Supporting Information

Sprowl et al. 10.1073/pnas.1305321110

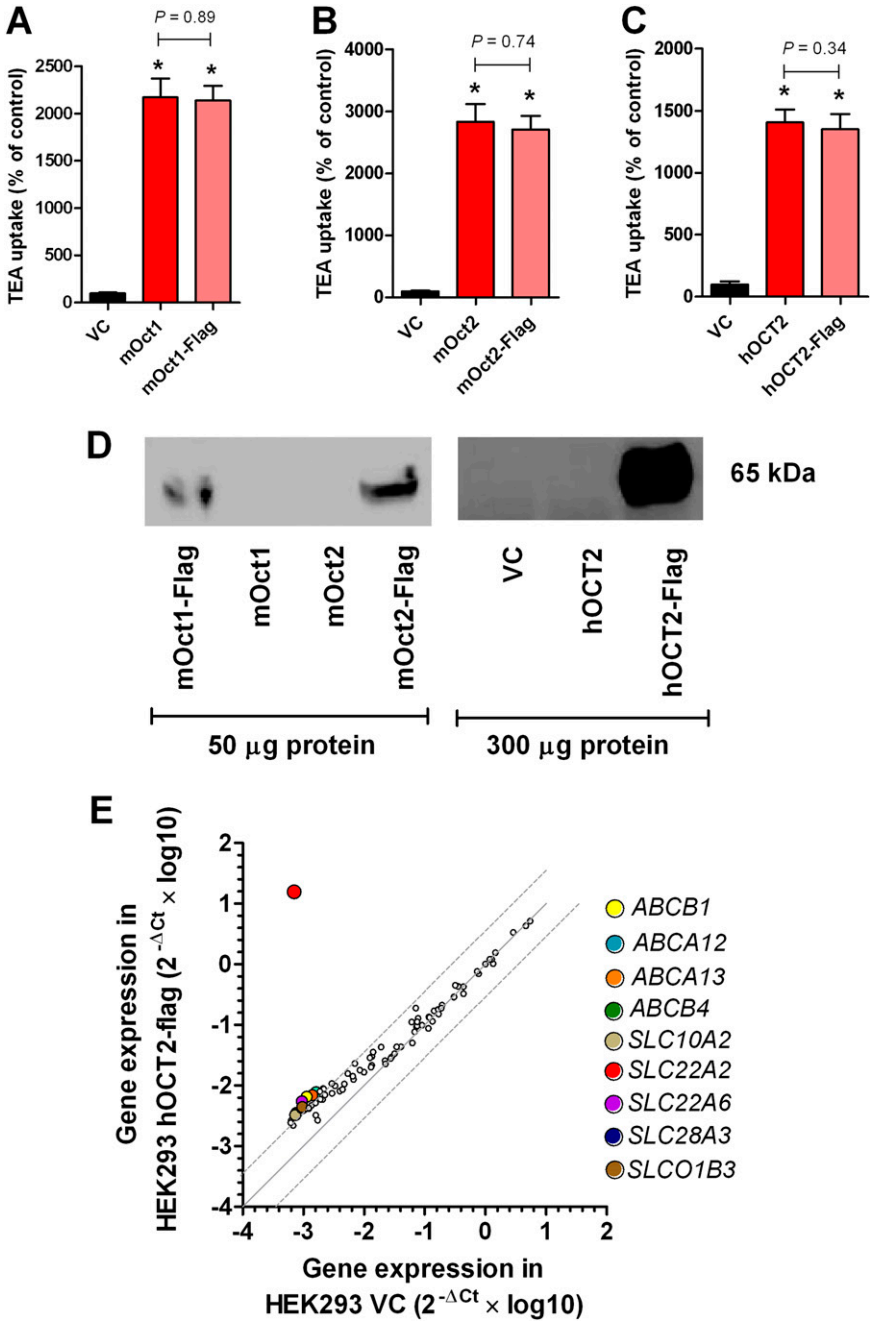

Fig. S1. Characterization of transfected cell lines. (*A*–*C*) Transport of tetraethylammonium (TEA), a positive control substrate, by mouse organic cation transporter 1 (mOct1) (*A*), mouse organic cation transporter 2 (mOct2) (*B*), and human OCT2 (hOCT2) (*C*) transfected (2 μM; 30-min incubations). Data represent the mean of triplicate observations from experiments performed on at least 3 separate occasions, and are expressed as the average percent of uptake values in cells transfected with an empty vector (VC). Error bars represent the SE. The asterisk denotes a significant difference from VC ($P < 0.05$), and *P* values above the bars denote statistical comparison between uptake data in cells transfected with the transporter or the corresponding flag-tagged transporter. (*D*) Expression of the tagged mOct1, mOct2, and hOCT2 proteins by Western blot. (*E*) Comparative expression of 84 transporter genes in HEK293 cells overexpressing hOCT2 or transfected with VC ($n = 3$ each). Each symbol represents an average reading for a single gene, the solid line is the line of identity, and the dotted lines are the 95% confidence intervals. Colored symbols represent transporter genes in HEK293 hOCT2 overexpressing cells with expression considered to be significantly different from VC. No genes other than the solute carrier family member 22a2 (*SLC22A2*) are associated with transport of platinum agents.

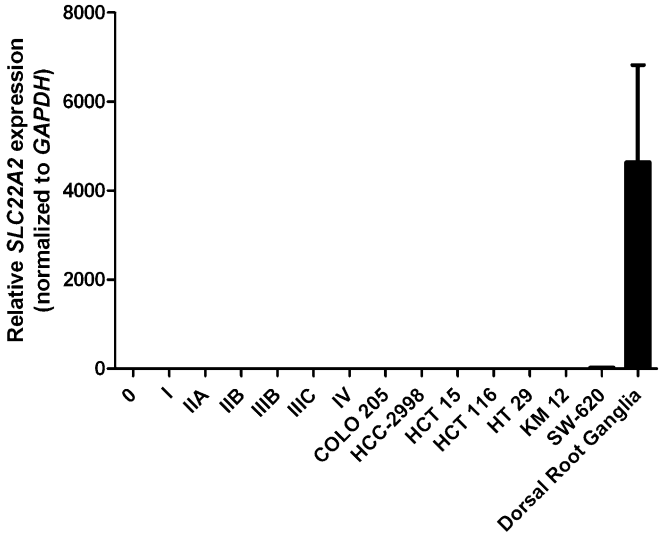

Fig. S2. OCT2 expression in colorectal tissue and dorsal root ganglia. Real-time PCR expression levels of *SLC22A2* (normalized to *GAPDH*) in 48 colorectal samples (stage 0: $n = 6$, stage I: $n = 3$, stage IIA: $n = 14$, stage IIB: $n = 2$, stage IIIB: $n = 8$, stage IIIC: $n = 8$, stage IV: $n = 7$), seven colorectal tumor cell lines, and human dorsal root ganglia ($n = 2$). Data are presented as the mean (bars) and SE (error bars).

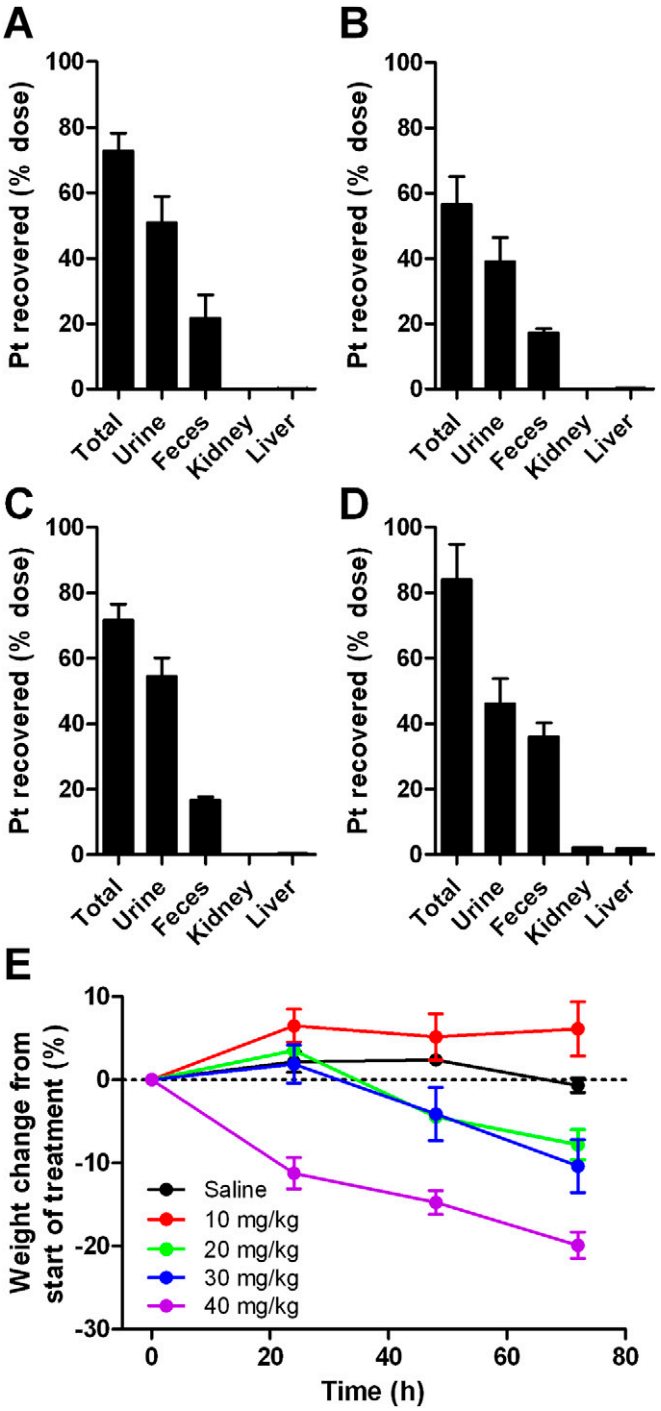

Fig. S3. Dose-dependence of oxaliplatin pharmacokinetics and toxicity. (*A–D*) Recovery of total platinum (Pt) in urine, feces, kidney, and liver in adult male wild-type mice at 72 h following a single i.p. administration of oxaliplatin at a dose of 10 mg/kg (*A*), 20 mg/kg (*B*), 30 mg/kg (*C*), or 40 mg/kg (*D*). Data are presented as the mean (bars) and SE (error bars) of 5 observations per group. (*E*) Oxaliplatin-dose-dependent toxicity as determined from the percentage loss in total body weight compared with baseline (time 0) at 1, 2, or 3 d after drug administration. Data are presented as the mean (symbols) and SE (error bars) of five observations per group.

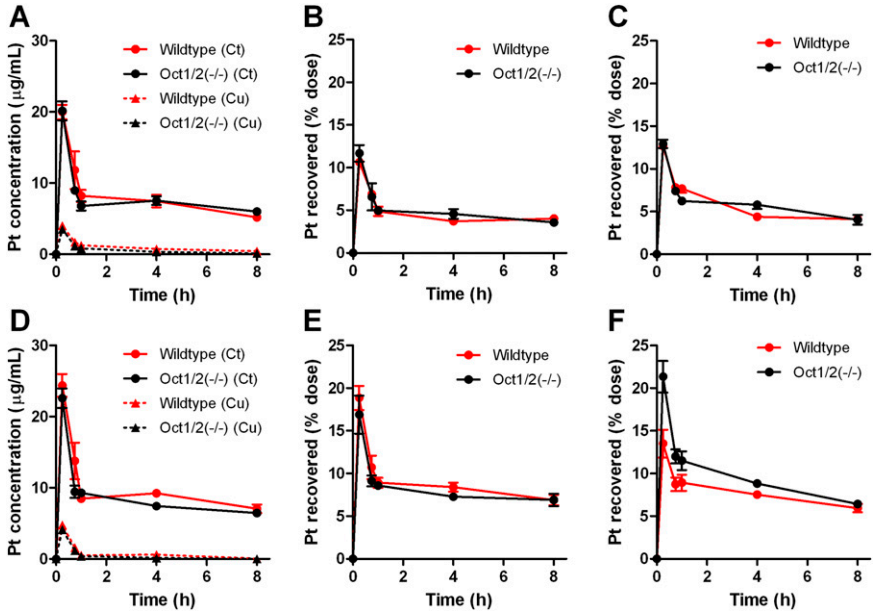

Fig. S4. Oxaliplatin disposition in male and female mice with a genetic deletion of the Oct1 and Oct2 transporters [Oct1/2($^{-/-}$) mice]. (*A*–*C*) Time course of total plasma concentrations (Ct) and unbound plasma concentrations (Cu) (*A*), liver concentrations (*B*), and kidney concentrations (*C*) of total platinum in male wild-type mice and Oct1/2($^{-/-}$) mice following a single i.p. administration of oxaliplatin at a dose of 40 mg/kg. (*D*–*F*) Time course of total plasma concentrations (Ct) and unbound plasma concentrations (Cu) (*D*), liver concentrations (*E*), and kidney concentrations (*F*) of total platinum in female wild-type mice and Oct1/2($^{-/-}$) mice following a single i.p. administration of oxaliplatin at a dose of 40 mg/kg. Data are presented as the mean (symbols or bars) and SE (error bars) of four observations per group per time point.

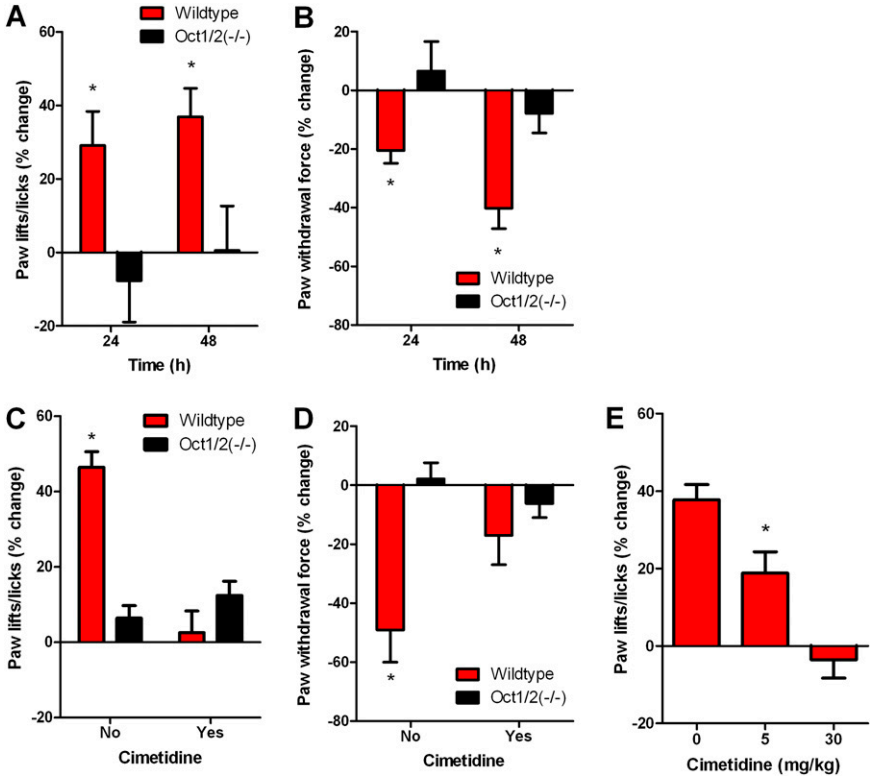

Fig. S5. OCT2 regulation of oxaliplatin-induced neuropathy. (*A*) Sensitivity to cold associated with a single dose of oxaliplatin (40 mg/kg) in wild-type and Oct1/2($^{-/-}$) mice, as determined by a cold-plate test. Data are presented as percentage change in the number of paw lifts or licks compared with baseline following exposure to a temperature of −4 °C for 5 min at 24 h [wild type: $n = 25$; Oct1/2($^{-/-}$): $n = 17$] or 48 h [wild type: $n = 25$; Oct1/2($^{-/-}$): $n = 16$] after drug administration. (*B*) Mechanical allodynia associated with a single dose of oxaliplatin (40 mg/kg) in wild-type and Oct1/2($^{-/-}$) mice, as determined by a Von Frey Hairs test. Data are presented as percentage change in the force required to promote paw withdrawal (referred to as "Paw withdrawal force") compared with baseline at 24 h [wild type: $n = 11$; Oct1/2($^{-/-}$): $n = 11$] or 48 h [wild type: $n = 11$; Oct1/2($^{-/-}$): $n = 10$] after drug administration. (*C*) Change in sensitivity to cold in wild-type ($n = 7$) and Oct1/2($^{-/-}$) ($n = 7$) mice 24 h after receiving oxaliplatin (5 mg/kg) alone or in combination with cimetidine (30 mg/kg, i.v. bolus). (*D*) Change in mechanical allodynia in wild-type ($n = 8$) and Oct1/2($^{-/-}$) ($n = 7$) mice 48 h after receiving oxaliplatin (5 mg/kg) alone or in combination with cimetidine (30 mg/kg, i.v. bolus). (*E*) Change in sensitivity to cold in wild-type ($n = 7$) 24 h after receiving oxaliplatin (5 mg/kg) alone ($n = 7$) or in combination with cimetidine (i.v. bolus) at a concentration of 5 ($n = 7$) or 30 mg/kg ($n = 9$). Bars represent the mean, and error bars are the SE. The asterisk denotes significant difference from baseline and between strains ($P < 0.05$).

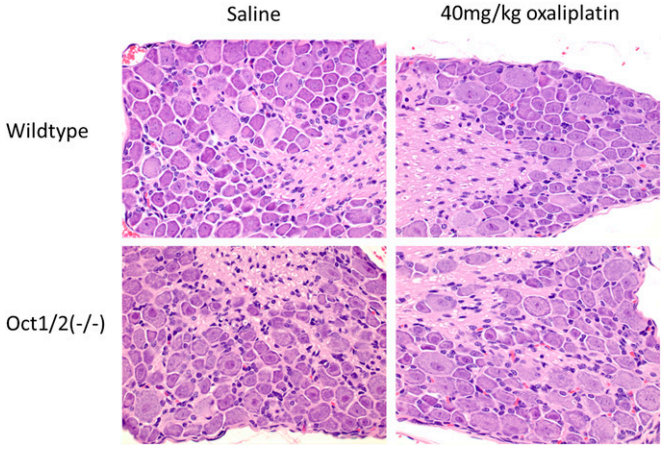

Fig. S6. Histology of dorsal root ganglia following administration of oxaliplatin. Histological images representing L4 dorsal root ganglia removed from wild-type or Oct1/2($^{-/-}$) mice following 72 h administration of saline or oxaliplatin (40 mg/kg). Images demonstrate a lack of cellular damage of the dorsal root ganglia following treatment.

Table S1. Genes included on the mouse transporter RT^2 profiles PCR array system

Number	Symbol	Number	Symbol	Number	Symbol	Number	Symbol	Number	Symbol
1	*Abca1*	21	*Abcc12*	41	*Slc5a1*	61	*Slc22a3*	81	*Slco3a1*
2	*Abca2*	22	*Abcd1*	42	*Slc5a4a*	62	*Slc22a6*	82	*Slco4a1*
3	*Abca3*	23	*Abcd3*	43	*Slc7a11*	63	*Slc22a7*	83	*Slco22a4*
4	*Abca4*	24	*Abcd4*	44	*Slc7a4*	64	*Slc22a8*	84	*Slco29a3*
5	*Abca9*	25	*Abcf1*	45	*Slc7a5*	65	*Slc22a9*	85	*Tap1*
6	*Abca12*	26	*Abcg2*	46	*Slc7a6*	66	*Slc25a13*	86	*Tap2*
7	*Abca13*	27	*Abcg8*	47	*Slc7a7*	67	*Slc28a1*	87	*Vdac1*
8	*Abcb1a*	28	*Aqp1*	48	*Slc7a8*	68	*Slc28a2*	88	*Vdac2*
9	*Abcb1b*	29	*Aqp7*	49	*Slc7a9*	69	*Slc29a1*	89	*Gusb**
10	*Abcb4*	30	*Aqp9*	50	*Slc10a1*	70	*Slc29a2*	90	*Hprt1**
11	*Abcb5*	31	*Atp6v0c*	51	*Slc10a2*	71	*Slc31a1*	91	*Hsp90ab1**
12	*Abcb6*	32	*Atp7a*	52	*Slc15a1*	72	*Slc38a2*	92	*Gapdh**
13	*Abcb11*	33	*Atp7b*	53	*Slc15a2*	73	*Slc38a5*	93	*Actb**
14	*Abcc1*	34	*Mvp*	54	*Slc16a1*	74	*Slco1a4*	94	*MGDC**
15	*Abcc2*	35	*Ralbp1*	55	*Slc16a2*	75	*Slco1a5*	95	*RTC**
16	*Abcc3*	36	*Slc2a1*	56	*Slc16a3*	76	*Slco1a6*	96	*PPC**
17	*Abcc4*	37	*Slc2a2*	57	*Slc19a1*	77	*Slco1b2*		
18	*Abcc5*	38	*Slc2a3*	58	*Slc19a2*	78	*Slco1c1*		
19	*Abcc6*	39	*Slc3a1*	59	*Slc22a1*	79	*Slco2a1*		
20	*Abcc10*	40	*Slc3a2*	60	*Slc22a2*	80	*Slco2b1*		

Abc, ATP binding cassette family of transporters; *Actb*, beta actin; *Aqp*, aquaporins; *Atp6v0c*, ATPase proton transporting lysosomal 16kDa V0 subunit c; *Atp7a* and *Atp7b*, ATPase copper transporting polypeptides; *Gapdh*, glyceraldehyde-3-phosphate dehydrogenase; *Gusb*, glucuronidase; *Hprt1*, hypozanthine phosphoribosyltransferase1; *Hsp90ab1*, heat shock protein 90kDa alpha (cytosolic) class B member 1; *MGDC*, monogalactosyldiacylglycerol synthase 3; *Mvp*, major vault protein; *PPC*, phosphoenolpyruvate carboxylase; *Ralbp1*, ralA binding protein 1; *RTC*, RNA 3′-terminal phosphate cyclase; *Slc*, solute carrier family of transporters; *Slco*, solute carrier family of organic anion transporters; *Tap1* and *Tap 2*, transporter 1 and 2; *Vdac1* and *Vdac2*, voltage-dependent anion channels.

*Included as controls/housekeeping genes.