

The *in vivo* effects of permeation enhancers on the epithelial transport and bioavailability of the Proteolysis Targeting Chimera (PROTAC) ARV-471

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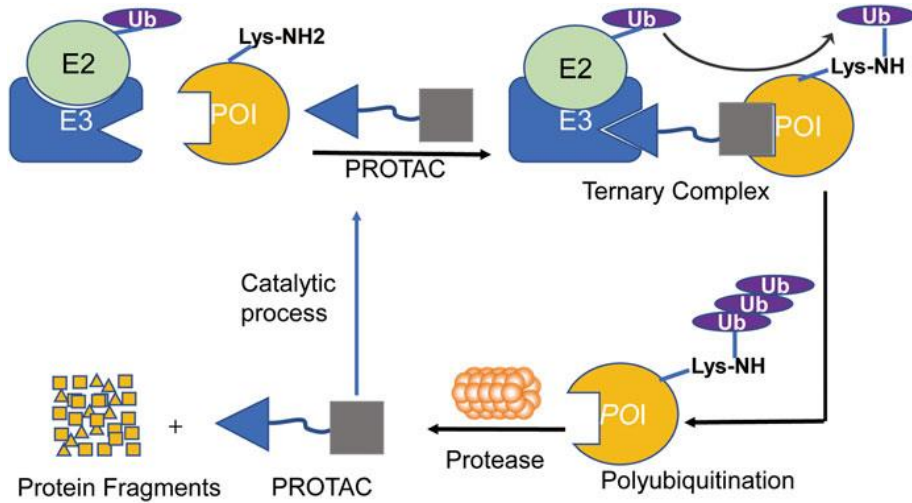


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PROTACs – Emerging therapeutic modality with limitations



PROTAC Promise – Unique Pharmacology

Drug the undruggable (expanding treatment possibilities)

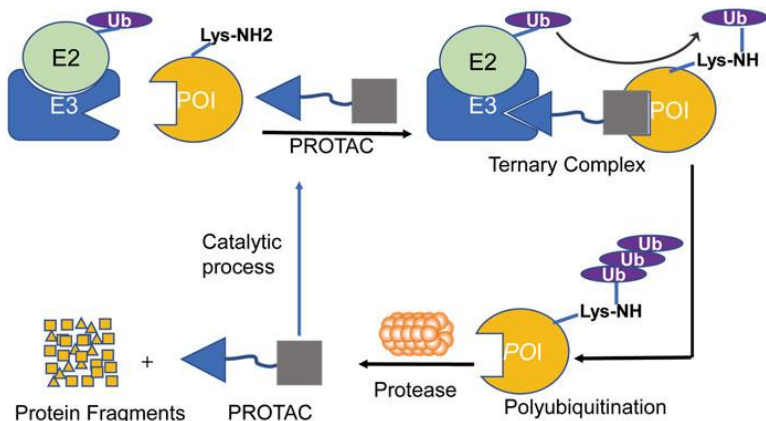
Overcoming resistances due to target point mutations

Reaching intracellular targets

Catalytic mode of action (1 molecule catalyzes > 1 protein degradation)

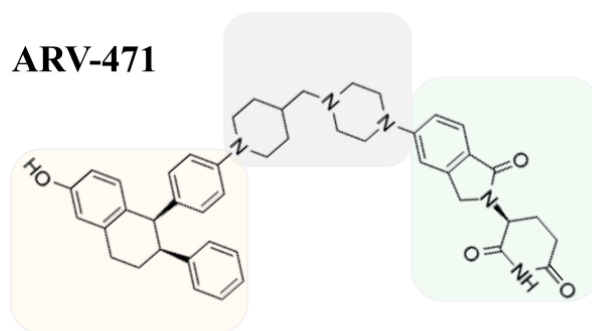
Elimination of entire protein incl pathogenic functions

PROTACs – Emerging therapeutic modality with limitations



ARV-471

ARV-471



Molecular Mass	724 Da
cLogP / chromLogD	6.8 / 5.3
tPSA / ePSA [Å ²]	96 / 146
HBA / eHBA	9 / 9
HBD / eHBD	2 / 2
RotB/eRotB	7 / 7
pKa	4.6, 8.5

Schade et al., 2024

PROTAC Promise – Unique Pharmacology

Major therapeutic potential across many indications: Unique, catalytic pharmacology that vastly expands the druggable proteome while enabling highly selective, sustained target degradation at low doses.

PROTAC Challenges – Clinical Translation

“Beyond rule of five” molecules: Implies **poor intestinal absorption & oral bioavailability** (BCS II or IV)

Poor mass balance recovery in standard *in vitro* assays

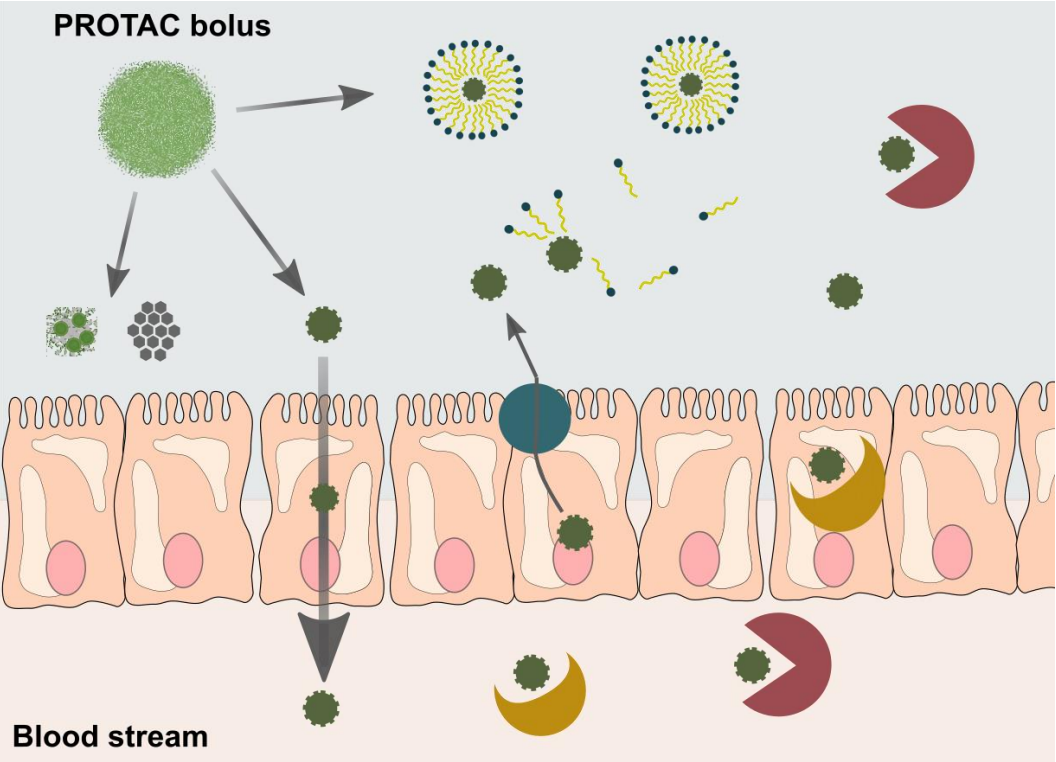
Often strong mismatch between *in silico/in vitro* predictions and *in vivo* outcomes

Poor understanding of intestinal absorption mechanisms complicates formulation development

PROTACs – What is governing PROTAC intestinal absorption?



Characterization



ARV-471

	LOW			HIGH
Dissolution/solubility:				
Permeability:				
Efflux:				
Luminal stability:				
First-pass stability:				
Bile excretion:				

Main absorption and bioavailability limitations

Aqueous amorphous solubility pH 6.8: 3.26 µg/mL

FaSSIF amorphous solubility pH 6.8: 19.9 µg/mL

Rat effective intestinal permeability: 0.23×10^{-4} cm/s

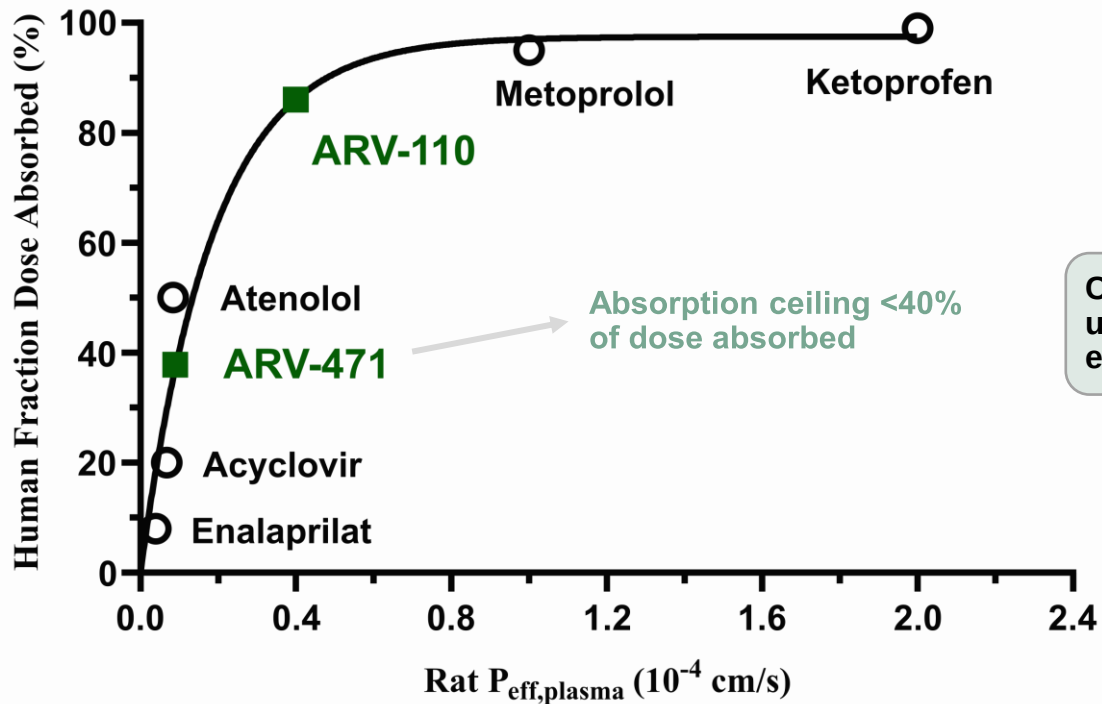
PROTACs – Overcoming the absorption limitation



Formulation

What could be the human f_{abs} potential of PROTACs based on their P_{eff} ?

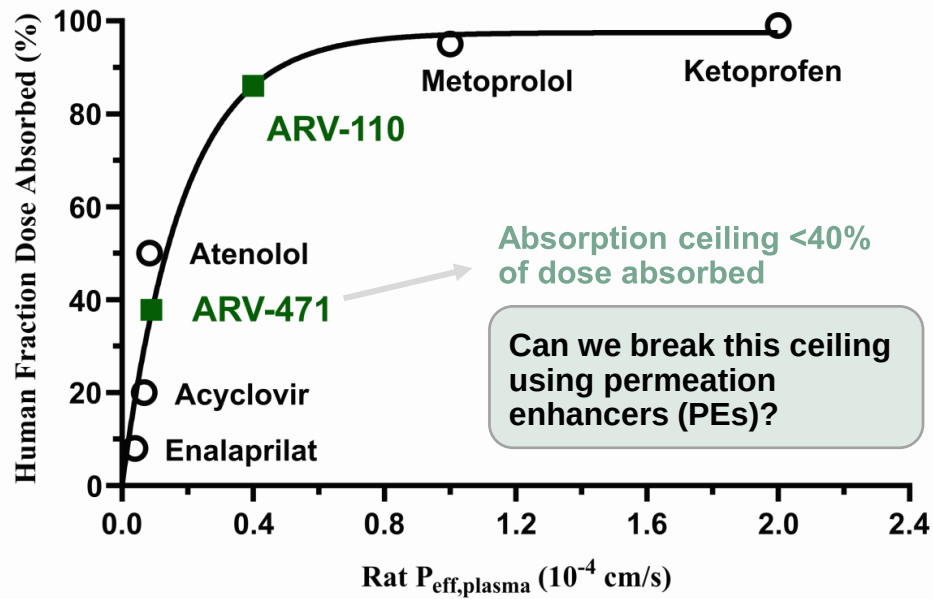
- Based on P_{eff} values generated in the same lab with the same method, assuming complete dissolution



PROTACs – Permeation enhancers (PEs) to boost *in vivo* intestinal absorption



Formulation

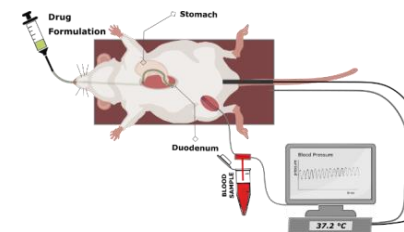


Permeation enhancers

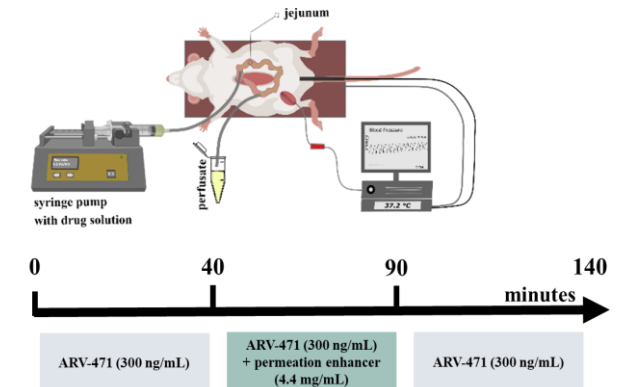


Rat *in vivo* study toolbox

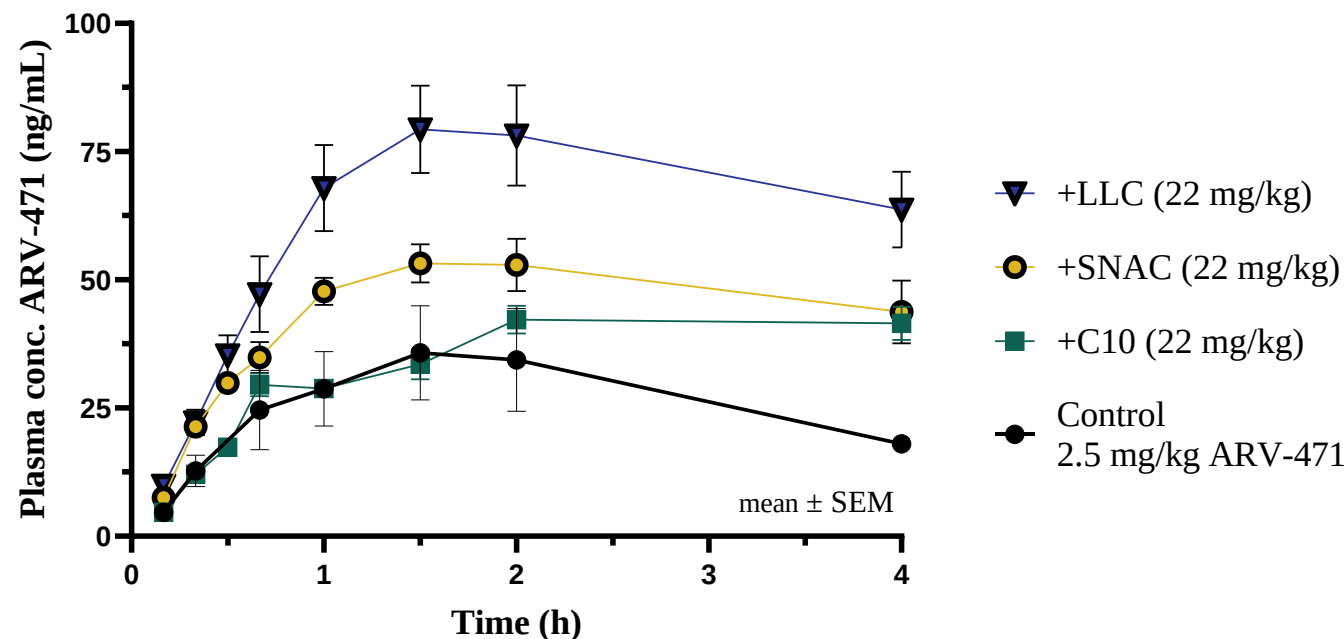
Intraduodenal bolus



Single pass intestinal perfusions (SPIP)



Effect of PEs on plasma exposure and absorptive flux of ARV-471



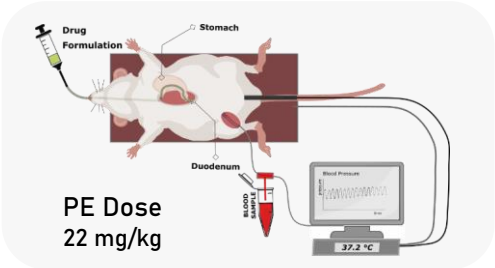
parameter	control	+ permeation enhancer		
	ARV-471 (2.5 mg/kg)	+ sodium caprate	+ SNAC	+ lauroyl-L-carnitine
$f_{abs\ 0-4h}$	0.10 ± 0.05	0.14 ± 0.02	0.17 ± 0.04	$0.25 \pm 0.08^{***}$
$J_{0-60min}$ (µg/min)	0.43 ± 0.28	0.44 ± 0.05	$0.72 \pm 0.14^*$	$0.90 \pm 0.25^{**}$



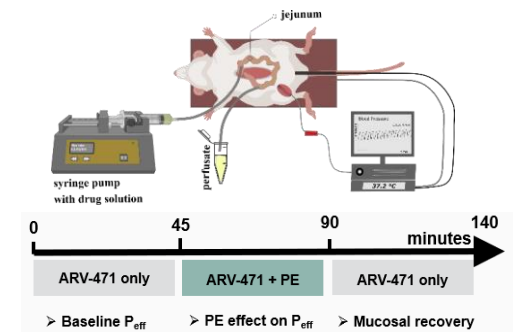
Key findings:

- Permeation enhancers increase systemic plasma exposure (AUC_{0-4h}) and absorption (C_{max}) of PROTACs
- Strong increase in **absorptive flux (J)** and **fraction of dose absorbed (f_{abs})**:
- **SNAC ($J \uparrow 67\%$ and $f_{abs} \uparrow 71\%$)** and **LLC ($J \uparrow 150\%$ and $f_{abs} \uparrow 109\%$)**

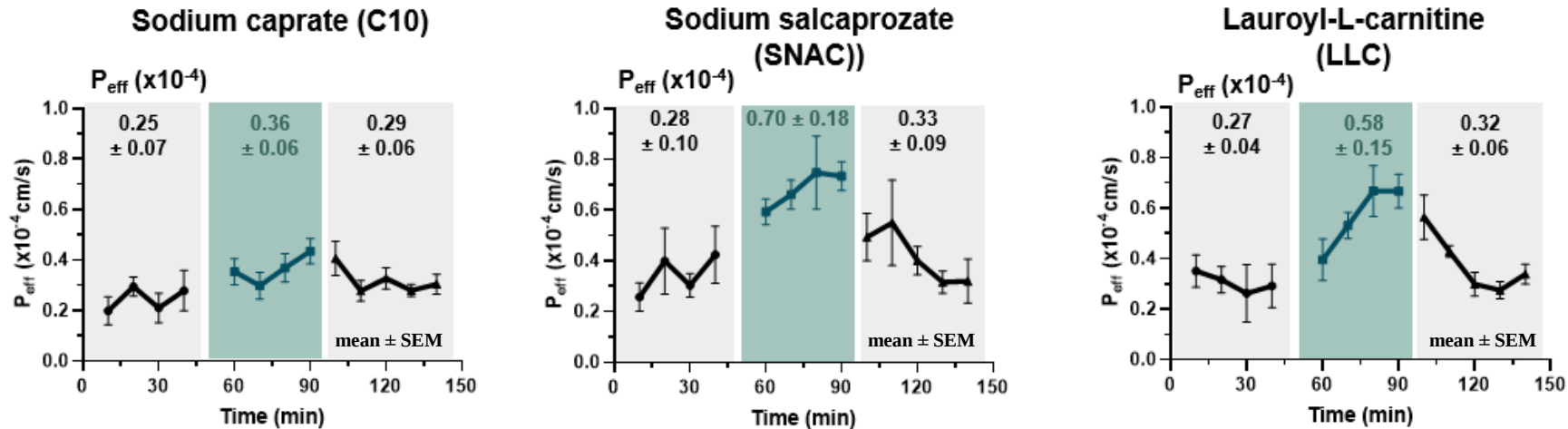
i.d. bolus studies



Effect of PEs on effective intestinal permeability (P_{eff})



Single pass intestinal perfusions (SPIP):



Membrane effects of PEs

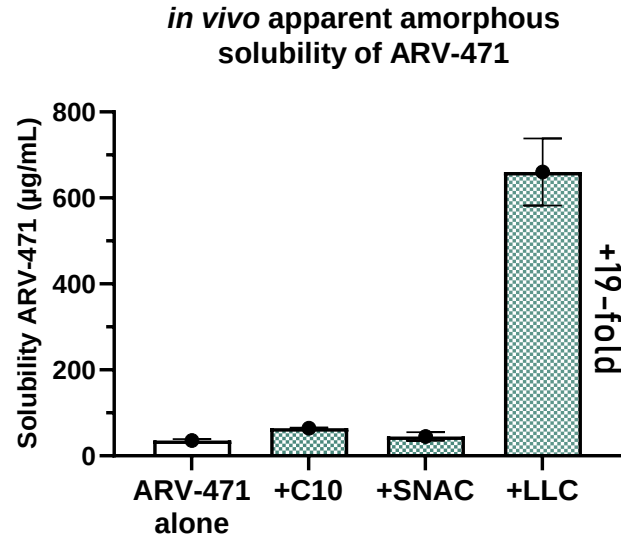
- C10: $\leftrightarrow$ 50% increase in P_{eff} , fast recovery
- SNAC: $\uparrow$ 150% increase in P_{eff} , 10-20 min recovery
- LLC: $\uparrow$ 120% increase in P_{eff} , 10-20 min recovery

Key findings:

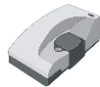
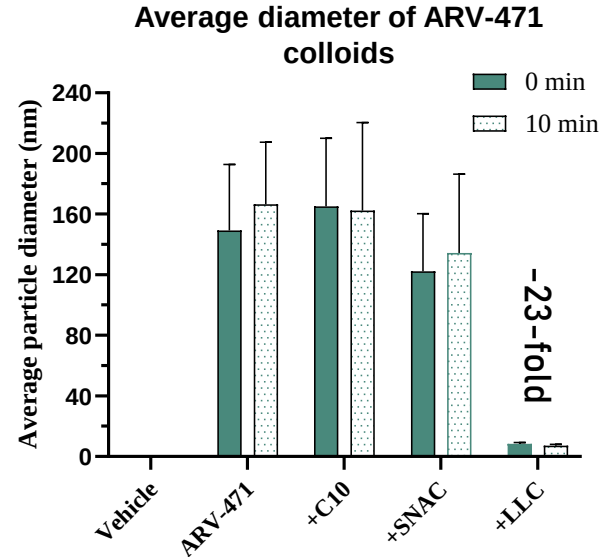
SNAC & LLC induce substantial membrane effect to increase absorptive flux

Effect of PEs on solubilization and colloidal dynamics

Solubilization effect of PEs on PROTACs *in vivo*:



Ultracentrifugation



Dynamic Light Scattering

Key findings:

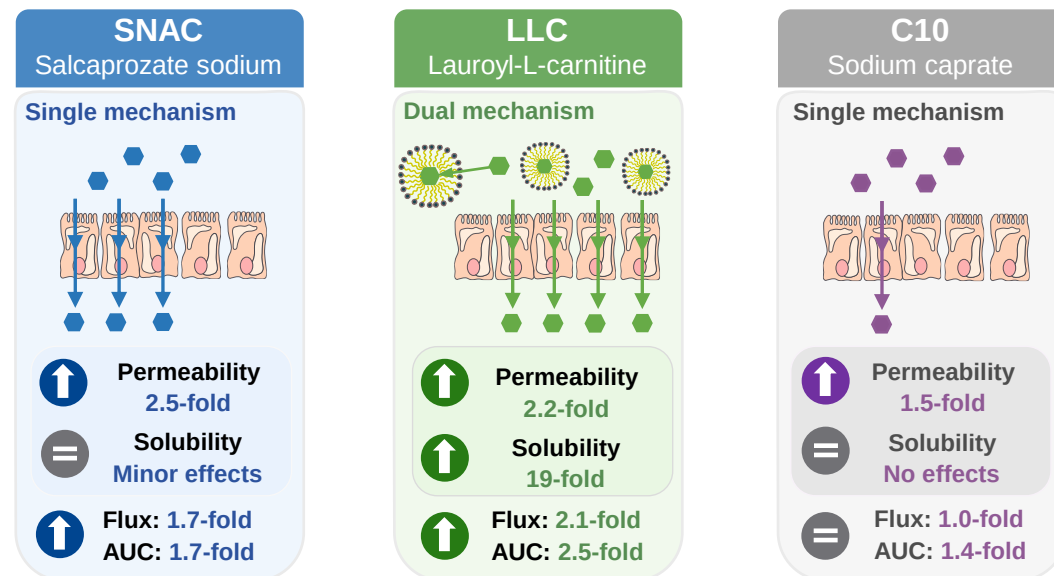
LLC massively impacts **solubilization** and luminal colloidal dynamics of ARV-471: **enhanced colloid transport across ABL**

Solubilization effects of PEs

- C10 & SNAC: Minimal increase in solubility, no effect on colloidal size
- LLC: **19-fold** increase in solubility, decrease in colloid size from 167 to 7 nm

Key take-aways – PEs as promising formulation strategy for PROTACs

- **Enhanced intestinal absorption by 40 – 150%** for the poorly permeable, poorly soluble PROTAC ARV-471
- Enhancement through two mechanisms:
 - Direct membrane effect ($\uparrow P_{\text{eff}}$) – SNAC & LLC**
 - Solubilization effects ($\uparrow$ solubility, $\downarrow$ colloid size) – LLC**
- **LLC promising PE for BCS class IV PROTACs via dual mechanism** (potent membrane interaction + low CMC)
- Choice of PE for formulation depends on the absorption-limiting process at clinically relevant doses



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