Intestinal 3D models to assess nanomaterial toxicity *in vitro*

For the uptake of engineered nanomaterials (ENM) the intestine is one of the main exposure routes to consider. Whereas it was long neglected in its role as entrance site and possible target organ for ENM, research efforts have increased recently.

In PATROLS two advanced *in vitro* systems were developed to represent different characteristics of the human intestinal tract (Figure 1). One model incorporates immuno-competent cells and can mimic the intestine in healthy or inflamed-like state. It is especially suitable to study the effects of impaired health on (nanomaterial) toxicity. The second model focuses on their inclusion of specialized cells for the uptake of macromolecules and particles, and is therefore particularly suitable to investigate the uptake of nanomaterials.

Outcome 1: Using these models, it was demonstrated that complex multi-cell type cultures are more robust towards the exposure to ENM than typically used enterocyte monocultures and show promising similarity to the outcomes from *in vivo* feeding studies. (Kämpfer et al., 2021; DOI 10.1002/smll.202004223)

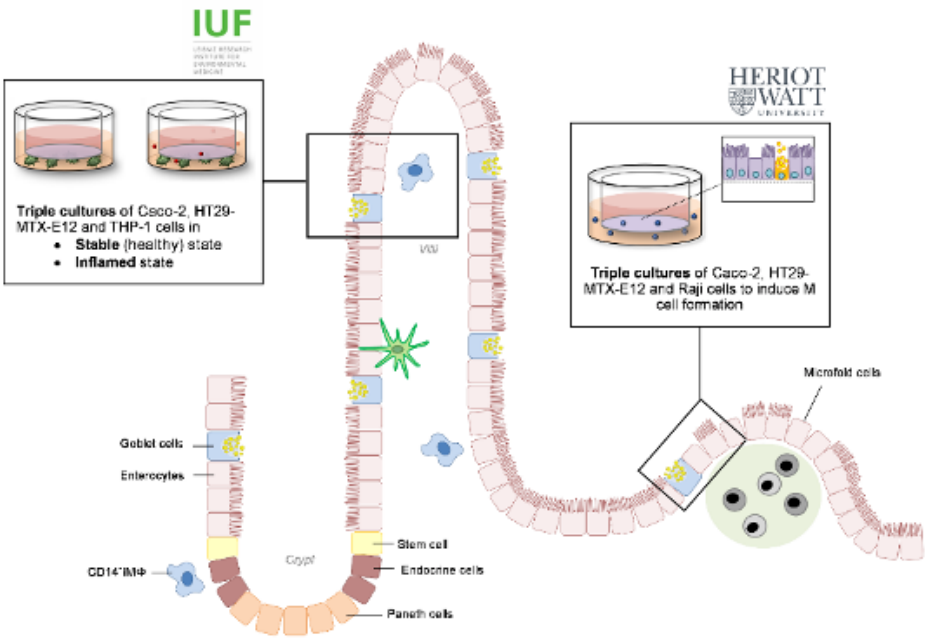

Figure 1. Schematic description of the intestinal *in vitro* models developed within PATROLS (adapted from Kämpfer et al, 2020; DOI 10.1021/acs.chemrestox.0c00079)

Outcome 2: It was shown again that impaired tissue integrity induced by an inflammation-like state can influence the effects of ENM in the intestinal *in vitro* model. This observation may suggest that individuals suffering from inflammatory health conditions involving the intestine, e.g. Crohn's disease or ulcerative colitis, could face a different risk from ingested ENM. (Kämpfer et al., 2021; DOI 10.1002/smll.202004223)

Outcome 3: The M cell model have been shown to be more sensitive to ENM and can translocate particulate substances more than the enterocyte monocultures. Therefore, our model may be more suitable for ENM toxicity and translocation studies than the enterocyte monocultures.

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