



平成18年度 日本薬物動態学会「奨励賞」

トランスポーター・アダプター分子群
による薬物動態制御

**Drug Disposition Governed by Transporters and
Adaptors**

加藤 将夫

Yukio Kato, Ph.D.

金沢大学大学院自然科学研究科(薬学系)

Kanazawa University

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Kanazawa University (2002~present)

Akira Tsuji, Ph.D

Yoshiyuki Kubo, Ph.D

Yoshimichi Sai, Ph.D
(Kyoritsu Univ of Pharmacy)

Students and
Collaborators

Tomohiko Wakayama, M.D

Lica Ishida



CBMB, NICHD, NIH (2001~2002)

Juan S Bonifacino, Ph.D



University of Tokyo (~1993~2001)

Yuichi Sugiyama, Ph.D

Hiroshi Suzuki, Ph.D

Kiyomi Ito, Ph.D (Hoshi Univ)

Students and

Masayo Yamazaki, Ph.D (Merck, USA)

Hiroyuki Kusuhara, Ph.D

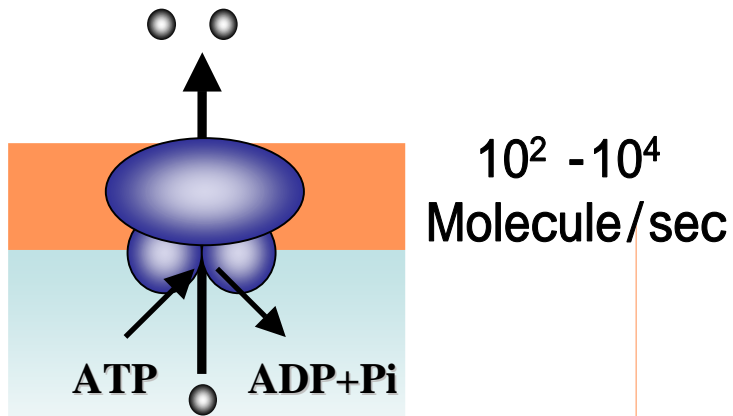
Collaborators

Tetsuya Terasaki, Ph.D (Tohoku Univ.)

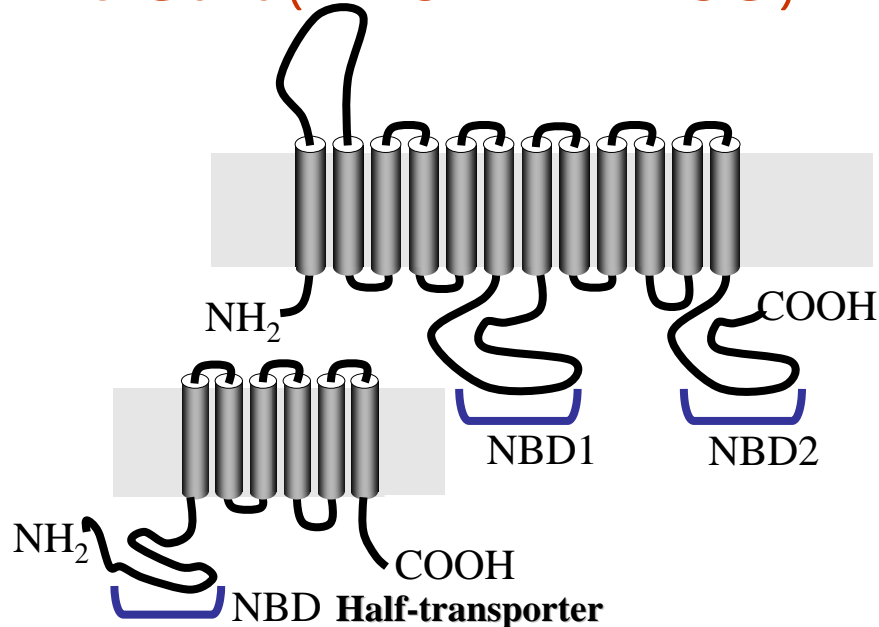
Transporter Families in Mammals

ABC Transporter Superfamily

ABC : ATP Binding Cassette

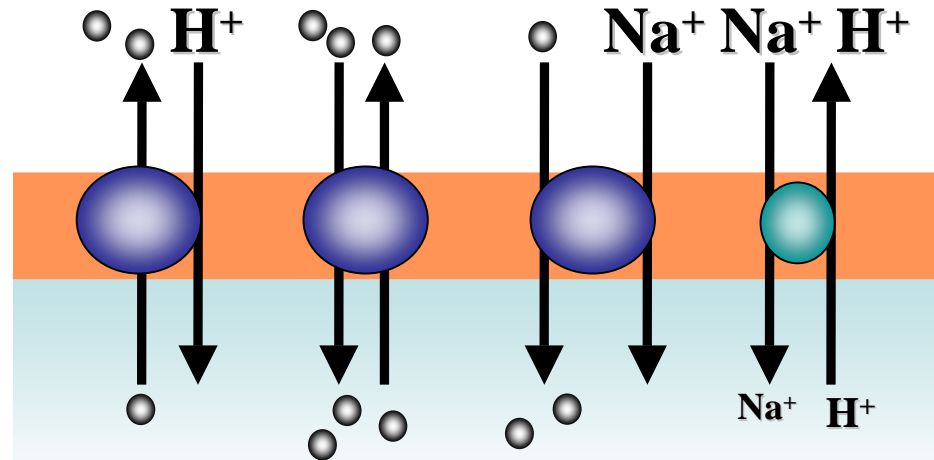


48 Gene (ABCA ~ ABCG)

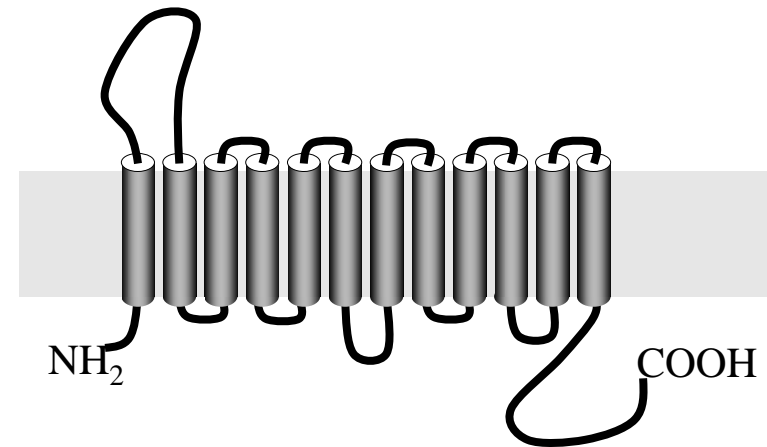


SLC Superfamily

SLC : Solute Carrier



319 Gene (SLC1 ~ SLC43)



<http://www.gene.ucl.ac.uk/nomenclature/>
<http://www.bioparadigms.org/slc/menu.asp>

Questions for Drug Transporters



How are the localization of xenobiotic transporters organized on cell-surface membranes ?



How are the function of xenobiotic transporters regulated ?



How are xenobiotic transporters sorted into the appropriate region of the membranes ?

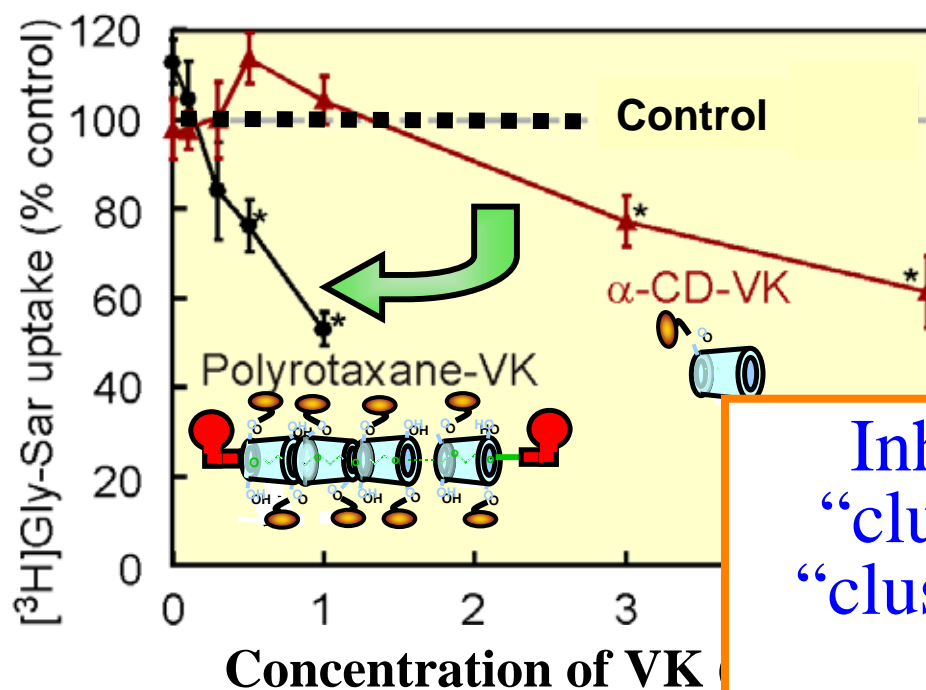


**Proten-Protein
Interaction**

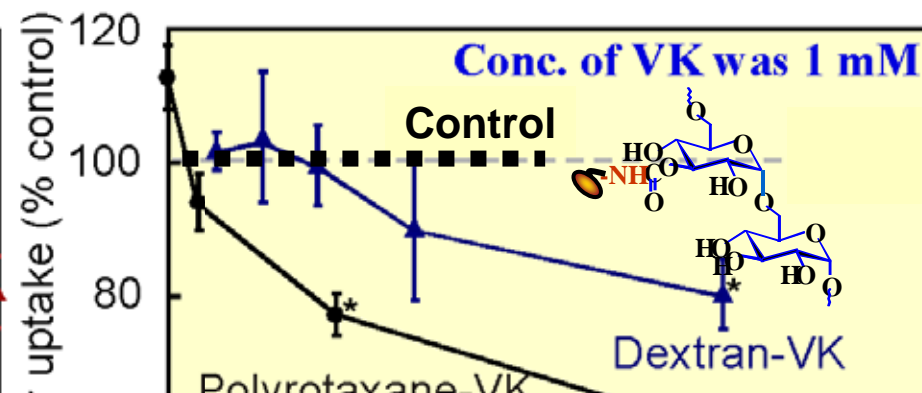


Inhibition of PEPT1-mediated Gly-Sar Uptake by VK-Polyrotaxane (VK-PRX)

VK-PRX vs α -CD-VK



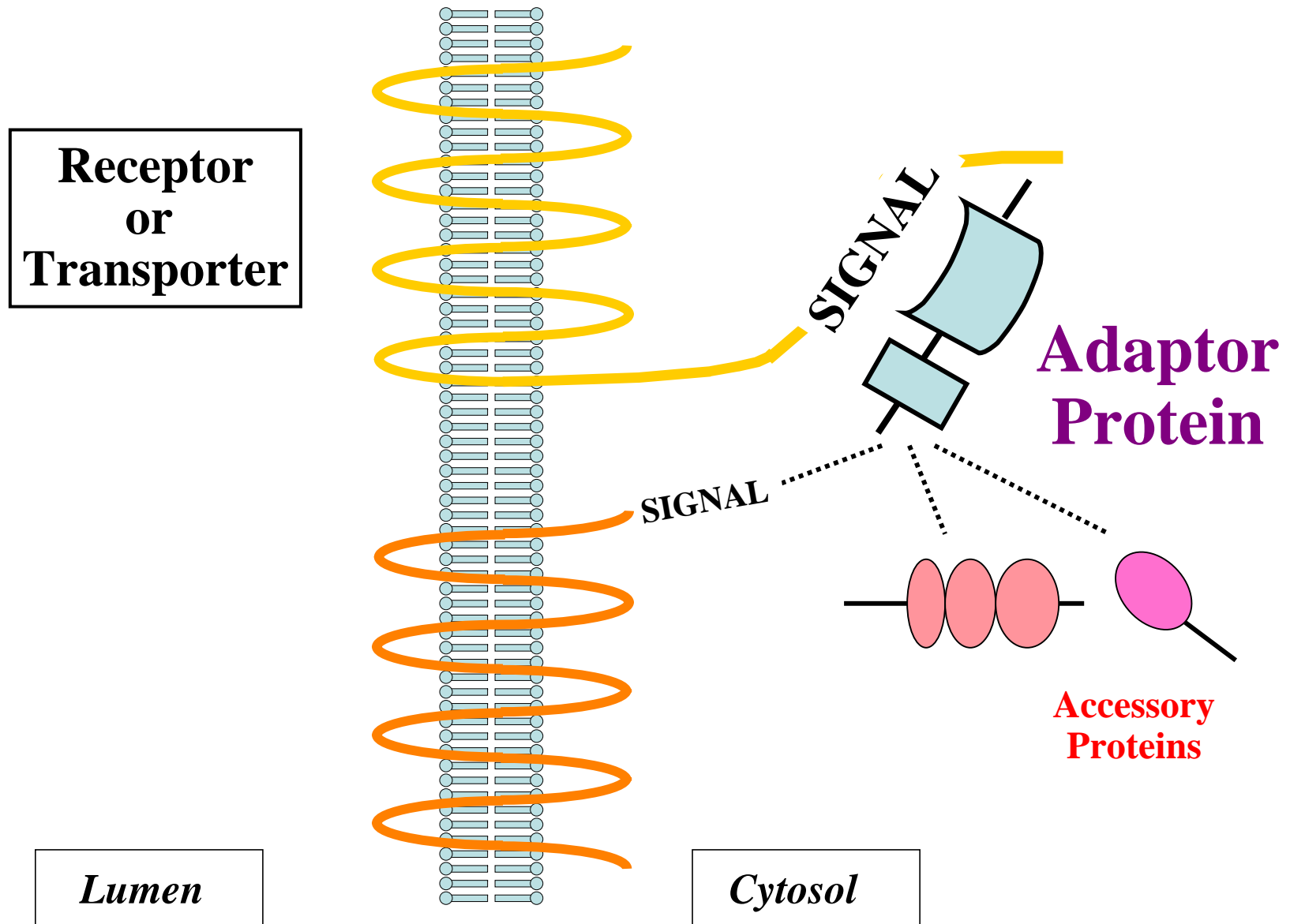
VK-PRX vs Dextran-VK

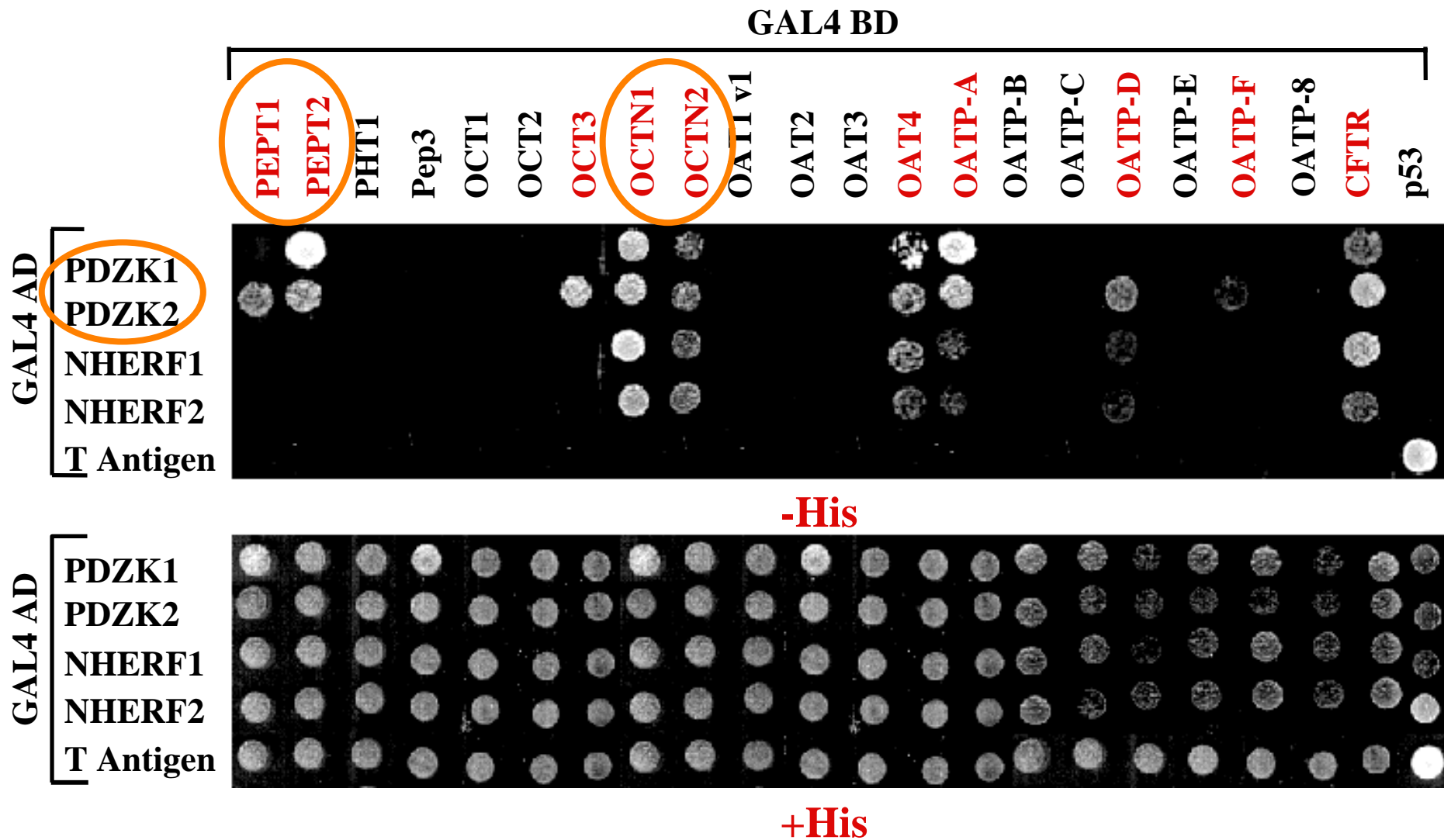


Inhibition of PEPT1 exhibited “clustering effect”, implying the “clustered” localization of PEPT1 on cell-surface.

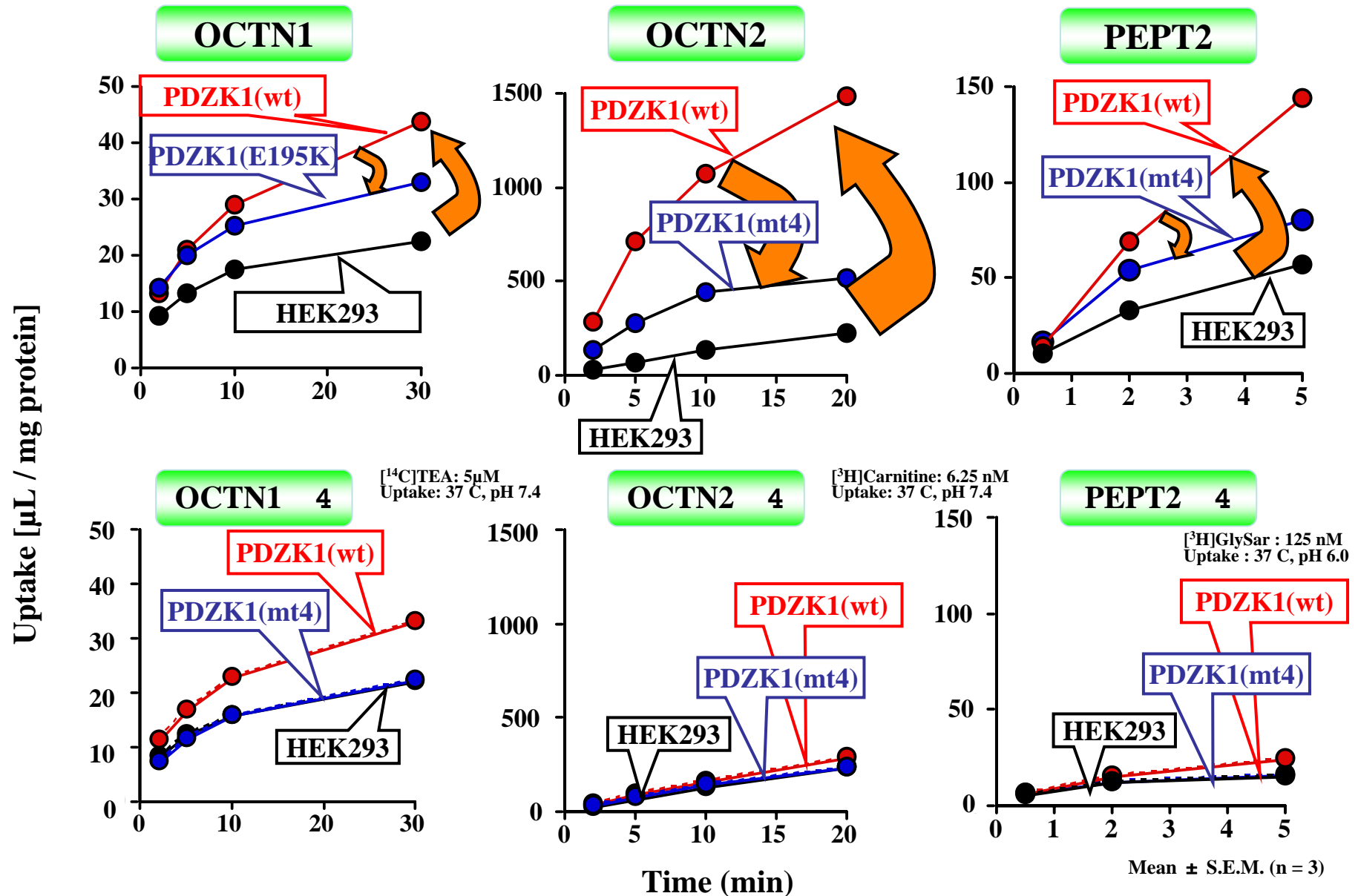
PEPT1-mediated dipeptide uptake is highly inhibited by polymer structure, compared with monomer one.

Sorting Signals in Integral Membrane Proteins



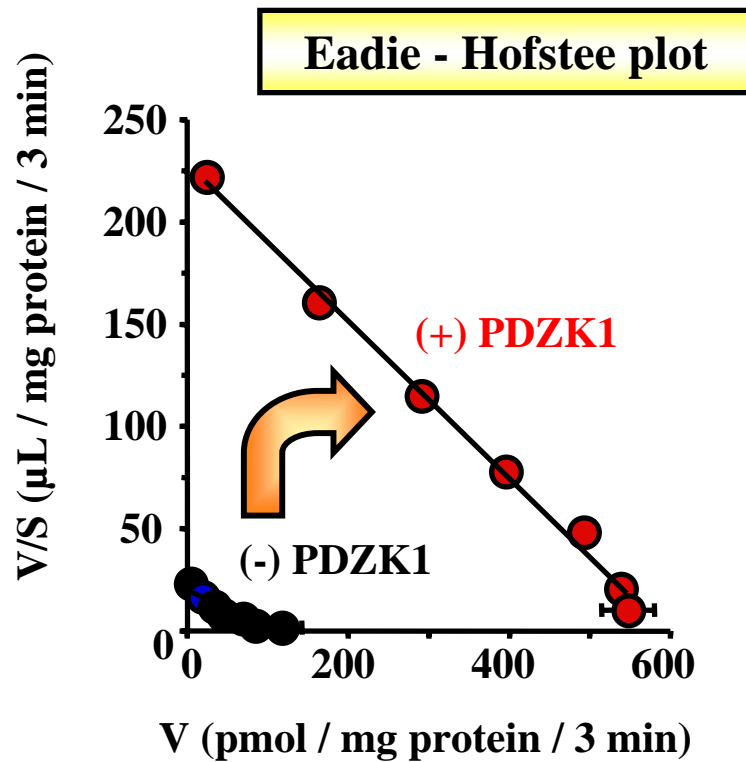


Yeast Two-Hybrid Analysis for Identifying Interaction between the Carboxyl-Terminus of Xenobiotic Transporters and PDZ Proteins



Effect of PDZK1 or Its Mutant on Transport Activity of OCTN1, OCTN2 and PEPT2 or Their Δ 4 Constructs

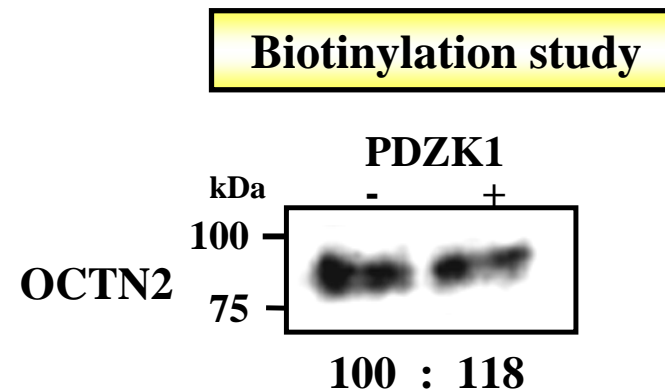
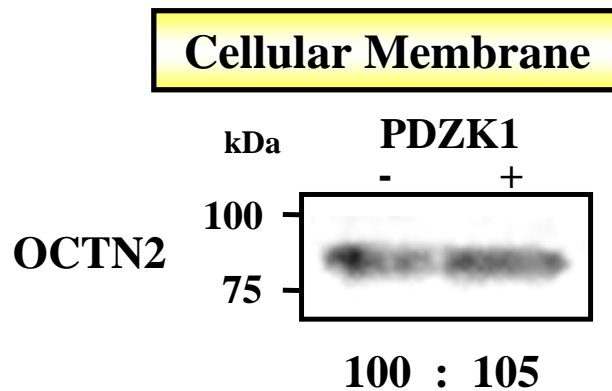
Sugiura T et al. *Drug Metab Pharmacokin* 21, 375, 2006.



Kinetic Parameters

	OCTN2	OCTN2 / PDZK1
K_m (μM)	3.06 ± 0.31	2.70 ± 0.10
V_{max} ($\text{pmol} / \text{mg protein} / 3 \text{ min}$)	103 ± 8	643 ± 17
V_{max} / K_m ($\mu\text{L} / \text{mg protein} / 3 \text{ min}$)	33.7	238

Mean \pm S.E.M. (n = 3)

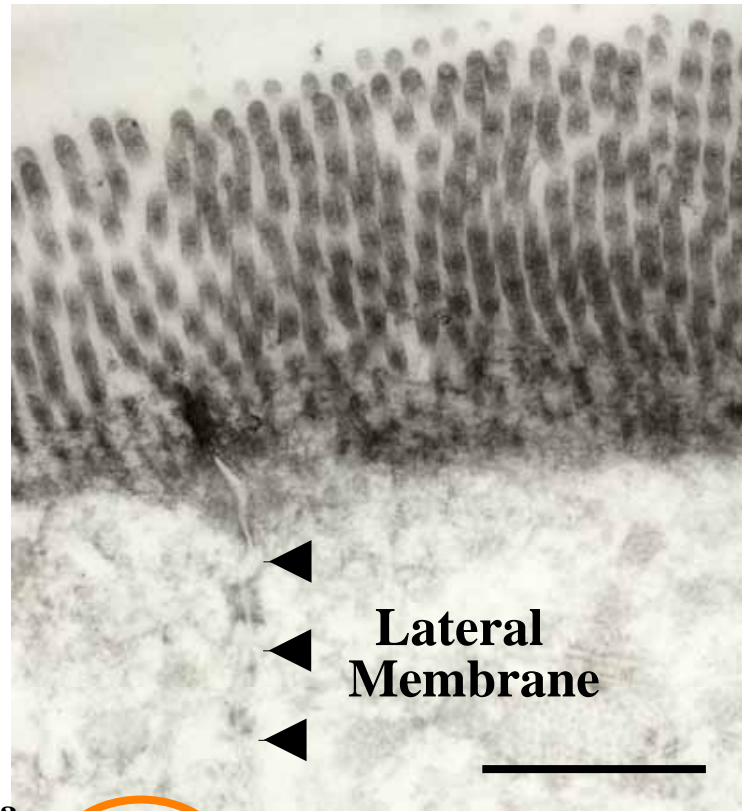


PDZK1 Increases V_{max}, but not K_m of L-[³H]Carnitine Uptake by OCTN2 with Minimal Effect on Its Cell-Surface Expression

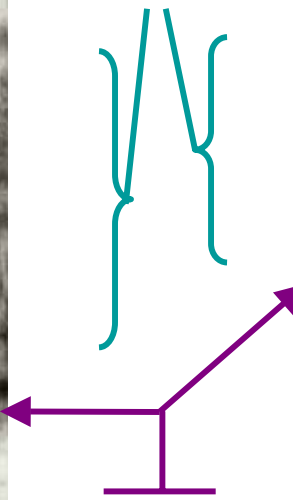
OCTN2 and PDZK1 are Colocalized in Microvilli of Mouse Small Intestine

OCTN2 (Transporter)

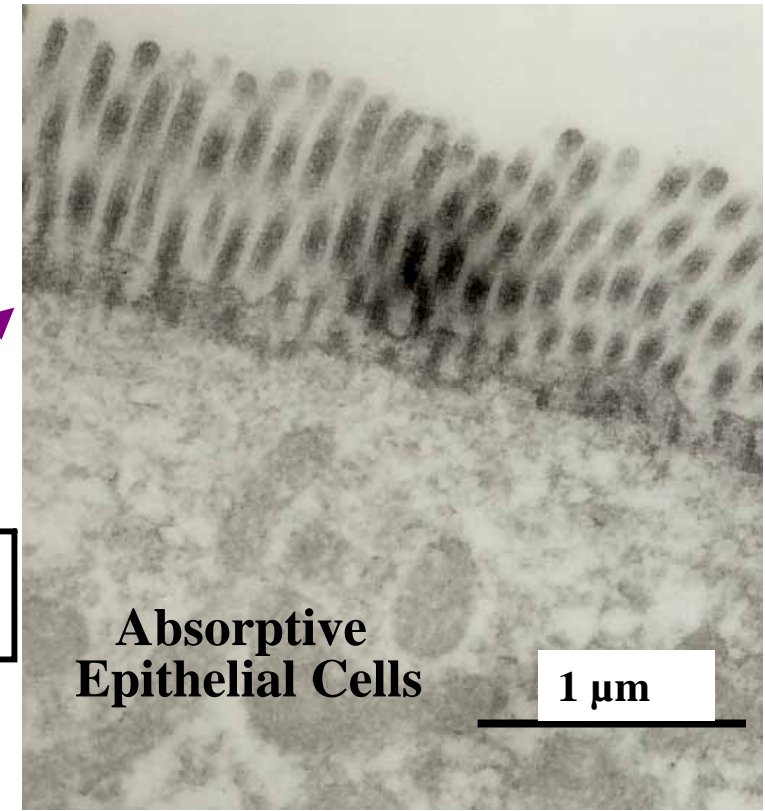
PDZK1 (Adaptor)



Microvilli



Base of Microvilli



Absorptive Epithelial Cells

1 μm

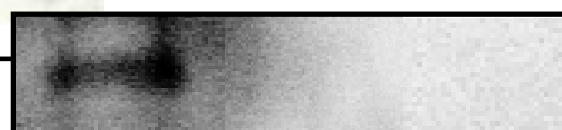
kDa

75



IP: **PDZK1** Preimmune GAPDH
 IB: **OCTN2** **OCTN2** **OCTN2**

75



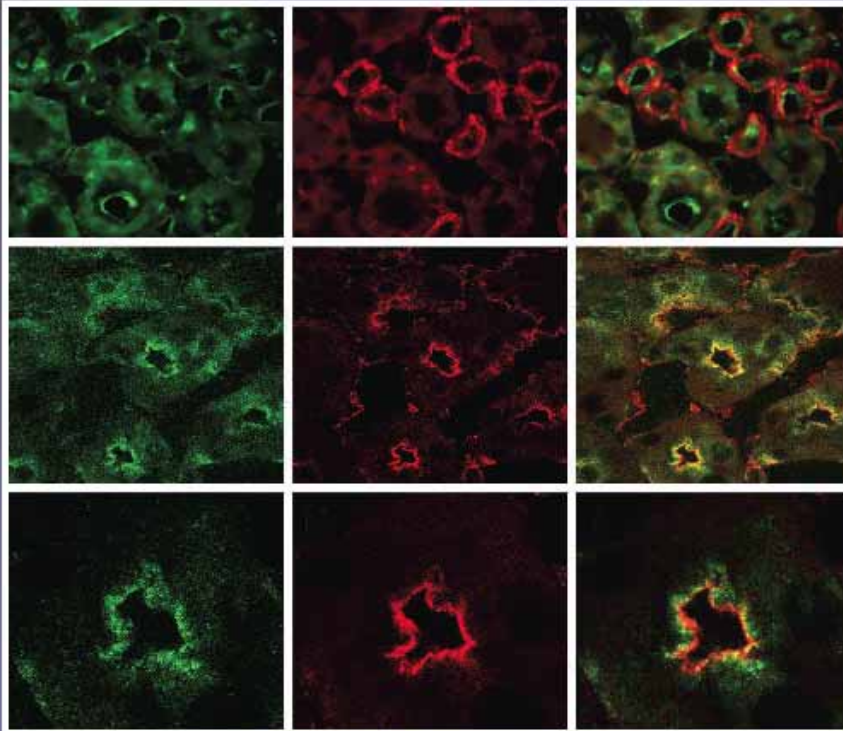
IP: **PDZK1** Preimmune GAPDH
 IB: **PDZK1** **PDZK1** **PDZK1**



IP: **PDZK1** Preimmune GAPDH
 IB: GAPDH GAPDH GAPDH

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DRUG METABOLISM AND DISPOSITION



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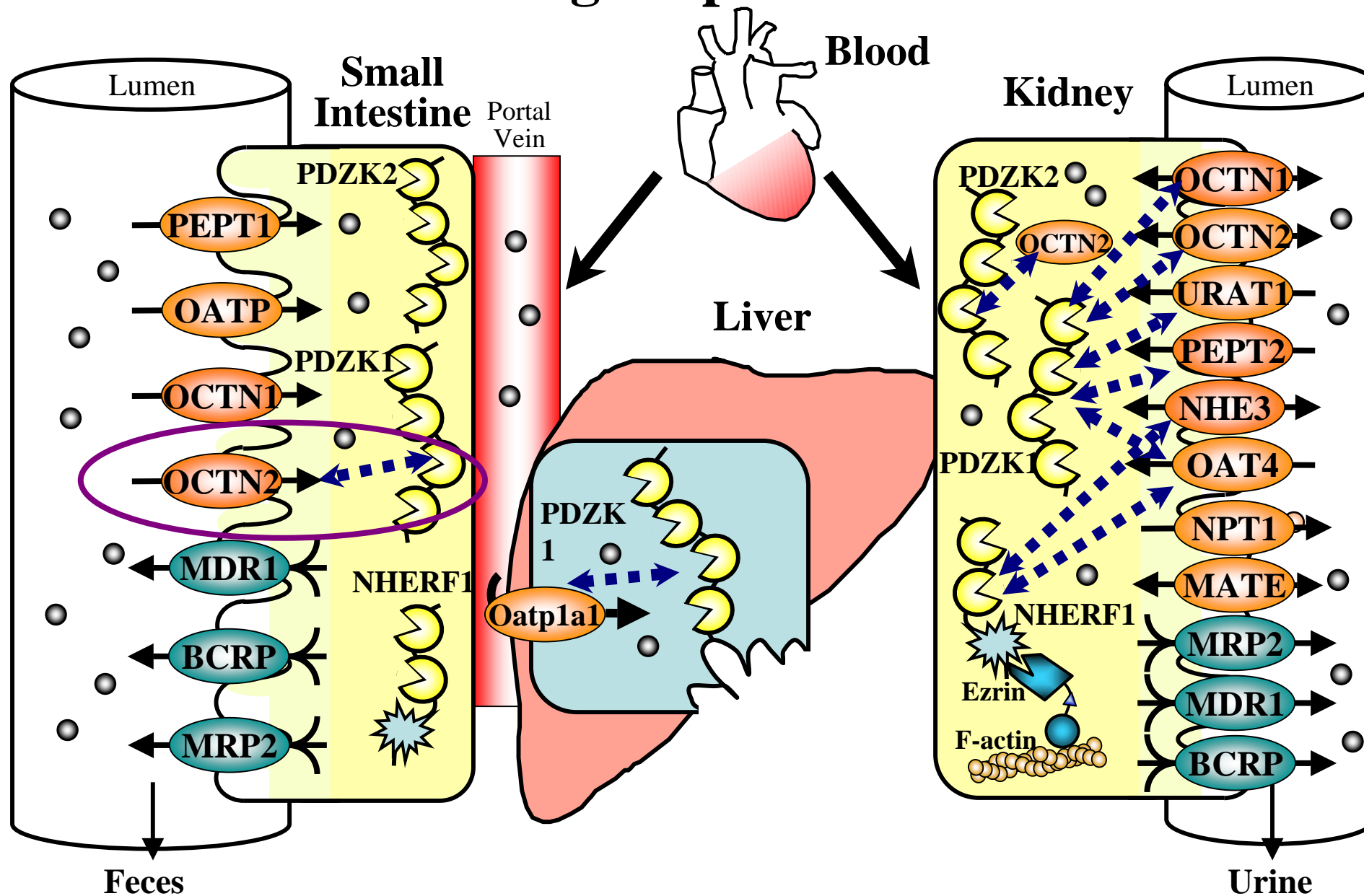
PDZK2

OCTN2

Merge

Cover Caption in *Drug Metab Dispos* 34 (11), 2006

Transporters and Adaptors-mediated Drug Disposition



A scenic view of a mountain range with snow-capped peaks and a valley below. The text "Thank you for your attention..." is overlaid in the center.

Thank you for your attention...