EVEREST – Intervention de l'ANR

- **Rappel de la contractualisation et des règles afférentes**
- **Présentation du suivi de projet**

Madame Emmanuelle SIMON

Responsable d'actions Santé & Biotechnologies
Direction des Grands Programmes d'Investissement de l'Etat
(DGPIE)

Agence Nationale de la Recherche

Madame Giulia GIRELLI ZUBANI

Chargée de Projets Scientifiques
Direction des Grands Programmes d'Investissement de l'Etat
(DGPIE)

Agence Nationale de la Recherche

EVEREST – Perspectives de recherche de l'IHU en 2024

- **Organisation et structuration de l'IHU (C. Oudin)**
- **Présentation des WPs (F. Zoulim)**
- **Highlights recherche**
  - Innovation en multiomique spatiale (S. Ayciriex)
  - Du profilage multiomique aux nouveaux biomarqueurs (M. Levrero)
  - Maladies stéatosiques hépatiques : mécanismes physiopathologiques (C. Caussy)
  - Innovation en transplantation hépatique (JY. Mabrut)
- **Plan d'action 2024 – 2025 (F. Zoulim)**
- **Table ronde (A. Blet, G. Mithieux)**

Organisation et structuration de l'IHU (C. Oudin)

Session

Perspectives de recherche de l' IHU en 2024

EVEREST – Gouvernance

Accord de consortium entre les Fondateurs : utilisation d'un modèle classique

Gouvernance: Présentation des comités, de leurs rôles, compositions et modalités

- **Conseil de Surveillance**: organe décisionnel, qui contrôle et entérine les décisions et propositions
  + Bureau des fondateurs: assiste le Directeur de l'IHU, assure le relais entre stratégie et management opérationnel

- **Comité de Direction** : définit les orientations scientifiques, met en œuvre, pilote les actions scientifiques, financières et de valorisation de l'IHU

- **Conseil Scientifique International** : suit, évalue les actions scientifiques, éducatives et technologiques, conseille sur la stratégie scientifique

- **Comités Opérationnels Techniques** : par thématiques
  - Comité scientifique
  - Comité clinique
  - Comité formation

EVEREST – Organisation et structuration de l'IHU

Conseil Scientifique International
8 scientifiques internationaux

Conseil de surveillance (>= 1 réunion/an)

4 Fondateurs
HCL, UCBL, Inserm, CLB

Partenaires académiques
(ULyon2, CNRS, INRAé)

4 membres invités: Directeur IHU, + 3 représentants des autorités
(représentants de l'Etat français, région AuRA, Métropole de Lyon)

3 représentants qualifiés :
- Associations de patients (ELPA)
- Sociétés savantes (AFEF)
- Acteurs économiques (Lyon Biopôle, …)

BUREAU des Fondateurs
4 réunions / an
1 représentant par Fondateur

Comité de Direction

Directeur de l'IHU

Directeur Adjoint
+ 4 scientifiques

+ Interface fondateurs:

Directeur de la DRS HCL
DGS Adjoint UCBL
Représentant Inserm
Représentant CLB

(>= 1 réunion/trimestre)

Comités Opérationnels Thématiques

Comité scientifique
Equipes pluridisciplinaires et inter-institutionnelles (WP leaders)

Groupe Valorisation

Comité Clinique
(équipes de recherche clinique)

Groupe Patients

Comité Formation

Un conseil scientifique international pour évaluer et guider nos stratégies

8 membres

- **Norah Terrault (USA, F); SAB chair**; clinical and translational Hepatology
- Marina Berenguer (Spain, F); ESLD & transplantation
- Anders Boyd (NL, M); Data science
- Amalia Gastaldelli (Italy, F); Metabolism
- Josep Llovet (Spain, M); HCC
- Mala Maini (UK, F); Immunology
- Arun Sanyal (USA, M); MASH
- John Tavis (USA, M); Virology

EVEREST – Comités internes

Cellule communication

Directeur:
F Zoulim

Directeur adjoint:
M Levrero

Comité de Direction
F Zoulim, M Levrero,
G Mithieux, S Ayciriex,
JY Mabrut, C Caussy

Cellule support
Directeur exécutif
Chef de projet
Assistant de Direction
Resp. adm et financier (UCBL)
Resp informatique

Comité Recherche et innovation

G. Mithieux, S. Ayciriex,
WP1: B. Testoni, D. Durantel
WP2: J. Rieusset, M. Zeisel
WP3: X. Muller, JY. Mabrut
WP4: S. Ayciriex, M. Levrero
WP5: C. Caussy, F. Zoulim
WP6: M. Préau, M. Viprey
WP7: L. Boussel, P. Roy
Plateformes techno:
C. Marquette, ML. Plissonnier,
Y. Clément, CLB translat, M. Rivoire

Comité recherche clinique

K. Mohkam, C. Caussy
F. Zoulim, F. Bailly, M. Levrero, P. Merle,
J. Dumortier, A. Blet, N. Laverdure,
JY. Mabrut, C. Guichon, P. Roy,
T. Antonini, V. Icard, H. Serrier,
V. Hervieu, A. Rode, C. Scholtès
CRB, CRC, paraméd. (J. Gonzalez)
Fast-track

Comité Formation

F. Lebossé, C. Moyret-Lalle
R. Parent, T. Antonini,
S. Ayciriex
F. Bailly, G. Rossignol

Groupe Valorisation

PO. Vidalain, C. Marquette
Représentants SATT et IT
+ consultants externes

Groupe Patients

M. Préau, G. Thual
Médecins, paraméd. et scientifiques
Associations de patients

EVEREST – Organisation et structuration de l'IHU

➢ Mise en place de la cellule support

Octavie Paris
Chef de projet

Christelle Couvrie
Assistante de Direction

Catherine Oudin
Directrice Exécutive

Accompagnement projets

- Gestion appels à projets interne
- Accompagnement projets scientifiques
- Veille des appels à projets
- Accompagnement collaborations

Animation scientifique

- Organisation des évènements IHU
- Animation Communication
- Organisation et suivi des comités

Suivi administratif et financier

- Gestion financière
- Suivi, tableaux de bord, rapports IHU
- Recrutements, suivi des contrats

Valorisation

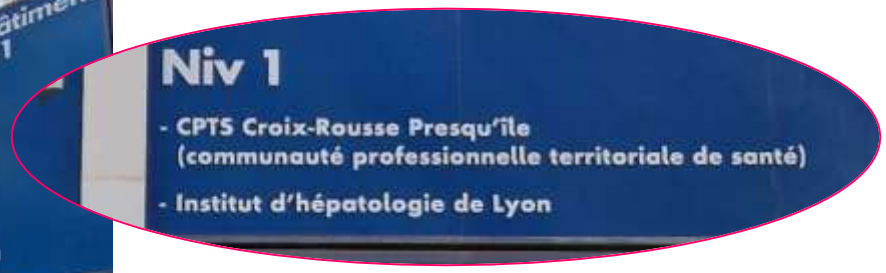
- Levée de fonds
- Sensibilisation PI
- Création de start-ups
- Recensements (publications, thèses, posters, brevets, start-ups…)

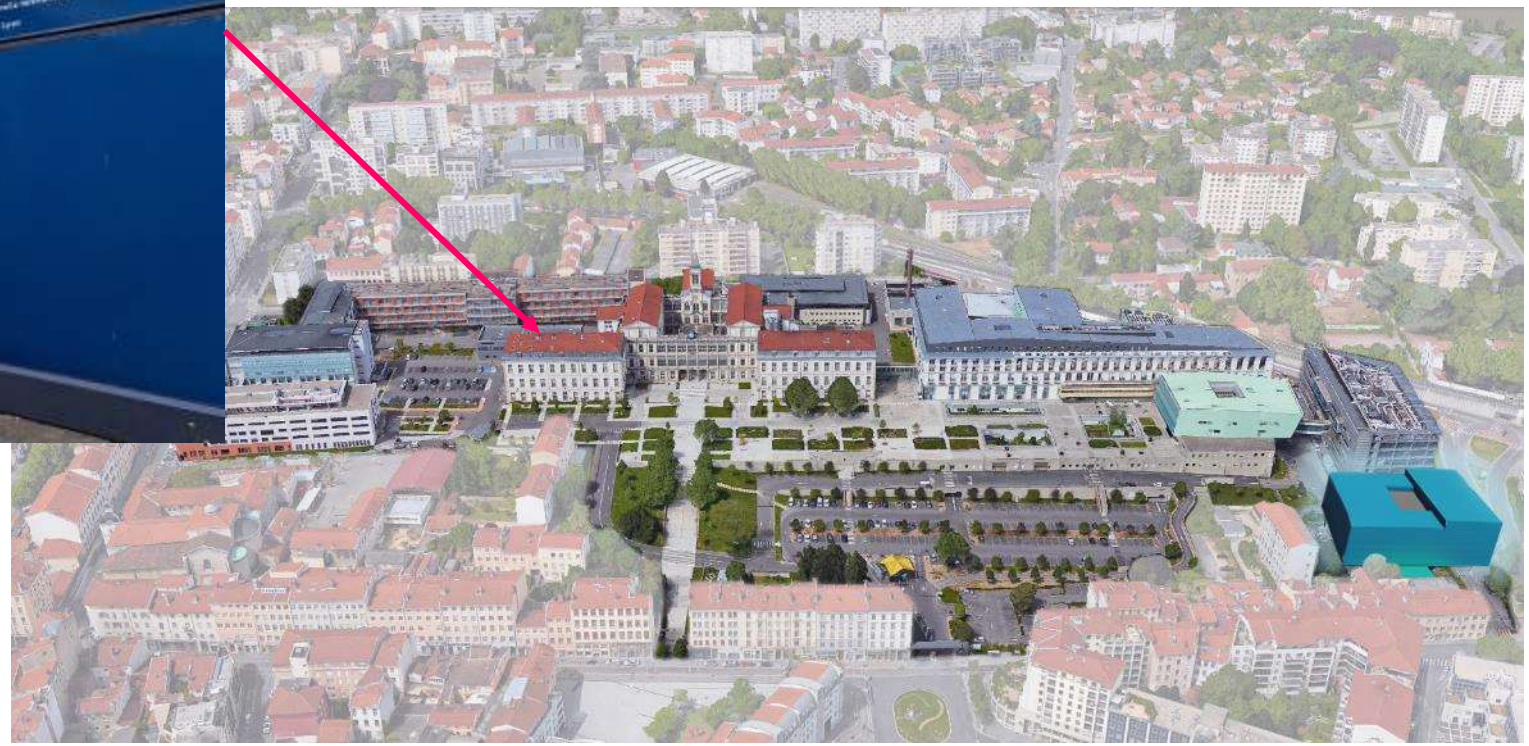
En lien avec les fondateurs, leurs filiales et structures supports

Lyon 1 · HCL · Inserm · Centre Léon Bérard · EZUS · Lyon Ingénierie Projets · PULSALYS · InsermTransfert

EVEREST – Organisation et structuration de l'IHU

➢ **Installation dans des bureaux dédiés sur l'hôpital de la Croix-Rousse**





- 3 bureaux - 40 m²
- 4 postes de travail
- un espace réunion

EVEREST – Organisation financière de l'IHU

Dotation ANR – IHU = 20 M€

RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

FRANCE 2030

anr agence nationale de la recherche

Etablissement gestionnaire

Université Claude Bernard Lyon 1

Création d'un SACD

Frais de gestion (10% = 1.818 M€)
Reversement de la part ANR à chaque fondateur

Lyon 1 — HCL — Centre Léon Bérard — Inserm

Redistribution des 10% (banalisés) selon les besoins IHU
Prioritairement sur la cellule opérationnelle

10% conservés en central par l'établissement

EVEREST – Gestion financière

➢ Utilisation de la dotation sur les 3 premières années

	Part UCBL	Part HCL	Part Inserm	Part CLB	**TOTAL**
Part ANR A1 à A3	2 911 k€	2 489 k€	960 k€	1 213 k€	7 573 k€
Frais de gestion A1 à A3	291 k€	249 k€	96 k€	121 k€	757 k€

8,2 M€
41% de la dotation

➢ **Financements complémentaires à l'ANR:** label IHU pour les projets d'hépatologie des différentes UMR et équipes cliniques

- **Enjeu d'attractivité de l'IHU et de démonstration de l'effet levier**
- Règles de gestion sur les recettes hors dotation non fixées dans l'AC, en cours de négociation avec les fondateurs
- Revenus concernés:
  - Subventions publiques (nationales et internationales)
  - Contrats industriels
  - Prestations de service

EVEREST – Pérennisation économique

Subvention ANR

ATTRACTION
3 packages :
Chaires junior, senior et KOL

RECHERCHE
Projets &
appels à projets

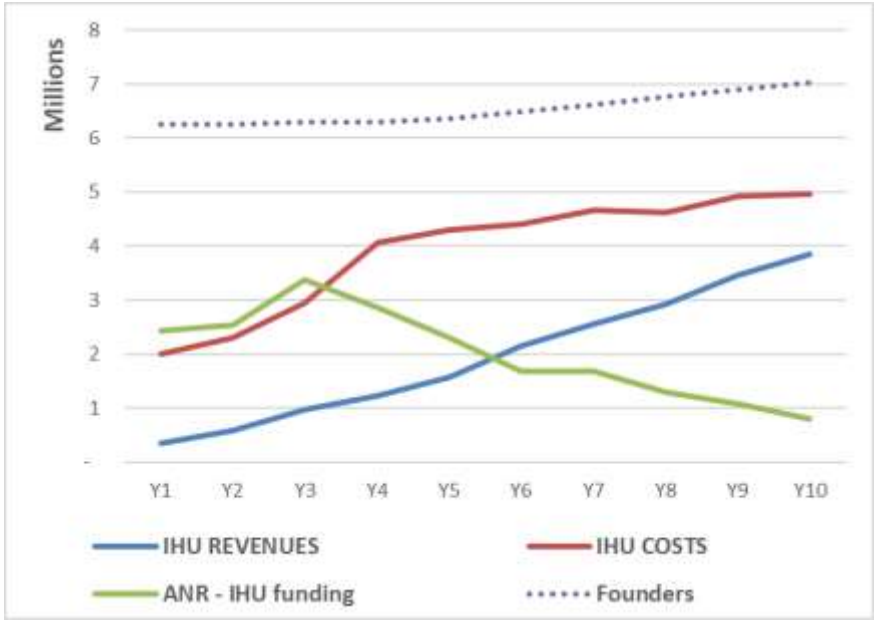
INNOVATION
- **CosMX**

Transcriptomique single cell

- **MALDI²-HiPlex**

Multiomique spatiale

Projections économiques



- **Utilisation majeure de la dotation ANR les 5 premières années**
- **Investissement fort et pérenne des fondateurs**
- **Accroissement constant des revenus**
- **Cible de ~4 M€ de recettes additionnelles en année 10**
- **Adaptation des recrutements et investissement selon financements captés**
- **Vers une autonomie financière**

Réinvestissement de tous les bénéfices de l'IHU EVEREST dans les projets de recherche et de formation :

i) attraction de scientifiques
ii) acquisition d'équipements innovants
iii) financement de projets high risk / high gain

EVEREST – Enjeux de ressourcement

Recherche fondamentale → Recherche translationnelle → Recherche clinique → Transfert industriel

1. **Exploitation des résultats des projets de recherche et de R&D**
   - Projets de recherche collaboratifs (collaborations directes, subventions nationales et internationales, France 2030, Horizon Europe …)
   - Partenariats privés
   - Brevets et licences
   - Start-ups

2. **Services supports aux projets industriels**
   - Prestations de services pour les sociétés privées
   - Valorisation des ressources, expertises et plateformes

3. **Formation**
   - e-training
   - Conférences (médecins, pharmaciens, biologistes, paramédicaux…)
   - Summer schools

4. **Dons, mécénat, levée de fonds et parrainage**

EVEREST – Plus d'informations

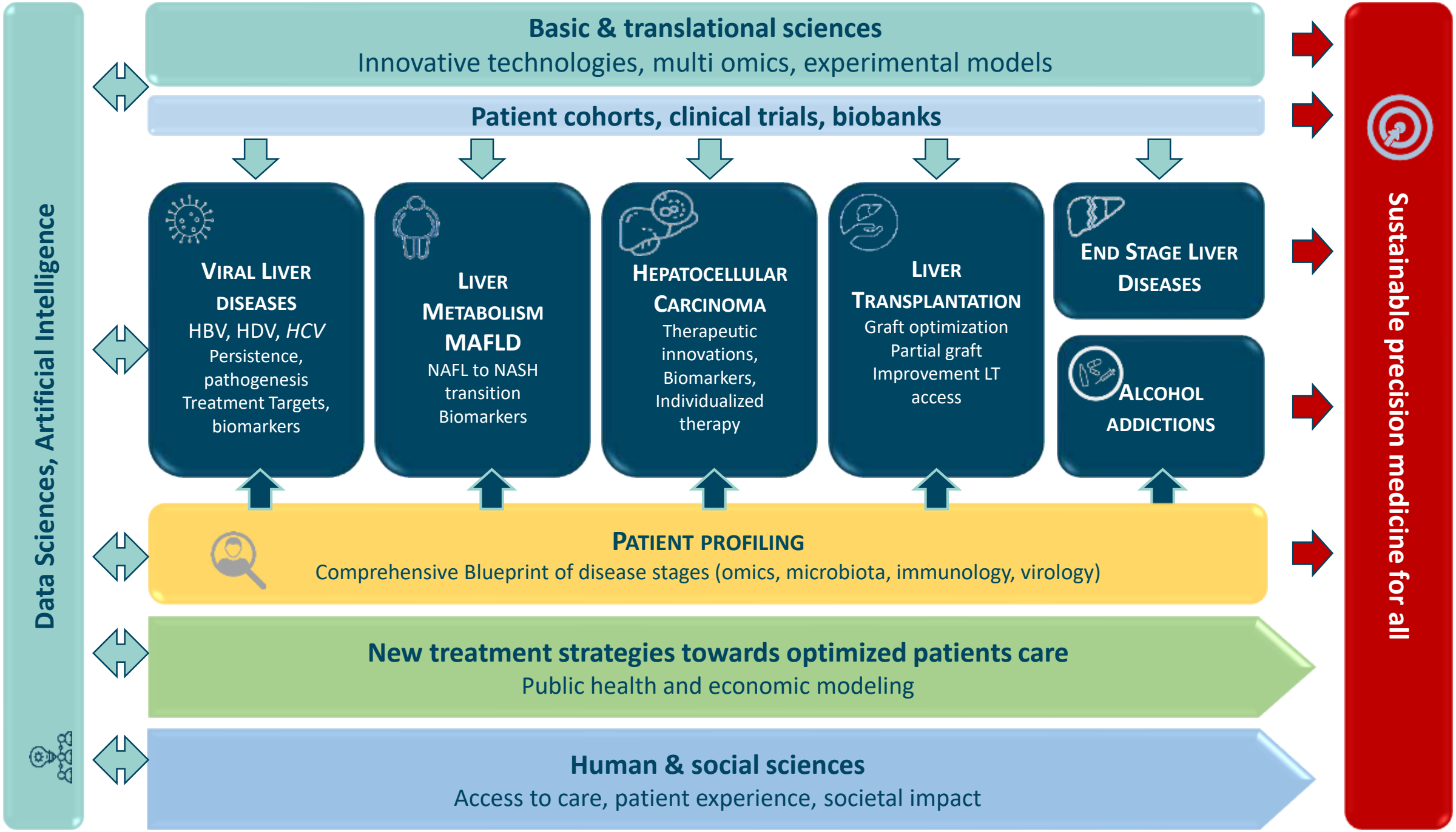
Notre site web est en ligne
https://www.ihu-hepatolyon.fr/
En français et en anglais

Nous contacter :
contact@ihu-hepatolyon.fr

Présentation des Work Packages (F. Zoulim)

Session

Perspectives de recherche de l' IHU en 2024


Data Sciences, Artificial Intelligence
Basic & translational sciences
Innovative technologies, multi omics, experimental models
Patient cohorts, clinical trials, biobanks
Viral Liver diseases
HBV, HDV, HCV
Persistence, pathogenesis
Treatment Targets, biomarkers
Liver Metabolism MAFLD
NAFL to NASH transition
Biomarkers
Hepatocellular Carcinoma
Therapeutic innovations, Biomarkers, Individualized therapy
Liver Transplantation
Graft optimization
Partial graft
Improvement LT access
End Stage Liver Diseases
Alcohol addictions
Patient profiling
Comprehensive Blueprint of disease stages (omics, microbiota, immunology, virology)
New treatment strategies towards optimized patients care
Public health and economic modeling
Human & social sciences
Access to care, patient experience, societal impact
Sustainable precision medicine for all

EVEREST - Workpackages

Basic and translational science

WP1 Curing HBV and HDV: *from virus persistance to innovative targets*

WP2 Liver integrative biology: *interplay between energetic metabolism, inflammation and epigenetics*

WP3 Hepatic critical care: *targeting perioperative liver injury*

Translational science for clinical research

WP4 Multiomics profiling: *towards an actionable blueprint of liver diseases*

WP5 Clinical cohorts and trials

WP6 Improving care: *impact of innovation on clinical care pathways and health system*

WP7 Data Science, data integration and modelling
Precision medicine, public health & economic assessment

WP8 Innovative Training and Education Programs

WP9 Exploitation and industrial translation

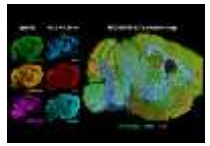
EVEREST – a cutting-edge platform for liver research

INSTITUT D'HEPATOLOGIE DE LYON

La Région Auvergne-Rhône-Alpes

INSTITUT DES SCIENCES ANALYTIQUES

BRUKER



MALDI²-HiPlex IHC

INSTITUT D'HÉPATOLOGIE DE LYON
CENTRE INTÉGRÉ DES MALADIES DU FOIE

nanoString

CosMx

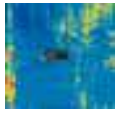
Lyon 1

MM FRANCE Microm Microtech

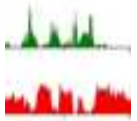
3DHISTECH

Translational Science Platform

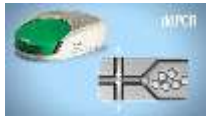
(Epi)genomics



Transcriptomics
Chromatin analysis

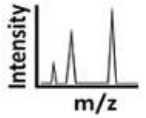


Single cell analysis
(RNA, Chromatin, Secretome)



ddPCR

High Resolution Multiomics MS



Microbiome

Cellular & animal Models
(PHH, PCLS, 3D bioprinting)

Spatial Multiomics

CosMx

nanoString

3d fab PRINTING FOR LIFE

Automated IHC platform

Computational biology

genoway

De l'innovation vers le transfert clinique

Hépatites virales
HBV, HDV, *HCV*

Foie Métabolique
MAFLD

Hépatites Alcooliques et Addictions

Défaillance Hépatique

Carcinome Hépatocellulaire

Transplantation Hépatique

Cohortes Cliniques

Hépatites B & Delta
MASLD
Hépatite alcoolique
Défaillance hépatique
Carcinome hépatocellulaire
Transplantation
Pédiatrie

Essais Cliniques

Phase I
Phase II
Phase III
Phase IV

Recherche Translationnelle

Échantillons Cliniques

Fixed & frozen biopsies

FNA
(Fine needle aspirate)

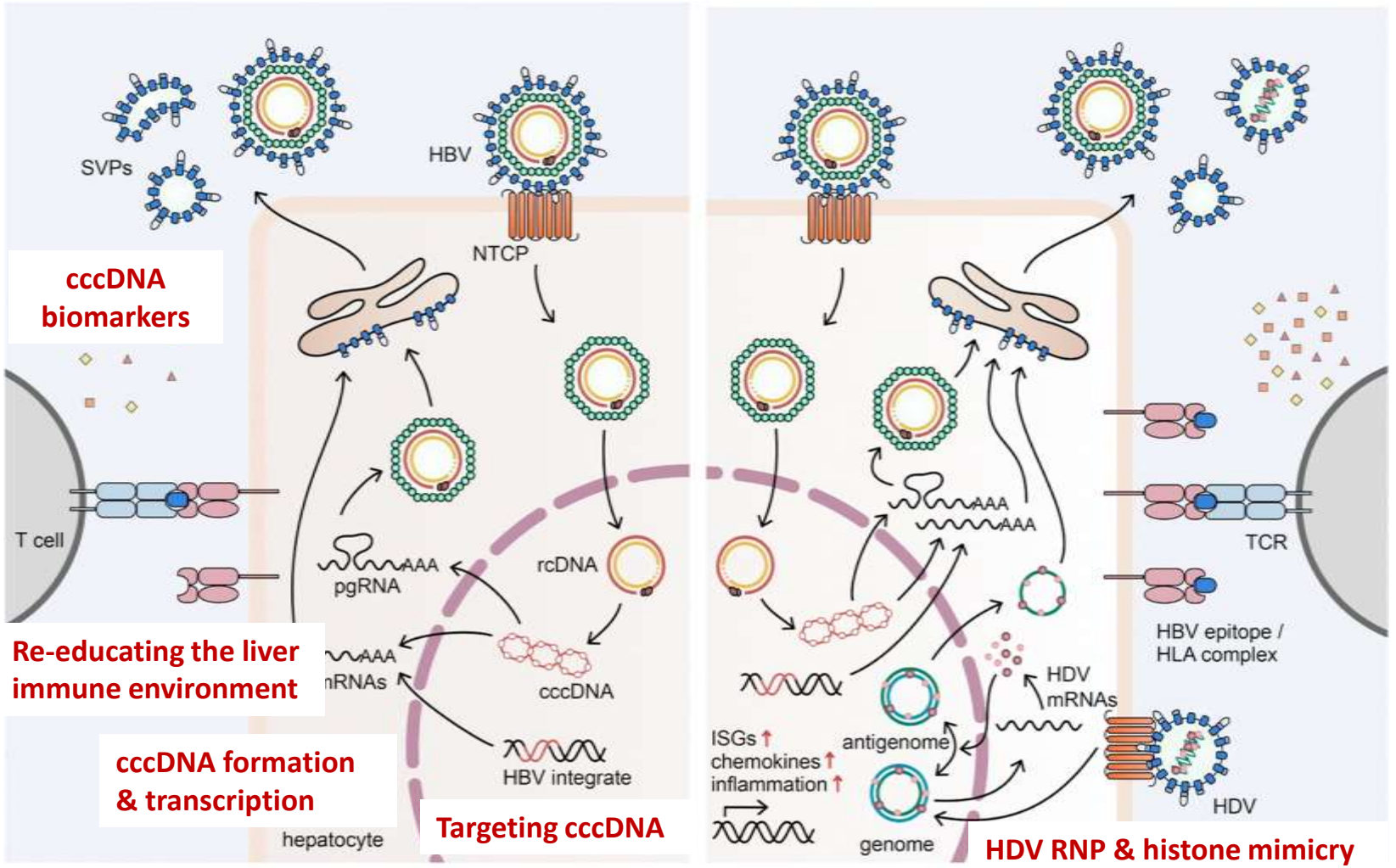
Liver resections

PCLS *(precision cut liver slices)*

Plasma, Serum, PBMCs

WP1 – Curing Hepatitis B and Delta: from virus persistence to innovative targets

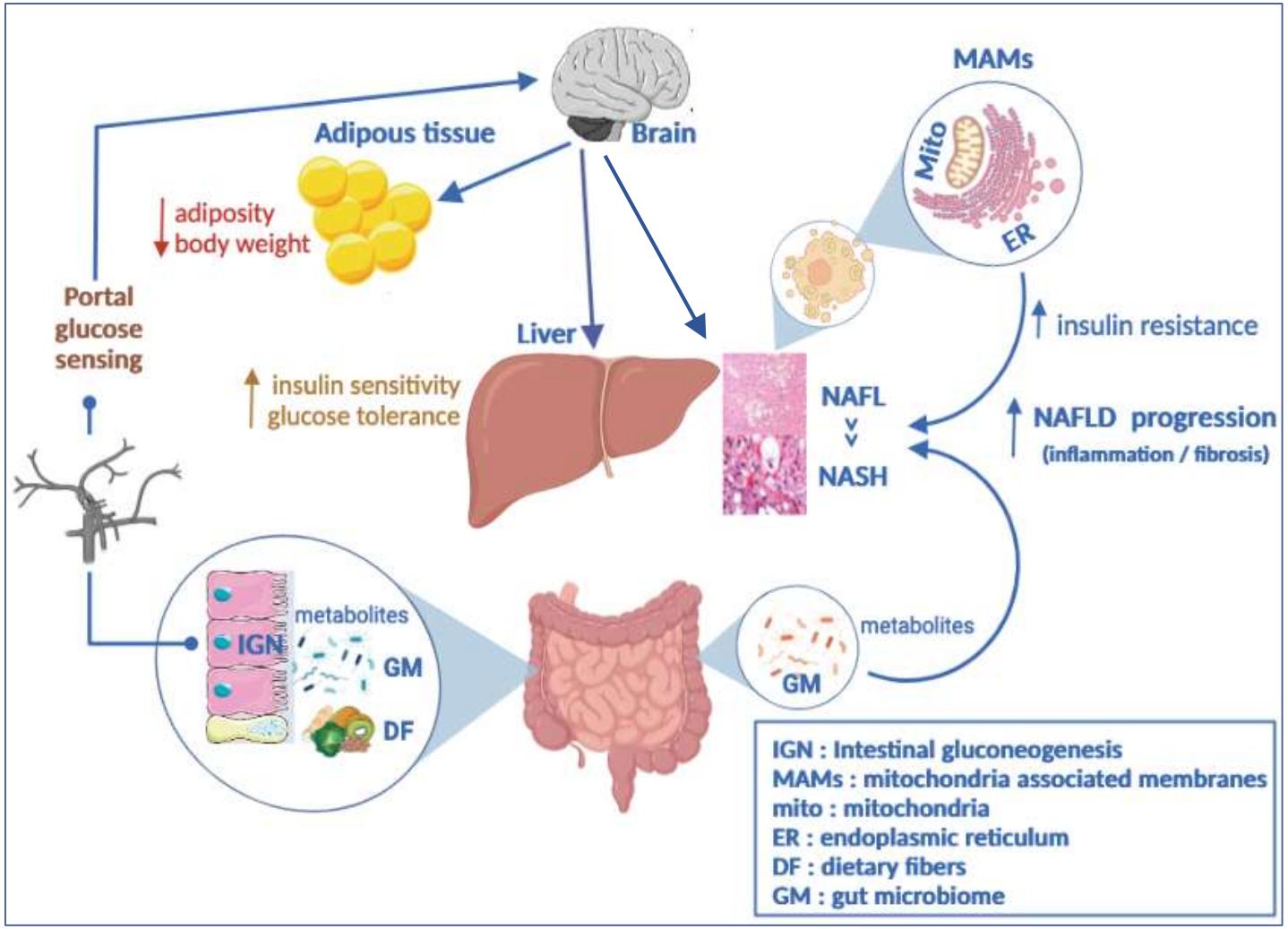
WP leaders: Barbara Testoni, David Durantel



Gene editing KO screen for new targets to cure HBV and HDV

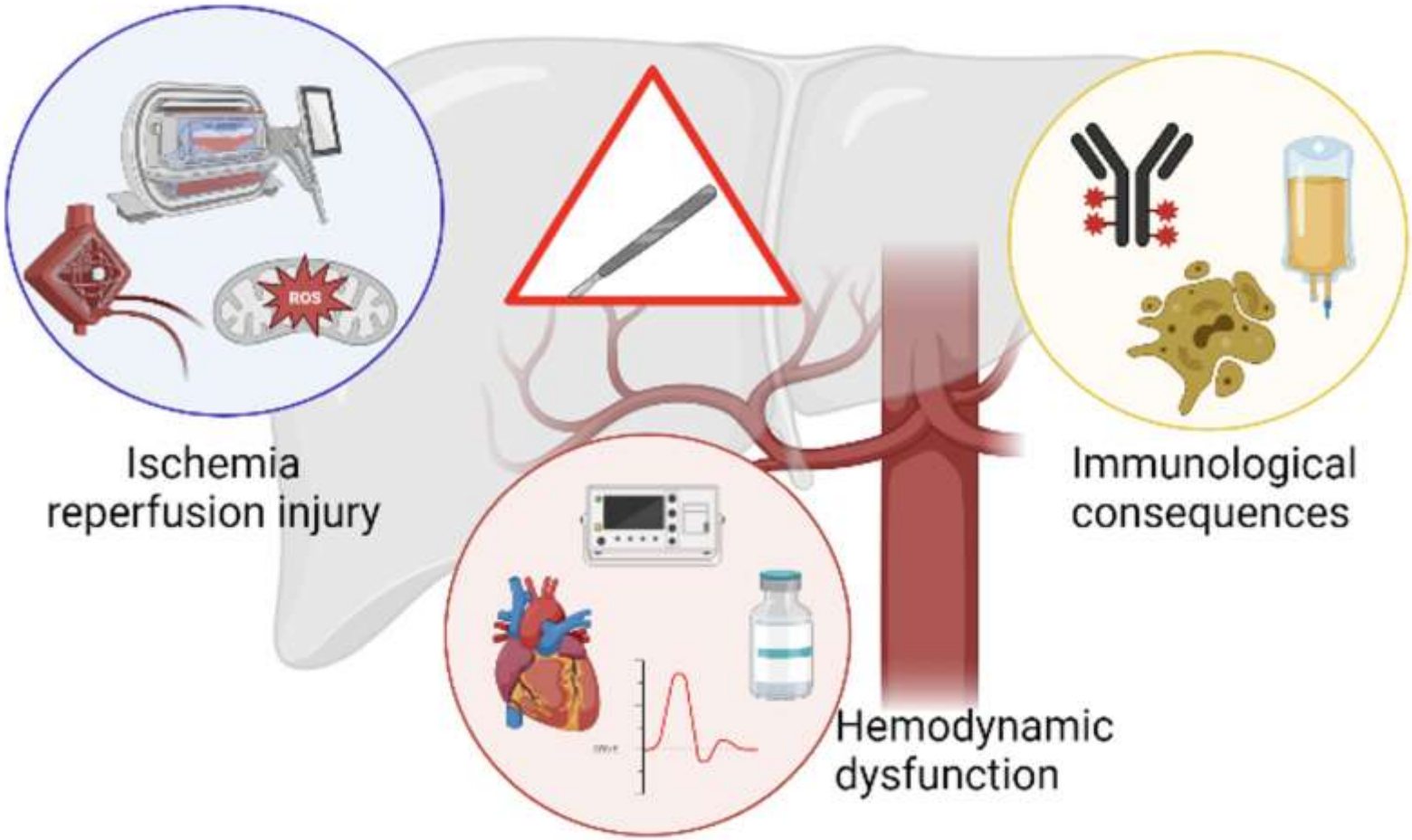
WP2 – Liver integrative biology: the interplay between energetic metabolism, inflammation and epigenetics

WP leaders: Jennifer Rieusset, Mirjam Zeisel



WP3 – Hepatic critical care: targeting perioperative injury

WP leaders: Xavier Muller, Jean-Yves Mabrut



WP4 – Multiomics profiling

WP leaders: Sophie Ayciriex, Massimo Levrero

Clinical samples

Fixed biopsies
FFPE blocks

Frozen core biopsies

FNA
Fine Needle Aspirate

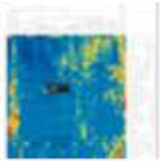
Liver resections

PCLS
Precision Cut Liver Slices

Plasma
Serum
PBMC

Omics

Transcriptomics
mRNAs ncRNAs
Nanostring, HTG EdgeSeq, NGS

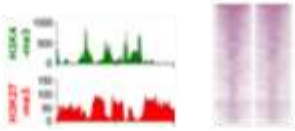


RNA-Seq
miR profiling

Single cell omics
10x Genomics, Isoplexis

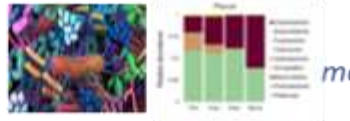
scRNA-Seq
Secretome
phosphoproteome

Chromatin analysis
NGS ChIP, ATAC, ChIRP, RIP



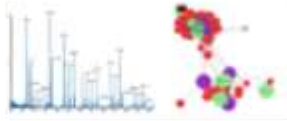
ChiP-Seq
ATAC-Seq

Microbiome
NGS



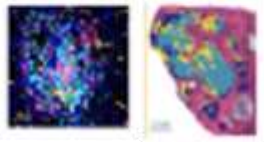
16S
metagenomics

Metabolomics
Lipidomics
Proteomics



LC-ESI-MS/MS

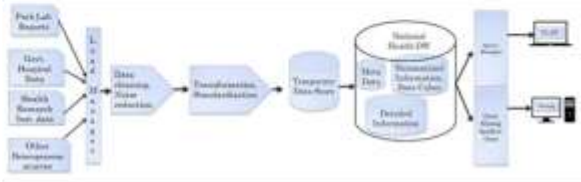
Spatial Omics
Nanostring digital spatial profiling
Bruker multiomic tissue imaging



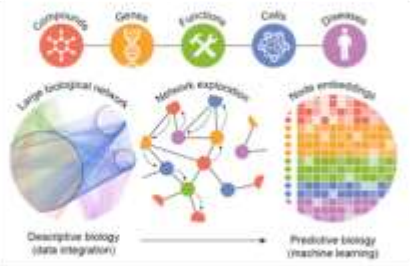
Digital spatial profiling (RNAs, proteins)
MALDI HIPLEX-IHC (proteins, metabolites)

Analysis

Healthcare data warehouse



Computational biology & artificial intelligence



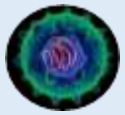
WP5 – Clinical studies

WP leaders: Cyrielle Caussy, Fabien Zoulim

Cohorts
Trials

HBV

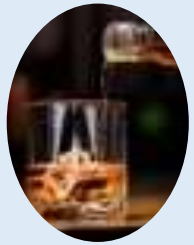
HDV



HCV

Viruses

NAFLD



Alcohol

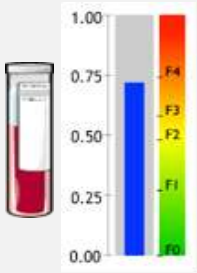
Rare diseases

HCC

Liver Failure

Liver Transplantation

Linkage to care
Patient trajectories



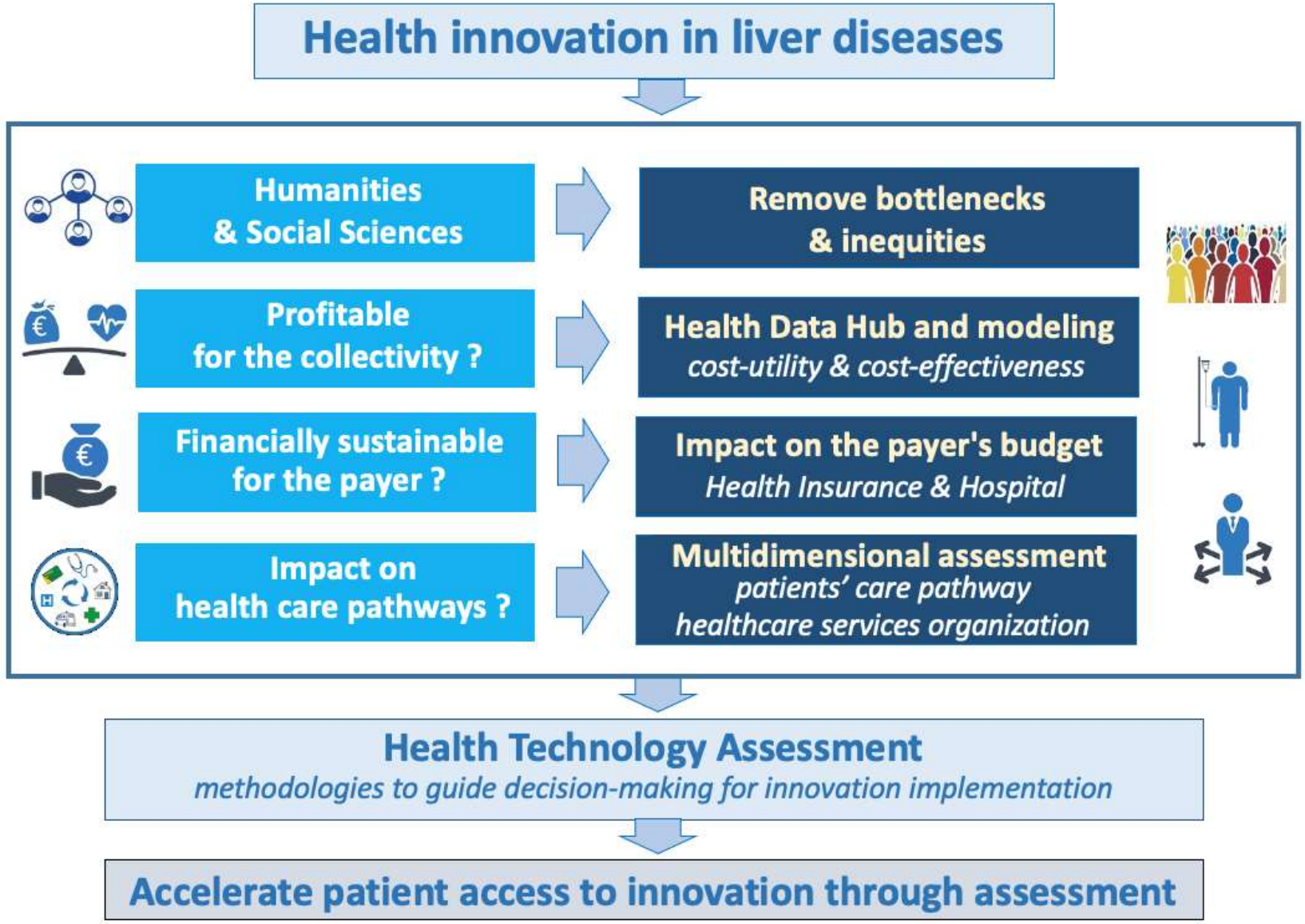
Deep phenotyping
Innovative Biomarkers
Disease staging

New therapies
Novel strategies
Individualized therapies

Pharmacoeconomics

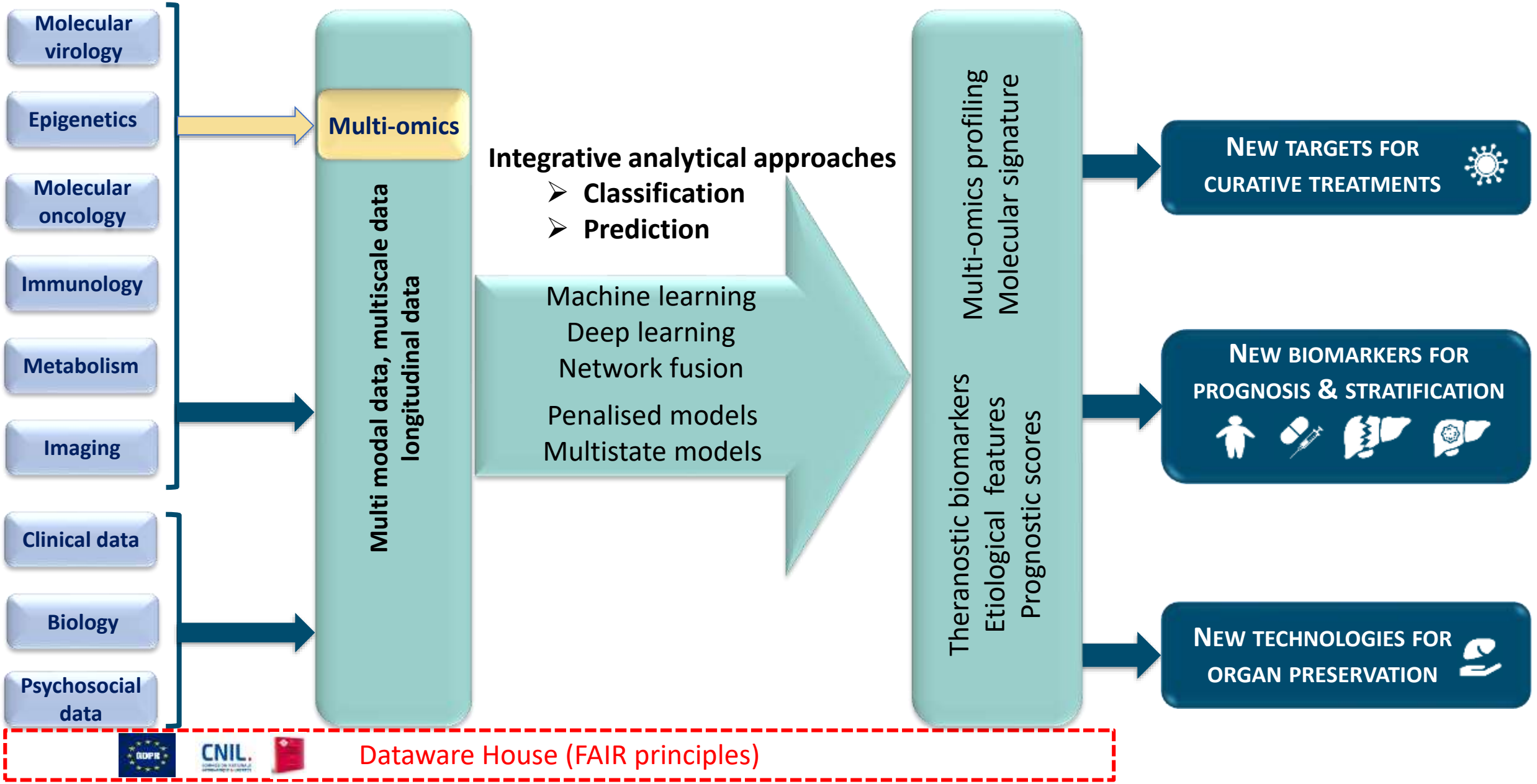
WP6 – Improving care: impact of innovation on clinical care pathways & health system

WP leaders: Marie Préau, Marie Viprey



WP7 – Data science, data integration and modeling

WP leaders: Pascal Roy, Loic Boussel



WP8 – Innovative training and education programs

WP leaders: Caroline Moyret-Lalle, Fanny Lebossé

1- New master courses

2- **Dual health sciences program**

3- **Post-graduate Hepatology certificate** for MD, PharmD, nurses and clinical research Associates

4- **« International Hepatology Summer school »** on innovation in Hepatology

5- PhD Training network

6- Dissemination : workshops & research think tanks

7- GP: education program on liver diseases

WP9 – Innovation, exploitation, transfer

WP leaders: C Marquette, C Oudin, PO Vidalain

Simple, responsive and efficient rules

- **Innovation and Valorization Committee (IVC)**
- **Unique mandate** for exploitation and technology transfer
  from innovation to licensing
- **Unique entry point** for all contract opportunities
  liaising with the Founders' legal and tech transfer offices to facilitate and accelerate contracts negotiation and signing
- **IP rules** in compliance with the founding members rules
- **Financial share of results exploitation between the founders and IHU EVEREST** (consortium agreement)

Advisory Group *H Brunar, G Fanning, L Fraisse*

Research Highlights

Session

Perspectives de recherche de l' IHU en 2024

Innovation en multiomique spatiale

Perspectives de recherche

Dr Sophie AYCIRIEX

IHU EVEREST - intEgratiVE RESearch in hepaTology
Centre Intégré des Maladies du Foie

Innovation en multi-omique spatiale

SPATIAL MULTI-OMICS PLATFORM
IHU EVEREST

Sophie AYCIRIEX, MCU UCBL

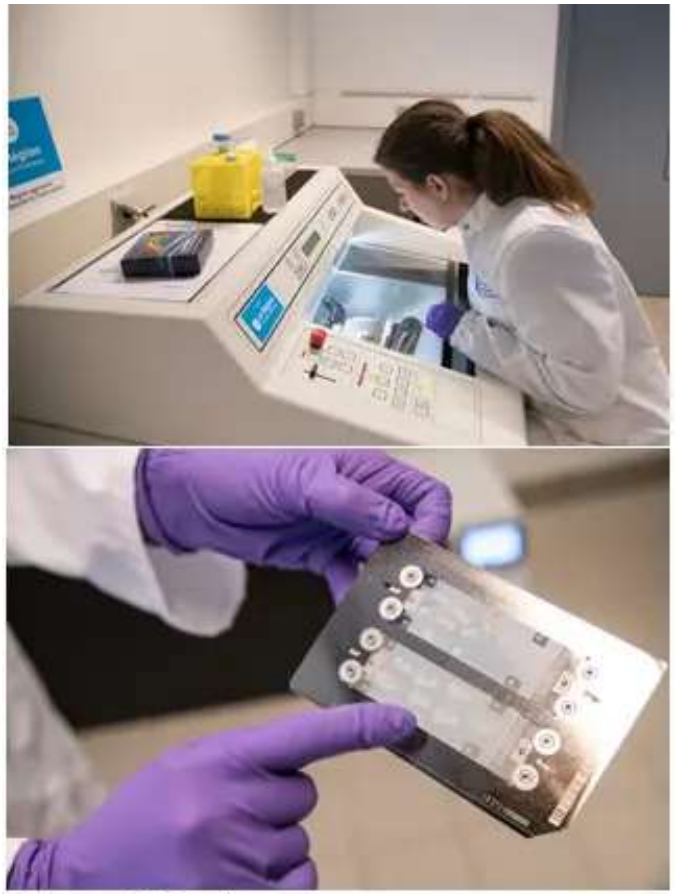
Responsable de la plateforme *Spatial multi-omics*

Imagerie par spectrométrie de masse

Plateforme *Spatial multi-omics* – IHU EVEREST

- Hébergée à l'Institut des Sciences Analytiques (CNRS UMR 5280)
- Site du *Cité lyonnaise de l'environnement et de l'analyse* (CLEA)

SPATIAL MULTI-OMICS PLATFORM
IHU EVEREST



- Spectromètre de masse MALDI-2 avec 2 chaînes de chromatographie liquide (nanoLC, UHPLC)
- Équipements pour la préparation des échantillons (M3+ sprayer, Sublimate)…

Photos: Eric Le Roux
Université Claude Bernard Lyon 1

La Région Auvergne-Rhône-Alpes

INSTITUT DES SCIENCES ANALYTIQUES

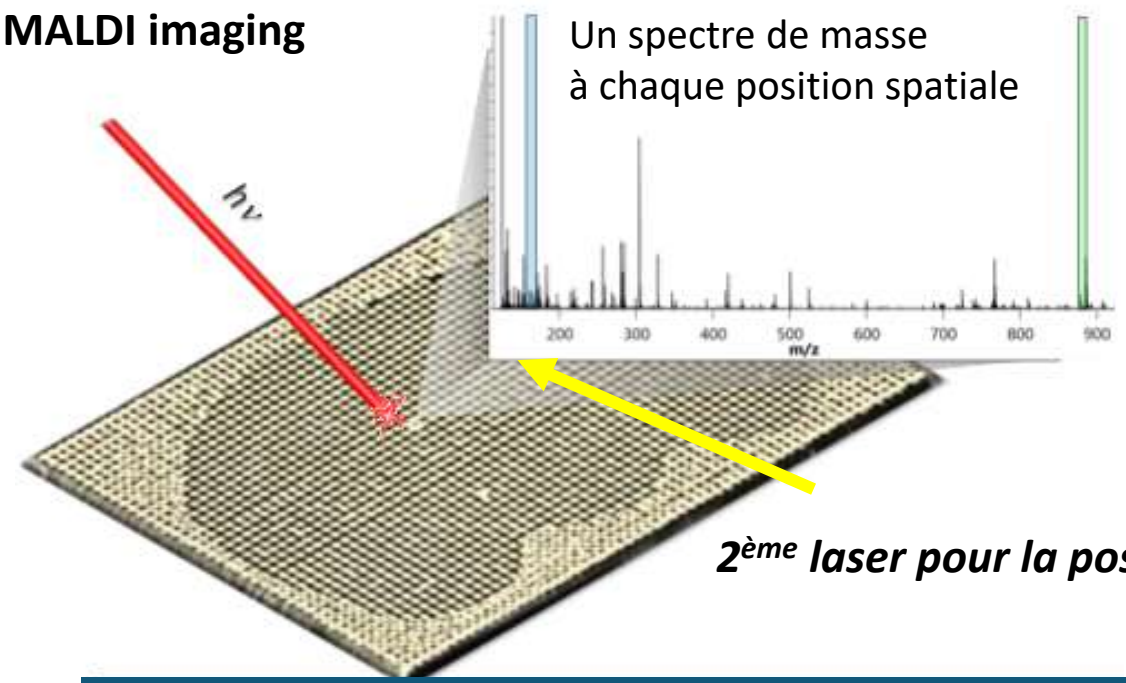
BRUKER

Imagerie MALDI par spectrométrie de masse (timsTOF *flex* MALDI-2)

Recherche fondamentale

Cryosections de tissus
12 µm d'épaisseur (-20°C)

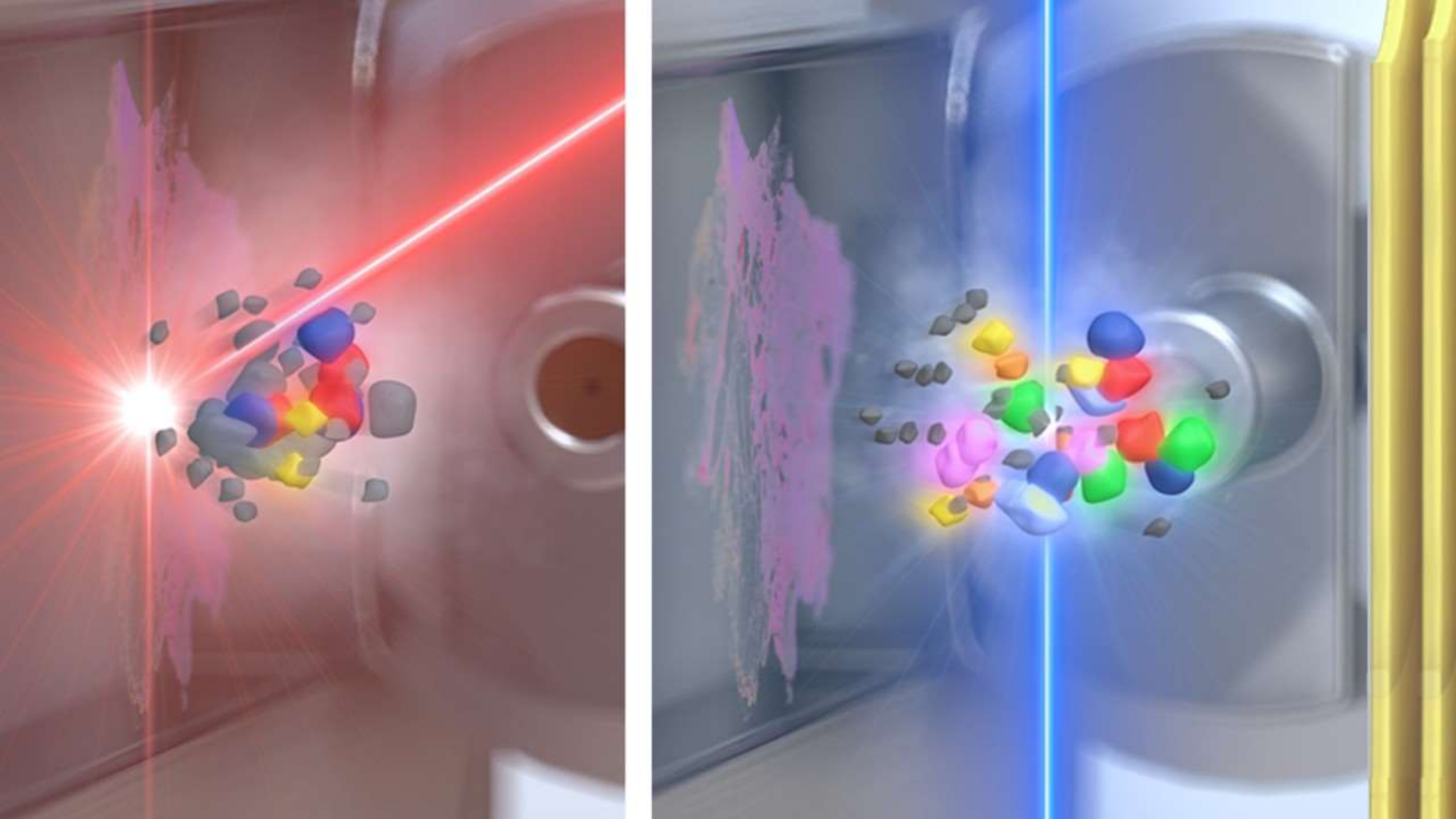
MALDI imaging



Un spectre de masse
à chaque position spatiale

2ème laser pour la post-ionisation

Les spectres de masse résolus spatialement sont enregistrés → Chaque signal (*m/z*) représente une molécule (protéine, lipide, métabolite…) → Reconstruction des images moléculaires de la distribution des composés

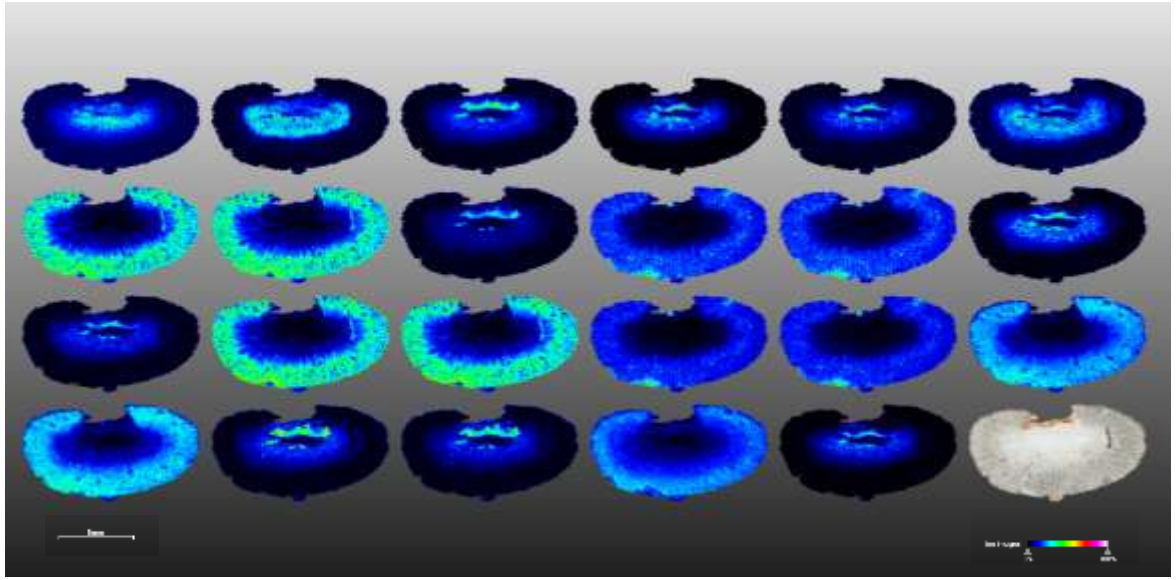


Imagerie MALDI par spectrométrie de masse (timsTOF *flex* MALDI-2)

Cryosections de tissus
12 µm d'épaisseur (-20°C)

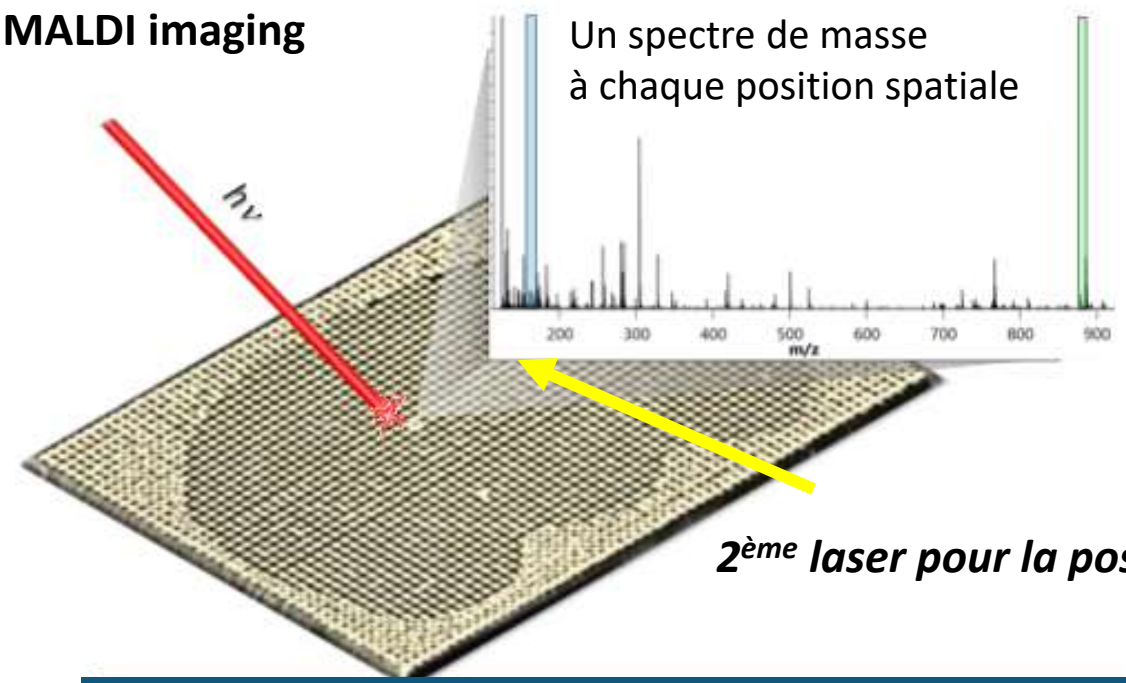
Recherche fondamentale

Distribution spatiale des molécules au niveau d'une coupe de rein de souris, avec une résolution spatiale de 20 µm



© IHU EVEREST – Calabrese V, Arquier D, Brunet T, André I, Clément Y, Ayciriex S *et al.*
Collaboration : **Laboratoire CarMeN**, INSERM U1060, Equipe MERISM, **Dr. J. Rieusset**

MALDI imaging



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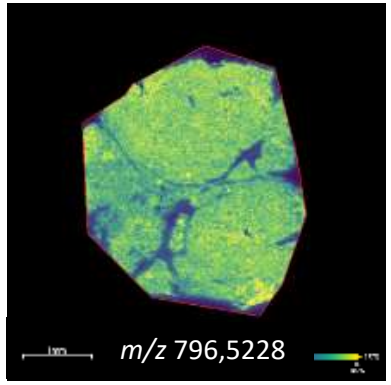
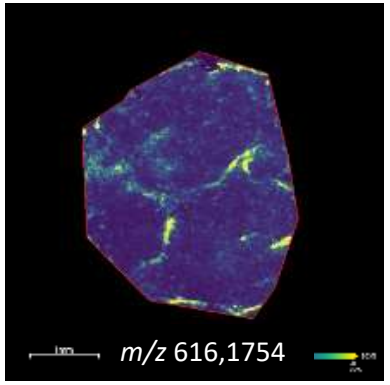
- ✓ **Label-free**
- ✓ **Multiplexage**
- ✓ **Vitesse : 10 pixels/sec**
- ✓ **Résolution spatiale (jusqu'à 5 µm)**

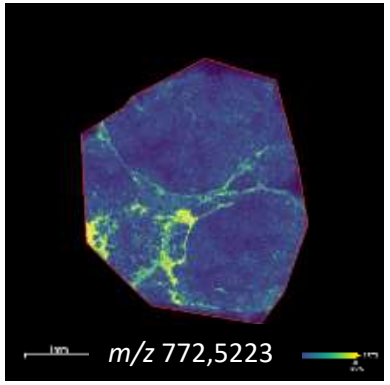
Exemples d'imagerie MALDI-2 sur des biopsies de foie

Recherche clinique et translationnelle

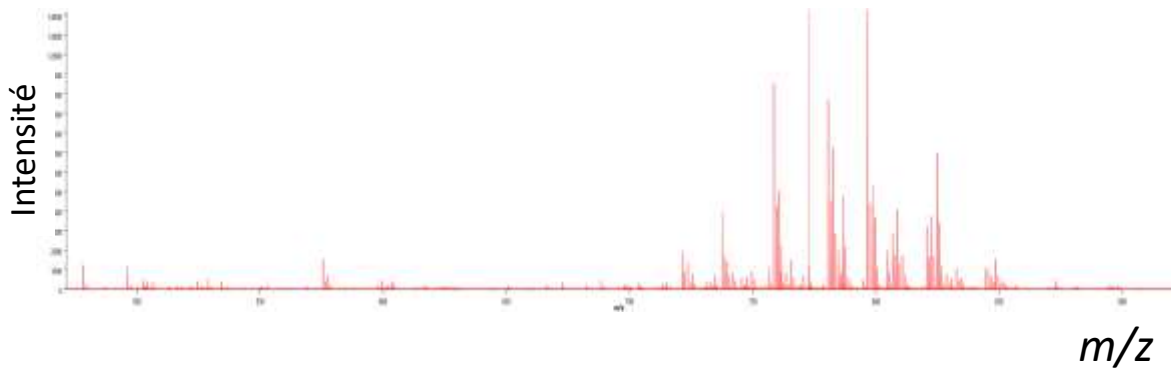
56 ans, F, greffe du foie en décembre 2022
cirrhose décompensée MASH (score Child B9; MELD 14) et CHC (1.5 cm)
Foie péri-tumoral (tissu congelé, coupe 12 µm d'épaisseur)



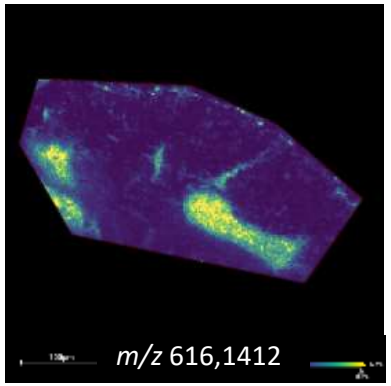


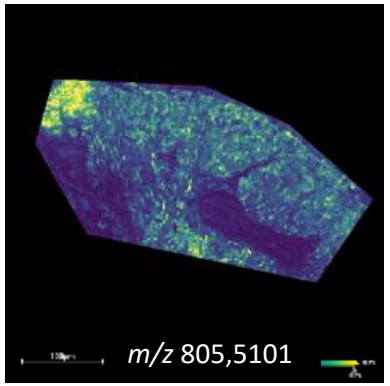


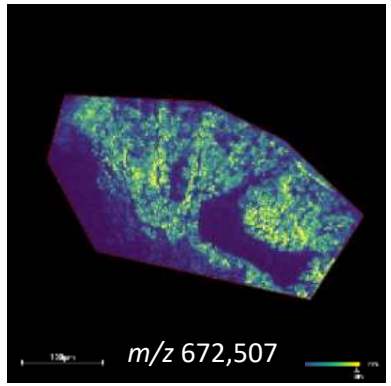
Spectre de Masse moyen de la coupe (DHB, 20 µm)



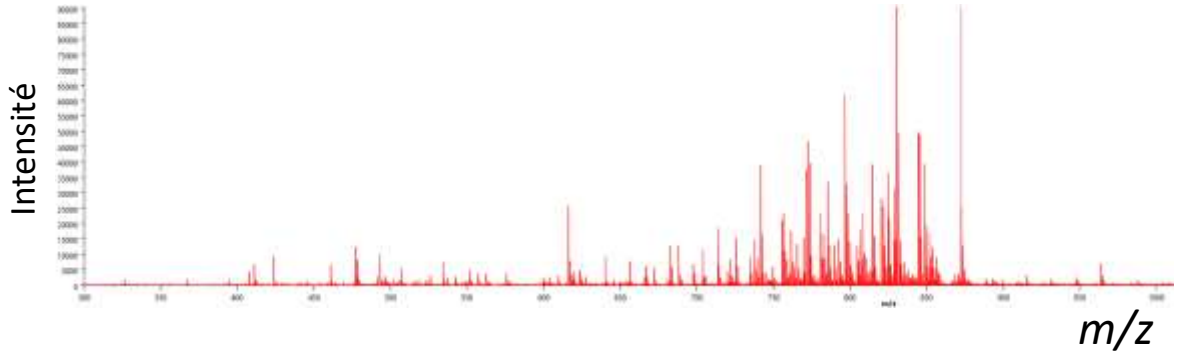
62 ans, F, greffe du foie en décembre 2022
VHB chronique avec fibrose avancée (F3/F4) et CHC traité avec succès par radiofréquence en avril 2022
Foie sans CHC résiduel (tissu congelé, coupe 12 µm d'épaisseur)





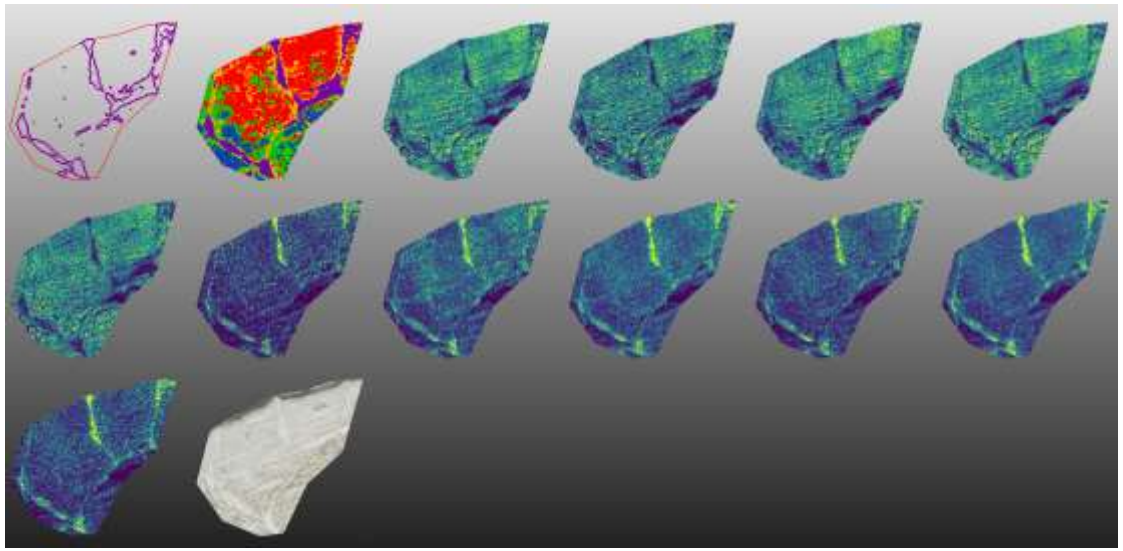


Spectre de Masse moyen de la coupe

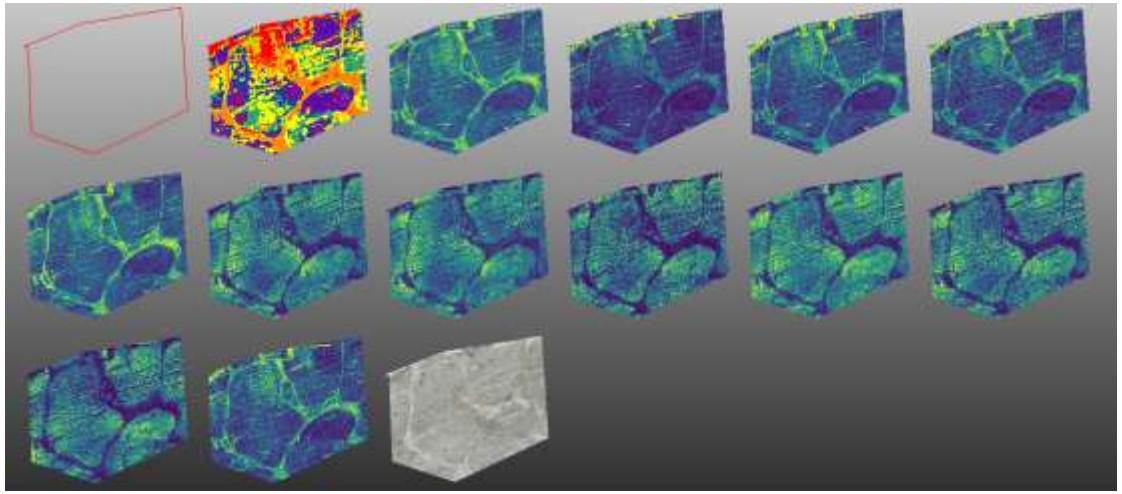


Optimisation du dépôt de la matrice MALDI

Biopsie de foie (12 µm; résolution spatiale 20 µm)
M3+



Biopsie de foie (12 µm; résolution spatiale 20 µm)
sublimate

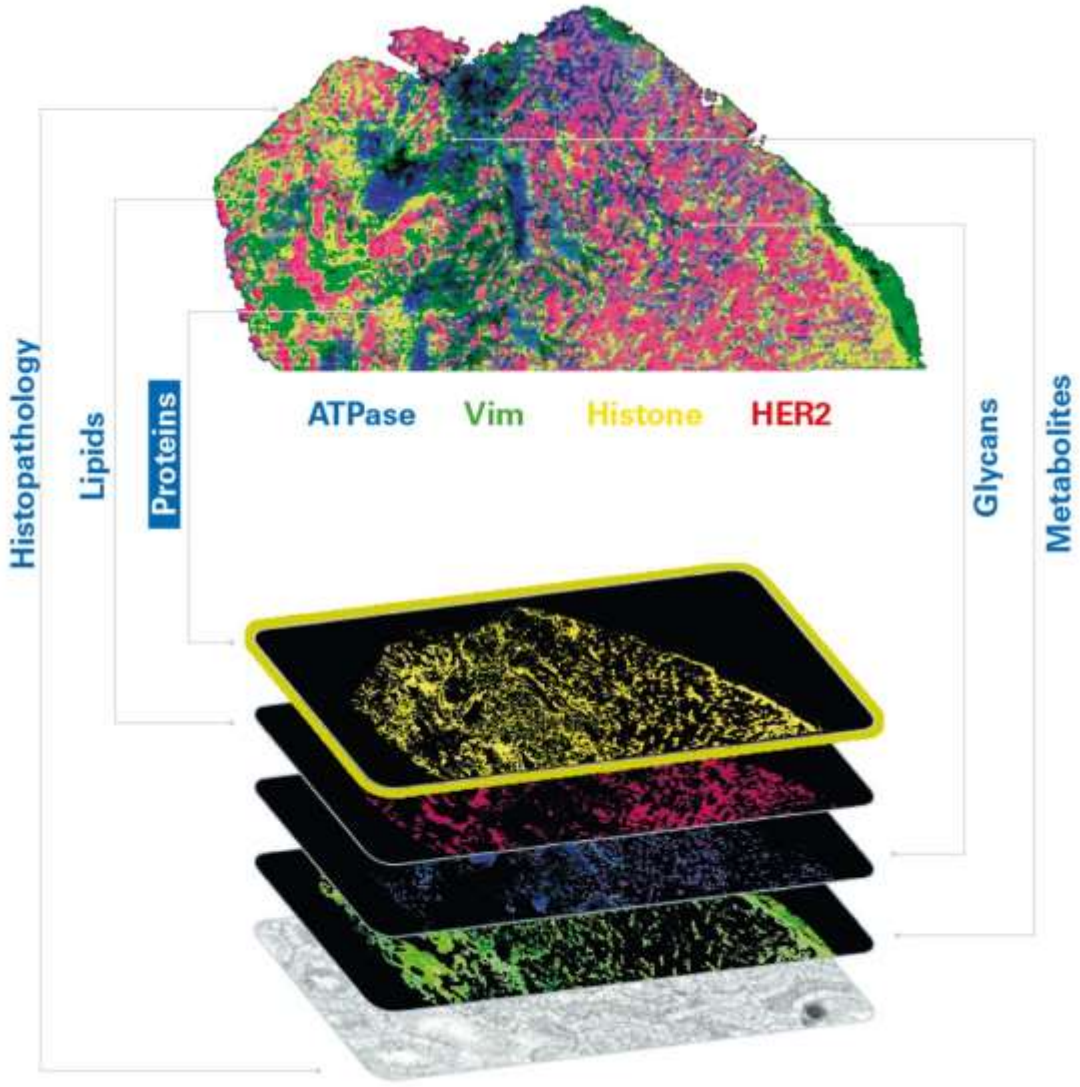


Collaboration: Dr. Marie-Laure Plissonnier & Prof. Massimo Levrero

Multi-omique spatiale par imagerie spectrométrie de masse

- Proteins (digested)
- RNA
- Proteins (Intact)
- N / O Glycans, intact
- N-Glycans, Released
- Lipids
- Metabolites
- Small Molecule Drug

MSI + AmberGen Miralys™

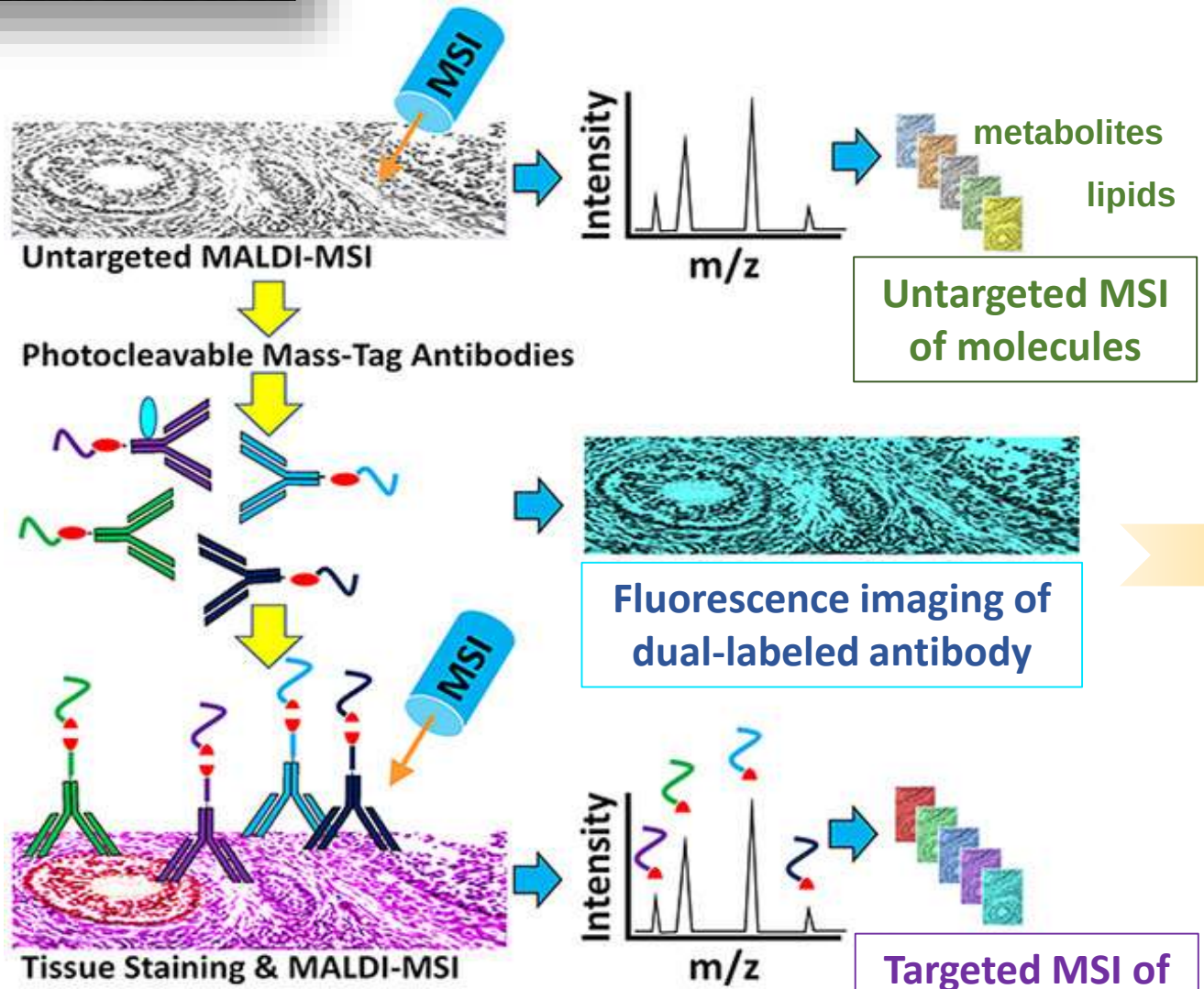


Possibilités de combiner différentes modalités spatiales : fluorescence, H&E, transcriptomics…

Multi-omique spatiale par MALDI MSI & validation

AmberGen

MALDI HiPLEX-IHC



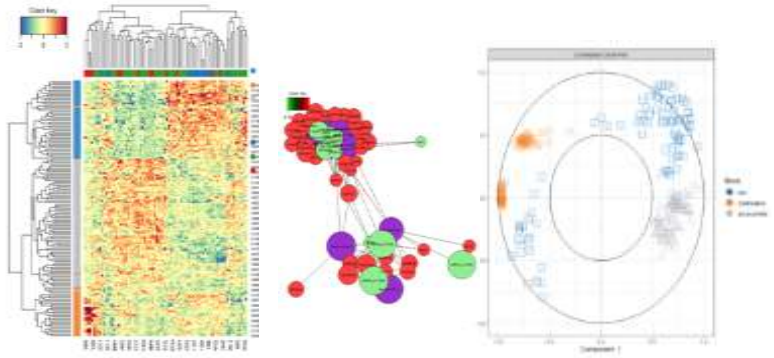
Untargeted MSI of molecules

Fluorescence imaging of dual-labeled antibody

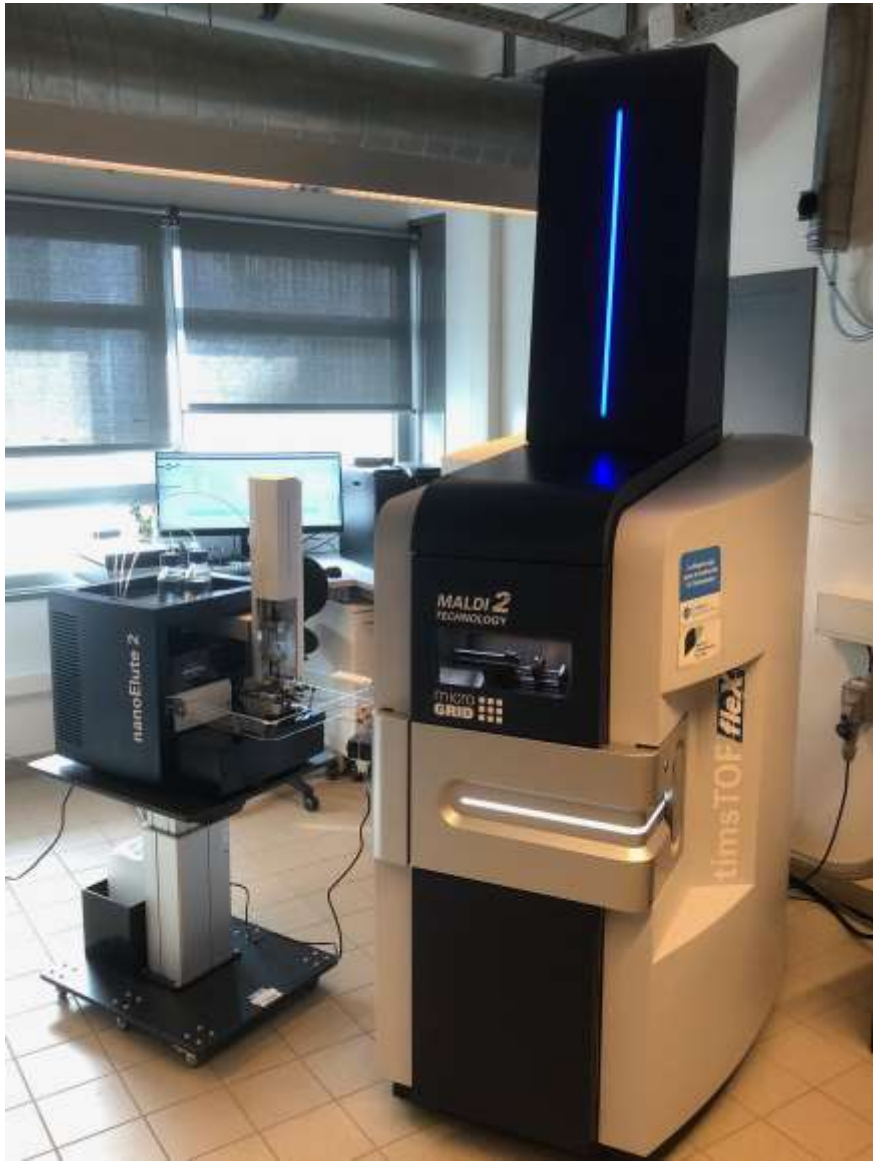
Targeted MSI of intact proteins

LC-ESI-MS/MS

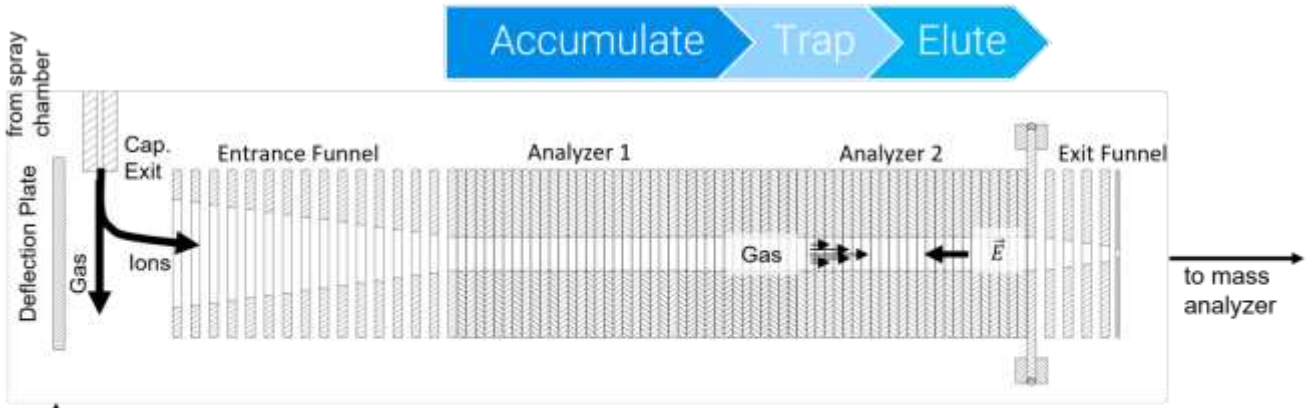
Biomarker's validation and quantification by LC-ESI-MS/MS

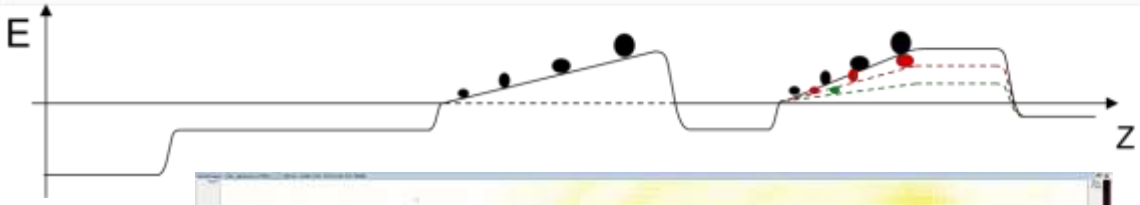


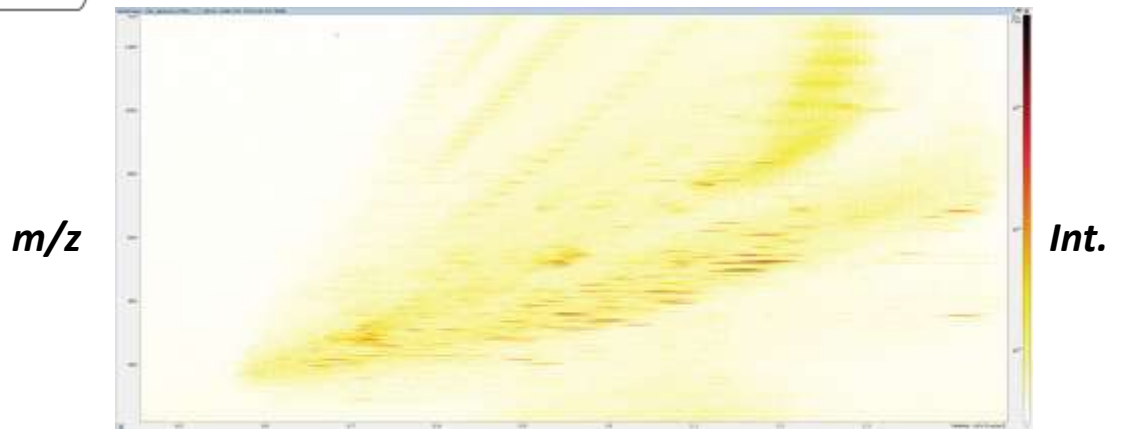
LC-ESI-HRMS (MS/MS) avec mobilité ionique (PASEF)



Mobilité ionique → Séparation des isomères







SPATIAL MULTI-OMICS PLATFORM

IHU EVEREST

Isabelle
Master 2

Delphine
IE CNRS

Yohann
IE UCBL

Thomas
PhD

Valentina
Post-doc

Justine
IE HCL

Plateforme CHEMOD (Yohann Clément, ISA)
- Traitement des données
- Data management

Projets en cours sur la plateforme
- Service de transplantation hépatiques (G. Rossignol) **CRN**
- Equipe Levrero (Marie-Laure Plissonnier) **MASH**
- Equipe Zoulim (Barbara Testoni & Maud Michelet) **HBV**

La Région Auvergne-Rhône-Alpes

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Merci de votre attention !

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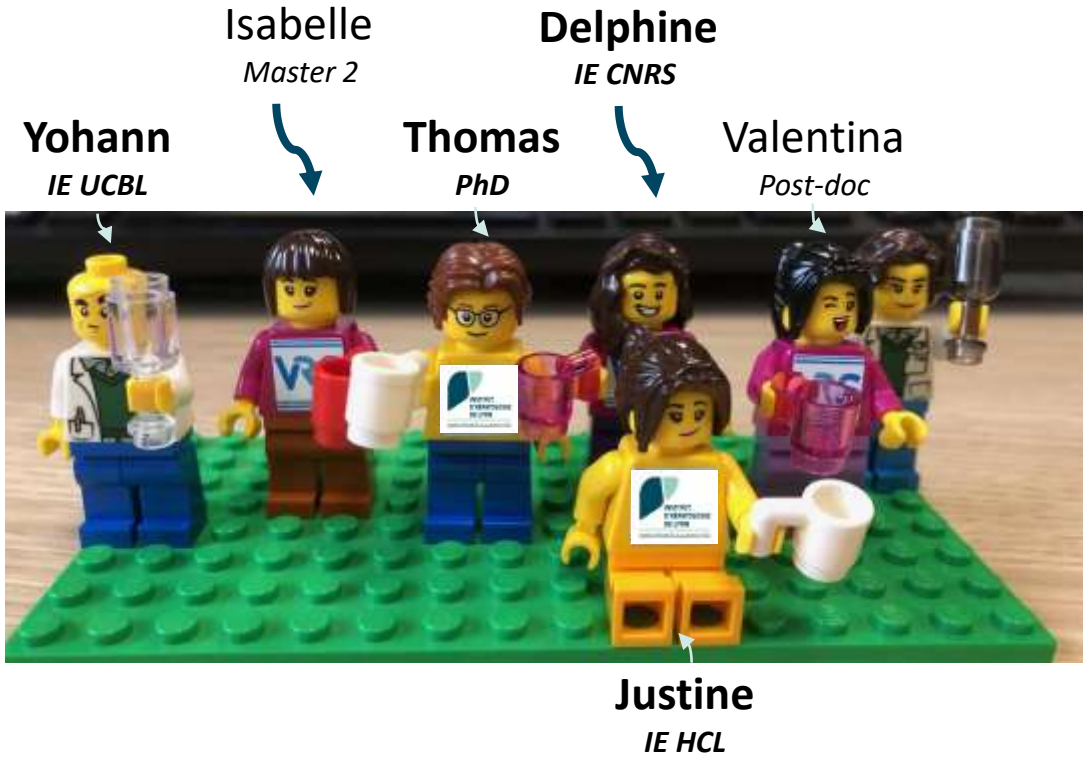
IHU EVEREST



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Du profilage multiomique aux nouveaux biomarqueurs

Perspectives de recherche
Pr Massimo LEVRERO

Du profilage multi-omique aux nouveaux biomarqueurs

Pr Massimo LEVRERO

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Cancer Research Center of Lyon (CRCL), INSERM U1052, CNRS UMR5286, Lyon, France
Department of Hepatology, Hôpital Croix-Rousse, Hospices Civils de Lyon, Lyon, France
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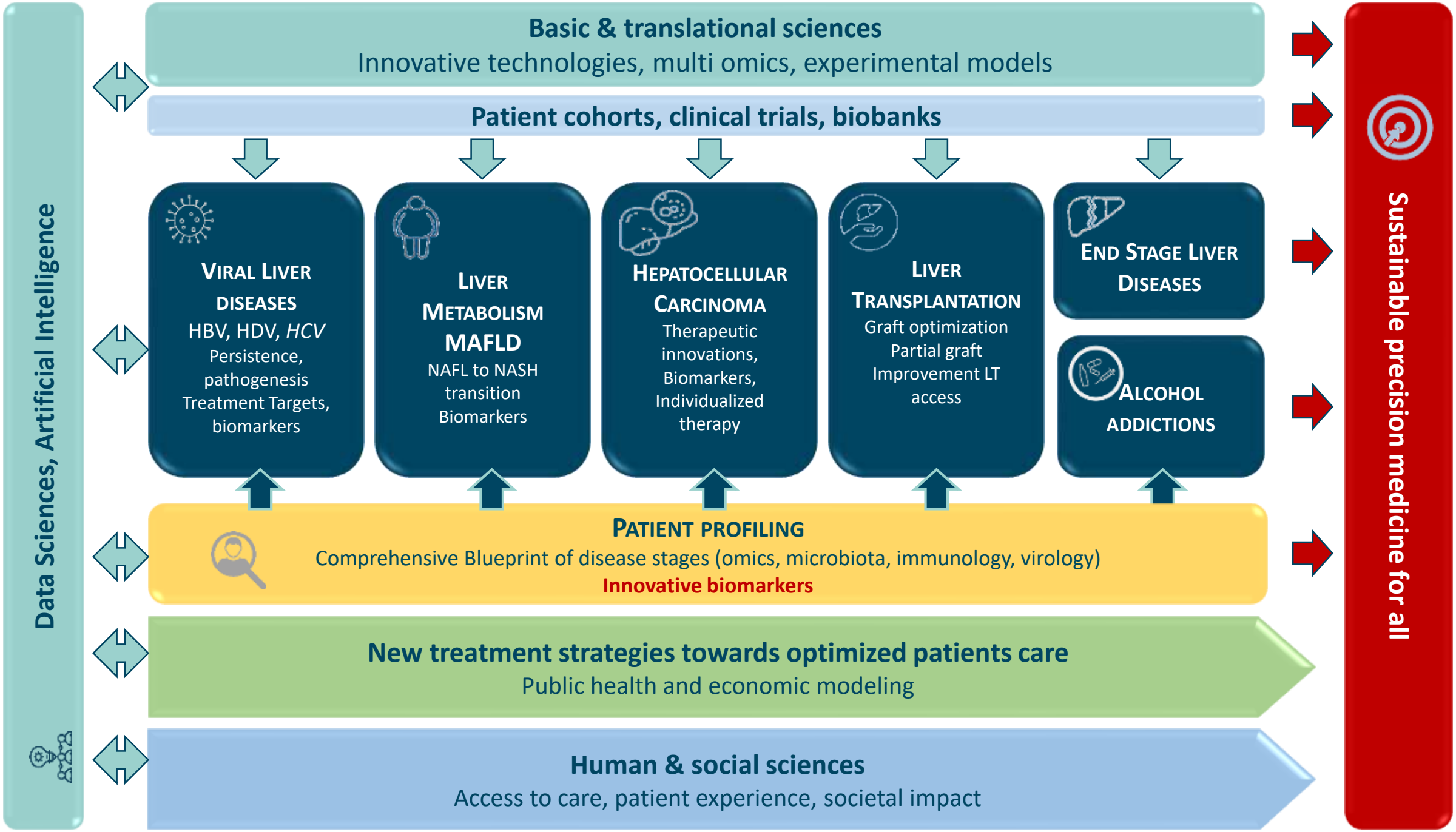

Data Sciences, Artificial Intelligence
Basic & translational sciences
Innovative technologies, multi omics, experimental models
Patient cohorts, clinical trials, biobanks
Viral Liver diseases
HBV, HDV, HCV
Persistence, pathogenesis
Treatment Targets, biomarkers
Liver Metabolism MAFLD
NAFL to NASH transition
Biomarkers
Hepatocellular Carcinoma
Therapeutic innovations, Biomarkers, Individualized therapy
Liver Transplantation
Graft optimization
Partial graft
Improvement LT access
End Stage Liver Diseases
Alcohol addictions
Patient profiling
Comprehensive Blueprint of disease stages (omics, microbiota, immunology, virology)
Innovative biomarkers
New treatment strategies towards optimized patients care
Public health and economic modeling
Human & social sciences
Access to care, patient experience, societal impact
Sustainable precision medicine for all

Du profilage multiomique aux nouveaux biomarqueurs

Clinical samples

Fixed biopsies
FFPE blocks

Frozen core biopsies

FNA
Fine Needle Aspirate

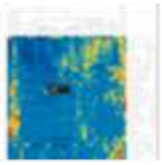
Liver resections

PCLS
Precision Cut Liver Slices

Plasma
Serum
PBMC

Omics

Transcriptomics
mRNAs ncRNAs
Nanostring, HTG EdgeSeq, NGS

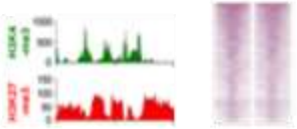


RNA-Seq
miR profiling

Single cell omics
10x Genomics, Isoplexis

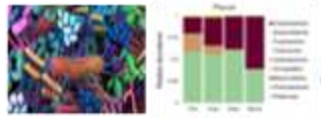
scRNA-Seq
Secretome
phosphoproteome

Chromatin analysis
NGS ChIP, ATAC, ChIRP, RIP



ChiP-Seq
ATAC-Seq

Microbiome
NGS

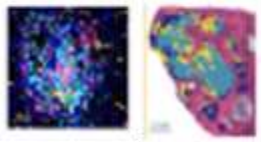


16S
metagenomics

Metabolomics
Lipidomics
Proteomics

LC-ESI-MS/MS

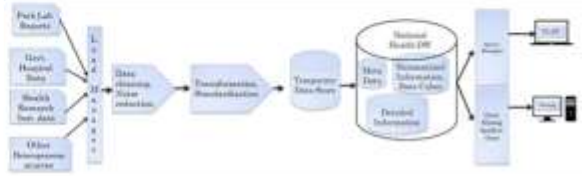
Spatial Omics
Nanostring digital spatial profiling
Bruker multiomic tissue imaging



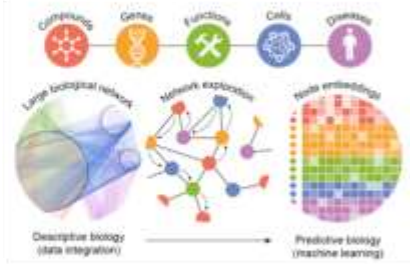
Digital spatial profiling (RNAs, proteins)
MALDI HIPLEX-IHC (proteins, metabolites)

Analysis

Healthcare data warehouse



Computational biology & artificial intelligence



Du profilage multiomique aux nouveaux biomarqueurs

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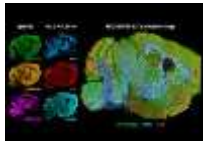
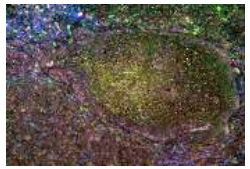


MALDI²-HiPlex IHC

INSTITUT D'HÉPATOLOGIE DE LYON
CENTRE INTÉGRÉ DES MALADIES DU FOIE

CosMx



nanoString

Lyon 1

MM FRANCE
Microm Microtech

3DHISTECH

Plateforme de Science Translationnelle

(Epi)genomics

Transcriptomics

Chromatin analysis

Single cell analysis (RNA, Chromatin, Secretome)

High Resolution Multiomics MS

Intensity

m/z

Microbiome

Spatial Multiomics

CosMx

nanoString

Cellular & animal Models
(PHH, PCLS, 3D bioprinting)

Automated IHC platform

3dFab

Computational biology

genoway

La revolution *spatiale*

BULK RNA-SEQ

Average expression level

scRNA-SEQ

Expression from individual cells

SPATIALLY RESOLVED TRANSCRIPTOMICS

identify the cellular organization and interactions of biological samples

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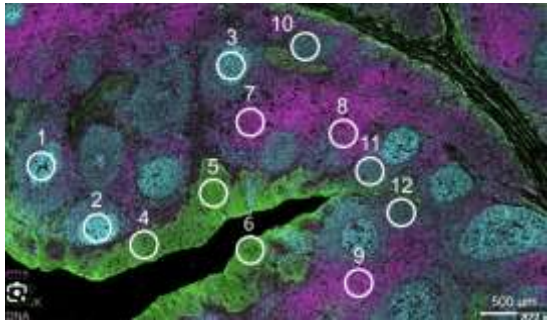

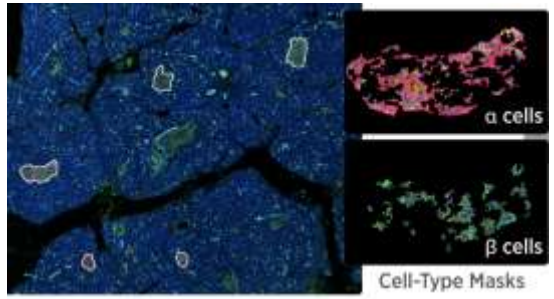

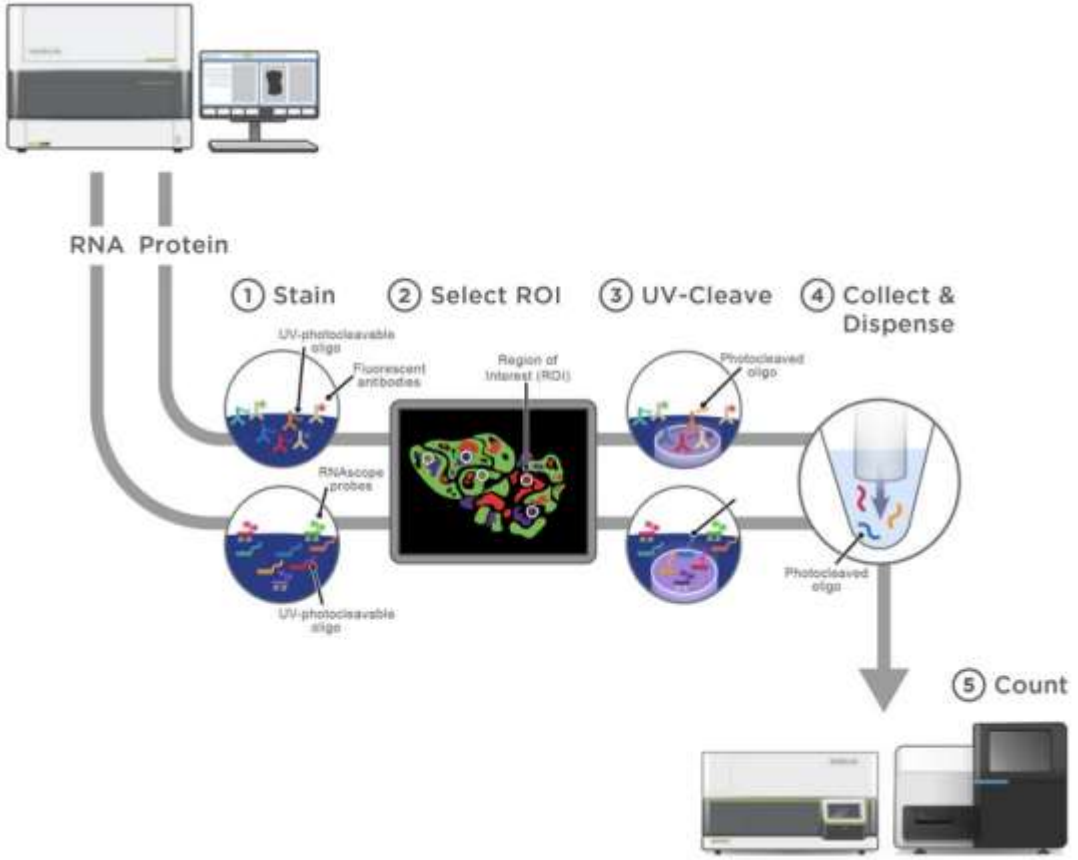

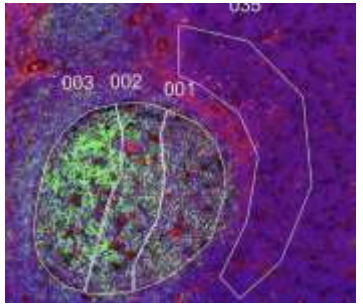

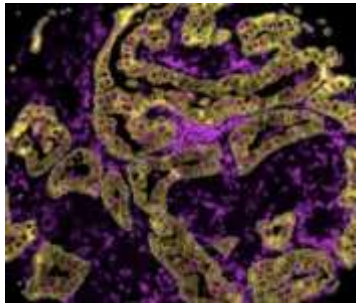

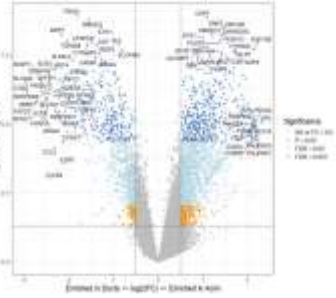

La revolution *spatiale*

BULK RNA-SEQ

Average expression level

scRNA-SEQ

Expression from individual cells

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identify the cellular organization and interactions of biological samples

nanoString
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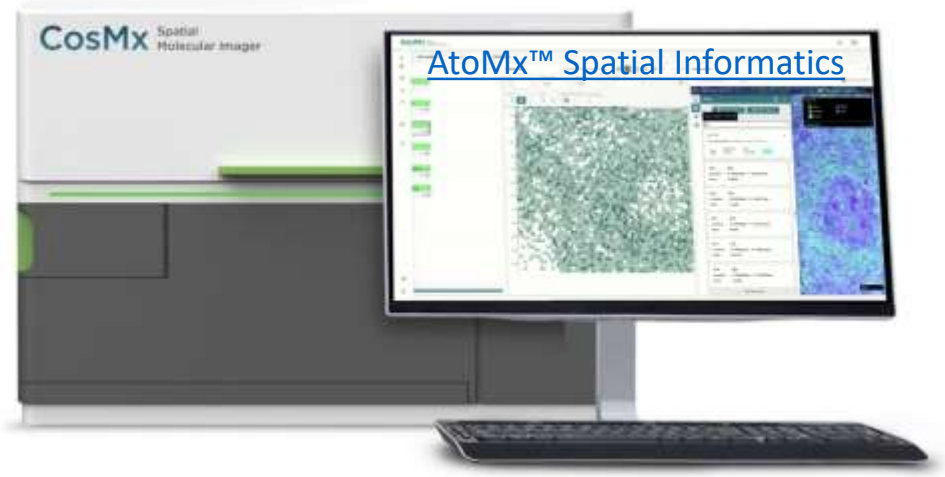


AtoMx™ Spatial Informatics

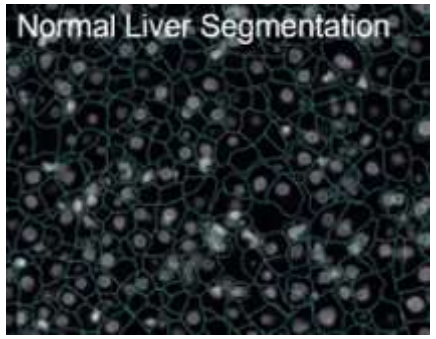
Image-based cell segmentation

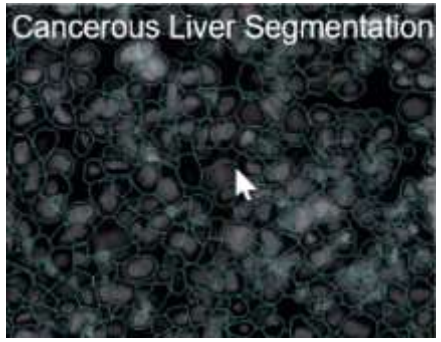
Image pre-processing

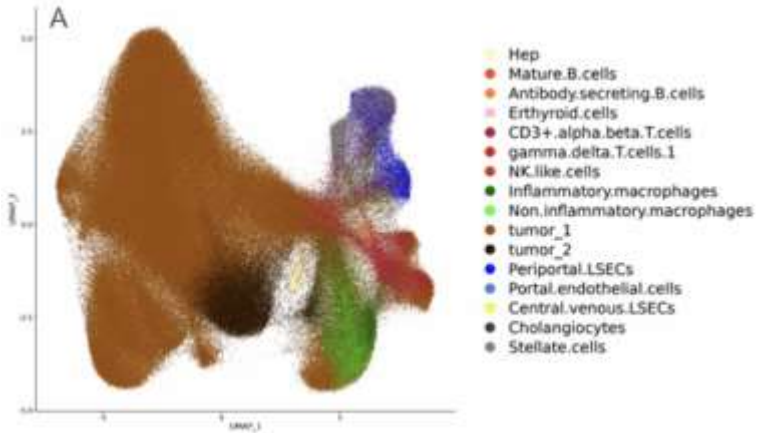
Improve image quality

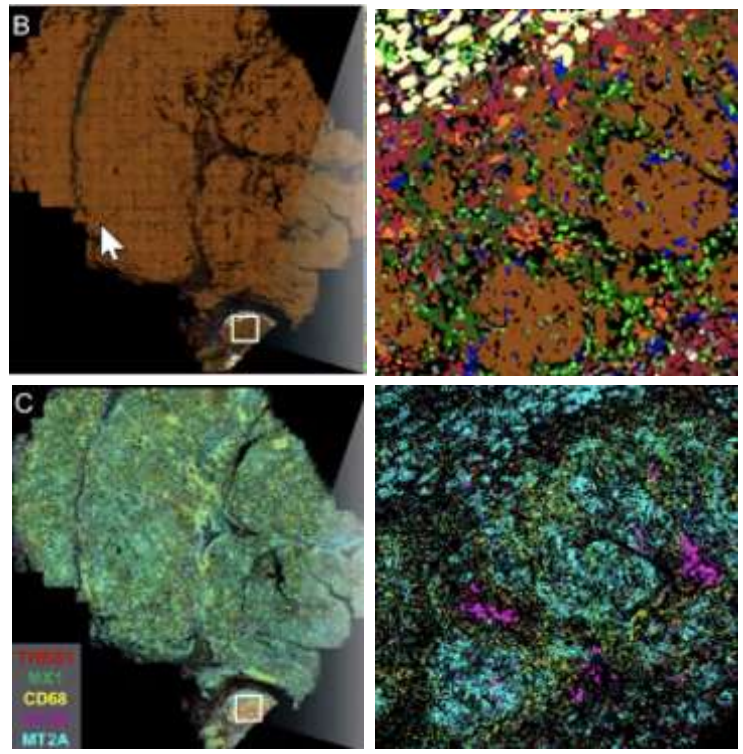
Machine learning (ML)-augmented cell segmentation

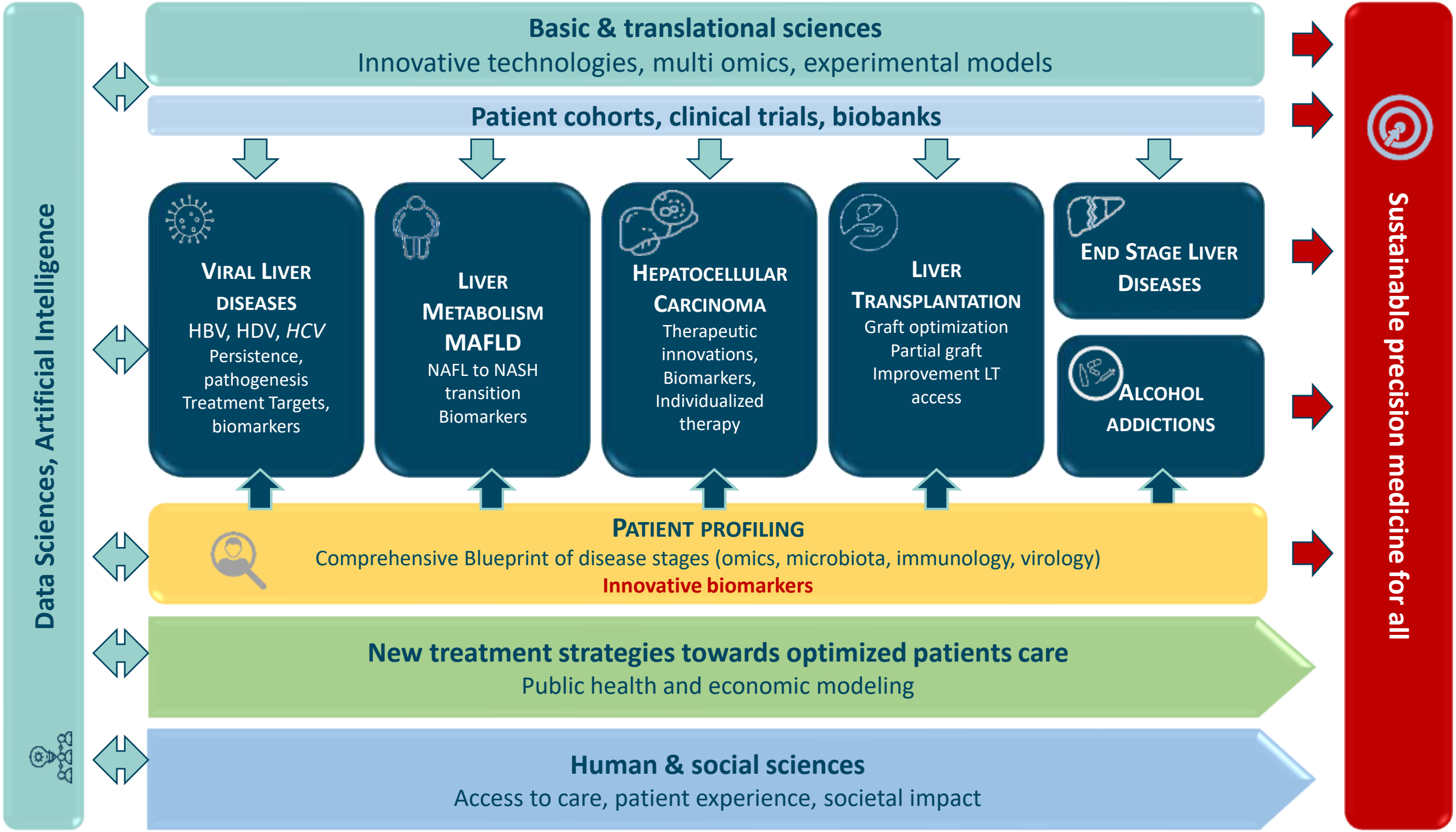
pre-trained Cellpose neural network models










Data Sciences, Artificial Intelligence
Basic & translational sciences
Innovative technologies, multi omics, experimental models
Patient cohorts, clinical trials, biobanks
Viral Liver diseases
HBV, HDV, HCV
Persistence, pathogenesis
Treatment Targets, biomarkers
Liver Metabolism MAFLD
NAFL to NASH transition
Biomarkers
Hepatocellular Carcinoma
Therapeutic innovations, Biomarkers, Individualized therapy
Liver Transplantation
Graft optimization
Partial graft
Improvement LT access
End Stage Liver Diseases
Alcohol addictions
Patient profiling
Comprehensive Blueprint of disease stages (omics, microbiota, immunology, virology)
Innovative biomarkers
New treatment strategies towards optimized patients care
Public health and economic modeling
Human & social sciences
Access to care, patient experience, societal impact
Sustainable precision medicine for all

Profil-MASH

Metabolic Liver Diseases (MAFLD)
patients referral, comprehensive profiling and therapeutic innovation

Patients Referral

Multidisciplinary MASH Board

Patients Cohorts

Goldmine NAFLD Care Steato-NORD

Clinical Research

RCTs (metabolic, inflammation and fibrosis targets)

Translational research

Multiomics characterization of liver metabolism and inflammatory ME

Plasma
Serum
PBMC

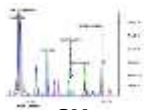
Fixed biopsies
FFPE blocks

Frozen core biopsies

FNA
Fine Needle Aspirate

PCLS
Precision Cut Liver Slices

New knowledge
Tailored therapies
Diagnostic Biomarkers
Prognostic biomarkers


SM


RNA Seq

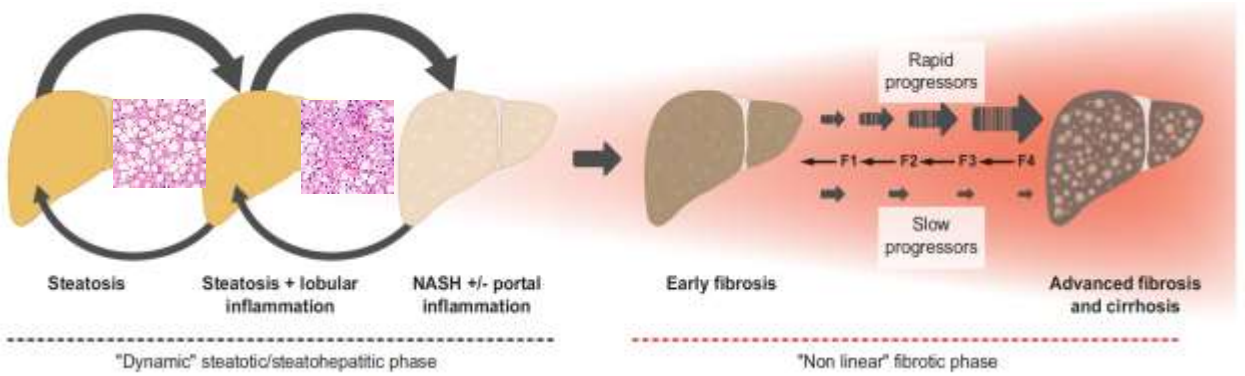

Multiplexed IF


single cell secretome /proteome


microbiome


CosMx DSP

Focus on transitions:
steatosis>MASH; MASH>early fibrosis progression



Challenges

- High prevalence (16-25 % in general population; 60 to 80% in diabetics and obese); ~1/3 dynamic progression of liver disease
- Comorbidities; several healthcare professionals/specialists involved
- Multiple cofactors (genetics, alcohol, life-style)
- Staging of liver disease (inflammation and fibrosis)

Hepatocellular Carcinoma (HCC)
Immunotherapies, Patients Profiling and Treatment Personalization

Profil-HCC

Patients Referral
Multidisciplinary HCC Board

Patients Cohorts
CHIEF
AURA HCC

Clinical Research
RCTs
academic
industrial

Translational research

PROFIL HCC
Multiomics characterization and inflammatory microenvironment
Liquid biopsy

Plasma
Serum
PBMC

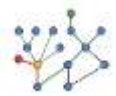
Fixed biopsies
FFPE blocks

Frozen core biopsies

FNA
Fine Needle Aspirate

PCLS
Precision Cut Liver Slices

New knowledge
Tailored therapies
Diagnostic Biomarkers
Prognostic biomarkers


RNA Seq

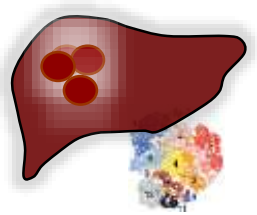

Multiplexed IF


single cell
secretome /proteome


microbiome


CosMx DSP

Innovative tools / biomarkers for HCC risk assessment and HCC classification based upon the « prevalent / causal etiology »



Curative treatments (RF, Surgery, OLT)
Chemio-Radio Embolization
Systemic therapies (MKIs, ICIs, VEGFi+ICI, ICI+ICI)

Challenges

- High heterogeneity (etiologic, genetic, epigenetic, phenotypic)
- ~1/3 of HBV and NASH-HCCs develop in non cirrhotic livers
- Multidisciplinary and multimodal treatment strategies
- Intrahepatic inflammation drives HCC development and treatment response
- Urgent need for:
  - -- > treatment response biomarkers (only 1/3 disease control)
  - -- > new treatments to combine with ICIs

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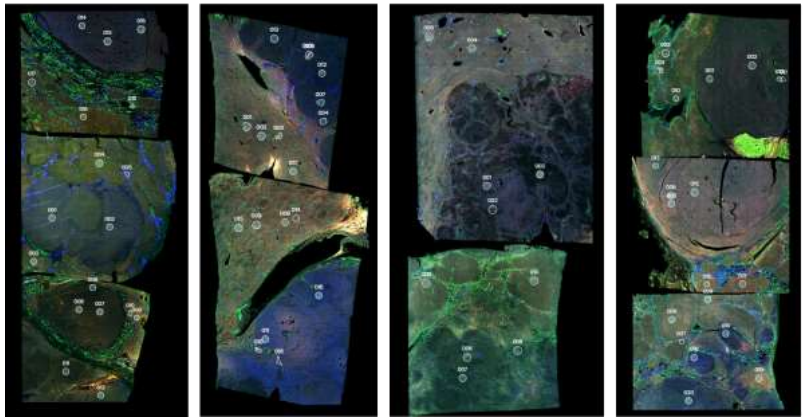
Hepatocellular Carcinoma (HCC) : Immunotherapies, Patients Profiling and Treatment Personalization

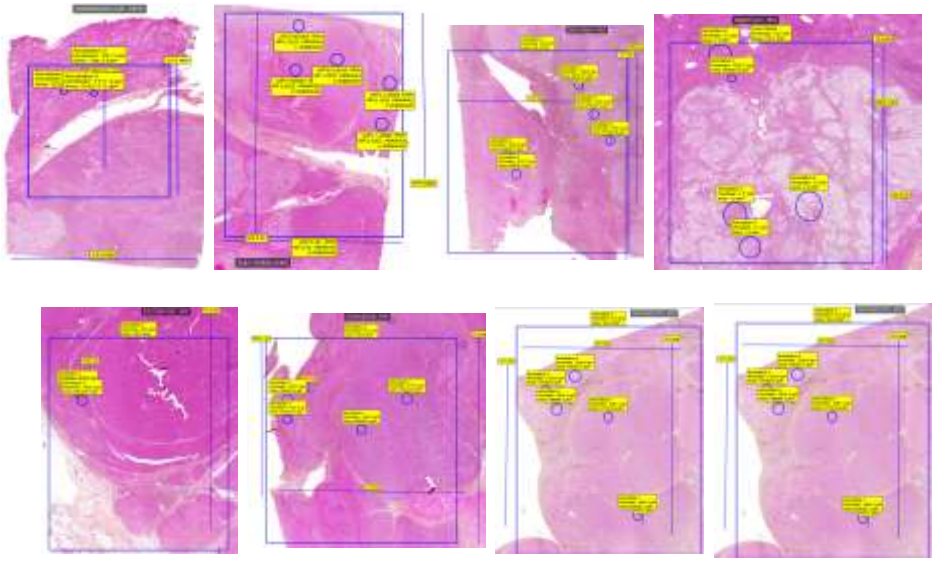
GeoMx

Slide 1 Slide 2 Slide 3 Slide 4



Slide	SegmentLabel	ROI_number	Average surface (um2) (min - max)	Average NucleiCount (min – max)
1	CD45	7	12060.53 (3436.62 - 24216.90)	203.00 (85 - 494)
1	PanCK	11	159565.23 (67254.51 - 220807.04)	649.82 (287 - 875)
2	CD45	4	5810.67 (3637.33 - 8859.24)	127.00 (73 - 192)
2	PanCK	9	150615.26 (81635.20 - 236919.98)	750.89 (559 - 1229)
3	CD45	12	8254.47 (2947.65 - 25320.90)	145.67 (65 - 407)
3	PanCK	15	158959.29 (52333.10 - 251678.08)	749.27 (295 - 1120)
4	CD45	6	5110.14 (2780.47 - 10049.33)	93.50 (59 - 125)
4	PanCK	18	152965.84 (43842.23 - 262932.01)	765.94 (172 - 1198)

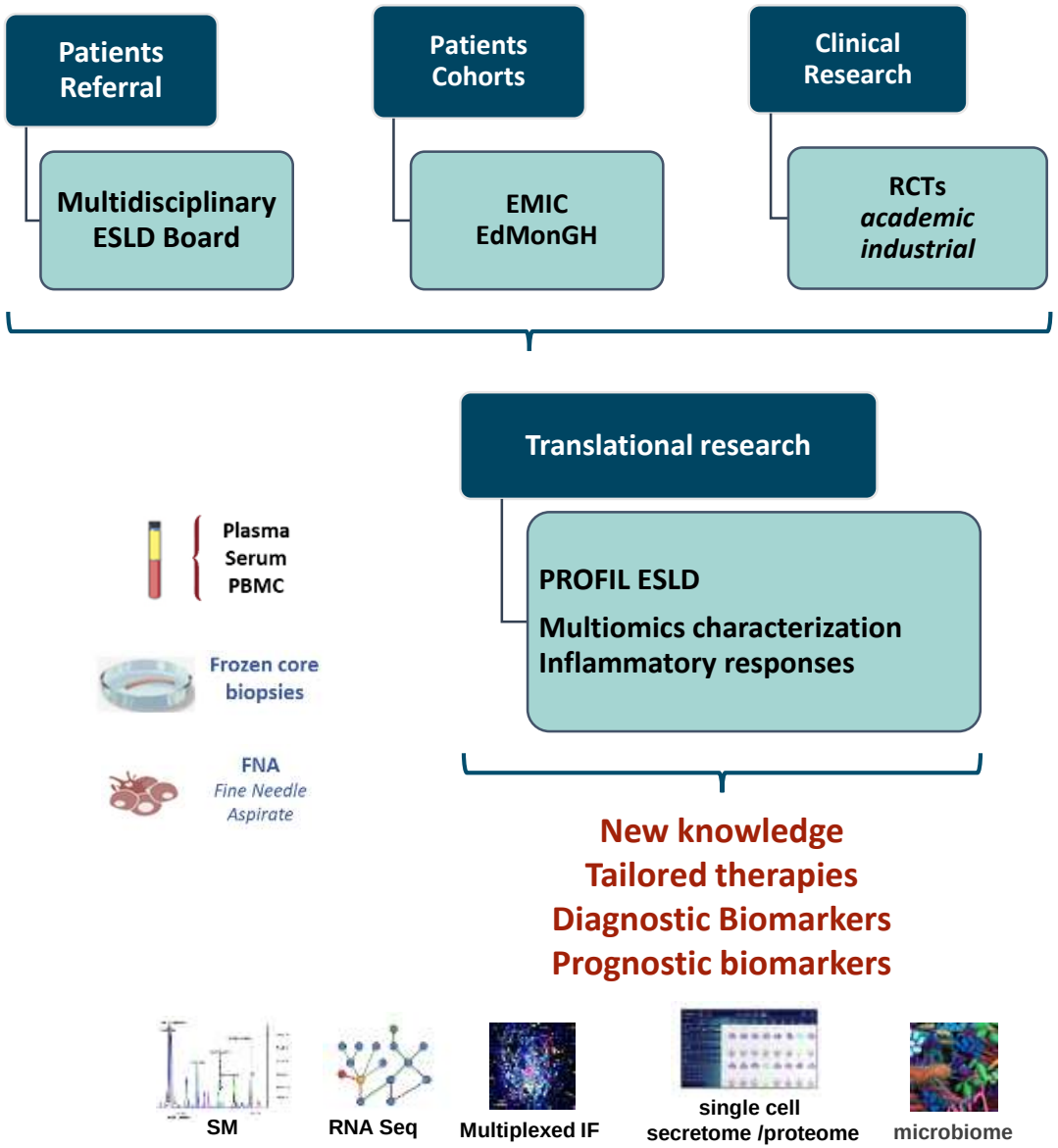
8 HCCs (4 cirrhosis)
5 MASH, 3 MetALD



Inflammatory infiltrate richer in nontumoral liver
Distinct transcriptional profiles in Tumor vs Non Tumor

End Stage Liver Diseases (ESLD)

Profil-ESLD



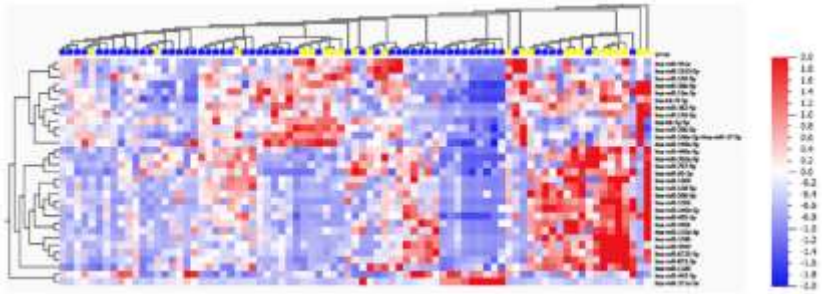
- **Identification of ESLD patients at higher risk of disease worsening**
- **Bacterial infections in ESLD**
- **Prediction of pre- and post-LT survival**
- **Diagnosis and prognostic stratification of AAH patients.**

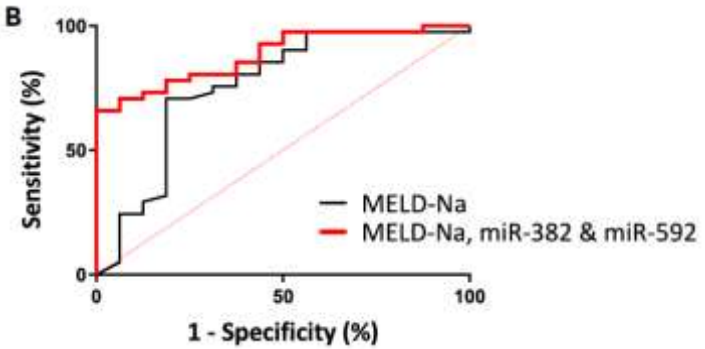
End Stage Liver Diseases (ESLD)

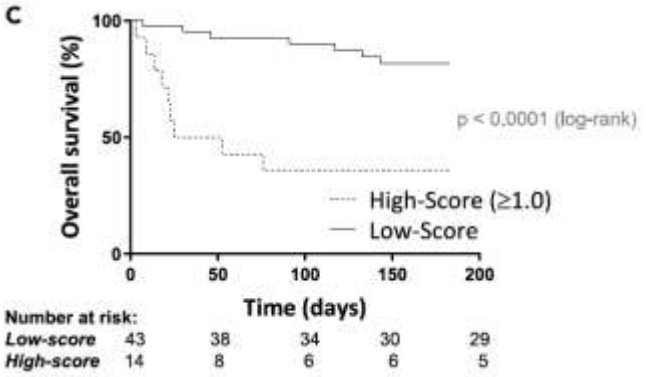
nanoString
A BRUKER COMPANY

NCounter

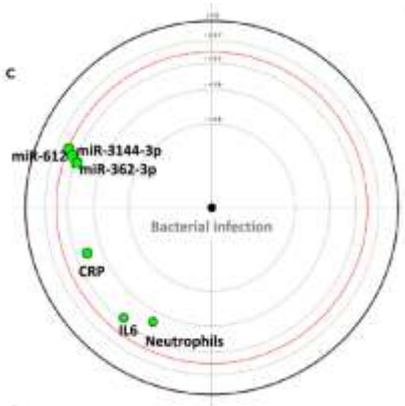
iScience
CellPress
OPEN ACCESS
Article
Circulating microRNAs improve bacterial infection diagnosis and overall survival prediction in acute decompensation of liver cirrhosis
iScience 26, 107427, August 18, 2023

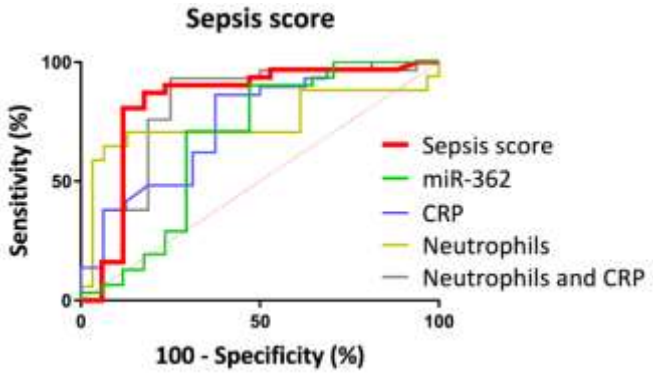






a composite score including miR-382-5p,miR-592 and MELD-Na improved 6-month survival prediction.





a composite score including absolute neutrophil count, C reactive protein and miR-362-3p diagnoses bacterial infection with an AUC of 0.825 [95% CI = 0.671–0.980; p < 0.001])

European Commission

LEOPARD - Liver Electronic Offering Platform with Artificial intelligence-based Devices

High density metabolomic profiling in MASH, MetALD and ALD compensated and decompensated cirrhosis

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CRCL CANCER RESEARCH CENTER OF LYON
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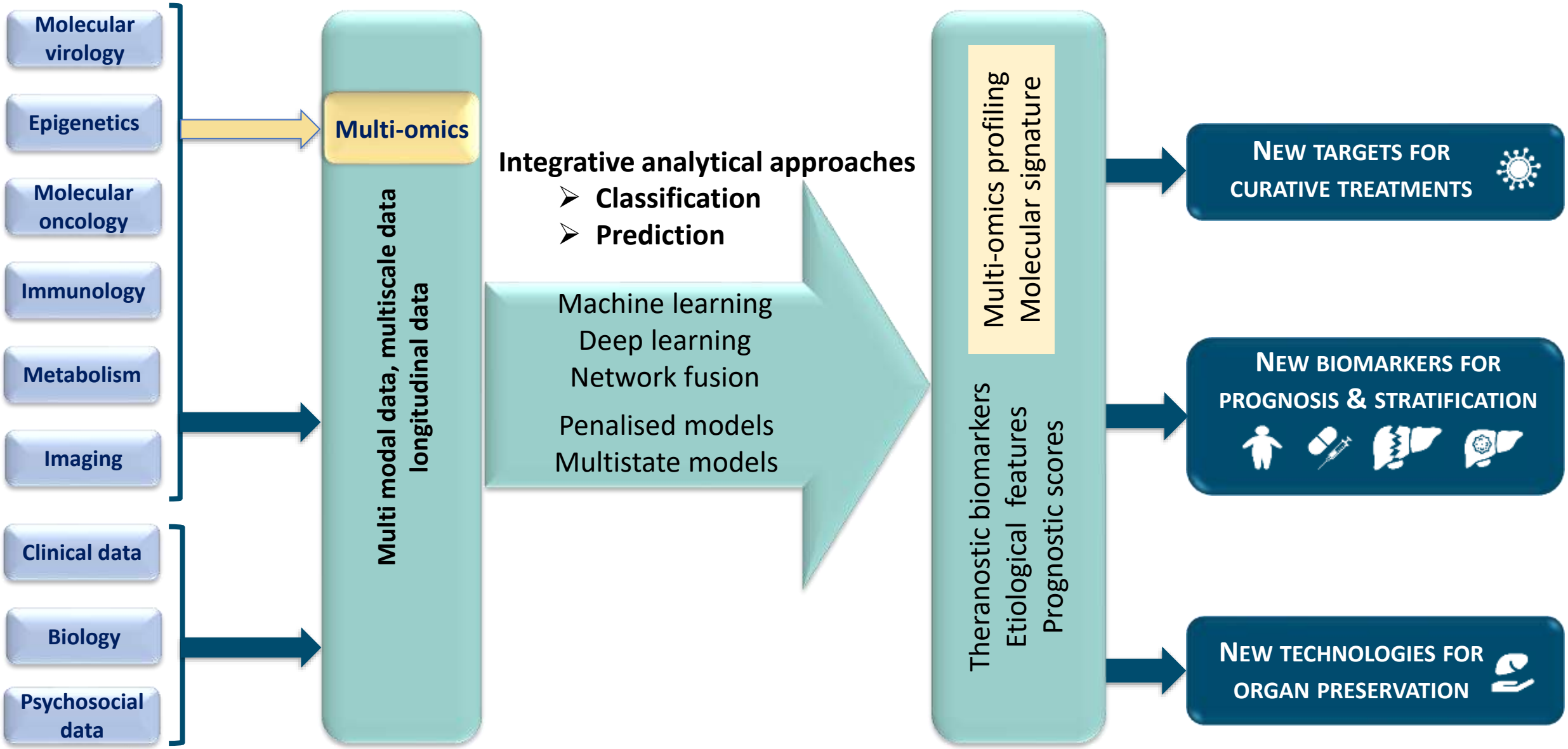
Data science, data integration and modeling

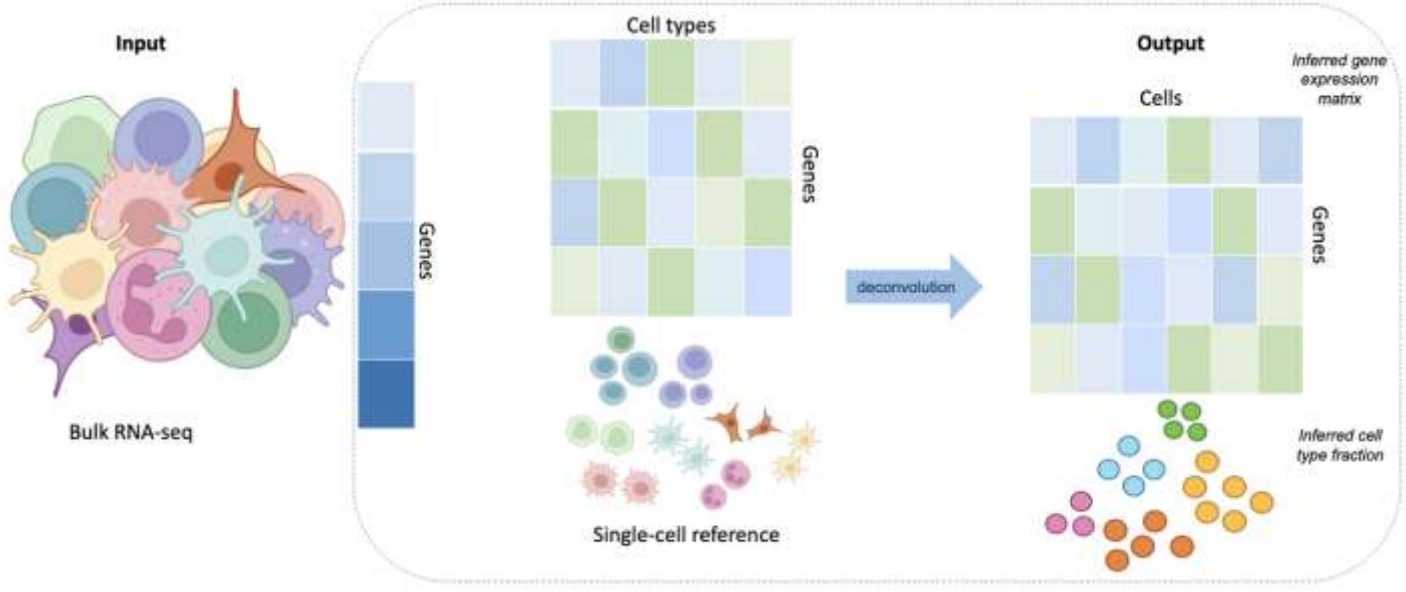


Data science, data integration and modeling

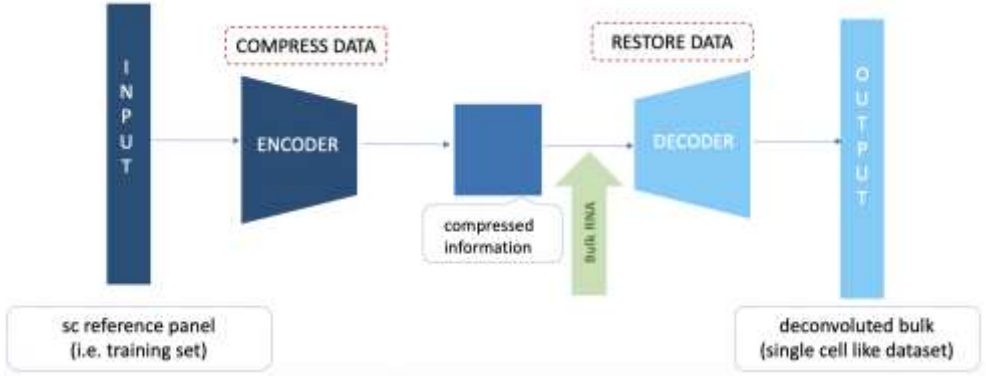
Next generation deconvolution tools

- fully exploit existing as well as newly generated transcriptomic datasets
- most clinical samples from large cohorts and RCTs are FFPE blocks

Empowering bulk RNA-seq deconvolution algorithms by integrating multiple transcriptomics datasets



BULK2SPACE AND VARIATIONAL AUTO ENCODER (VAE) ARCHITECTURE



Thanks to the clinicians and scientists who contributed to the proof-of-concept studies presented in detail

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Philippe Merle
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Guillaume Rossignol
Xavier Muller

Marie Laure Plissonnier
Massimiliano Cocca

Mirjam Ziesel
Barbara Testoni
Andres Roca Suarez

Sophie Ayciriex
Clement Yohann

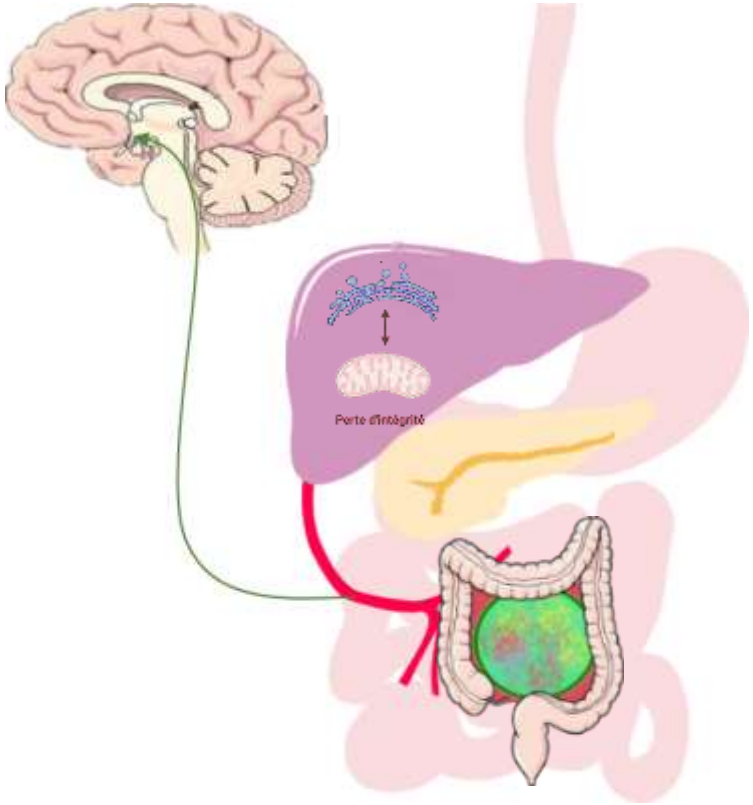
and thank you for your attention

Maladies stéatosiques hépatiques : mécanismes physiopathologiques

Perspectives de recherche

Pr Cyrielle CAUSSY

Maladies stéatosiques hépatiques : mécanismes physiopathologiques

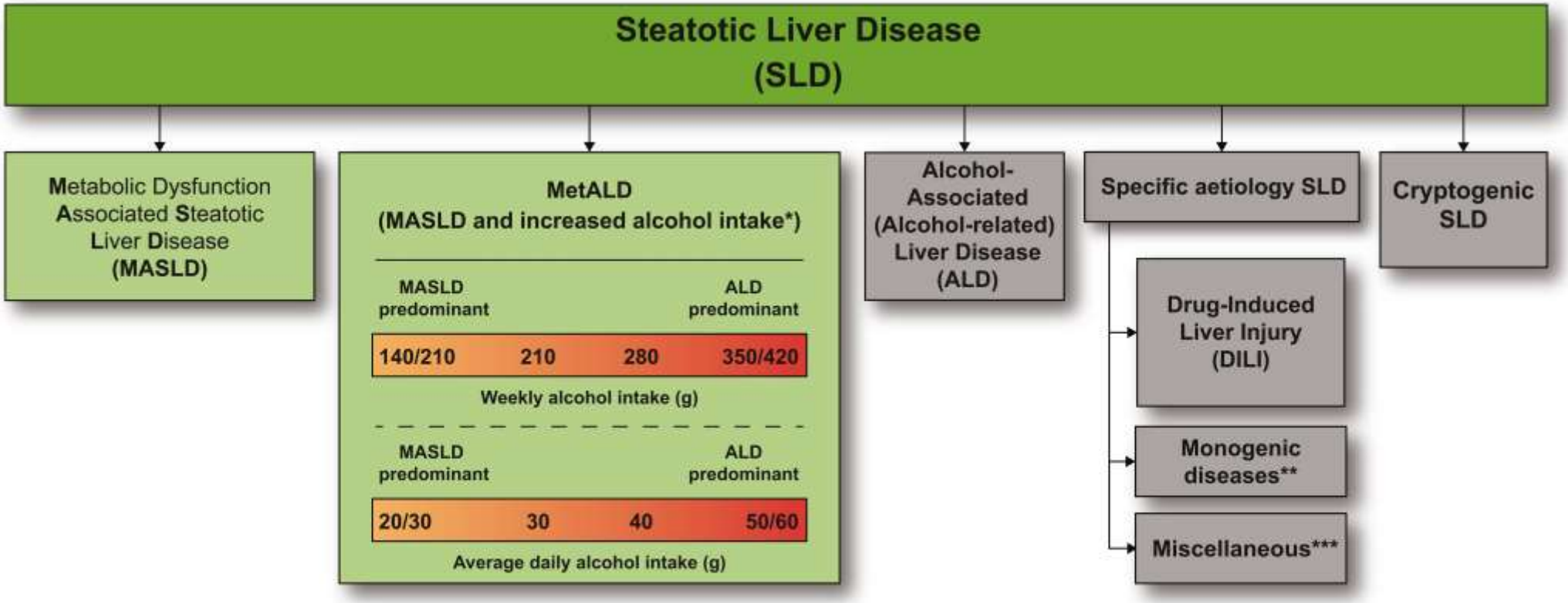


Perspectives de recherche

Pr Cyrielle Caussy

Endocrinologie Diabète et Nutrition, Hôpital Lyon Sud,
Hospices Civils de Lyon,
CRNH Rhône Alpes, Laboratoire CarMen INSERM 1060

Maladies stéatosiques hépatiques



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

Rinella M. et al. Hepatology : June 24, 2023

Maladies stéatosiques hépatiques

Maladie stéatosique du foie = Steatotic liver disease (**SLD**)

Maladie stéatosique du foie liée à une dysfonction métabolique (MASLD)

Au moins 1 critère cardio-métabolique

Dyslipidémie

Hypertension

surpoids
IMC ≥ 25 kg/m2

Intolérance au glucose /DT2

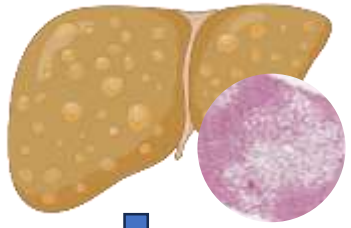
Rinella M. et al. Hepatology : June 24, 2023

Maladies stéatosiques hépatiques

Obésité
Syndrome métabolique

Aggrave l'insulino-résistance, la dyslipidémie …

MASLD



Diabète de type 2

Augmente les risques d'aggravation de la MASLD

Maladies cardiovasculaires

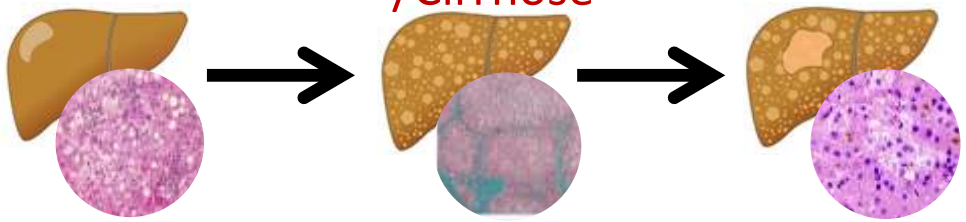
Maladies rénales

Forte prévalence
30% de la population adulte mondiale

Fibrose Avancée /Cirrhose

MASH

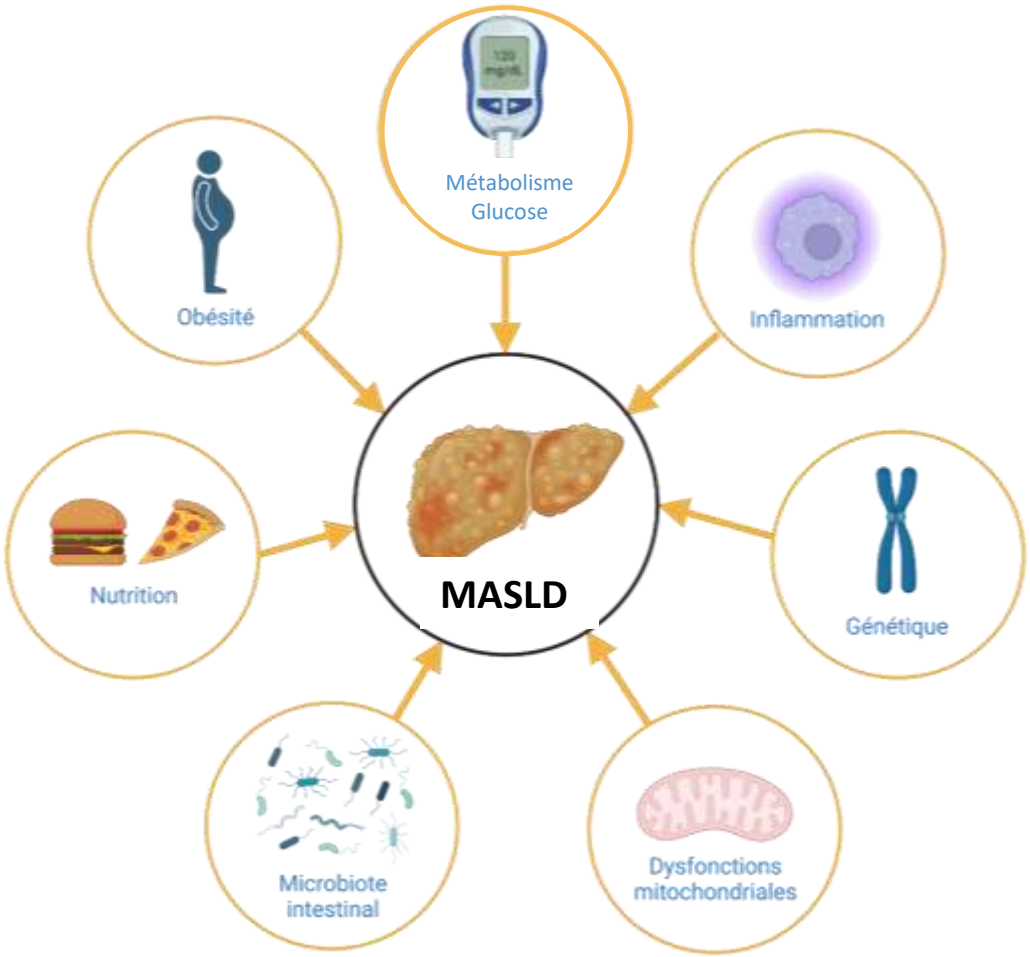
CHC



ENJEUX:

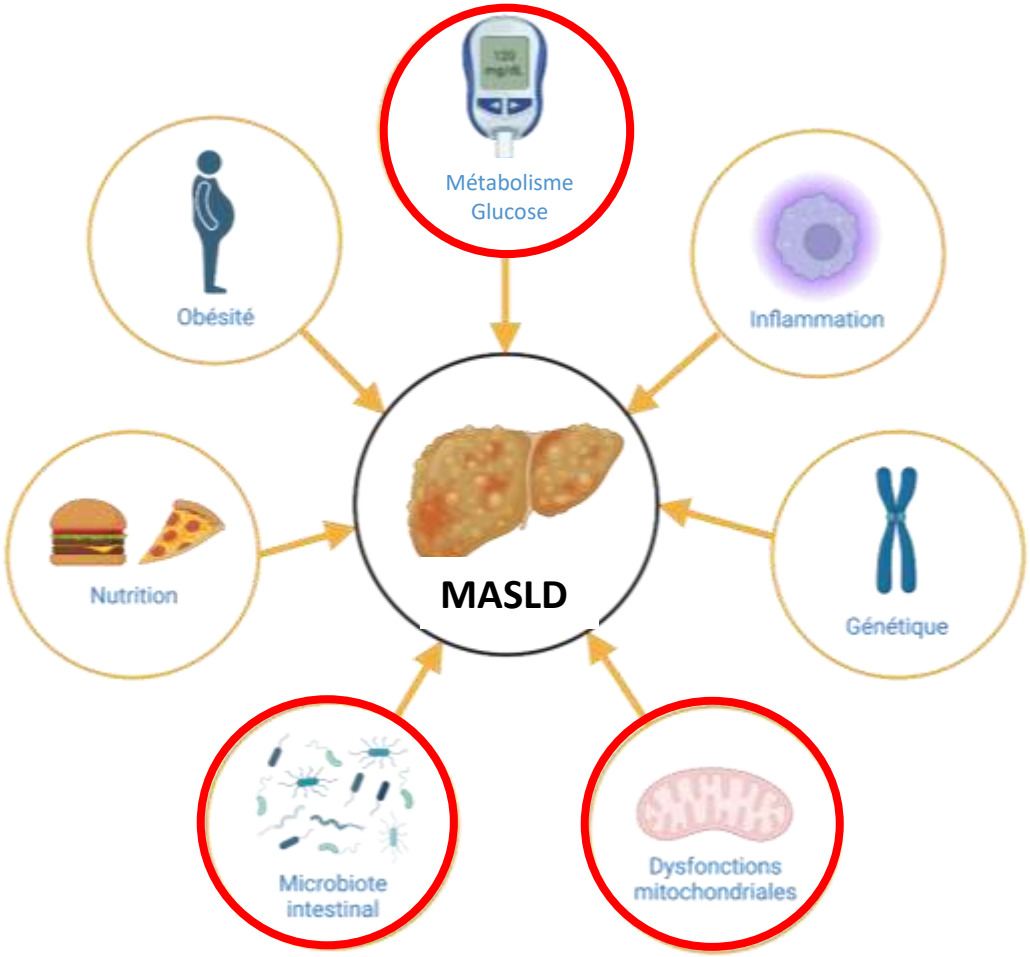
- **Nouveaux mécanismes physiopathologiques**
  cibles thérapeutiques potentielles

Mécanismes multifactoriels



Maladies stéatosiques hépatiques

Mécanismes multifactoriels



Equipe NUDICE
G.Mithieux
F. Rajas
A. Gautier-Stein

Equipe MERISM
J. Rieusset
C. Caussy

Maladies stéatosiques hépatiques

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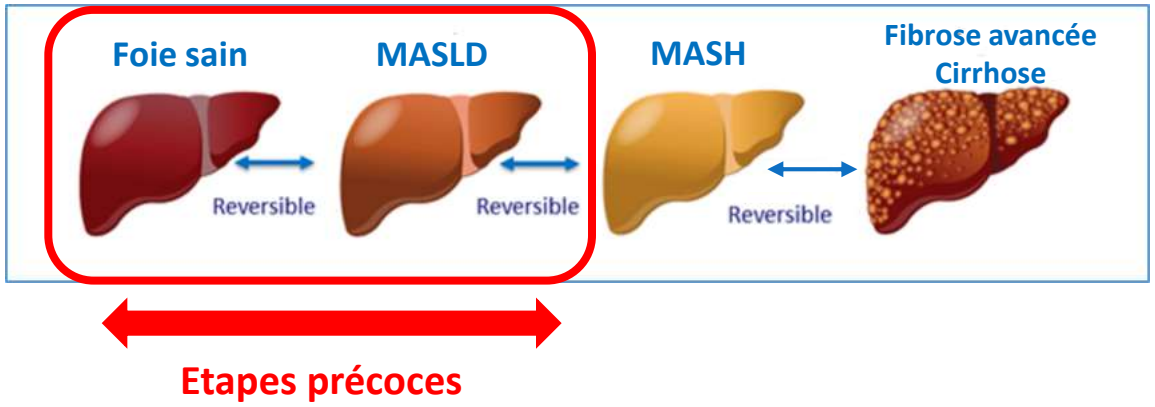

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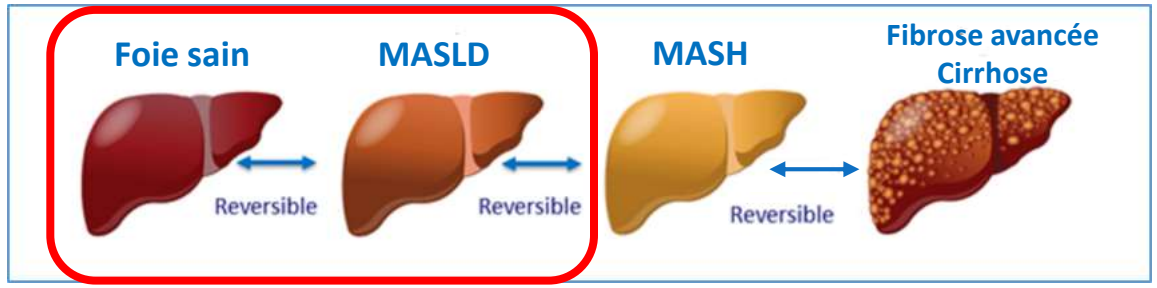
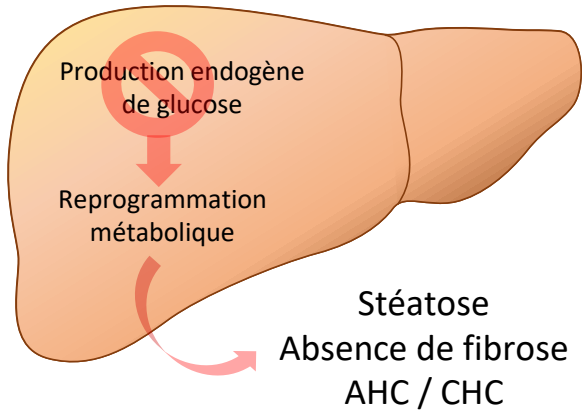


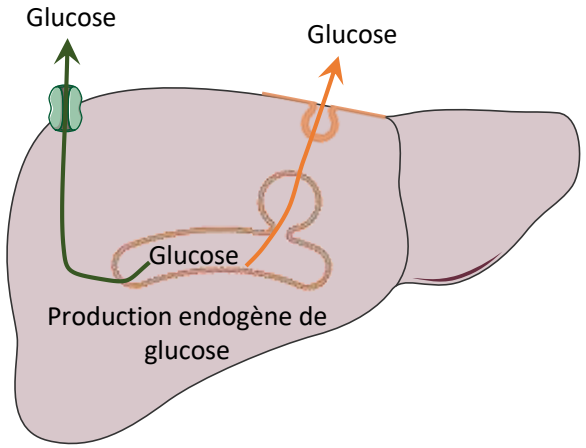
Etapes précoces

La glycogénose de type 1 : modèle métabolique original de MASLD

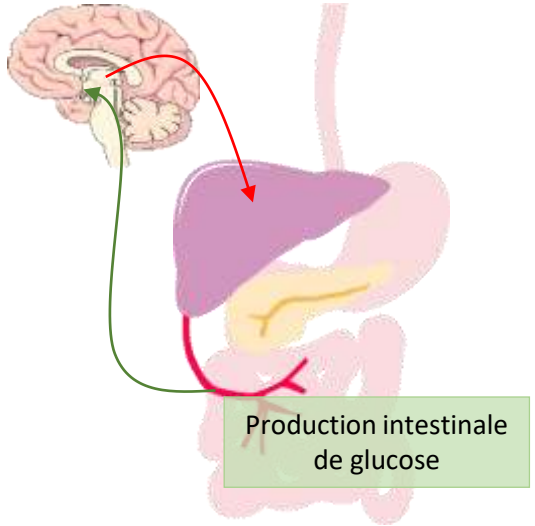


Gjorgjieva et al, J Hepatol 2018

Nouvelle voie de production hépatique de glucose

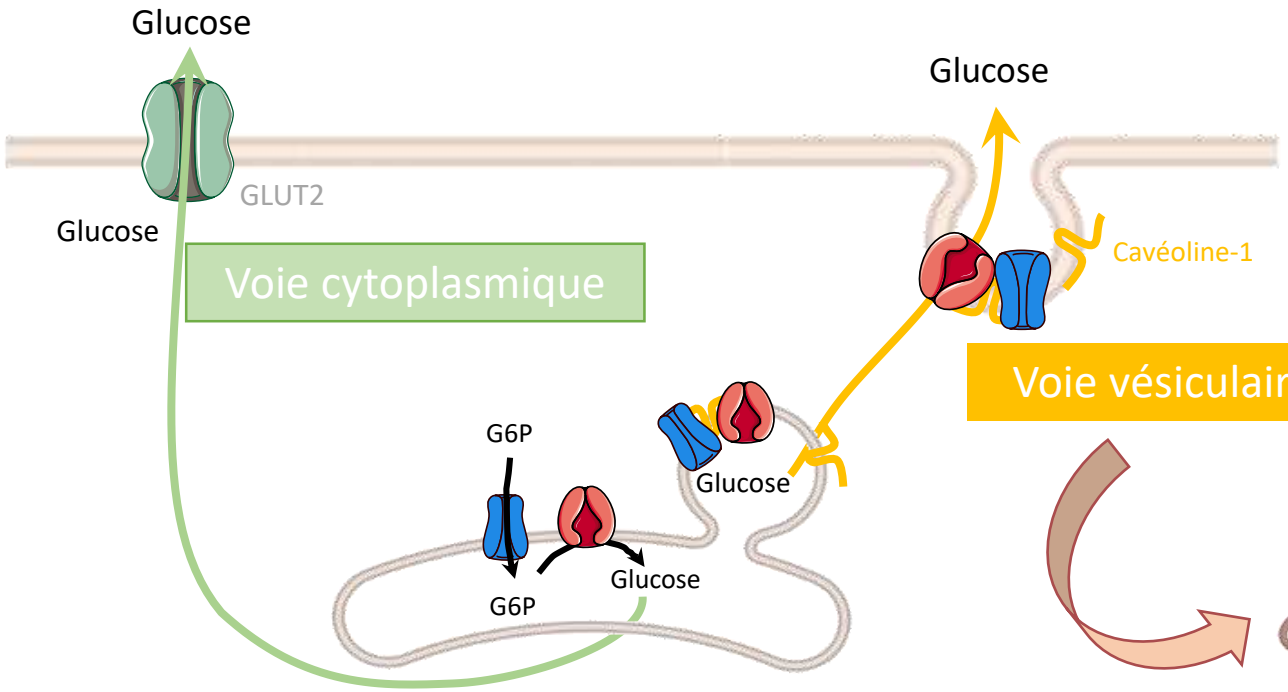


Production intestinale de glucose : fonction anti-diabète et anti-obésité



Maladies stéatosiques hépatiques

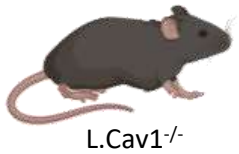
Equipe NUDICE
A. Gautier-Stein



Protège du diabète

Da Costa et al. unpublished data

Protège de l'insulino-résistance hépatique



L.Cav1$^{-/-}$

Régime pro-fibrotique

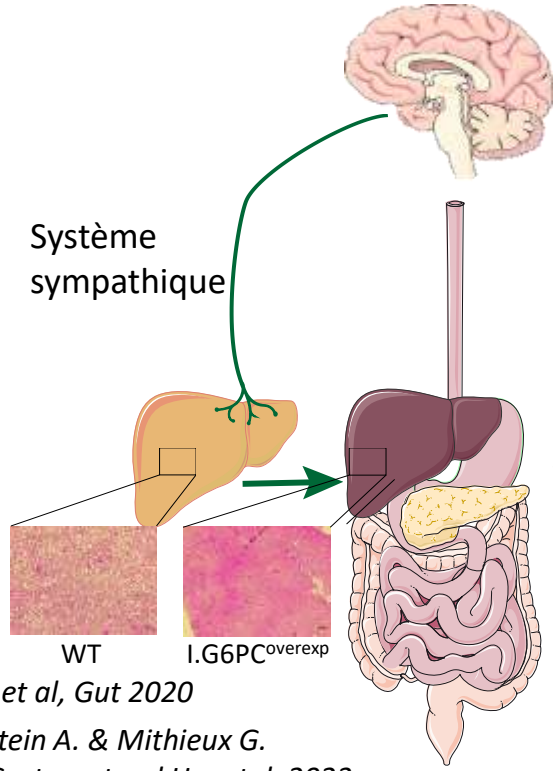
Protection de l'inflammation et de la fibrose ?

Gautier-Stein et al, Mol Metab 2023

Rôle dans le développement des SLD ?

Maladies stéatosiques hépatiques

Equipe NUDICE
G. Mithieux



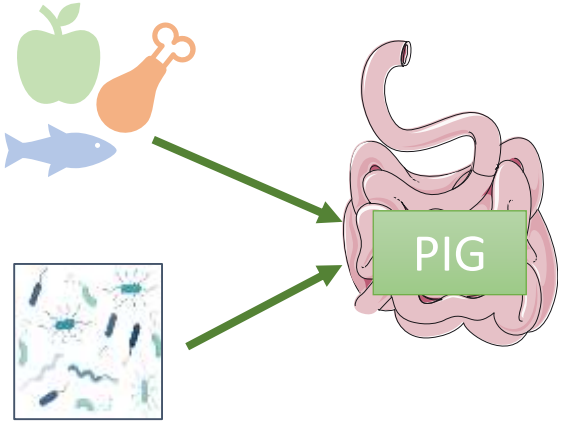
Vily-Petit et al, Gut 2020

Gautier-Stein A. & Mithieux G.
Nat Rev Gastroenterol Hepatol. 2023

I.G6PC^overexp

Régime pro-fibrotique

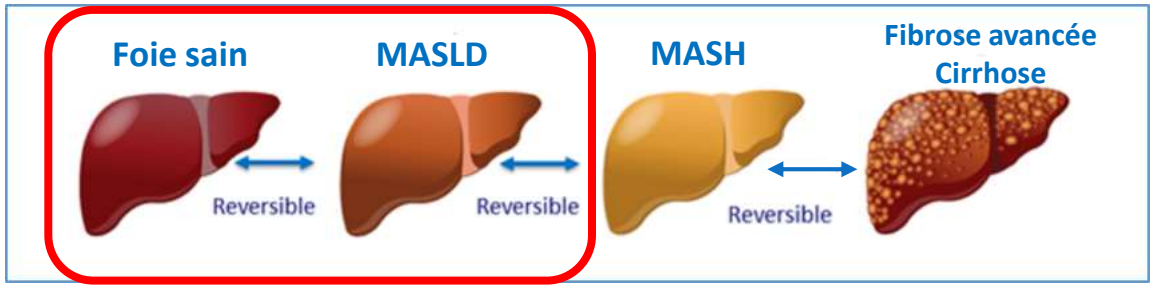
Protection de l'inflammation et de la fibrose ?



Nouveaux inducteurs de la production intestinale de glucose

European Research Council

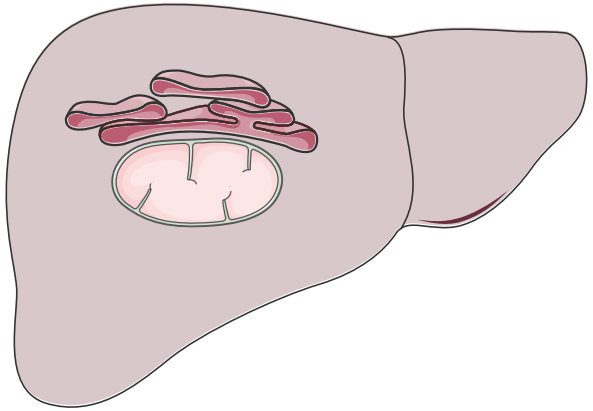
Maladies stéatosiques hépatiques



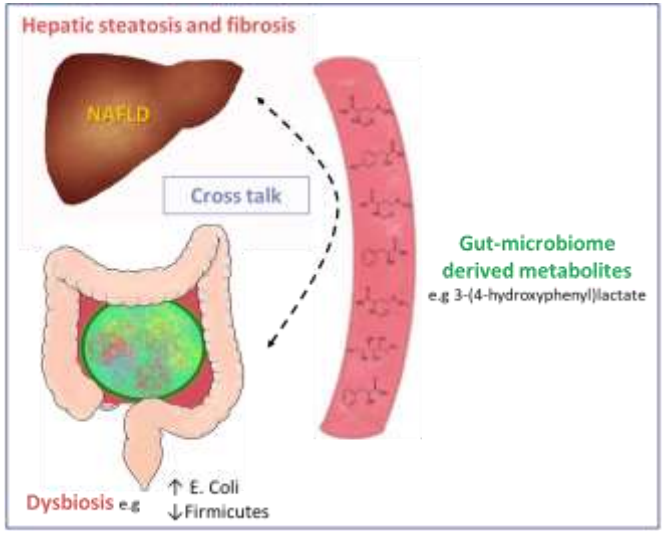
Etapes précoces

Equipe MERISM
J Rieusset
C Caussy

Communication mitochondrie-RE et insulin-résistance hépatique et stéatose

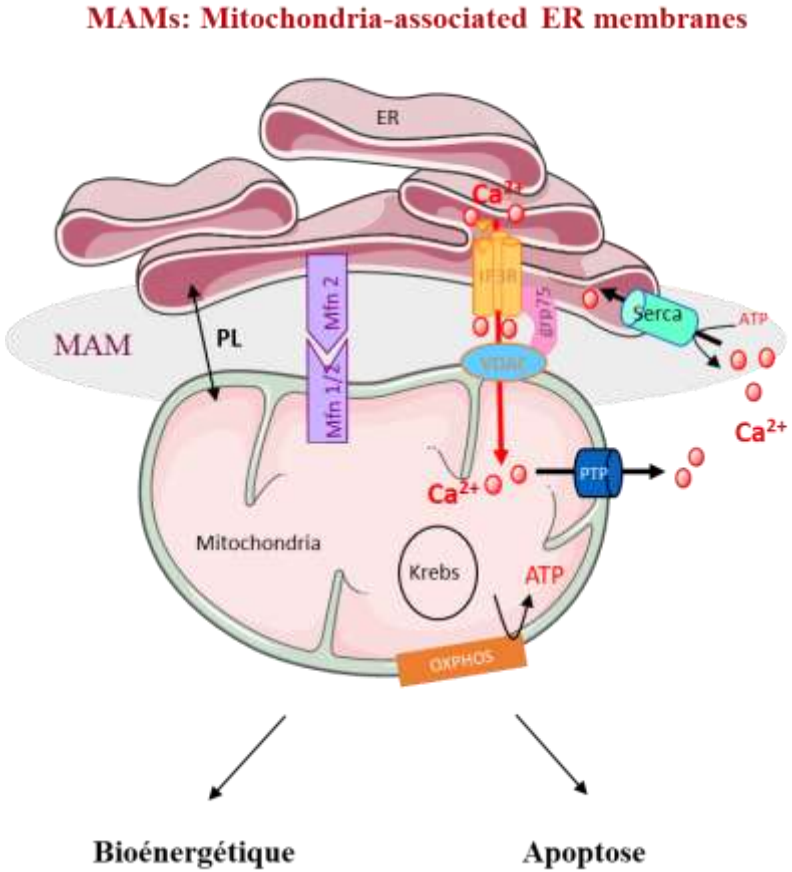


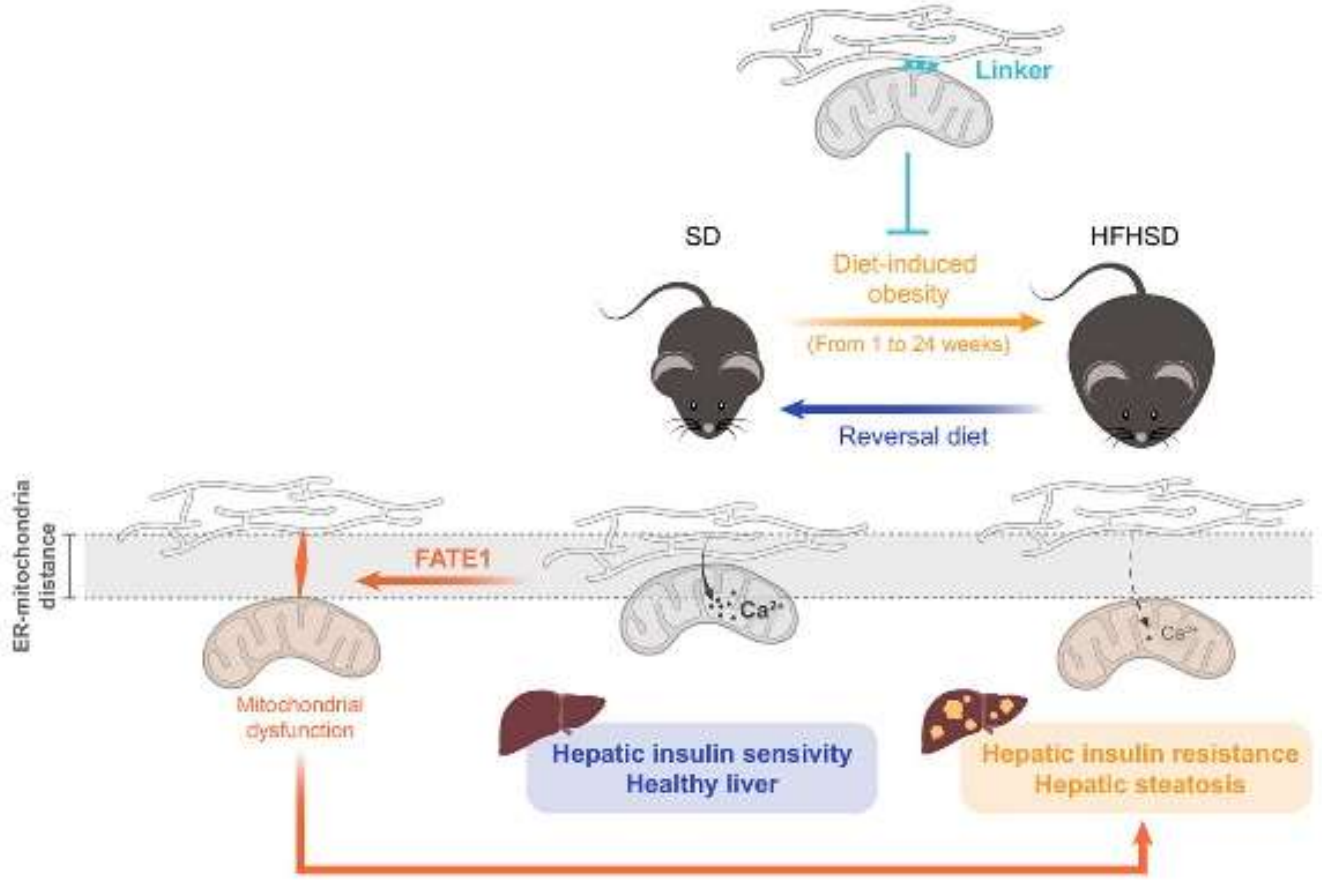
Axe intestin-foie et communication via métabolites dérivés du microbiote



Maladies stéatosiques hépatiques

Equipe MERISM
J Rieusset

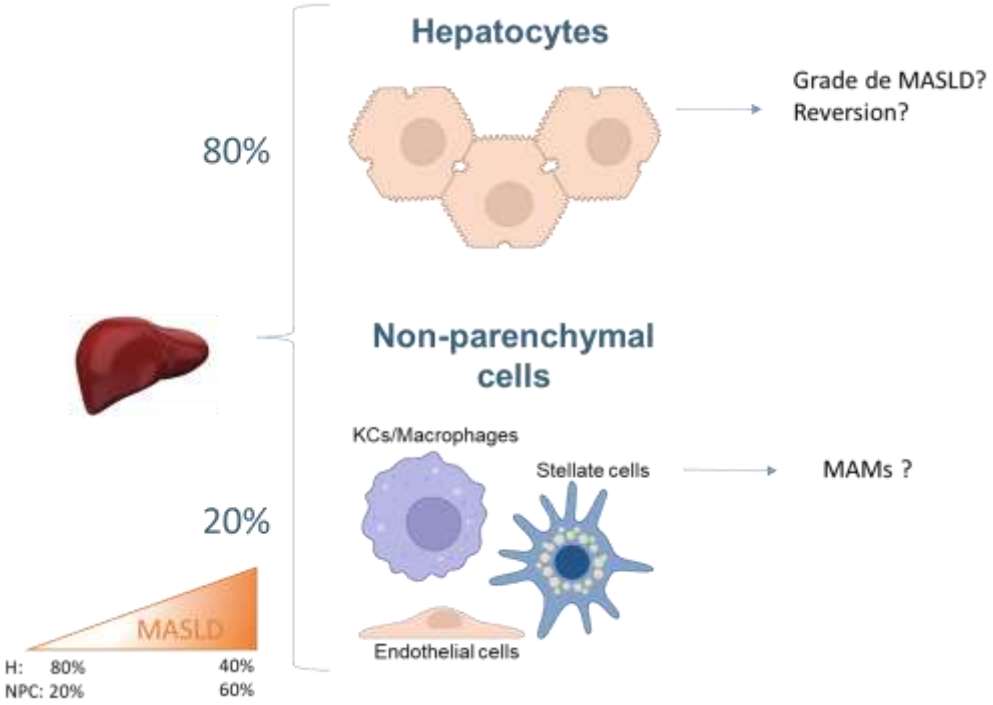


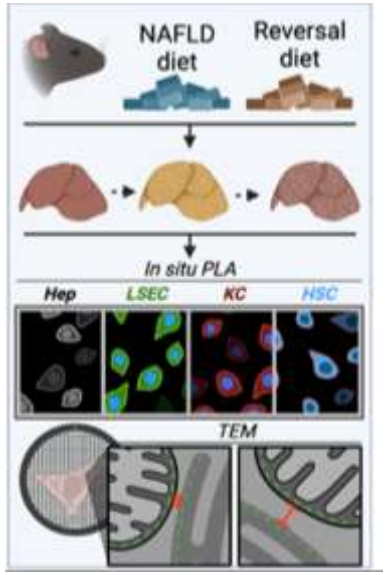


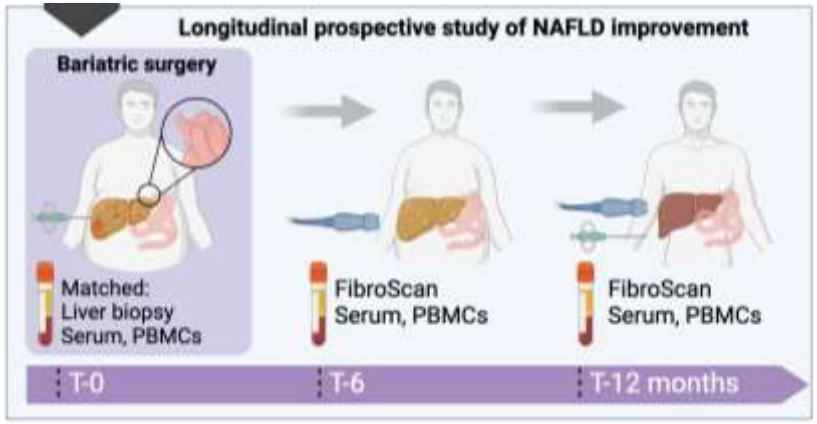
Beaulant et al. J Hep. 2022

Maladies stéatosiques hépatiques

Project CEMPR: Cell-type-specific ER-Mitochondria contact sites in NAFLD Progression and Recovery







HCL HOSPICES CIVILS DE LYON

anr agence nationale de la recherche

DFG Deutsche Forschungsgemeinschaft

CarMen Lyon

INEM Paris

Fawaz Alzaid

CRC Paris

Marie Lagouge

University of Munich

Hans Zischka

Maria Paula Macedo (Portugal)

Maladies stéatosiques hépatiques

Cohorte de patients : recherche translationnelle

Biobanque

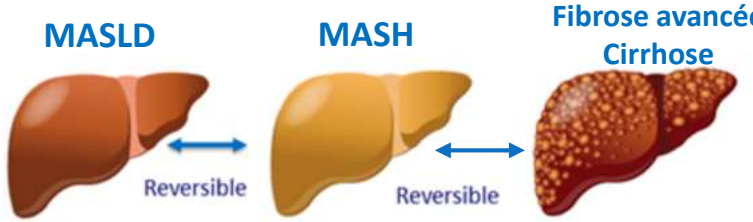
Sérum
Plasma
Sang total
Selles (sous-groupe)
Tissu hépatique (sous-groupe)

Patients avec Diabètes de type 2 et/ou Obésité et MASLD (IMC 30-40 kg/m2)

800 patients
40-80 ans

Suivi longitudinal
à 4 ans

500 patients DT2



- ✓ Progression de la MASLD
- ✓ Evènements cliniques
  - Complications DT2
  - Cardiovasculaire
  - Hépatique

Etude prospective multicentrique

- ✓ Lyon
- ✓ Nantes
- ✓ Dijon

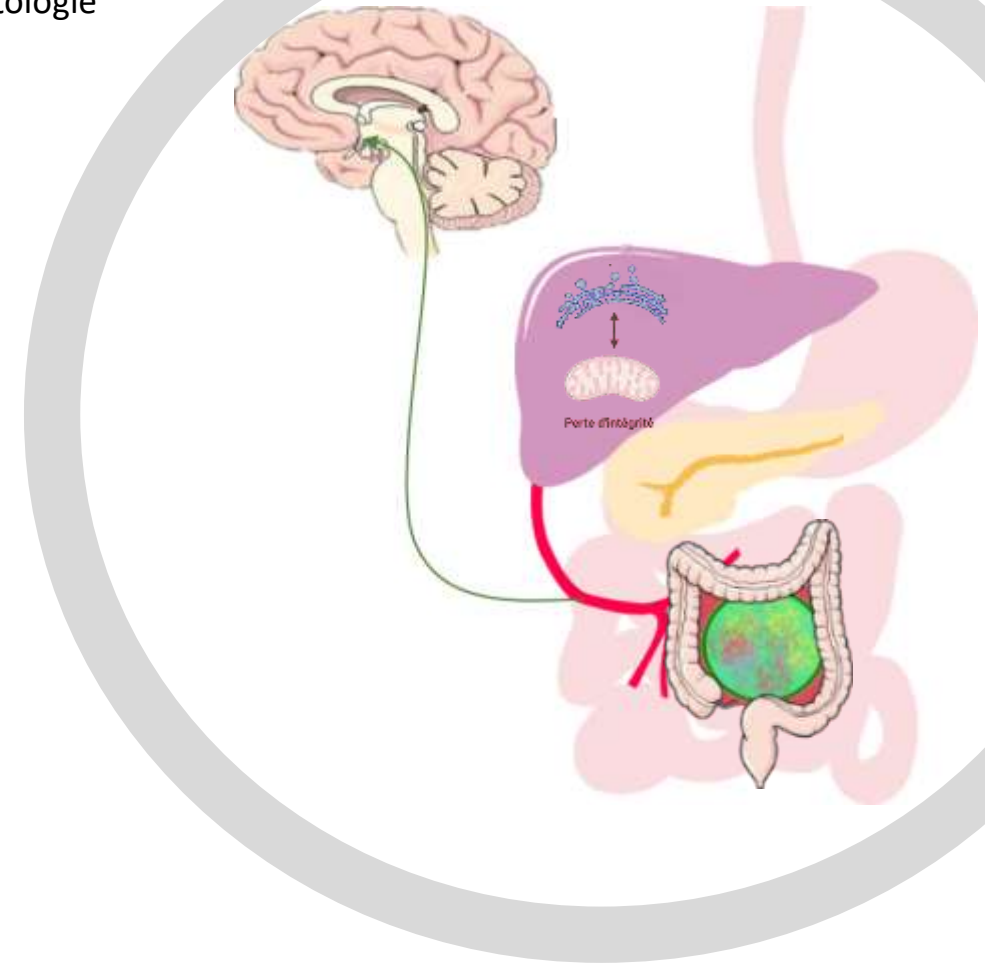
NCT04435054, PI C. CAUSSY HCL

Maladies stéatosiques hépatiques

HCL HOSPICES CIVILS DE LYON

Endocrinologie Diabète et Nutrition
Hôpital Lyon Sud

Service Hépatologie
Croix Rousse



Equipe NUDICE
G.Mithieux
F. Rajas
A. Gautier-Stein

CarMeN LYON

Equipe 2 MERISM
J. Rieusset
C. Caussy

Métabolomique

INSTITUT DES SCIENCES ANALYTIQUES

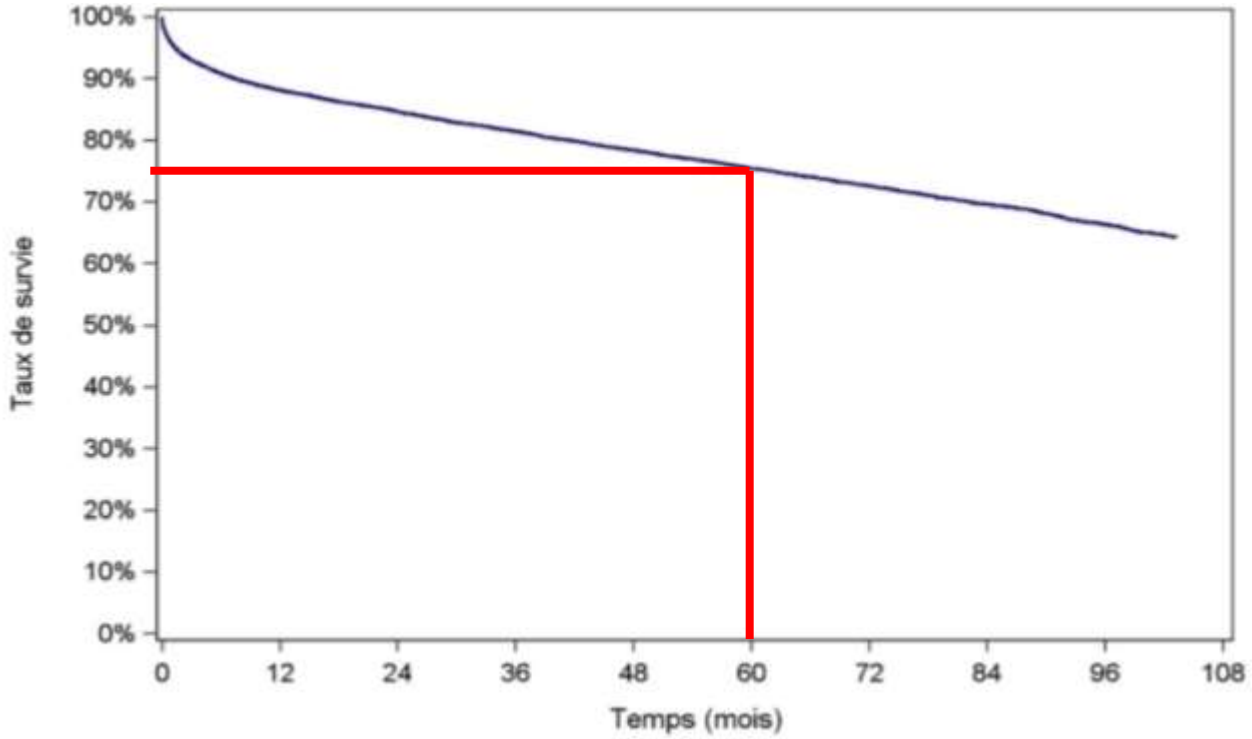
S. Ayciriex

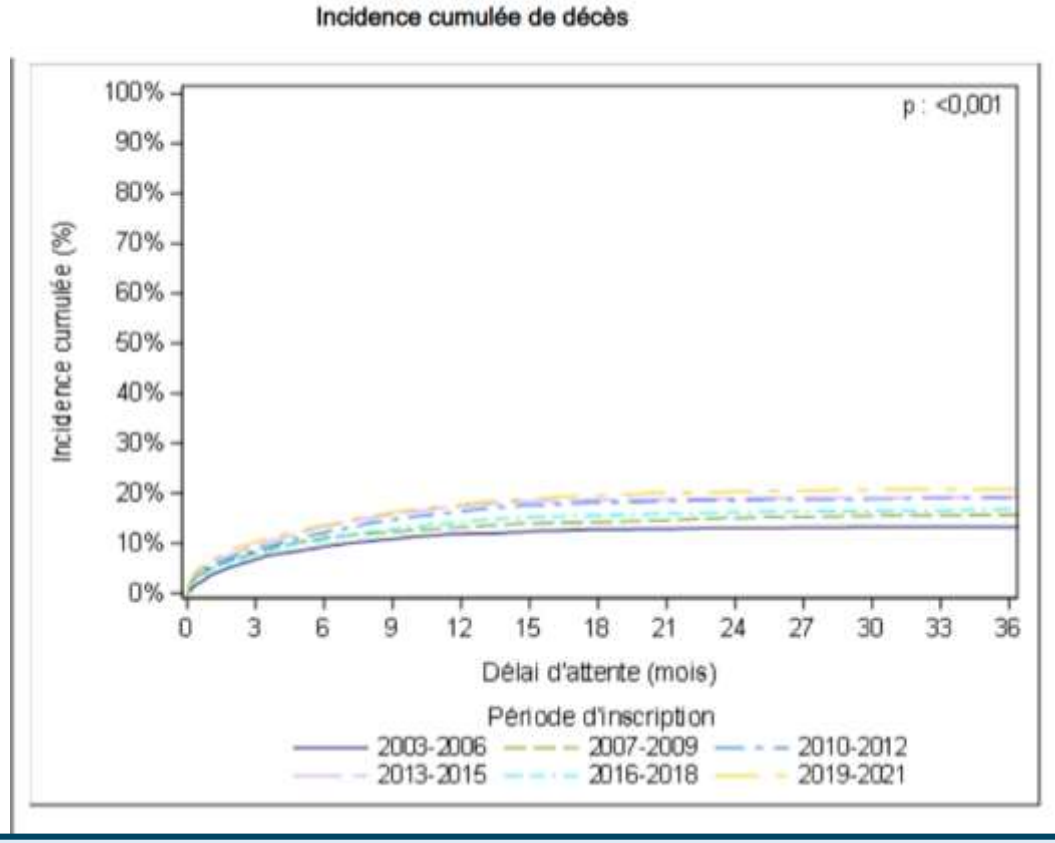
Innovation en transplantation hépatique

Perspectives de recherche

Pr Jean-Yves MABRUT

Survie: 88% à 1 an, 75% à 5 ans



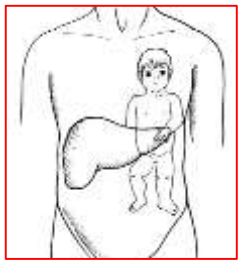


Décès sur liste d'attente: 18% à 1 an

CENTRE TRANSPLANTATION HEPATIQUE - HCL

INSTITUT D'HÉPATOLOGIE DE LYON

Perfusion normothermique & rewarming

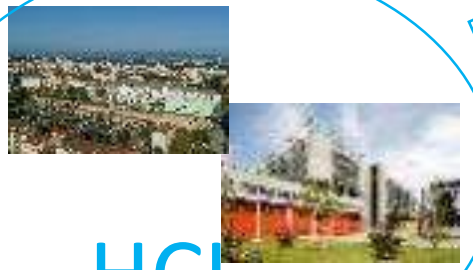


Donneur vivant pédiatrique & adulte

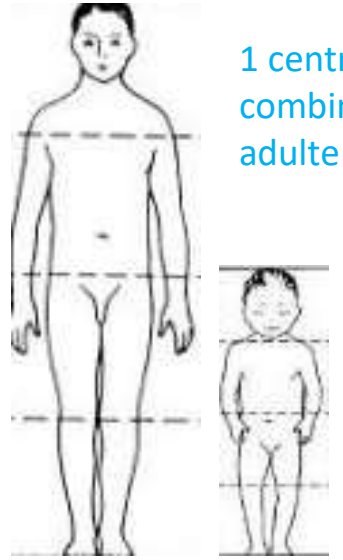
IHU EVEREST

Perfusion hypothermique

Bi-partition ex-situ & in-situ



HCL



1 centre unique combinant les expertises adulte et pédiatrique

Réduction

Recherche expérimentale

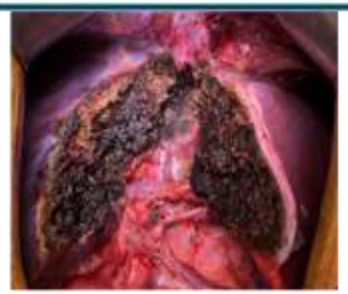
Recherche clinique PHRC & innovations

GREFFONS PARTIELS

Adulte

Enfant

Donneurs vivants



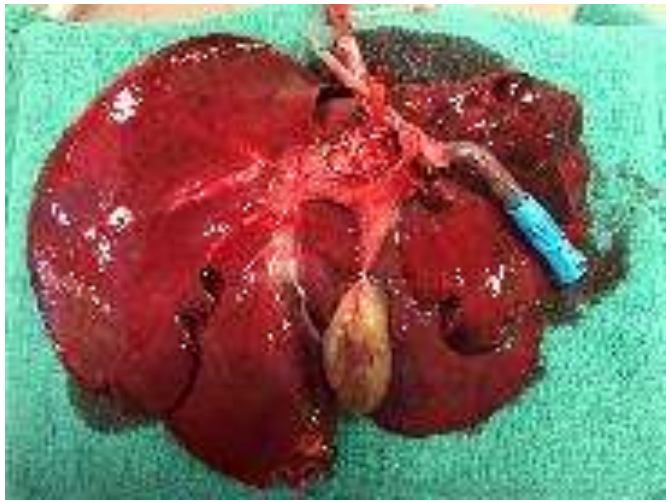
Réduction

Split

Split ex-situ

Split in-situ

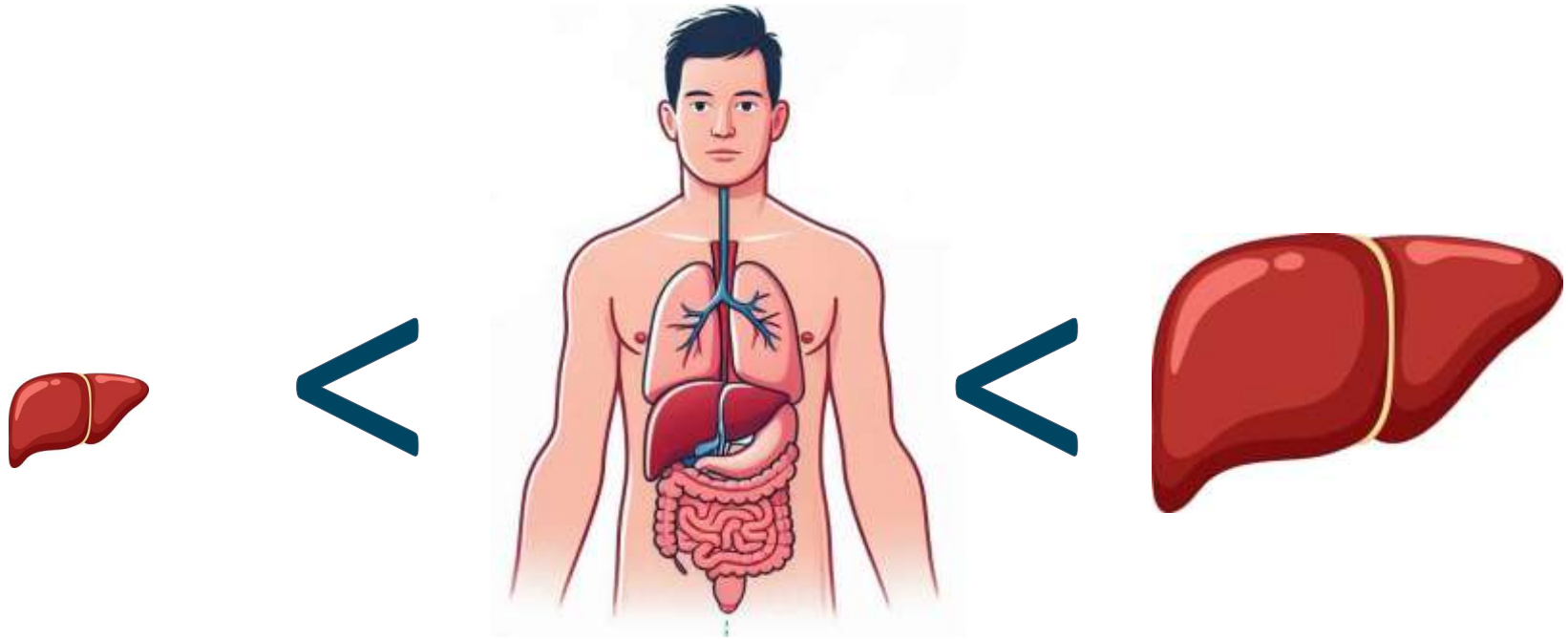
Plateforme de Chirurgie Expérimentale (Gros Animal)



Etudes Pré-Cliniques

MATCHING MORPHOLOGIQUE

SMALL FOR SIZE	LARGE FOR SIZE



REDUCTION HEPATIQUE FOIE ENTIER

ADULTE

PEDIATRIC TRANSPLANTATION
The Official Journal of the International Pediatric Transplant Association

CASE REPORT

Optimizing graft-recipient size matching in adolescent liver transplantation: Don't forget ex situ right posterior sectionectomy

Guillaume Rossignol ✉ Xavier Muller, Remi Dubois, Agnes Rode, Jean-Yves Mabrut, Kayvan Mohkam

First published: 15 March 2023 | https://doi.org/10.1111/petr.14510

PEDIATRIE

LETTERS TO THE EDITOR

Letter to the Editor: Reduced whole liver grafts from pediatric donors as an alternative for small recipients

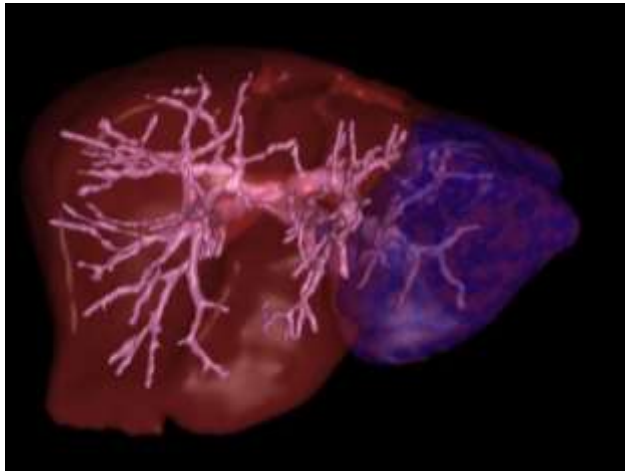
Rossignol, Guillaume[1,2,3,4]; Muller, Xavier[2,3,4]; Dubois, Remi[1]; Mabrut, Jean-Yves[2,3]; Mohkam, Kayvan[1,2,3]

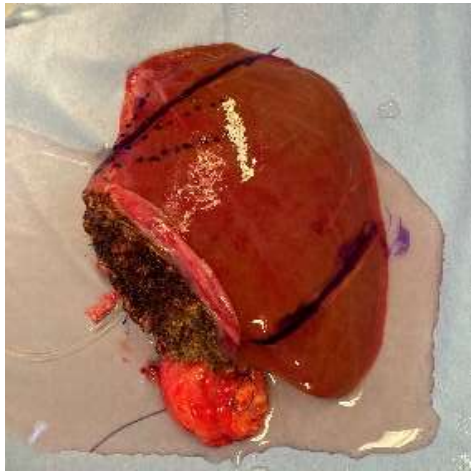
Author Information

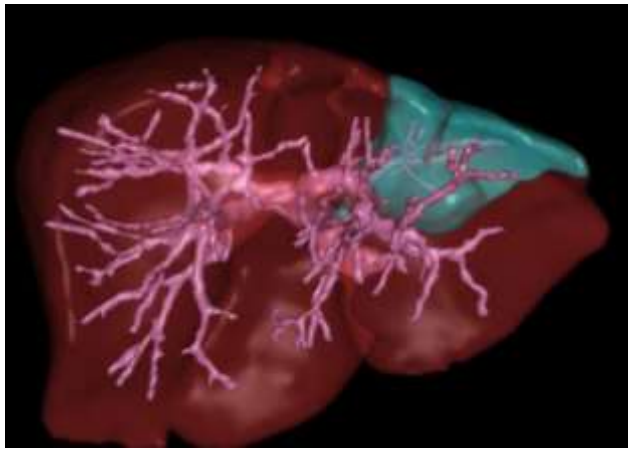
Liver Transplantation 29(6):p E11-E12, June 2023. | **DOI:** 10.1097/LVT.0000000000000076

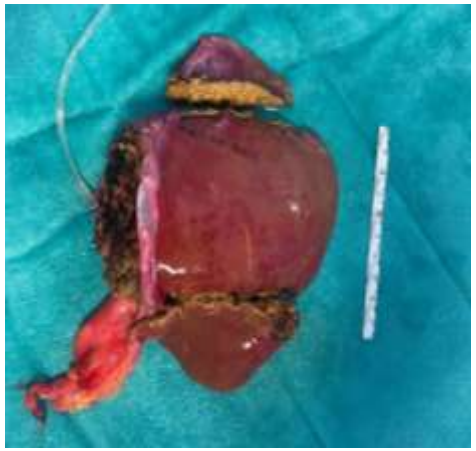
REDUCTION HEPATIQUE FOIE PARTIEL

PEDIATRIE

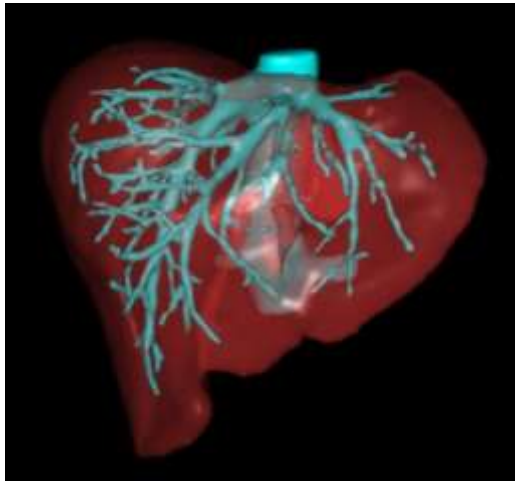








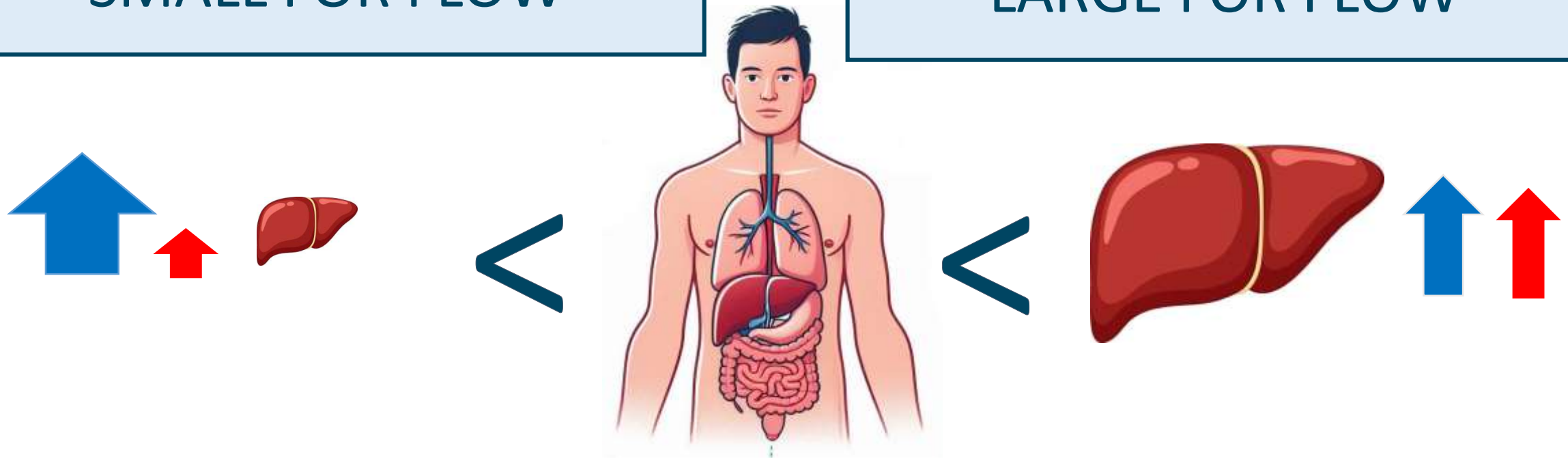
DONNEUR VIVANT
Modélisation 3D



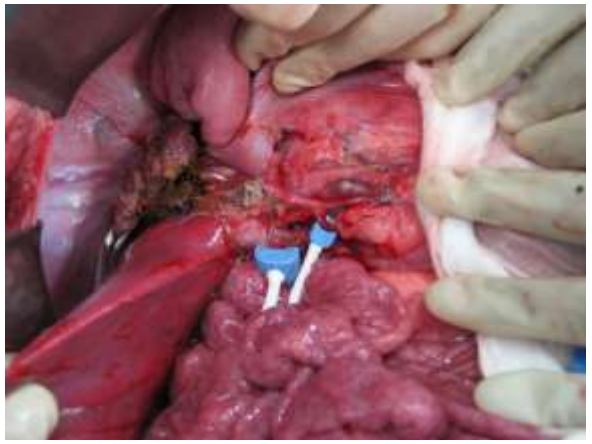
MATCHING HEMODYNAMIQUE

SMALL FOR FLOW

LARGE FOR FLOW



MODELE ANIMAL



ELSEVIER

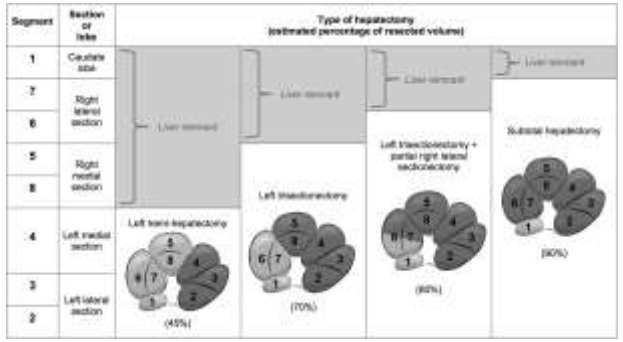
The American Journal of Surgery

Volume 212, Issue 2, August 2016, Pages 321-326

Research

Successful modulation of portal inflow by somatostatin in a porcine model of small-for-size syndrome

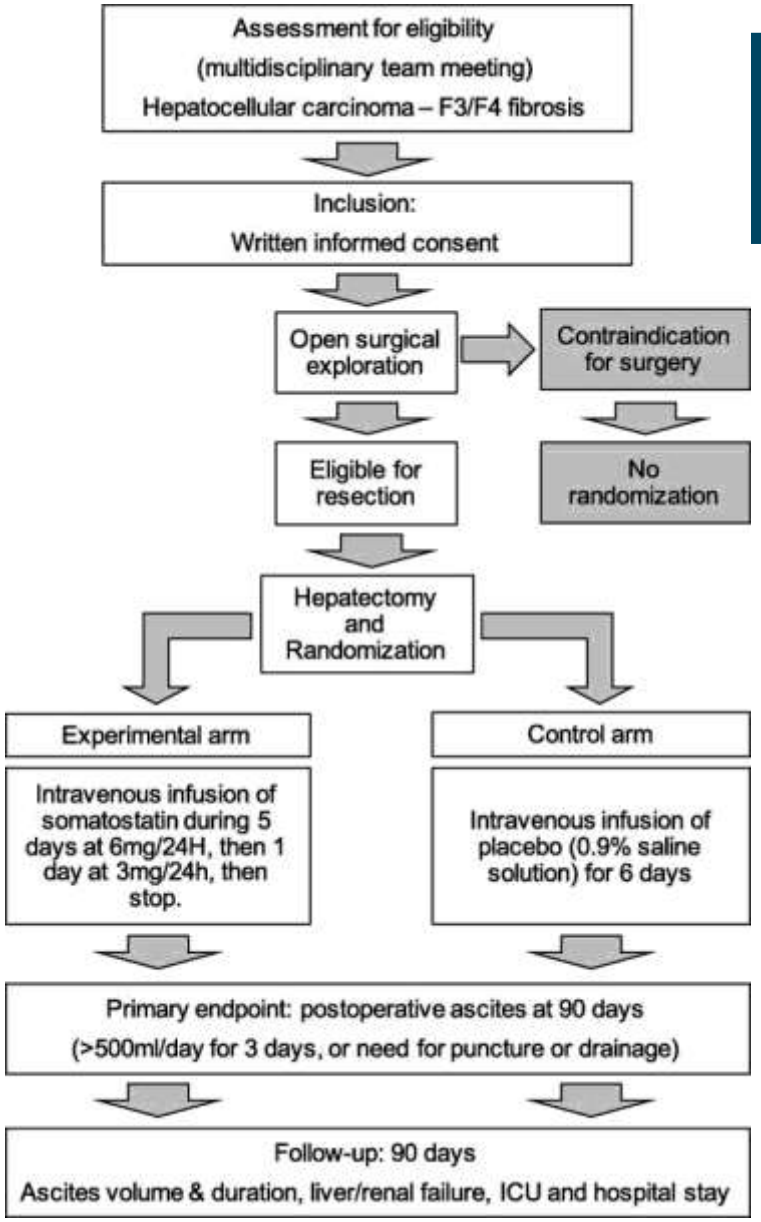
Kayvan Mohkam M.D. [a b c], Benjamin Darnis M.D. [a c], Zoé Schmitt M.D. [c d], Serge Duperret M.D., Ph.D. [c d], Christian Ducerf M.D., Ph.D. [a c], Jean-Yves Mabrut M.D., Ph.D. [a b c]



Modulation Flux porte

Thèse de Doctorat =1
Master 2 =3

TRANSLATIONNEL
Modulation Flux Porte



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MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

BMC Cancer. 2018; 18: 844.
Published online 2018 Aug 23. doi: 10.1186/s12885-018-4667-0
PMCID: PMC6108122
PMID: 30139340

Evaluation of postoperative ascites after somatostatin infusion following hepatectomy for hepatocellular carcinoma by laparotomy: a multicenter randomized double-blind controlled trial (SOMAPROTECT)

Kayvan Mohkam,[1,2] Michel Rayar,[3] Jean-Philippe Adam,[4] Fabrice Muscari,[5] Agnès Rode,[6] Philippe Merle,[7] Pierre Pradat,[8] Stéphanie Bauler,[9] Isabelle Delfour,[8] Laurence Chiche,[4] Christian Ducerf,[1] Karim Boudjema,[3] Mickaël Lesurtel,[1] Christophe Laurent,[4] and Jean-Yves Mabrut[1,2]

HEMODYNAMIQUE

APPLICATION CLINIQUE

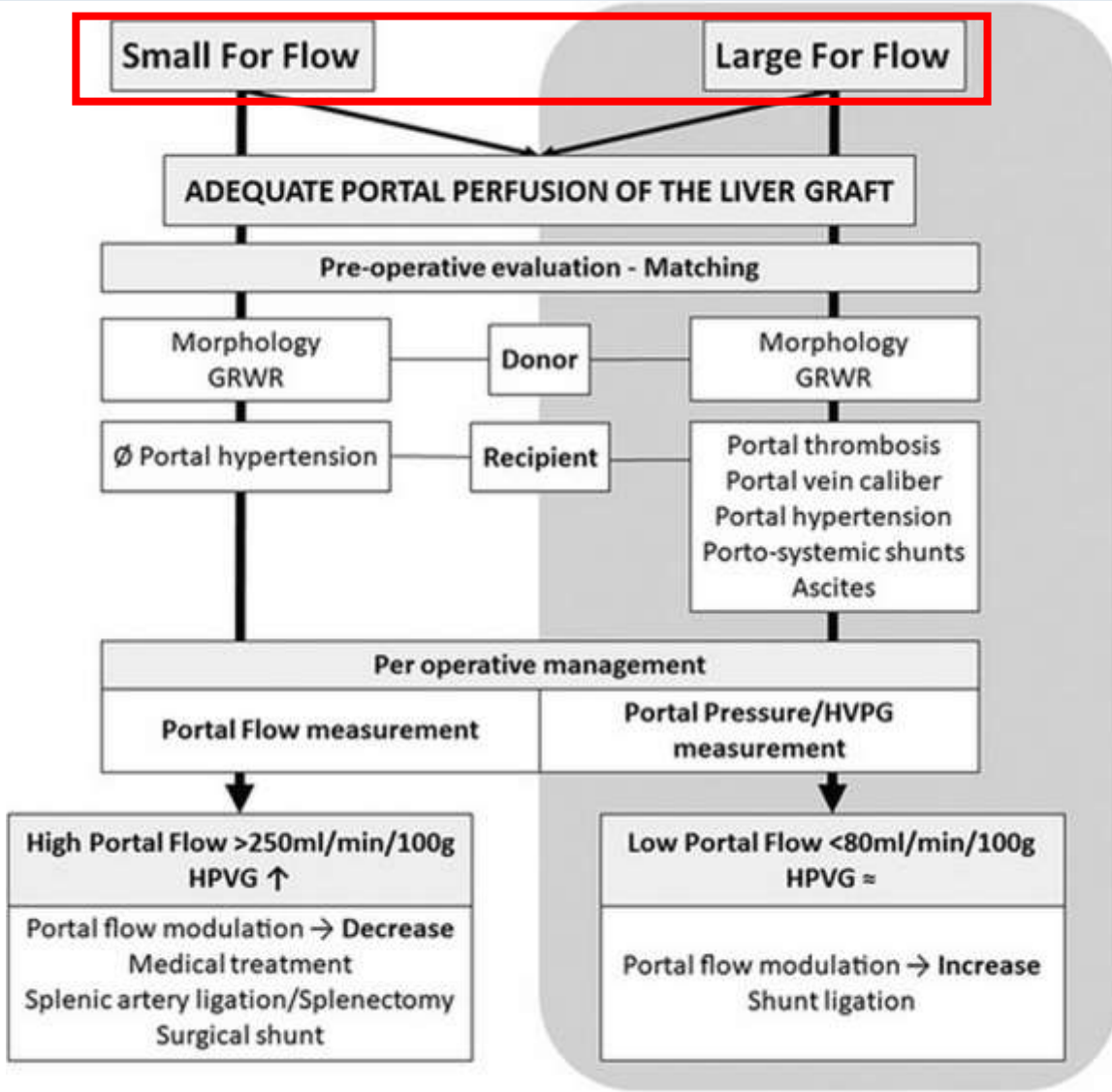
ORIGINAL ARTICLES: LIVER SURGERY AND ORGAN PRESERVATION

From large-for-size to large-for-flow: A paradigm shift in liver transplantation

Rossignol, Guillaume[1,2,3,4]; Muller, Xavier[2,3,4]; Couillerot, Joris[3]; Lebosse, Fanny[5]; Delignette, Marie-Charlotte[6]; Mohkam, Kayvan[1,2,4]; Mabrut, Jean-Yves[1,2]

Author Information

Liver Transplantation 30(3):p 277-287, March 2024. | **DOI:** 10.1097/LVT.0000000000000150



Modulation Flux porte

CONSERVATION - EVALUATION

MACHINES A PERFUSION

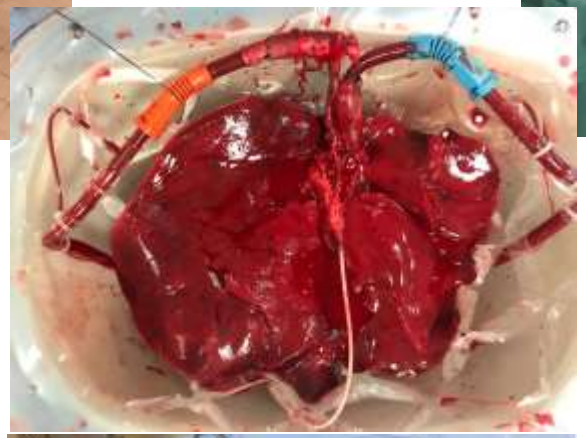
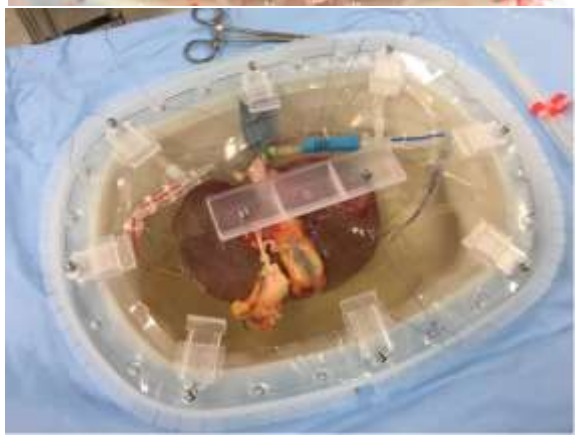
Conservation

Evaluation / Viabilité

Optimisation

CONSERVATION - EVALUATION



PhD

Xavier Muller 2023
Guillaume Rossignol 2024
Natacha Boulanger 2026

Master

Antoine Breton
Joris Couillerot
Natacha Boulanger
Charles De Matteis
Rithya Ou
Emma Mulet

CONSERVATION - EVALUATION

COLLABORATION INDUSTRIE

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XVIVO

IGL

to BridgeLife

COLLABORATION SCIENTIFIQUE

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HCL HOSPICES CIVILS DE LYON

HOPExt

MAASTR3BOLOMIC

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FONDATION DE L'AVENIR

EVALUATION

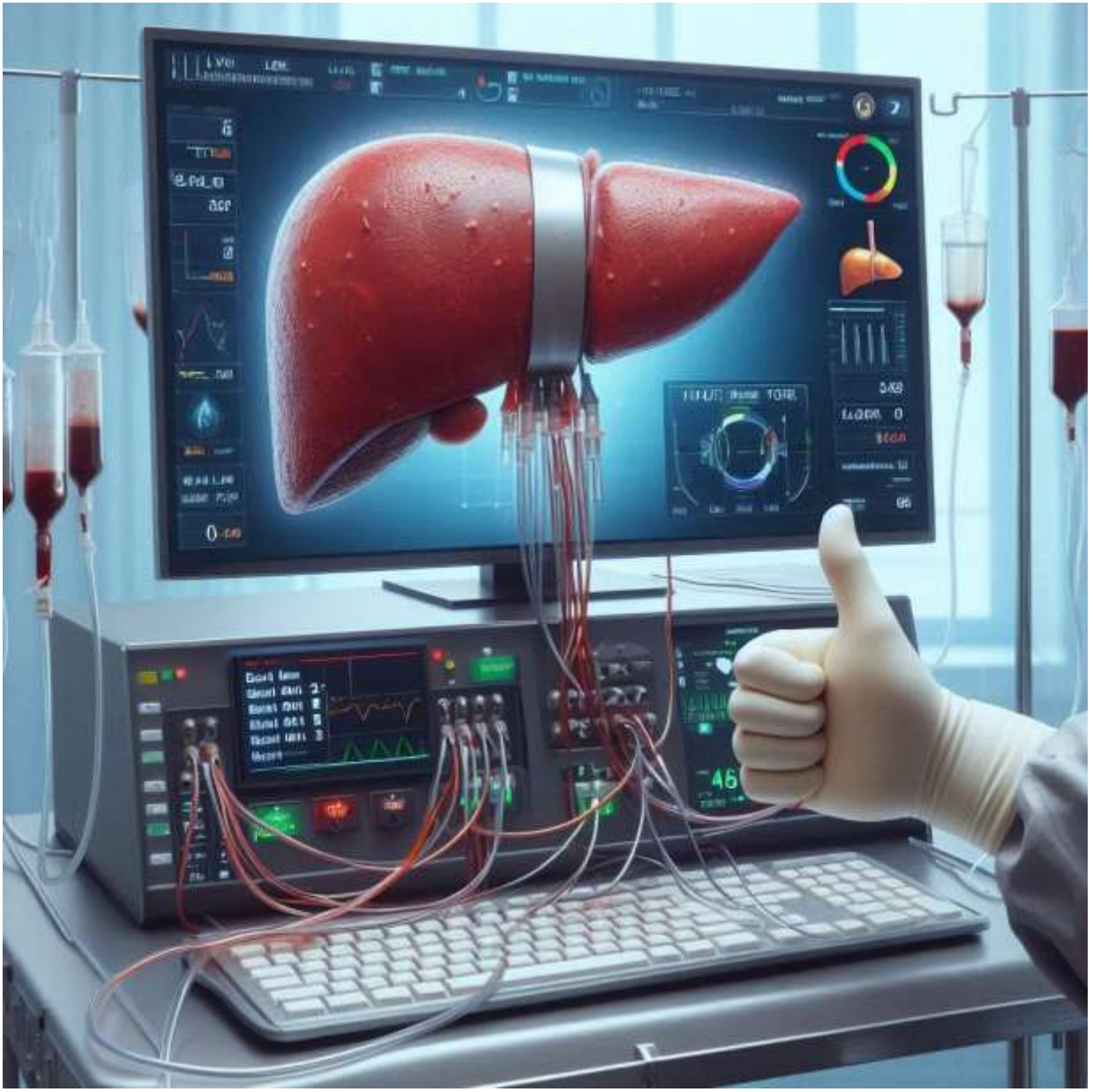
INSTITUT D'HÉPATOLOGIE DE LYON

INSTITUT DES SCIENCES ANALYTIQUES

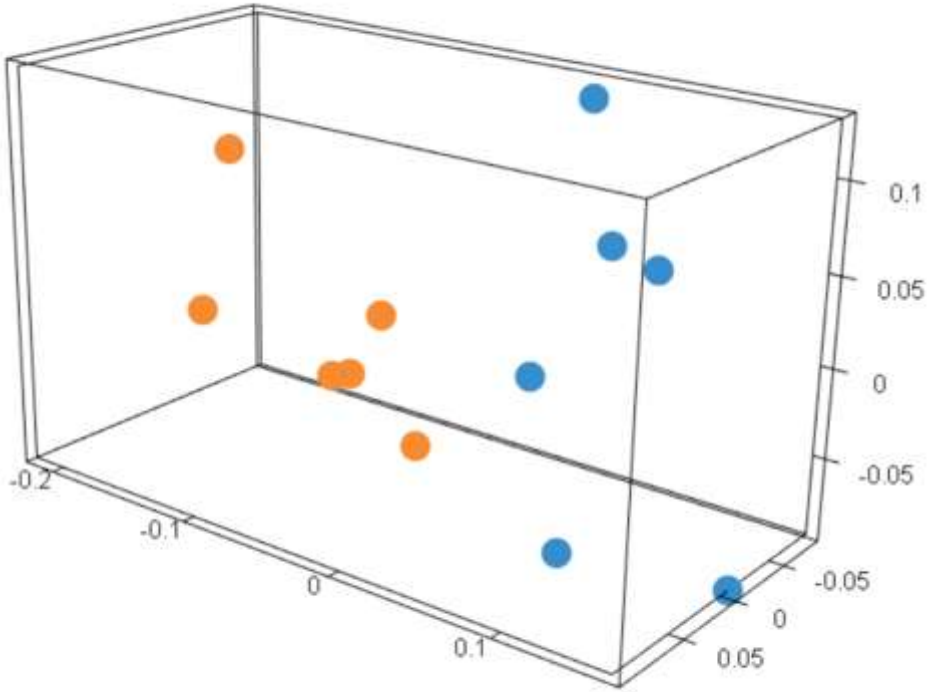
La Région Auvergne-Rhône-Alpes

INSTITUT D'HÉPATOLOGIE DE LYON

EVALUATION



INSTITUT DES SCIENCES ANALYTIQUES



METABOLOMIQUE

CONSERVATION - EVALUATION

Original Basic Science—Liver

A Single Preservation Solution for Static Cold Storage and Hypothermic Oxygenated Perfusion of Marginal Liver Grafts: A Preclinical Study

Xavier Muller, MD,[1,2,3] Guillaume Rossignol, MD,[1,2,3] Joris Couillerot, MSc,[1,2] Antoine Breton, MSc,[1,2] Valérie Hervieu, MD, PhD,[4] Mickaël Lesurtel, MD, PhD,[1] Kayvan Mohkam, MD, PhD,[1,2] and Jean-Yves Mabrut, MD, PhD[1,2]

Article | Open access | Published: 29 January 2024

Comprehensive bile acid pool analysis during ex-vivo liver perfusion in a porcine model of ischemia-reperfusion injury

Guillaume Rossignol, Xavier Muller, Thomas Alexandre Brunet, Valeska Bidault, Valerie Hervieu, Yohann Clement, Sophie Ayciriex, Jean-Yves Mabrut, Arnaud Salvador & Kayvan Mohkam

Scientific Reports **14**, Article number: 2384 (2024) | Cite this article

576 Accesses | **1** Altmetric | Metrics

Evaluation of liver viability for transplantation by fluorescence spectroscopy

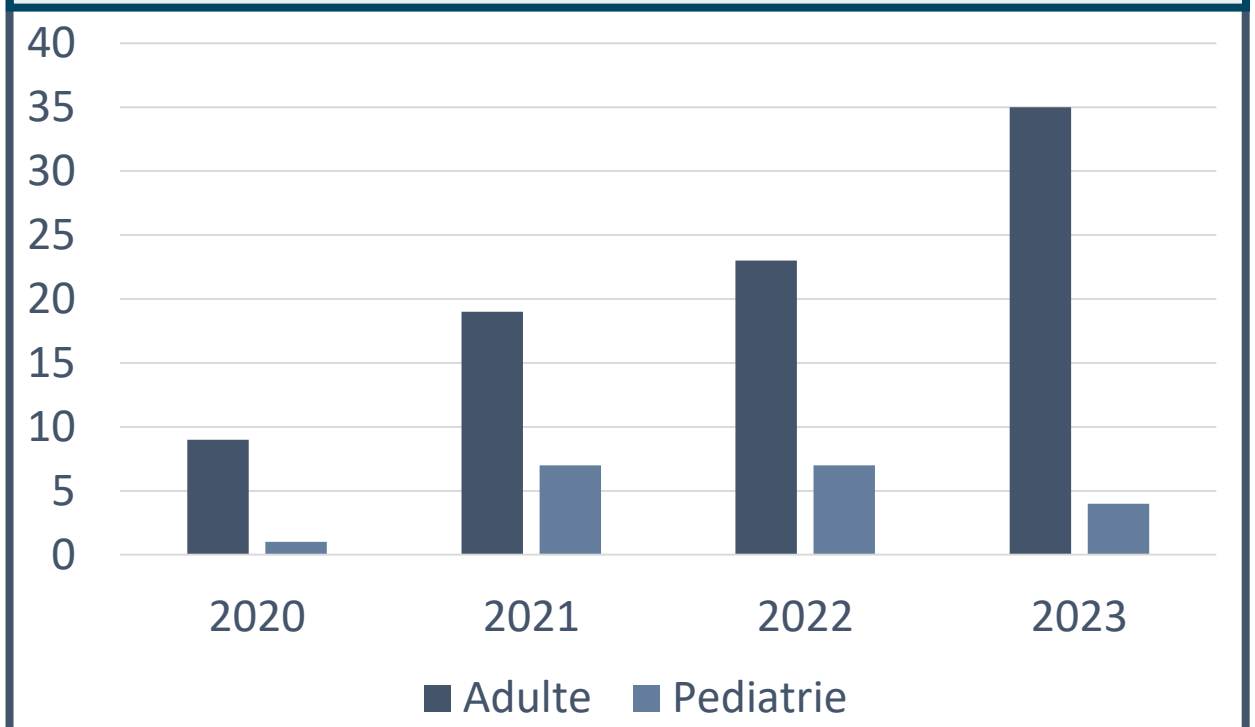
Antoine Uzel, *Olivier Lopez*, *Arthur Gautheron*, *Guillaume Rossignol*, *Xavier Muller*, *Michaël Sdika*, *Bruno Montcel*

Author Affiliations +

UNE DYNAMIQUE D'INNOVATION - PERFUSION

DYNAMIQUE DE PERFUSION +++

SOUTIEN INNOVATION HCL



PHRC Recherche hospitalo- universitaires

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

HOPExt
1,1 M €

INSTITUT D'HÉPATOLOGIE DE LYON

DYNAMIQUE D'INNOVATION

PHRC Recherche hospitalo- universitaires

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

PERFUSION

SOUTIEN HCL

HCL HOSPICES CIVILS DE LYON

HOPE SPLIT

CREATING

Evaluation describes the new intervention in its first live demonstration: what it is, how it works and what the first experience taught us.

AGREEING

Evaluation focuses on defining the **intervention**it's **indications**, and the standards for acceptable **quality of delivery** by collaborative prospective cohort study by multiple groups, including analysis of learning curves.

MONITORING

Evaluation involve**slarge-scale surveillance of outcomes in routine use** of the intervention, looking for trends, and unexpected late or rare effects.

Idea → Development → Exploration → Assessment → Long-term Study

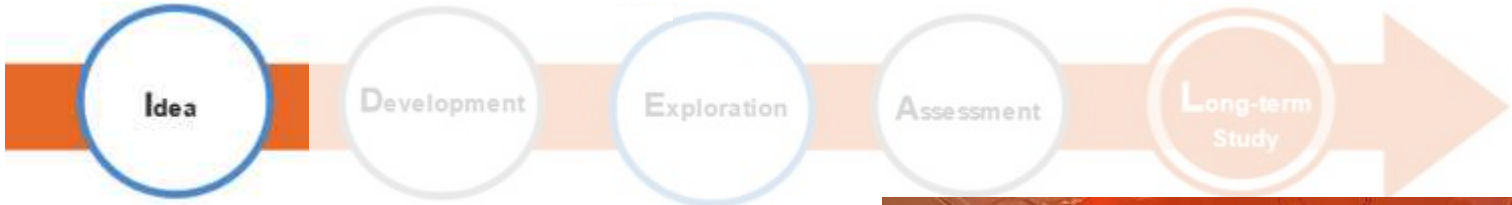
REFINING

Evaluation records the **iterative improvement of the intervention** until it reaches a**stable form**. What was changed, when, why, and with what impact on outcomes?

COMPARING

Evaluation of the intervention against current practiceis now possible, preferably in an RCT. Mechanisms to neutralize effects of any deficit in investigator equipoise are important.

IDEAL FRAMEWORK



Transplantation

Ex Vivo Liver Splitting and Hypothermic Oxygenated Machine Perfusion: Technical Refinements of a Promising Preservation Strategy in Split Liver Transplantation

Jean-Yves Mabrut, MD, PhD,[1,2] Mickaël Lesurtel, MD, PhD,[1,2] Xavier Muller, MD,[1,2] Rémi Dubois, MD,[3] Christian Ducerf, MD, PhD,[1] Guillaume Rossignol, MD,[2,3] and Kayvan Mohkam, MD, PhD[1,2,3]

PEDIATRIC TRANSPLANTATION
The Official Journal of the International Pediatric Transplant Association

CASE REPORT | Full Access

Full left/full right liver graft ex situ split during hypothermic oxygenated perfusion

Guillaume Rossignol, Xavier Muller, Kayvan Mohkam, Remi Dubois, Mickaël Lesurtel, Jean-Yves Mabrut

HEPATOLOGY AASLD

CORRESPONDENCE

Letter to the editor: Is there a place for machine perfusion strategies in pediatric liver transplantation?

Guillaume Rossignol, Xavier Muller, Kayvan Mohkam, Remi Dubois, Jean-Yves Mabrut

First published: 13 January 2022 | https://doi.org/10.1002/hep.32343 | Citations: 2

IDEAL FRAMEWORK

Liver Transplantation

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

ORIGINAL ARTICLE

Liver transplantation of partial grafts after ex-situ splitting during Hypothermic Oxygenated Perfusion – The HOPE-Split Pilot Study

Guillaume Rossignol, Xavier Muller, Valérie Hervieu, Sophie Collardeau-Frachon, Antoine Breton, Natacha Boulanger, Mickaël Lesurtel, Remi Dubois, Kayvan Mohkam, Jean-Yves Mabrut

First published: 18 May 2022 | https://doi.org/10.1002/lt.26507

BRIEF RESEARCH REPORT

Transpl Int, 07 June 2024
https://doi.org/10.3389/ti.2024.12686

HOPE Mitigates Ischemia-Reperfusion Injury in Ex-Situ Split Grafts: A Comparative Study With Living Donation in Pediatric Liver Transplantation

Guillaume Rossignol[1,2,3,4,*†], Xavier Muller[1,2,3], Mathias Ruiz[5], Sophie Collardeau-Frachon[6], Natacha Boulanger[1], Celia Depaulis[7], Teresa Antonini[8], Remi Dubois[4], Kayvan Mohkam[1,2,4] and Jean-Yves Mabrut[1,2,3]

IDEAL FRAMEWORK

HOPE mitigates ischemia-reperfusion injury in ex-situ split grafts:

A comparative study with living donation in pediatric liver transplantation

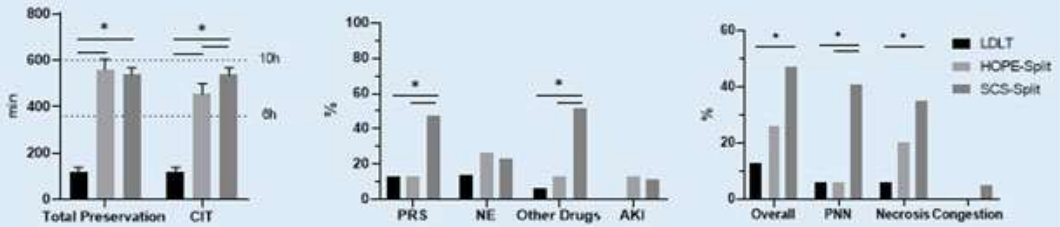
Impact of HOPE on ischemia-reperfusion injury
Ex-situ split grafts – Pediatric liver transplantation

- **HOPE-Split** n=15
- **Static cold Storage split (SCS-Split)** n=17
- **Living donor (LDLT)** n=15

Ischemia Reperfusion Injury
- *Post Reperfusion Syndrome*
- *Reperfusion Biopsy*
- *Preservation time*

Post-operative outcomes

GRAFT PRESERVATION	REPERFUSION	ISCHEMIA REPERFUSION INJURY



HOPE-Split vs SCS-Split

↓ Cold ischemia time
↓ Post reperfusion syndrome
↓ Ischemia reperfusion injury

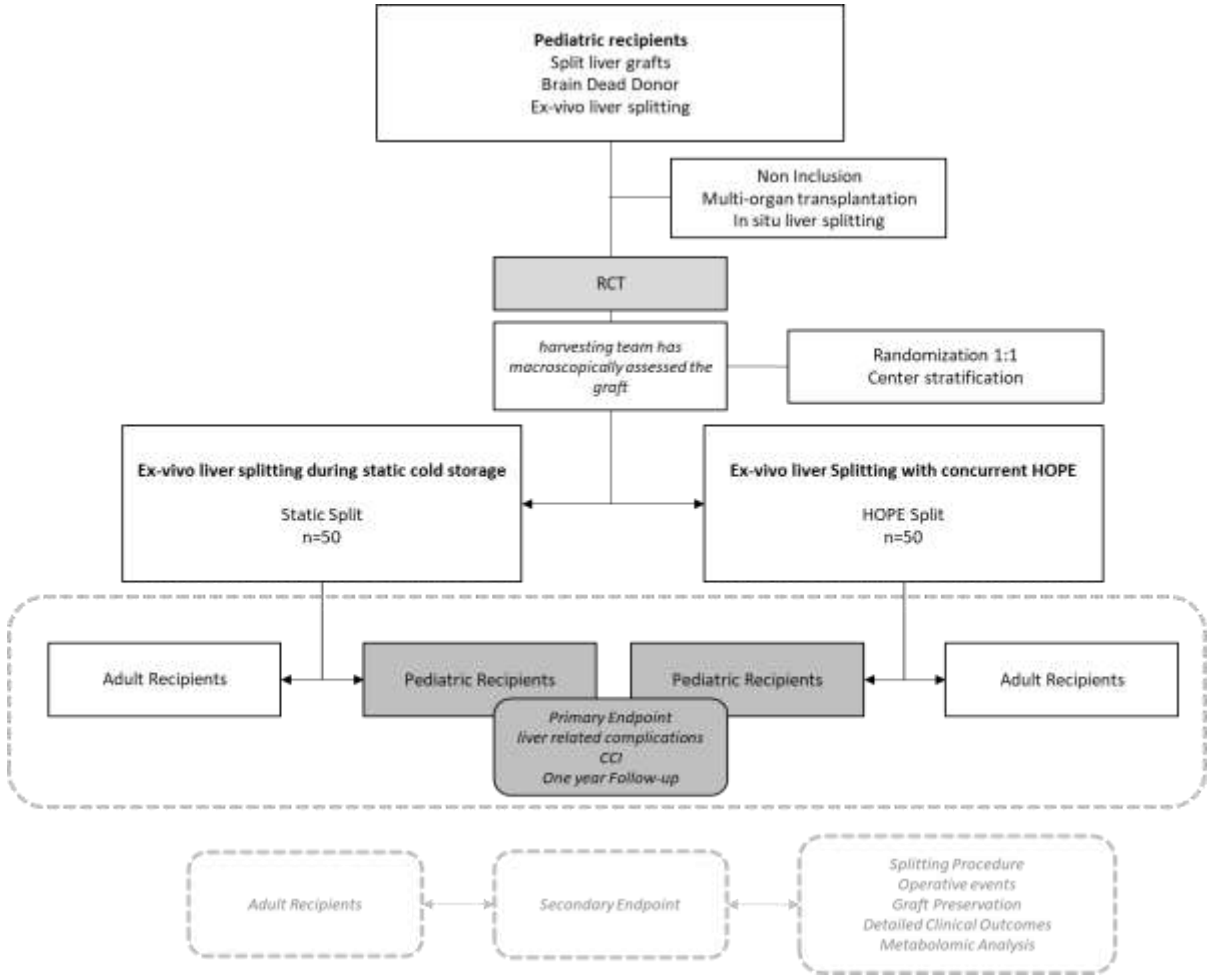
HOPE-Split vs LDLT

↑ Cold ischemia time
≈ Post reperfusion syndrome
≈ Ischemia reperfusion injury

HOPE-Split mitigates early IRI in pediatric recipients in comparison to SCS-Split, resulting in early IRI profiles comparable to LDLT.

Rossignol et al. *Transpl. Int.* 2024
doi: 10.3389/ti.2024.12686

IDEAL FRAMEWORK



PHRC Recherche hospitalo- universitaires

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

HOPE-Split

900 000€

UNE DYNAMIQUE D'INNOVATION

2015

1er Maastricht 3

2020

1er Maastricht 3 Perfusé

2021

1er Perfusion Pédiatrique

2023

1er Donneur Vivant Robot

DONNEUR VIVANT PEDIATRIQUE

HCL HOSPICES CIVILS DE LYON

ROBOT4HPB

1ST INTERNATIONAL CONSENSUS CONFERENCE ON ROBOTIC HEPATO-PANCREATO-BILIARY SURGERY

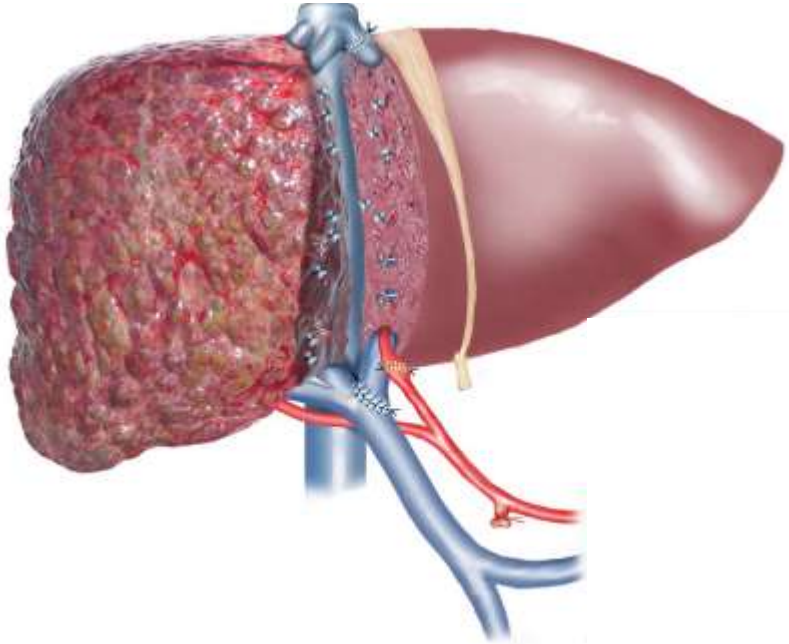
7 - 9 DECEMBER 2023

NOVOTEL PARIS CENTRE TOUR EIFFEL

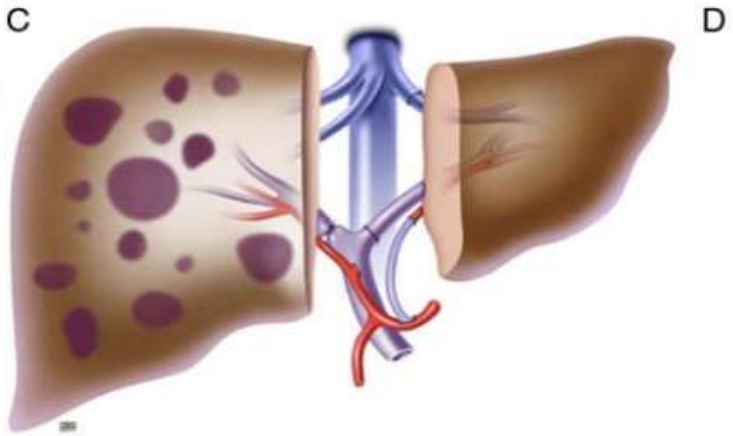
PERSPECTIVES

FOIE PARTIEL

SPLIT / PERFUSION



DV / ROBOTIQUE



HEMODYNAMIQUE

CONCEPT GREFFE AUXILIAIRE RAPID

PERSPECTIVES

FOIE PARTIEL

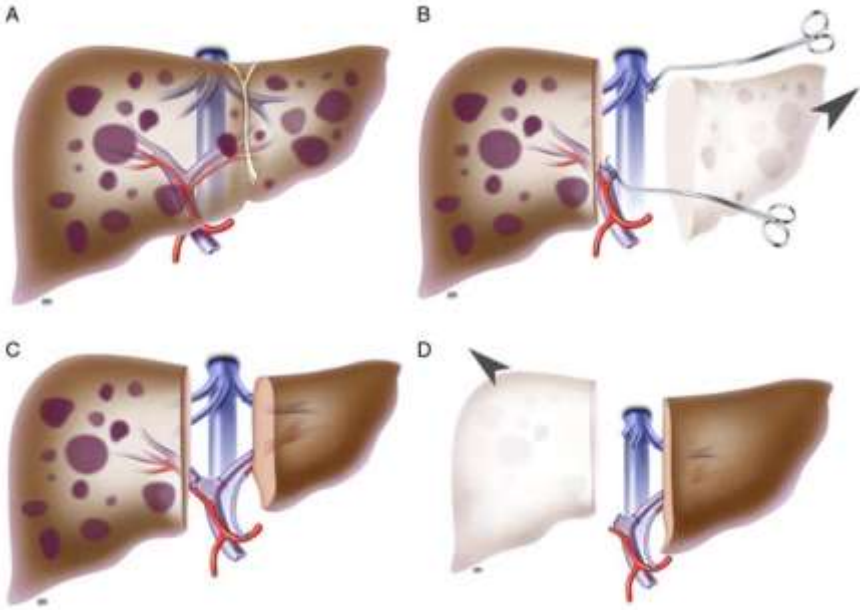
SPLIT / PERFUSION

DV / ROBOTIQUE

HEMODYNAMIQUE

Safety and feasibility of chemotherapy followed by liver transplantation for patients with definitely unresectable colorectal liver metastases: insights from the TransMet randomised clinical trial

René Adam,[a,*] David Badrudin,[a,b] Laurence Chiche,[c] Petru Bucur,[d] Olivier Scatton,[e] Victoire Granger,[f] Michel Ducreux,[g] Umberto Cillo,[h] François Cauchy,[e] Mickael Lesurtel,[i] Jean-Yves Mabrut,[j] Chris Verslype,[j] Laurent Coubeau,[k] Jean Hardwigsen,[l] Emmanuel Boleslawski,[m] Fabrice Muscari,[n] Heithem Jeddou,[o] Denis Pezet,[p] Bruno Heyd,[q] Valerio Lucidi,[r] Karen Geboes,[s] Jan Lerut,[k] Pietro Majno,[t] Lamiae Grimaldi,[e] Nadjia Boukhedouni,[e] Céline Piedvache,[e] Maximiliano Gelli,[g] Francis Levi,[a] and Maité Lewin[a]



ORIGINAL ARTICLE

Auxilliary Liver Transplantation According to the RAPID Procedure in Noncirrhotic Patients

Technical Aspects and Early Outcomes

Utz Settmacher, MD,* Aladdin Ali-Deeb, MD,* Laurent Coubeau, MD,† Umberto Cillo, MD,‡ Pål-Dag Line, MD,§‖ Markus Guba, MD,¶ Silvio Nadalin, MD,# and Falk Rauchfuß, MD*‖

NOUVELLES INDICATIONS TH
Métastases de Cancer Colo-rectal

PERSPECTIVES

XENOTRANSPLANTATION ??

Nature. 2024 Jun;630(8015):18. doi: 10.1038/d41586-024-01613-4.

First pig-to-human liver transplant recipient 'doing very well'

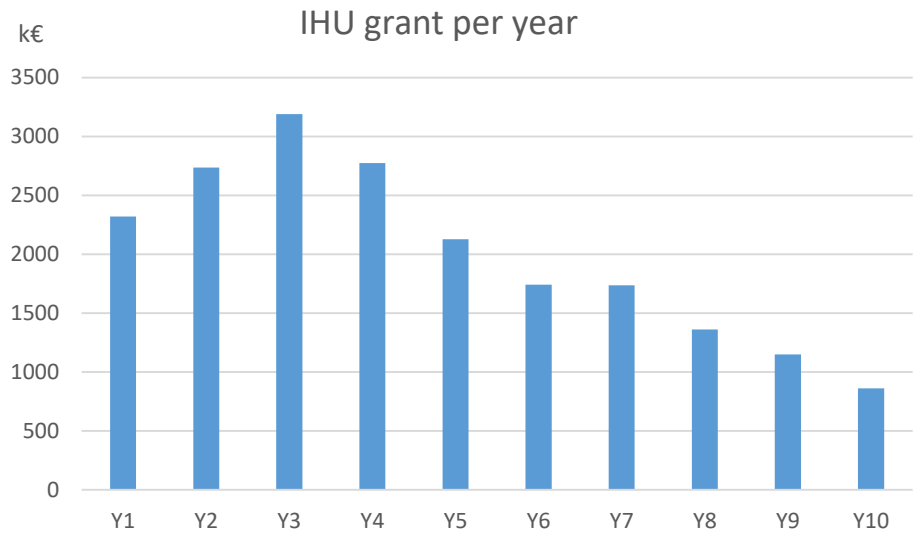
Plan d'action 2024 – 2025 (F. Zoulim)

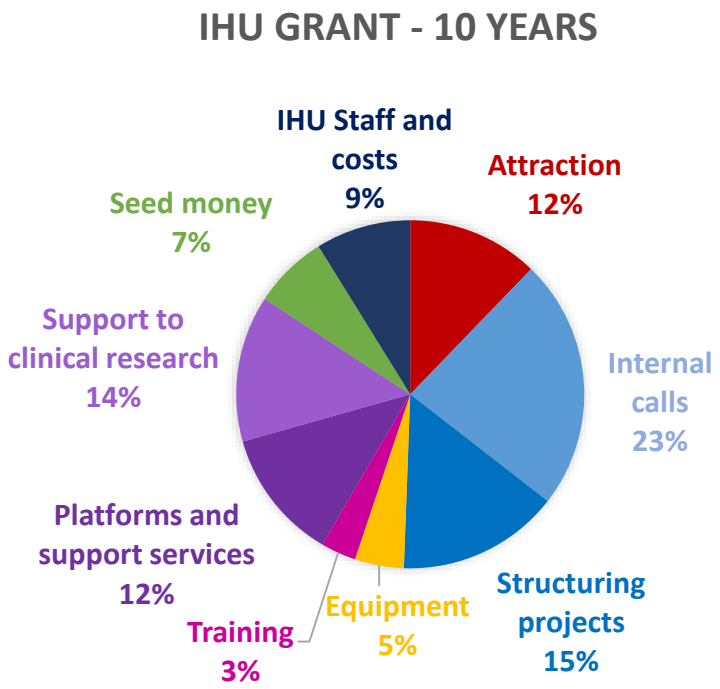
Session

Perspectives de recherche de l' IHU en 2024

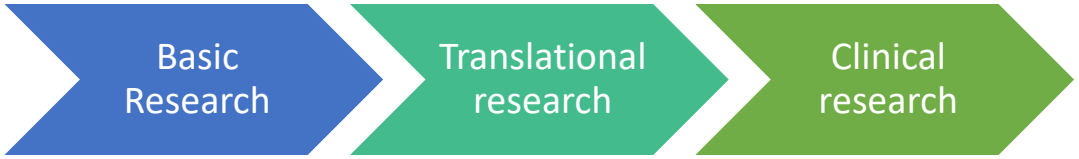
Projection d'utilisation de la dotation ANR IHU

- **10 year budget distribution**





- **5 year budget for research projects**
  - Internal call for proposals : 2.6 M€
  - Top down projects : 1.6 M€
  - Chairs : 2.5 M€



Appel à projets

Call for proposals

- Applications: 3 page template (+ scientific references, + CV and publications of the PI)
- SAB recommendation on a predetermined template
- List of criteria and ranking: innovation, feasibility, scientific quality
- Priority assessment of the project
- Template for scoring and ranking
- Call: summer 2024
- Starting: January 2025

Chair of excellence positions

- Applications to be preselected by the Steering committee
- Selection of the top candidates by the SAB
- Interview with project presentations for final selection

Appel à projets interne

3 942 k€
25% running costs
65% HR

Deux types de projets
- Initiation
- Classique
  avec et sans
  cofinancement

Plafond par projet (à définir)

	Year 1	Year 3	Year 5
	1526 k€	1208 k€	1208 k€
	• 350 k€ running costs • 2 PhD (2 x 3 years) • 2 post-docs (2 x 3 years) • 2 Techs (2 x 3 years) • 2 biostat (2 x 3 years) • 2 x 0.5 CRA (2 x 3 years – half time)	• 350 k€ running costs • 2 PhD (2 x 3 years) • 2 post-docs (2 x 3 years) • 1 Tech (3 years) • 1 biostat (3 years) • 0.5 CRA (3 years – half time)	• 350 k€ running costs • 2 PhD (2 x 3 years) • 2 post-docs (2 x 3 years) • 1 Tech (3 years) • 1 biostat (3 years) • 0.5 CRA (3 years – half time)
For example	4 scientific projects (75 k€ running costs) 2 clinical projects (25 k€ running costs)	4 scientific projects (75 k€ running costs) 1 clinical project (25 k€ running costs)	4 scientific projects (75 k€ running costs) 1 clinical project (25 k€ running costs)

EVEREST – Plan d'action 2024 – 2025

➢ Assurer le déploiement, le ressourcement et la pérennisation de l'IHU

- Appels à projet interne: création de valeur, génération de collaborations, source d'innovation, pluridisciplinarité
- Financements complémentaires
- Partenariats industriels
- Développement de l'IHU sur une logique de cercle vertueux
- Appels à projets cibles pour le déploiement, en capitalisant sur l'effet levier
  - CPJ
  - ERC individuels et synergies
  - Horizon Europe
  - Chaires d'excellence
  - RHU
  - ANR
  - INCa
  - PHRC
  - PHRIP
  - iDemo (national /régional)
- Cellule d'aide aux AO (coordination, relecture, répétition des oraux, etc.). Coordination G. Mithieux

EVEREST – Evènements locorégionaux 2025

- **Journée annuelle de l'IHU** (en continuité de la journée d'hépatologie)
  - 1 jour recherche fondamentale
  - 1 jour recherche translationnelle et clinique
  - Le soir entre les 2 = AG de l'IHU

- **Séminaires mensuels**
  - Alternativement recherche fondamentale / recherche translationnelle
  - Intervenants externes et internes à l'IHU
  - En présentiel et en visioconférence

- **Séminaire dédié au paramédical**

EVEREST – Evènements internationaux 2025

- **Workshop HBV Cure** (avec l'ANRS)

- **Symposium Falk Foundation: Experimental Hepatology Days (24 – 26 Avril 2025 à Lyon)**

- **EASL (7 au 10 mai 2025 – Amsterdam)**

TABLE RONDE