Transporteurs des acides aminés:
rôles physiopathologiques dans les MHM et au-delà

Jean-François Benoist

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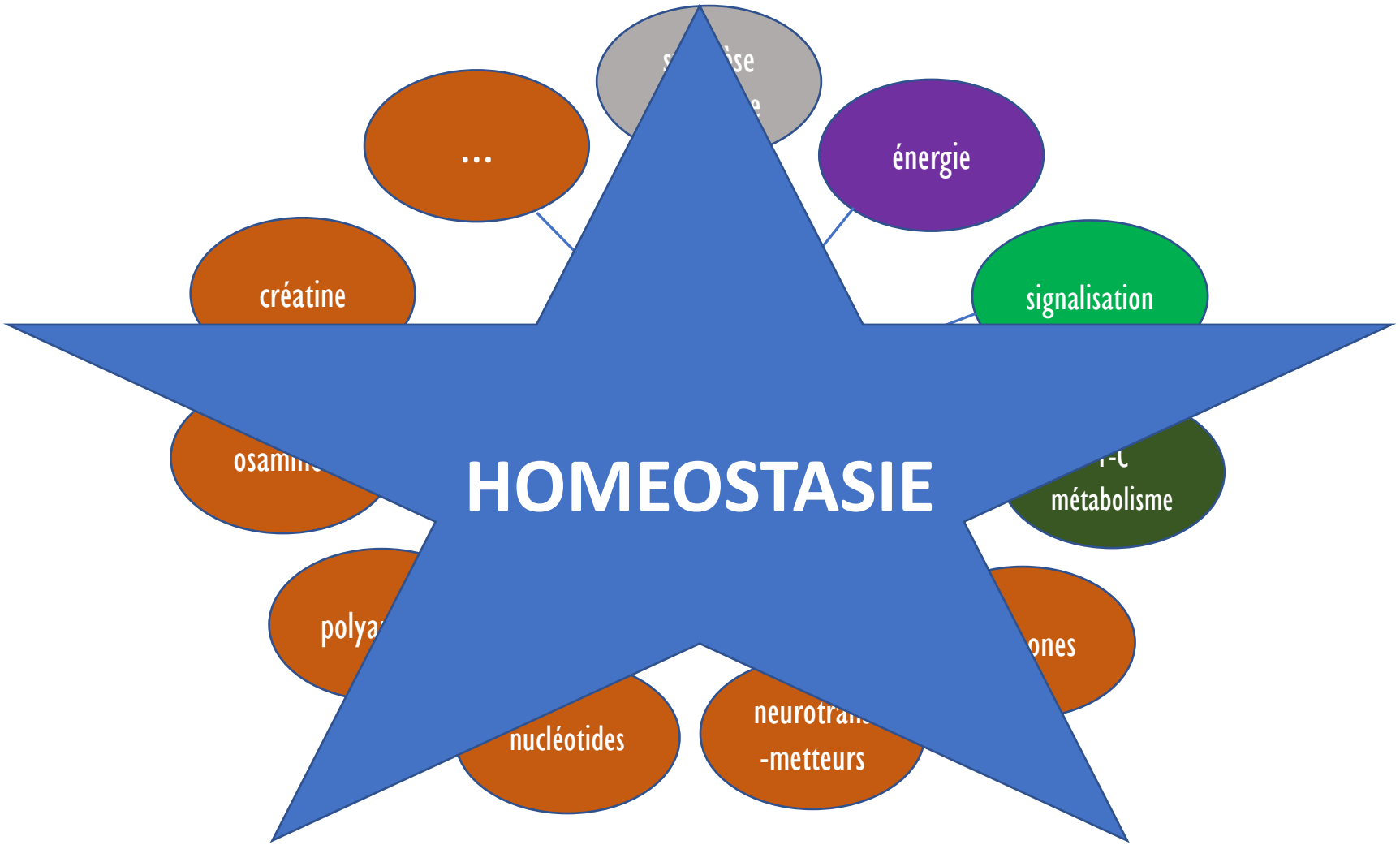
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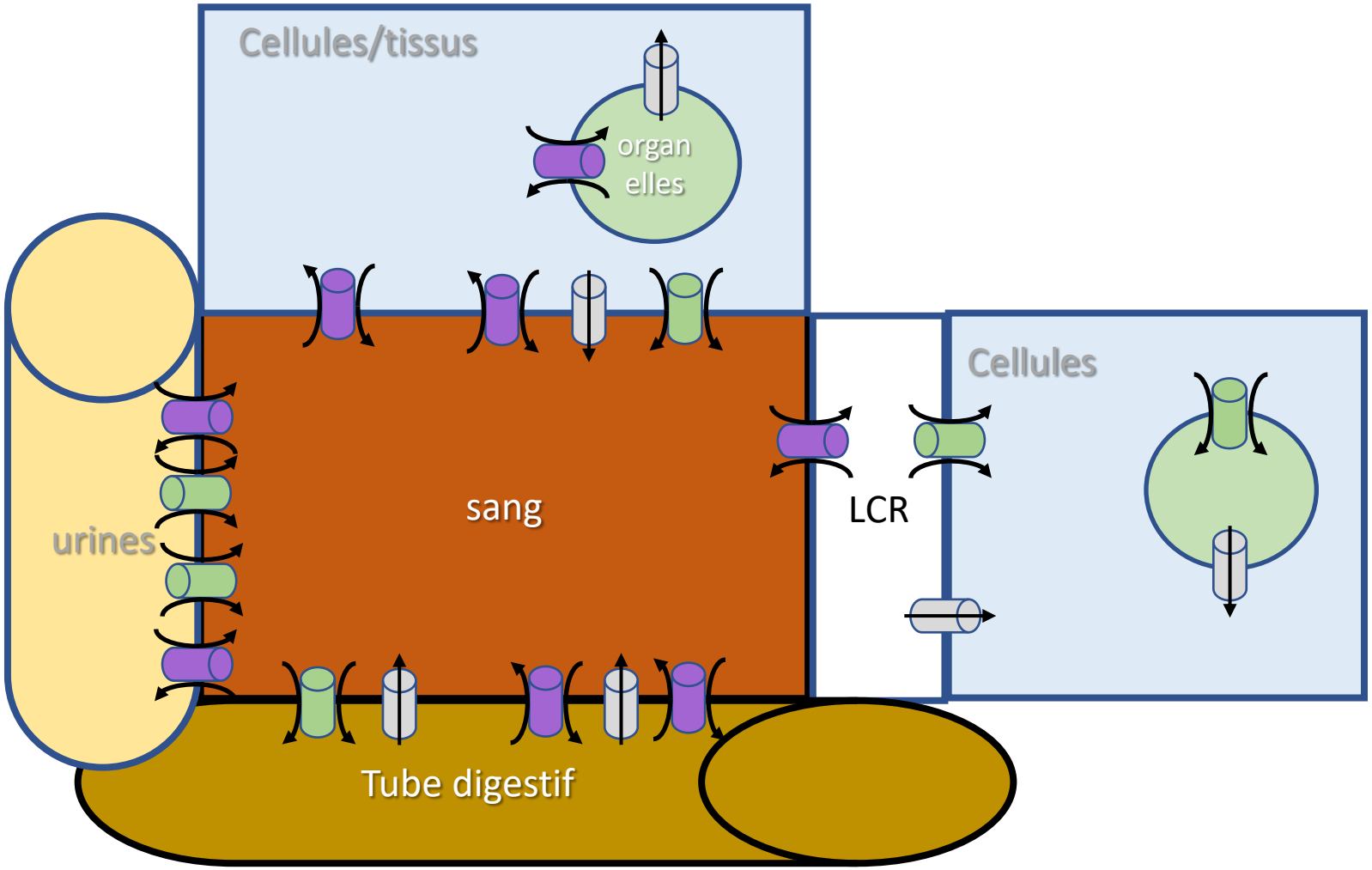
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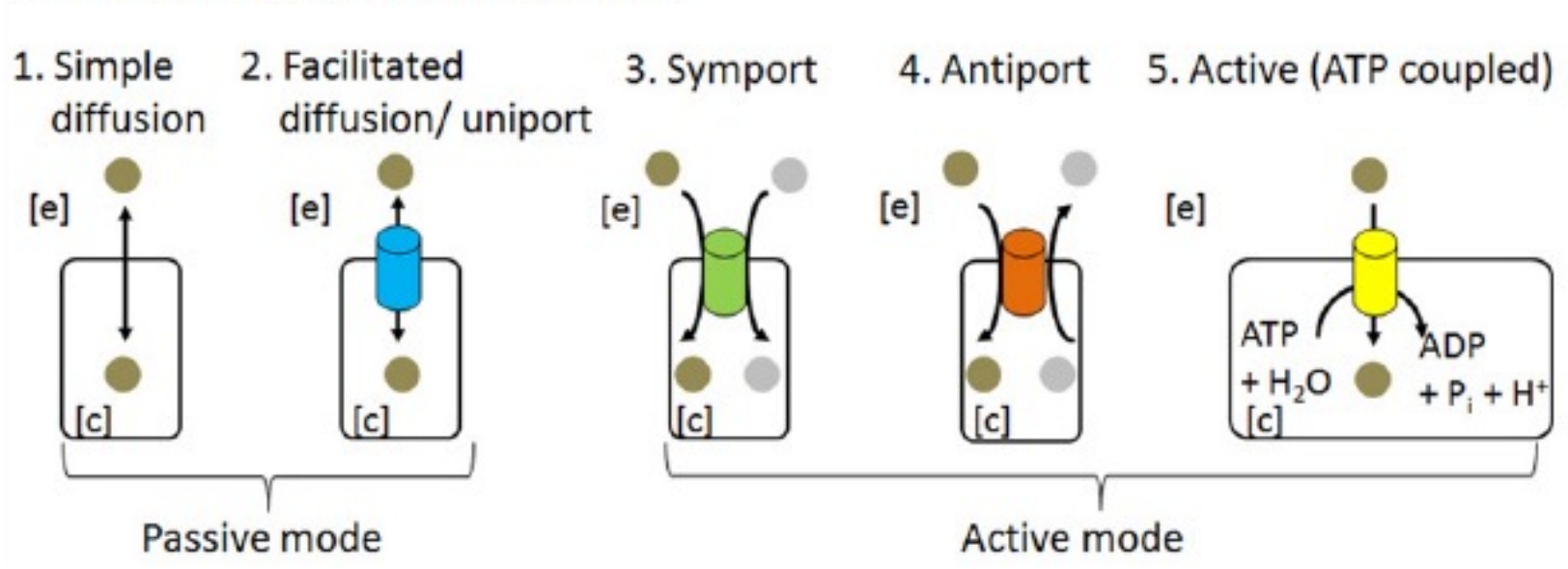
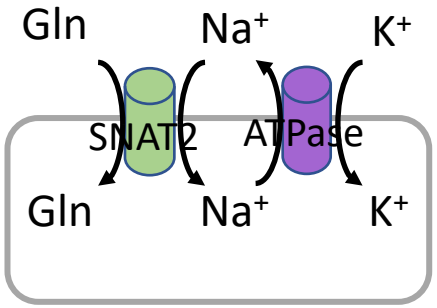
Cellules
Tube digestif

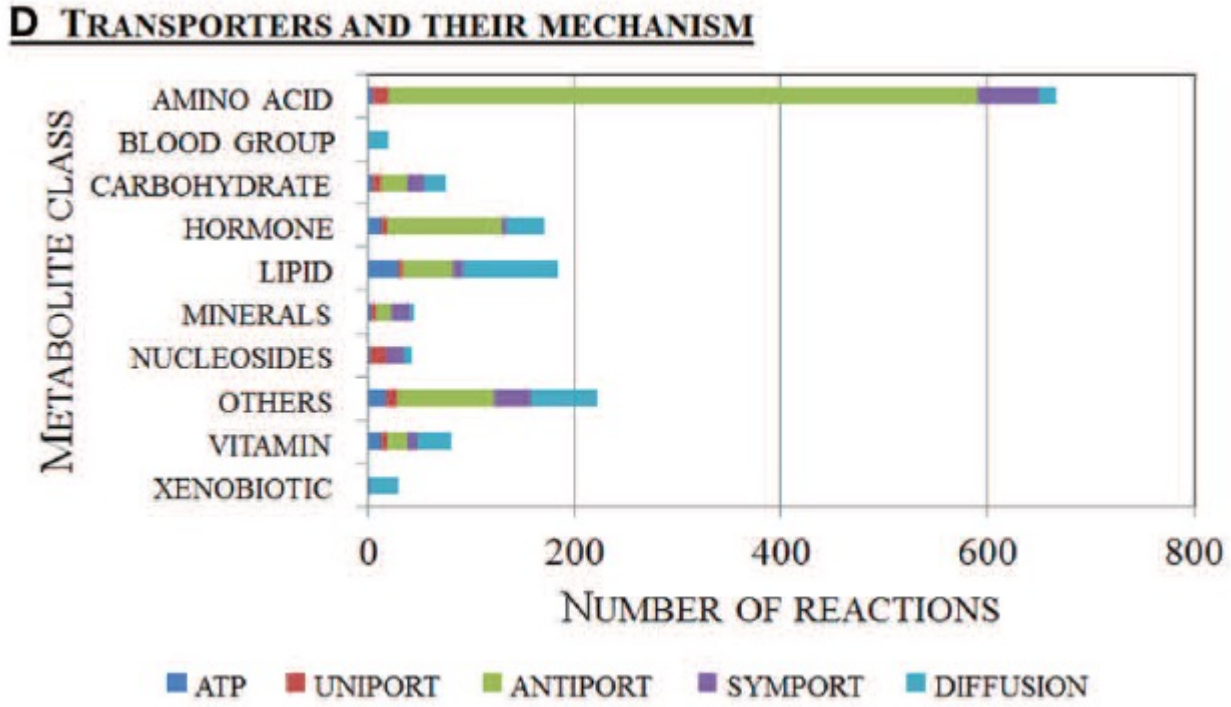
Classification des transporteurs



doi: 10.3389/fphys.2014.00091

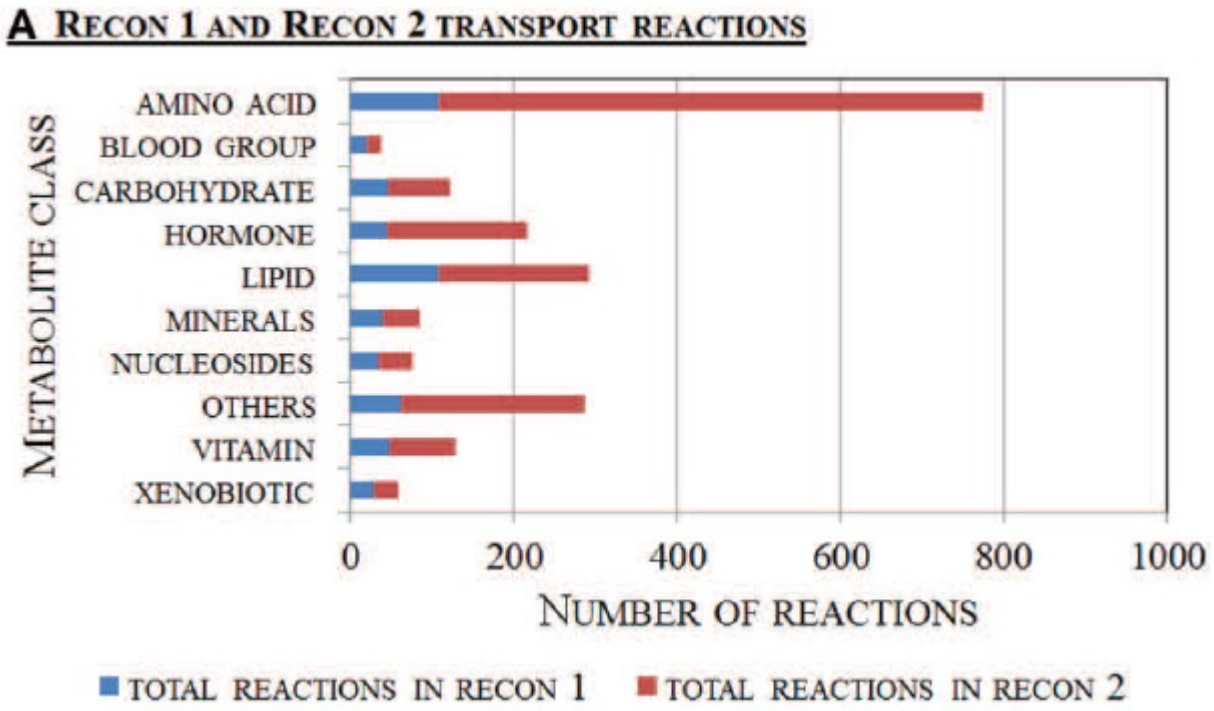


Sodium-dependent neutral amino acid transporter-2



Recon 2: nature biotechnology VOLUME 31 NUMBER 5 MAY 2013

doi: 10.3389/fphys.2014.00091



Recon 2: nature biotechnology VOLUME 31 NUMBER 5 MAY 2013

doi: 10.3389/fphys.2014.00091

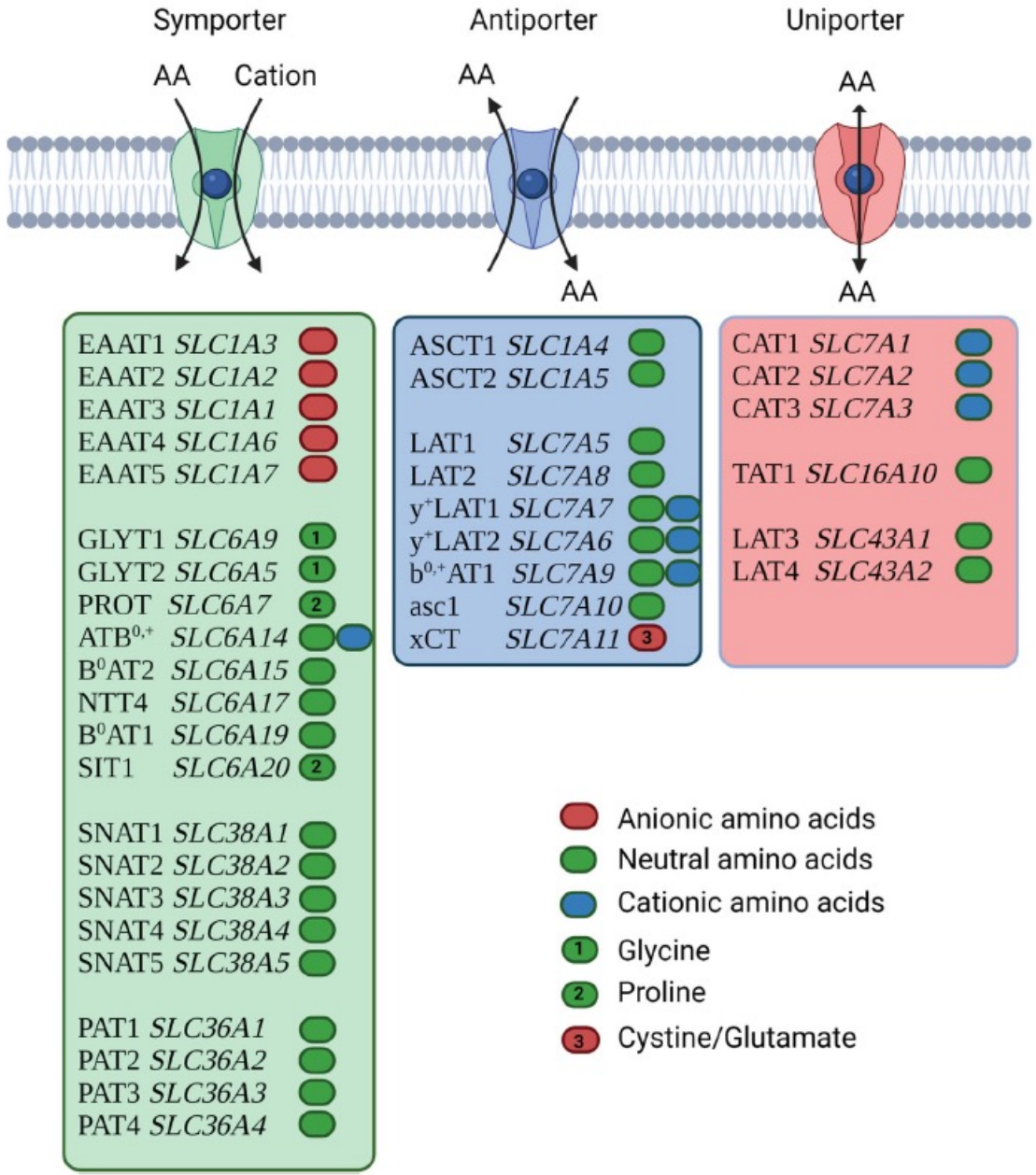
Classification par similarité entre les gènes codant pour ces transporteurs : famille des solute carriers SLC

[+]	SLC1	High-affinity glutamate and neutral amino acid transporter family	SLC1A1→ SLC1A7
[+]	SLC3	Heavy subunits of the heteromeric amino acid transporters	SLC3A1→ SLC3A2
[−]	SLC6	Sodium- and chloride-dependent neurotransmitter transporter family	SLC6A1→ SLC6A21
[+]	SLC7	Cationic amino acid transporter/glycoprotein-associated family	SLC7A1→ SLC7A14
[−]	SLC15	Proton oligopeptide cotransporter family	SLC15A1→ SLC15A4
[+]	SLC16	Monocarboxylate transporter family	SLC16A10 (autres pas AA)
[+]	SLC25	Mitochondrial carrier family	SLC25A2; 12-15 ; 18 ; 22 ; 26; 29
[+]	SLC36	Proton-coupled amino acid transporter family	SLC36A1 → SLC36A4
[+]	SLC38	System A and System N sodium-coupled neutral amino acid transporter family	SLC38A1 → SLC38A11
[−]	SLC43	Na+-independent, system-L-like amino acid transporter family	SLC43A1 → SLC43A3
[−]	SLC66	PQ-loop amino acid transporters	SLC66A1 → SLC66A4

TABLE 1. *Epithelial amino acid transport systems and their mediators*

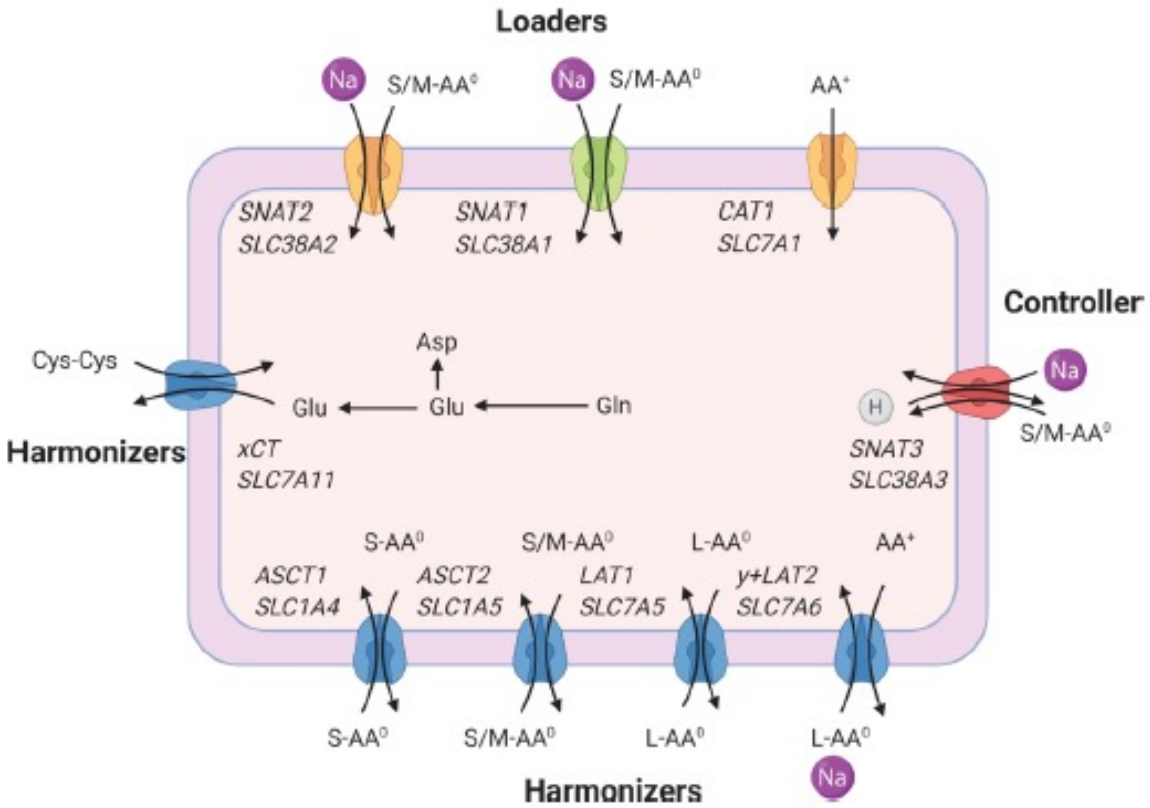
System	cDNA	SLC	Amino Acid Substrates	Analogs	Affinity	Mechanism	Ions	Expression*
A	SNAT2	SLC38A2	G,P,A,S,C,Q,N,H,M	MeAIB	Medium	S	Na^+	Ub
	SNAT4	SLC38A4	G,A,S,C,Q,N,M,AA^+	MeAIB	Medium	S	Na^+	K
ASC	ASCT1	SLC1A4	A,S,C	Cysteic acid	High	A	Na^+	K
	ASCT2	SLC1A5	A,S,C,T,Q		High	A	Na^+	K,I (AM)
asc	4F2 hc/asc1	SLC3A2/SLC7A10	G,A,S,C,T	D-AA^0	High	A		K
B^0	B^0AT1	SLC6A19	AA^0	BCH	Low	S	Na^+	K,I (AM)
	B^0AT2	SLC6A15	P,L,V,I,M	BCH	High	S	Na^+	K
$B^{0,+}$	$ATB^{0,+}$	SLC6A14	AA^0, AA^+, β-Ala	BCH	High	S	Na^+, Cl^-	I (AM)
$b^{0,+}$	rBAT/$b^{0,+}AT$	SLC3A1/SLC7A9	R,K,O,cystine		High	A		K,I (AM)
β	TauT	SLC6A6	Tau, β-Ala		High	S	Na^+, Cl^-	K (AM,BM)
Gly	XT2	SLC6A18	G		NR	NR	NR	K (AM)
IMINO	IMINO	SLC6A20	P, HO-P	MeAIB	Medium	S	Na^+, Cl^-	K,I (AM)
L	4F2hc/LAT1	SLC3A2/SLC7A5	H,M,L,I,V,F,Y,W	BCH	High	A		
	4F2hc/LAT2	SLC3A2/SLC7A8	AA^0 except P	BCH	Medium	A		K,I (BM)
	LAT3	SLC43A1	L,I,M,F	BCH	Low	U		K
	LAT4	SLC43A2	L,I,M,F	BCH	Low	U		
N	SNAT3	SLC38A3	Q,N,H		Low	S	Na^+(S), H^+(A)	K (BM)
	SNAT5	SLC38A5	Q,N,H,S,G		Low	S	Na^+(S), H^+(A)	K
PAT (Imino acid)	PAT1	SLC36A1	P,G,A GABA, β-Ala	MeAIB	Low	S	H^+	K,I (AM)
	PAT2	SLC36A2	P,G,A	MeAIB	Medium	S	H^+	K
T	TAT1	SLC16A10	F,Y,W		Low	U		K,I (BM)
X^-_{AG}	EAAT2	SLC1A2	E,D	D-Asp	High	S	Na^+,H^+(S), K^+(A)	K (BM)
	EAAT3	SLC1A1	E,D	D-Asp	High	S	Na^+,H^+(S), K^+(A)	K,I (AM)
x^-_c	4F2 hc/xCT	SLC3A2/SLC7A11	E, $cystine^-$		High	A		Ub
y^+	CAT-1	SLC7A1	R,K,O,H		Medium	U		Ub
y^+L	4F2hc/y^+LAT1	SLC3A2/SLC7A7	K,R,Q,H,M,L		High	A	Na^+(S-AA^0)	K,I (BM)
	4F2hc/y^+LAT2	SLC3A2/SLC7A6	K,R,Q,H,M,L,A,C		High	A	Na^+(S-AA^0)	K,I (BM)

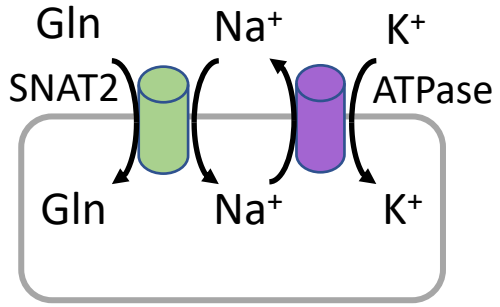
NR, not reported; A, antiport; AA^0, neutral amino acids; AA^+, cationic amino acids; U, uniport; S, symport; S-AA^0, symport together with neutral amino acids; K, kidney; I, intestine; AM, apical membrane; BM, basolateral membrane; Ub, ubiquitous. Amino acids are given in one-letter codes. O, ornithine; HO-P, hydroxyproline. Affinity: high, <100 μM; medium, 100 μM to 1 mM; low, >1 mM. * Expression in epithelial cells of kidney and intestine.



NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-021-25563-x

contrôle physiologique de l'homéostasie intracellulaire des concentrations d'AA





SNAT1 : Q A N C H S
SNAT2 : Q A N C H S G M S

NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-021-25563-x

« MHM » et anomalies des transporteurs d'acides aminés

pathologie	transporter	AA°	gène	localisation
maladie de Hartnup	B°AT1	AA°	SLC6A19	mb pl pôle apical
LPI	y+LAT1	K,R,O,Q,H M,L	SLC7A7	mb pl pôle basolatéral
Cystinurie lysinurie	$b^{°,+}$ AT1	K,R,O,cystine	SLC3A1/SLC7A9	mb pl pôle apical
Citrine	AGC2	D,E	SLC25A13	mb mito
HHH	ORC1	O,C,D,E	SLC25A15	mb mito
Cytopathie mito	SAMc	SAM, SAH	SLC25A26	mb mito
cystinose	CTNS	cystine	SLC66A4	mb lyso

<u>entités reconnues comme traits biochimiques & non-maladies :</u>

- Aminoacidurie dicarboxyllique SLC1A 1 (OMIM#222730)
- Imminoglycinurie ou hyperglycinurie SLC36A2 (OMIM#242600 & #138500)

Maladies «neurologiques/neurosensorielles» et anomalies des transporteurs d'acides aminés

pathologie	transporter	AA	gène	localisation
Enceph. épileptique	EAAT2	E,D	SLC1A2	mb pl
Ataxie récurrente	EAAT1	E,D	SLC1A3	mb pl
Tétraplégie spastique	ASCT1	A,S,C	SLC1A4	mb pl
Hyperplexie	GLYT2	G	SLC6A5	mb pl
Dégéneresc. rétienene et cardiomyopathie	Taut	taurine	SLC6A6	mb pl
Encéphalopathie	GLYT1	G	SLC6A9	mb pl
surdité	VGLUT3	E	SLC17A8	mb vesicule neuronale
Enceph. épileptique	ARALAR	D,E	SLC25A12	mb mito
Enceph. épileptique	GC1	E	SLC25A22	mb mito
Enceph. épileptique	SNAT3	Q,N,H,A	SLC38A3	mb pl
Hypoplasie foveale	SNAT8	Q,N,H,A	SLC38A8	mb pl
Synd. neurodégén.	CTL1	choline	SLC44A1	mb pl
Syndrome autistique	*LAT1*	*AA°*	*SLC7A5*	*mb pl (BHE)*

Utilisation des propriétés de ces transporteurs en thérapeutique pour les MHM

Phénylcétonurie

- Traitement par acides aminés neutres : compétition pour le passage des acides aminés neutres au niveau de la BBB
- Intérêt de l'utilisation d'inhibiteurs du transport de la phénylalanine ?
  quel transporteur cibler ?

JCI insight

RESEARCH ARTICLE

Inhibiting neutral amino acid transport for the treatment of phenylketonuria

Adam M. Belanger, Malgorzata Przybylska, Estelle Gefteas, Matthew Furgerson, Sarah Geller, Alla Kloss, Seng H. Cheng, Yunxiang Zhu, and Nelson S. Yew

Sanofi, Framingham, Massachusetts, USA.

The neuropathological effects of phenylketonuria (PKU) stem from the inability of the body to metabolize excess phenylalanine (Phe), resulting in accumulation of Phe in the blood and brain. Since the kidney normally reabsorbs circulating amino acids with high efficiency, we hypothesized that preventing the renal uptake of Phe might provide a disposal pathway that could lower systemic Phe levels. SLC6A19 is a neutral amino acid transporter responsible for absorption of the majority of free Phe in the small intestine and reuptake of Phe by renal proximal tubule cells. Transgenic KO mice lacking SLC6A19 have elevated levels of Phe and other amino acids in their urine but are otherwise healthy. Here, we crossed the *Pah*^{enu2} mouse model of PKU with the *Slc6a19*-KO mouse. These mutant/KO mice exhibited abundant excretion of Phe in the urine and an approximately 70% decrease in plasma Phe levels. Importantly, brain Phe levels were decreased by 50%, and the levels of key neurotransmitters were increased in the mutant/KO mice. In addition, a deficit in spatial working memory and markers of neuropathology were corrected. Finally, treatment of *Pah*^{enu2} mice with *Slc6a19* antisense oligonucleotides lowered Phe levels. The results suggest that inhibition of SLC6A19 may represent a novel approach for the treatment of PKU and related aminoacidopathies.

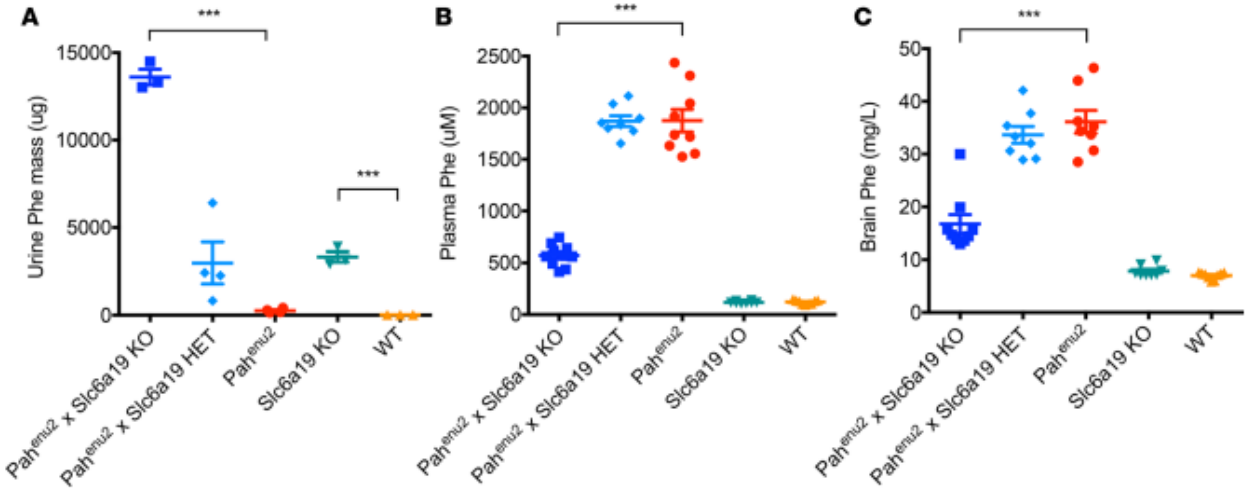


Figure 2. Decreased Phe levels in *Pah*^{enu2} mice lacking *Slc6a19*. (**A**) Excretion of Phe in the urine of *Pah*^{enu2} × *Slc6a19*-KO mice. Mice were placed in metabolic cages, and urine was collected for 24 hours. (**B**) Phe levels in plasma. (**C**) Phe levels in the brain. Animals were perfused with PBS and whole brains were harvested. Phe was quantitated by HPLC/tandem MS/MS. Phe is expressed as milligram Phe per liter of brain homogenate. n = 8–10 animals/group. One-way ANOVA was performed, follow by Tukey's multiple comparisons test. ***$P < 0.0001$. Mean ± SEM is shown.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 28 February 2020
doi: 10.3389/fphar.2020.00140

Novel Chemical Scaffolds to Inhibit the Neutral Amino Acid Transporter B^0AT1 (SLC6A19), a Potential Target to Treat Metabolic Diseases

Aditya Yadav[1†], Nishank Shah[1†], Praveen Kumar Tiwari[2], Kiran Javed[1], Qi Cheng[1], Indrapal Singh Aidhen[2] and Stefan Bröer[1]*

[1] Research School of Biology, Australian National University, Canberra, ACT, Australia, [2] Department of Chemistry, Indian Institute of Technology Madras, Chennai, India

JNT-517 de JNANA Therapeutics essais préclinique

Utiliser la machinerie des transporteurs d'acide aminés pour acheminer des principes actifs vers une cible

Déjà utilisé en thérapeutique :

- L-DOPA parkinson (SLC6A19 - SLC7A5)
- Anti épileptique gabapentin (SLC7A5)
- antibiotique (PEPT1)
- imagerie du cancer (PETscan)

LAT1 (SLC7A5) : forte expression au niveau du **cortex cérébral, la BBB, la barrière sang/rétine**, moelle osseuse et certaines cellules cancéreuses

→ Nombreux test de couplage AA-PA sont en court d'étude (*in vitro*) pour vectoriser des PA via LAT1 notamment pour favoriser l'action au niveau du SNC

molecular pharmaceutics

dx.doi.org/10.1021/mp2001878 | Mol. Pharmaceutics 2011, 8, 1857–1866

ARTICLE

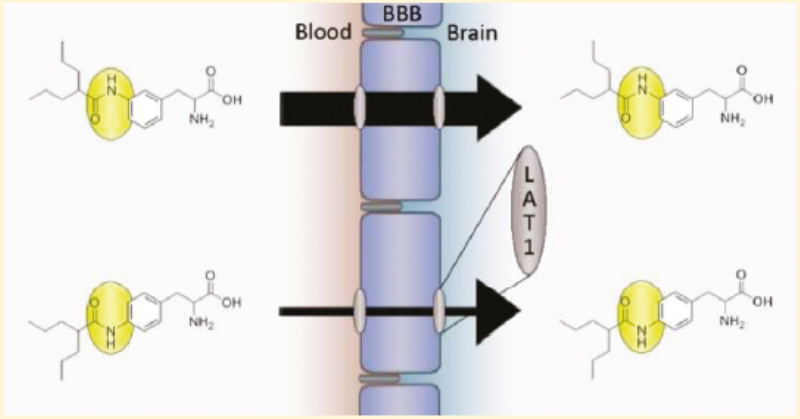
pubs.acs.org/molecularpharmaceutics

Large Amino Acid Transporter 1 (LAT1) Prodrugs of Valproic Acid: New Prodrug Design Ideas for Central Nervous System Delivery

Lauri Peura,*,† Kalle Malmioja,† Krista Laine, Jukka Leppänen, Mikko Gynther,‡ Antti Isotalo, and Jarkko Rautio

School of Pharmacy, University of Eastern Finland, P.O. Box 1627, FI-70211, Kuopio, Finland

ABSTRACT: Central nervous system (CNS) drug delivery is a major challenge in drug development because the blood−brain barrier (BBB) efficiently restricts the entry of drug molecules into the CNS at sufficient amounts. The brain uptake of poorly penetrating drugs could be improved by utilizing the transporters at the BBB with a prodrug approach. In this study, we designed four phenylalanine derivatives of valproic acid and studied their ability to utilize a large amino acid transporter 1 (LAT1) in CNS delivery with an aim to show that the meta-substituted phenylalanine prodrugs bind to LAT1 with a higher affinity compared with the affinity of the para-substituted derivatives. All of the prodrugs crossed the BBB carrier mediatedly via LAT1 in *in situ* rat brain perfusion. For the first time, we introduced a novel meta-substituted phenylalanine analogue promoiety which improved the LAT1 affinity 10-fold and more importantly the rat brain uptake of the prodrug 2-fold compared with those of the para-substituted derivatives. Therefore, we have characterized a new prodrug design idea for CNS drug delivery utilizing a transporter-mediated prodrug approach.



Utiliser la signalisation par les AA et leur transporteur comme cible thérapeutique : reprogrammation des cellules cancéreuses

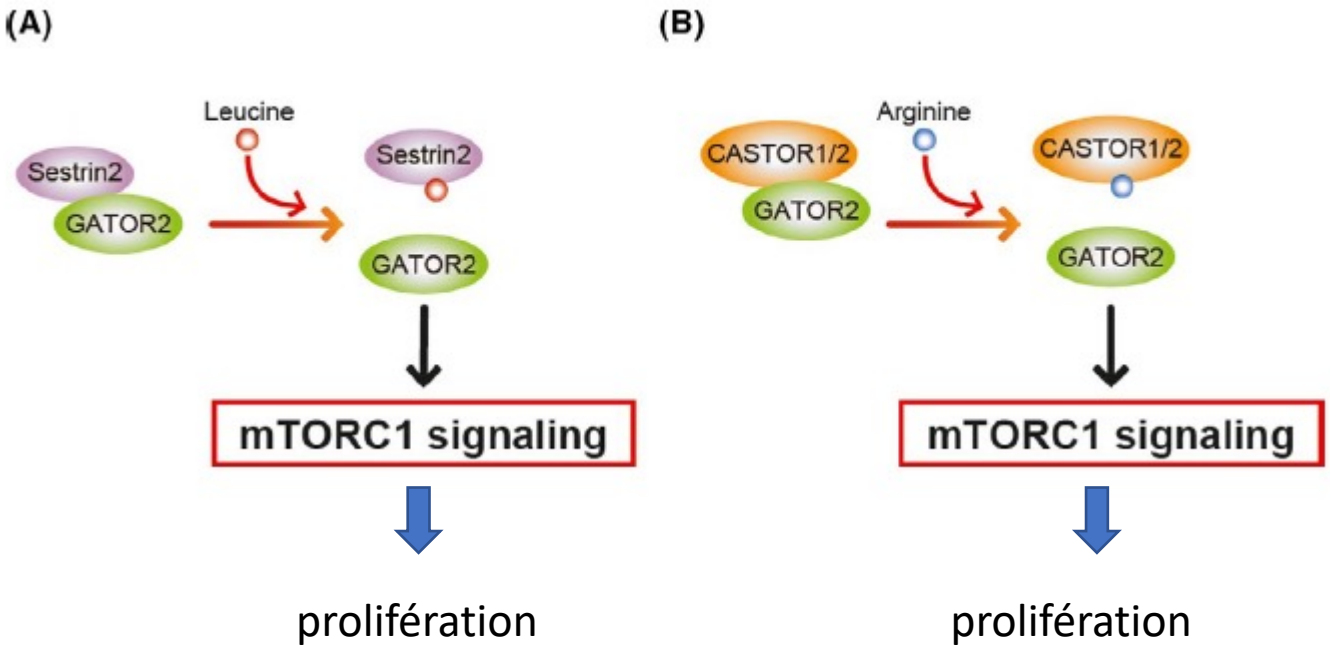
Cellules incapables de synthétiser AA essentiels et capacité limitée pour les autres.
L'adaptabilité des cellules en cas de prolifération rapide repose sur les capacités d'uptake

Certains acides aminés sont spécifiquement utilisés ou sont limitants dans certains type de cellules cancéreuses pour stimuler leur croissance
Expression aberrante de certains transporteurs dans les cellules cancéreuses = cibles thérapeutiques

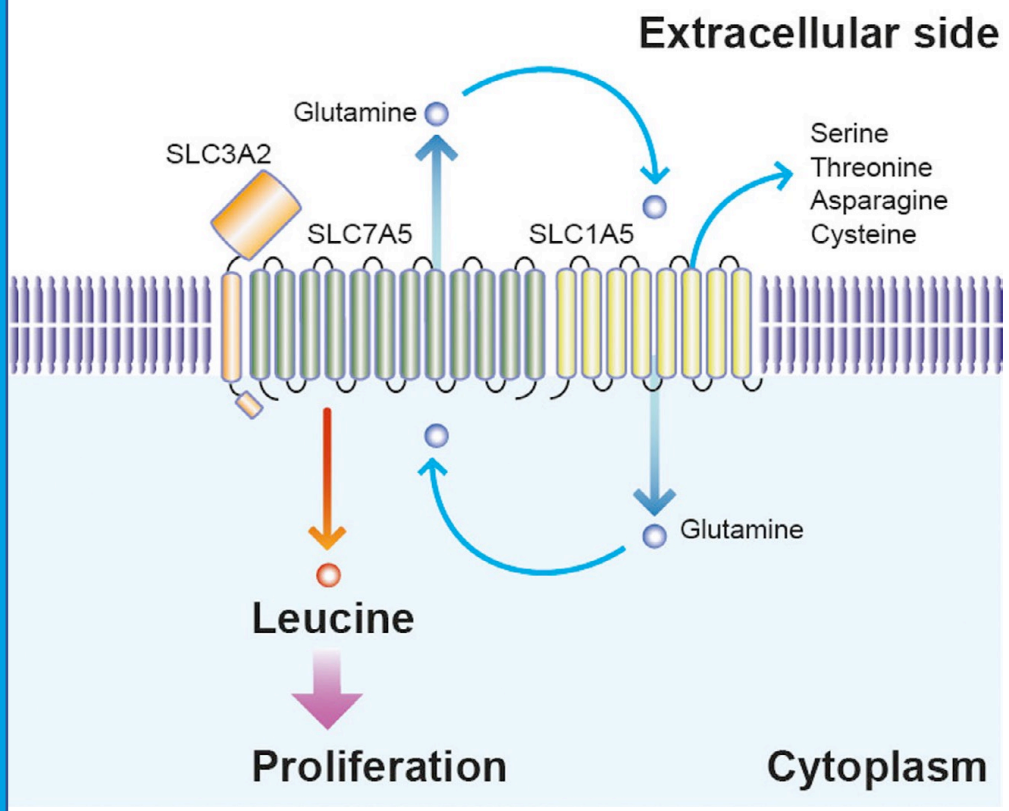
Ex : l'asparagine pour les lymphoblastes → L-asparaginase utilisée en 1er ligne des chimio LAL depuis plus de 50 ans

Dans un grand nombre de tumeurs la croissance cellulaire est dépendante de la concentration en leucine

Certains acides aminés contrôlent la croissance cellulaire via le complexe mTORC1



Adapté de Cancer science DOI: 10.1111/cas.15006



Ex cancer du sein cellule ER+ surexpriment SLC1A5 (important Gln) et possèdent plus de transporteurs SLC7A5 à leur surface que les cellule ER-

Tissue	Type of cancer cells	SLC7A5 inhibitors used in	Patient data (IHC or K-M plot)	Relationship to therapeutic resistance	References
Breast	Estrogen receptor (ER)-positive breast cancer	BCH, JPH203	Yes	Yes	[16]
	Luminal type of breast cancer	-	Yes	Yes	[29]
	Luminal type of breast cancer	-	Yes	-	[30]
	Endocrine therapy-treated patients	-	Yes	Yes	[31]
Lung	NSCLC	-	Yes	-	[32]
	NSCLC	BCH	-	-	[33]
Prostate	Prostate cancer	-	Yes	Yes	[34]
Biliary tract	Cholangiocarcinoma	BCH	Yes	-	[35]
	Cholangiocarcinoma	JPH203	-	-	[36]
	Biliary tract cancer	-	Yes	-	[37]
Gastrointestinal cells	Gastric cancer cell line/colon cancer cell line	JPH203	-	-	[38]
	Gastric cancer cell line	Knockdown	Yes	-	[39]
	Esophageal squamous cell carcinoma	-	Yes	-	[40]
Colon	KRAS-mutant CRC	-	-	-	[41]
Pancreas	Pancreatic ductal adenocarcinoma	-	Yes	-	[42]
	Pancreatic ductal adenocarcinoma	-	Yes	Yes	[43]
	Pancreatic ductal adenocarcinoma	-	Yes	-	[44]
Skin	Basal cell carcinoma	-	Yes	-	[45]
	Melanoma	-	Yes	-	[46]
Ovary	Ovarian cancer	-	Yes	Yes	[47]
	Ovarian cancer	BCH	-	-	[48]
Uterine	Endometrioid carcinoma	-	Yes	Yes	[49]
	Endometrioid carcinoma	BCH	Yes	-	[50]
Thyroid	Anaplastic thyroid cancer	JPH203	Yes	-	[51]
	Anaplastic thyroid cancer	JPH203	Yes	-	[52]
	Papillary thyroid cancer	-	Yes	-	[53]
Liver	hepatocellular carcinoma	-	Yes	-	[54]
Neuroendocrine tissue	Pheochromocytoma/medullary thyroid carcinoma	-	Yes	-	[55]
	Medulloblastoma	JPH203	-	-	[56]
Blood	T-cell acute lymphoblastic leukemia/T-cell lymphoblastic lymphoma	BCH, JPH203	Yes	-	[57]
Kidney	Renal cell carcinoma	JPH203	Yes	-	[58]
Bone	Rhabdomyosarcoma, synovial	-	Yes	-	[59]

Cancer science DOI: 10.1111/cas.15006