# Interactions of Oral Molecular Excipients with Breast Cancer Resistance Protein, BCRP

**Ling Zou** (ling.zou@ucsf.edu), Joshua Pottel, Natalia Khuri, Huy X. Ngo, Mark S. Warren, Yong Huang, Brian K. Shoichet, Kathleen M. Giacomini

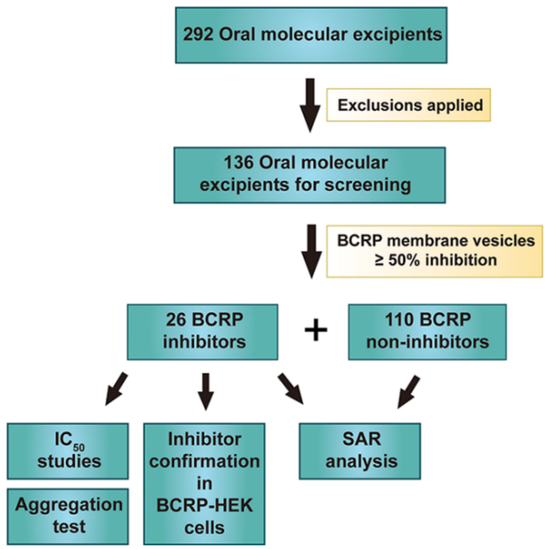
University of California San Francisco

## BACKGROUND

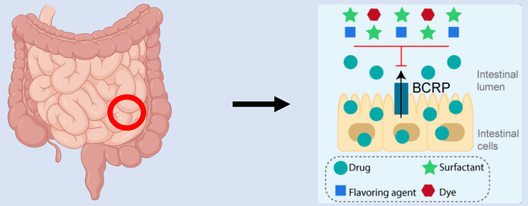
- Molecular excipients are a major component of oral drug products, yet their effects on enzymes and transporters involved in drug absorption and disposition have been poorly characterized.
- BCRP plays a critical role in drug absorption with potential implications for drug safety and efficacy.
- **Goal**: Investigate the effects of molecular excipients present in orally administered FDA-approved drug products on the intestinal efflux transporter, BCRP (ABCG2).

## METHODS

**Figure 1**. Experimental design.

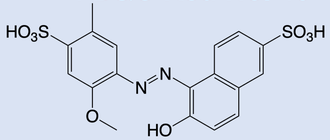



- **Intestinal transporters may be the targets for some formulation-dependent drug interactions.**




- **Most excipients tested in vitro are not expected to inhibit BCRP at concentrations hypothesized to be achieved in the intestine following single oral doses of therapeutic medications.**
- **However, some excipients, particularly food dyes, which are present in dosage formulations and processed foods, may inhibit BCRP clinically, potentially increasing the oral bioavailability of some drugs. Because of their higher intake of processed foods, especially candies, children may be at higher risk for potential excipient-drug interactions.**

**FD&C Red No. 40**




Adults

[I] / $IC_{50\text{-}BCRP}$: 1.58

Higher risks?

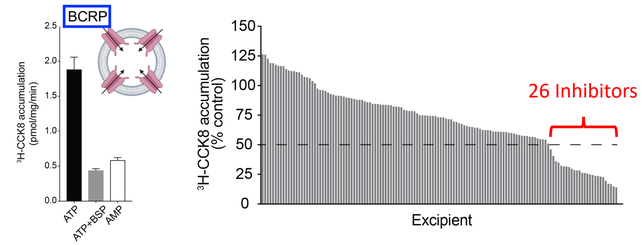
Children

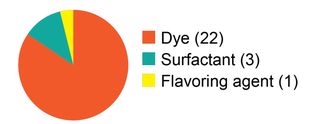
[I] / $IC_{50\text{-}BCRP}$: **4 - 16**

We acknowledge that this publication was made possible by Grant U01FD004979/ U01FD005978 from the US Food and Drug Administration (FDA), which supports the University of California, San Francisco–Stanford Center of Excellence in Regulatory Sciences and Innovation (UCSF-Stanford CERSI).

## RESULTS

**Figure 2**. Identification of oral molecular excipients as inhibitors of BCRP in membrane vesicles.




85% of BCRP-inhibiting excipients were dyes

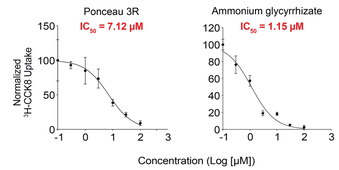


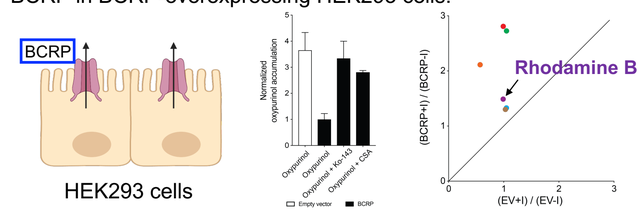

**Table 1**. Estimated Daily Intake and Intestinal Concentrations of Dyes for the US Population.

| Excipient | EDI (μg/kg/day) | [I] (μM) | $IC_{50\text{-}BCRP}$ (μM) | [I] / $IC_{50\text{-}BCRP}$ |
|---|---|---|---|---|
| FD&C Red 40 | 11.2 | 6.97 | 4.42 | 1.58 |
| FD&C Yellow 5 | 5.1 | 3.07 | 5.61 | 0.55 |
| FD&C Blue 1 | 2.1 | 0.79 | 1.97 | 0.40 |

EDI: Estimated daily intake for the US population (the mean of the maximum use level)
[I]: Estimated intestinal concentration

The EDI of FD&C Red 40 for children between 2 and 5 years old is about **3−10 times** greater than the EDI for adults.

**Figure 3**. Identification of oral molecular excipients as inhibitors of BCRP in BCRP-overexpressing HEK293 cells.




**Only Rhodamine B inhibited BCRP-mediated $^3$H-oxypurinol uptake by more than 50%.**