Metabolomics in cancer epidemiology

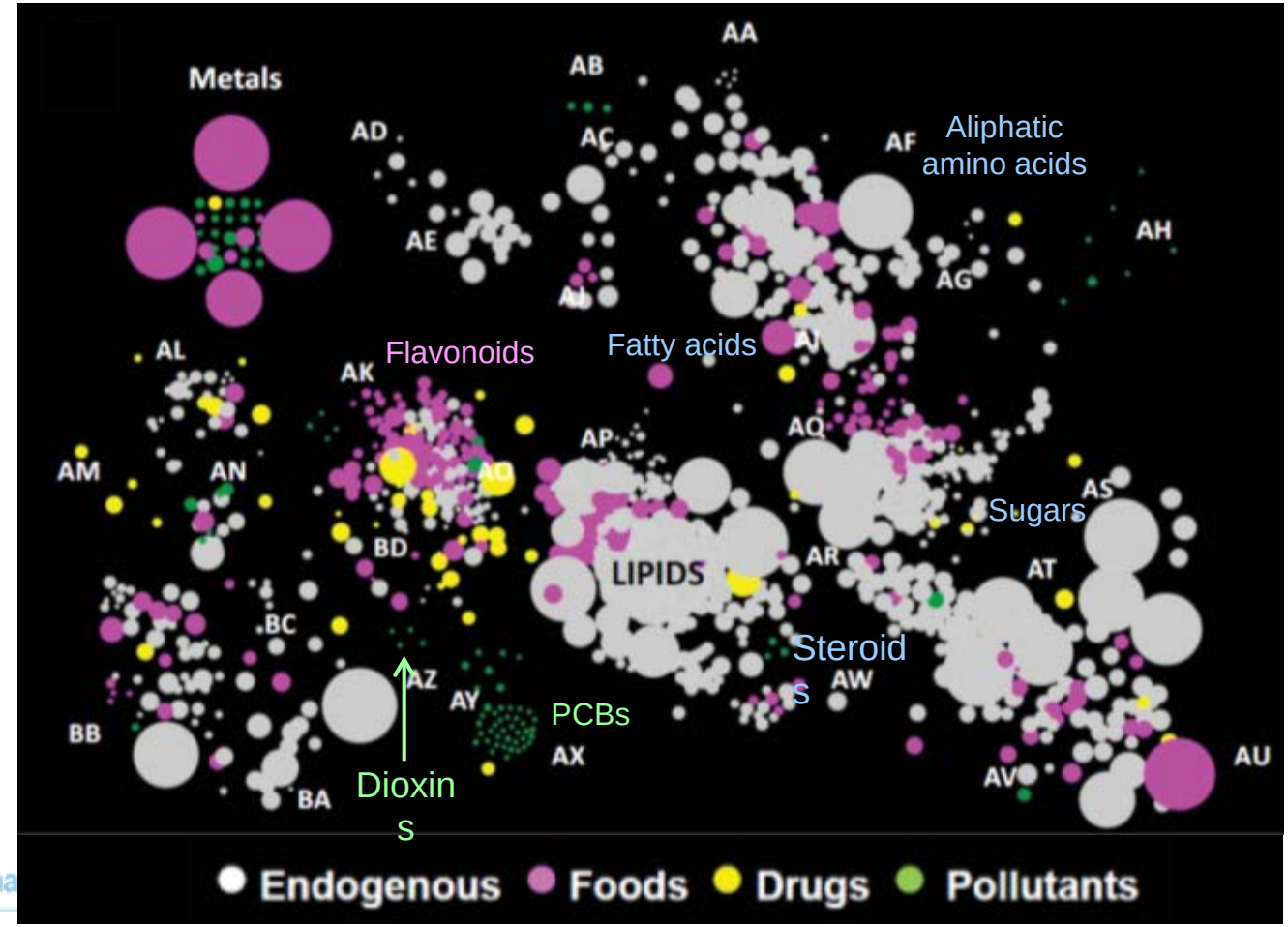
Augustin SCALBERT

Biomarkers Group

International Agency for Research on Cancer
Lyon, France

The blood exposome

- Exposome = the totality of environmental exposures received by an individual during life

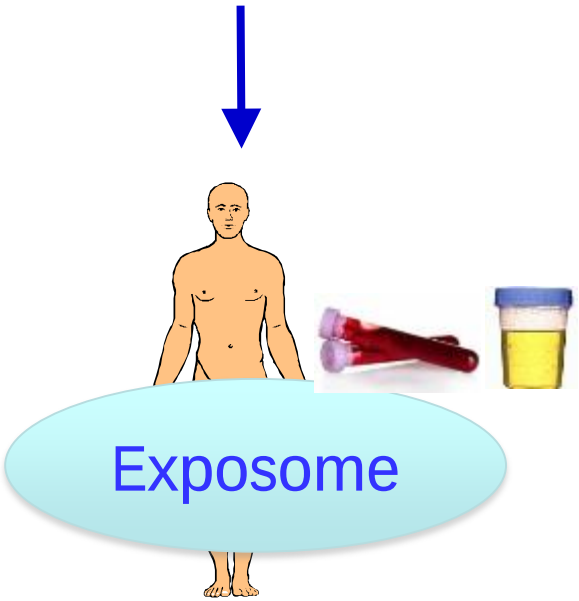


International World Health Organization

Rappaport et al., 2014, *Environ. Health Perspect.*

Exposome-Wide Association Studies (EWAS)

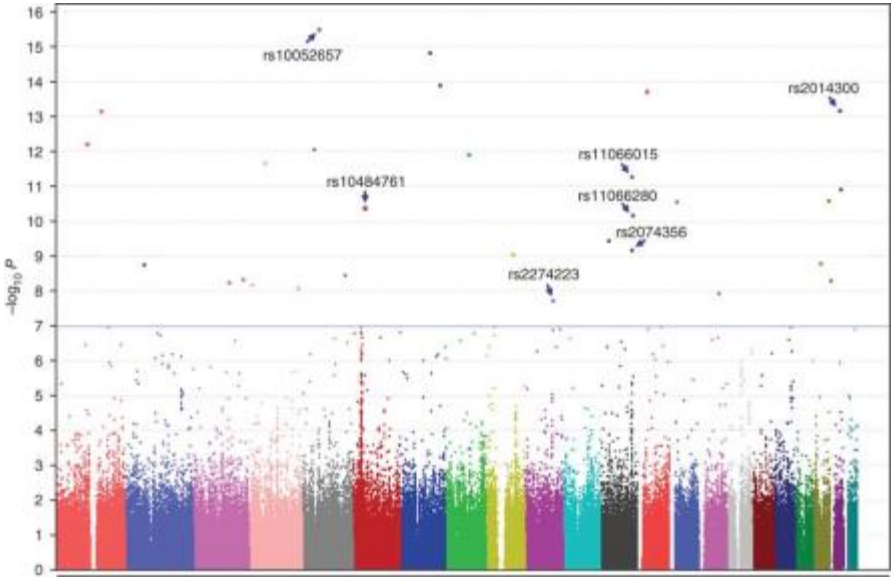
Exposures



(Nested)
case-control studies

Disease risk

Association with disease risk



Chemicals

Patel et al., 2010, *Plos One*
Rappaport, 2012, *Biomarkers*

- New risk factors for diseases

International Agency for Research on Cancer
World Health Organization

AML and metabolomics

A distinct glucose metabolism signature of acute myeloid leukemia with prognostic value

Wen-Lian Chen,[1,2] Jing-Han Wang,[1] Ai-Hua Zhao,[1,3] Xin Xu,[1] Yi-Huang Wang,[1,2] Tian-Lu Chen,[1,3] Jun-Min Li,[1] Jian-Qing Mi,[1] Yong-Mei Zhu,[1] Yuan-Fang Liu,[1] Yue-Ying Wang,[1] Jie Jin,[4] He Huang,[5] De-Pei Wu,[6] Yan Li,[7] Xiao-Jing Yan,[7] Jin-Song Yan,[8] Jian-Yong Li,[9] Shuai Wang,[9] Xiao-Jun Huang,[10] Bing-Shun Wang,[11] Zhu Chen,[1,2] Sai-Juan Chen,[1,2] and Wei Jia[1,3,12]

Chen W.L. et al., 2015, *Blood*

229 de novo AML patients
260 matched controls
Serum
GC-TOF-MS
100 metabolites identified

Table 2. A panel of 6 metabolites with prognostic value for CN-AML

Metabolite‡	Importance score for OS and EFS*
Lactate	74.17
2-Oxoglutarate	57.12
Pyruvate	53.89
2-HG	12.3
Glycerol-3-phosphate	8.05
Citrate	−23.54

International Agency for Research on Cancer
World Health Organization

- A prognosis risk score to predict patients with poor survival

Trade-off between metabolite coverage and quality

Quantitative analyses

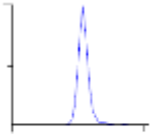
Semi-quantitative analyses

Data quality

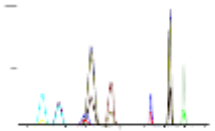
Metabolite coverage

1 | 10's | 100's | 1,000's

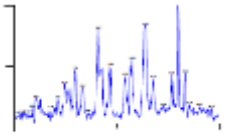
Number of metabolites analysed



Single assay



Target analysis

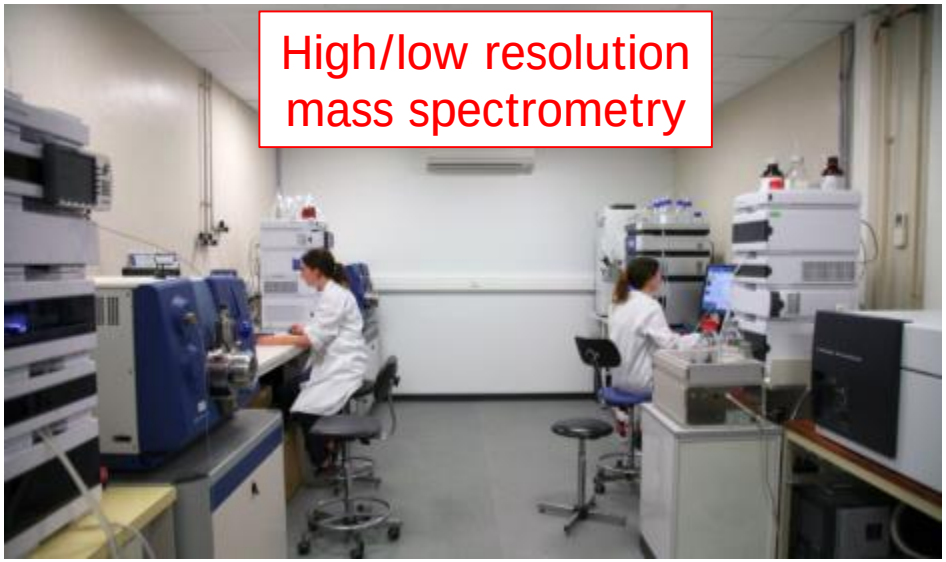


Metabolite profiling

Targeted metabolomics

Untargeted metabolomics

Metabolomics at IARC



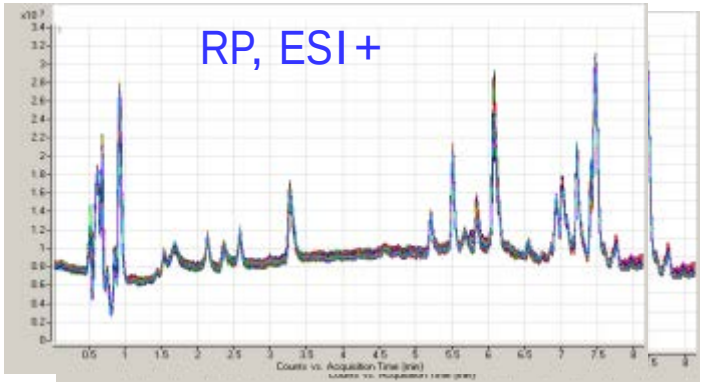
- Several analytical methods needed to analyze the metabolome
- LC-MS → ~ 15,000 signals
- ~ 8,000 known metabolites in blood but 200 to 800 commonly annotated in LC-MS profiles

hmdb
The Human Metabolome Database

UHPLC-QTof - Methods

Conditioning
Conditioning
SST
SST
SST
SST
SST
SST
SST
SST
SST
SST
Blank
QC
MS/MS 10V
MS/MS 20V
MS/MS 30V
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Blank
QC
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Sample
Blank
QC

- Plasma samples
  - 50 uL aliquots
  - Protein precipitation (ACN)
- UHPLC
  - Reverse-phase
  - HILIC
  - 13.5 min runs
- Agilent Qtof 6550
- Robust QC procedure
  - Agilent MPP, Profinder
  - Up to 500 samples/batch
- Data-dependant MS/MS
- Targeted MS/MS analysis

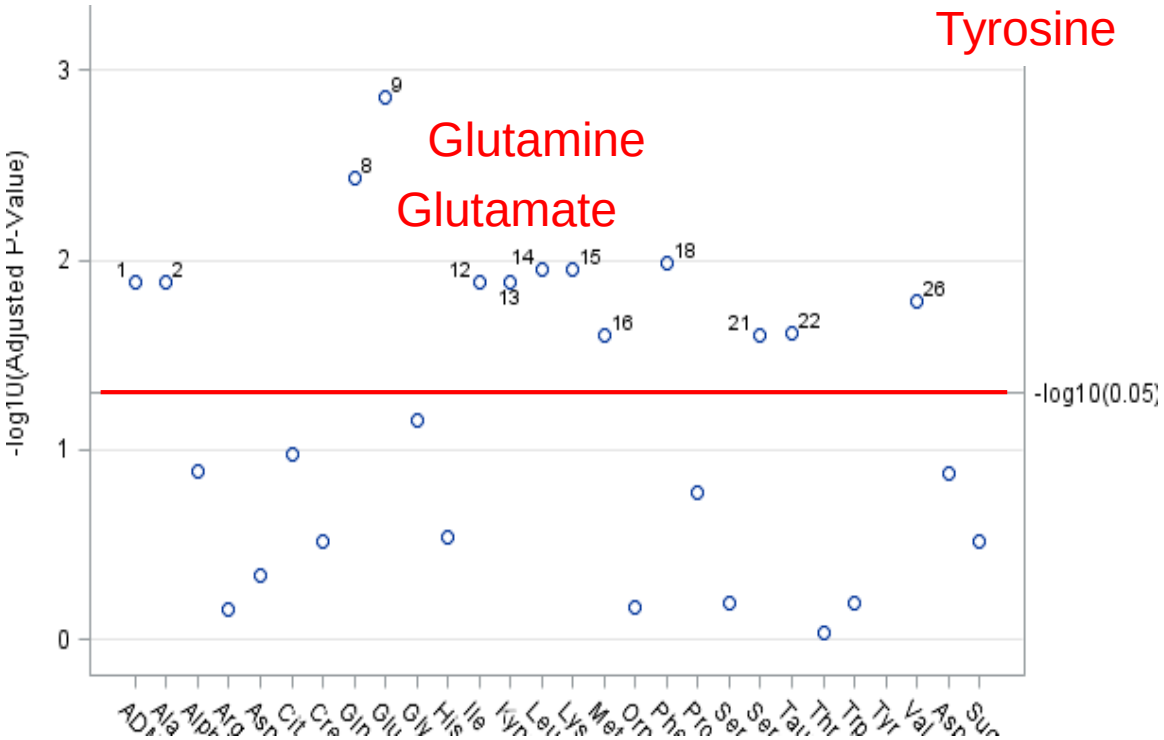


International Agency for Research on Cancer
World Health Organization

A prospective study on hepatocellular carcinoma in the EPIC cohort

147 HCC cases, 147 controls
Serum samples
Avg. follow-up time: 9.6 yrs
28 Amino acids, biogenic amines, hexoses measured by LC-ESI-MS-MS
Adjusted for multiple variables
Corrected for multiple-hypothesis testing

Associations with risk of liver cancer



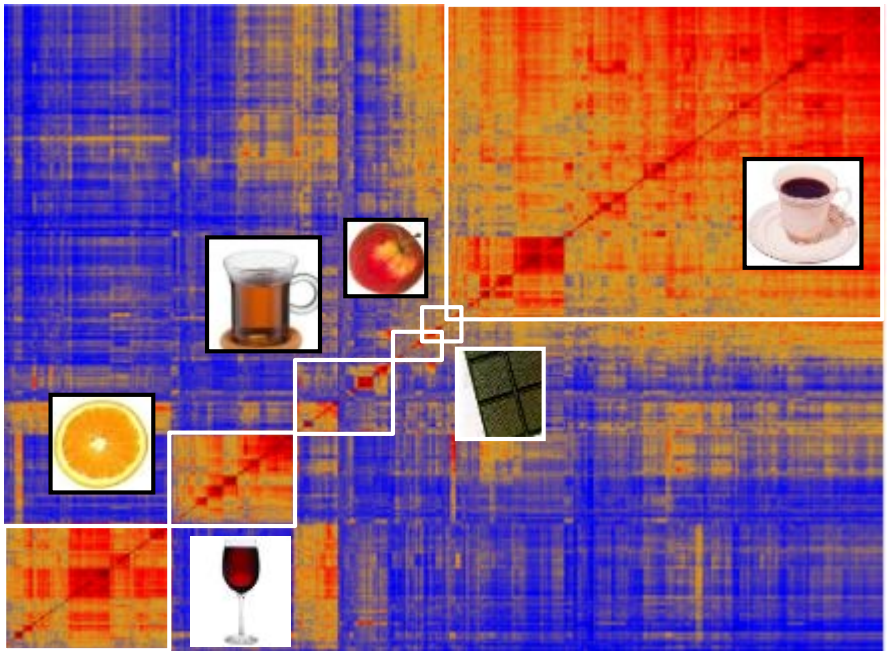
International Agency for Research on Cancer

World Health Organization

- 16 metabolites associated to cancer risk

Stepien et al., 2015, *Int J Cancer*

Xenometabolome

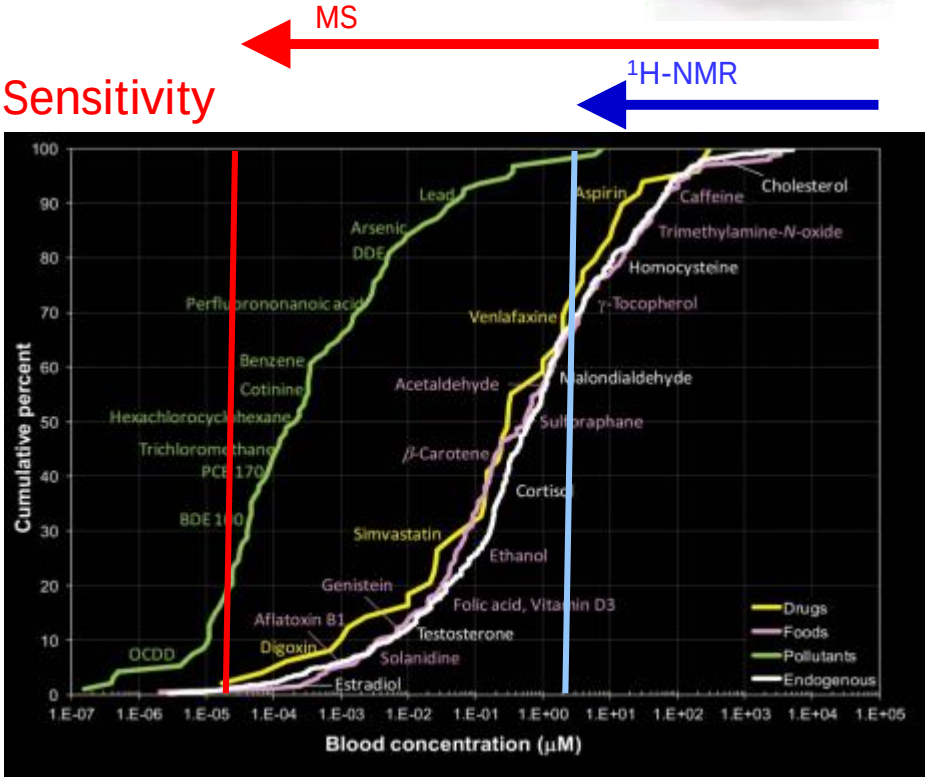


- 83 food-derived metabolites identifed in urine

International Agency for Research on Cancer

World Health Organization

Edmands et al., 2015, *Am J Clin Nutr*



- Limits of concentrations to measure the xenometabolome not yet evaluated

Rappaport et al., 2014, *Environ. Health Perspect.*

Biomarkers Group, IARC

Craig Knox
David Wishart
Liang Li

Rashmi Sinha
Erikka Loftfield
Neal Freedman

Paolo Vineis
Marc Gunter

Tim Key

Bernardo Bonnani

Neli Ulrich
Nina Haberman