Engineering Nanotherapeutics for Local Intestinal Delivery Responding to Oxidative Cues in the Gut Microenvironment

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CRS 2025 ANNUAL MEETING & EXPOSITION
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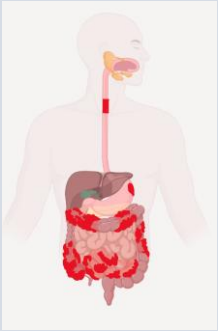
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

Inflammatory Bowel Disease as a burden

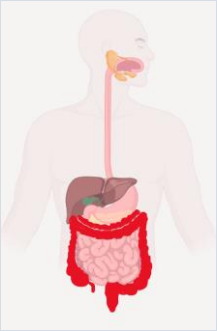
IBD

Crohn's Disease



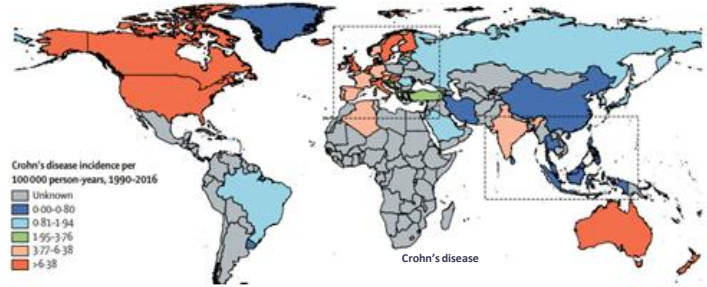
- ✓ Can affect any part of the Gastrointestinal tract (GIT)
- ✓ Discontinuous inflammation pattern with a thicker mucus layer

Ulcerative Colitis



- ✓ Affects mainly the large intestine
- ✓Continuous superficial inflammatory lesion with thin mucus layer

Crohn's Disease



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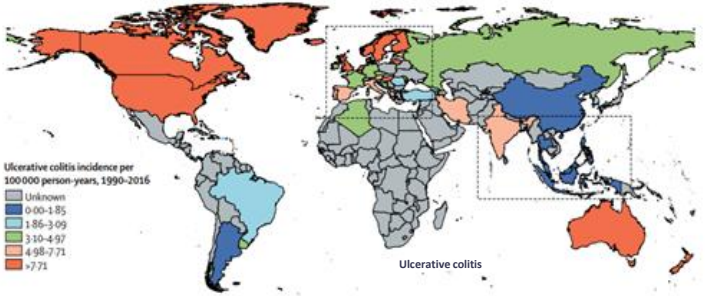
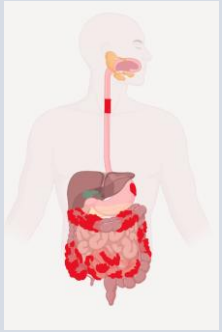
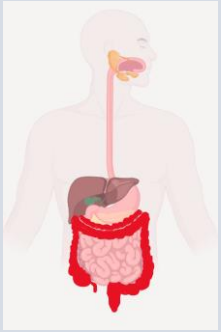


- Incidence rate increase of 85.1% worldwide
- IBD direct cost in USA: ~$5000 per person/year
- IBD direct cost in Europe: ~€2000 per person/year

Inflammatory Bowel Disease as a burden

IBD

Crohn's Disease	Ulcerative Colitis
	
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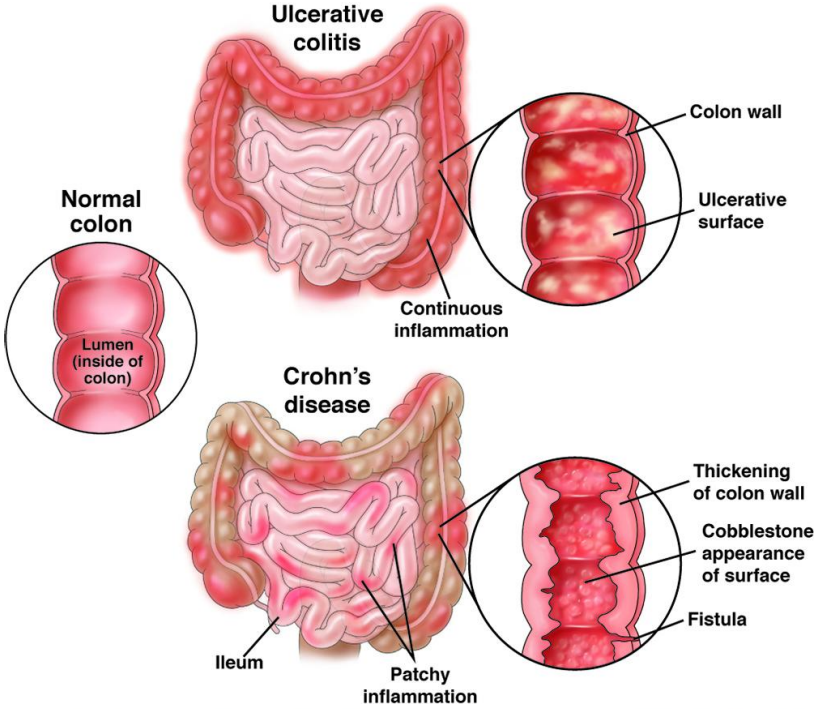
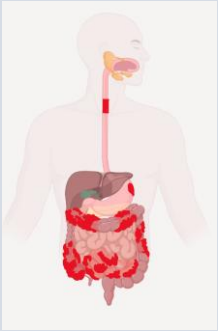


Inflammatory Bowel Disease as a burden

IBD

Crohn's Disease



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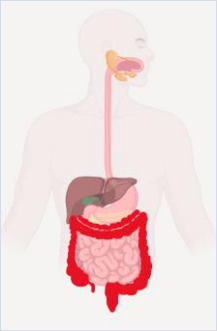

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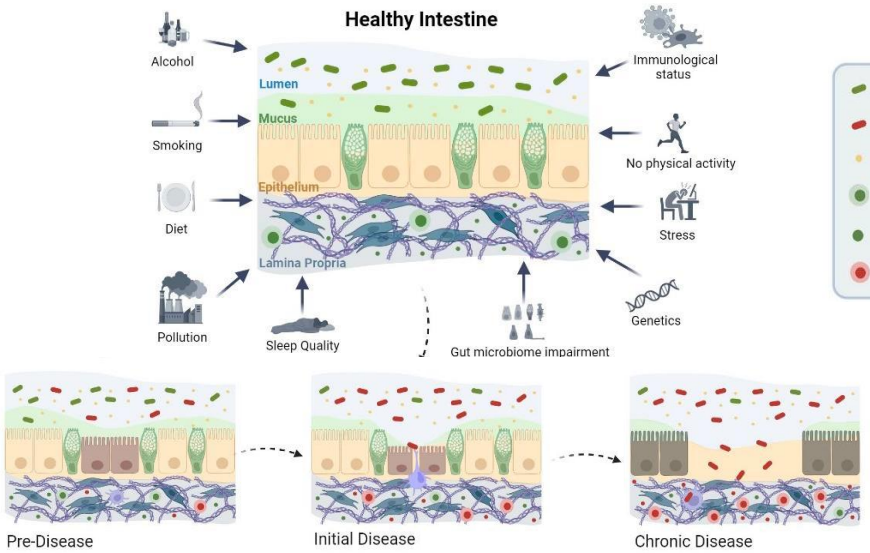

Inflammatory Bowel Disease as a burden

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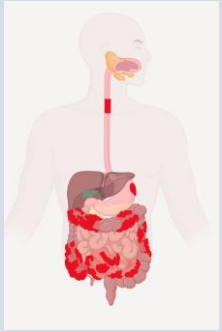	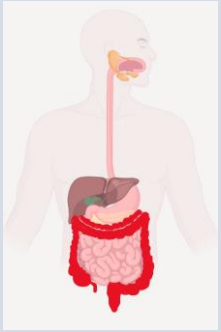
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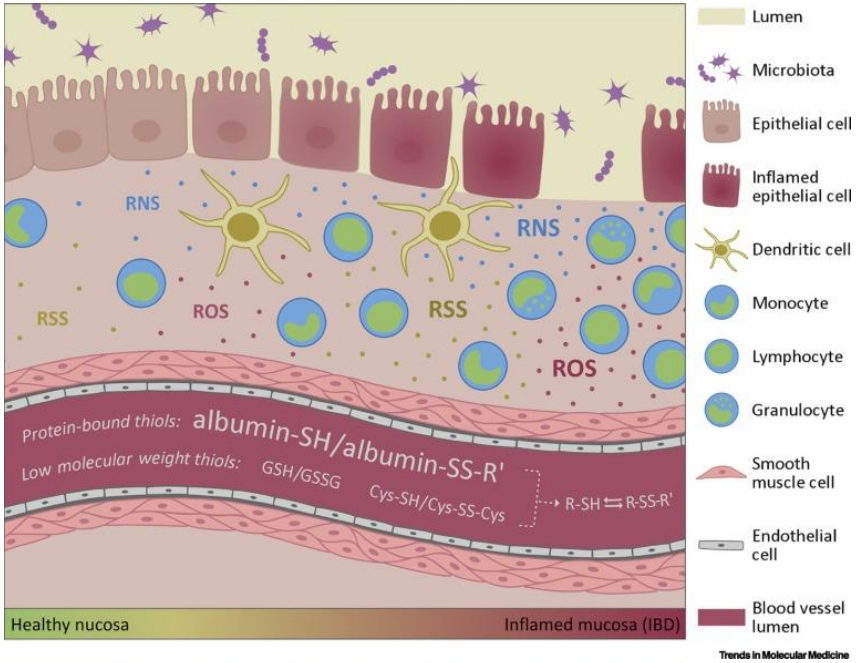
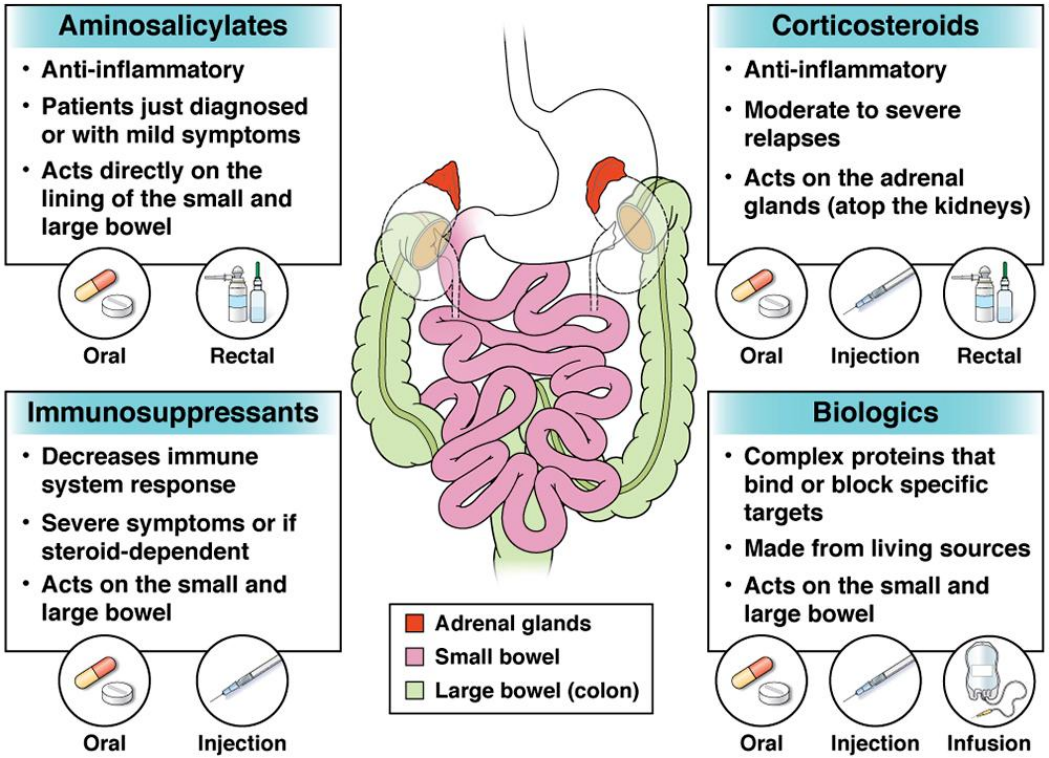
Intestinal Reactive Species Interactome (RSI) and Systemic Redox Status in Healthy and Inflamed Intestinal Mucosa



Therapeutic toolkit for inflammatory bowel disease



Therapeutic toolkit for inflammatory bowel disease

Corticosteroids

- Anti-inflammatory
- Moderate to severe relapses
- Acts on the adrenal glands (atop the kidneys)

Oral Injection Rectal

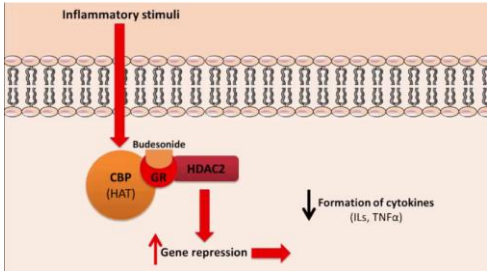
Prednisolone

Budesonide

Rapid control of flares	Long-term limitations
Versatile administration	Adverse effects

Therapeutic toolkit for inflammatory bowel disease

Budesonide

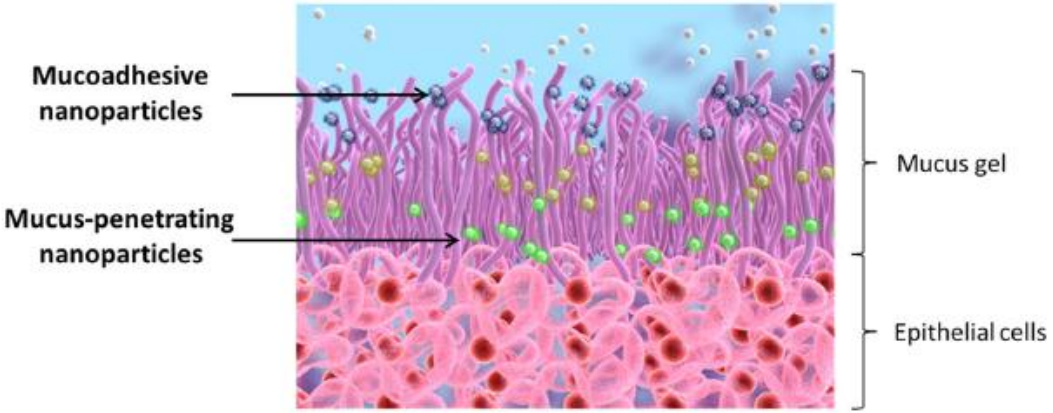


Acts directly on the affected area of the bowel, causes fewer side effects.

Still... inferior efficacy compared to systemic steroids

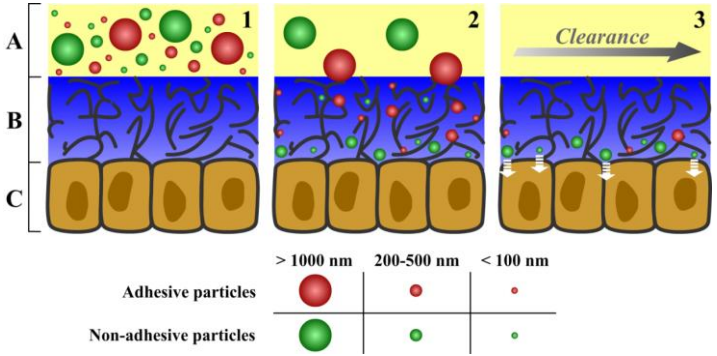
Site specific drug delivery can lead to avoidance of first pass metabolism, which is a limitation for its oral bioavailability

Oxidative intestinal environment as an opportunity

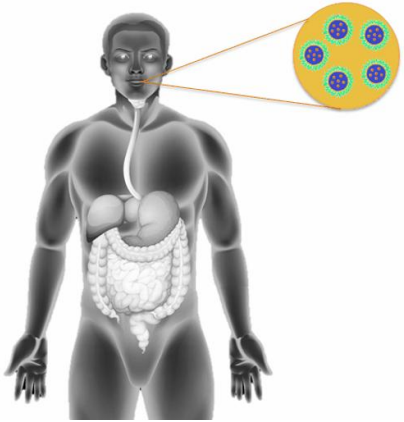


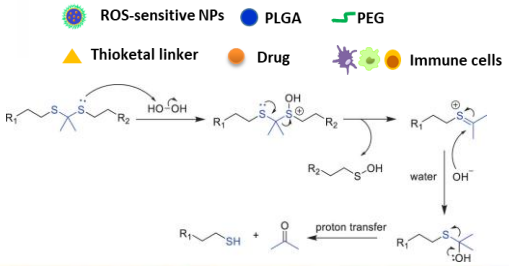
Nanomedicines

- Provide stability to payload
- Mucopenetration
- Cross physiological barriers
- Enhance intracellular uptake

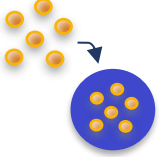


ROS-based stimulus-responsive nanomedicines

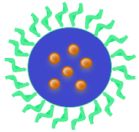




Drug



PLGA matrix

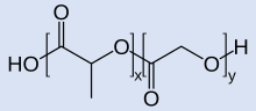


Poly(lactic-*co*-glycolic) acid - PLGA

-Biodegradable

-Biocompatible

-Hydrophobic

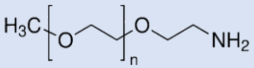


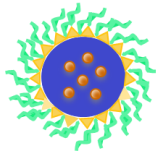
PEGylation

Polyethylene glycol - PEG

-Biocompatible

-Hydrophilic

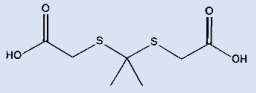


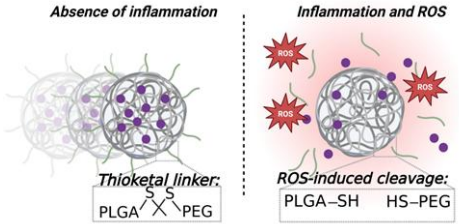


ROS-sensitive linker

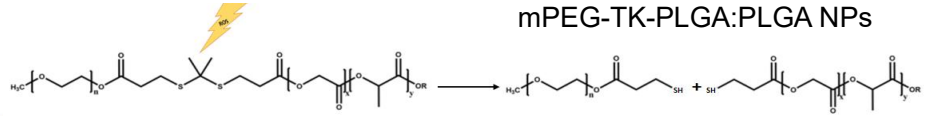
Thioketal - TK

- ROS-sensitive linker

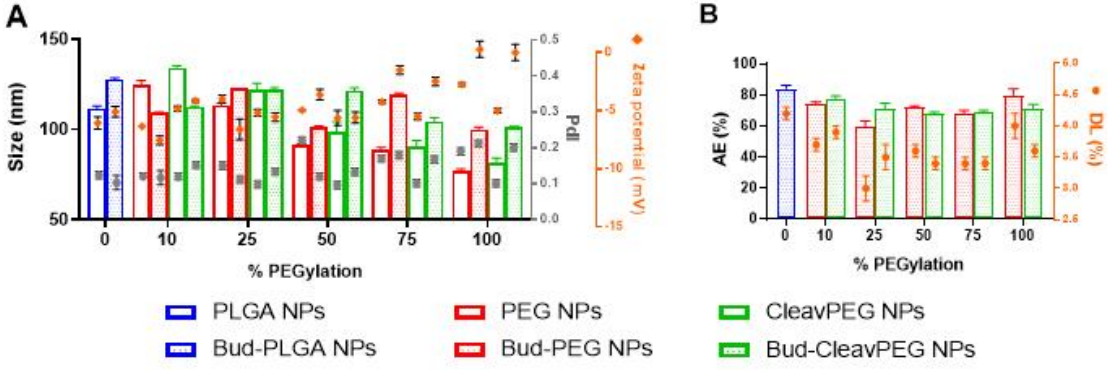


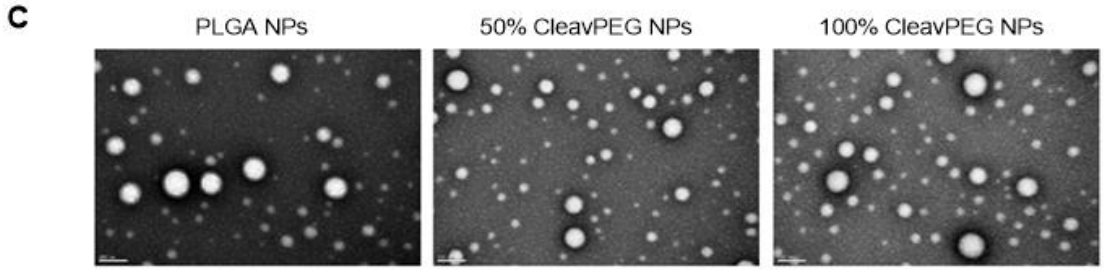


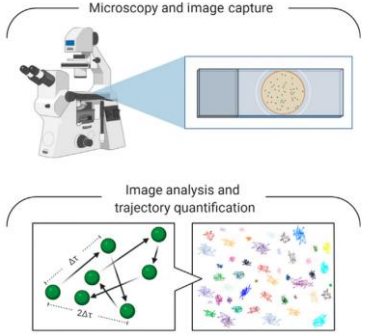
mPEG-TK-PLGA:PLGA NPs

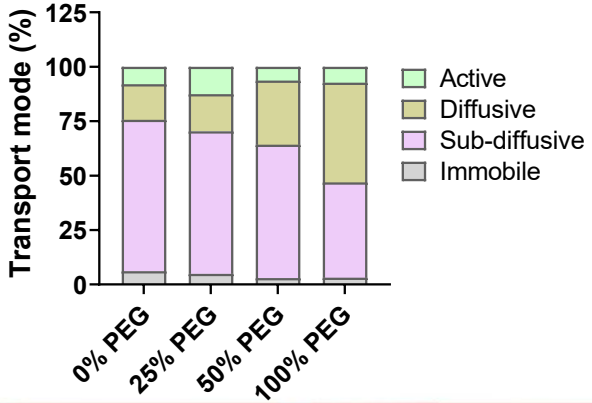


Stimulus-responsive nanomedicines for oral delivery of budesonide



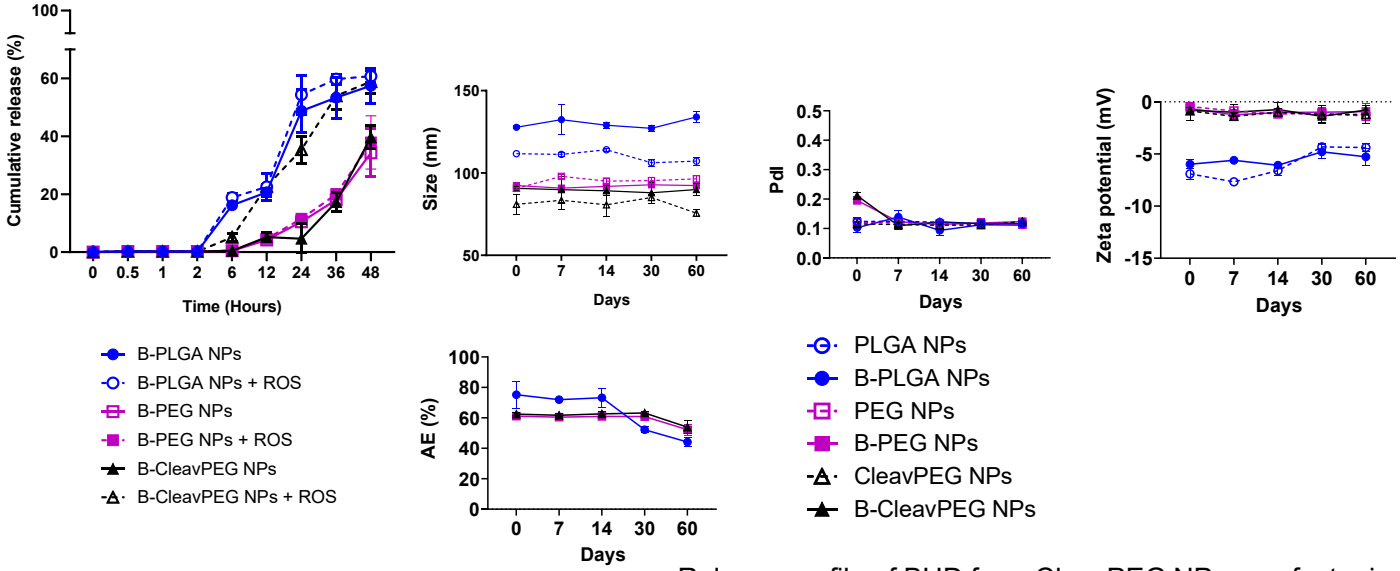






Cristelo *et al.* J Control Rel, 384, 113948, 2025

Stimulus-responsive nanomedicines for oral delivery of budesonide – Release and stability

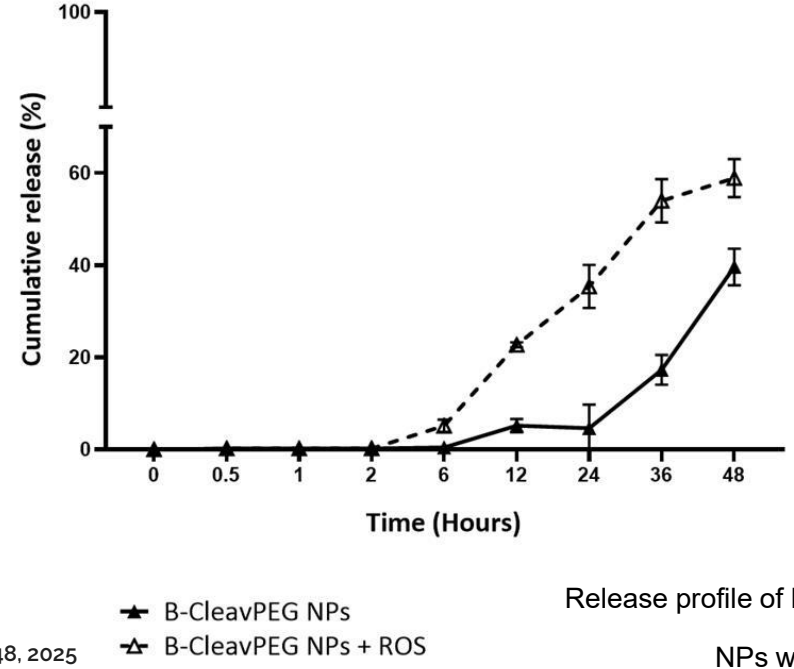


Release profile of BUD from CleavPEG NPs was faster in presence of ROS

NPs were stable under normal and ROS conditions

Cristelo *et al.* J Control Rel, 384, 113948, 2025

Stimulus-responsive nanomedicines for oral delivery of budesonide – Release and stability



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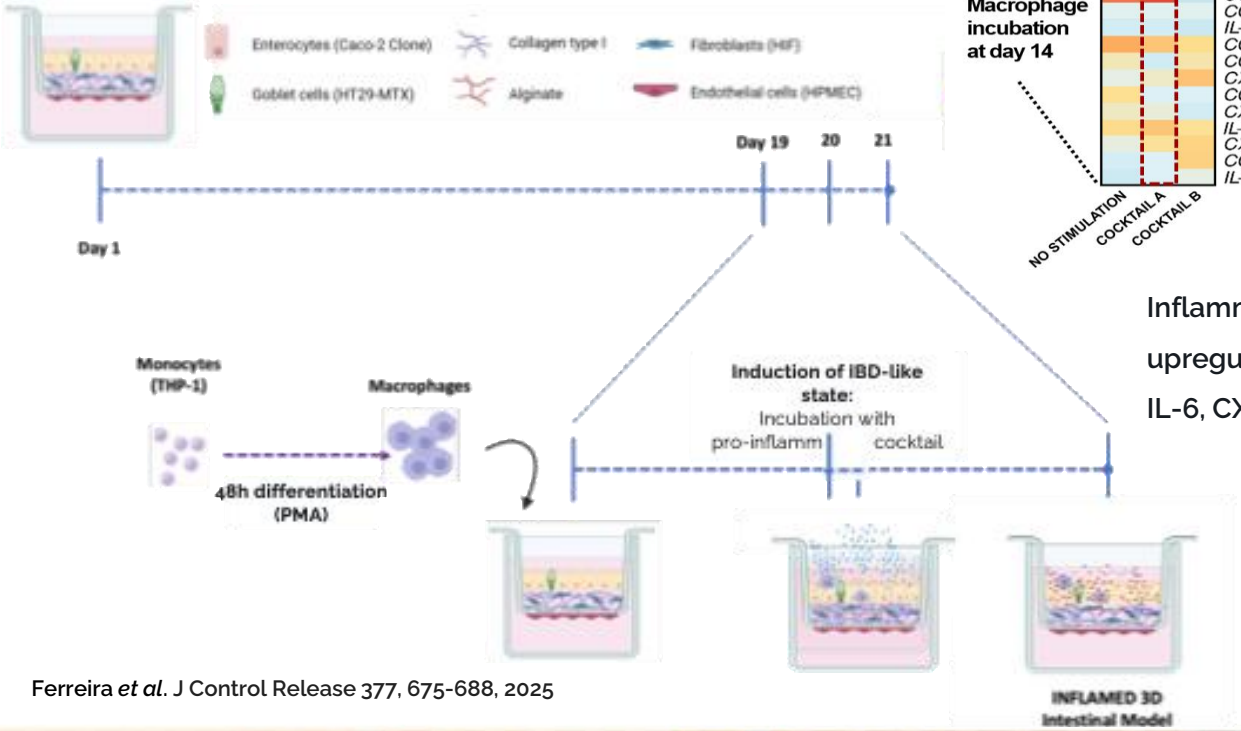
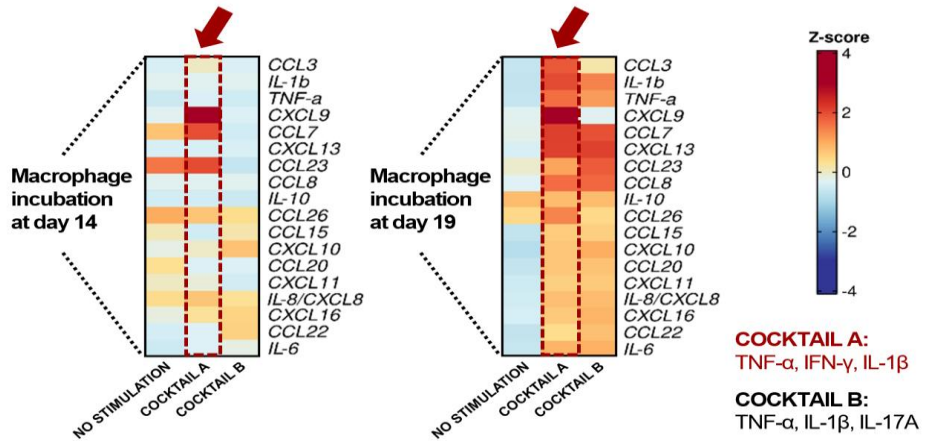
In vitro IBD 3D model

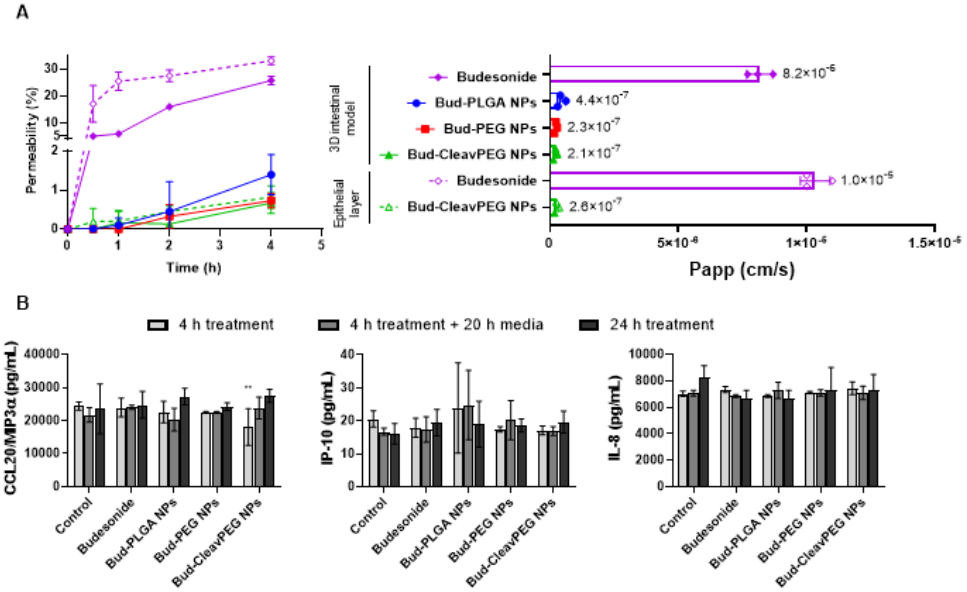


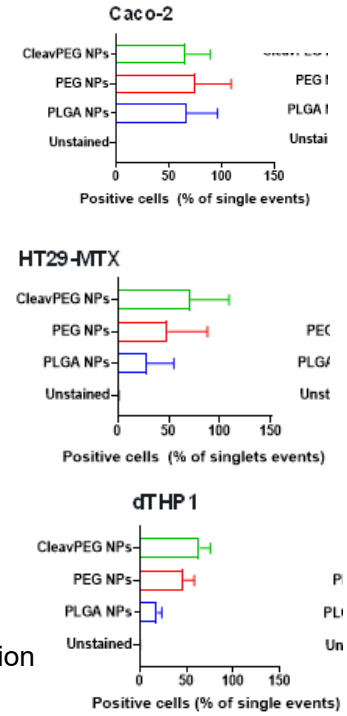


Inflammation was successfully induced by Cocktail A, upregulating pro-inflammatory cytokines such as CCL20, IL-6, CXCL9, and CXCL10, associated with IBD onset

Ferreira *et al.* J Control Release 377, 675-688, 2025

Stimulus-responsive nanomedicines for oral delivery of budesonide – Cell interactions





Encapsulation reduced BUD absorption, demonstrating its local action
Budesonide-CleavPEG NPs reduced CCL20/MIP3α levels

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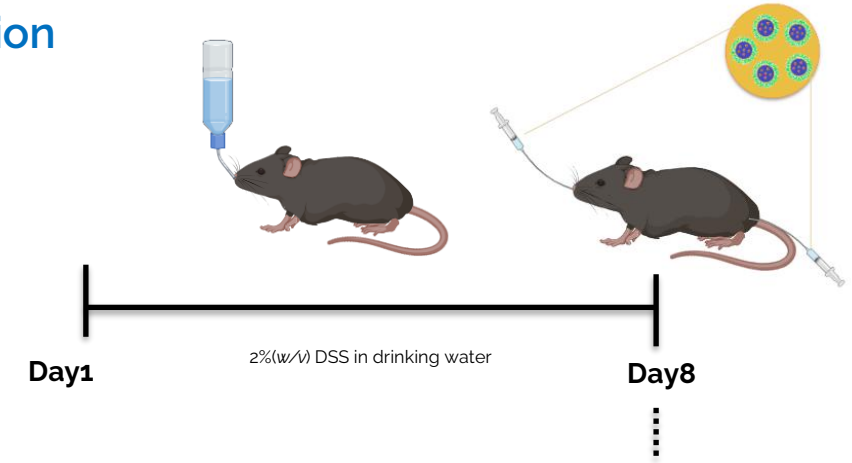
Stimulus-responsive nanomedicines for oral delivery of budesonide – In vivo distribution

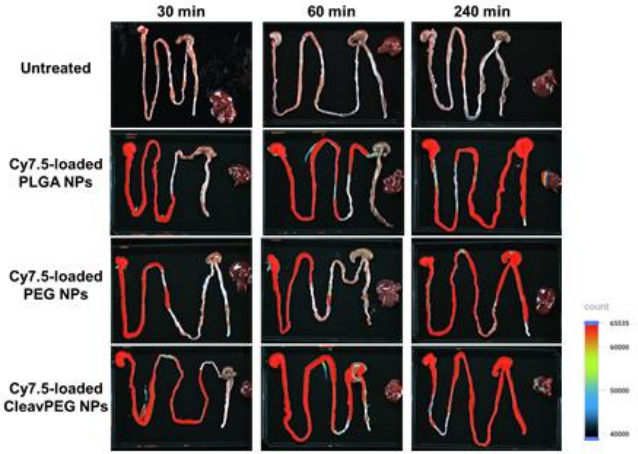


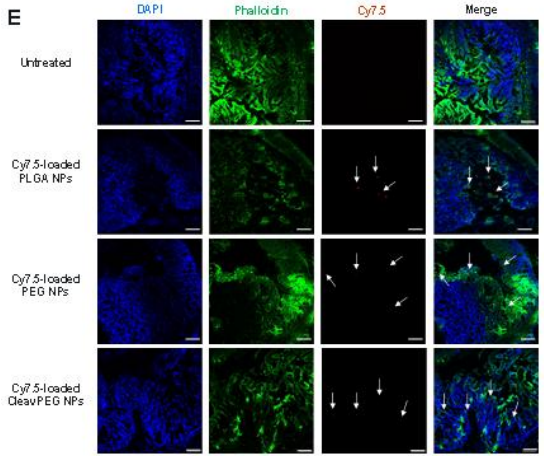
Dextran sodium sulfate - DSS

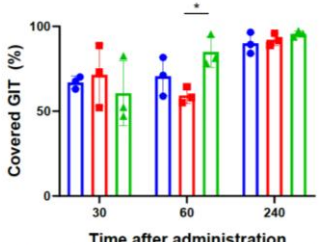
Cy7.5 – loaded NPs administration (orally or rectally)

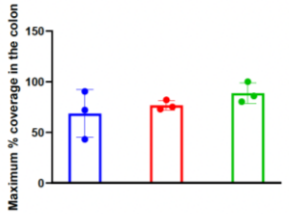
After 30, 60 and 240 min: Euthanasia; IVIS imaging and organ collection

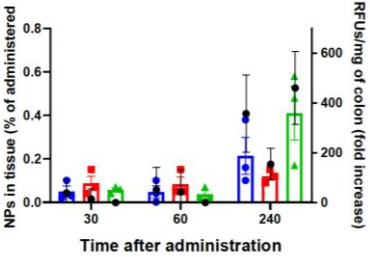
Stimulus-responsive nanomedicines for oral delivery of budesonide – In vivo distribution











CleavPEG NPs were more retained in inflamed colon

- PLGA NPs
- PEG NPs
- CleavPEG NPs

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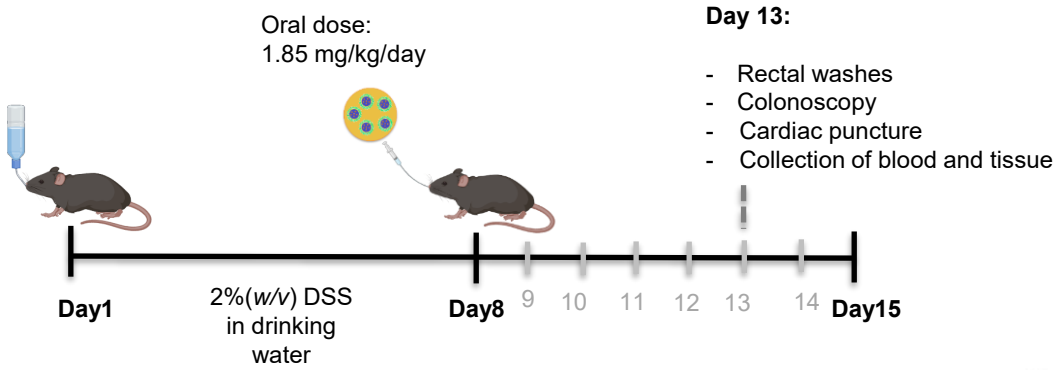
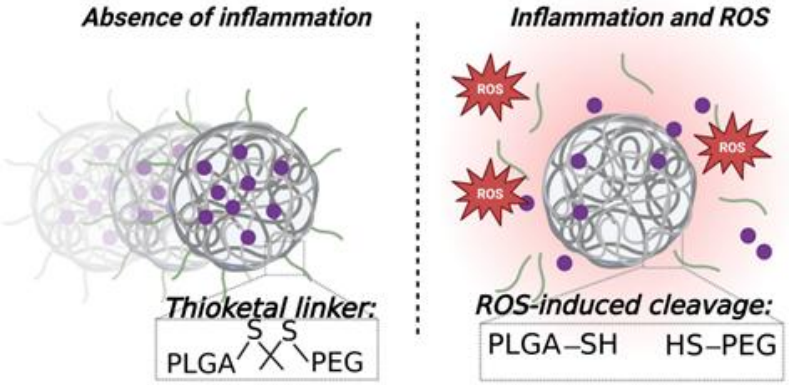
Stimulus-responsive nanomedicines for oral delivery of budesonide – In vivo efficacy

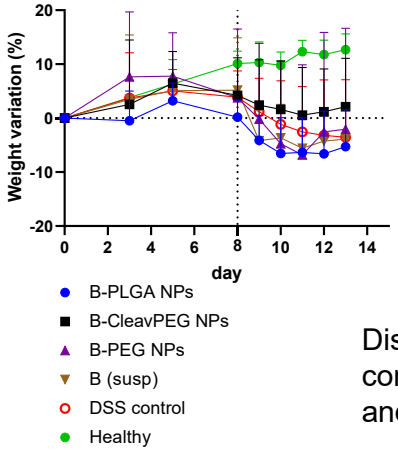


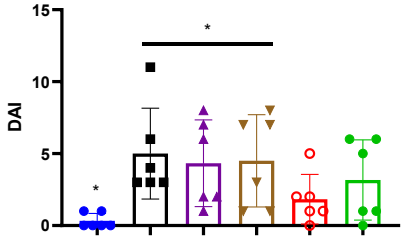
Treatment groups:

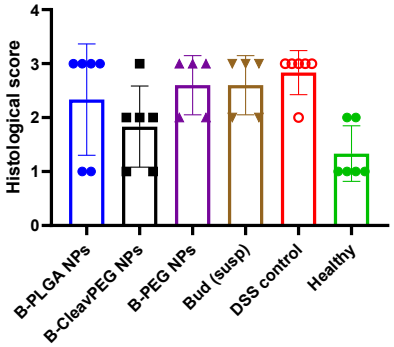
- Free BUD oral
- BUD-loaded PLGA NPs
- BUD-loaded mPEG-TK-PLGA:PLGA NPs
- BUD-loaded mPEG-PLGA NPs
- Healthy
- Non-treated disease



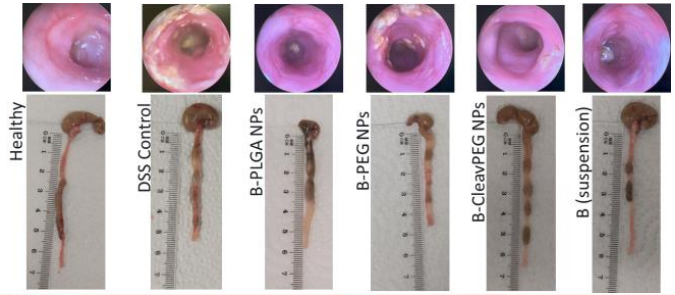
Stimulus-responsive nanomedicines for oral delivery of budesonide– In vivo efficacy







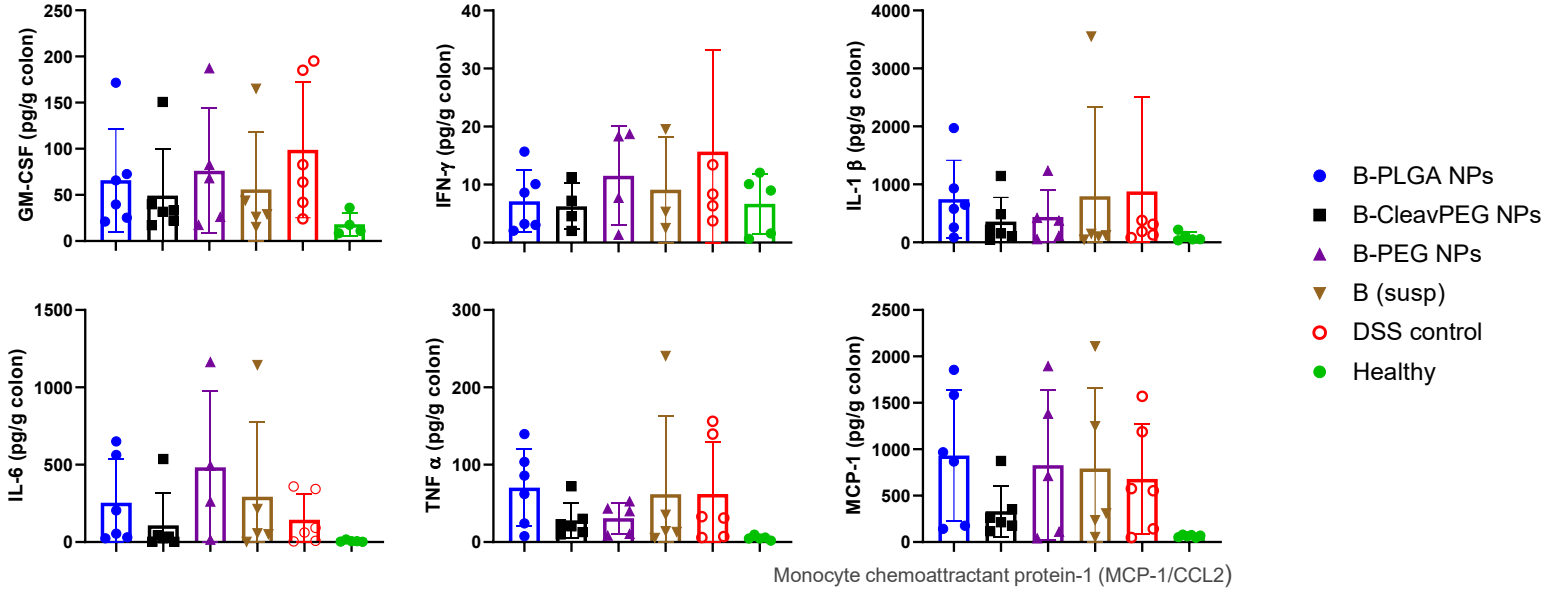
Disease activity index (DAI) on day 12, considering weight loss, stool consistency and presence of blood in feces



Bud-loaded CleavPEG NPs presented both DAI and histological scores similar to healthy animals

Cristelo *et al.* J Control Rel, 384, 113948, 2025

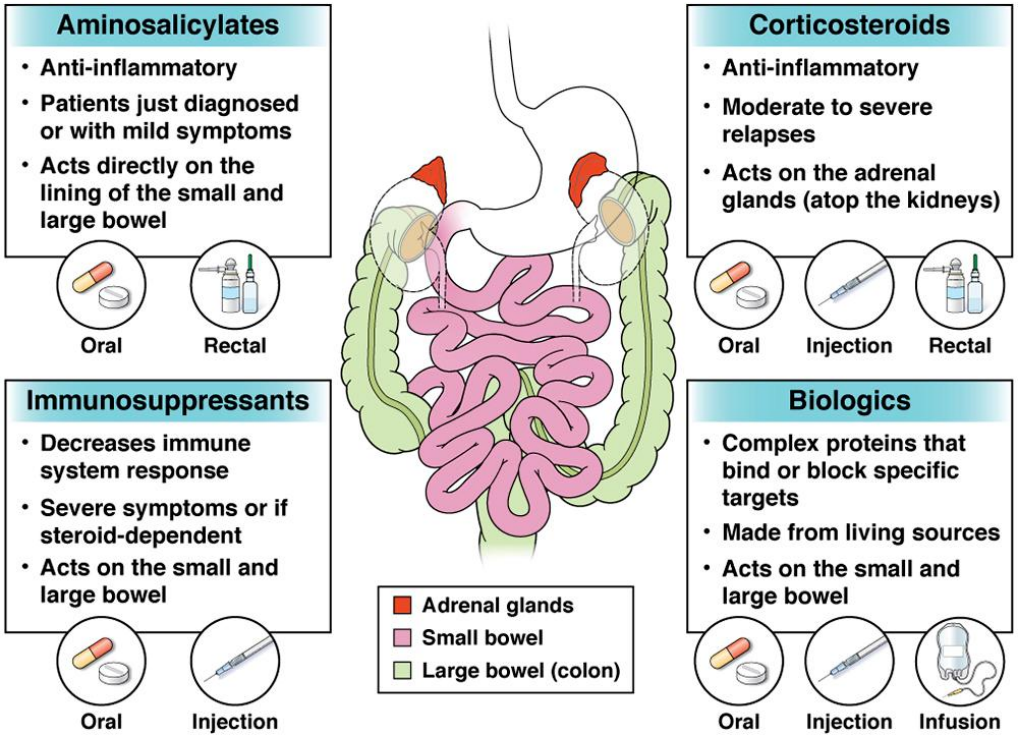
Stimulus-responsive nanomedicines for oral delivery of budesonide – In vivo efficacy



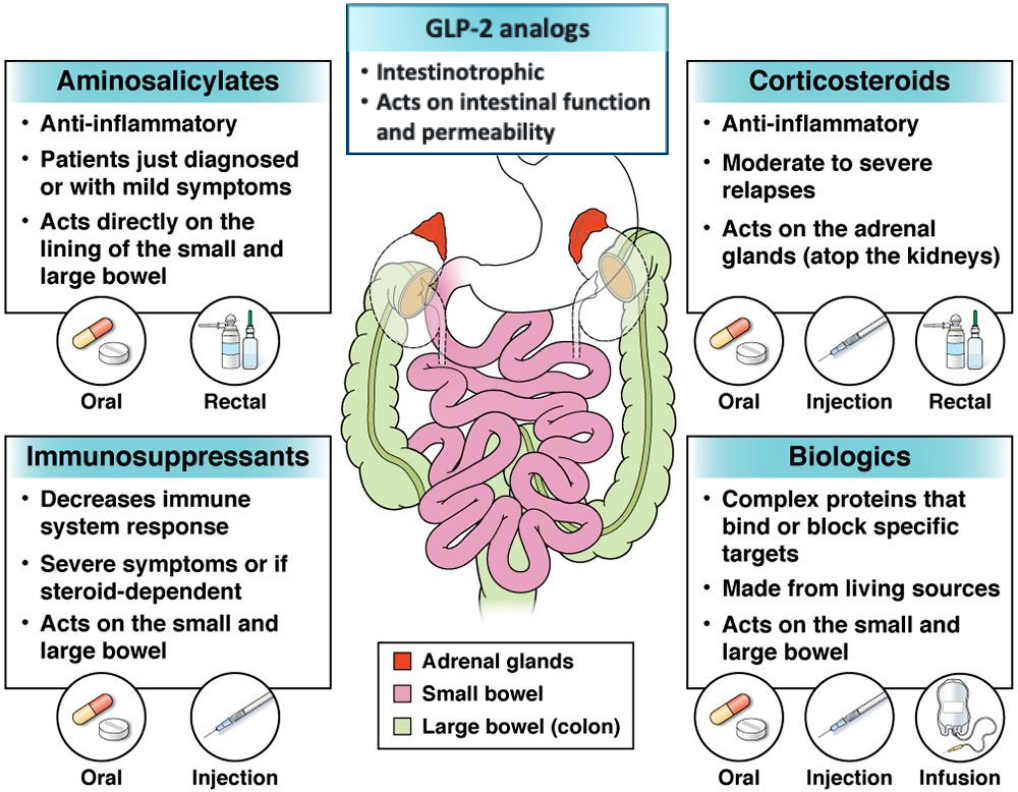
Bud-loaded CleavPEG NPs decreased inflammatory markers

Cristelo *et al.* J Control Rel, 384, 113948, 2025

Therapeutic toolkit for inflammatory bowel disease



Therapeutic toolkit for inflammatory bowel disease

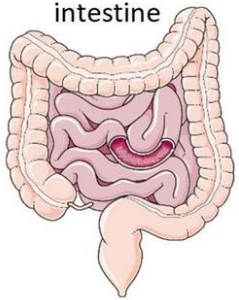


Therapeutic toolkit for inflammatory bowel disease

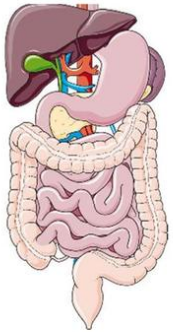
GLP-2 analogs

- Intestinotrophic
- Acts on intestinal function and permeability

Teduglutide
Glepaglutide
Apraglutide



GLP-2



gastrointestinal tract

Intestinotrophic actions

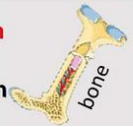
- ✓ ↑ cytoprotection & proliferation
- ✓ ↑ elongation of the enterocytes
- ✓ ↑ epithelial surface expansion

Gastrointestinal properties

- ✓ ↓ gastric acid secretion & ↓ gastric emptying
- ✓ ↑ intestinal & portal blood flow
- ✓ ↑ intestinal barrier function & ↓ intestinal permeability
- ✓ ↑ nutrient absorption

Bone metabolism

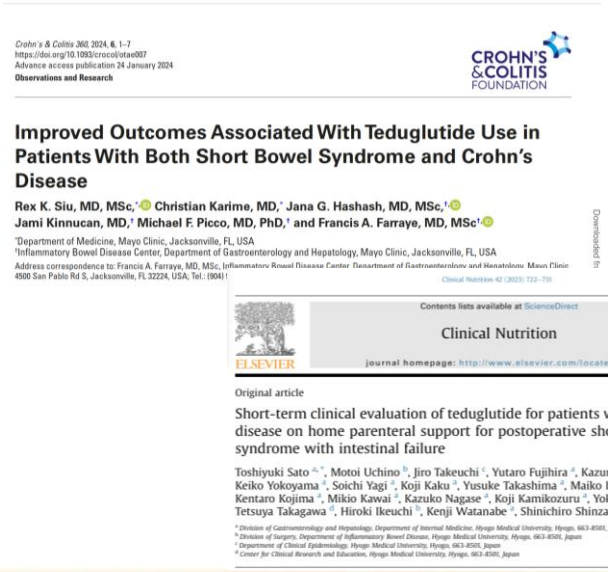
- ✓ ↓ bone resorption



Therapeutic toolkit for inflammatory bowel disease

Teduglutide is used in adults and children 1 year of age and older with short bowel syndrome (SBS)

Teduglutide



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Observations and Research

CROHN'S & COLITIS FOUNDATION

Improved Outcomes Associated With Teduglutide Use in Patients With Both Short Bowel Syndrome and Crohn's Disease

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Original article

Short-term clinical evaluation of teduglutide for patients with Crohn's disease on home parenteral support for postoperative short bowel syndrome with intestinal failure

Toshiyuki Sato [a, *], Motoi Uchino [b], Jiro Takeuchi [c], Yutaro Fujihira [a], Kazuma Shimizu [a], Keiko Yokoyama [a], Soichi Yagi [a], Koji Kaku [a], Yusuke Takashima [a], Maiko Ikenouchi [a], Kentaro Kojima [a], Mikio Kawai [a], Kazuko Nagase [a], Koji Kamikozuru [a], Yoko Yokoyama [a], Tetsuya Takagawa [d], Hiroki Ikeuchi [b], Kenji Watanabe [a], Shinichiro Shinzaki [a]

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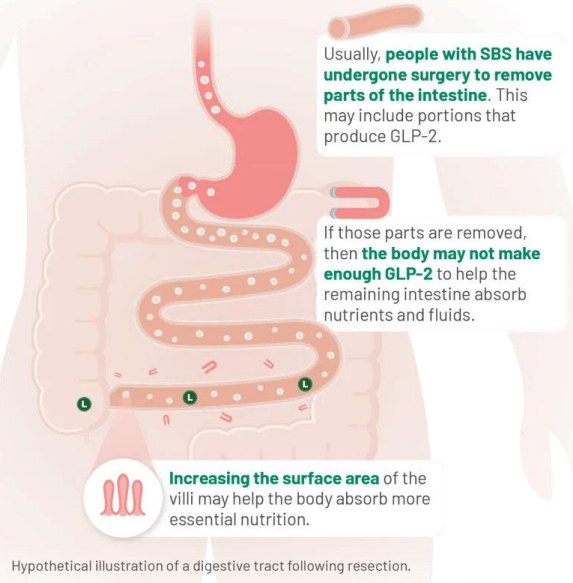
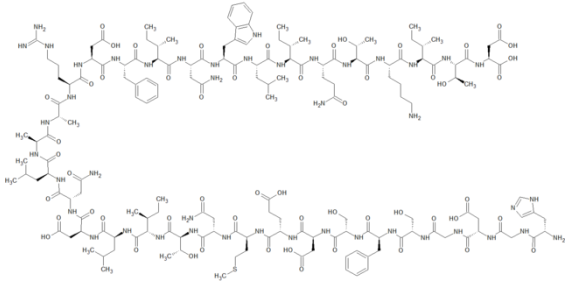
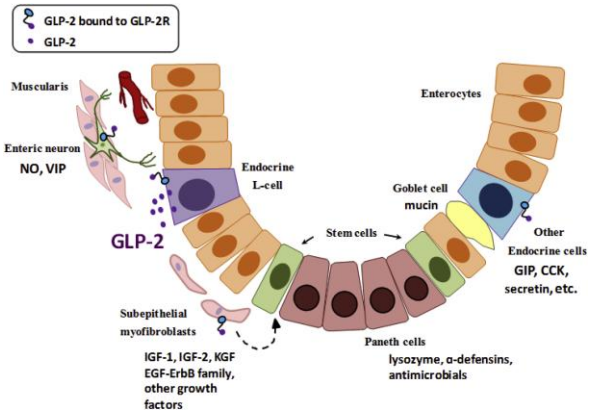


Hypothetical illustration of a digestive tract following resection.

Therapeutic toolkit for inflammatory bowel disease



Teduglutide



GLP-2 analog (33 aa) with higher half-time (from 7 min to 2-3h)

Intestinotrophic and anti-inflammatory properties

Increases intestinal absorption

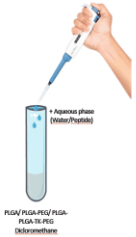
Enhances the intestinal barrier functions

Easily degradable

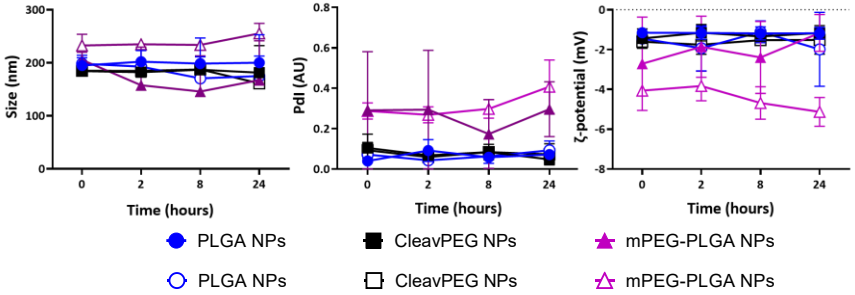
Injectable administration is inconvenient for patients

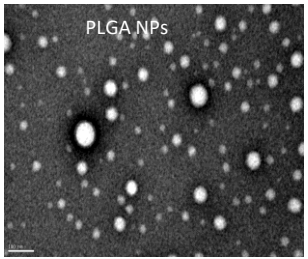
Low local concentration

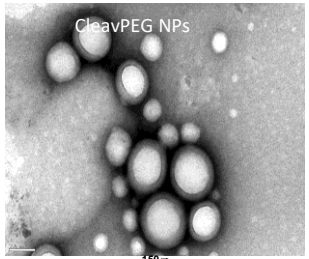
Stimulus-responsive nanomedicines for oral delivery of teduglutide

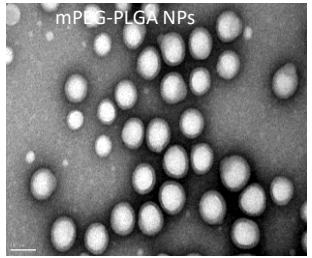


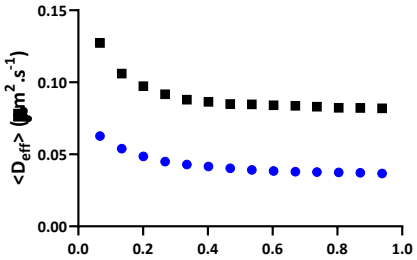
Samples	Size (nm)	PdI	ζ-potential (mV)	AE (%)	DL (%)
PLGA NPs	203 ± 5	0.113 ± 0.042	-1.0 ± 0.5	---	---
mPEG-PLGA NPs	194 ± 7	0.125 ± 0.029	-1.6 ± 0.2	---	---
CleavPEG NPs	205 ± 5	0.097 ± 0.041	-0.9 ± 0.3	---	---
TED-loaded CleavPEG NPs	222 ± 4	0.217 ± 0.036	-0.8 ± 0.3	71 ± 14	7.1 ± 1.4

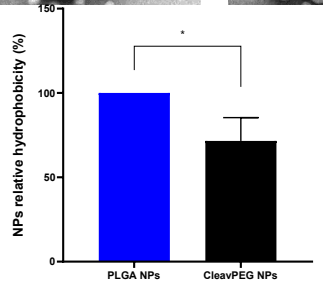






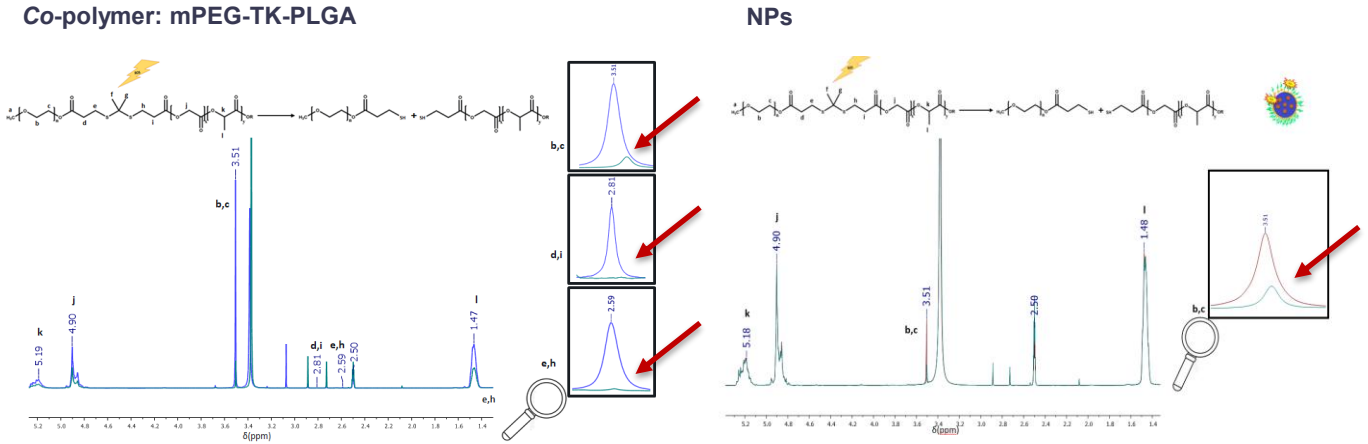






Barros *et al*. Small 20, 2402502, 2024

ROS-responsive profile



Absence of the TK characteristic ^{1}H NMR peak after ROS exposure

Decrease of PEG characteristic ^{1}H NMR peaks after ROS exposure

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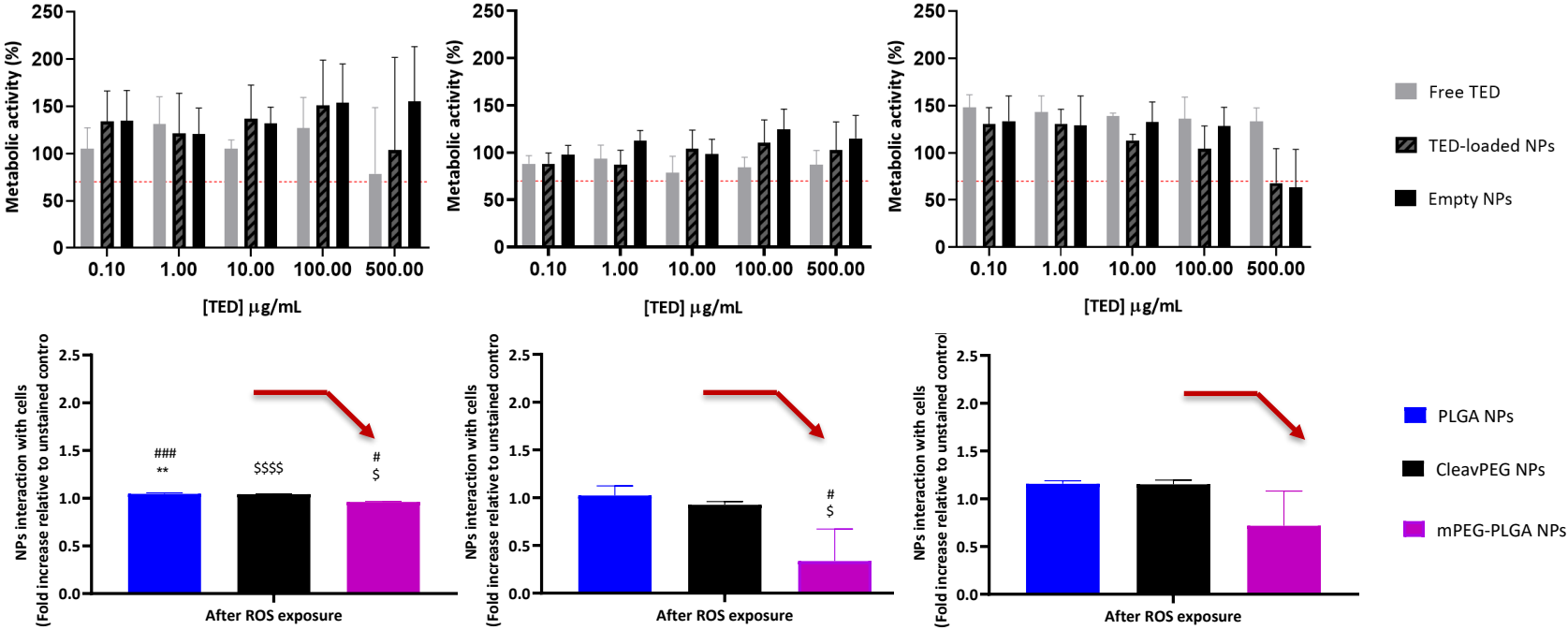
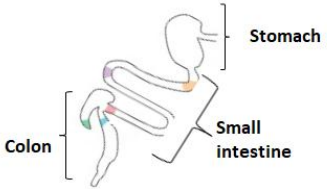
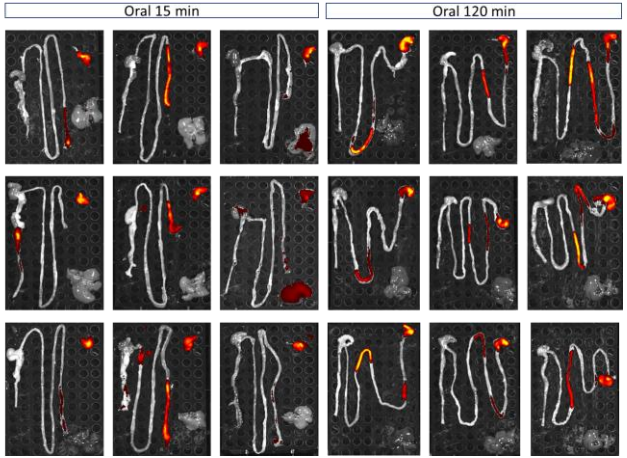
Interaction of NPs with cells

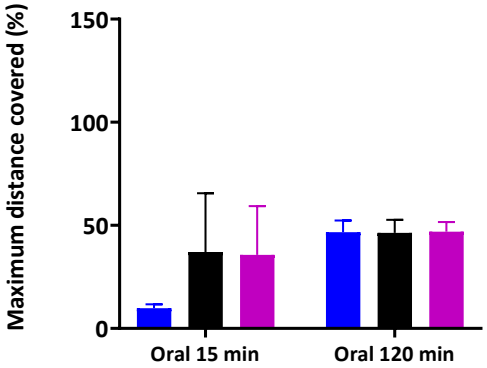


ROS-sensitive NPs have a higher interaction profile with cells than PEGylated NPs, after ROS exposure

In vivo oral biodistribution

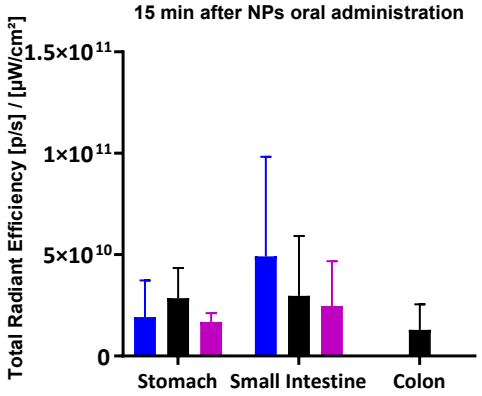


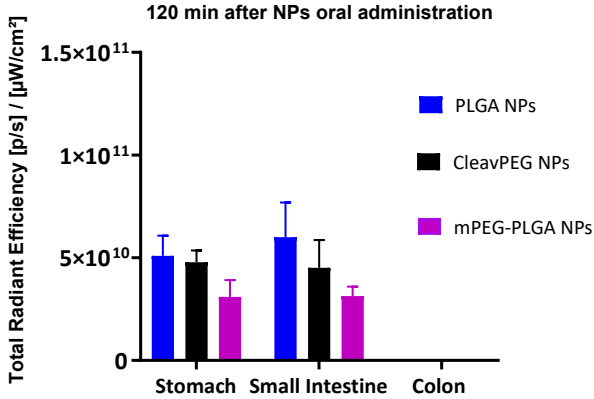




Cy7.5 – loaded NPs administration (orally or rectally)

After 15 and 120 min: Euthanasia; IVIS imaging and organ collection





ROS-responsive NPs reached the target (inflamed colon) after 15 min of oral administration

PEGylated NPs have a higher GIT covered area compared to PLGA NPs

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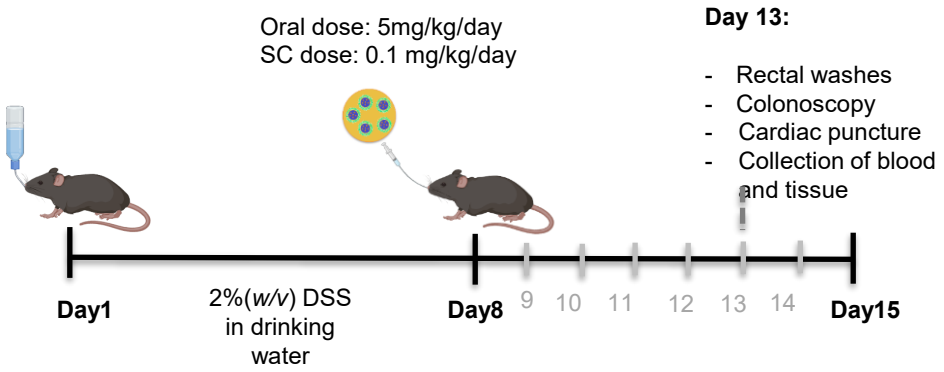
In vivo efficacy

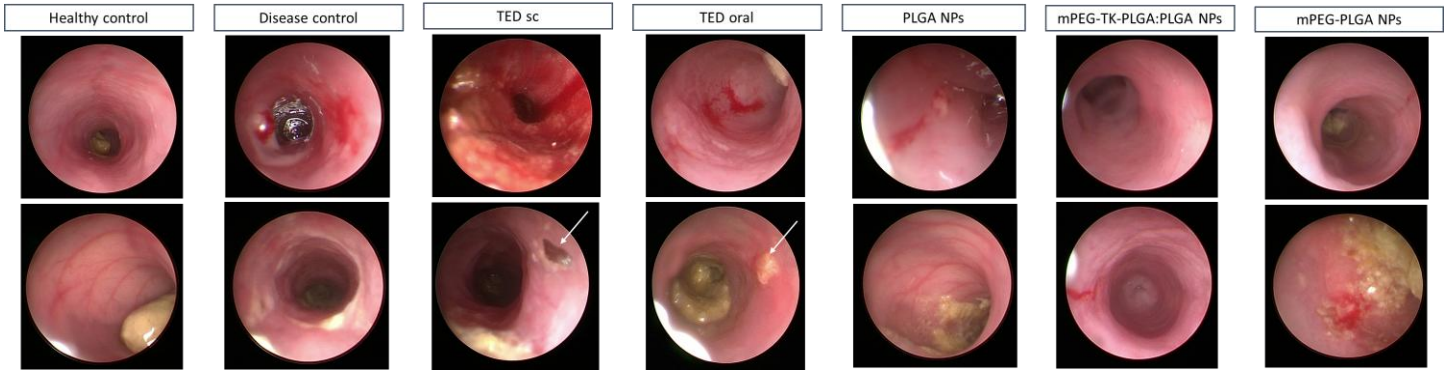


Treatment groups:

- Free TED oral
- Free TED sc
- TED-loaded PLGA NPs
- TED-loaded mPEG-TK-PLGA:PLGA NPs
- TED-loaded mPEG-PLGA NPs
- Healthy
- Non-treated disease

In vivo efficacy

Colonoscopy evaluation



TED-loaded NPs resulted in better recover scores compared to free TED, both oral and s.c.

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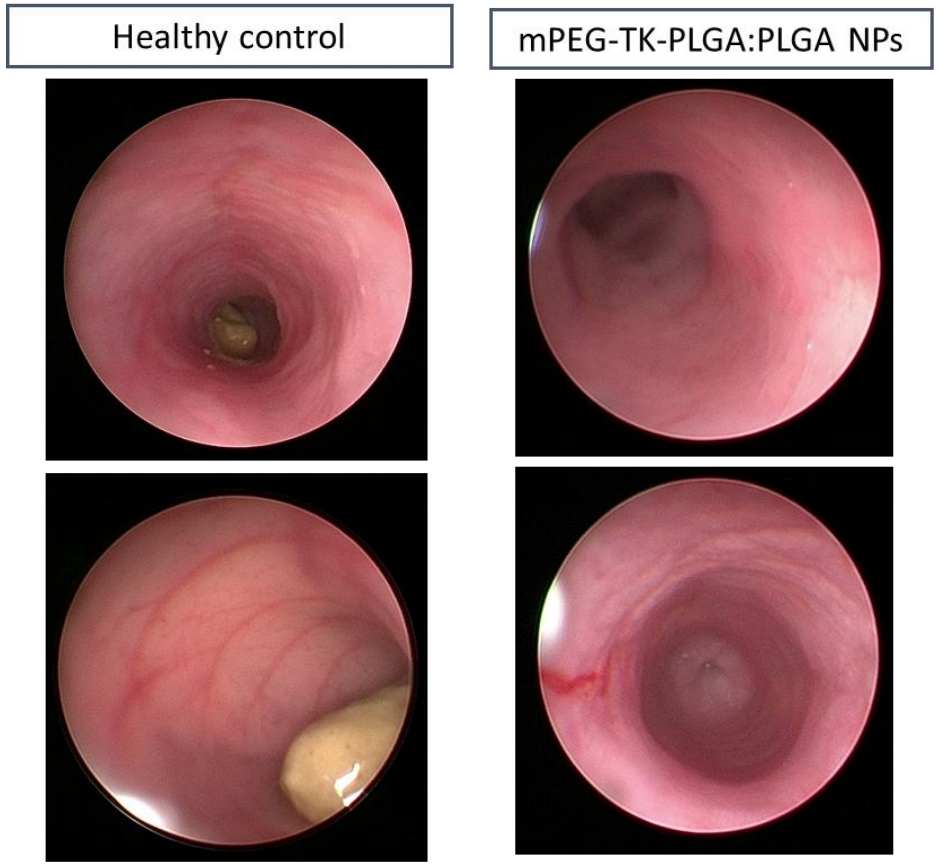
In vivo efficacy

Colonoscopy evaluation



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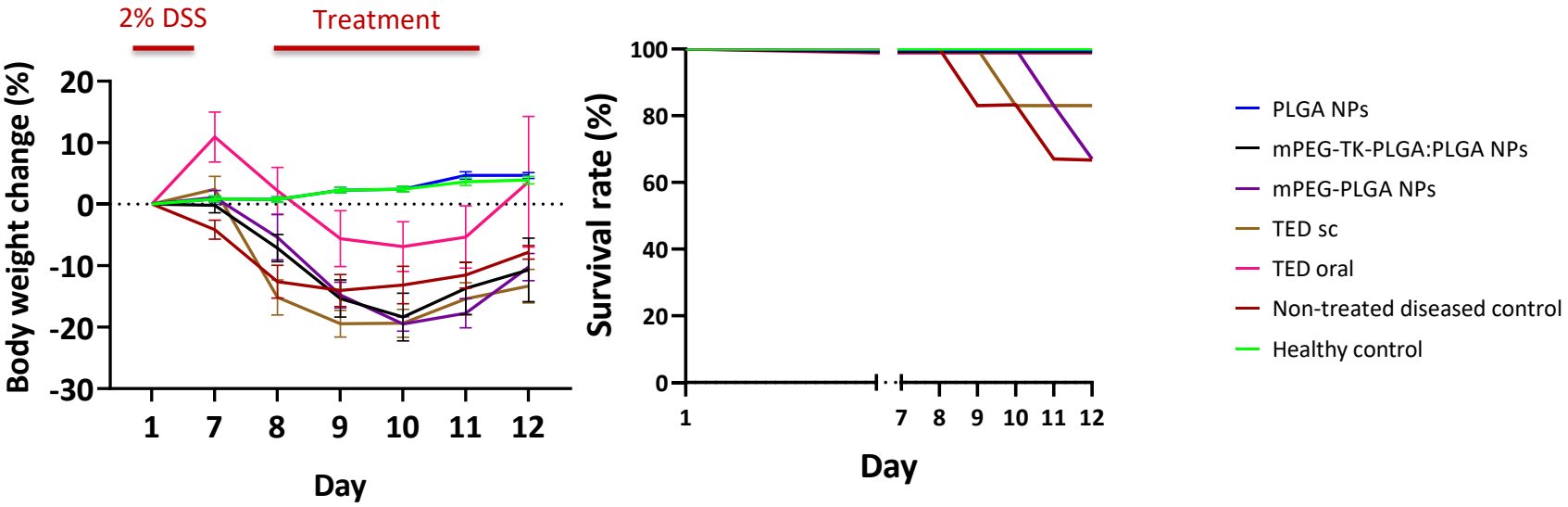
In vivo efficacy



Body weight decrease after DSS treatment and an increase with TED treatment

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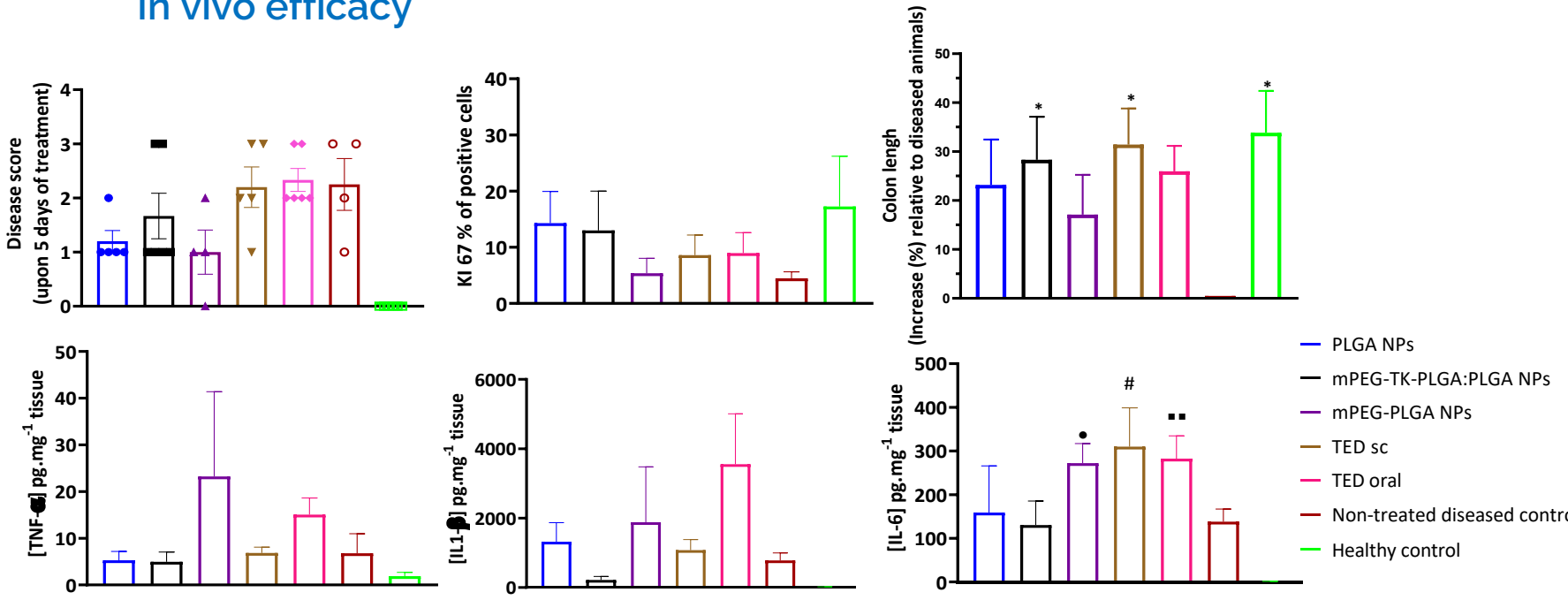
In vivo efficacy



ROS-responsive NPs decreased inflammatory markers and promote mucosal healing

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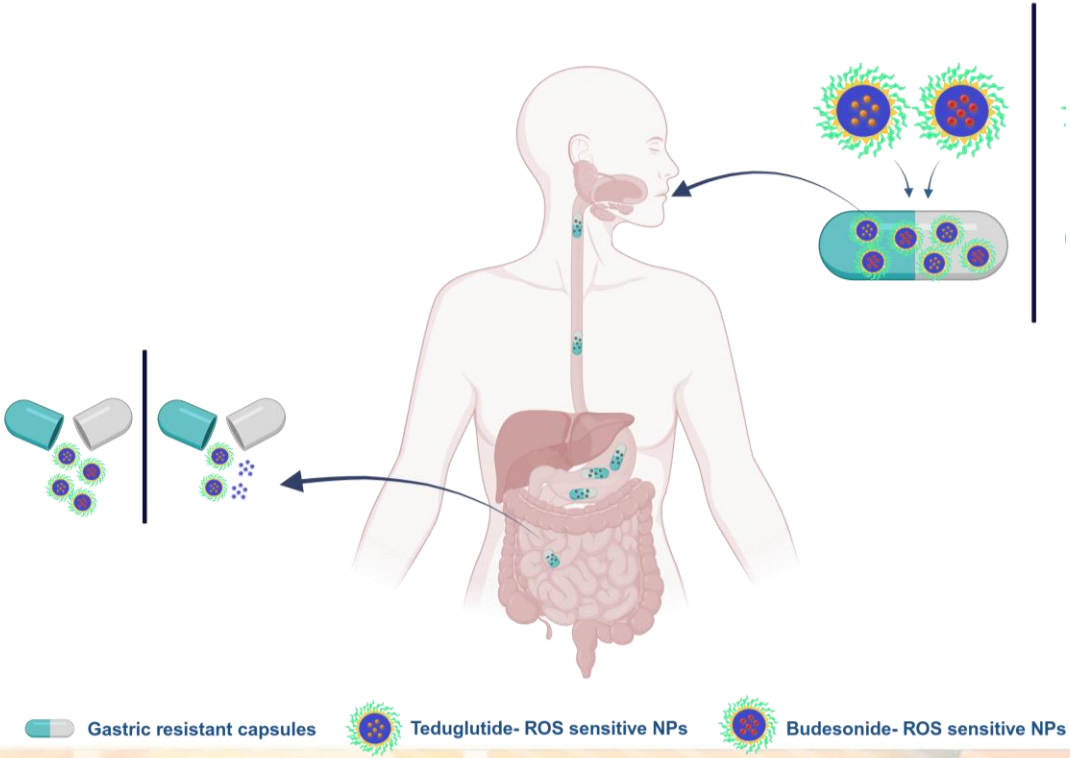
ROS-based stimulus-responsive nanomedicines – on going work



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