ADME Profiling of Targeted Oral Peptide JNJ-77242113 (Icotrokinra)

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Key Takeaways

- Icotrokinra is a first-in-class, targeted oral peptide that potently and selectively blocks the IL-23R
- Icotrokinra showed high stability compared to typical peptides
- Due to its high potency, icotrokinra resulted in systemic target inhibition even with low oral bioavailability (typical of peptides)
- Icotrokinra also demonstrated:
  - Wide distribution to disease-relevant tissues
  - No DDI risk
  - Main route of elimination through feces as unchanged drug

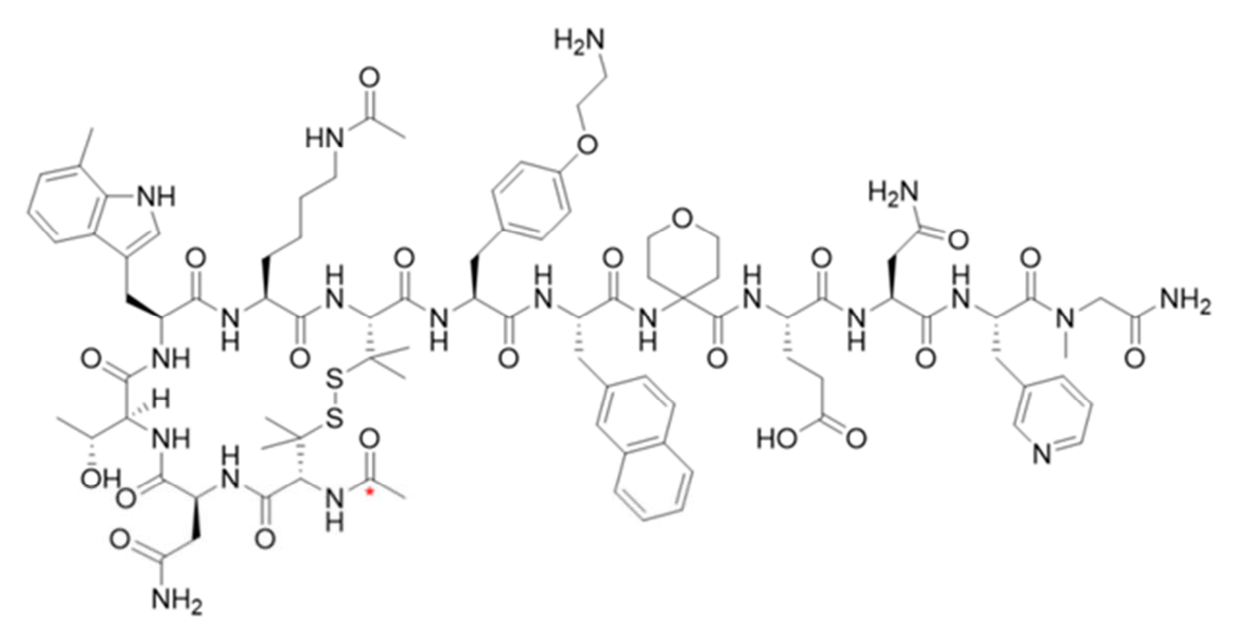
Background

The interleukin (IL)-23 pathway plays a key role in the pathogenesis of psoriasis (PsO), psoriatic arthritis, and inflammatory bowel disease (IBD)[1]

IL-23 signaling inhibition via monoclonal antibodies has demonstrated efficacy and safety in patients with psoriatic disease[2] and IBD[3]

Icotrokinra (formerly JNJ-77242113)

- A first-in-class, targeted oral peptide that inhibits IL-23 signaling by binding to the IL-23 receptor (R)
- Induced selective IL-23 pathway inhibition in preclinical models (in vitro and in vivo), and pharmacodynamic response in healthy volunteers[4]
- Demonstrated significant, durable skin clearance with no safety signals through 1 year in Phase 2 PsO studies[5,6]



Objectives

Profile icotrokinra in vitro and in vivo to elucidate:

- Absorption, distribution, metabolism, and excretion (ADME) properties
- Drug-drug interaction (DDI) potential

Methods

In vitro ADME characterization

Property	Assay
Bi-directional membrane permeability	**System:** LLC-PK1-MDR1/mock-transfected cell monolayers seeded in 24-well inserts (100,000 cells/cm²) **Conditions:** ±valspodar at 37°C for 4 h **Analysis method:** Liquid scintillation counter
Plasma protein binding	**System:** Classical equilibrium dialysis (Dianorm) **Conditions:** 37°C for 16 h **Analysis method:** LC-MS/MS
Blood-to-plasma partitioning	**System:** Whole blood from rat, dog, monkey, and human **Conditions:** 37°C for up to 2 h **Analysis method:** LC-MS/MS
Metabolic stability	**System:** (1) hepatocytes (1.0 million cells/mL) from rat, monkey, and human; (2) GI mucosa (20% [w:v]) from rat, monkey, and human; (3) fecal homogenates (6.25% [w:v]) from rat, monkey, and human **Conditions:** 37°C (1) up to 120 min; (2 & 3) up to 24 h **Analysis method:** LC-MS/MS
DDI	**System:** Transfected cell systems or vesicles **Conditions:** Triplicates prototypical substrates and ± inhibitors at 37°C for 0.5 h to 4 h depending on the assay **Analysis method:** LSC or LC-MS/MS

GI=gastrointestinal; h=hour; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLC-PK1-MDR1=multidrug resistance-transfected Lilly Laboratories cell-porcine kidney; LSC=liquid scintillation counting; w:v=weight to volume ratio.

In vivo ADME characterization

Property	Rat	Monkey
PK evaluation	**Animals:** Sprague Dawley; N=3 fasted/group **Tissue collected:** Blood through 24 h **Analysis method:** LC-MS/MS[a]	**Animals:** Cynomolgus; N=4 fasted/group **Tissue collected:** Blood through 24 h **Analysis method:** LC-MS/MS[a]
Tissue distribution	**Animals:** Lister Hooded; N=6 **Tissue collected:** Freeze dried sections up to 72 h **Analysis method:** QWBA[b]	**Animals:** Cynomolgus; N=2/time point **Dose and route:** IV (1 mg/kg) icotrokinra **Tissue collected:** Various tissues at 1.5 and 6 h **Analysis method:** LC-MS/MS[c] **Animals:** Cynomolgus; N=4 **Dose and route:** Single IV (2mg/kg) risankizumab **Tissue collected:** Various tissues at day 7 **Analysis method:** Immunoassay[d]
Metabolism	**Animals:** Sprague Dawley (intact); N=2 fasted **Tissue collected:** Plasma, urine, and feces through 24 h **Analysis method:** LC-radiometric detection system coupled with tandem MS[e]	**Animals:** Cynomolgus; N=2 fed **Tissue collected:** Blood through 48 h and excreta through 96 h **Analysis method:** Total radioactivity by LSC; Metabolic profiles by LC-radiometric detection system coupled with tandem MS[e]
Excretion	**Animals:** Sprague Dawley (intact); N=3 fed **Tissue collected:** Cage wash, urine, and feces through 96 h **Analysis method:** Total radioactivity by LSC	

- Metabolic profiling by LC-MS/MS was also conducted on plasma and urine samples collected from 10 healthy volunteers from the phase 1 FIH study of icotrokinra[4]

[a]LLOQ=1 ng/mL. [b]Limit of reliable measurement=0.1-0.2 µg equiv/g. [c]LLOQ=5 ng/mL for tissue samples. [d]LLOQ=10 ng/mL. [e]LLOQ=0.5 ng/mL for plasma, 1 ng/mL for urine, and 100 mg/mL for feces. FIH=first in human. IV=intravenous; LLOQ=lower limit of quantification; PK=pharmacokinetic; QWBA=quantitative whole-body autoradiography.

Results

Icotrokinra exhibited low non-saturable permeability in LLC-PK1 cell monolayers

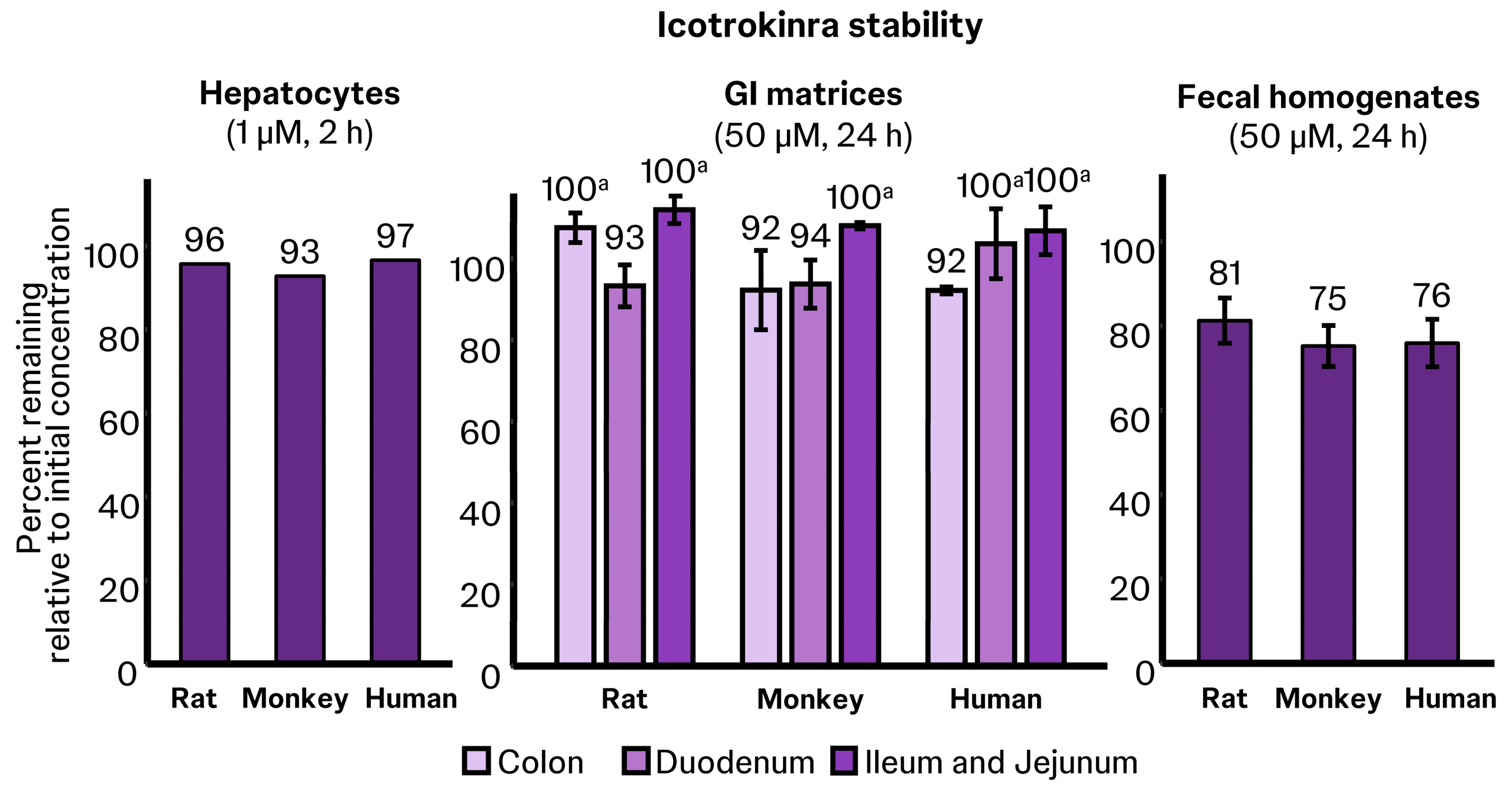
- Efflux ratios in LLC-PK1-MDR1 were <2, indicating that icotrokinra is not a P-gp substrate

Bi-directional transport of [14C]-icotrokinra in the absence or presence of a P-gp inhibitor (valspodar)

[14C]-icotrokinra concentration, µM	Valspodar (2 µM)	LLC-PK1-MDR1			LLC-PK1-Mock		
		P_{app} (A-B)[a], nm/sec	P_{app} (B-A)[b], nm/sec	ER[c]	P_{app} (A-B)[a], nm/sec	P_{app} (B-A)[b], nm/sec	ER[c]
1	–	1.96	1.98	**1.0**	1.90	3.40	**1.8**
3	–	1.61	1.56	**1.0**	1.67	2.58	**1.5**
10	–	1.25	1.55	**1.2**	1.64	1.64	**1.0**
30	–	1.23	1.43	**1.2**	1.40	1.91	**1.4**
100	–	1.02	0.69	**0.7**	1.30	1.29[d]	**1.0**
300	–	0.90	0.61	**0.7**	1.38	2.51	**1.8**
1	+	1.67	1.88	**1.1**	1.77	1.93	**0.8**
3	+	1.47	1.84	**1.3**	1.91	1.79	**0.9**
[3H] digoxin (10 µM)	-	8.47	118.5	**14**	20.3	79.4	**3.9**
[3H] digoxin (10 µM)	+	35.1	31.6	**0.9**	33.2	36.6	**1.1**

Data presented as mean of triplicate measurements. [a]P_{app} from apical-to-basolateral direction (A-B). [b]P_{app} from basolateral-to-apical direction (B-A). [c]ER=P_{app}(B-A)/P_{app}(A-B). [d]n=2. A=apical; B=basolateral; ER=efflux ratio; P_{app}=apparent permeability; P-gp=P-glycoprotein; sec=second.

Icotrokinra was stable in relevant tissues across species, including human


Icotrokinra stability
Hepatocytes
(1 µM, 2 h)
GI matrices
(50 µM, 24 h)
Fecal homogenates
(50 µM, 24 h)
Percent remaining
relative to initial concentration
96
93
97
100ᵃ
93
100ᵃ
92
94
100ᵃ
92
100ᵃ
100ᵃ
81
75
76
Rat
Monkey
Human
Colon
Duodenum
Ileum and Jejunum

[a]Actual measurements exceeded 100% due to instrument variation. Error bars represent percent coefficient of variation.

Icotrokinra exhibited dose-proportional pharmacokinetics with F<1%

Plasma pharmacokinetics of icotrokinra in rats and monkeys following intravenous or oral dosing

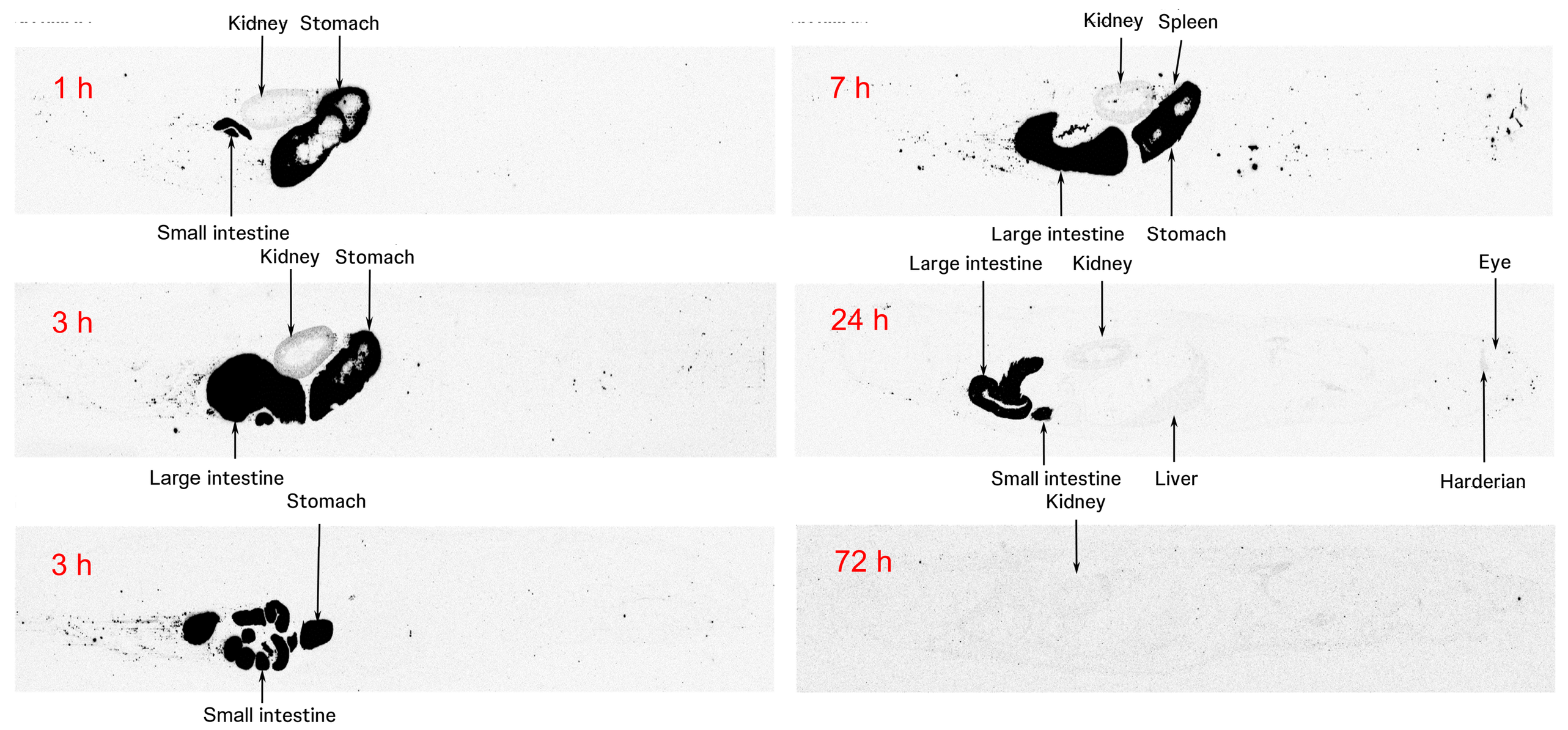
Dosing Route	Animal	Dose, mg/kg	CL, mL/min/kg	V_{ss}, mL/kg	C_{max}, ng/mL	t_{max}, h	$AUC_{0-\infty}$, ng*h/mL	$t_{1/2}$, h	F, %
IV	Rat[a]	2	8.77	459	--	--	3,810	0.762	**--**
	Monkey[b,c]	1	1.44	299	--	--	12,000	3.47	**--**
PO	Rat[a]	20	--	--	8.68	2[d]	44.2[e]	2.36[f]	**0.12[e]**
	Rat[a,g]	30	--	--	134	0.5	181	1.76	**0.32**
	Rat[a,g]	100	--	--	76.3	1	317	--[h]	**0.17**
	Rat[a,g]	300	--	--	134	1	1,120	--[h]	**0.11**
	Monkey[b]	2.5	--	--	11.0	2[d]	82.2[e]	5.58[e]	**0.27[e]**
	Monkey[b]	7.5	--	--	27.8	1[d]	226[i]	6.41[i]	**0.25[i]**
	Monkey[b]	22.5	--	--	84.3	1.5[d]	812[i]	5.60[i]	**0.30[i]**

Values are presented as mean except as noted. [a]N=3. [b]N=4. [c]N=3: One animal showed an extravascular administration profile rather than a typical IV PK profile and so was excluded from PK analysis. [d]Median. [e]N=2: Other animal(s) did not have sufficient data in elimination phase. [f]N=1: Other animals did not have sufficient time points for $t_{1/2}$ estimation. [g]For rats dosed orally at 30, 100, and 300 mg/kg, sparse sampling was used, with 3 rats/time point, and composite profiles were used for PK parameter estimation. [h]Insufficient elimination phase to calculate $t_{1/2}$. [i]N=3: Other animals did not give sufficient data in elimination phase. $AUC_{0-\infty}$=area under the plasma concentration-time curve from time zero extrapolated to infinity; CL=clearance; C_{max}=maximum plasma concentration; F=bioavailability; IV=intravenous; min=minute; PO= per os (oral gavage); $t_{1/2}$= plasma elimination half-life; t_{max}=time to reach maximum plasma concentration; V_{ss}=volume of distribution at steady state.

Icotrokinra distributed mainly to the GI tract and kidneys of rats

- Drug was largely undetectable after 72 h

Distribution of [14C]-icotrokinra in rat following oral dosing (300 mg/kg)

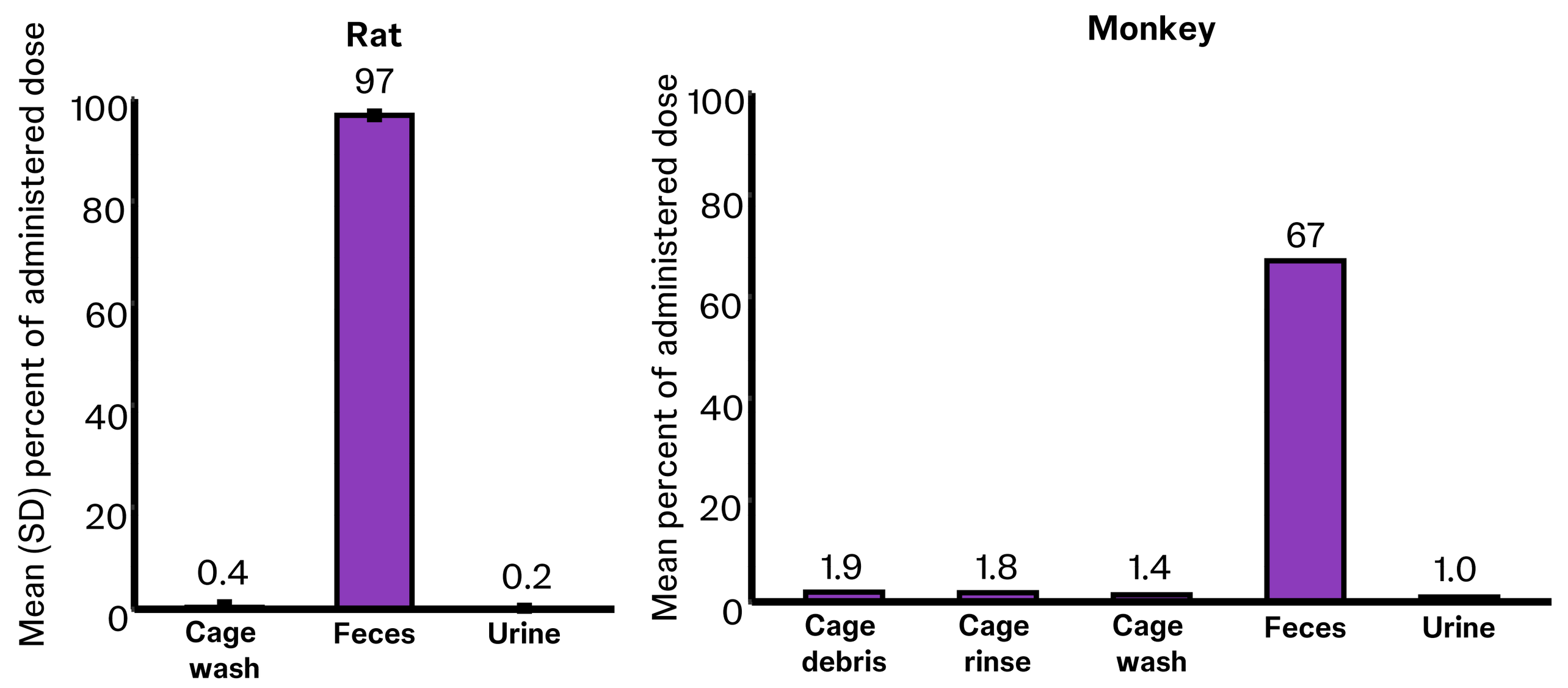


Presence of icotrokinra in tissues is depicted in black.

Fecal excretion of unabsorbed icotrokinra was the main route of elimination

- Renal excretion contributed to clearance of systemic drug (<1% of dose is bioavailable)

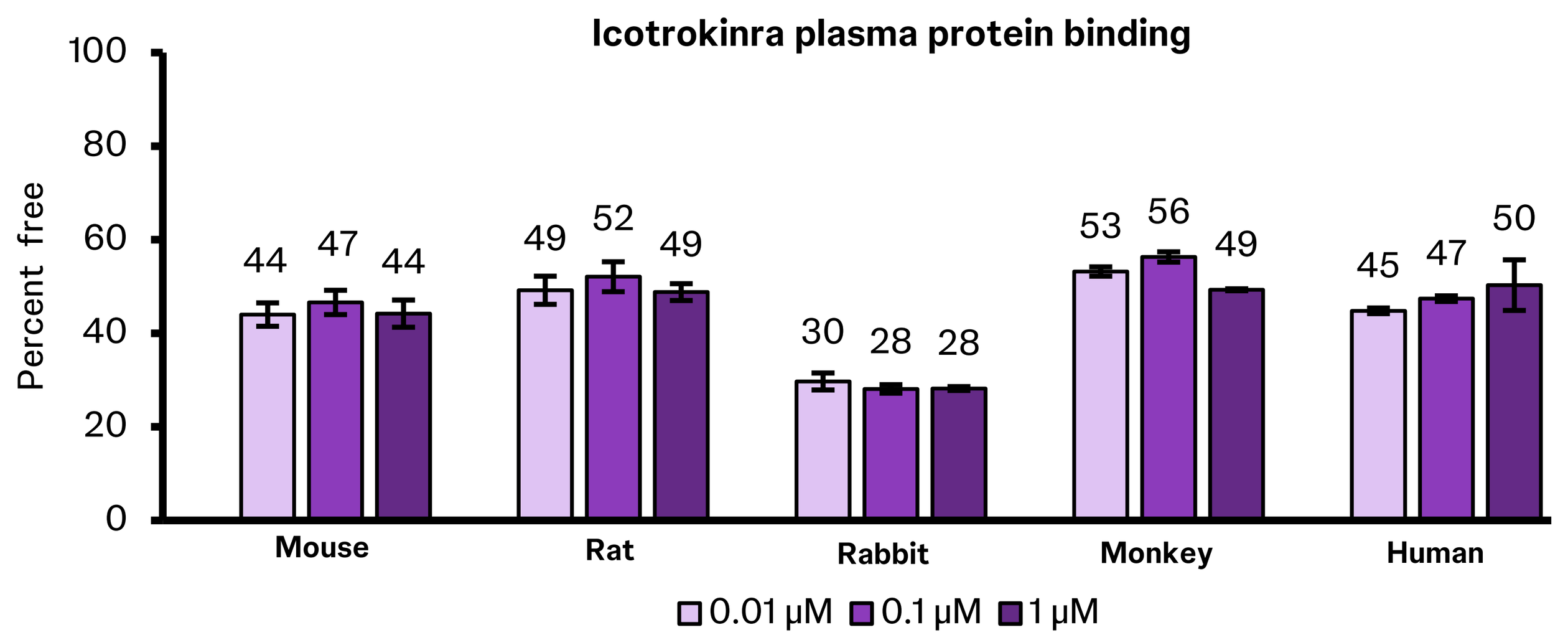
Excretion of [14C]-icotrokinra through 96 h following oral administration



Dose=300 mg/kg with target radioactivity of ~400 µCi/kg in rats and ~100 µCi/kg in monkeys.

Icotrokinra showed low and non-saturable protein binding across species

- Icotrokinra (0.0013 -0.13 µM) also exhibited low blood partitioning and no preferential binding to RBCs, with mean observed $K_{WB/P}$ and $K_{RBC/P}$ values of <1 across species



Data presented as mean of triplicate samples ± SD. $K_{WB/P}$=whole blood-to-plasma ratio; $K_{RBC/P}$=red blood cell-to-plasma ratio; RBC=red blood cell; SD=standard deviation.

Icotrokinra was not a substrate or inhibitor of CYP enzymes or drug transporters

- Minor inhibition of OATP1B1/3 was observed, but no impact expected at clinical concentrations

Substrate/inhibition potential of icotronkinra towards transporters

Transporter	Substrate (Yes/No)	Inhibitor (Yes/No)	Maximum Inhibition, %[a]
OATP1B1	No	No	44[b]
OATP1B3	No	No	48[c]
OAT1	No	No	-14[d]
OAT3	No	No	5[e]
OCT2	No	No	-2[f]
MATE1	No	No	-4[d]
MATE2-K	No	No	9[g]
BSEP	NT	No	14[h]
BCRP	No	No	15[i]
P-gp	No	No	9[j]

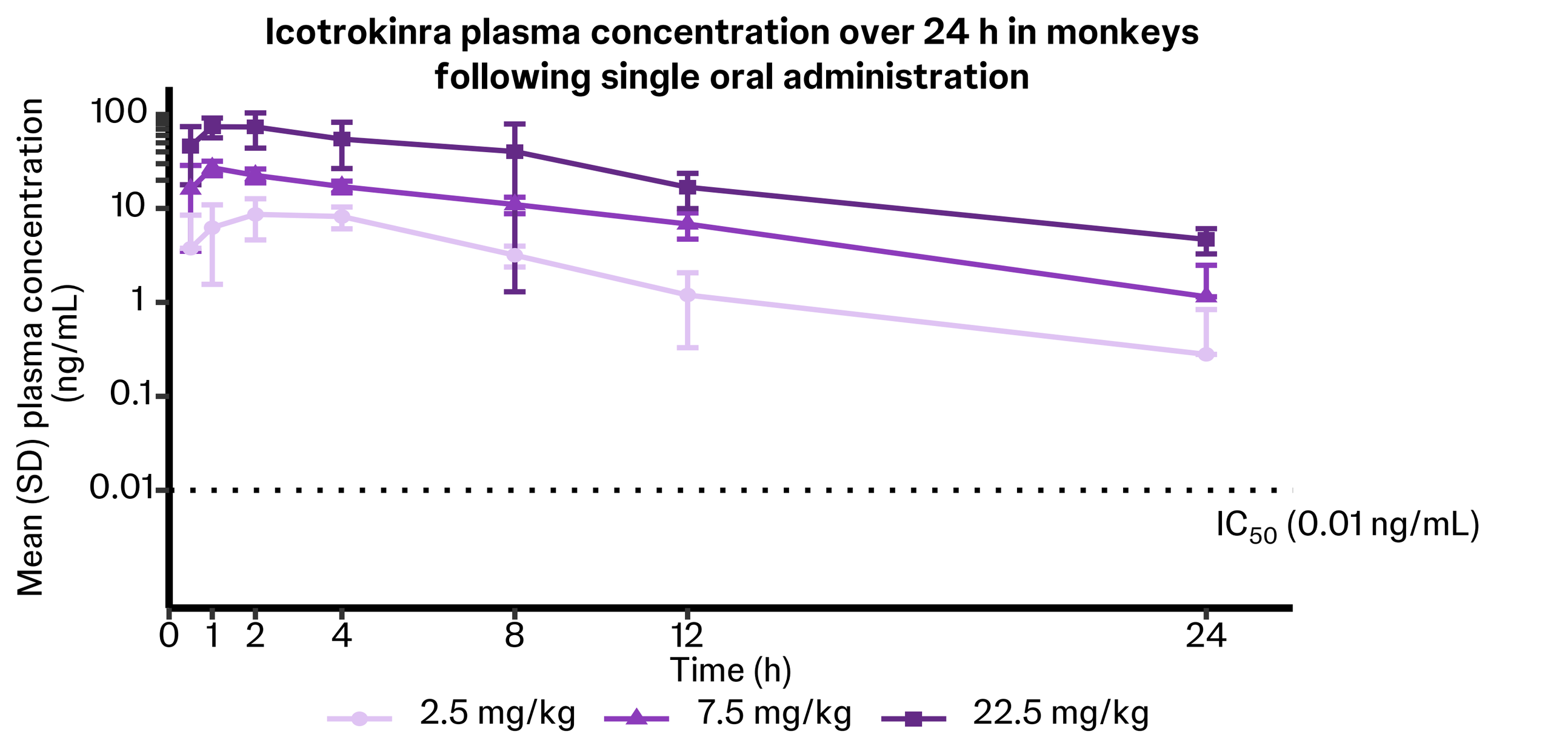
Inhibitory potency of icotrokinra towards CYP450 isoforms in human hepatocytes

CYP enzyme	Probe substrate	Inhibitor (Yes/No)	Inhibition at 100 µM, %
1A2	20 µM Phenacetin	No	19
2B6	10 µM Bupropion	No	<10
2C8	3 µM Amodiaquine	No	<10
2C9	5 µM Diclofenac	No	<10
2C19	5 µM S-(+)-Mephenytoin	No	<10
2D6	2 µM Dextromethorphan	No	<10
2E1	45 µM Chlorzoxazone	No	30
3A4	2 µM Midazolam	No	<10

[a]Results are presented as mean of triplicate measurements unless otherwise noted. Icotrokinra measured concentrations: [b]24.7 µM. [c]24.2 µM. [d]22.5 µM. [e]26.2 µM. [f]22.7 µM. [g]22.2 µM. [h]29.7 µM. [i]24.8 µM. [j]1 µM. Icotrokinra concentration in P-gp inhibition assay: 1-600 µM; additional transporter assays (inhibition: 0-30 µM; substrate: 0.25-5 µM); CYP inhibition assay: 0-100 µM. BCRP= breast cancer resistance protein; BSEP=bile salt export pump; CYP=cytochrome P450; MATE=multidrug and toxin extrusion; min=minute; NT=not tested; OAT=organic anion transporter; OATP=organic anion transporting polypeptide; OCT=organic cation transporter.

Plasma concentrations in monkey exceeded IC_{50} for inhibition of IL-23 signaling

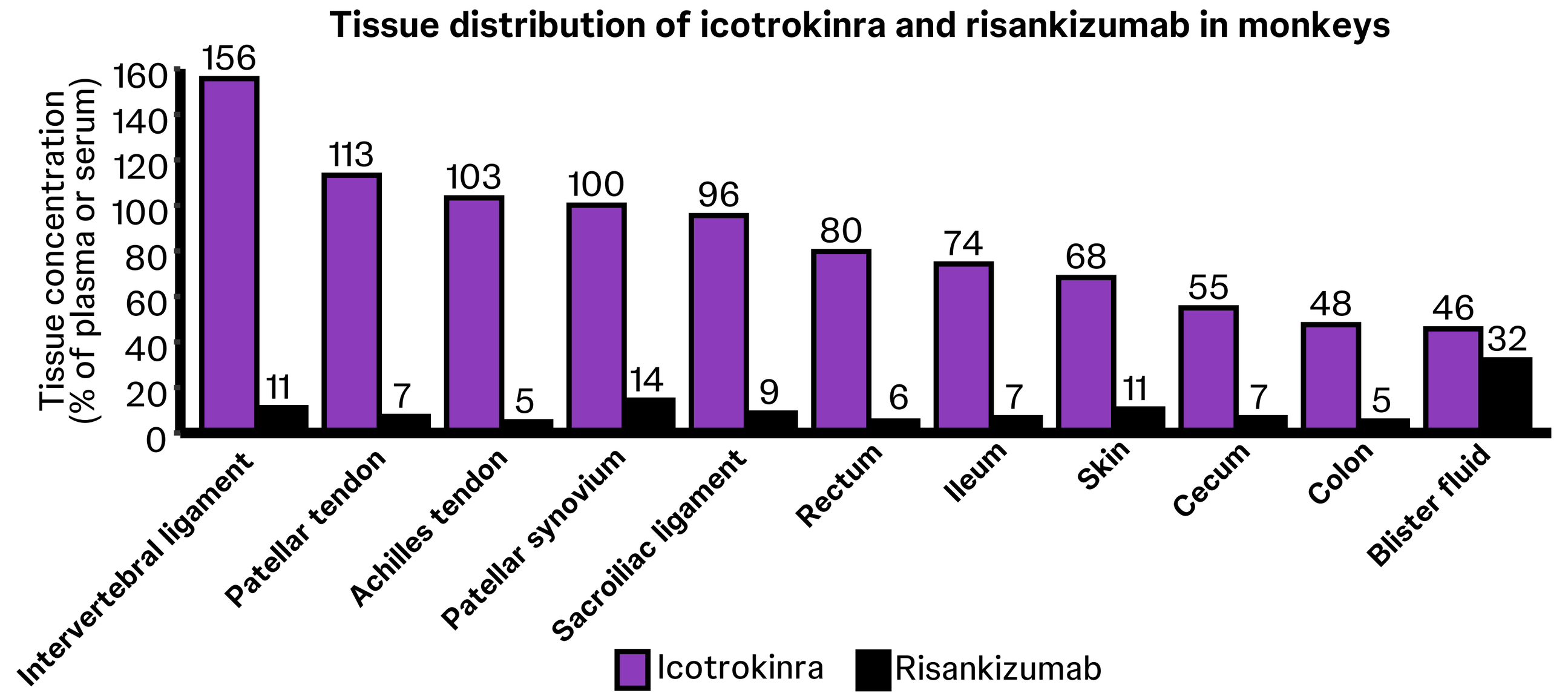
- Due to high potency, target coverage was achieved for 24 h for doses ≥2.5 mg/kg



Dotted line represents the icotrokinra IC_{50} for IL-23-induced STAT3 phosphorylation in human peripheral blood mononuclear cells after 24 h (0.01 ng/mL). SD values below 0 are not plotted. IC_{50}=half-maximal inhibitory concentration; STAT=signal transducer and activator of transcription.

Icotrokinra was freely distributed to tissues relevant to inflammatory diseases

- Icotrokinra distributed to disease-relevant tissues more extensively than risankizumab


Tissue distribution of icotrokinra and risankizumab in monkeys
Tissue concentration
(% of plasma or serum)
156
11
113
7
103
5
100
14
96
9
80
6
74
7
68
11
55
7
48
5
46
32
Intervertebral ligament
Patellar tendon
Achilles tendon
Patellar synovium
Sacroiliac ligament
Rectum
Ileum
Skin
Cecum
Colon
Blister fluid
Icotrokinra
Risankizumab

Icotrokinra tissue concentration presented as tissue:plasma percentage. Risankizumab tissue concentration presented as tissue:serum percentage.

Unchanged icotrokinra was the main drug-related component in urine and feces

- Mostly unchanged drug was detected in rat and monkey plasma
- In humans (Phase 1)
  - Fecal excretion increased with dose (ranging from 37.2% at 10 mg to 80.7% at 1000 mg)
  - Urinary excretion of unchanged drug was low (<0.001%)
  - No metabolites were detected in human plasma or urine

Mass balance of [14C]-icotrokinra and its main metabolites after oral administration

Analyte	Rat (0-24 h), % of dose			Monkey (0-96 h), % of dose		
	Feces	Urine	Total	Feces	Urine	Total
Up to 14 metabolites	2.7	0.099	2.80	2.87	0.11	2.98
Unchanged icotrokinra	**72.8**	**0.056**	**72.9**	**64.2**	**0.86**	**65.1**
Sum	**75.5**	**0.155**	**75.7**	**67.1**	**0.97**	**68.1**

Dose=300 mg/kg with target radioactivity of ~400 µCi/kg in rats and ~100 µCi/kg in monkeys.

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