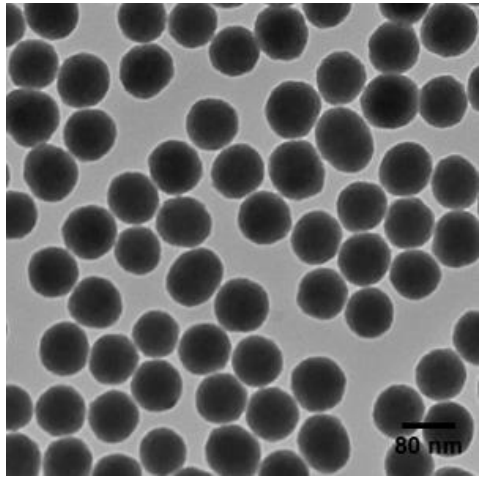
3. Pelargonidin enables especially potent oral insulin delivery.

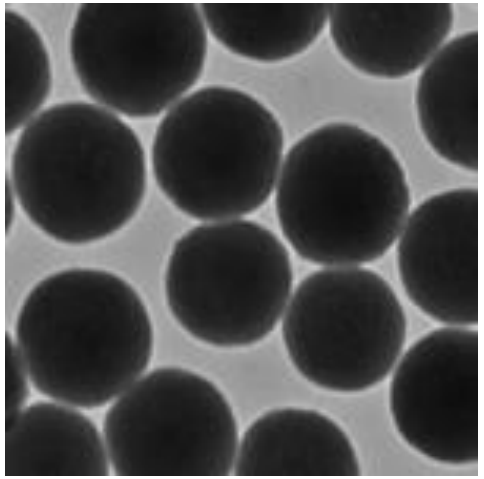
4. Effects are transient & non-toxic.

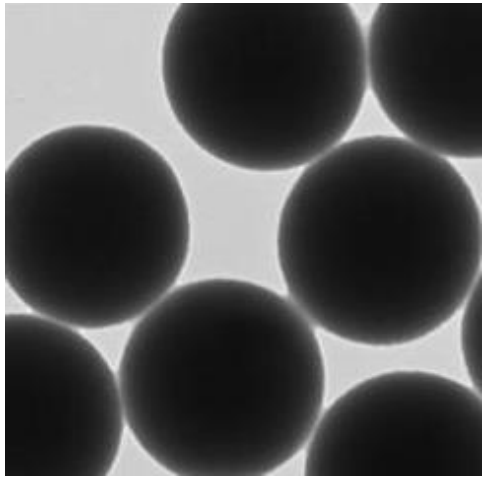
Stray observation:
Smoothie colloidal size might be important.

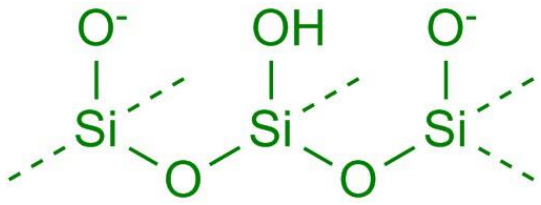
We examined silica nanoparticles.





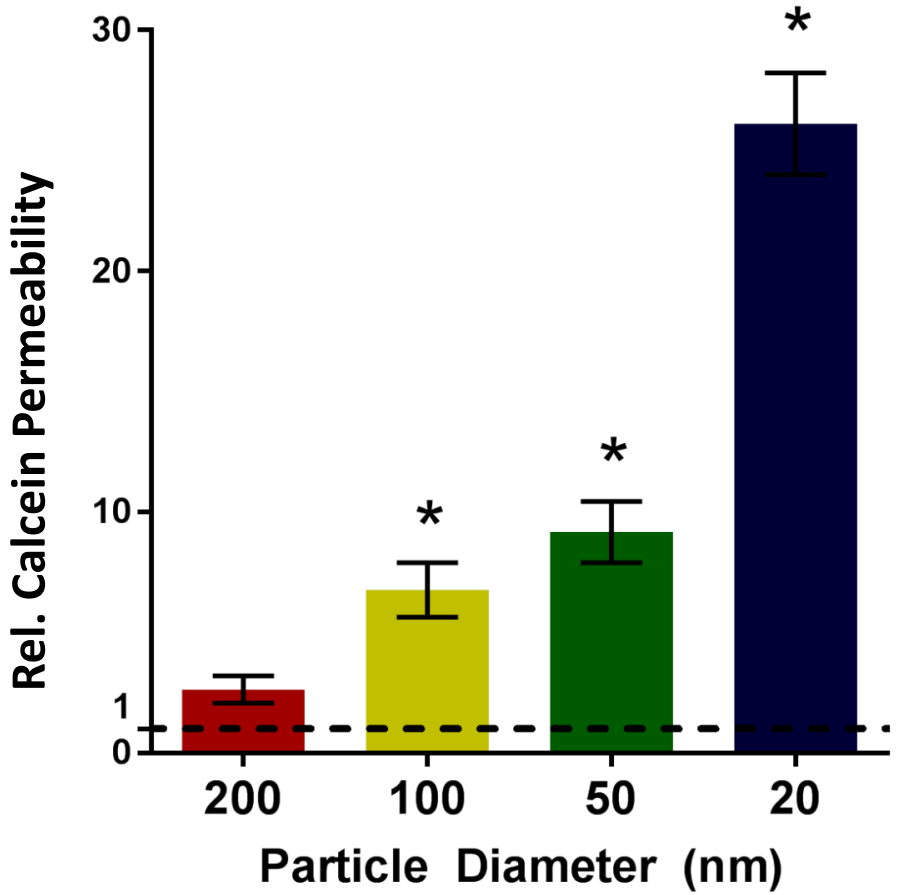






Sizes: 20 nm – 1.2 μm
Zeta: -40 mV

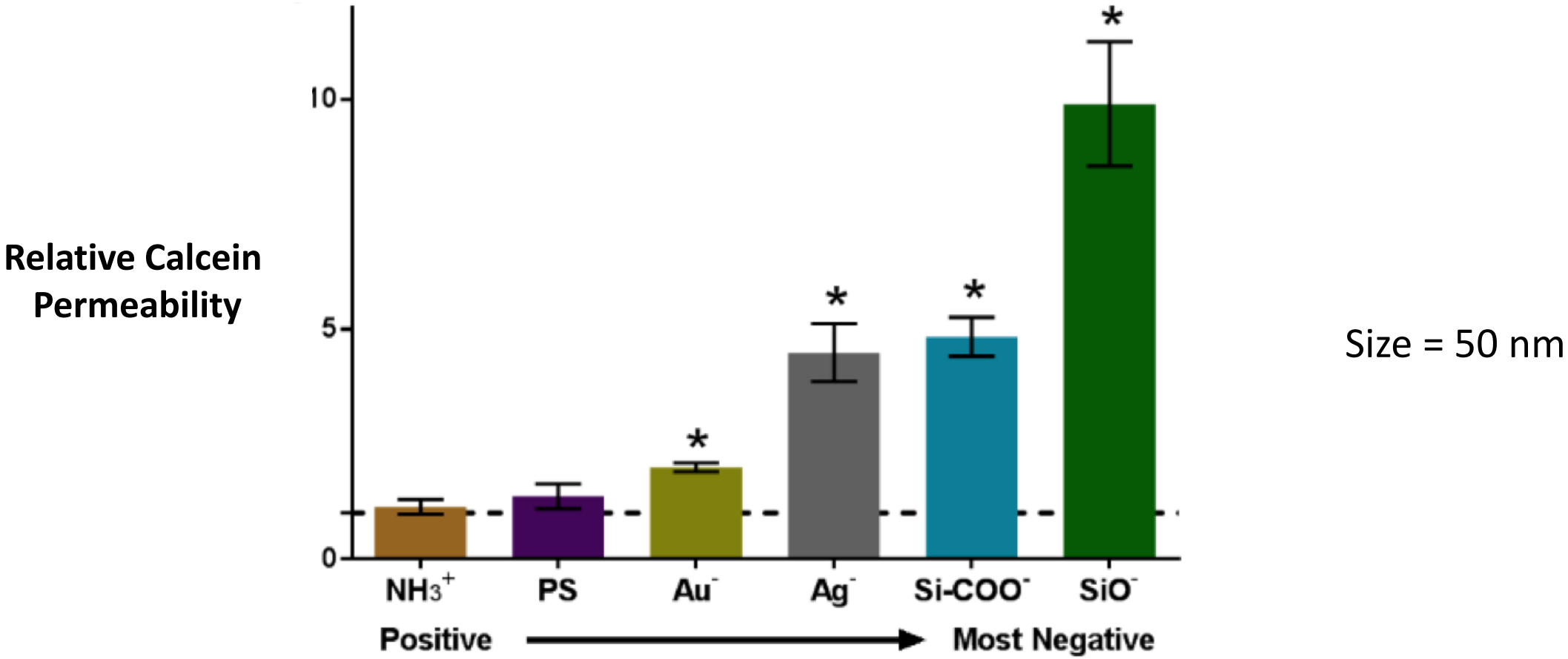
Small silica nanoparticles increased permeability of intestinal cell monolayers.



Lamson et al., *Nature BME* 2019

Does nanoparticle chemistry also matter?

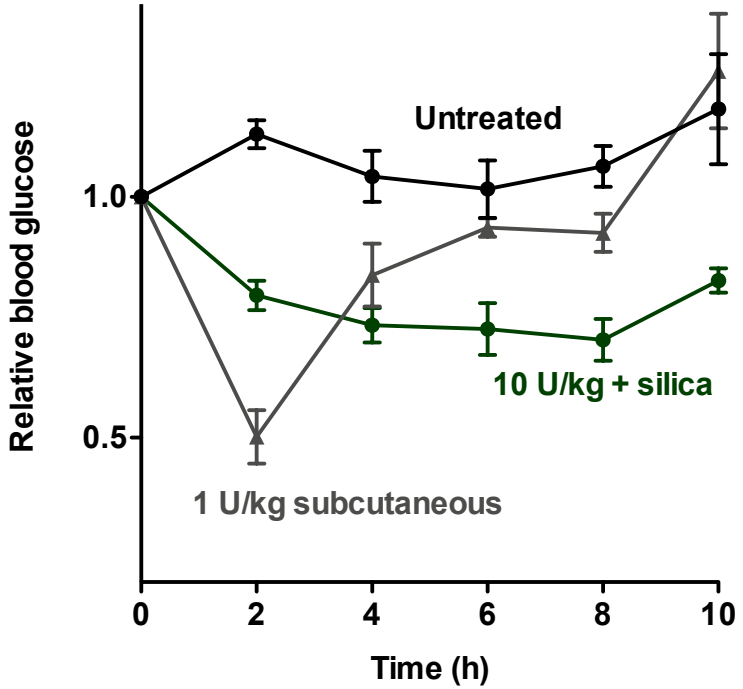
Only anionic particles enhance permeability.

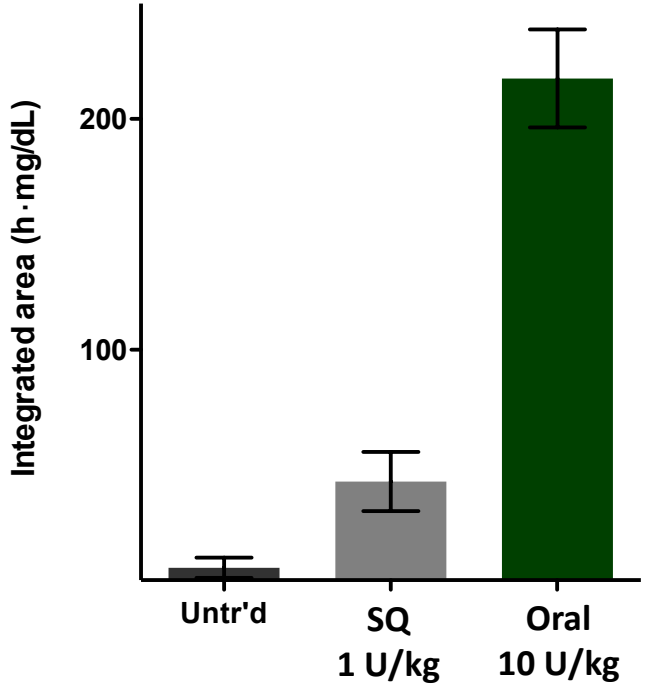


Lamson et al., *Nature BME* 2019

Can silica nanoparticles enable oral delivery of a therapeutic drug?

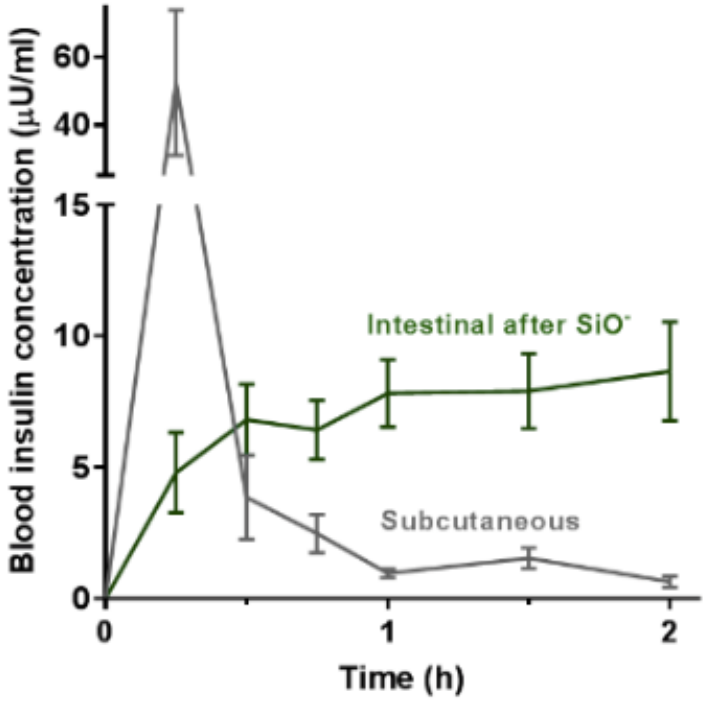
Silica nanoparticles facilitated oral insulin delivery with ~35% bioactivity.

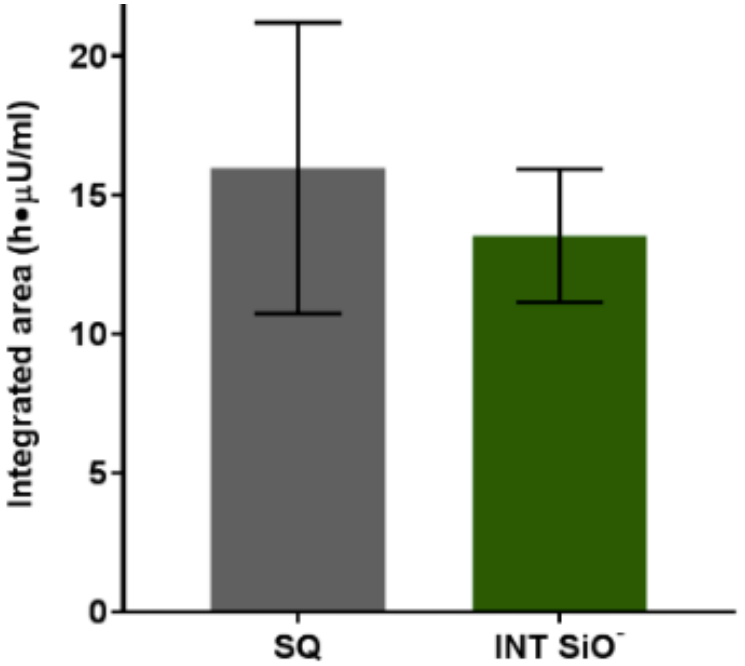




Lamson et al., *Nature BME* 2019

Silica nanoparticles sustainably increased insulin blood concentrations.

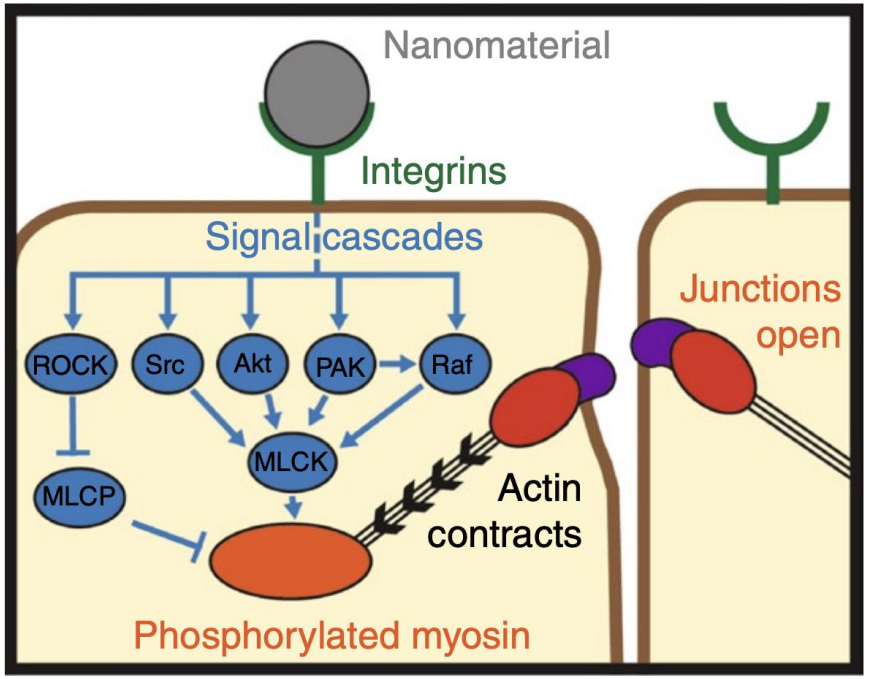


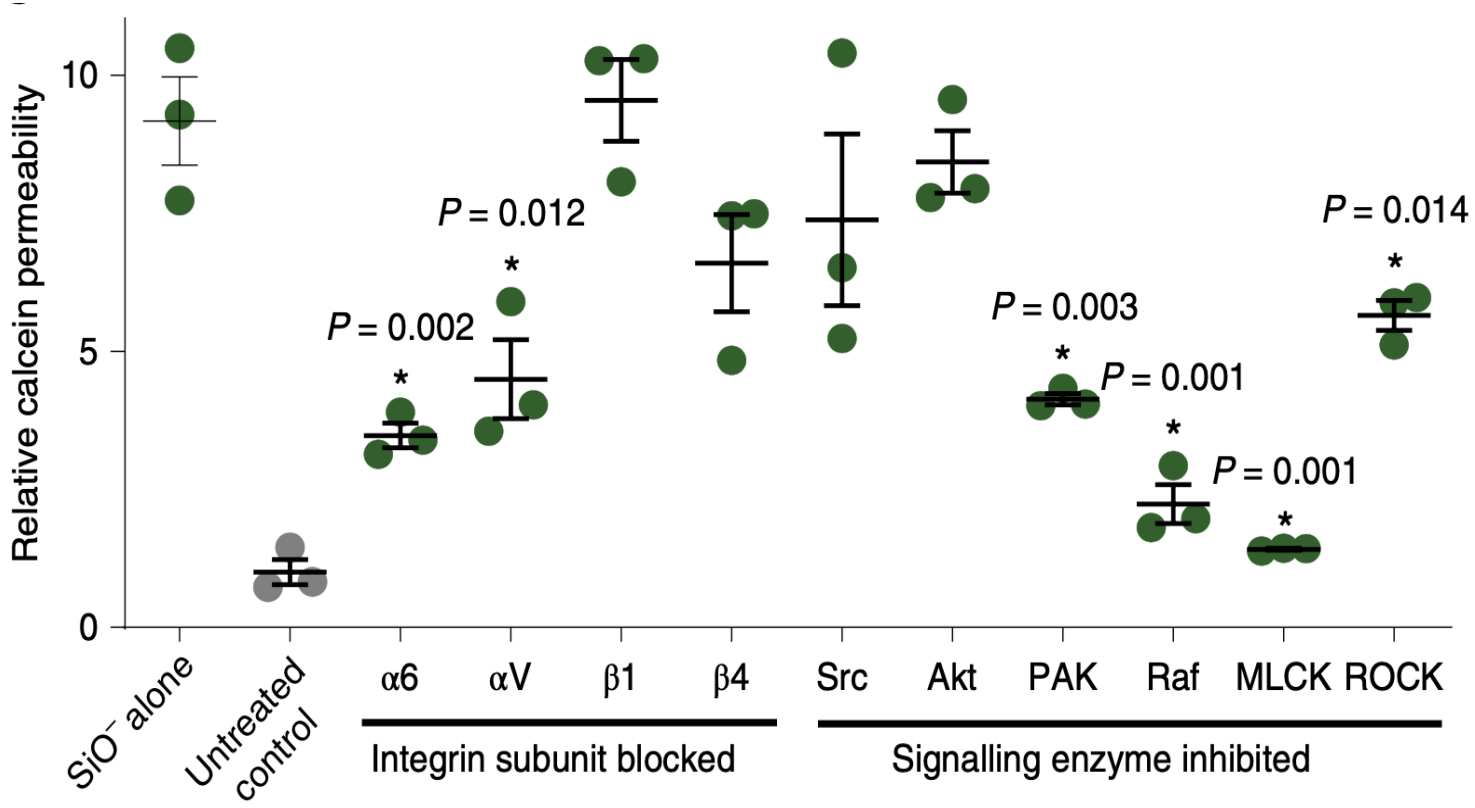


Lamson et al., *Nature BME* 2019

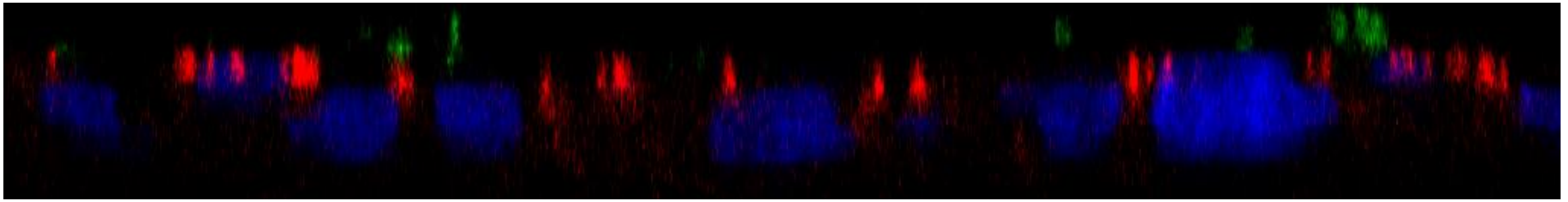
How do the particles work?

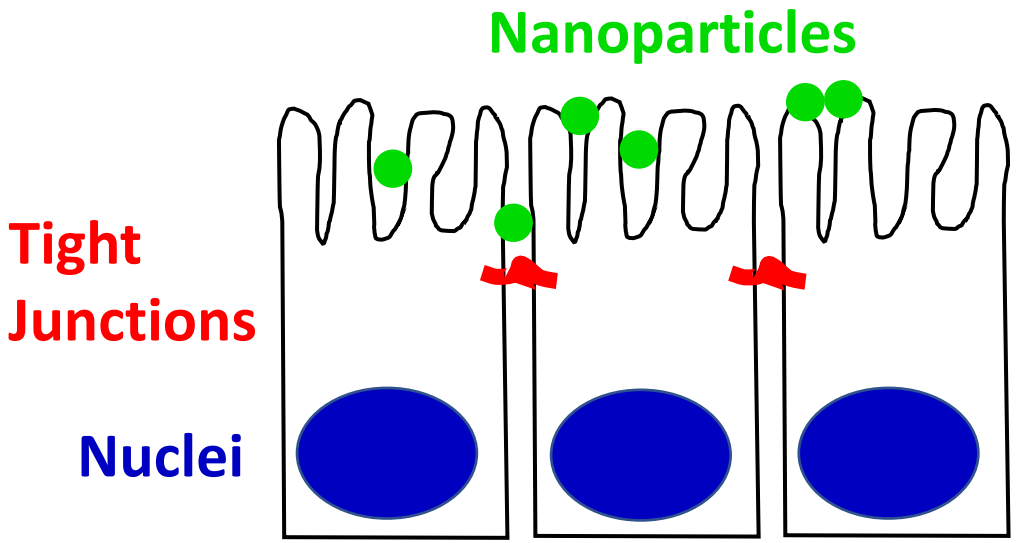
Particles act through the integrin pathway.





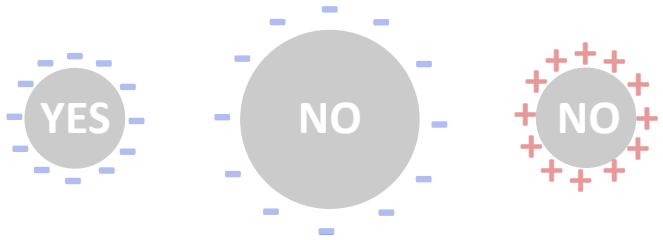
Silica nanoparticles did not cross intestinal monolayers.



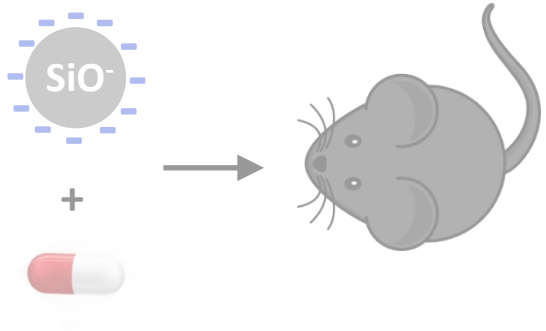


Particle summary

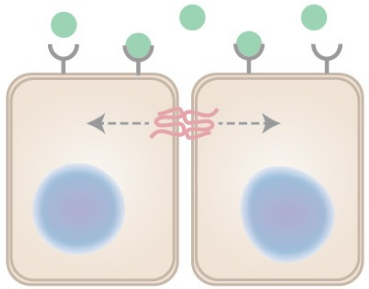
1. Small & negative nanoparticles enable oral protein delivery.



2. Silica facilitates oral insulin delivery with high bioactivity.



3. Silica binds integrin receptors to open tight junctions.



4. Effects are transient & do not damage the intestine.

Science =  + 

(what you love) (what you wonder)

Good science comes from good people.

Mariah Arral
Rebecca Ball
Warren Callen
Namit Chaudhary
Dhruv Chotaliya
Kyle Cochran
Rose Doerfler
Katherine Fein
John Gleeson
Khalid Hajj
Lisa Kasiewicz
Julie Kim
Chris Knapp
Nick Lamson
Sam LoPresti
Jilian Melamed
Naseeha Mohammed
Catalina Montoya
Alexandra Newby
Saurav Padhye
Daria Strelkova
Ryan Weiss
Samantha Yang
Sai Yerneni

Collaborator: Gloria Silva

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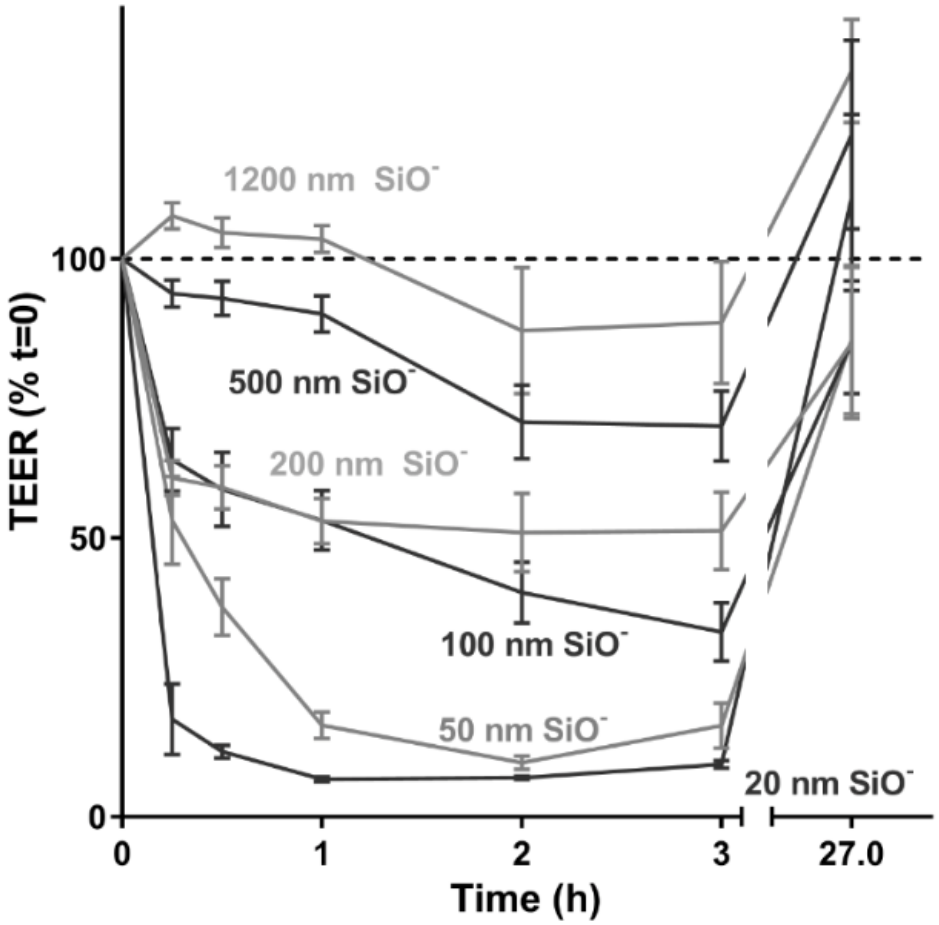
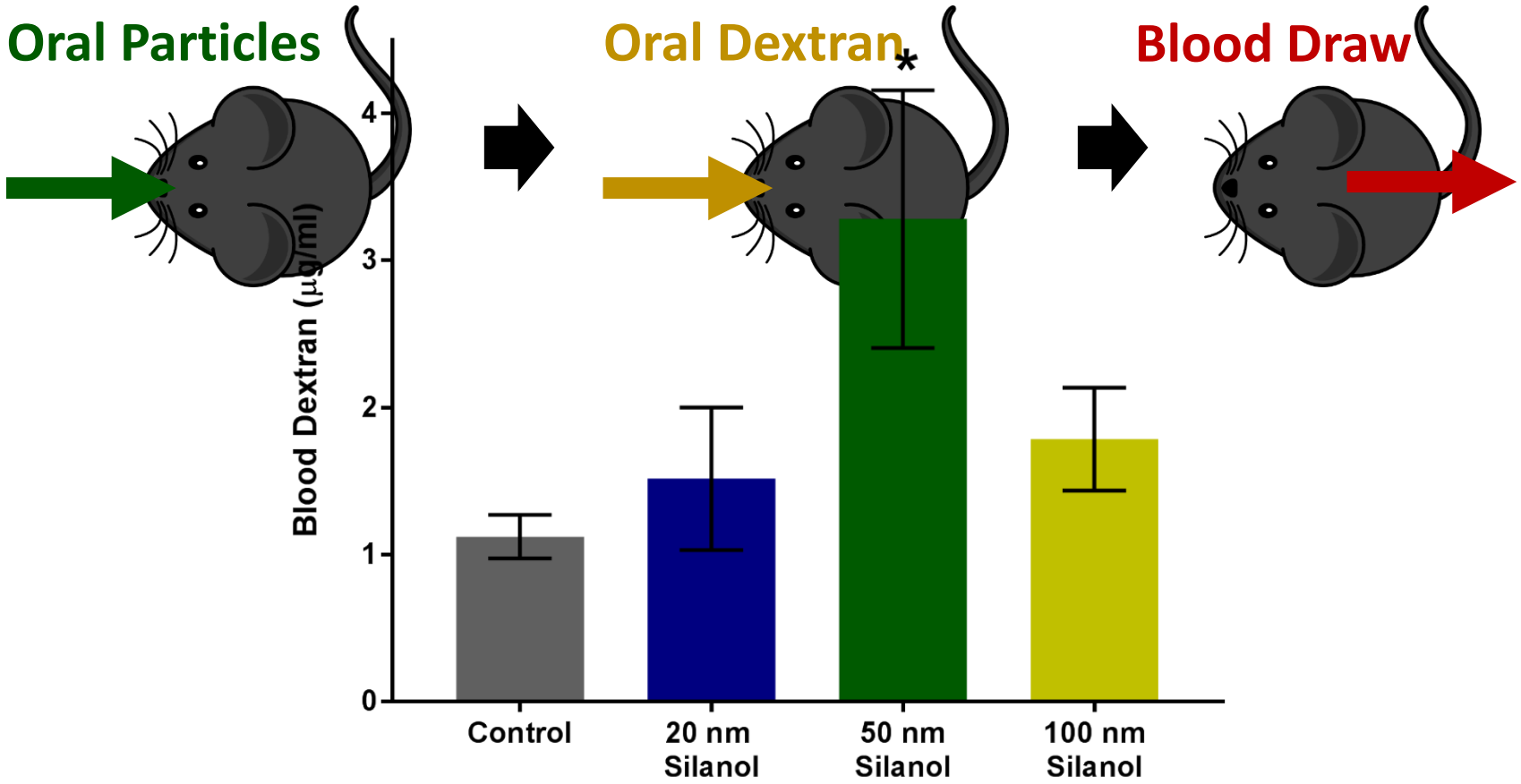
Smaller silica nanoparticles caused greater reductions in TEER on Caco-2 monolayers.

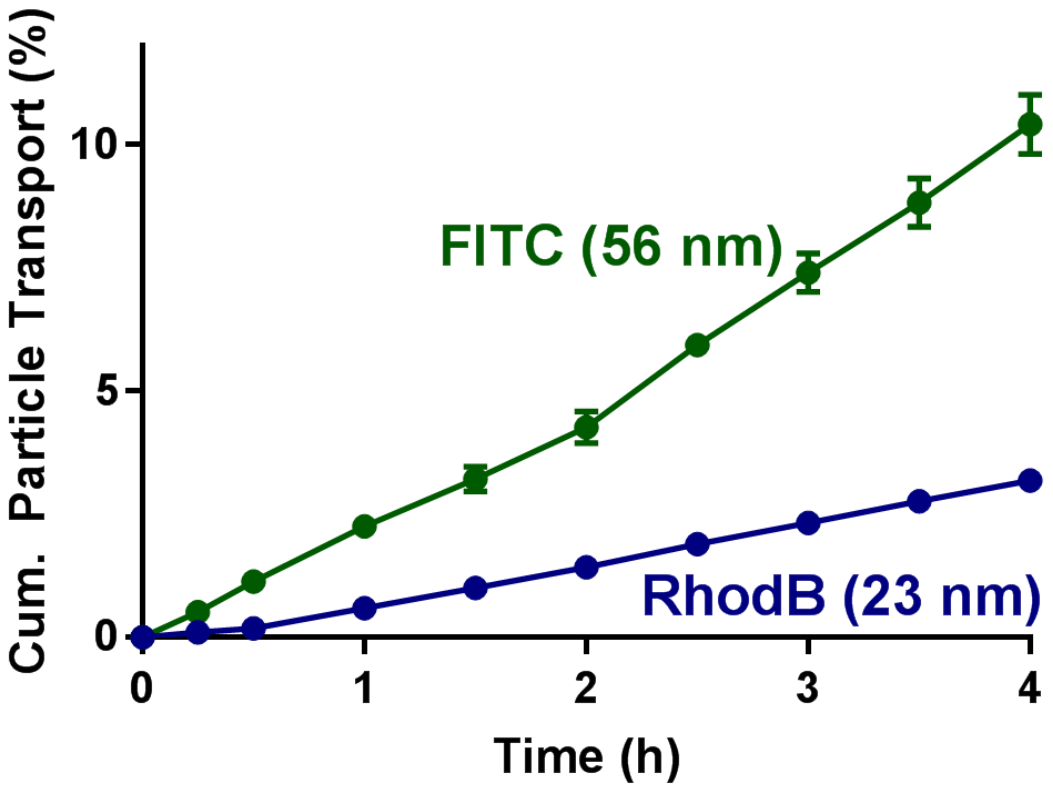


Small silica nanoparticles increased permeability in mice.



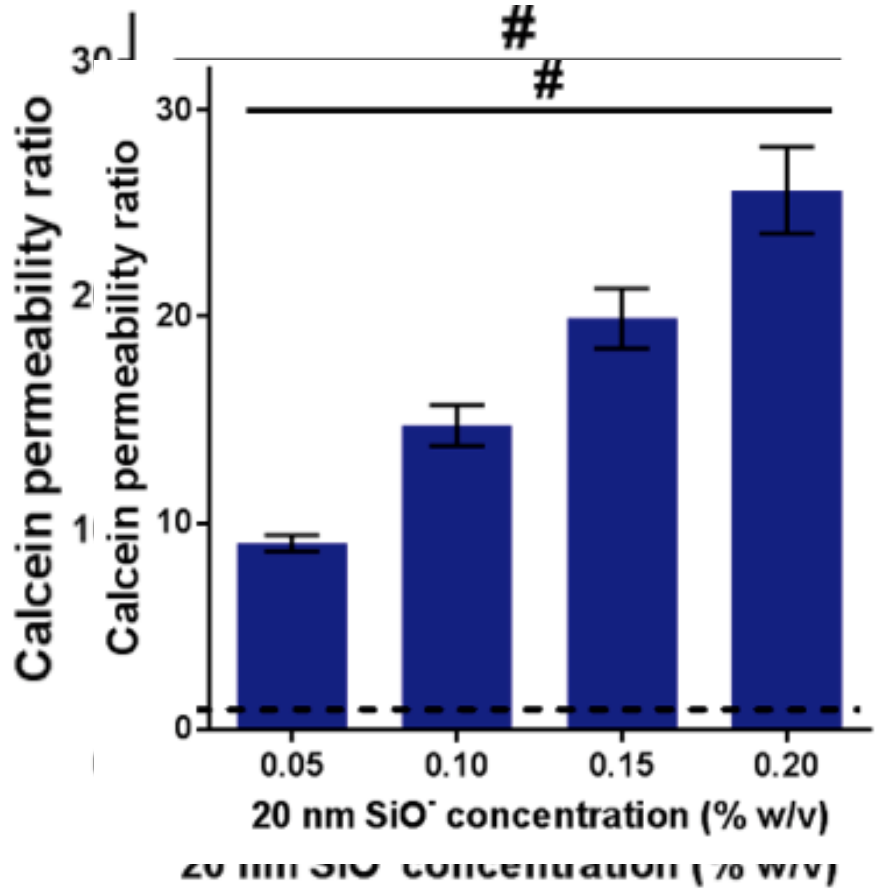
Lamson, Berger, & Whitehead, *Submitted*.

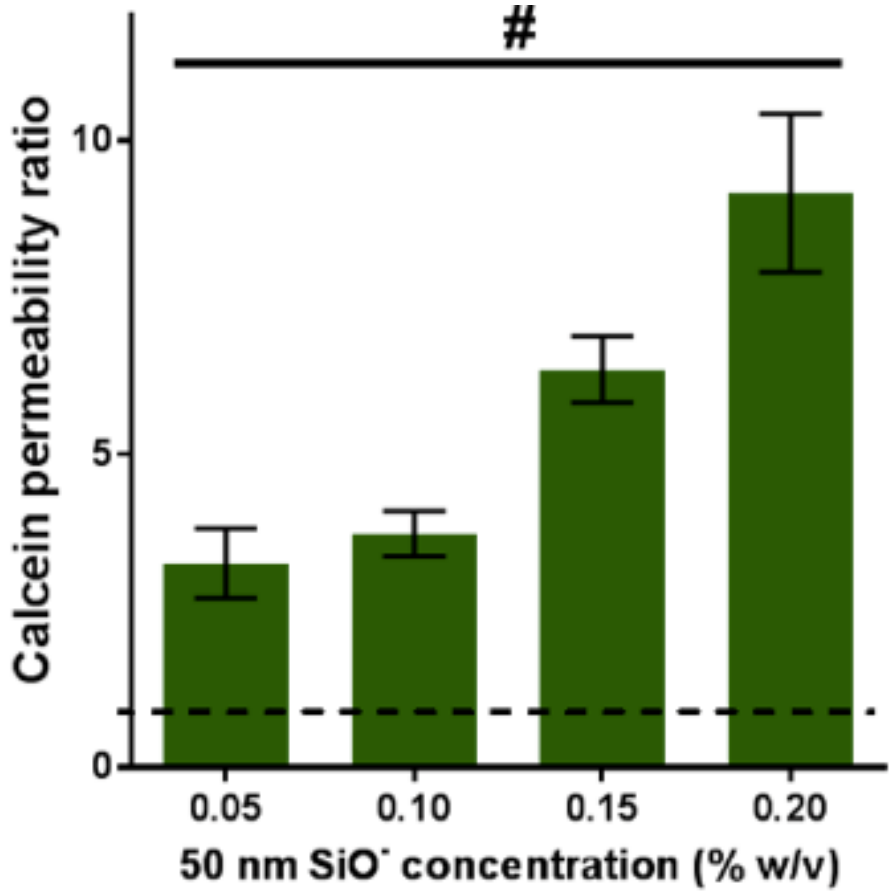
Diffusion of 20 nm particles is hindered by mucus.



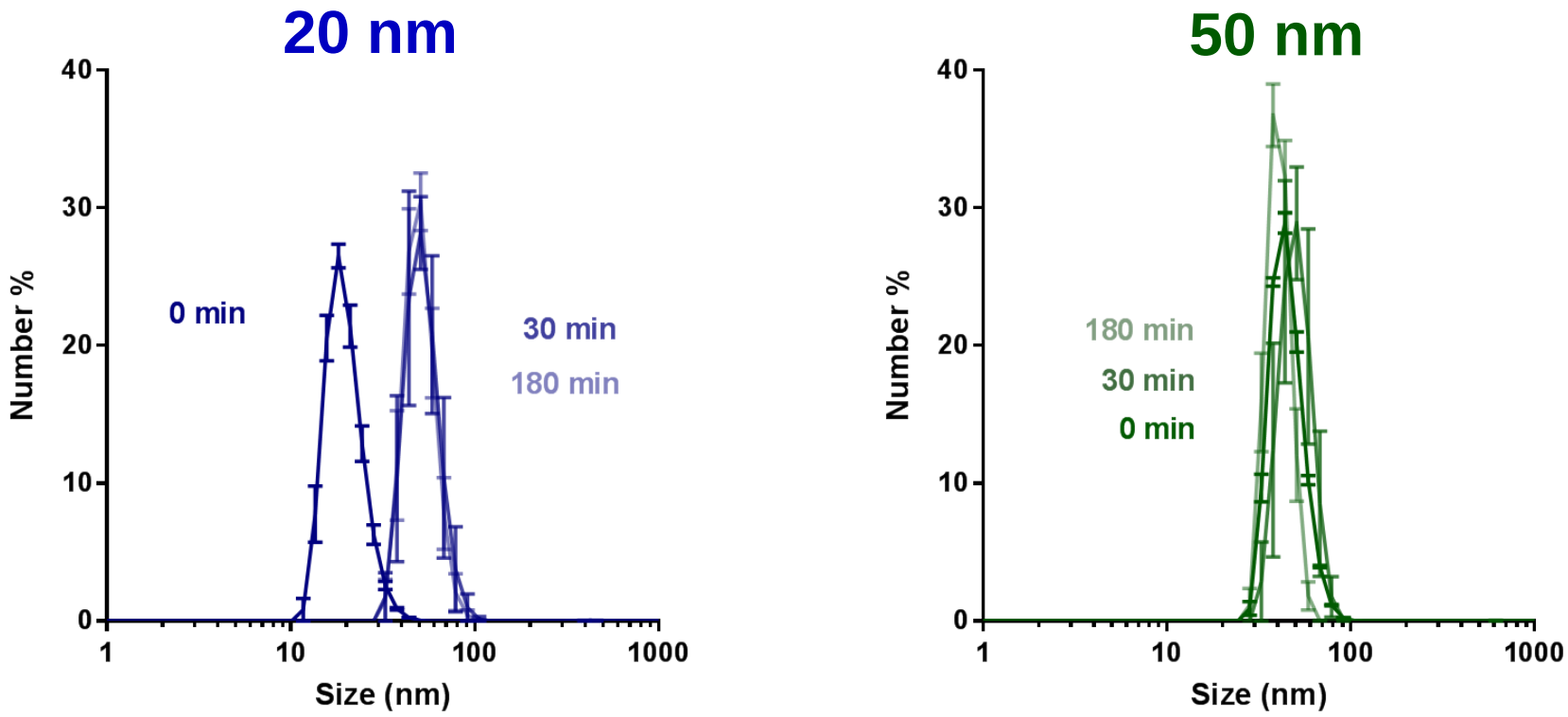
Lamson, Berger, & Whitehead, *Submitted*.

Particle effects on permeability were dose-dependent.



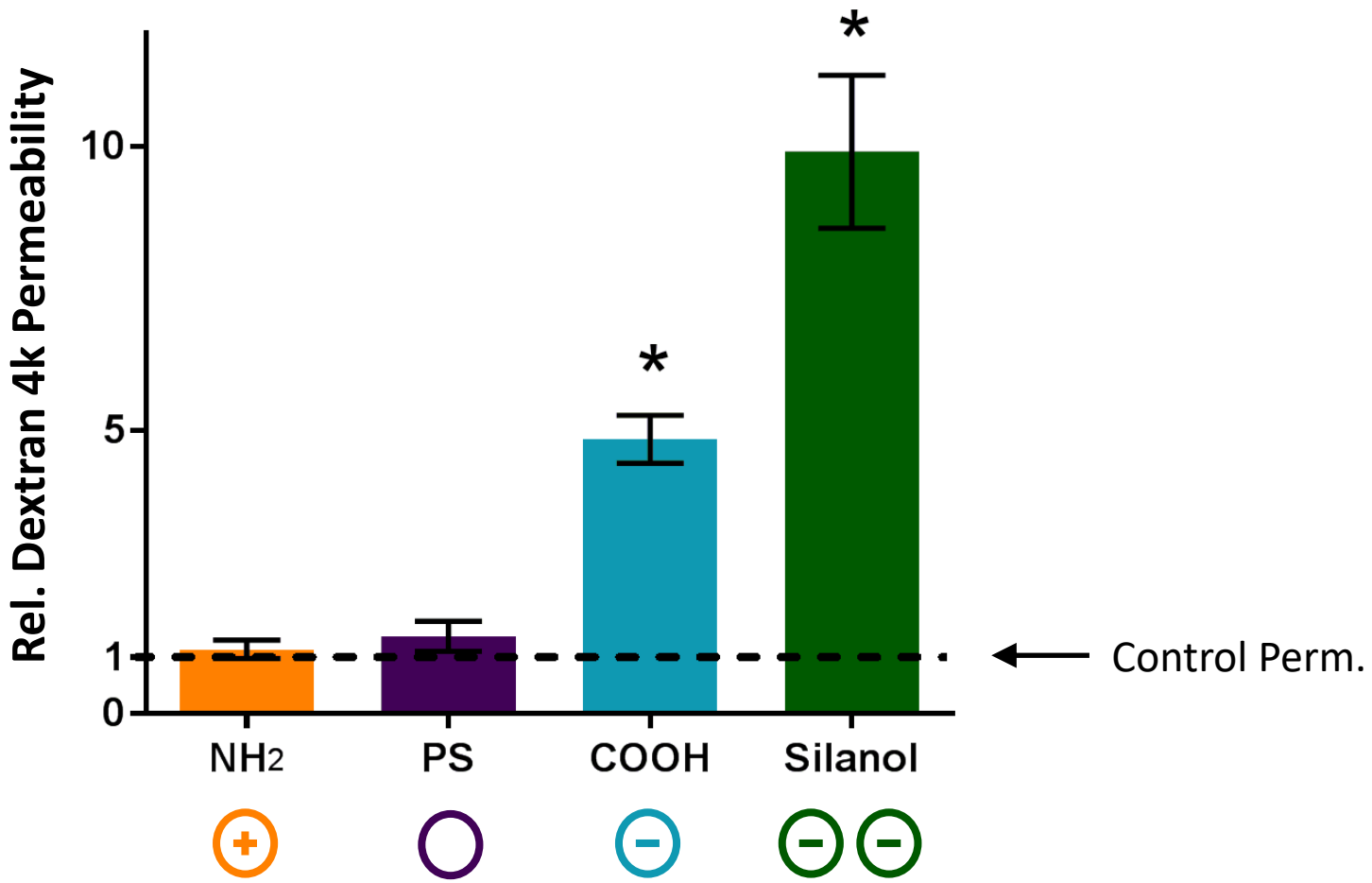


20 nm silica particles bind mucus, limiting efficacy in mice.

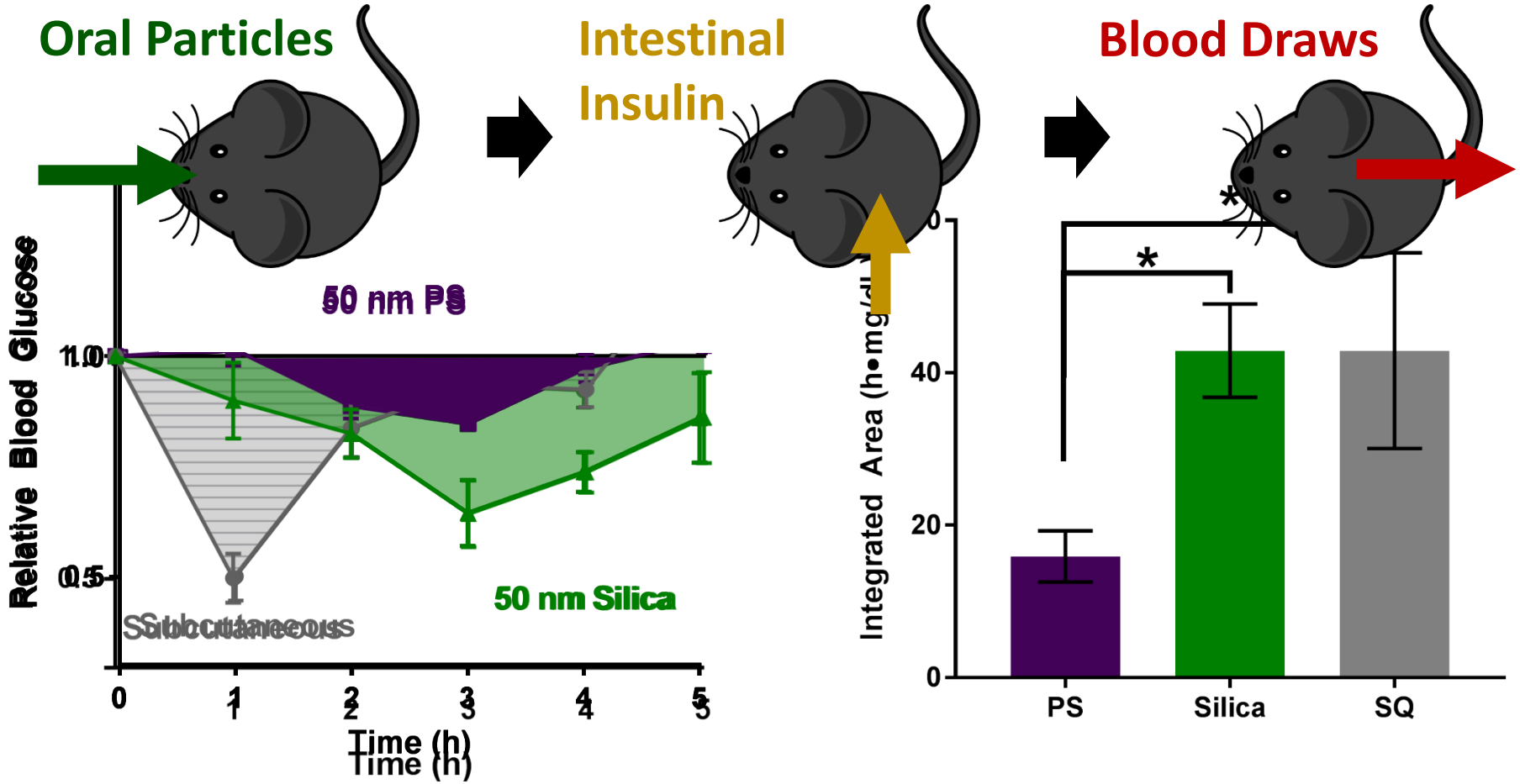


Lamson, Berger, & Whitehead, *Submitted*.

Only anionic particles are effective oral permeation enhancers in mice.

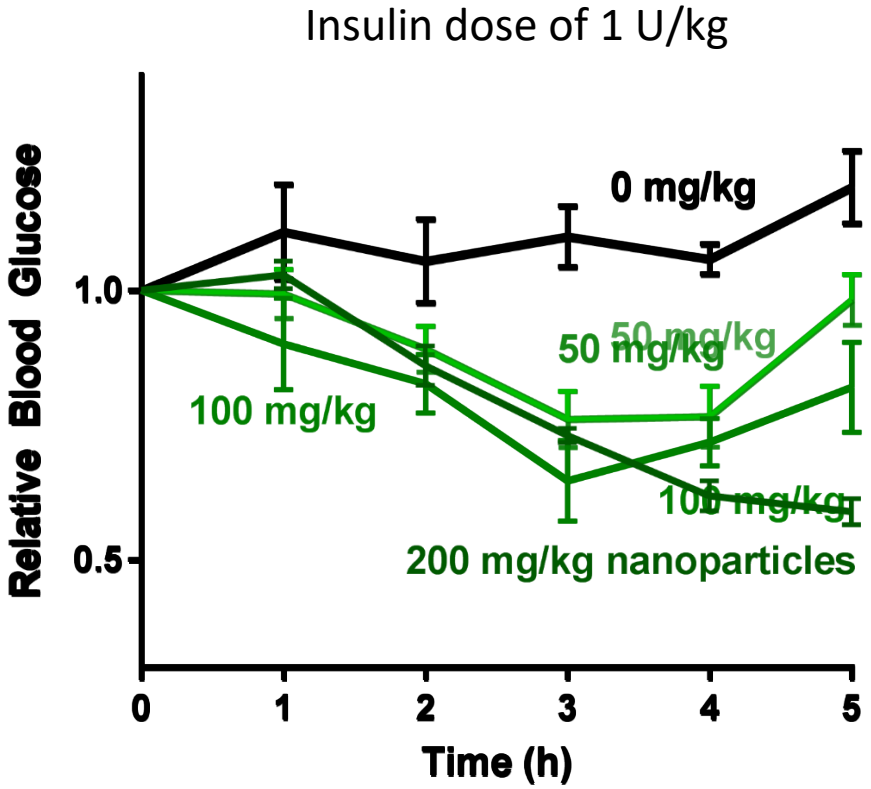


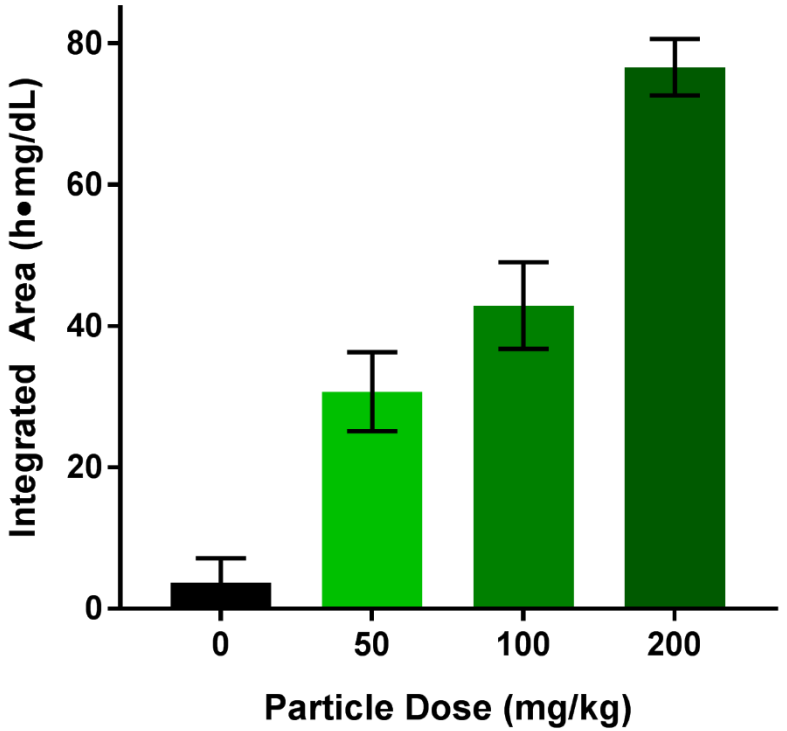
Silica nanoparticles enabled intestinal insulin absorption in mice.



Lamson, Berger, & Whitehead, *Submitted*.

Insulin delivery was nanoparticle dose-dependent.

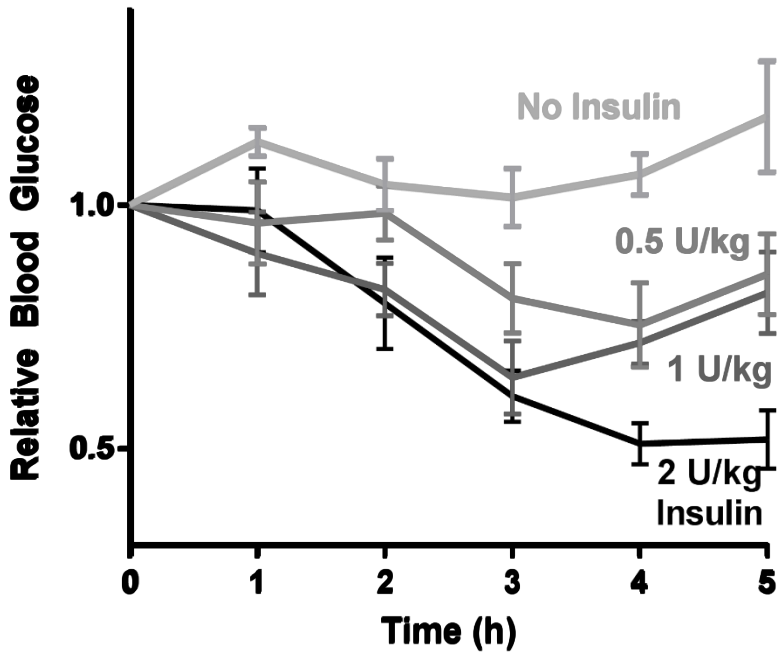


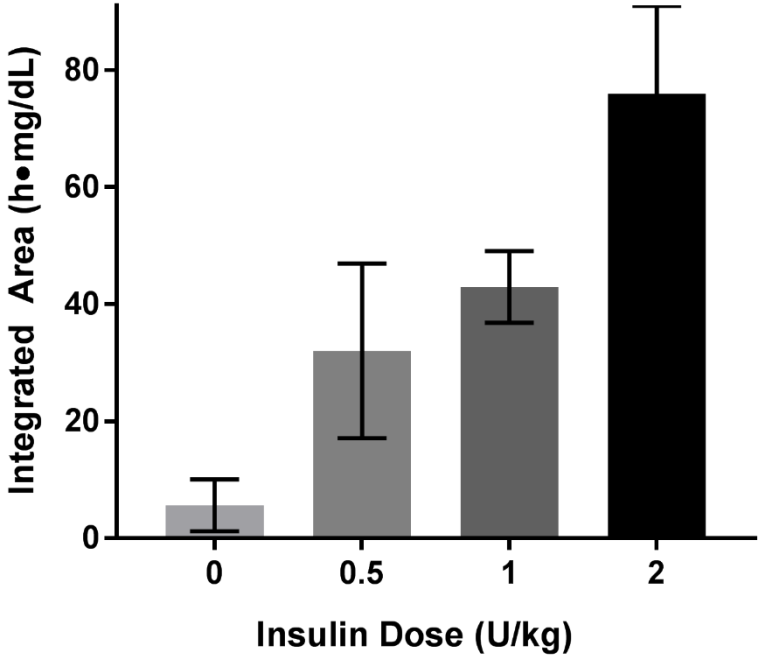


Lamson, Berger, & Whitehead, *Submitted*.

Pharmacodynamics were insulin dose-dependent.

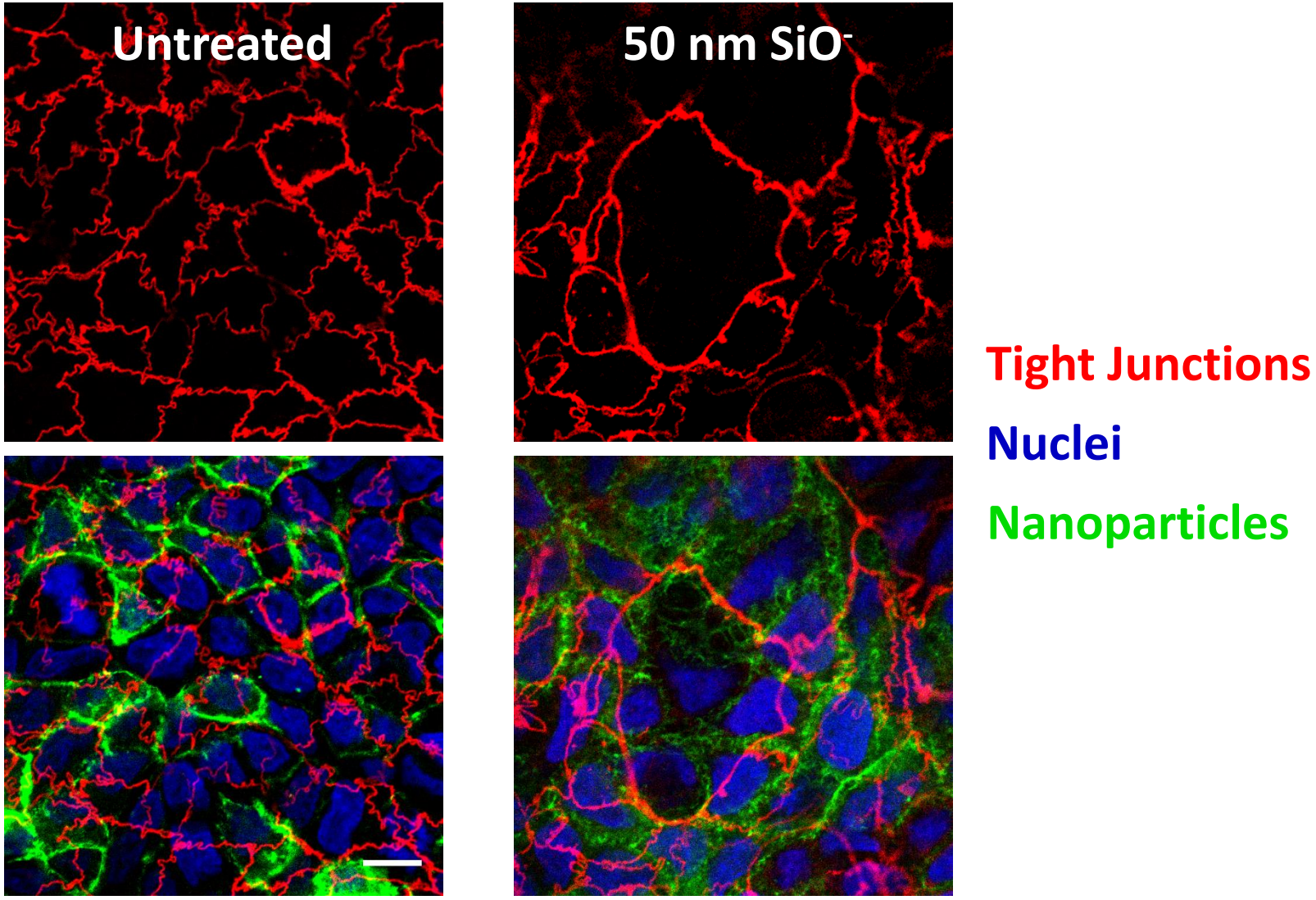
Particle dose of 100 mg/kg



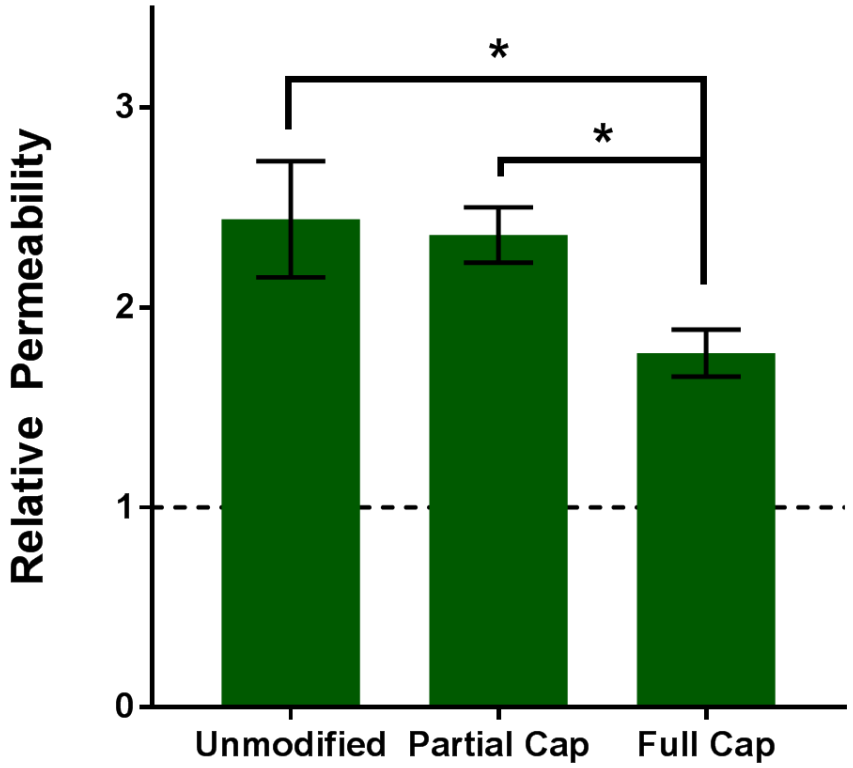


Lamson, Berger, & Whitehead, *Submitted*.

Particle treatment rearranged intestinal tight junctions.

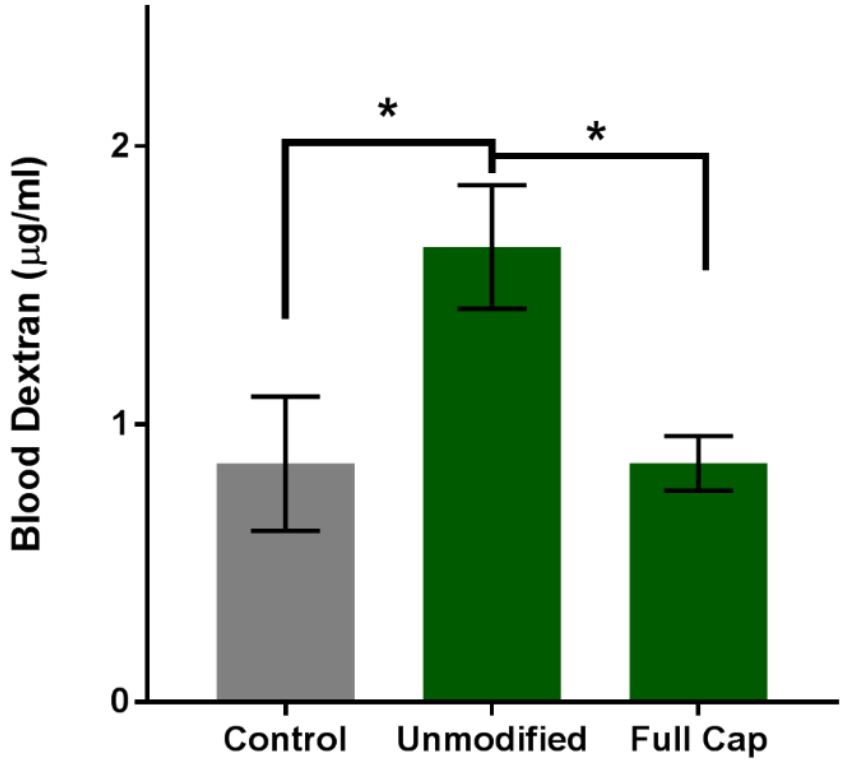


Capping anionic surface groups removes particles' *in vitro* efficacy.



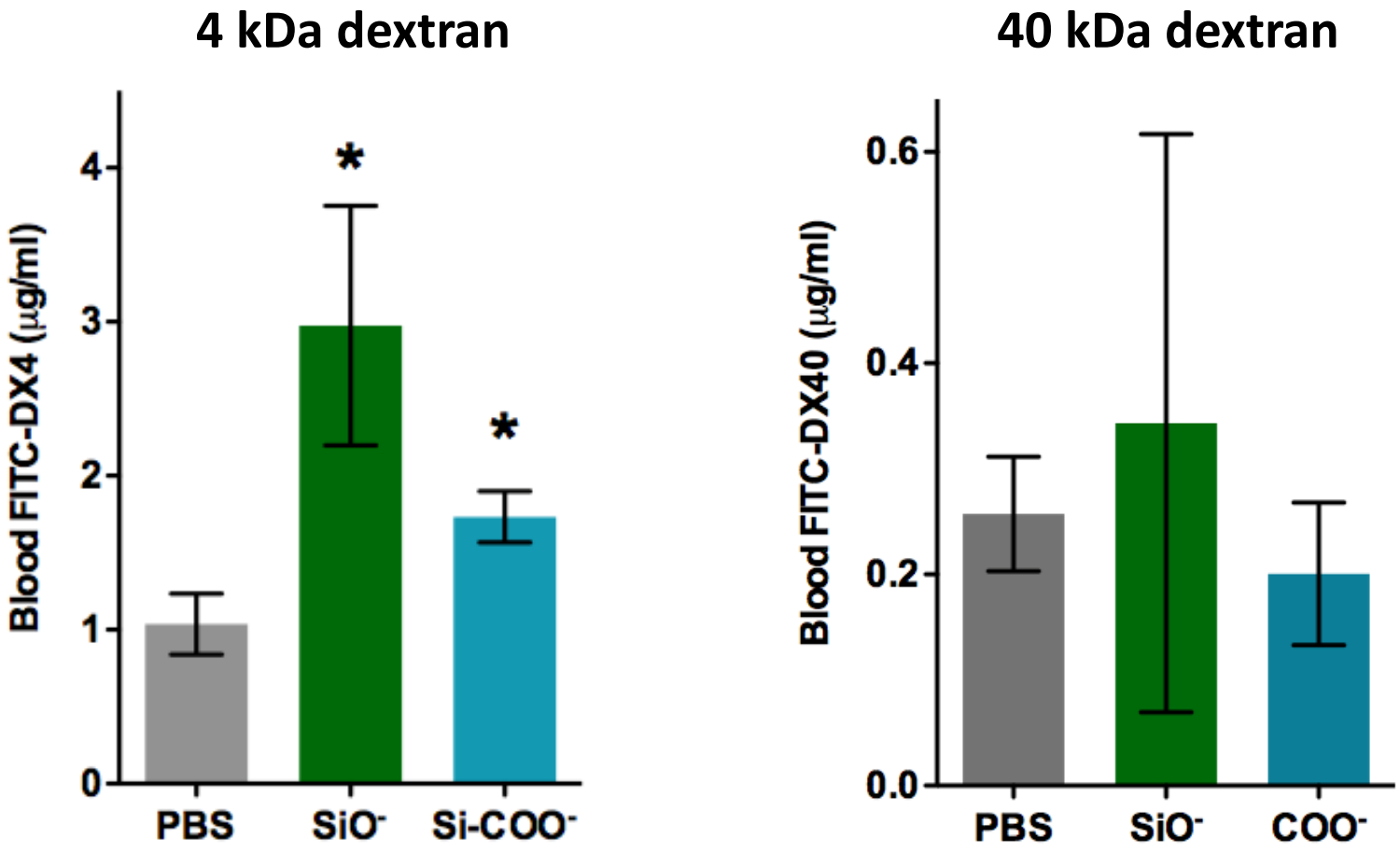
Diameter (nm)	**54.0**	**54.6**	**54.4**
Zeta Potential (mV)	**-33**	**-27**	**-13**

Capping anionic surface groups also removes particles' *in vivo* efficacy.



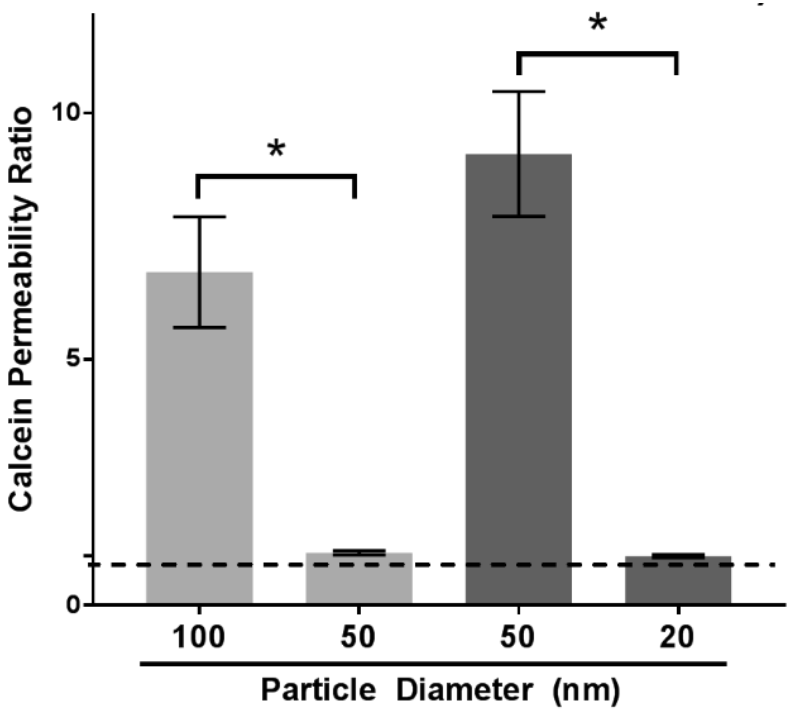
Diameter (nm)	**54.0**	**54.4**
Zeta Potential (mV)	**-33**	**-13**

Anionic nanoparticles improve transport only of small macromolecules.

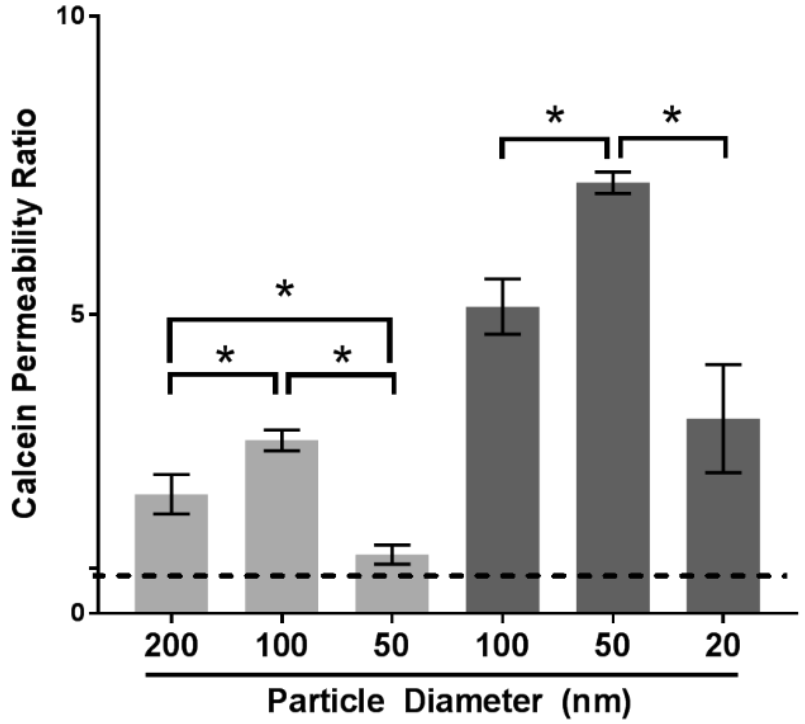


Nanoparticle efficacy is dictated by neither osmosis nor charge balance.

Same number of particles

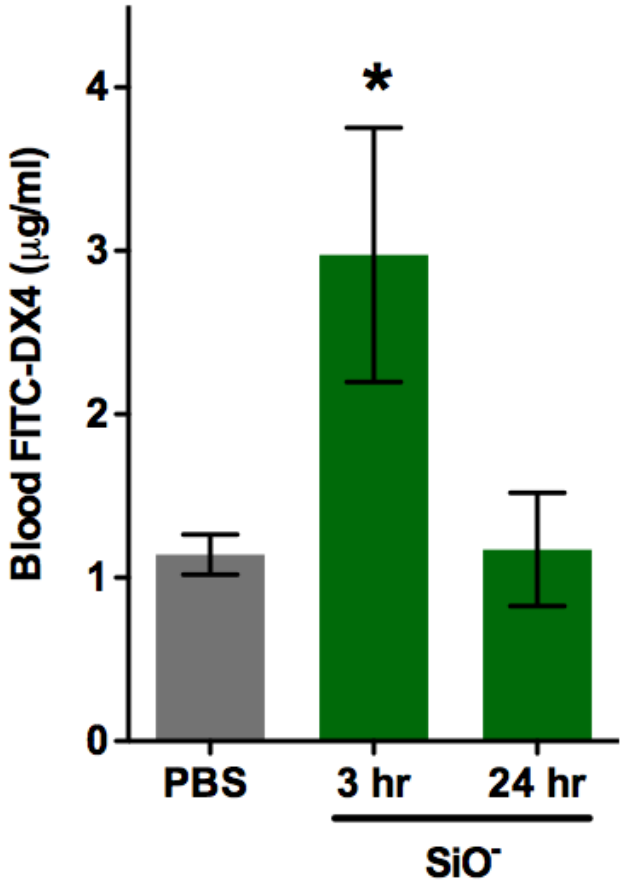


Same cumulative surface charge of particles



Are effects reversible and non-toxic?

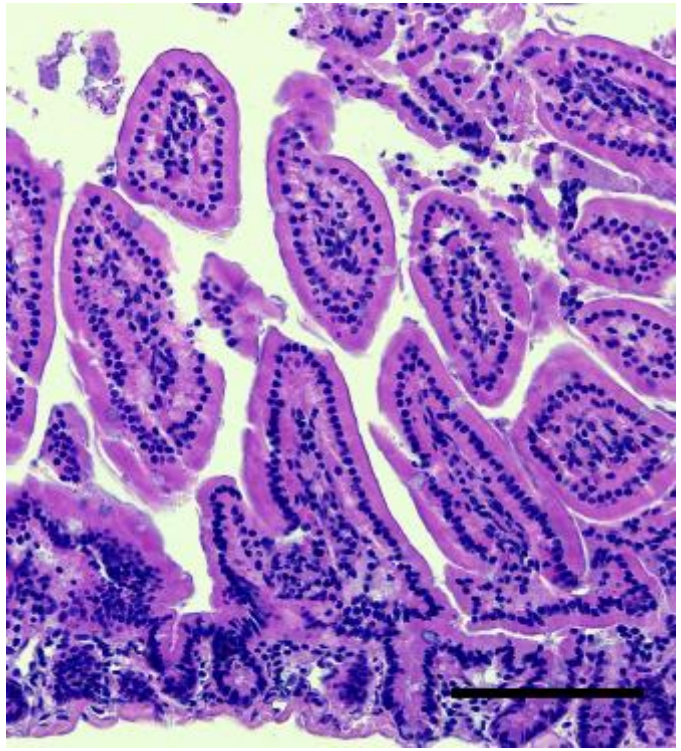
Silica nanoparticles induced *transient* intestinal permeability.



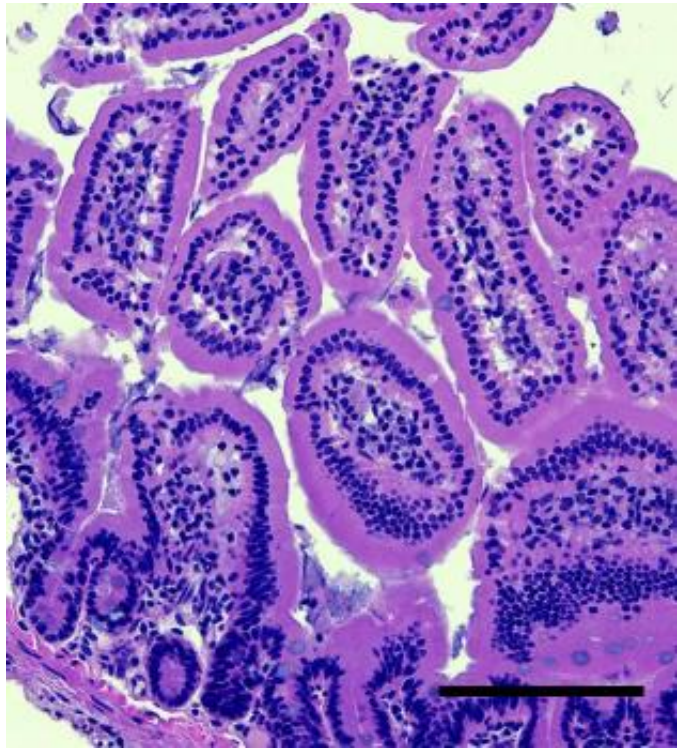
Lamson et al., *Nature BME* 2019

Particles did not induce inflammation or change intestinal architecture.

Untreated



50 nm Silica NPs



scale bar = 100 μm

Good science comes from good people.

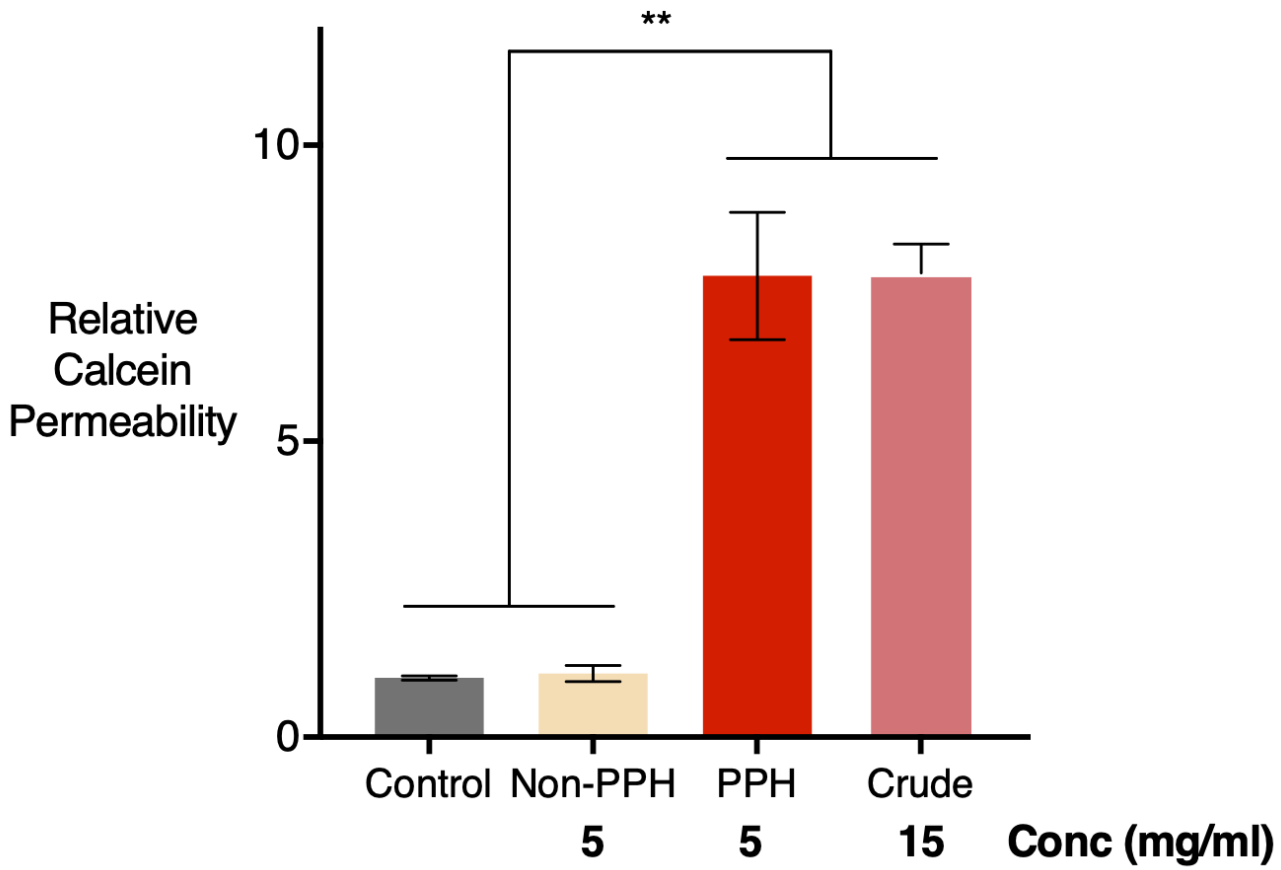
Mariah Arral
Rebecca Ball
Namit Chaudhary
Kyle Cochran
Rose Doerfler
Katherine Fein
John Gleeson
Khalid Hajj
Lisa Kasiewicz
Chris Knapp
Nick Lamson
Sam LoPresti
Jilian Melamed
Alexandra Newby
Daria Strelkova
Ryan Weiss
Sai Yerneni
Prof. Gloria Silva
Dr. Brigette Schmidt

NIH

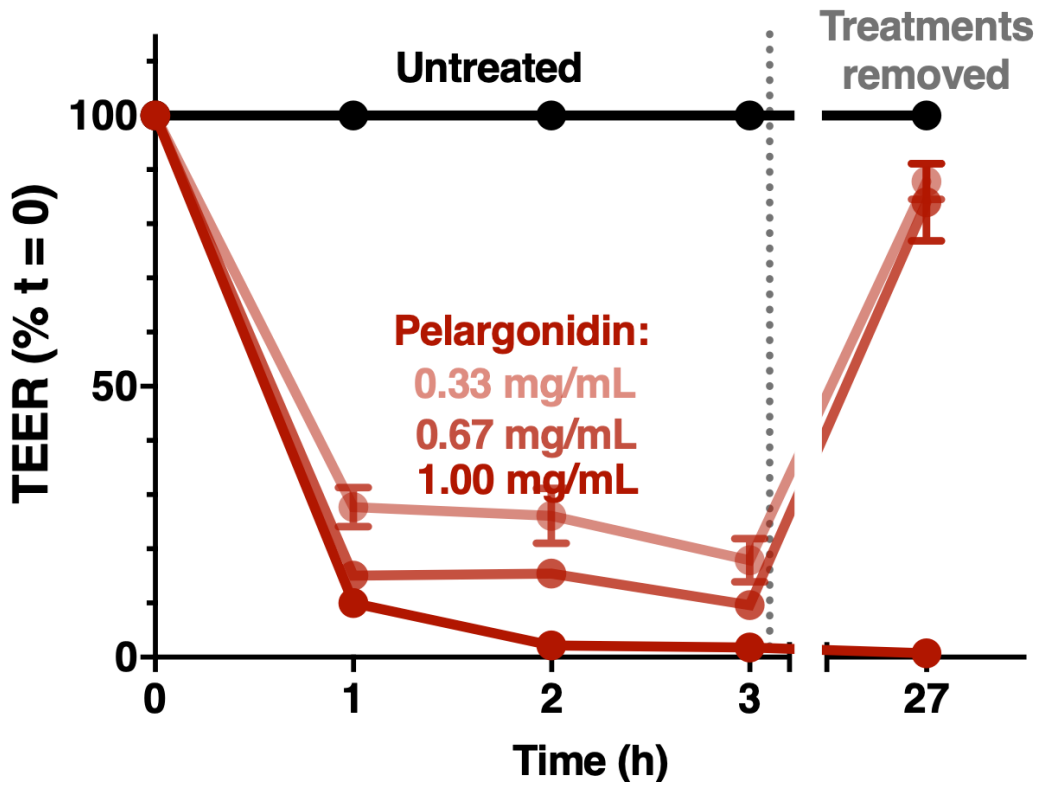
TED

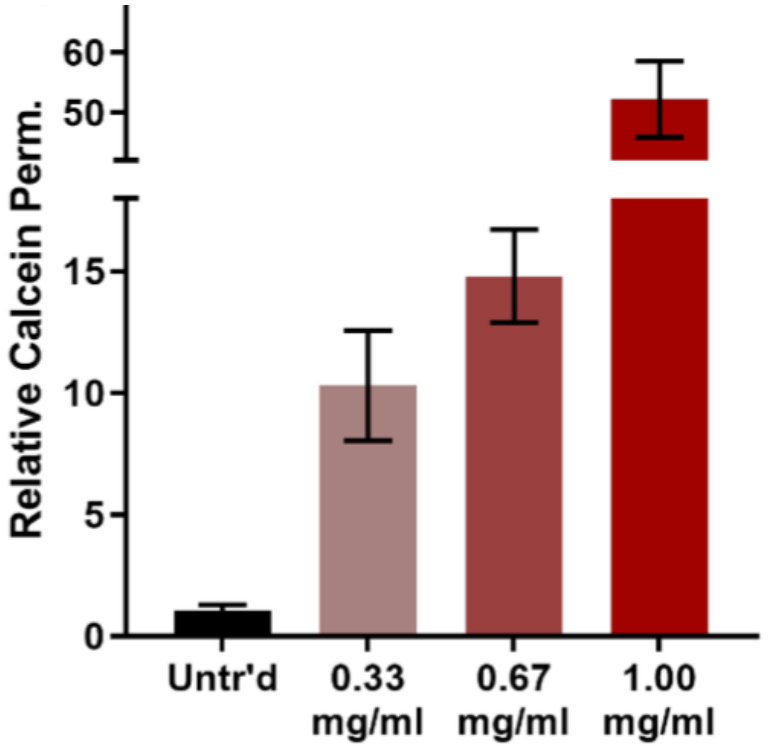
“Fat balls”

Strawberry polyphenols increase permeability of intestinal cells in culture.



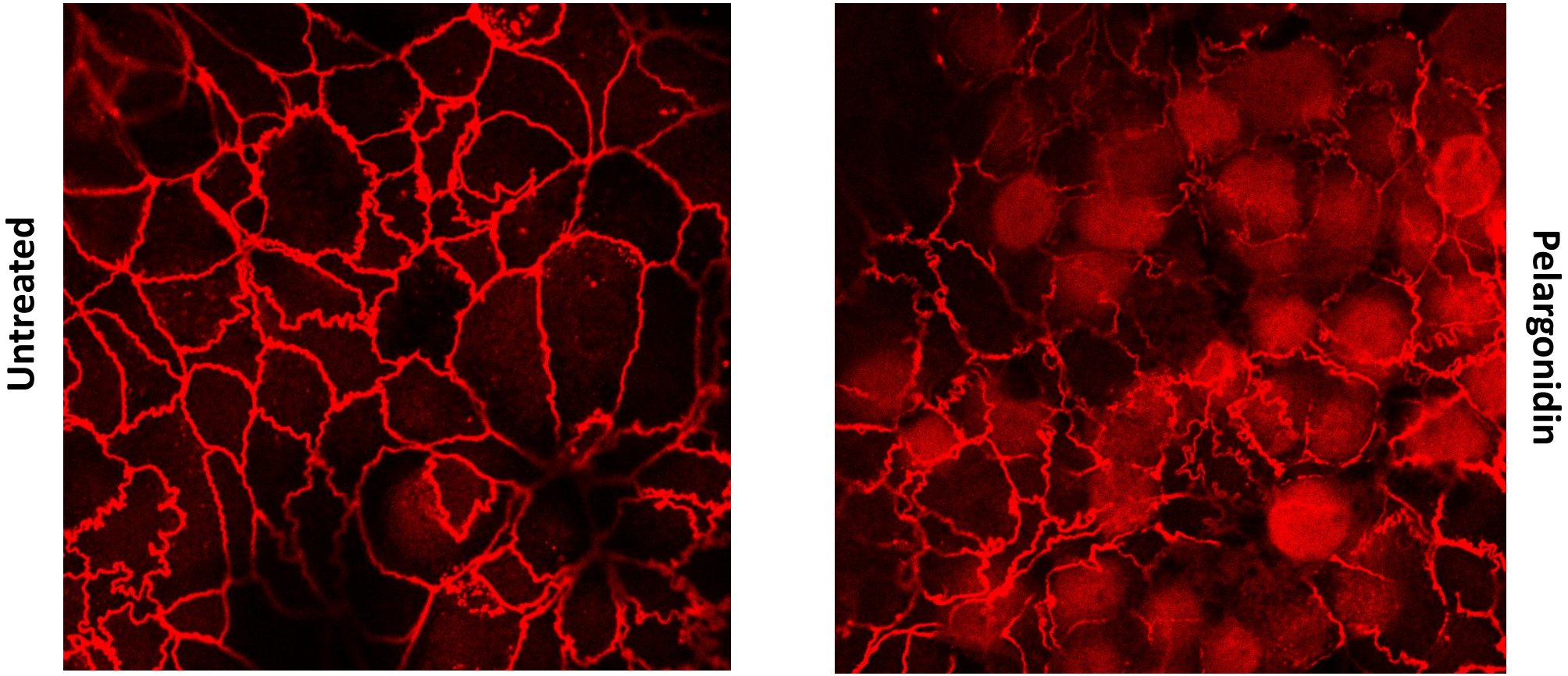
The effect of pelargonidin on intestinal cells is dose-dependent.



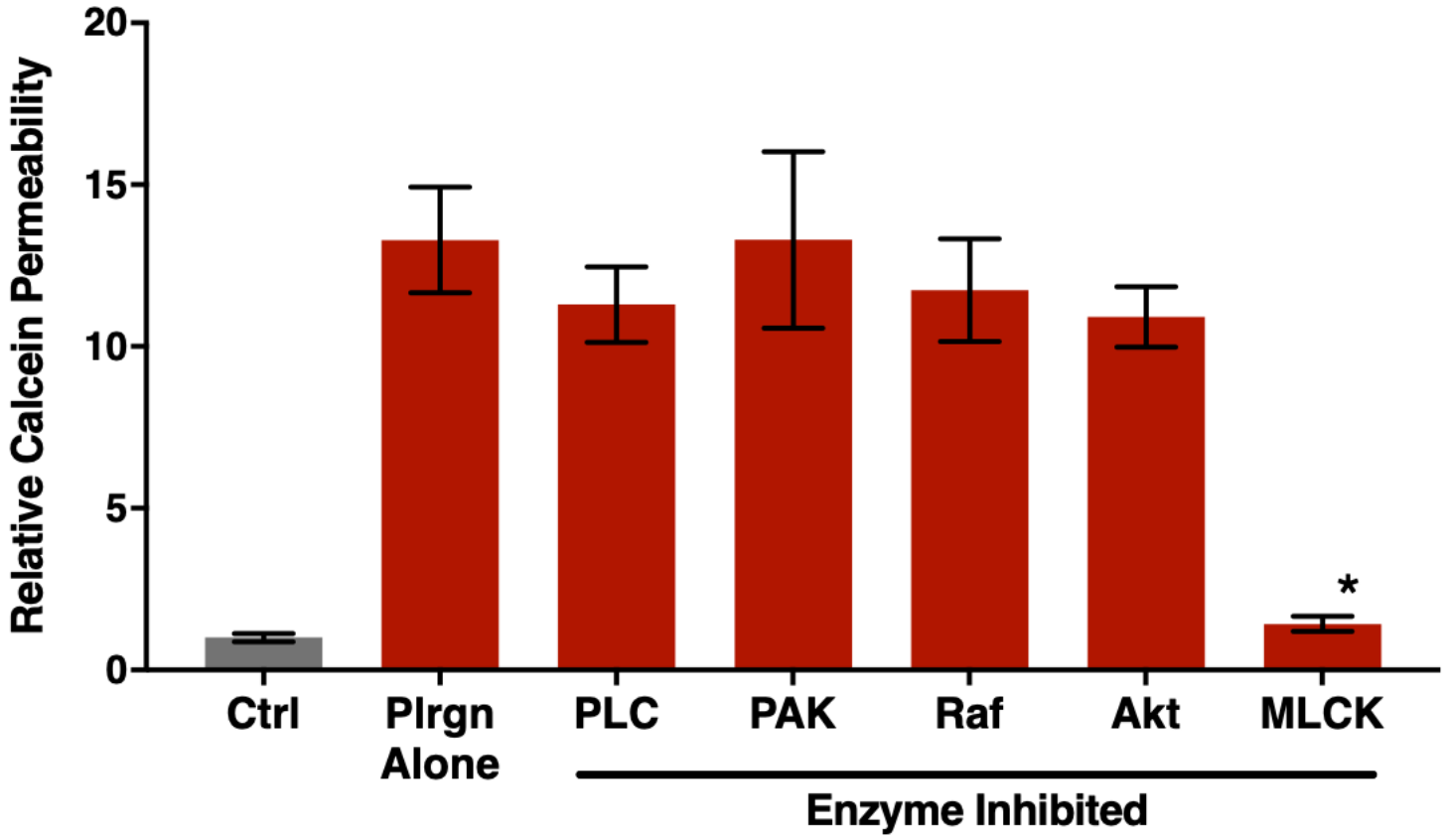


How does pelargonidin work?

Pelargonidin induces ZO-1 rearrangement in Caco-2 cells.

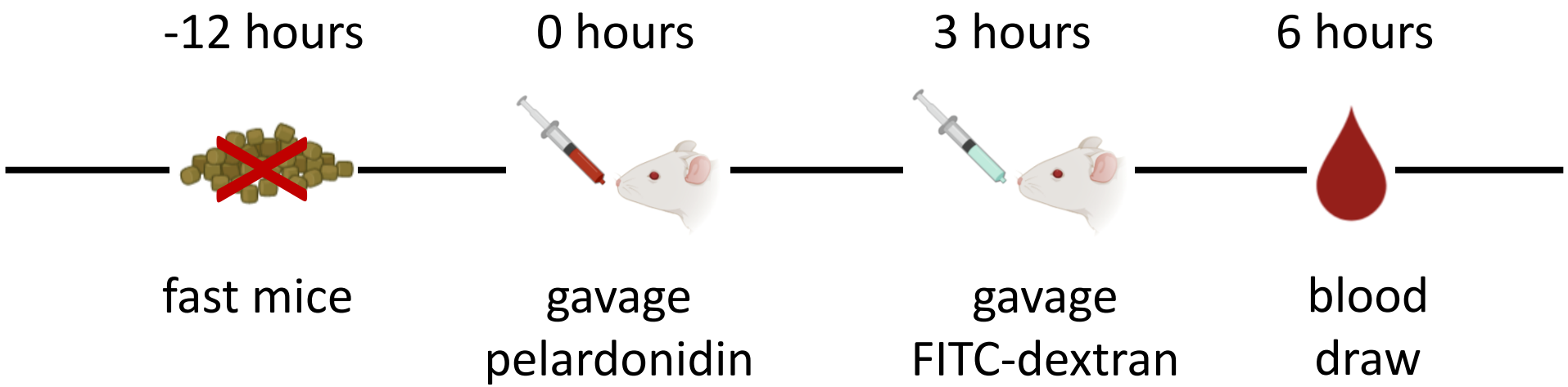


The protein MLCK plays a critical role in pelargonidin effect.

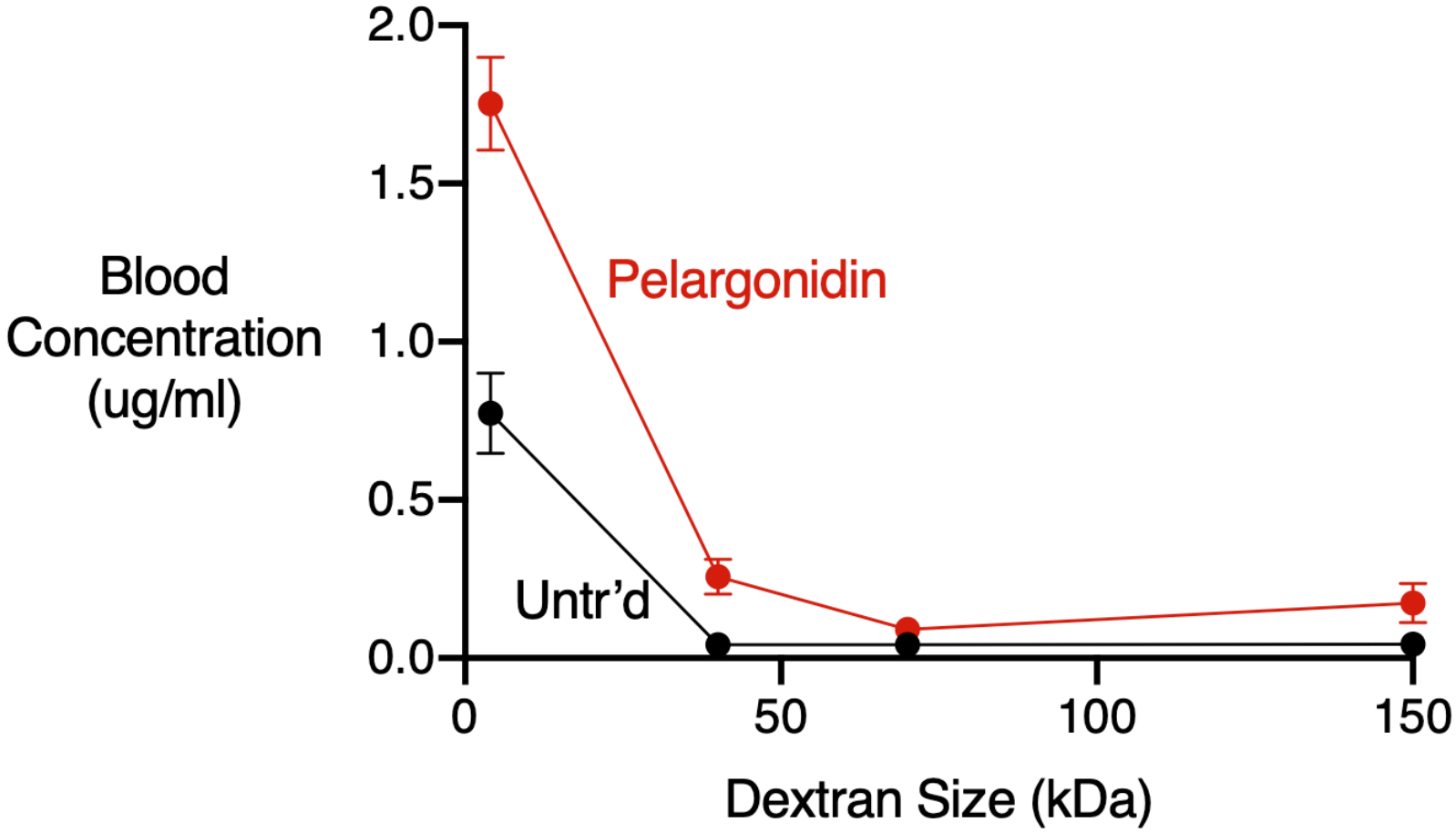


How large of a macromolecule can pelargonidin deliver?

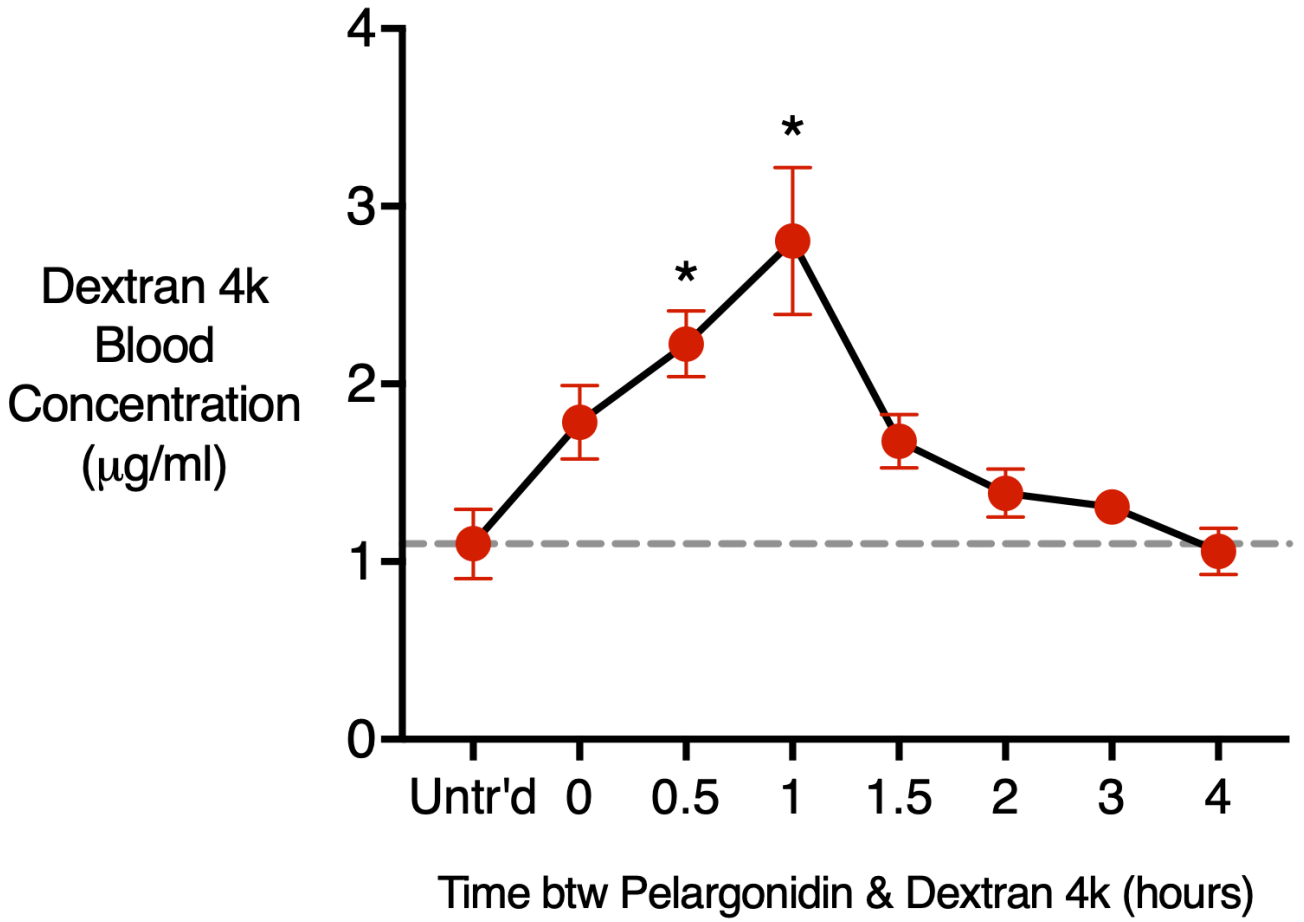
We used dextrans as model oral drugs.



Pelargonidin enables oral delivery of macromolecules.



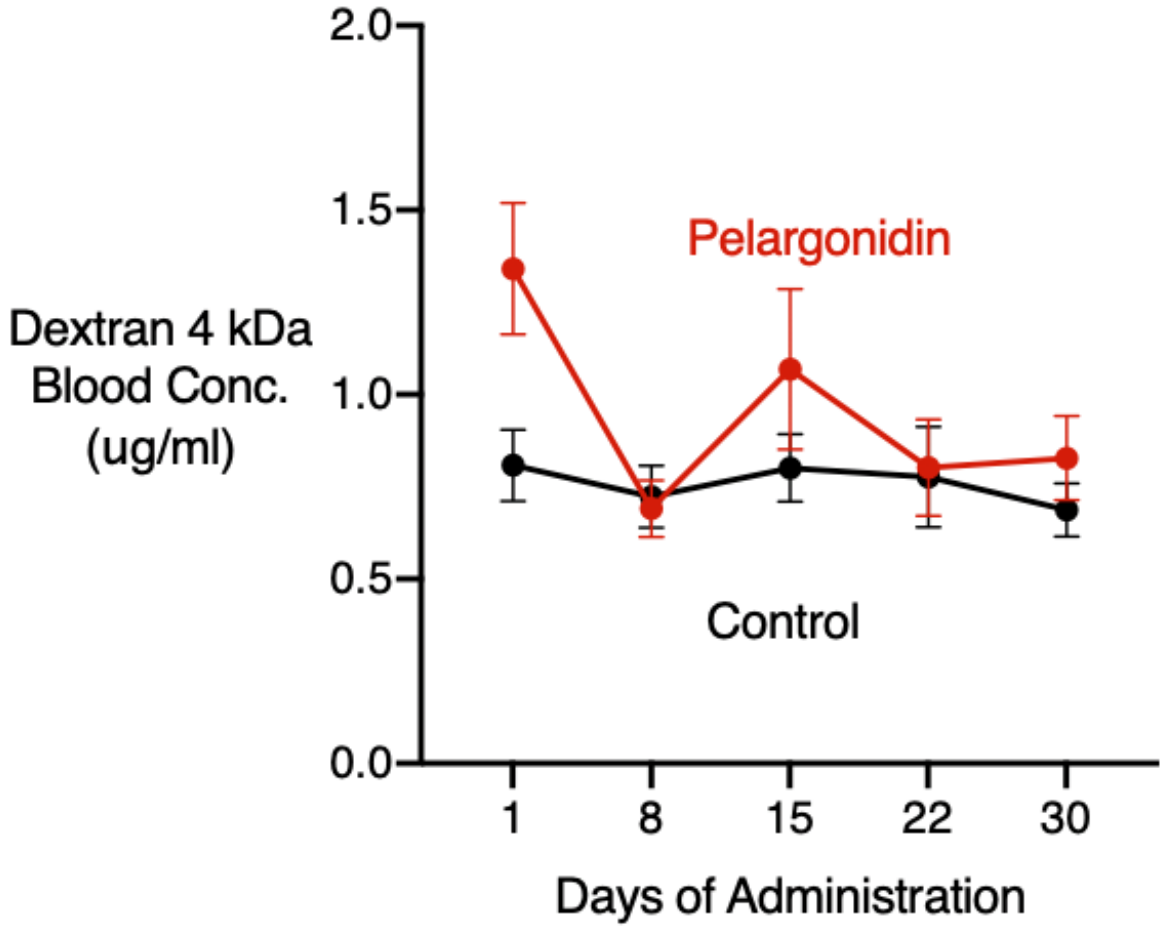
Pelargonidin effects reverse within 1 hour.



Lamson et al., *PNAS* 2022

Is pelargonidin safe?

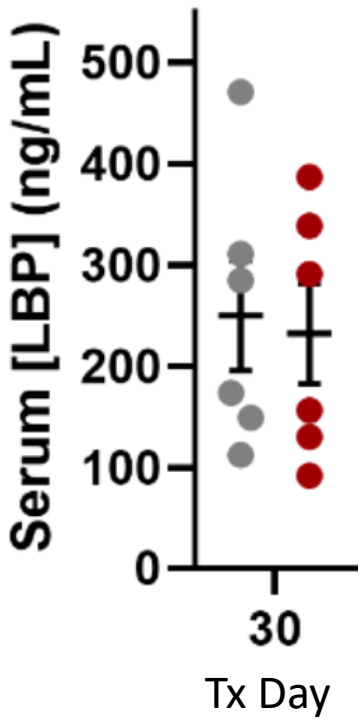
One month of daily treatment did not change baseline intestinal permeability.



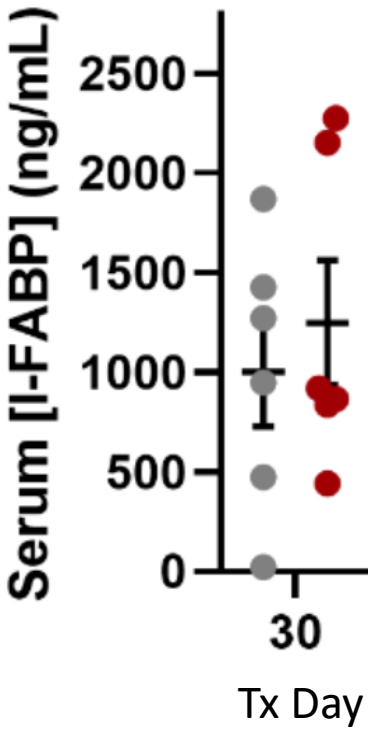
Lamson et al., *PNAS* 2022

One month of daily treatment did not cause inflammation.

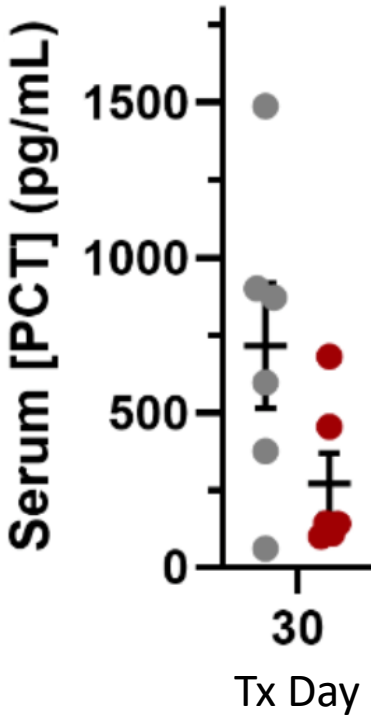
Liposaccharide binding protein



Intestinal fatty acid binding protein

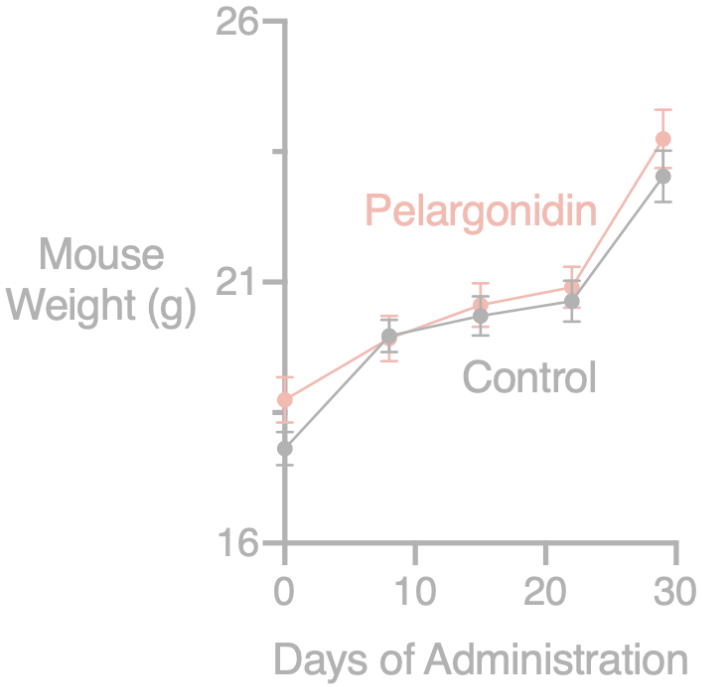


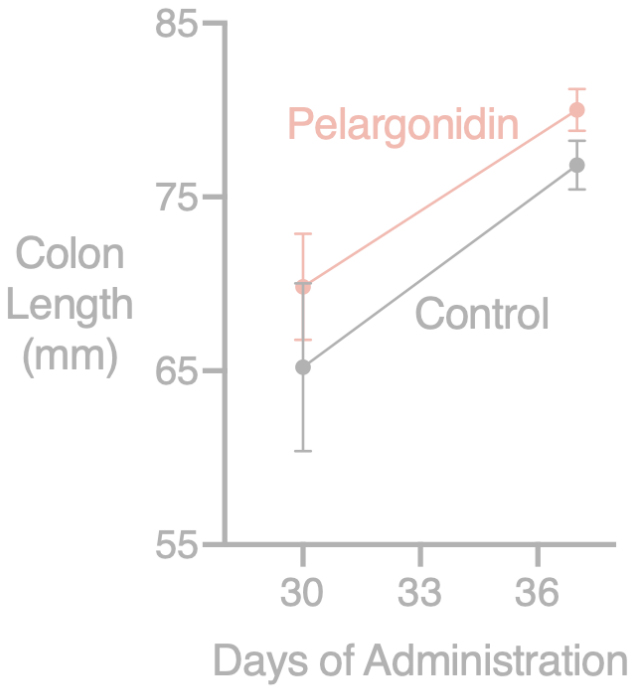
Procalcitonin

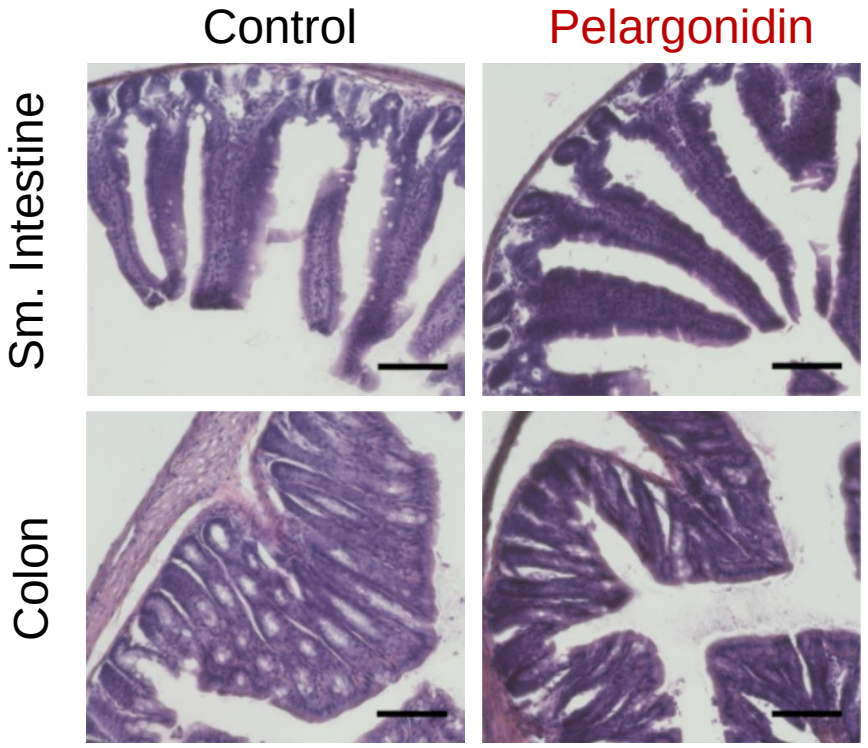


Control (Saline)
Pelargonidin

One month of daily pelargonidin treatment did not cause gross toxicity.







scale bars = 100 um

Lamson et al., *PNAS* 2020