Découverte de biomarqueurs par analyse du métabolome

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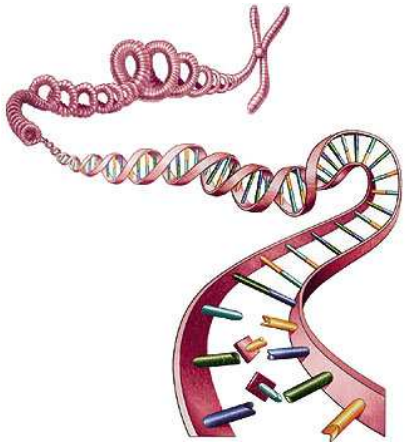
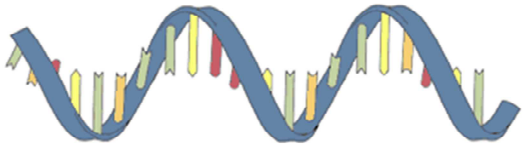
Les approches globales «omiques»



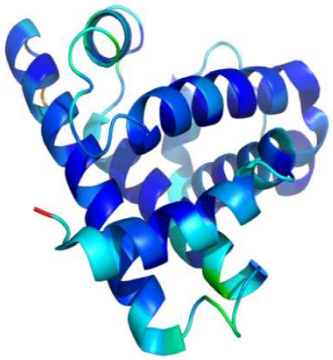
Les gènes
Le génome

génomique
polymorphisme



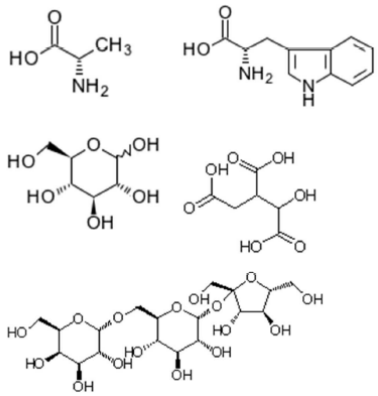
Les ARN messagers
Le transcriptome

transcritomique



Les protéines
Le protéome

protéomique



Les métabolites
Le métabolome

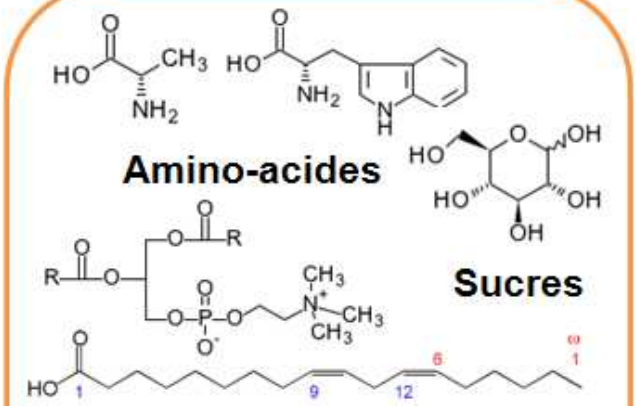
métabolomique

GENOTYPE

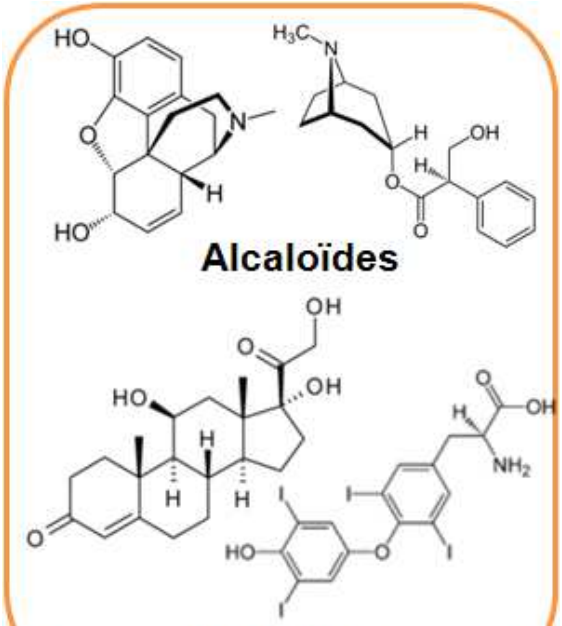
PHENOTYPE

Métabolites et métabolome

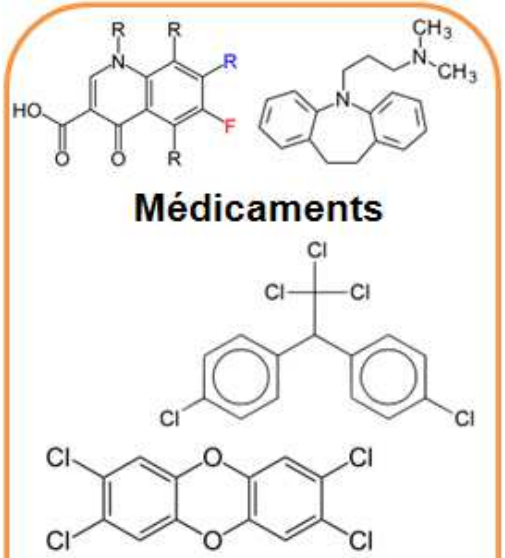
Métabolites primaires



Métabolites secondaires



Xénobiotiques

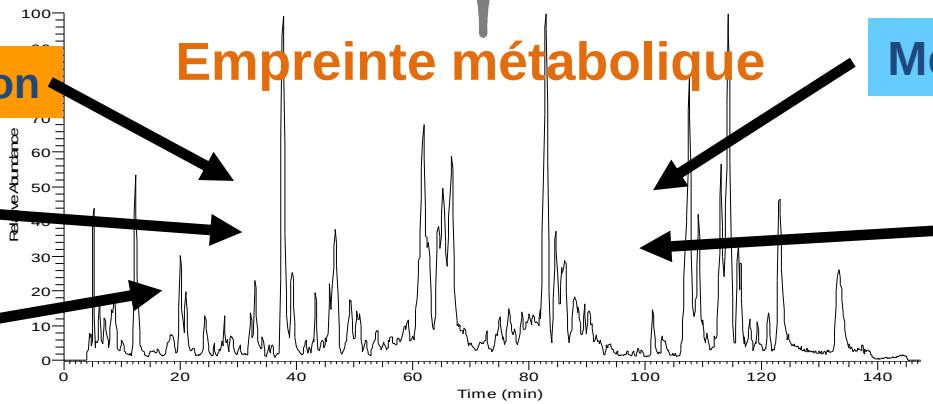


Empreinte métabolique

Alimentation / Boisson

Flore intestinale

Pathologie

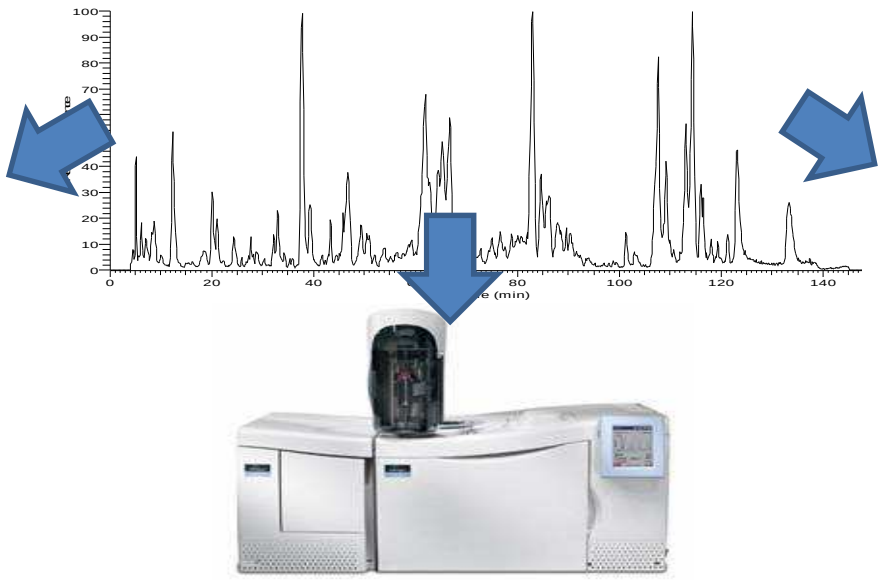


Métabolisme «central»

Environnement : xénobiotiques (polluants, médicaments…)

Acquisition des empreintes métaboliques

Empreinte métabolique



RMN

- Simple, non invasif
- Rapide
- Applicable à des biomatériaux intacts et aux grandes séries

Mais :

- Sensibilité limitée
- Difficulté d'identification de composés inconnus

GC-EI-MS

- Sensible
- Reproductible
- Bibliothèques de spectres de masse

Mais :

- Modification chimique requise pour les composés non volatils
- Composés non thermosensibles

API-MS

- Accès à la masse moléculaire (identification)
- Analyse des molécules thermolabiles
- sensible

Mais:

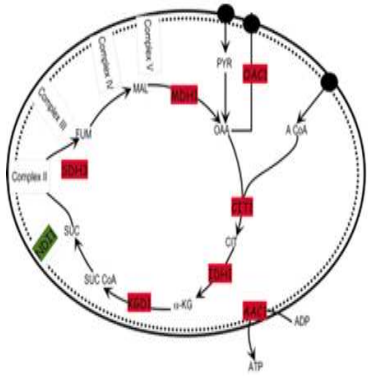
peu reproductible

Déroulement d'une analyse métabolomique

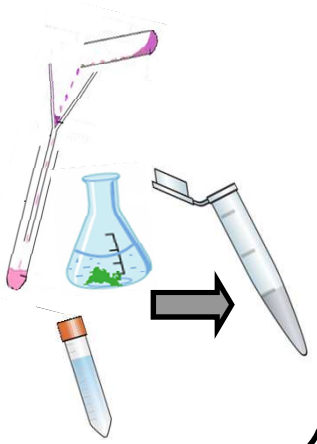
Biological context

Biological investigation

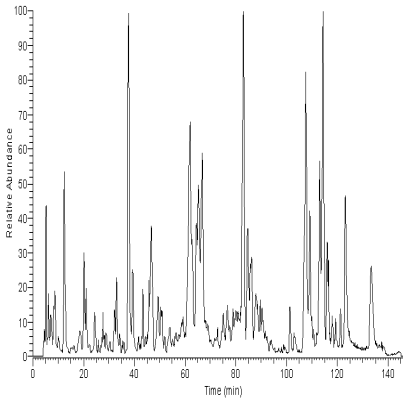
Metabolic network



Sample preparation



Fingerprinting

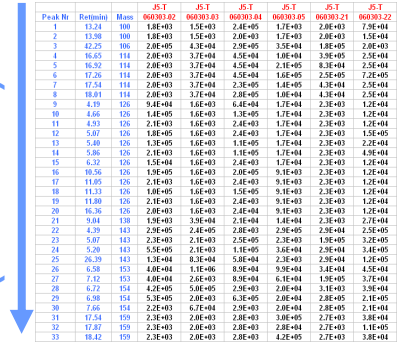


Data analysis

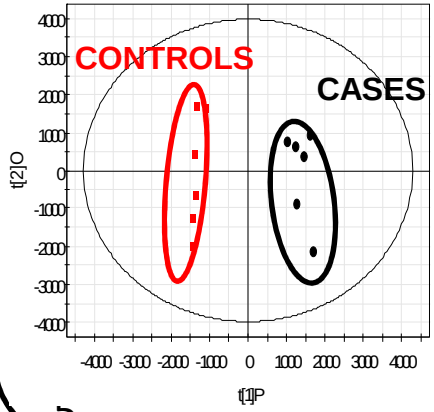
Automatic peak detection

Samples

VARIABLES (RT-MASSES)

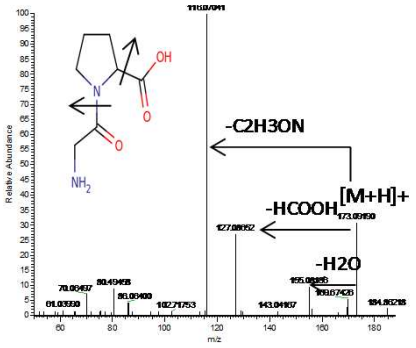


Statistical analysis

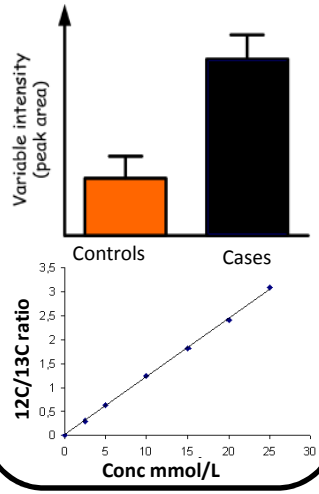


Biomarker identification

Databases, MS/MS …



Quantification



«Metabolome Wide Association Studies»
(Holmes E., Cell, 2008)
(Gieger C, Plos Genetics, 2008)

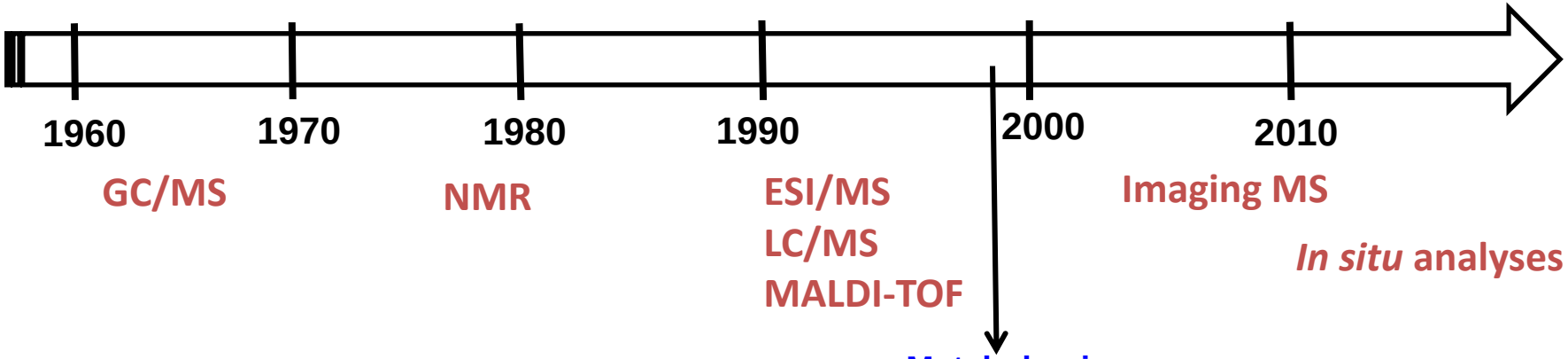
Biomarker discovery (cohort size<100)

Intermap study (NMR)
4630 participants
(Holmes E., Nature, 2008)

Sarcosine as a biomarker of aggressive prostate cancers
(Skreekumar, Nature 2009)

Microbiome interaction

Chronobiology, epigenetics



Metabolomics
Metabonomics: The metabolic response of living systems to physiopathological stimuli via multivariate statistical analysis of biological NMR spectra.
(Nicholson et al., 1999)

Quelle information tirer de la métabolomique?

Des biomarqueurs:

de diagnostic,
de suivi d'évolution (ex. agressivité de cancers…)
d'activité des thérapies
de toxicité des thérapies

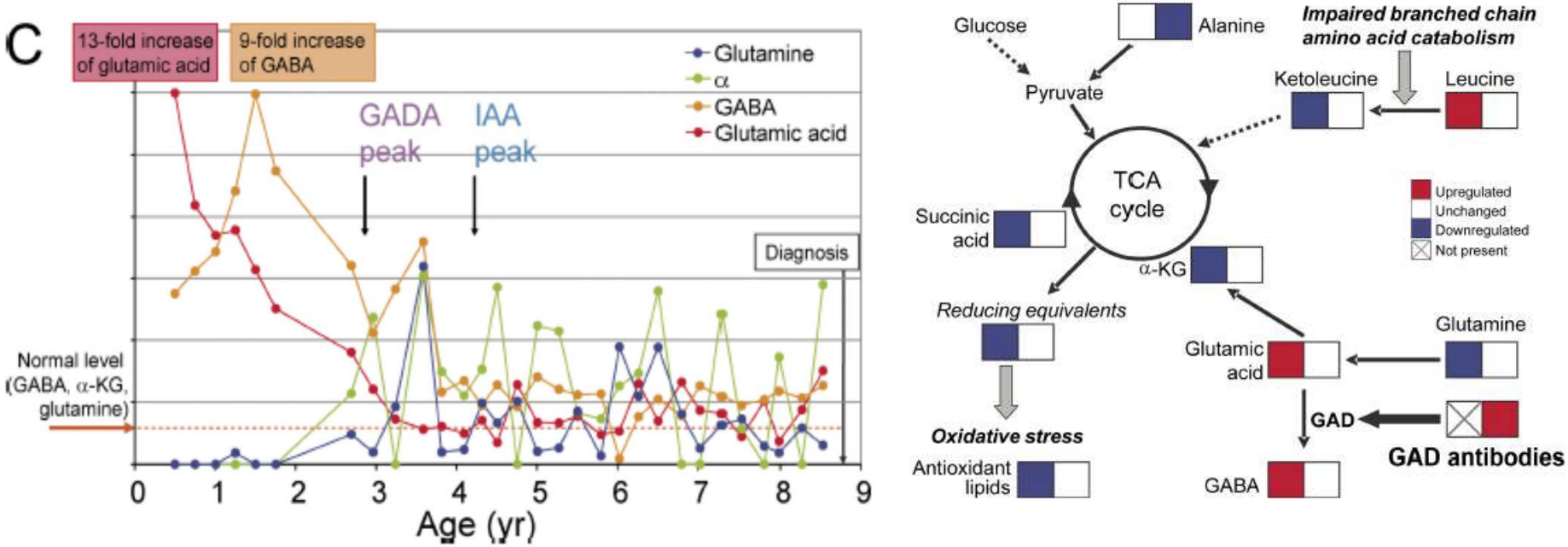
Aspects mécanistiques:

modèles cellulaires et animaux

Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes

J. Exp. Med. Vol. 205 No. 13 2975-2984

Matej Orešič,[1] Satu Simell,[2] Marko Sysi-Aho,[1] Kirsti Näntö-Salonen,[2] Tuulikki Seppänen-Laakso,[1] Vilhelmiina Parikka,[2] Mikko Katajamaa,[1] Anne Hekkala,[4] Ismo Mattila,[1] Päivi Keskinen,[5] Laxman Yetukuri,[1] Arja Reinikainen,[6] Jyrki Lähde,[5] Tapani Suortti,[1] Jari Hakalax,[2] Tuula Simell,[2] Heikki Hyöty,[7,8] Riitta Veijola,[4] Jorma Ilonen,[3,9] Riitta Lahesmaa,[6] Mikael Knip,[5,10] and Olli Simell[2]



(2011) nature medicine

Metabolite profiles and the risk of developing diabetes

Thomas J Wang[1–3], Martin G Larson[3,4], Ramachandran S Vasan[3,5], Susan Cheng[2,3,6], Eugene P Rhee[1,7,8], Elizabeth McCabe[2,3], Gregory D Lewis[1,2,8], Caroline S Fox[3,9,10], Paul F Jacques[11], Céline Fernandez[12], Christopher J O'Donnell[2,3,8], Stephen A Carr[8], Vamsi K Mootha[8,13,14], Jose C Florez[8,13], Amanda Souza[8], Olle Melander[15], Clary B Clish[8] & Robert E Gerszten[1,2,8]

Emerging technologies allow the high-throughput profiling of metabolic status from a blood specimen (metabolomics). We investigated whether metabolite profiles could predict the development of diabetes. Among 2,422 normoglycemic individuals followed for 12 years, 201 developed diabetes. Amino acids, amines and other polar metabolites were profiled in baseline specimens by liquid chromatography–tandem mass spectrometry (LC-MS). Cases and controls were matched for age, body mass index and fasting glucose. Five branched-chain and aromatic amino acids had highly significant associations with future diabetes: isoleucine, leucine, valine, tyrosine and phenylalanine. A combination of three amino acids predicted future diabetes (with a more than fivefold higher risk for individuals in top quartile). The results were replicated in an independent, prospective cohort. These findings underscore the potential key role of amino acid metabolism early in the pathogenesis of diabetes and suggest that amino acid profiles could aid in diabetes risk assessment.

61 metabolites monitored using LC-MS/MS

1. Framingham study: 189 diabetes patients with 189 matched controls
2. Replication analysis (Malmö diet and cancer study): 163 cases and 163 controls

BCAA as modulators of insuline secretion
Circulating BCAA may promote insuline resistance / are an early manisfestation of insuline resistance

Genetics Meets Metabolomics: A Genome-Wide Association Study of Metabolite Profiles in Human Serum

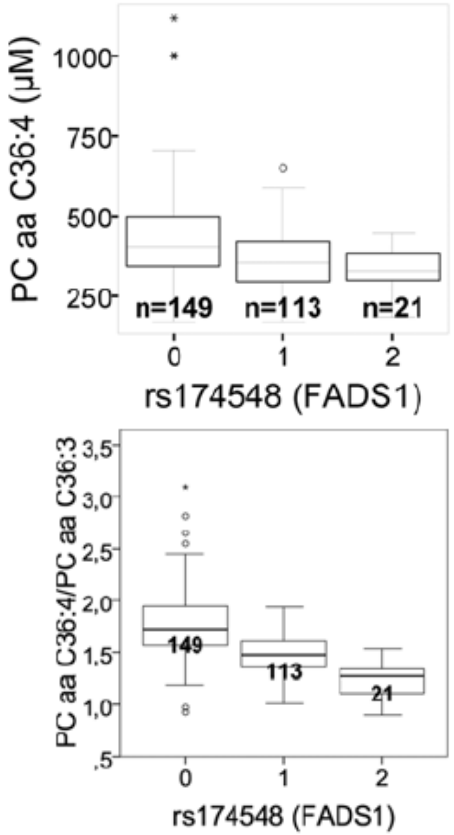
PLoS GENETICS (2008)

Christian Gieger[1,2], Ludwig Geistlinger[1], Elisabeth Altmaier[3,4], Martin Hrabé de Angelis[5,6], Florian Kronenberg[7], Thomas Meitinger[8,9], Hans-Werner Mewes[3,10], H.-Erich Wichmann[1,2], Klaus M. Weinberger[11], Jerzy Adamski[5,6], Thomas Illig[1], Karsten Suhre[3,4]*

«Genetically determined metabotypes»

Quantitative measurement of 363 metabolites in 284 human serum samples

Polymorphism in the *FADS1* (fatty acid delta 5 desaturase) gene



enumerator	denominator	mean	ncases	p-value	estimate	explained variance
Single metabolites (four double bonds)						
PC a C20:4*	1	5.094	284	5.3×10^{-7}	−0.293	8.58%
PC aa C34:4	1	3.249	284	3.3×10^{-3}	−0.174	3.04%
PC aa C36:4	1	399.407	284	4.5×10^{-8}	−0.318	10.11%
PC aa C38:4	1	209.050	284	4.9×10^{-6}	−0.268	7.17%
PC ae C36:4	1	35.160	284	1.7×10^{-3}	−0.186	3.46%
PC ae C38:4	1	30.117	284	1.4×10^{-4}	−0.224	5.03%
PE aa C38:4	1	5.357	284	0.13	−0.090	0.81%
PI aa C38:4*	1	27.025	284	0.012	−0.149	2.22%
Single metabolites (three double bonds)						
PC a C20:3*	1	2.461	208	0.86	−0.013	0.02%
PC aa C34:3	1	30.751	284	0.21	0.075	0.56%
PC aa C36:3	1	250.496	284	0.56	0.035	0.12%
PC aa C38:3	1	123.002	284	0.66	−0.027	0.07%
PC ae C36:3	1	19.697	284	0.17	0.081	0.66%
PC ae C38:3	1	10.641	284	0.74	0.020	0.04%
PE aa C38:3	1	1.623	132	0.92	−0.009	0.01%
PI aa C38:3*	1	7.791	221	0.077	0.120	1.43%
Ratios between metabolite concentrations						
PC a C20:4*	PC a C20:3*	2.224	208	2.9×10^{-8}	−0.374	13.98%
PC aa C34:4	PC aa C34:3	0.107	284	4.2×10^{-7}	−0.295	8.72%
PC aa C36:4	PC aa C36:3	1.613	284	2.4×10^{-22}	−0.535	28.62%
PC aa C38:4	PC aa C38:3	1.708	284	2.1×10^{-17}	−0.476	22.66%
PC ae C36:4	PC ae C36:3	1.832	284	7.3×10^{-8}	−0.313	9.81%
PC ae C38:4	PC ae C38:3	2.888	284	9.7×10^{-9}	−0.333	11.07%
PE aa C38:4	PE aa C38:3	3.693	132	0.013	−0.216	4.64%
PI aa C38:4*	PI aa C38:3*	3.582	221	1.5×10^{-8}	−0.370	13.69%

Symbiotic gut microbes modulate human metabolic phenotypes

PNAS
February 12, 2008

Min Li*, Baohong Wang†, Menghui Zhang*, Mattias Rantalainen‡, Shengyue Wang§, Haokui Zhou*, Yan Zhang*, Jian Shen*, Xiaoyan Pang*, Meiling Zhang*, Hua Wei*, Yu Chen†, Haifeng Lu†, Jian Zuo†, Mingming Su*, Yunping Qiu*, Wei Jia*, Chaoni Xiao¶‖, Leon M. Smith‡, Shengli Yang*, Elaine Holmes‡, Huiru Tang¶**, Guoping Zhao§**, Jeremy K. Nicholson‡**, Lanjuan Li†**, and Liping Zhao*,**

Fecal and urinary samples from 7 chinese individuals (NMR / 16S RNA gene sequencing / multivariate statistical analyses)

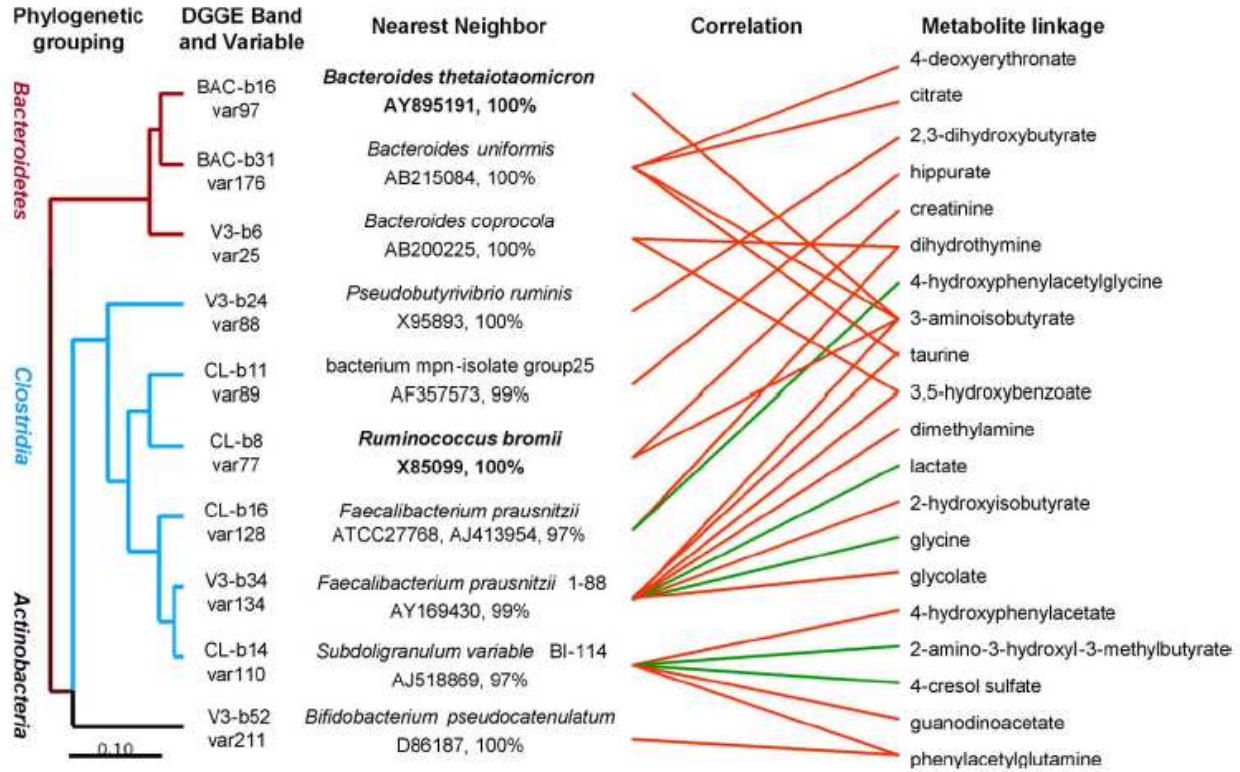


Fig. 3. Dendrogram of OTUs from DGGE bands, which are well predicted by metabolic variation, labeled as the nearest known neighbor with similarity value. Associations with specific urine metabolites are shown for each OTU with the direction of correlation indicated by red (positive) or green (negative) lines. Gender-related bands predicted by OPLS-DA are denoted by bold text.

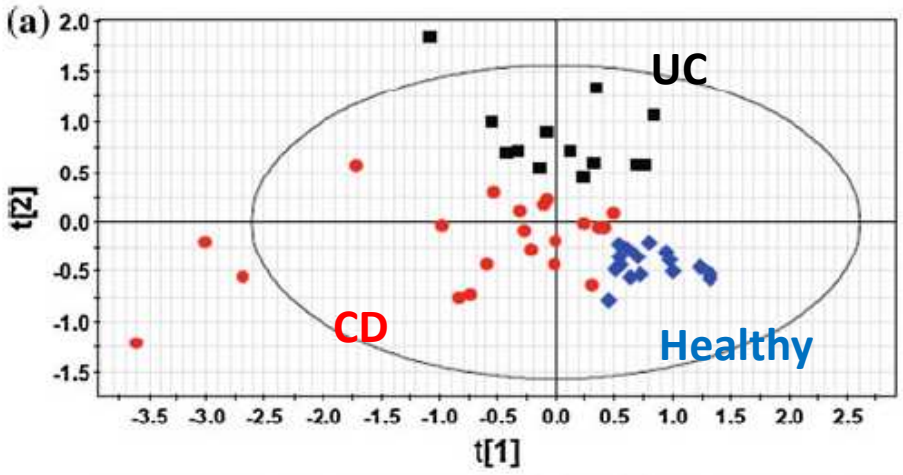
Inflamm. Res. (2011) 60:831–840

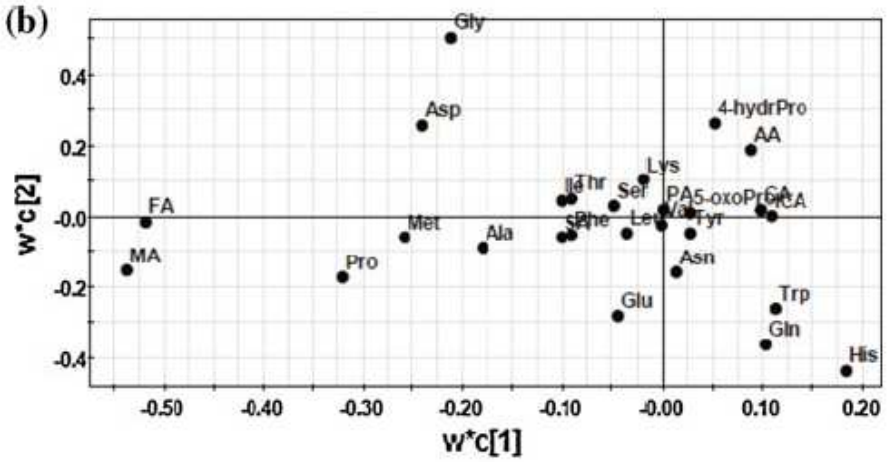
GC/MS-based profiling of amino acids and TCA cycle-related molecules in ulcerative colitis

Makoto Ooi · Shin Nishiumi · Tomoo Yoshie · Yuuki Shiomi · Michitaka Kohashi · Ken Fukunaga · Shiro Nakamura · Takayuki Matsumoto · Naoya Hatano · Masakazu Shinohara · Yasuhiro Irino · Tadaomi Takenawa · Takeshi Azuma · Masaru Yoshida

Disease induced changes in metabolic profiles

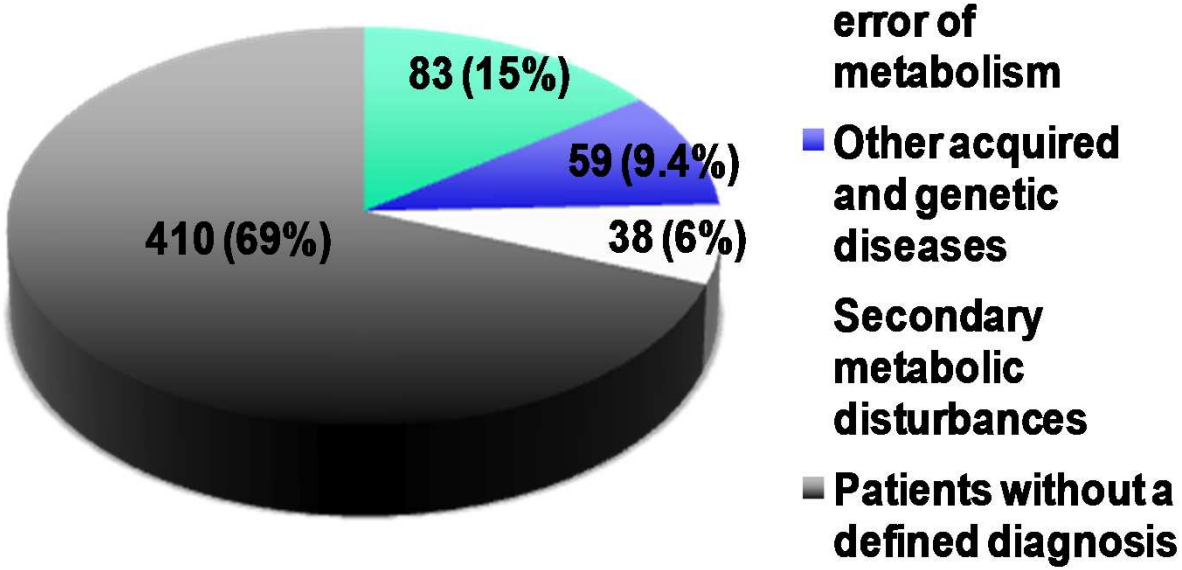
Materials and methods Colonic biopsy samples from 22 UC patients were used, as well as serum samples from UC patients ($n = 13$), Crohn's disease (CD) patients ($n = 21$), and healthy volunteers ($n = 17$).





Inborn Errors of Metabolism (IEM), neurology and metabolomics

Pitié-Salpétrière Hospital: 593 patients referred for a suspicion of «metabolic disease» without an initial diagnosis

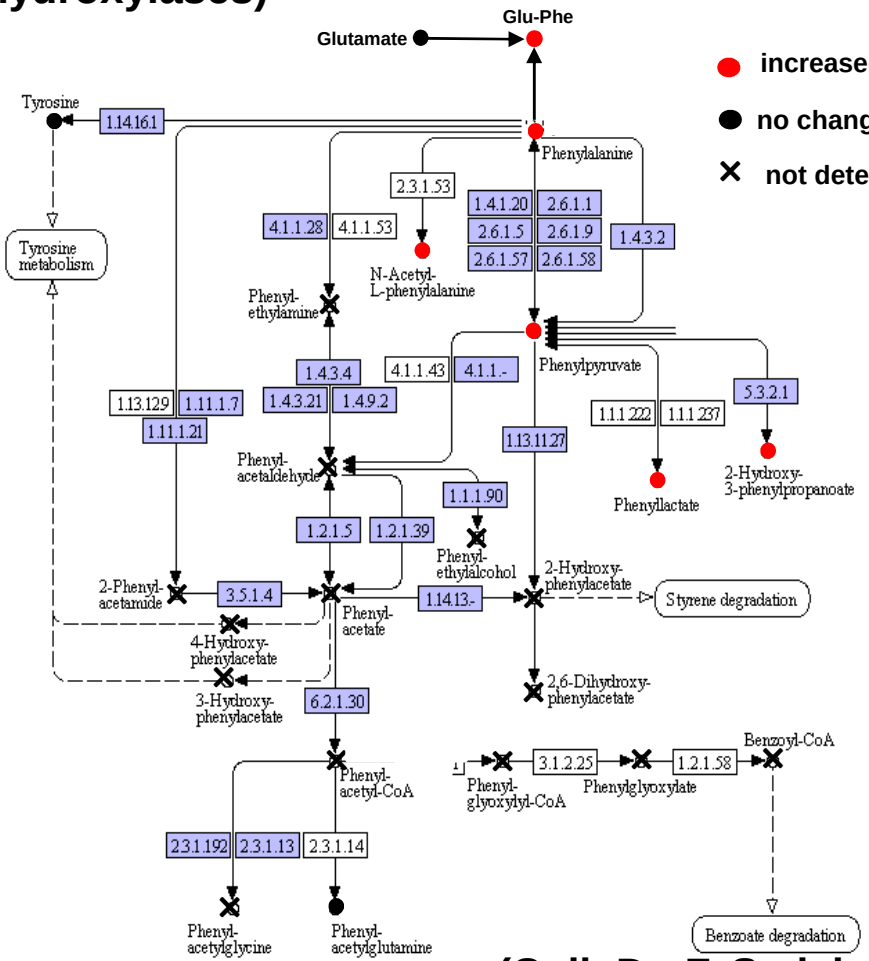


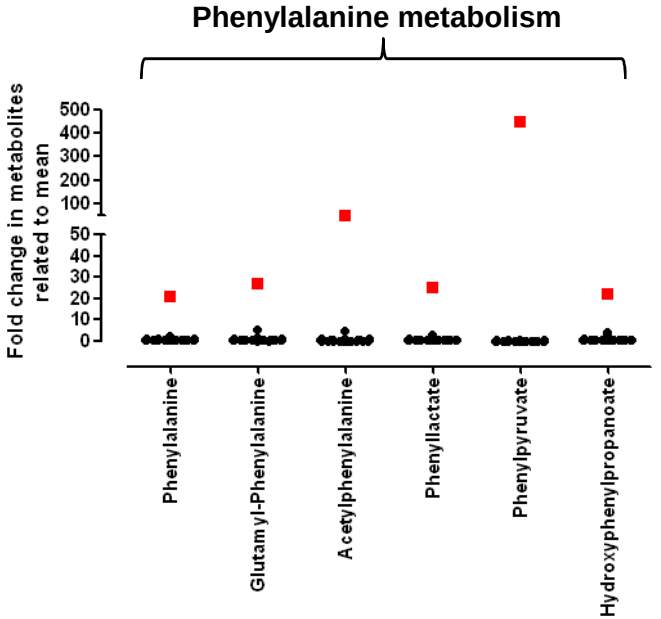
(Coll. Drs. F. Sedel, F. Mochel et F. Lamari, G.H. Pitié-Salpétrière ; Pr. F. Seguin, Poitiers)

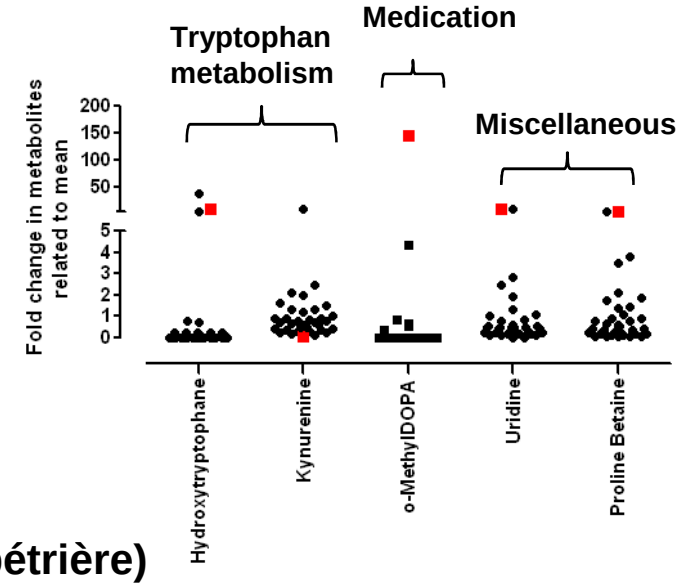
P.H.R.C «SPECMET 2»

CSF metabotype of a Dihydropteridine reductase (DHPR) deficient patient

Autosomal recessive genetic disorder.
Hyperphenylalaninemia due to tetrahydrobiopterine deficiency (malfunctioning Tyr and Trp hydroxylases)

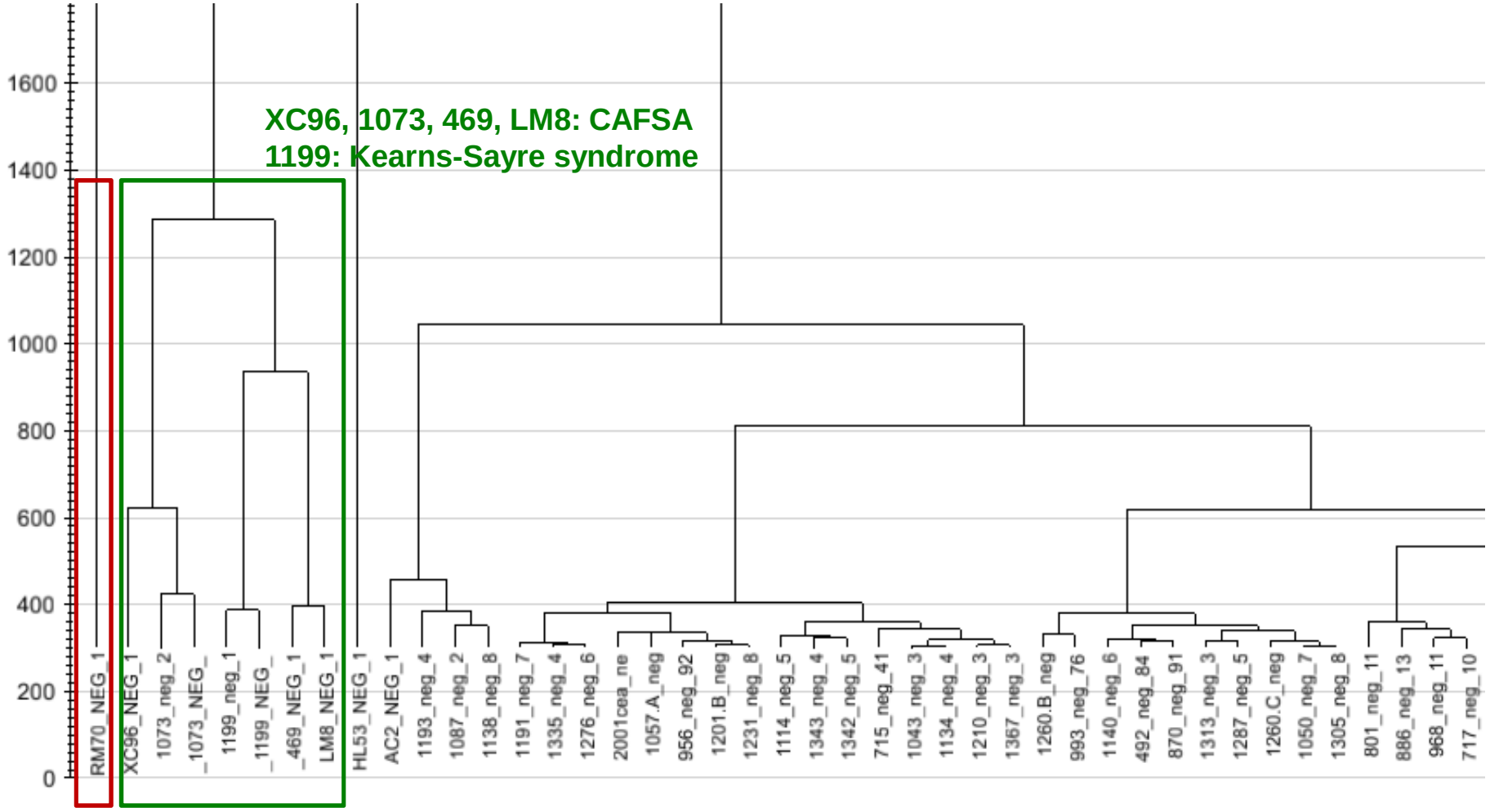






(Coll. Dr. F. Sedel, G.H. Pitié-Salpétrière)

Stratification de patients atteints d'encéphalopathies inexpliquées. Analyses de LCRs

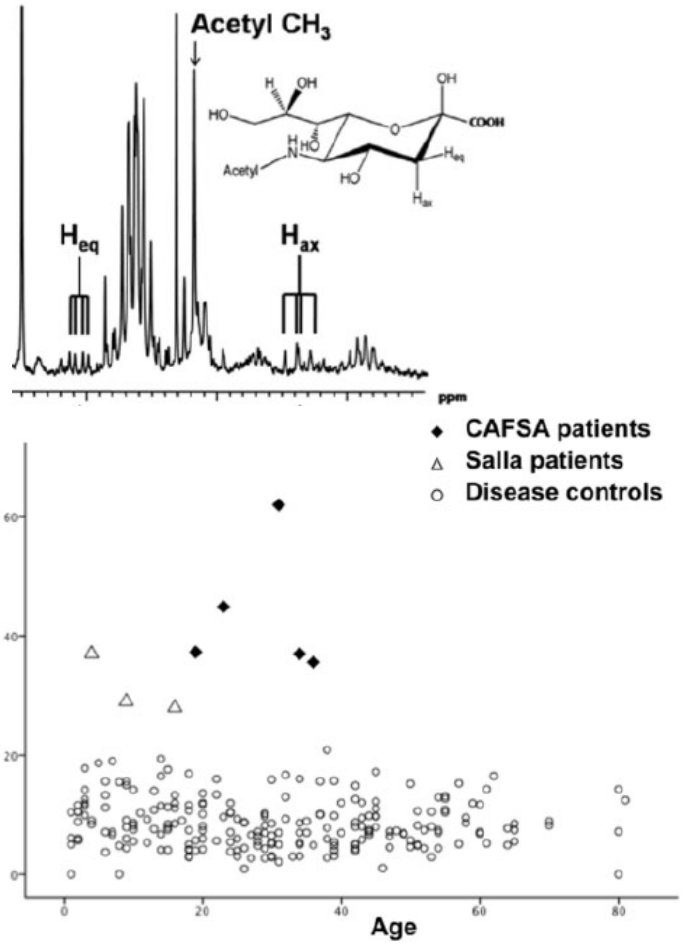


Portosystemic shunt

BRAIN
A JOURNAL OF NEUROLOGY
2009: 132; 801–809

Cerebellar ataxia with elevated cerebrospinal free sialic acid (CAFSA)

F. Mochel,[1,2] F. Sedel,[3,*] A. Vanderver,[4,*] U. F. H. Engelke,[5] J. Barritault,[6] B. Z. Yang,[2] B. Kulkarni,[4] D. R. Adams,[7] F. Clot,[1] J. H. Ding,[2] C. R. Kaneski,[2] F. W. Verheijen,[8] B. W. Smits,[9] F. Seguin,[6] A. Brice,[1,10] M. T. Vanier,[11] M. Huizing,[7] R. Schiffmann,[2] A. Durr[1,10] and R. A. Wevers[5]



- **Cerebellar ataxia, with peripheral neuropathy and cognitive decline or behavioural changes**
- **Free sialic acid elevated only in CSF, using NMR spectroscopy**
- **Significant hyposialylation of transferrin in CSF of all patients**
  →New free sialic acid syndrome
- **Four candidate genes sequencing did not reveal any mutation**

Laboratoire d'Etude du Métabolisme des Médicaments, DSV/iBiTec-S/SPI

Kearns-Sayre syndrome

CAFSA

Values are fold changes related to control value

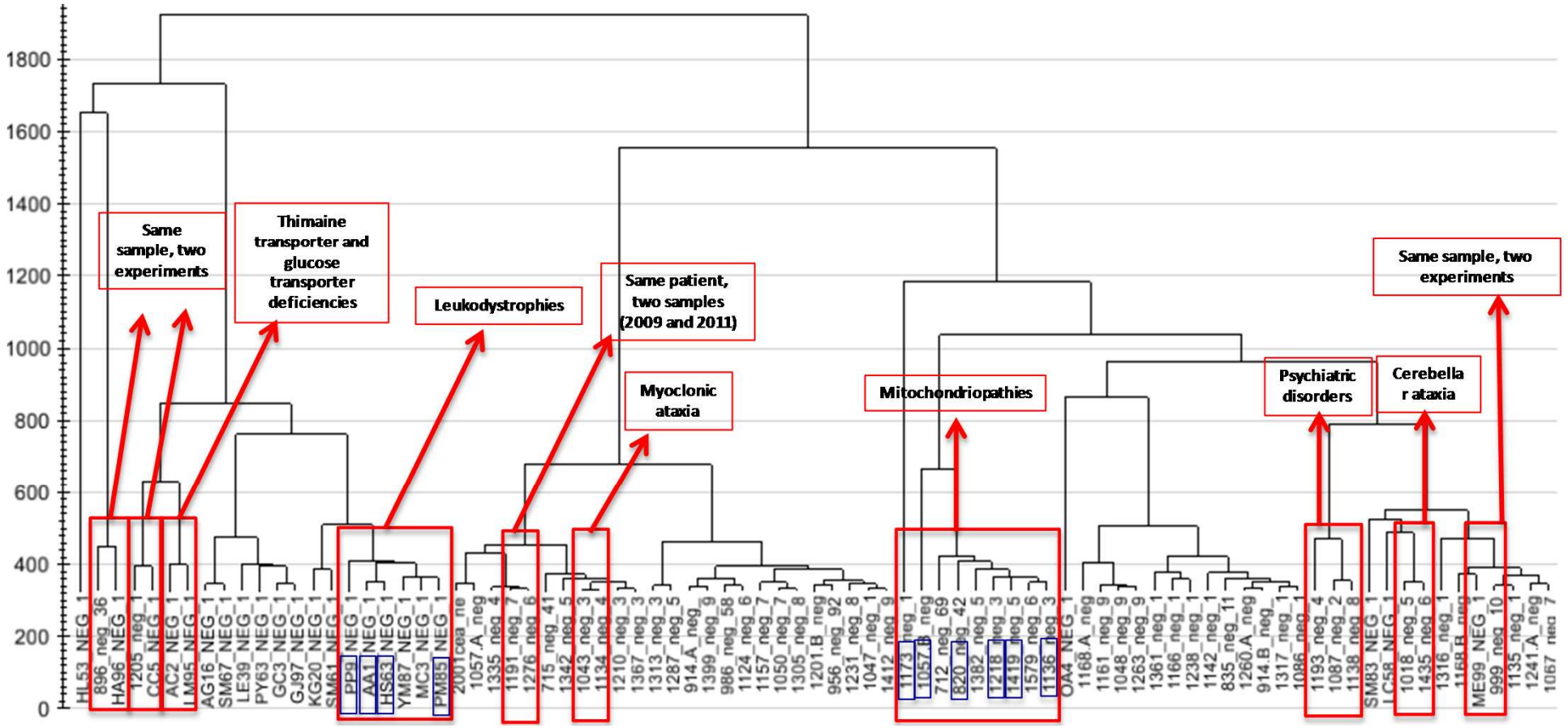
value >mean+2SD

Mean+SD<value <mean+2SD

		Patients with unexplained encephalopathy																																
		1018_55	1043_31	1047_127	1048_95	1050_71	1052_46	1057.A_88	1057.B_133	1058_107	1061_32	1067_74	469	XC96	LM8	1073_29	1199_121	1074_80	1086_114	1087_27	1113_28	1114_50	1124_67	1134_43	1135_131	1136_39	1138_89	1140_68	1142_125	1148_77	1157_79	1161_90	1166_117
sugar acid	N-acetylneuraminic acid	0.9	0.5	10	0.5	11	14	0.3	10	12	10	0.9	5.9	7.7	7.8	4.4	5.0	15	0.8	0.6	12	0.5	0.8	0.9	0.7	12	0.7	0.8	0.7	12	0.7	0.8	12
Carbohydrates	Deoxyribose	0.6	0.4	0.5	0.5	0.6	15	0.3	10.2	10	0.8	0.7	9.1	6.3	8.1	4.0	5.0	0.9	0.7	0.5	10	0.4	0.7	0.5	0.7	17	0.5	0.6	0.7	13	0.5	0.5	0.7
	Pentose	14	0.7	0.6	0.4	0.6	3.9	0.3	11	17	10	0.9	8.3	2.2	11	4.1	2.0	3.0	0.7	0.6	2.1	10	10	0.6	0.6	12	0.5	0.6	0.8	12	0.7	0.6	0.7
	Mannitol or isomers	0.9	0.6	11	0.4	0.8	18	0.6	13	11	0.8	0.7	2.2	4.4	3.3	2.5	8.1	13	0.8	0.6	0.9	0.6	10	0.6	0.7	10	0.5	0.4	15	17	0.6	0.6	13
Hydroxy acids	Threonic acid	0.8	11	0.7	0.6	0.9	2.5	0.5	11	13	10	0.8	12	19	16	3.3	3.3	11	0.7	10	17	0.8	0.8	0.7	0.6	10	0.5	0.9	11	12	14	0.6	11
	Quinic acid	3.4	0.3	0.6	0.0	0.0	4.7	0.0	0.9	5.0	16	0.8	4.8	4.0	15	2.3	3.2	5.3	11	0.4	9.3	2.3	3.1	0.1	11	0.3	0.0	0.6	12	0.7	0.0	11	0.0
nucleoside derivative	Succinyladenosine	0.8	0.6	0.7	0.5	0.8	17	0.4	13	12	10	11	8.0	3.9	6.2	4.1	2.3	15	0.9	0.7	13	0.6	10	0.7	0.8	12	0.8	0.9	0.7	14	0.6	0.6	13
Aminoacid and derivatives	Proline Betaine	0.7	0.5	2.5	0.5	0.8	2.1	0.4	17	3.0	2.3	0.1	0.1	5.7	0.1	4.1	0.8	0.1	0.9	19	4.3	0.6	10	0.9	0.2	0.9	0.1	2.3	0.8	0.7	3.2	0.3	2.1
	Glutamic acid	0.6	0.5	0.9	0.5	0.9	15	0.4	12	11	0.8	0.8	3.6	0.7	3.4	2.3	2.8	18	0.9	0.8	12	0.7	0.9	0.7	0.8	11	0.8	0.9	0.7	12	0.8	0.9	11
	Aminoadipic acid	0.8	0.6	0.8	0.6	0.9	14	0.4	11	12	0.8	0.8	2.2	18	3.2	2.6	2.9	17	0.9	0.8	12	0.7	0.9	0.7	0.9	12	0.6	10	0.8	15	0.7	0.8	11
	N-acetyl-L-glutamic acid	0.5	0.5	0.7	0.5	10	14	10	2.8	12	0.8	0.8	48.6	0.6	11.9	0.7	2.0	0.8	12	14	10	0.4	0.9	0.7	16	13	13	0.8	0.4	0.8	13	13	12
	N-Acetyl-D-allo-isoleucine	0.6	0.5	10	0.7	10	15	0.5	14	12	10	11	2.8	13	2.3	12	2.0	17	0.9	12	12	0.6	0.7	0.7	10	11	0.8	0.8	0.8	11	0.9	10	14
Pyrimidine derivated	Dihydroorotic acid	0.9	0.7	0.8	0.4	0.9	2.2	0.4	13	0.9	0.8	10	16	5.5	2.7	2.2	5.0	13	0.5	0.7	11	0.8	10	0.7	0.5	14	0.6	0.7	11	14	0.5	0.6	13
Acylcarnitines	Acetyl-carnitine	18	0.7	0.6	11	0.5	0.9	0.6	0.9	2.7	10	15	12	2.1	15	2.0	11	15	10	0.4	15	12	0.9	0.6	15	0.9	0.9	0.3	0.7	15	0.8	0.8	0.8
	Propionyl-carnitine	19	0.5	0.5	10	0.5	16	0.8	0.8	2.3	13	15	0.8	3.7	12	2.1	0.8	0.8	10	0.7	13	12	0.8	0.6	19	0.8	10	0.2	0.4	18	11	0.9	0.9
	Butyryl-carnitine	0.9	0.5	0.5	0.7	0.8	16	0.6	0.6	14	16	15	10	3.3	13	2.2	13	0.6	0.8	0.8	12	11	0.9	0.6	12	10	0.9	0.3	0.6	16	0.7	0.9	11
	Methylbutyroyl-carnitine	13	0.4	0.6	0.9	0.8	19	0.5	0.9	15	14	13	10	2.5	11	2.4	0.7	0.7	0.8	10	13	0.9	0.7	0.6	11	0.8	0.9	0.3	0.4	17	0.9	0.8	10
Bile acids	Glycochenodeoxycholic acid	4.4	0.1	10	0.2	0.2	2.6	0.6	0.1	10	0.9	0.0	0.0	11.0	0.0	11.1	6.7	7.4	0.3	0.0	0.6	2.8	13	0.0	12	13	0.1	0.0	0.0	0.6	0.1	0.7	0.2
	Glycocholic acid	17	0.0	10	0.2	0.2	5.5	0.1	0.0	0.6	0.6	0.0	0.0	16.0	0.0	9.6	4.8	6.2	0.1	0.4	0.4	19	2.2	0.1	0.5	18	0.2	0.5	0.0	0.2	0.2	12	0.9

(Coll. Dr. F. Sedel, G.H. Pitié-Salpétrière)

Stratification de patients atteints d'encéphalopathies inexpliquées. Analyses de LCRs



Le futur?

Le profilage métabolique à haut débit pour l'épidémiologie et la médecine personnalisée

To improve and standardize metabolite detection and quantification

To improve metabolite identification

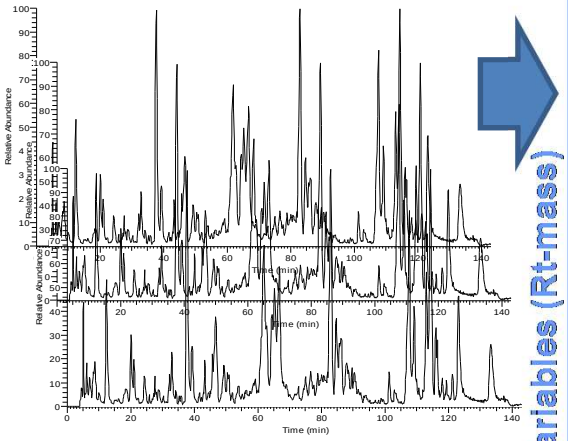
- Data set annotation
- Spectral databases

Informatics and bioinformatics

- Data analysis tools
- Data visualization tools
- Standard data formats
- Spectral databases
- Metabotype databases

The issue of confounding factors

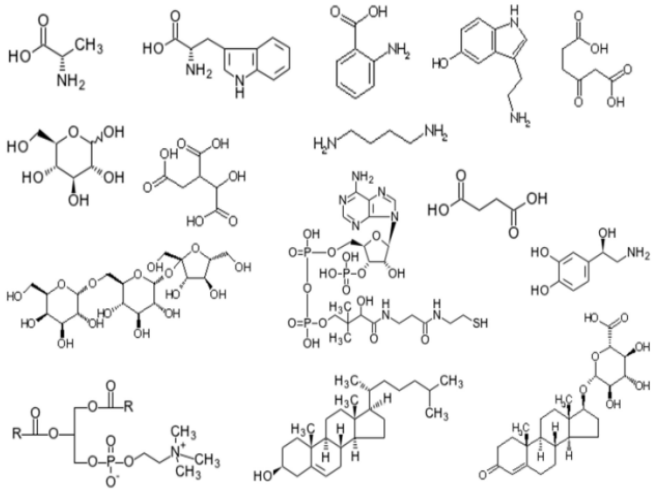
Annotation of peak lists is required to help for metabolite identification



Samples

Variables (Rt-mass)

Peak Nr	Ret(min)	Mass	J5-T 060303-02	J5-T 060303-03	J5-T 060303-04	J5-T 060303-05	J5-T 060303-21	J5-T 060303-22
1	13.24	100	1.8E+03	1.5E+03	2.4E+05	1.7E+03	2.0E+03	7.9E+04
2	13.98	100	1.8E+03	1.5E+03	2.0E+03	1.7E+03	2.0E+03	1.5E+04
3	42.25	106	2.0E+05	4.3E+04	2.9E+05	3.5E+04	1.8E+05	2.0E+03
4	16.65	114	2.0E+03	3.7E+04	4.5E+04	1.0E+04	3.9E+05	2.5E+04
5	16.92	114	2.0E+03	3.7E+04	4.5E+04	2.1E+05	8.3E+04	2.5E+04
6	17.26	114	2.0E+03	3.7E+04	4.5E+04	1.6E+05	2.5E+05	7.2E+05
7	17.54	114	2.0E+03	3.7E+04	2.3E+05	1.4E+05	4.3E+04	2.5E+04
8	18.01	114	2.0E+03	3.7E+04	2.8E+05	1.0E+04	4.3E+04	2.5E+04
9	4.19	126	9.4E+04	1.6E+03	6.4E+04	1.7E+04	2.3E+03	1.2E+04
10	4.66	126	1.4E+05	1.6E+03	1.3E+05	1.7E+04	2.3E+03	1.2E+04
11	4.93	126	2.1E+03	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.2E+04
12	5.07	126	1.8E+05	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.5E+05
13	5.40	126	1.3E+05	1.6E+03	1.1E+05	1.7E+04	2.3E+03	2.2E+04
14	5.86	126	2.1E+03	1.6E+03	1.1E+05	1.7E+04	2.3E+03	4.9E+04
15	6.32	126	1.5E+04	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.2E+04
16	10.56	126	1.9E+05	1.6E+03	2.0E+05	9.1E+03	2.3E+03	1.2E+04
17	11.05	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
18	11.33	126	1.0E+05	1.6E+03	1.5E+05	9.1E+03	2.3E+03	1.2E+04
19	11.80	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
20	16.36	126	2.0E+03	1.6E+03	2.4E+04	9.1E+03	2.3E+03	1.2E+04
21	9.04	138	1.9E+03	3.9E+04	2.1E+04	1.4E+04	2.3E+03	2.7E+04
22	4.39	143	2.9E+05	2.4E+05	2.8E+03	2.9E+05	2.9E+04	2.5E+05
23	5.07	143	2.3E+03	2.1E+03	2.5E+05	2.3E+03	1.9E+05	3.2E+05
24	5.20	143	5.5E+05	2.1E+03	1.1E+05	3.6E+04	2.9E+04	3.4E+05
25	26.39	143	1.3E+04	8.3E+04	5.8E+04	2.3E+03	2.9E+04	1.2E+05
26	6.58	153	4.0E+04	1.1E+06	8.9E+04	9.9E+04	3.4E+04	4.5E+04
27	7.12	153	4.0E+04	2.6E+03	8.9E+04	6.1E+04	1.9E+05	3.7E+04
28	6.72	154	4.2E+05	5.0E+05	2.9E+03	2.0E+04	3.1E+03	3.9E+04
29	6.98	154	5.3E+05	2.0E+03	6.3E+05	2.0E+04	2.8E+05	2.1E+05
30	7.66	154	2.2E+03	6.7E+04	2.9E+03	2.0E+04	2.8E+05	2.1E+04
31	17.54	159	2.3E+03	2.0E+03	2.8E+03	3.0E+05	2.7E+03	3.8E+04
32	17.87	159	2.3E+03	2.0E+03	2.8E+03	2.8E+04	2.7E+03	1.1E+05
33	18.42	159	2.3E+03	2.0E+03	2.8E+03	4.2E+05	2.7E+03	3.8E+04



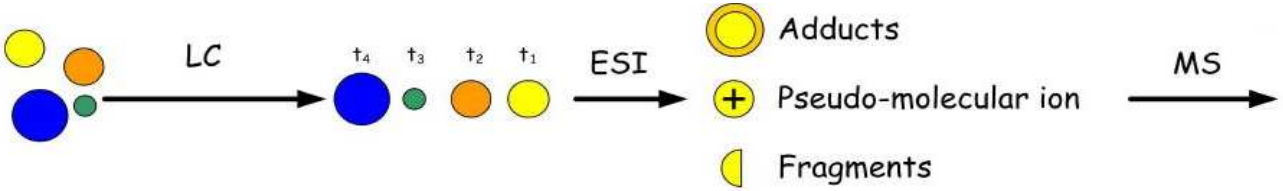
Few thousands of variables…

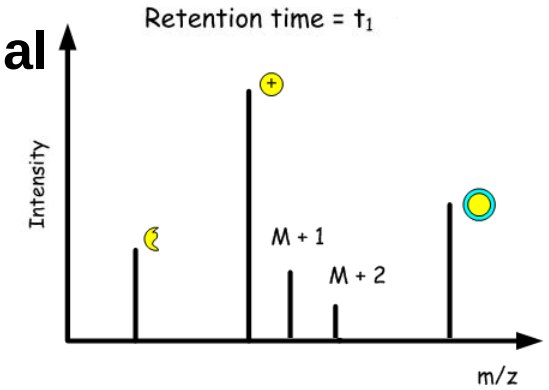
…Few hundreds of metabolites ??

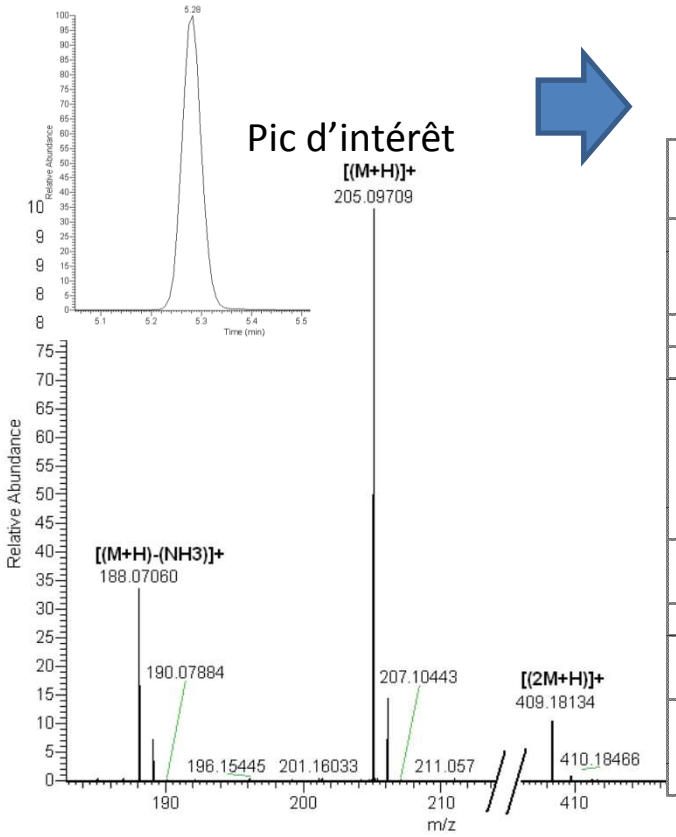
- **Chemical and biochemical databases: KEGG (**www.genome.jp/kegg**), Metlin (**www.metlin.scripps.edu**), HMDB (**www.hmdb.ca)
- **spectral databases**

Pourquoi une base de données spectrale ?

Une molécule = plusieurs ions = redondance du signal





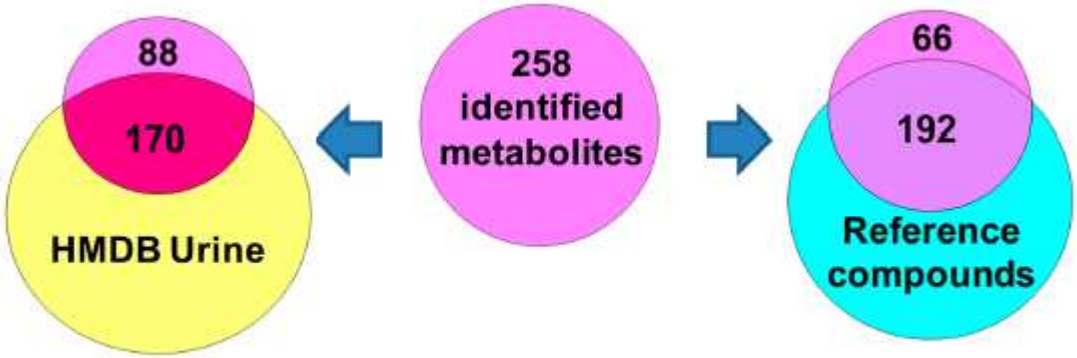


Extraction des ions : liste de variables annotese

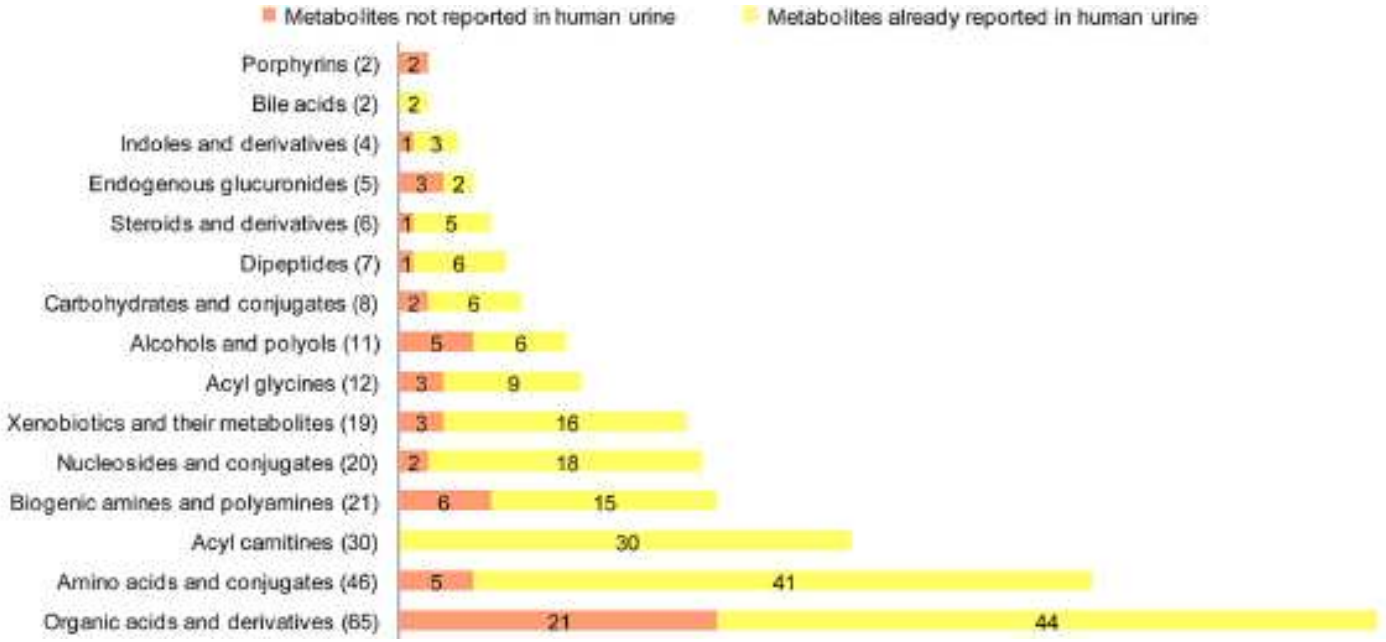
M/Z	RT	Formula	Compound	Attribution	Annotations (HMDB, KEGG, METLIN)
188.0709	5.28	C11H10NO2	Tryptophan	[(M+H)-(NH3)]+	Deethylatrazine
					3-amino-2-naphthoic acid
					Indoleacrylic acid
189.0757	5.28	C10[13C]H10NO2	Tryptophan	[(M+H)-(NH3)]+ (13C)	Ethyl Oxalacetate
190.0787	5.28	C9[13C]2H10NO2	Tryptophan	[(M+H)-(NH3)]+ (13C2)	
205.0975	5.28	C11H13N2O2	Tryptophan	[(M+H)]+	Tryptophan
					ethotoin
					Vasicinol
					Idazoxan
					Nirvanol
206.1010	5.28	C10[13C]H13N2O2	Tryptophan	[(M+H)]+ (13C)	N-Acetyl-D-fucosamine
					N-Acetyl-D-quinovosamine
207.1051	5.28	C9[13C]2H13N2O2	Tryptophan	[(M+H)]+ (13C2)	
409.1902	5.28	C22H25N4O4	Tryptophan	[(2M+H)]+	Gly Trp Phe (and isomers)
					Lys Met Met (and isomers)
410.1938	5.28	C21[13C]H25N4O4	Tryptophan	[(2M+H)]+ (13C)	Tyr Leu Asp (and isomers)
					Ile Tyr Asp (and isomers)
					Val Tyr Glu (and isomers)

(Thèse Aurélie Roux 2008-2011)

Annotation du métabolome urinaire humain



Distribution of the 258 identified metabolites among chemical families



(Roux A. et al., Anal. Chem., 2012)

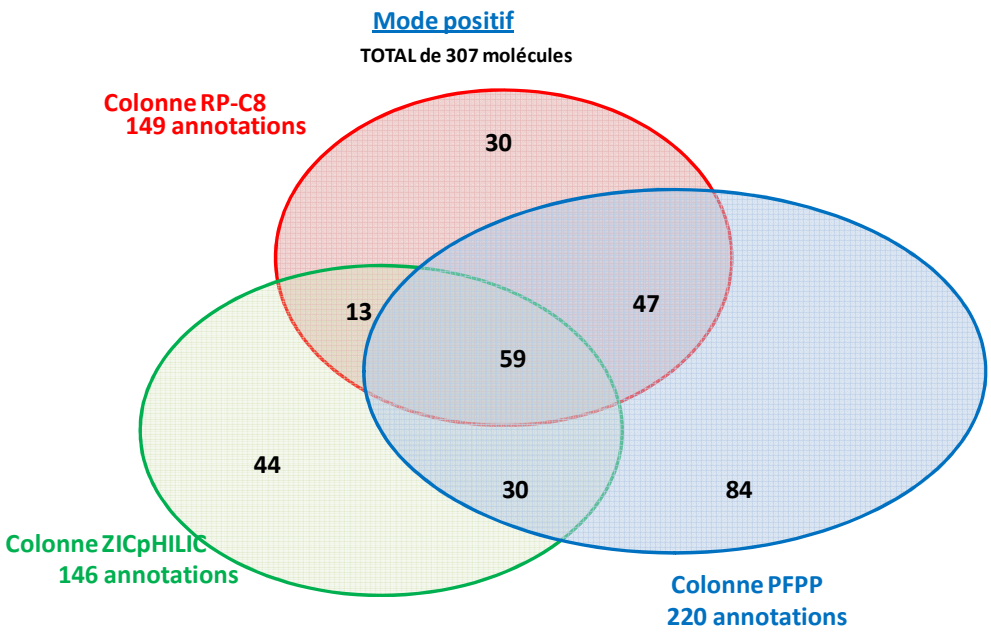
Several LC/MS methods have to implemented in order to achieve an optimal metabolome coverage

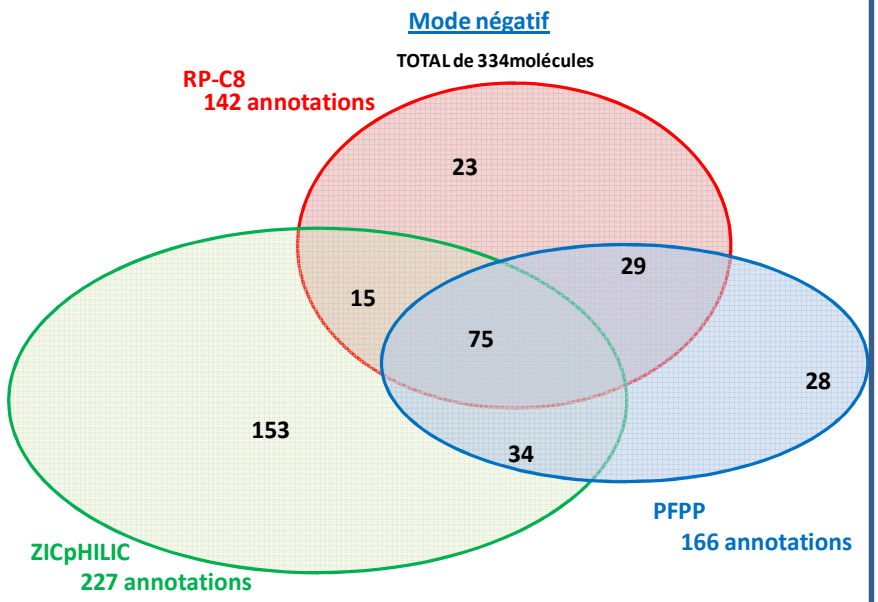
dx.doi.org/10.1021/ac2030738 | Anal. Chem. 2012, 84, 1994–2001

Evaluation of Coupling Reversed Phase, Aqueous Normal Phase, and Hydrophilic Interaction Liquid Chromatography with Orbitrap Mass Spectrometry for Metabolomic Studies of Human Urine

Tong Zhang,*,† Darren J. Creek,‡,§ Michael P. Barrett,‡ Gavin Blackburn,† and David G. Watson†

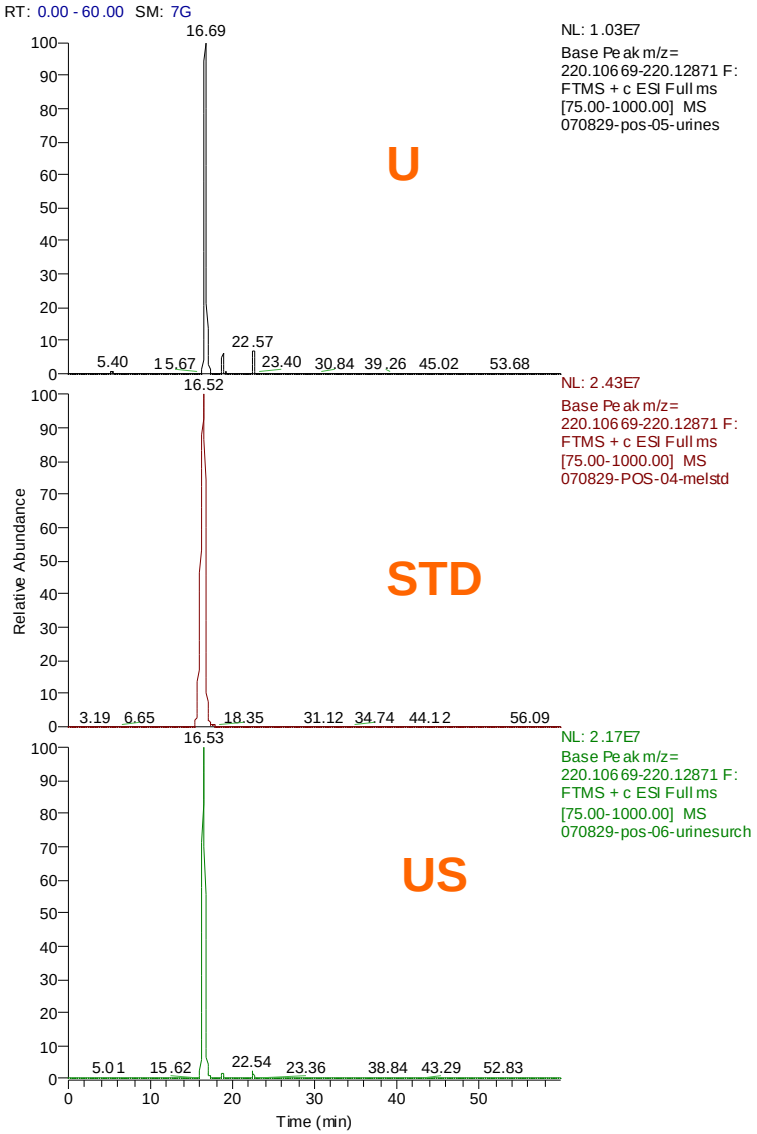
Annotation du métabolome plasmatique humain

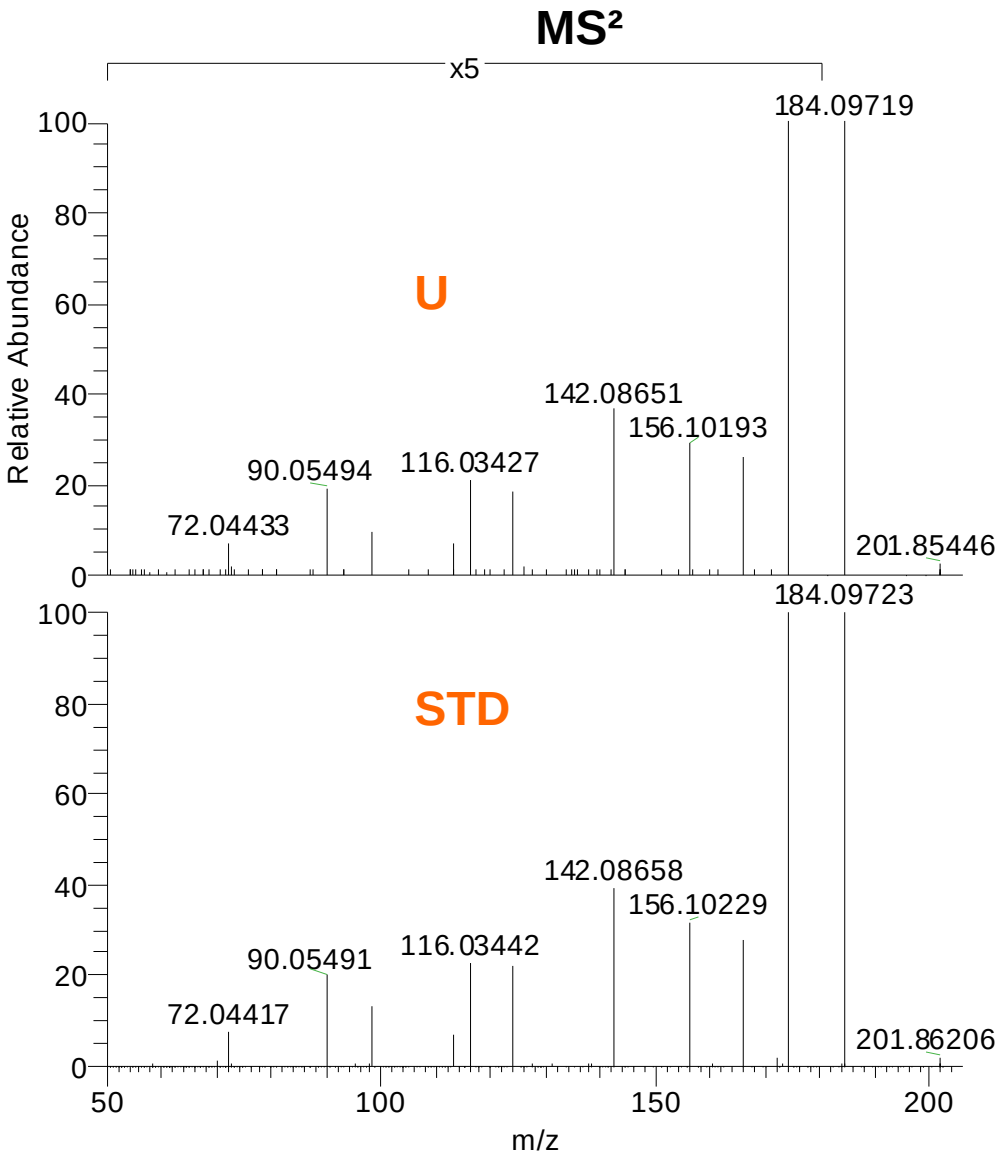




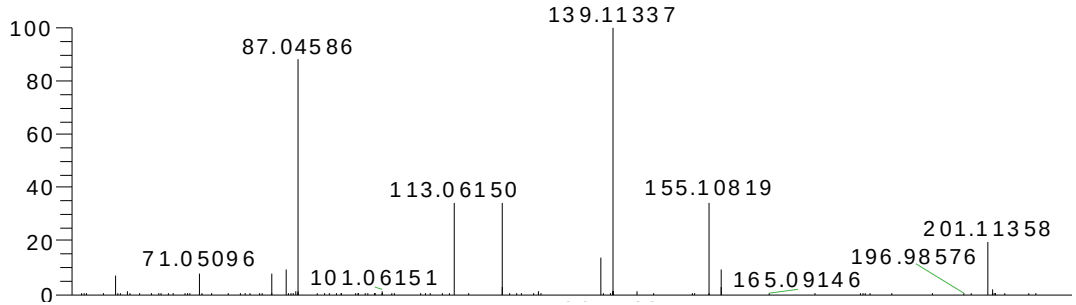
(Thèse Samia Boudah, 2012-2013)

Identification of pantothenic acid in rat urine

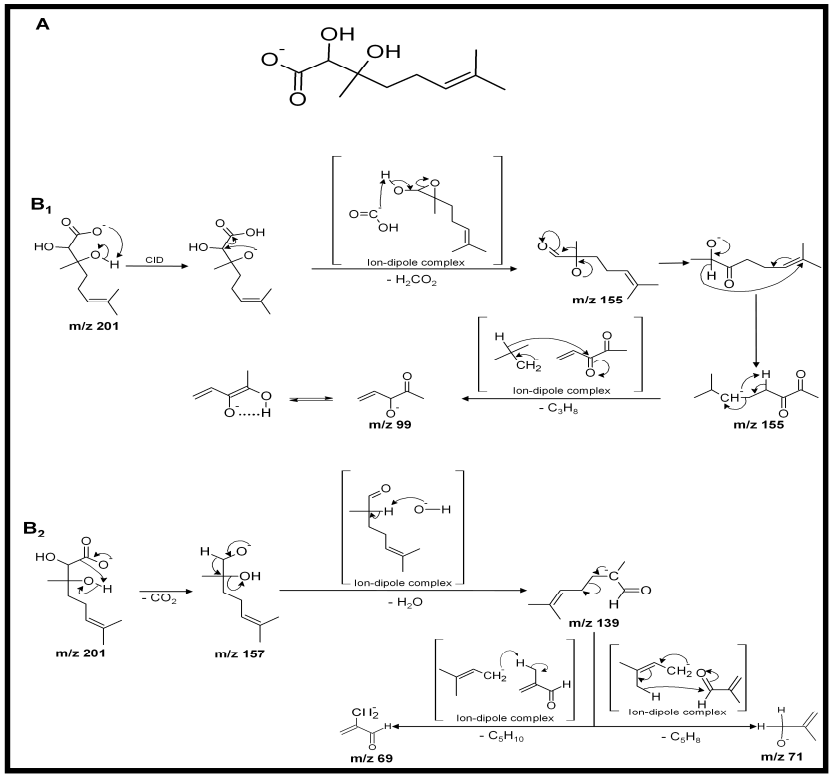




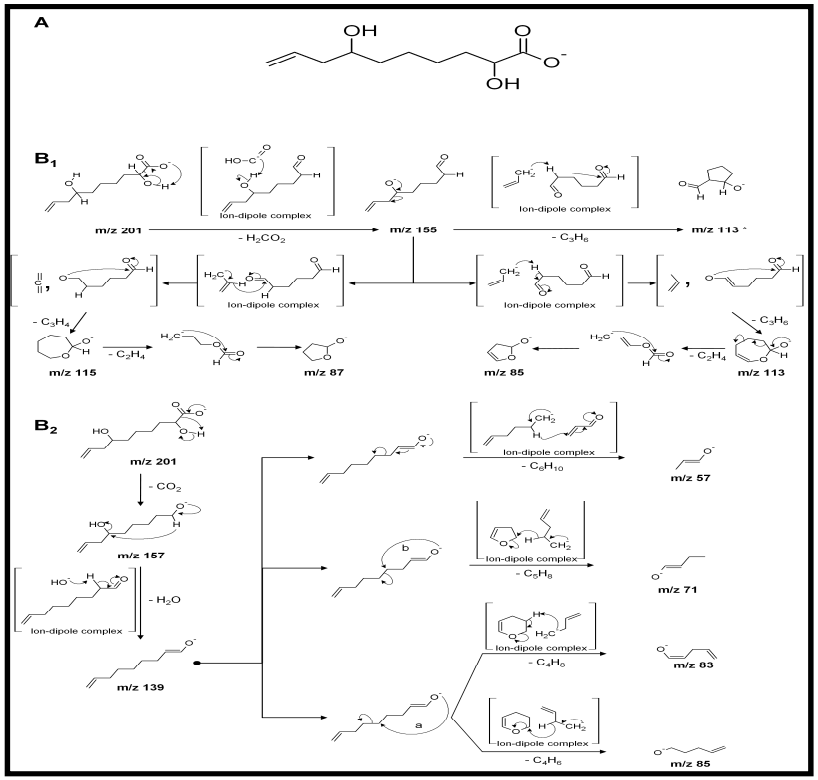
Characterization of unknown metabolites using MS^n



Proposed by CAS



Proposed (MS^n, H/D)



(Werner E. et al., 2008)

Metabolomics (2007) 3:211–221
DOI 10.1007/s11306-007-0082-2

ORIGINAL ARTICLE

Proposed minimum reporting standards for chemical analysis

Chemical Analysis Working Group (CAWG) Metabolomics Standards Initiative (MSI)

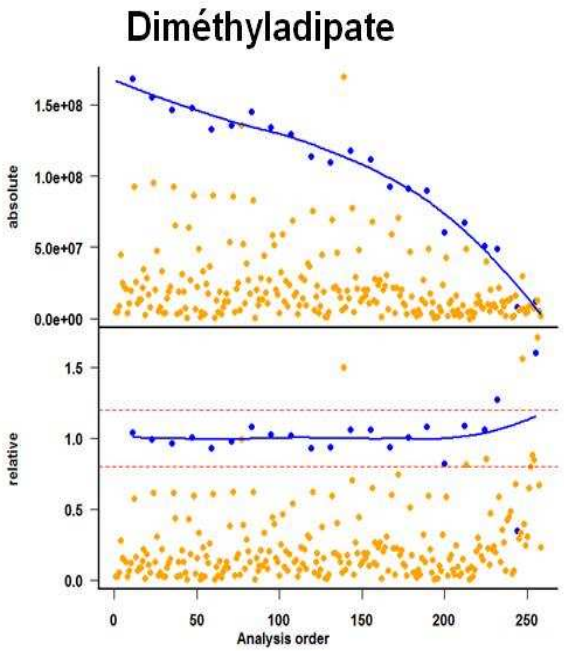
Lloyd W. Sumner · Alexander Amberg · Dave Barrett · Michael H. Beale · Richard Beger · Clare A. Daykin · Teresa W.-M. Fan · Oliver Fiehn · Royston Goodacre · Julian L. Griffin · Thomas Hankemeier · Nigel Hardy · James Harnly · Richard Higashi · Joachim Kopka · Andrew N. Lane · John C. Lindon · Philip Marriott · Andrew W. Nicholls · Michael D. Reily · John J. Thaden · Mark R. Viant

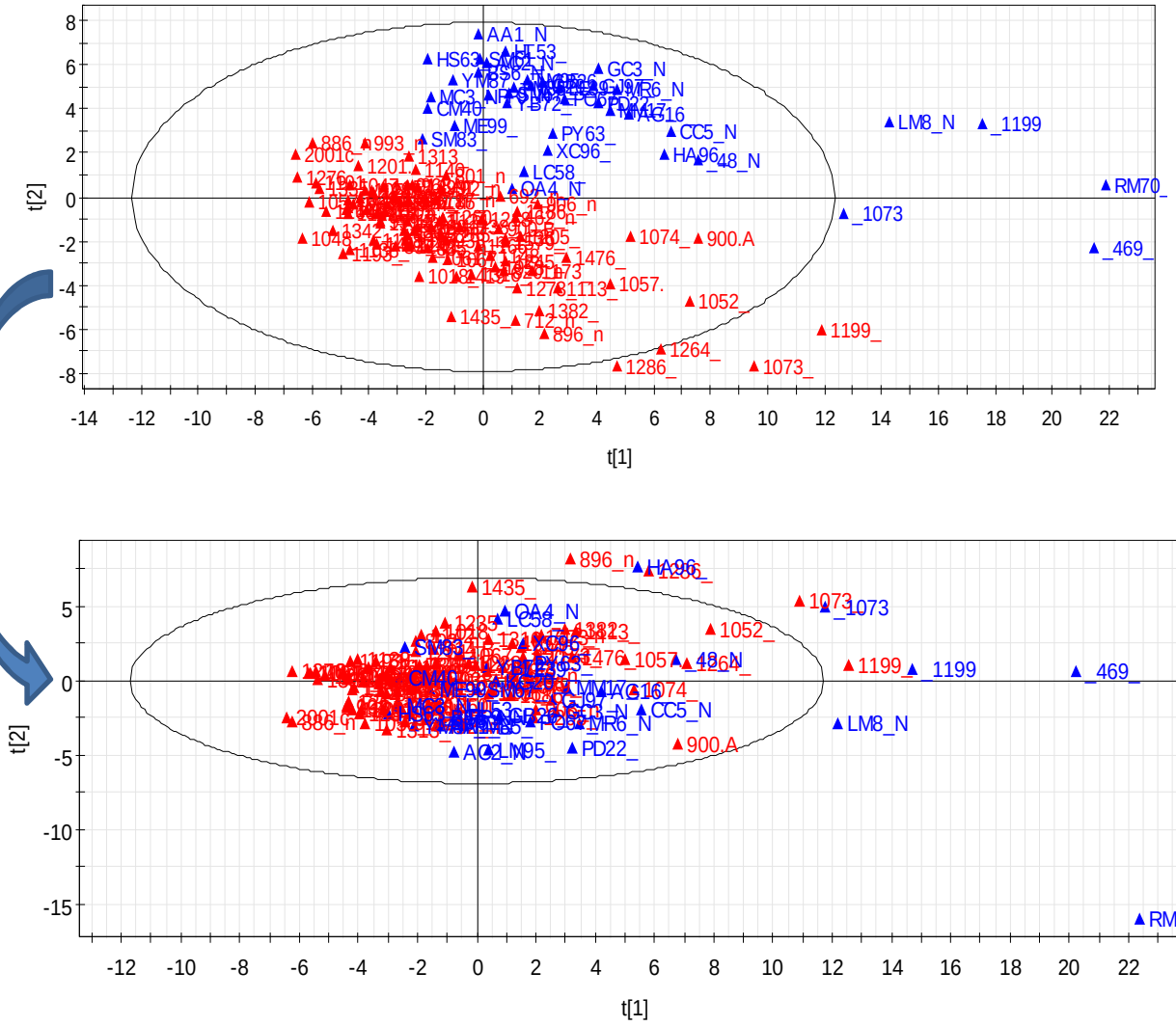
1. Identified compounds (see below).
2. Putatively annotated compounds (e.g. without chemical reference standards, based upon physicochemical properties and/or spectral similarity with public/commercial spectral libraries).
3. Putatively characterized compound classes (e.g. based upon characteristic physicochemical properties of a chemical class of compounds, or by spectral similarity to known compounds of a chemical class).
4. Unknown compounds—although unidentified or unclassified these metabolites can still be differentiated and quantified based upon spectral data.

Les facteurs confondants:

S'affranchir des biais analytiques

Algorithmes de correction des signaux LOWESS (Dunn WB, 2011)

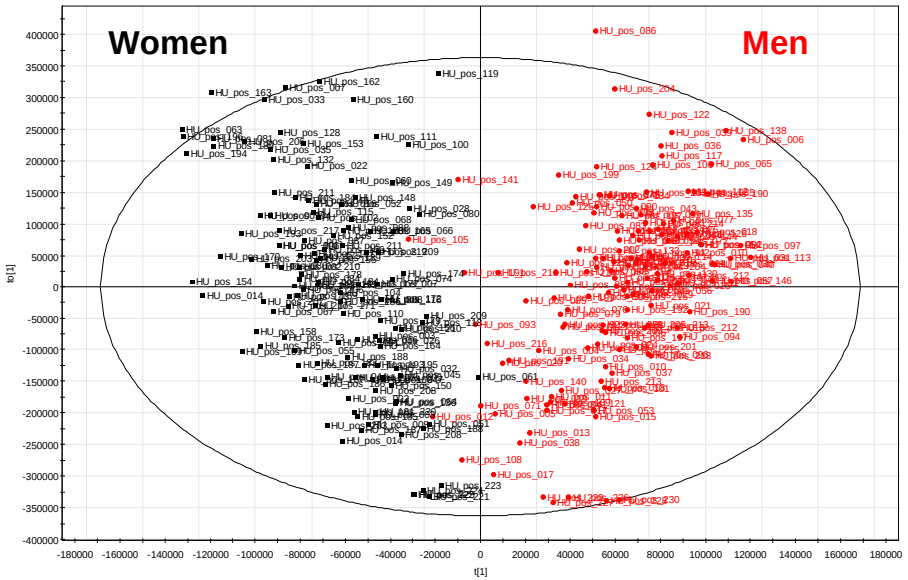


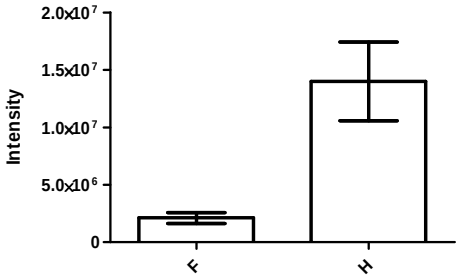


Les facteurs confondants:

Facteurs physiologiques

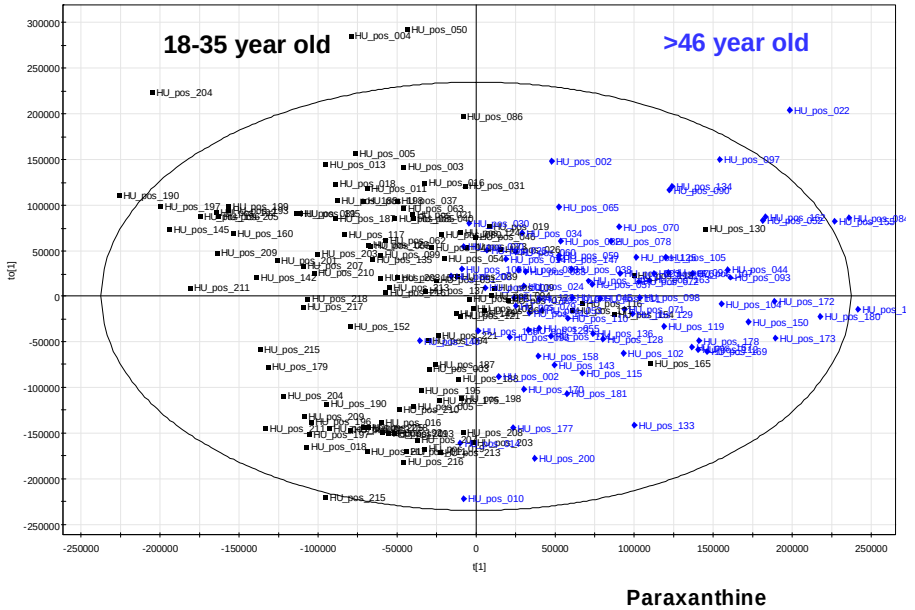
Impact du genre sur le métabolome urinaire

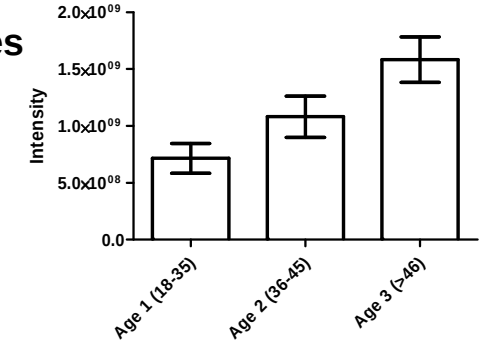




Hormones stéroïdiennes
Nucléosides
Polyamine
Carnitines
Aminoacides
Peptides

Impact de l'âge sur le métabolome urinaire





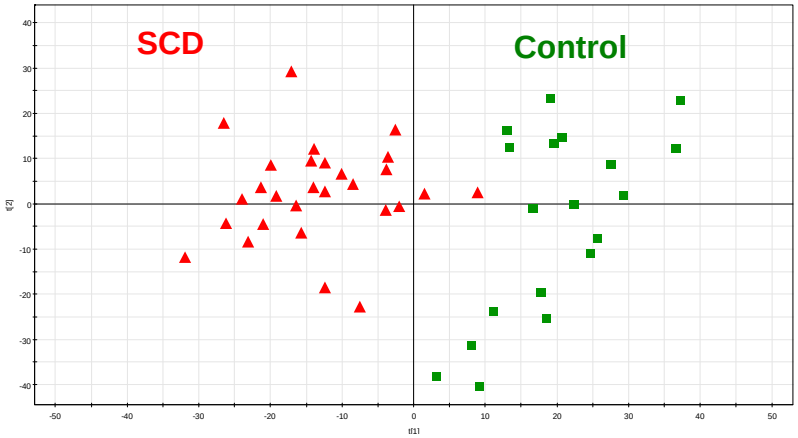
Hormones stéroïdiennes
Purines
Aminoacides

(Thèse Aurélie Roux 2008-2011)

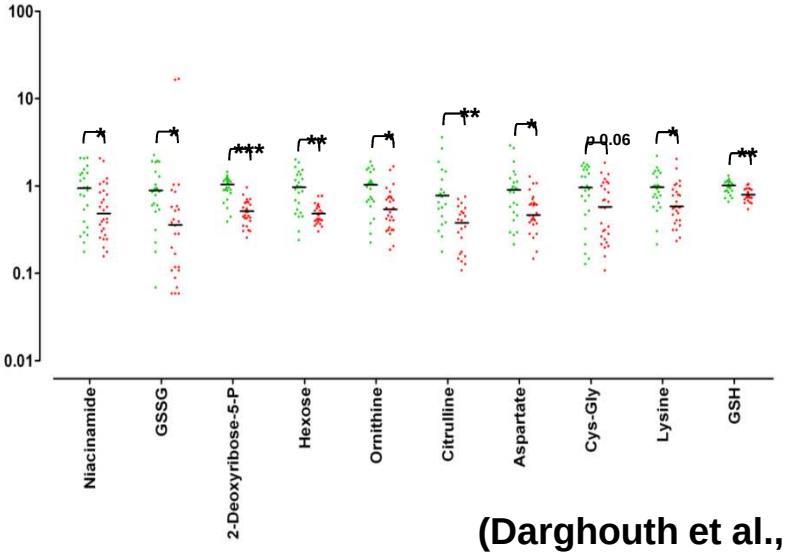
Les facteurs confondants:

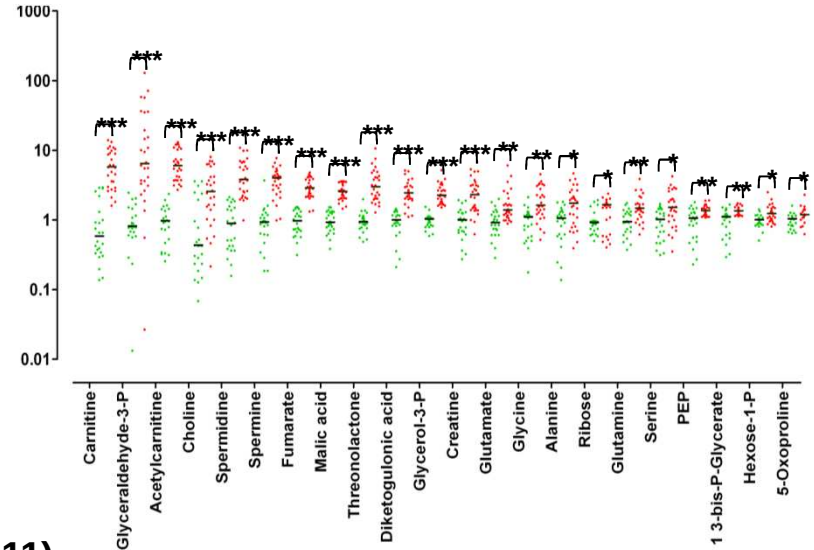
Facteurs physiologiques

Red blood cell metabolomics in sickle cell disease patients



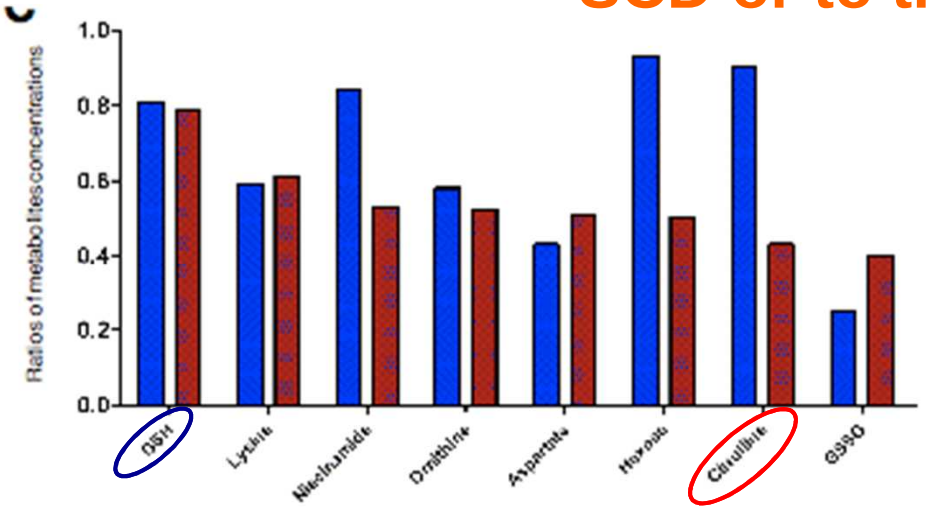
Signature de la drépanocytose ou de la différence d'âge des globules rouges entre les 2 groupes??

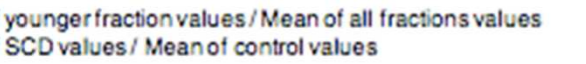


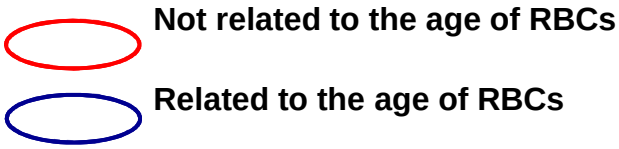


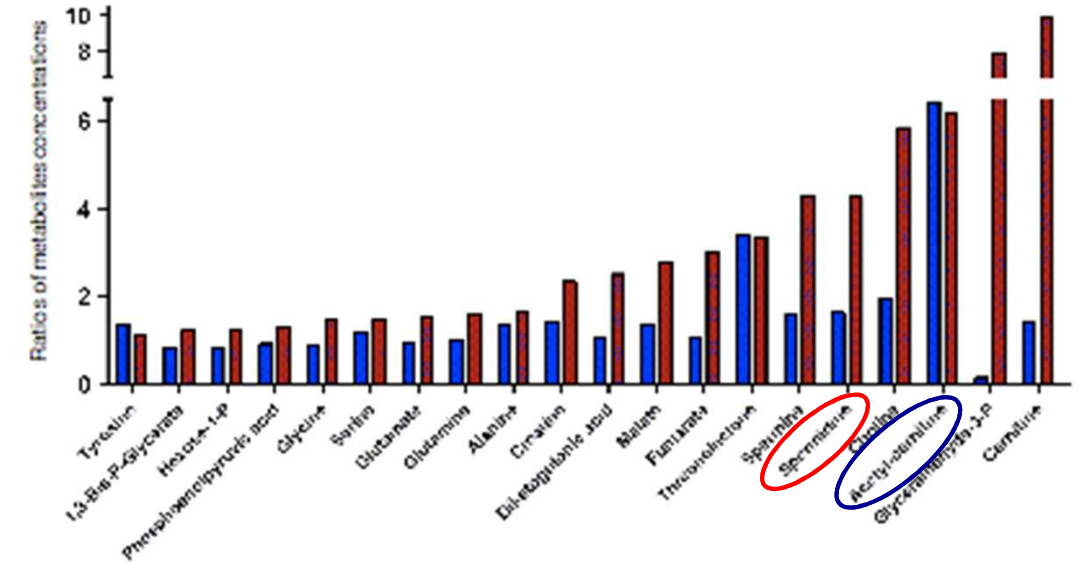
(Darghouth et al., Blood, 2011)

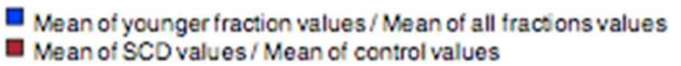
Separation of metabolites directly related to SCD or to the age of the RBCs







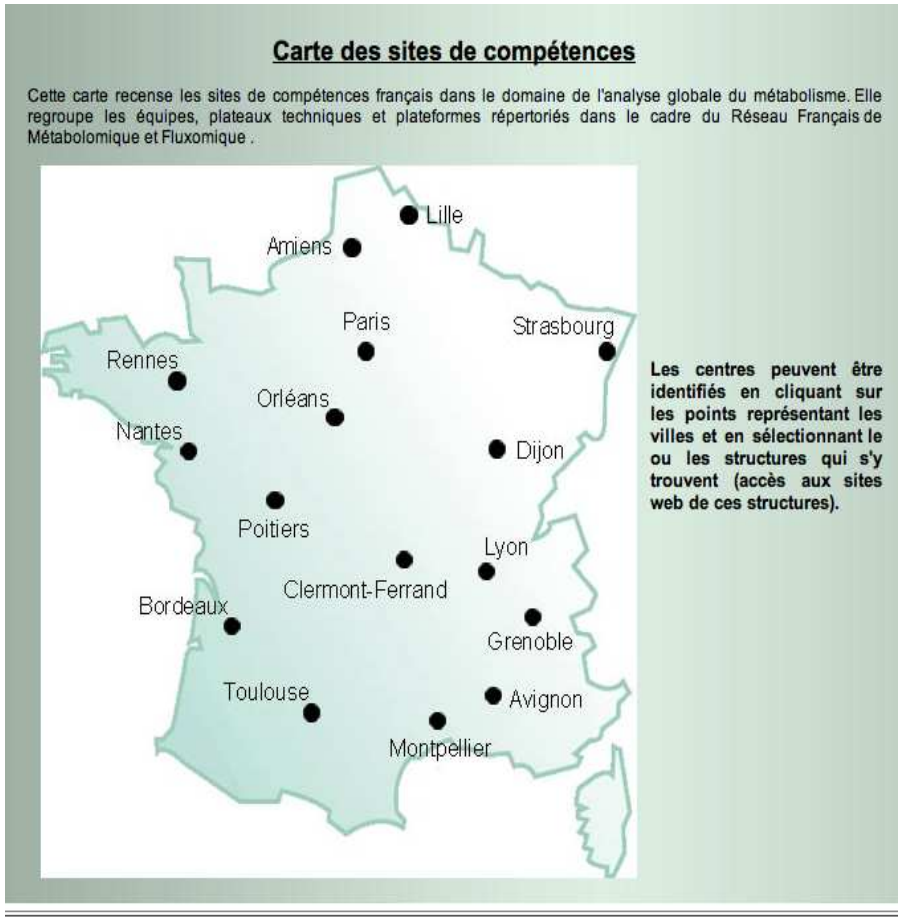




RFMF

RÉSEAU FRANÇAIS DE MÉTABOLOMIQUE ET FLUXOMIQUE

Créé en 2005



Contribuer au développement de la M-F

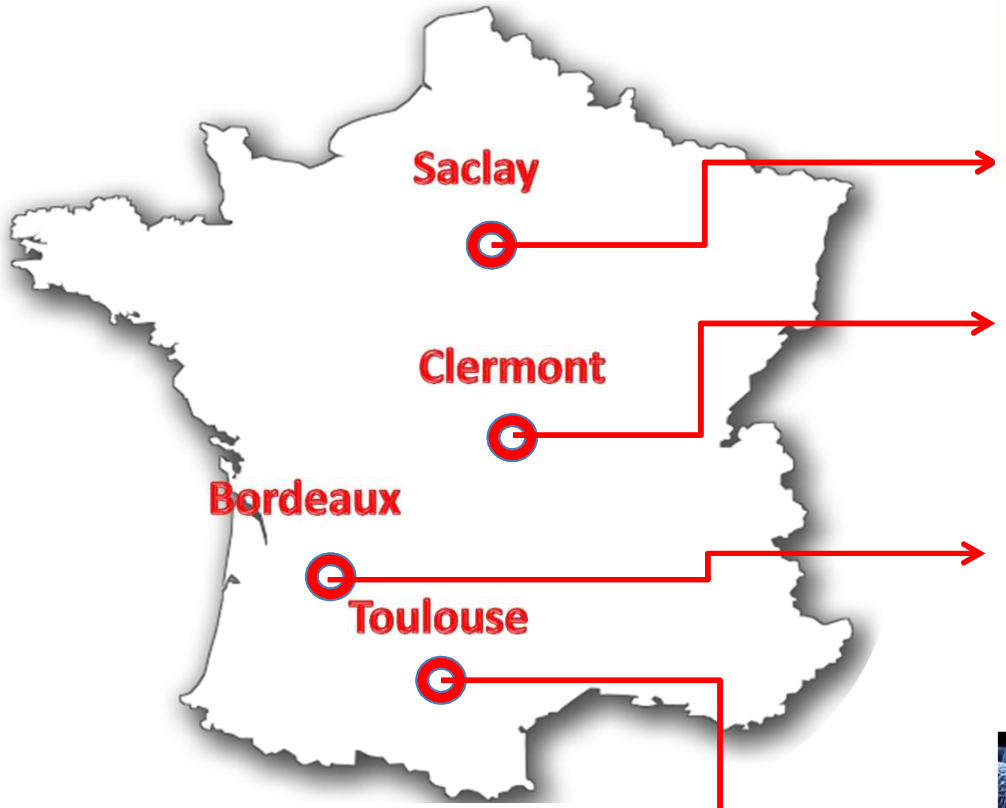
Favoriser les échanges entre les chercheurs

Favoriser / structurer l'enseignement et la formation

Organiser ou soutenir l'organisation de congrès/colloques

Favoriser la participation des jeunes chercheurs aux congrès

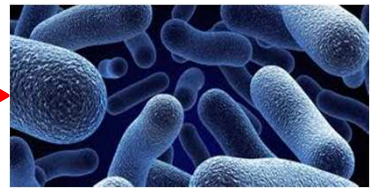
MetaboHUB: building a national infrastructure for metabolomics in France



Pharmacology & Clinical diagnostic

Nutrition and Health

Plant Biology & Biotechnology



Microbiology & Biotechnology

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