Perfusion hépatique ex vivo
Perspectives en France

O Scatton

Service de Chirurgie Hépatobiliaire et transplantation hépatique
Hôpital Pitié-Salpêtrière
FRANCE

La perfusion ex-vivo des greffons hépatiques : État des lieux

Hypothermie

- **4°C, logistique simple**
- Seule ou avant normothermie
- **Protection mitochondriale**, restockage ATP
- Prévention de la non-fonction primaire et de la cholangite ischémique


The NEW ENGLAND JOURNAL of MEDICINE

Hypothermic Machine Perfusion in Liver Transplantation — A Randomized Trial

Rianne van Rijn, M.D., Ph.D., Ivo J. Schurink, B.Sc., Yvonne de Vries, M.D., Ph.D., Aad P. van den Berg, M.D., Ph.D., Miriam Cortes Cerisuelo, M.D., Ph.D., Sarwa Darwish Murad, M.D., Ph.D., Joris I. Erdmann, M.D, Ph.D., Nicholas Gilbo, M.D., Ph.D., Robbert J. de Haas, M.D., Ph.D., Nigel Heaton, M.D., Ph.D., Bart van Hoek, M.D., Ph.D., Volkert A.L. Huurman, M.D., Ph.D., et al., for the DHOPE-DCD Trial Investigators*

N=78 vs 78, greffons de **donneurs en arrêt cardiaque** (à risque)
Sténoses biliaires non anastomotiques : **6% vs 18%** (p=0.03)
Sd reperfusion : 12% vs 27%
Dysfonction précoce : 26% vs 40%

Validée en clinique pour les greffons à risque (marginaux) : DDAC ++

Normothermie

- Conditions physiologiques : **métabolisme à 37°**
- Nécessité d'un **transporteur d'O2** (sang/Hb de synthèse)
- Test de viabilité en temps réel
- Permet interventions pharmacologiques (corrections metaboliques, défatting)


nature

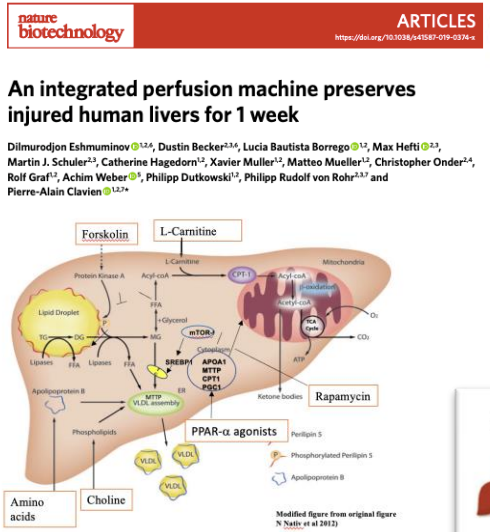
A randomized trial of normothermic preservation in liver transplantation

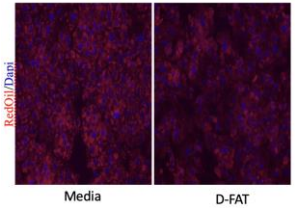
David Nasralla[1]*, Constantin C. Coussios[2]*, Hynek Mergental[3], M. Zeeshan Akhtar[4,5], Andrew J. Butler[3,6], Carlo D. L. Ceresa[1], Virginia Chiocchia[3,7], Susan J. Dutton[8], Juan Carlos García-Valdecasas[9], Nigel Heaton[10], Charles Imber[11], Wayel Jassem[12], Ina Jochmans[13,14], John Karani[10,14], Simon R. Knight[15,16], Peri Kocabayoglu[16], Massimo Malago[11], Darius Mirza[3], Peter J. Morris[3,17], Arvind Pallan[18], Andreas Paul[19], Mihai Pavel[8], M. Thamara P. R. Perera[4], Jacques Pirenne[13,14], Reena Ravikumar[3], Leslie Russell[10], Sara Upponi[10], Chris J. E. Watson[3,20], Annemarie Weissenbacher[3], Rutger J. Ploeg[8], Peter J. Friend[4]* for the Consortium for Organ Preservation in Europe

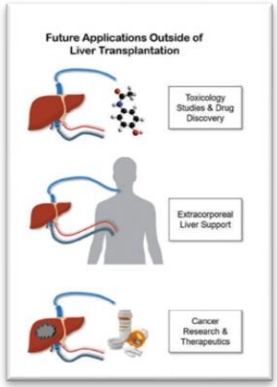
N=170 vs 164, tous greffons dont en arrêt cardiaque
Transaminases J7 moins élevées après perfusion
Refus greffe après évaluation ultime diminué: 11.7% vs 24.1%
Complications et survie comparables

Faisable pour évaluer la viabilité des greffons très marginaux (stéatose ++)

La perfusion ex-vivo des greffons hépatiques : Perspectives







Futur proche :

- Délai supplémentaire de gestion de greffon
- Testing métabolique à 37°

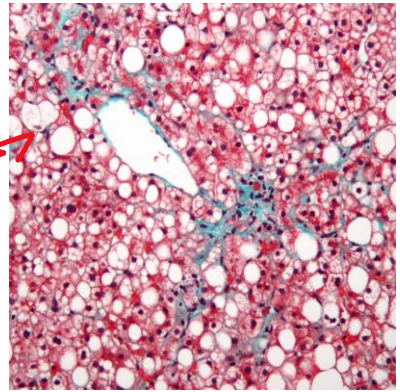
En cours d'évaluation :
Cocktails défattants

An effective defatting cocktail to reduce liver graft steatosis before transplantation. **L Aoudjehane, et al.(Sorbonne U, PSL)** – *Dis. Mod & Mech 2020*

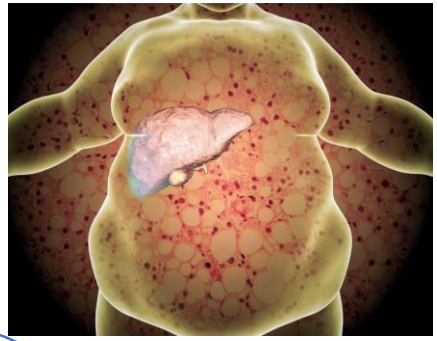
A plus long terme :

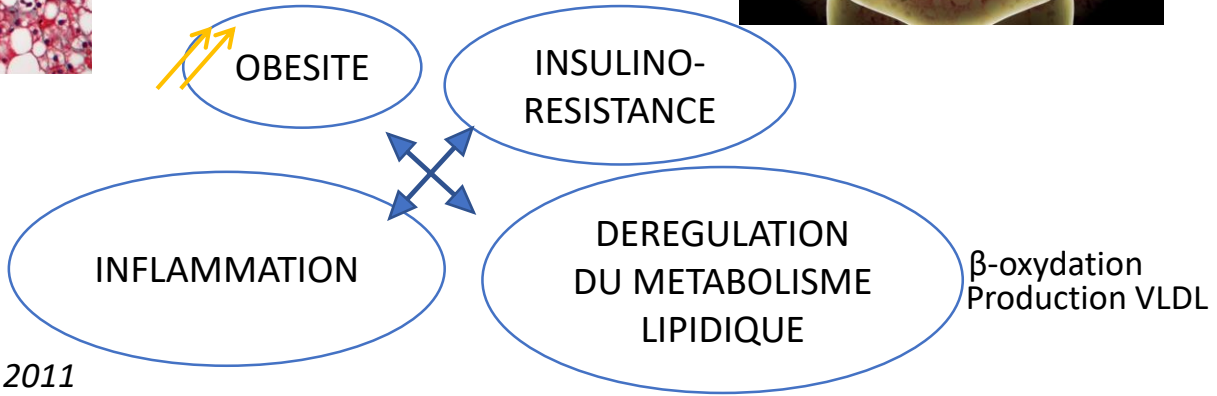
- Support hépatique ex-vivo
- Plateforme de recherche thérapeutique in vivo

Greffons stéatosiques



STEATOSE HEPATIQUE

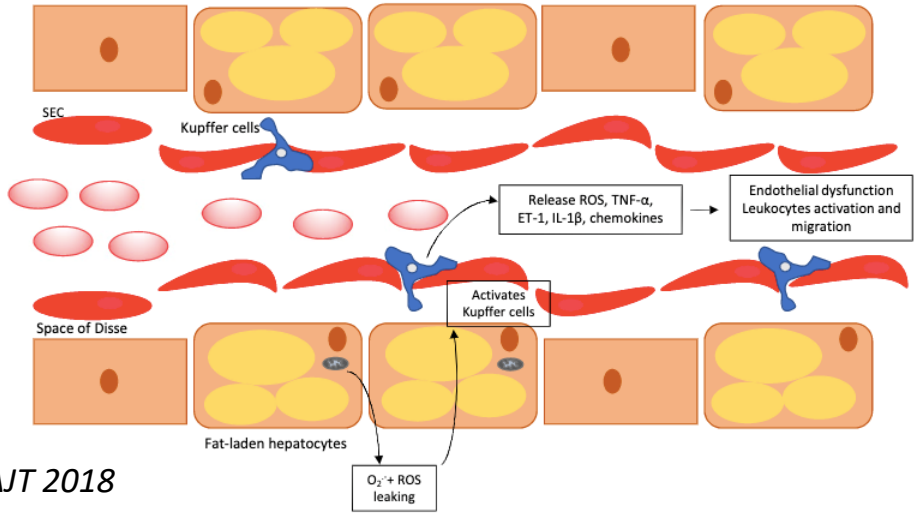




Cohen et al, Nature 2011

Principal motif de refus de greffons hépatiques en France
130-150 greffons par an

Greffons stéatosiques en conservation statique
De l'huile à la motte de beurre…



Boteon et al., AJT 2018

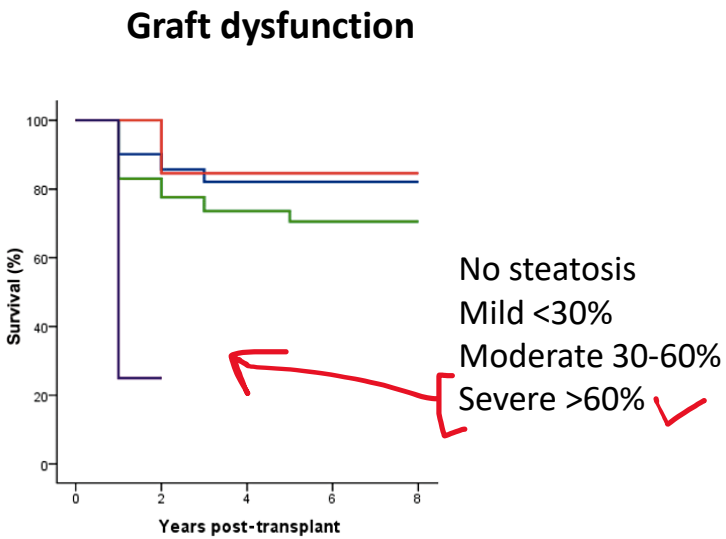
1. **Metabolisme mitochondrial** altéré – stocks d'ATP bas - production ROS
2. **Microcirculation altérée** : réduction spatiale dans les sinusoïdes
3. **Micro-environnement pro-inflammatoire**

DeGraaf, J Gastroenterol Hepatol 2012

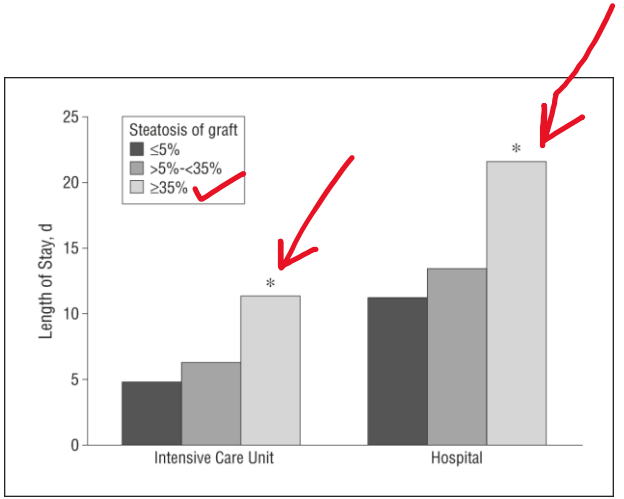
Seuil de tolérance à l'ischémie reperfusion : bas ++

Greffons stéatosiques

Stéatose > 30% : transplantation à haut risque



DeGraaf, J Gastroenterol Hepatol 2012



Doyle et al. Arch Surg 2010

Principes de la perfusion hépatique

Métabolisme anaérobie 10%

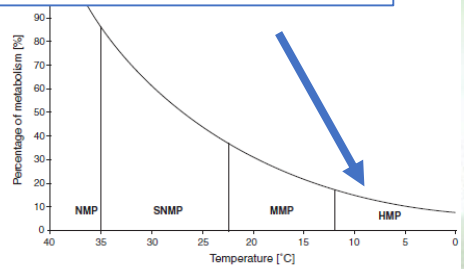
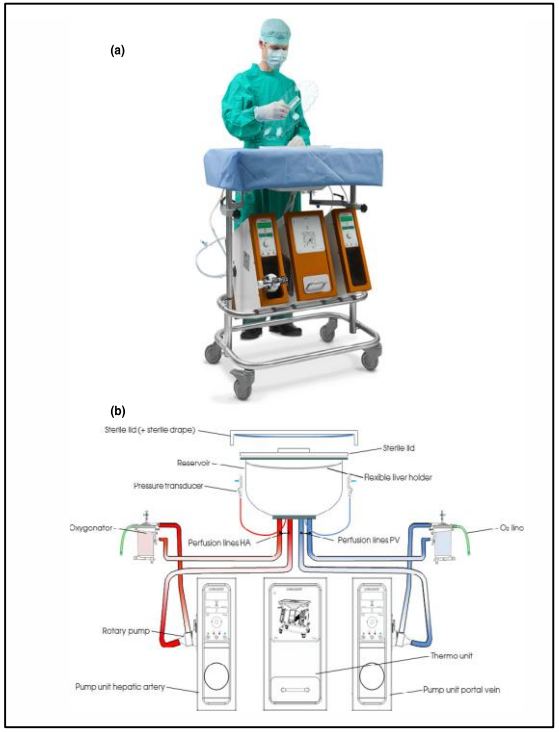


Figure 3: Graphic presentation of the change in the rate of metabolism with decreasing temperature. Based on Van't Hoff's principle (expressed as $Q_{10} = (k_2/k_1)^{10/(t_2-t_1)}$), this graph demonstrates the significantly reduced metabolism at hypothermic temperatures (0°C–12°C). The vertical lines in the graphs indicate the lower endpoint of temperature ranges of the different types of MP proposed. NMP; normothermic machine perfusion (35°C–38°C); SMP, subnormothermic machine perfusion (25°C–34°C); MMP, mid-thermic machine perfusion (13°C–24°C); HMP, hypothermic machine perfusion (0°C–12°C).

D'après Karangswa AJT 2016



Apport dynanique d'oxygène

PLUSIEURS POSSIBILITÉS

Perfusion hypothermique

- En perfusion isolée ou avant normothermie
- Prévention de la non-fonction primaire et de la **cholangite ischémique**

Perfusion normothermique

- Métabolisme en conditions physiologiques
- Permet d'évaluer la viabilité de l'organe en temps réel
- Permet des interventions pharmacologiques dynamiques (corrections métaboliques, défatting…)

Marecki et al Liver transplantation 2017
Schlegel et al, Curr Op Org Transplant 2017

Hypothermie seule améliore mais ne corrige pas « Booster » la mitochondrie en ATP

Hypothermic oxygenated perfusion (HOPE) for fatty liver grafts in rats and humans

Philipp Kron[†], Andrea Schlegel[†], Leandro Mancina, Pierre-Alain Clavien, Philipp Dutkowski[*]

Department of Surgery & Transplantation, University Hospital Zurich, Switzerland

Table 1. Transplantation of matched (donor & recipient age, preservation time) human liver grafts with severe macrosteatosis with and without HOPE Perfusion.

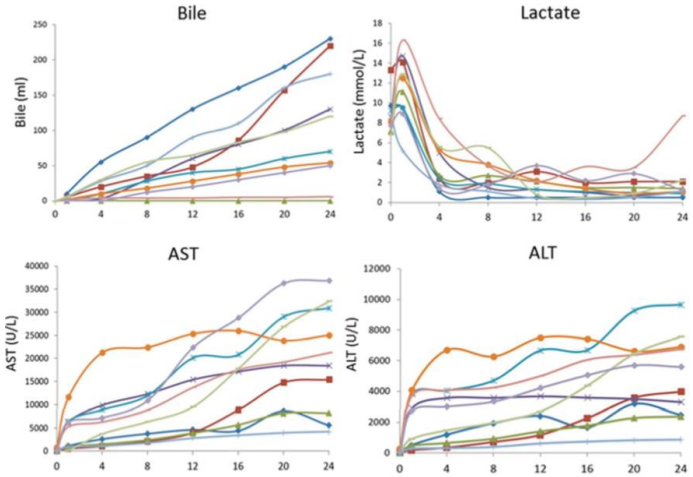
	Donor					Preservation		Recipient		Outcome					
	Age (yr)	Total WI (min)	Functional WI (min)	Asyst. WI (min)	Steatosis macro/micro (%)	HOPE (h)	Total cold preservation (h)	Age (y)	Lab MELD	AUC ALT (U/L)	RRT (y/n)	ICU stay (days)	PNF (y/n)	Re-transplant (y/n)	1-year patient survival (y/n)
Steatosis + CS + HOPE (with/without additional warm ischemia [DCD, n = 6])															
1	66	-	-	-	40/90	4.0	9	56	16	5,304	0	4	0	0	Yes
2	86	41	38	17	20/70	4.8	7.3	53	10	9,131	0	2	0	0	Yes
3	63	41	40	21	30/30	1.8	7	53	13	7,851	0	2	0	0	Yes
4	55	36	22	16	30/50	2.0	4.5	59	6	3,453	0	6	0	0	Yes
5	64	43	41	17	20/30	1.8	5	50	6	2,687	Yes	5	0	0	Yes
6	73	40	37	21	30/30	2.6	7.1	60	12	8,470	0	2	0	0	Yes
Median	65	41	38	17	30/40	2.3	7	55	11	6,578	17%	3	0	0	100%
Steatosis + CS (n = 12)															
1	59	-	-	-	40/30	-	6.8	73	25	3,043	Yes	40	0	0	yes
2	55	-	-	-	60/50	-	9.0	45	12	19,140	0	6	0	0	yes
3	68	-	-	-	30/30	-	6.1	63	8	5,913	Yes	49	0	0	0
4	58	-	-	-	30/30	-	6.8	61	6	16,061	0	5	0	0	0
5	54	-	-	-	20/80	-	7.1	55	30	8,001	Yes	84	Yes	0	0
6	70	-	-	-	20/10	-	6.2	55	7	22,433	0	1	0	0	Yes
7	62	-	-	-	50/30	-	7.3	53	21	20,307	Yes	20	0	0	0
8	66	-	-	-	30/40	-	7.0	53	23	11,163	Yes	10	0	Yes	0
9	60	-	-	-	40/40	-	7.1	62	34	39,822	Yes	2	Yes	0	0
10	59	-	-	-	25/10	-	8.9	48	28	15,262	Yes	57	Yes	Yes	0
11	69	-	-	-	40/20	-	7.4	53	18	3,629	Yes	6	0	0	Yes
12	54	-	-	-	40/20	-	7.0	42	14	48,587	Yes	56	0	Yes	Yes
Median	59	-	-	-	35/30	-	7	54	19	15,662	75%	15	25%	25%	42%
	0.17	-	-	-	0.06/0.16	-	0.73	1	0.07	0.04	0.04	0.03	0.5	0.5	0.04

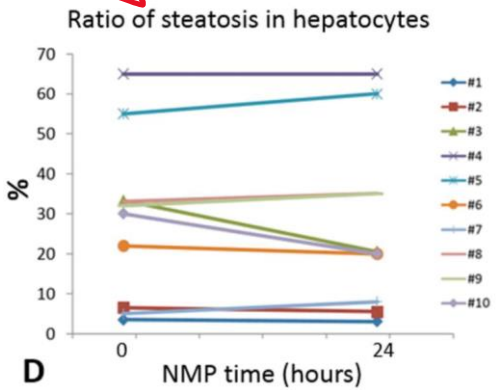
AUC, area under curve during seven days after OLT. ALT, alanine aminotransferase; CS, cold storage; HOPE, hypothermic oxygenated perfusion; ICU, intensive care unit; MELD, model for end-stage liver disease; OLT, orthotopic liver transplantation; PNF, acute graft failure; RRT, renal replacement therapy; WI, warm ischemia.

1. **Metabolisme mitochondrial** altéré – stocks d'ATP bas - production ROS
2. **Microcirculation altérée** : réduction spatiale dans les sinusoïdes
3. **Micro-environnement pro-inflammatoire**

J Hepatol 2017

Normothermie seule améliore et teste la viabilité… mais ne diminue pas la stéatose : sélection ?





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Liver Transpl. 2018 Feb;24(2):233-245. doi: 10.1002/lt.24972.

Lipid metabolism and functional assessment of discarded human livers with steatosis undergoing 24 hours of normothermic machine perfusion.

Liu Q[1], Nassar A[1], Buccini L[1], Iuppa G[1], Soliman B[1], Pezzati D[1], Hassan A[1], Blum M[1], Baldwin W[1], Bennett A[1], Chavin K[2], Okamoto T[1], Uso TD[1], Fung J[1], Abu-Elmagd K[1], Miller C[1], Quintini C[1].

WILEY LIVER TRANSPLANTATION
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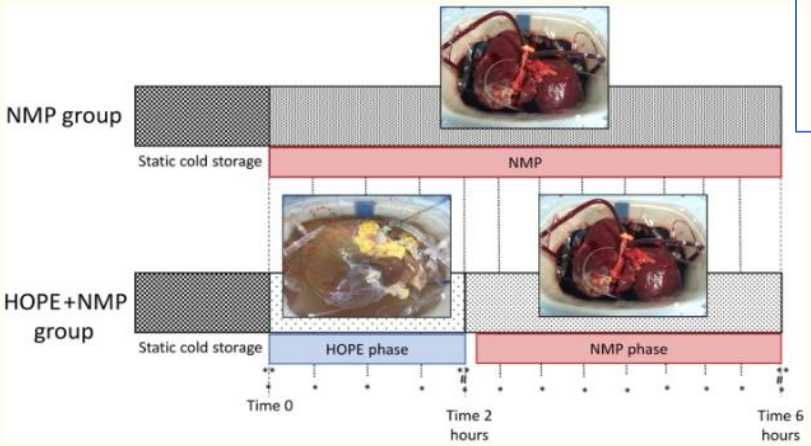
Liver Transpl. 2018 Dec; 24(12): 1699–1715. PMCID: PMC6588092
Published online 2018 Dec 4. doi: 10.1002/lt.25315 PMID: 30058119

Combined Hypothermic and Normothermic Machine Perfusion Improves Functional Recovery of Extended Criteria Donor Livers

Yuri L. Boteon, [1,3] Richard W. Laing, [1,3,†] Andrea Schlegel, [1,†] Lorraine Wallace, [3] Amanda Smith, [1] Joseph Attard, [1] Ricky H. Bhogal, [1,3] Desley A. H. Neil, [2] Stefan Hübscher, [2] M. Thamara P. R. Perera, [1] Darius F. Mirza, [1,3] Simon C. Afford, [3,†] and Hynek Mergental [1,3,†]



10 discarded livers
6h NMP vs 2h HOPE+4h NMP

ESA Paper

Transplantation of High-risk Donor Livers After Ex Situ Resuscitation and Assessment Using Combined Hypo- and Normothermic Machine Perfusion

A Prospective Clinical Trial

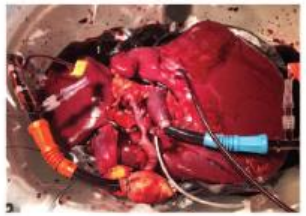
Otto B. van Leeuwen, BSc,* Yvonne de Vries, MD,* Masato Fujiyoshi, MD, PhD,* Maarten W. N. Nijsten, MD, PhD,† Rinse Ubbink, MSc,‡ Gert Jan Pelgrim, PhD,‡ Maureen J. M. Werner, MD,* Koen M. E. M. Reyntjens, MD,§ Aad P. van den Berg, MD, PhD,‖ Marieke T. de Boer, MD, PhD,* Ruben H. J. de Kleine, MD,* Ton Lisman, PhD,¶ Vincent E. de Meijer, MD, PhD,* and Robert J. Porte, MD, PhD*¶

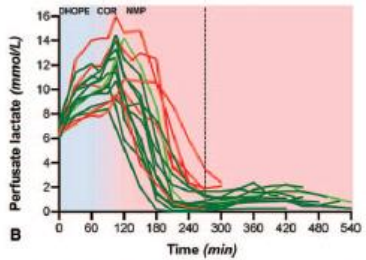
Hypo
puis
normo

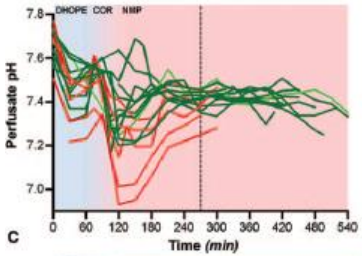
49 propo

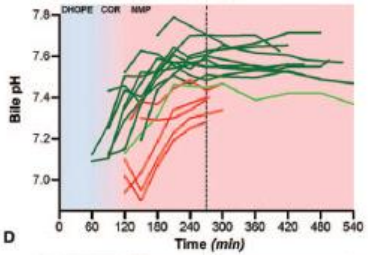
↓

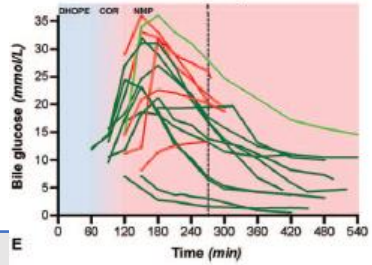
11 TH

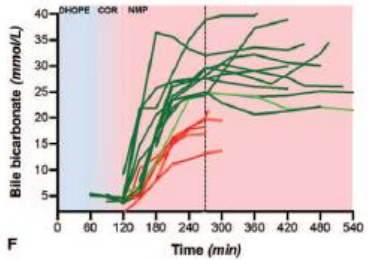








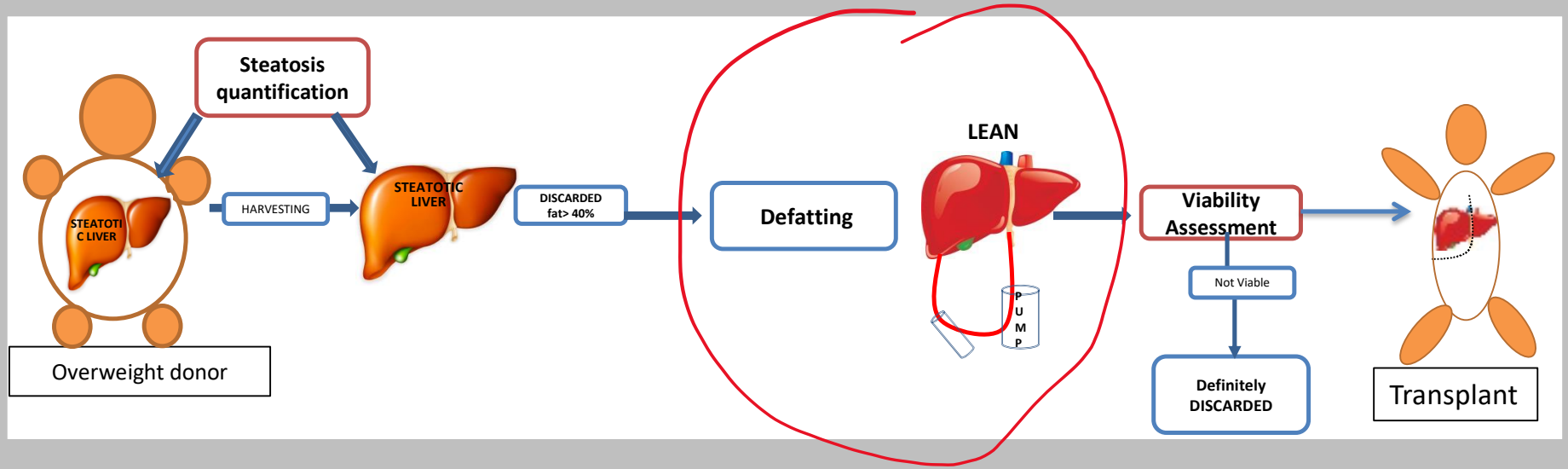




Viability criteria after 150 min	
Perfusate lactate	<1.7 mmol/L
Perfusate pH	7.35-7.45
Bile production (cumulative)	>10 mL
Bile pH*	>7.45*
Difference between perfusate glucose and bile glucose	>10 mmol/L

Objectives in Pitié-Salpêtrière

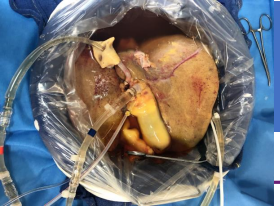
Innovative strategies to rescue discarded fatty livers



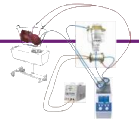
Atteindre ces objectifs…

Créer une machine capable
. De passer de Hypo à la normothermie
. Stratégie de perfusion
NORMOPERF…GRAFFITI
UTC-Sorbonne/SATT LUTECH/LIVANOVA

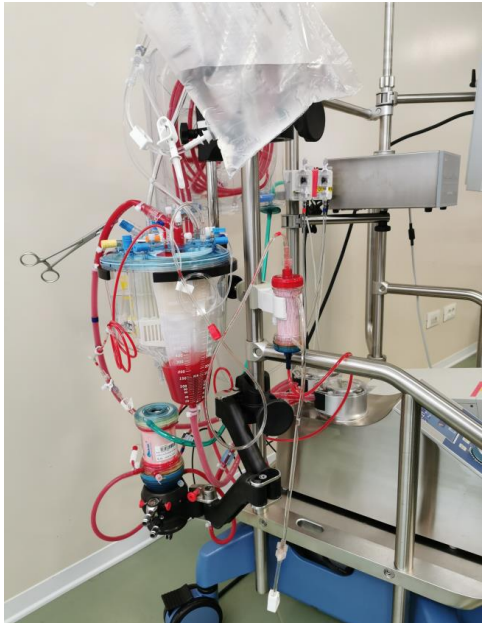
Créer Cocktail « défattant »
D-FAT - RAPAPERF – RIPA56
UMRS-ICAN
AGEPS
ANR/SATT LUTECH/



Quelle machine pour quoi faire ?



	OrganOx	Organ Assist	TransMedics	Graffiti - LvNa
Hypothermic		▯		▯
Normothermic	▯	▯	▯	▯
Sub-Normo				▯
Reservoir	▯		▯	▯
Gas, Psi, flow monitoring	▯	▯ *No gas*	▯	▯
Arterial Filter	▯		▯	▯
Infusion of meds/ nutrients	▯			▯
OR staff set up / simple				▯
Intuitive operating system				▯
LT Perfusion performance				▯
Cost Effective		▯		▯
Portable for >8hr transport	▯		▯	



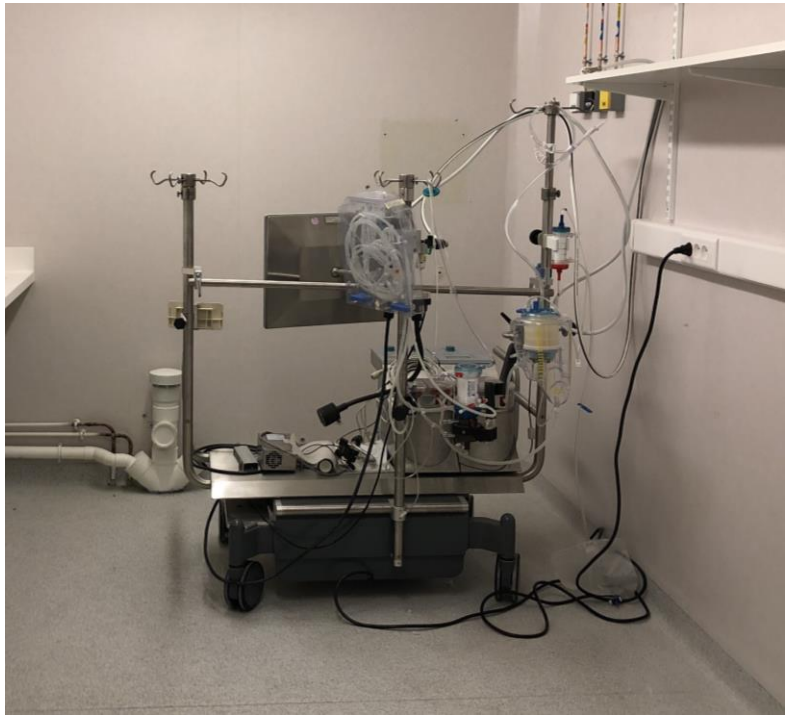
https://doi.org/10.1016/j.hpb.2020.04.001 HPB

Cold-to-warm machine perfusion of the liver: a novel circuit for an uninterrupted combined perfusion protocol

C. Goumard[1], E. Savier[1], J. Danion[1], J. Pellissier[2], Cécile Legallais[3] & O. Scatton[1]

[1]Sorbonne Université, INSERM Centre de Recherche Saint Antoine UMR S-938, Department of Hepatobiliary Surgery and Liver Transplantation, [2]Department of Extracorporeal Perfusion and Vascular Surgery, Hôpital Pitié-Salpêtrière, Assistance Publique-Hopitaux de Paris, and [3]Technological University of Compiegne (UTC), UMR CNRS 7338 Biomechanics and Bioengineering, Compiègne, France

LE CIRCUIT : PROJET *NORMOPERF*

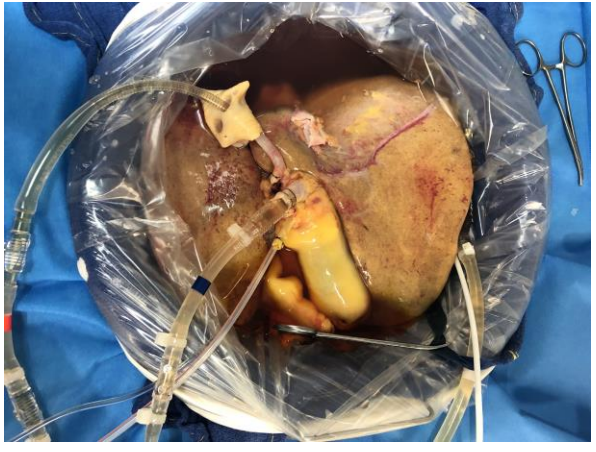


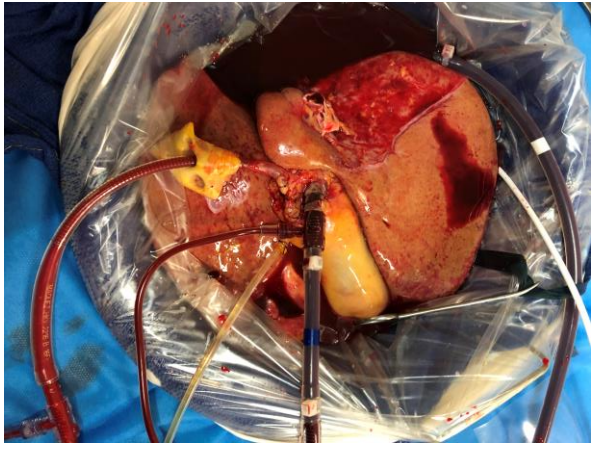
UTC –Sorbonne

SATT LUTECH

LivaNova
Health innovation that matters

LE CIRCUIT : PROJET *NORMOPERF*





Defatting pharmacologique?

Journal of *Clinical Medicine*

MDPI

Review

Ex-Vivo Pharmacological Defatting of the Liver: A Review

EX VIVO Machine…

Claire Goumard [1,2,*], Célia Turco [1,2], Mehdi Sakka [3], Lynda Aoudjehane [2], Philippe Lesnik [4], Eric Savier [1,2], Filomena Conti [2] and Olivier Scatton [1,2]

	Model	*n*	Defatting Agents	Main Outcomes
Yarmush et al., 2015 [21]	HepG2 cells	3	combination of visfatin, forskolin, hypericin and nuclear receptor ligands (GW7, GW5, scoparone)	decrease of TG content
Boteon et al., 2018 [23]	human hepatocytes from discarded donor livers HIEC, cholangiocytes	4	combination of visfatin, forskolin, hypericin, L-carnithine, PPARα ligand and nuclear receptor ligands (GW7, GW5, scoparone)	reduction of intracellular TG induction of fatty acids β-oxidation
Aoudjehane et al., 2020 [24]	human hepatocytes from fatty livers	6	forskolin, L-carnitine and PPARα agonist	reduction of intracellular TG
Madji et al., 2020 [20]	mice livers human steatotic hepatocytes	10 10	RIPA-56	decrease of intracelliular lipid droplets and TG content decreased inflammation and liver injury

AMP: cyclic adenosine monophosphate; TG: triglycerides; HIEC: human intra-hepatic endothelial cells.

IN VITRO

Table 2. Drugs used in experimental models for ex-vivo defatting of steatotic livers.

	Model	*n*	Perfusion	Length of Perfusion (hours)	Defatting Agents	Main Outcomes
Nagrath et al., 2009 [18]	rat	7	NMP	3	combination of visfatin, forskolin, hypericin and nuclear receptor ligands (GW7, GW5, scoparone)	decrease of TG rate improvement of bile production
Liu et al., 2013 [25]	rat	NA	SNMP	6	combination of amino acids, visfatin, forskolin, hypericin and nuclear receptor ligands (GW7, GW5, scoparone)	higher rate of TG (non significance)
Raigani et al., 2020 [26]	rat	6	NMP	6	combination of amino acids, visfatin, forskolin, hypericin and nuclear receptor ligands (GW7, GW5, scoparone)	decrease of pro inflammatory markers (NF-κB, TNF-α, IL-6) decrease of pro-apoptotic markers (CASP3, CD95) decrease of combined VLDL/LDL level
Taba Taba Vakili et al., 2016 [27]	mice	4	NMP	4	glial cell line–derived neurotrophic factor	reduction of TG content in liver no liver damage (no increase of apoptosis)
Banan et al., 2016 [31]	human discarded livers	2	NMP	8	L-carnithine and exendin-4	decrease of TG and LDL level in the perfusate reduction of Mas
Boteon et al., 2019 [32]	human livers discarded	5	NMP	12	combination of L-carnithine, visfatin, forskolin, hypericin and nuclear receptor ligands (GW7, GW5, scoparone)	decrease of T-TG level decrease of MaS increase of P-TG level higher bile production

LDL: low-density lipoprotein; MaS: macrovesicular steatosis; NMP: normothermic perfusion; P-TG: SNMP: subnormothermic perfusion; TG: triglycerides; T:TG: tissue-TG; VLDL: very low-density lipoprotein.

DEFATTING : D-FAT Cocktail

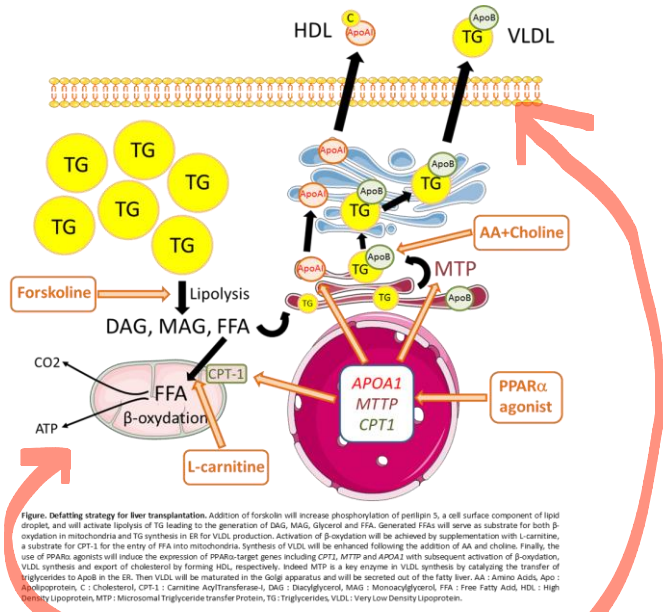
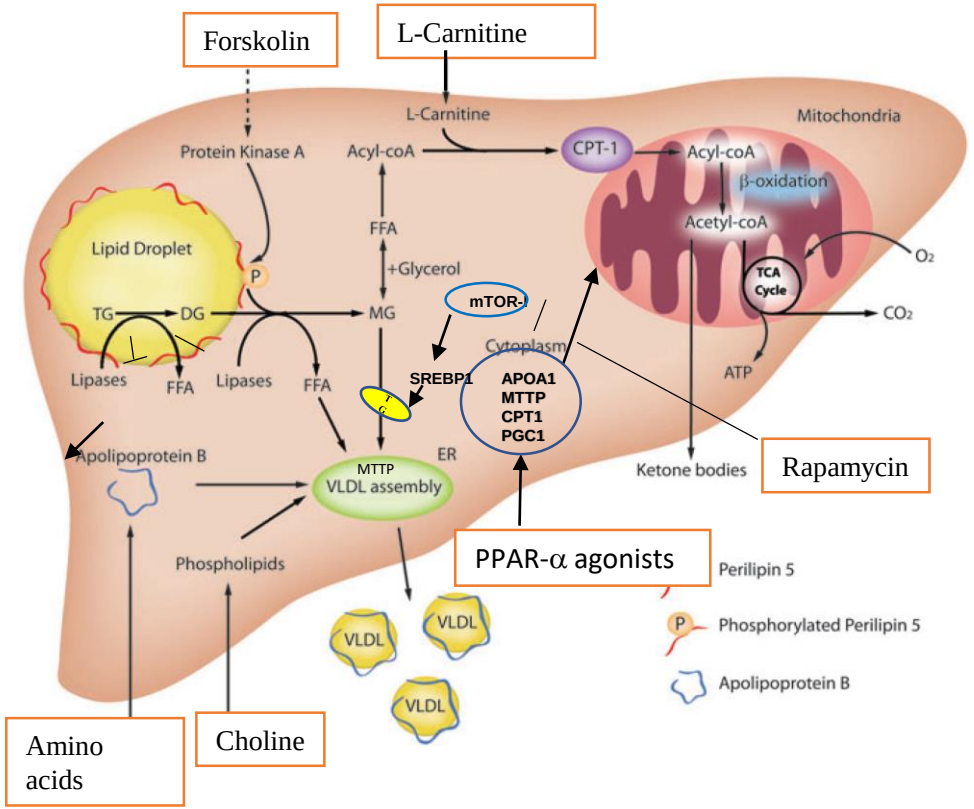


Figure. Defatting strategy for liver transplantation. Addition of forskolin will increase phosphorylation of perilipin 5, a cell surface component of lipid droplet, and will activate lipolysis of TG leading to the generation of DAG, MAG, Glycerol and FFA. Generated FFAs will serve as substrate for both β-oxydation in mitochondria and TG synthesis in ER for VLDL production. Activation of β-oxydation will be achieved by supplementation with L-carnitine, a substrate for CPT-1 for the entry of FFA into mitochondria. Synthesis of VLDL will be enhanced following the addition of AA and choline. Finally, the use of PPARα agonists will induce the expression of PPARα-target genes including *CPT1, MTTP* and *APOA1* with subsequent activation of β-oxydation, VLDL synthesis and export of cholesterol by forming HDL, respectively. Indeed MTP is a key enzyme in VLDL synthesis by catalyzing the transfer of triglycerides to ApoB in the ER. Then VLDL will be maturated in the Golgi apparatus and will be secreted out of the fatty liver. AA : Amino Acids, Apo : Apolipoprotein, C : Cholesterol, CPT-1 : Carnitine AcylTransferase-I, DAG : Diacylglycerol, MAG : Monoacylglycerol, FFA : Free Fatty Acid, HDL : High Density Lipoprotein, MTP : Microsomal Triglyceride transfer Protein, TG : Triglycerides, VLDL : Very Low Density Lipoprotein.

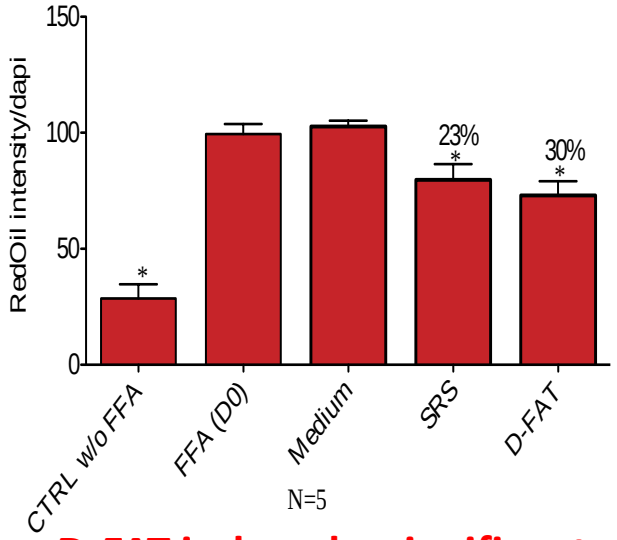
B oxydation

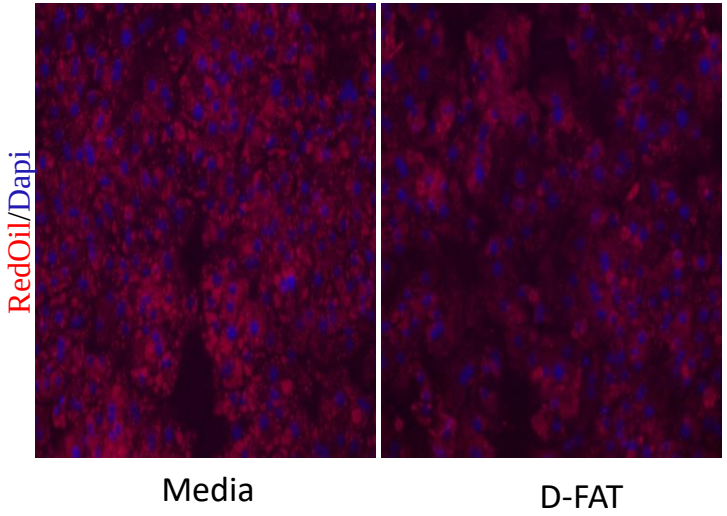
Export



Modified figure from original figure N Nativ et al 2012

Defatting – in vitro



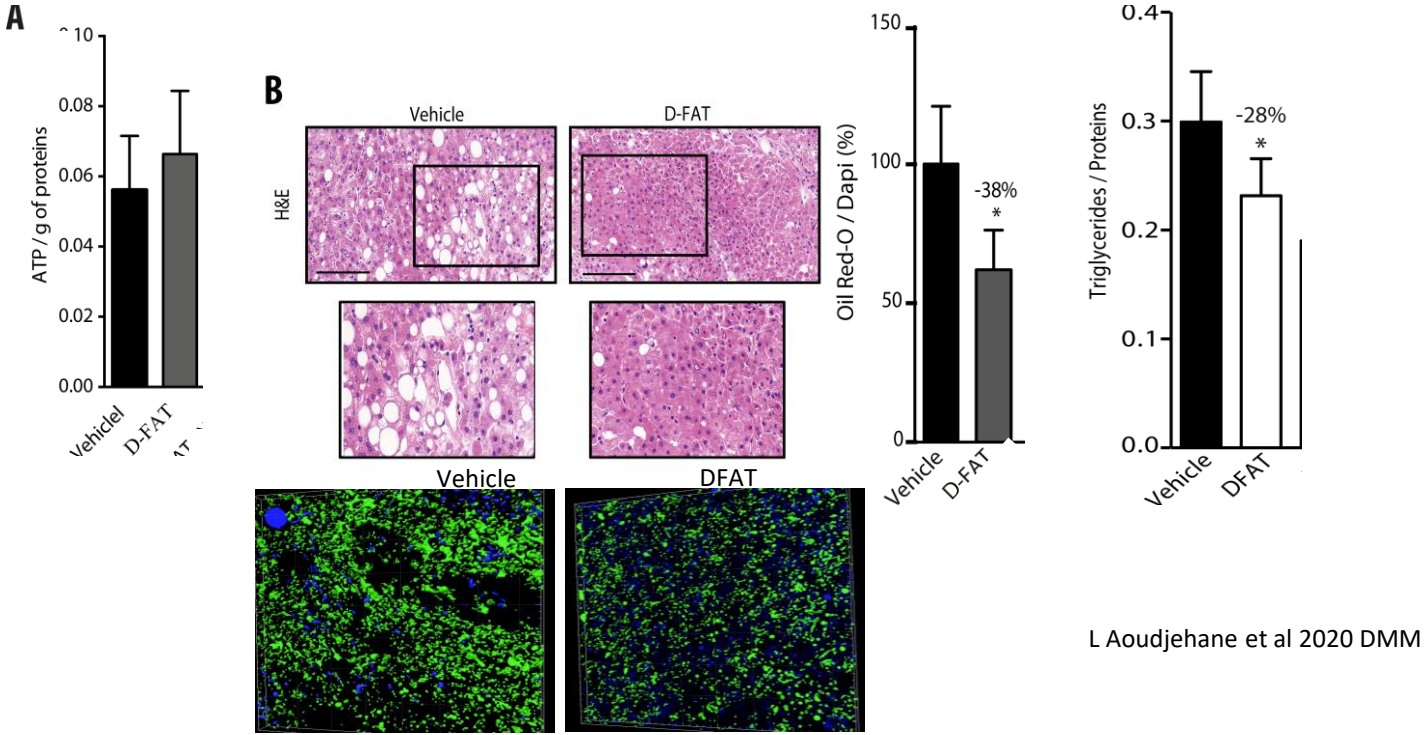


D-FAT induced a significant reduction of intracellular lipid droplets

An effective defatting cocktail to reduce liver graft steatosis before transplantation
L Aoudjehane, et al. - Disease Models & Mechanisms 2020

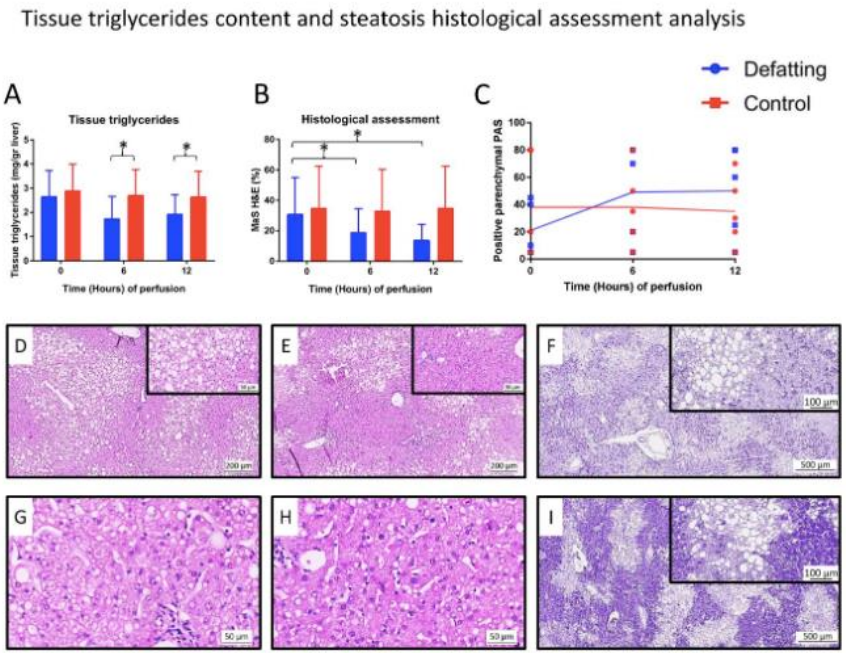
ICAN
HUMAN HepCell

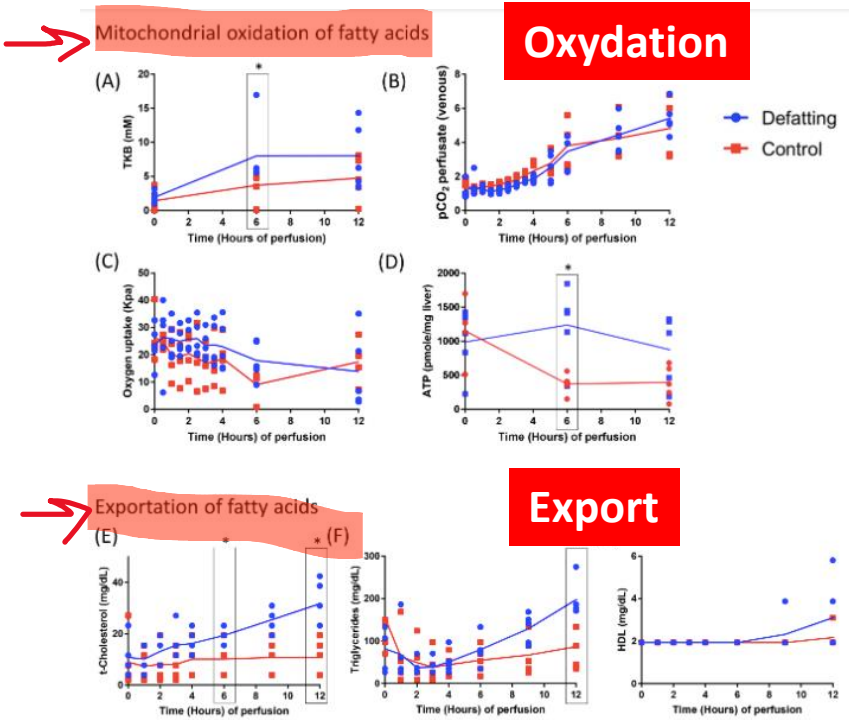
Efficacy of defatting cocktails in human steatotic precision-cut liver slices (PCLS)



L Aoudjehane et al 2020 DMM

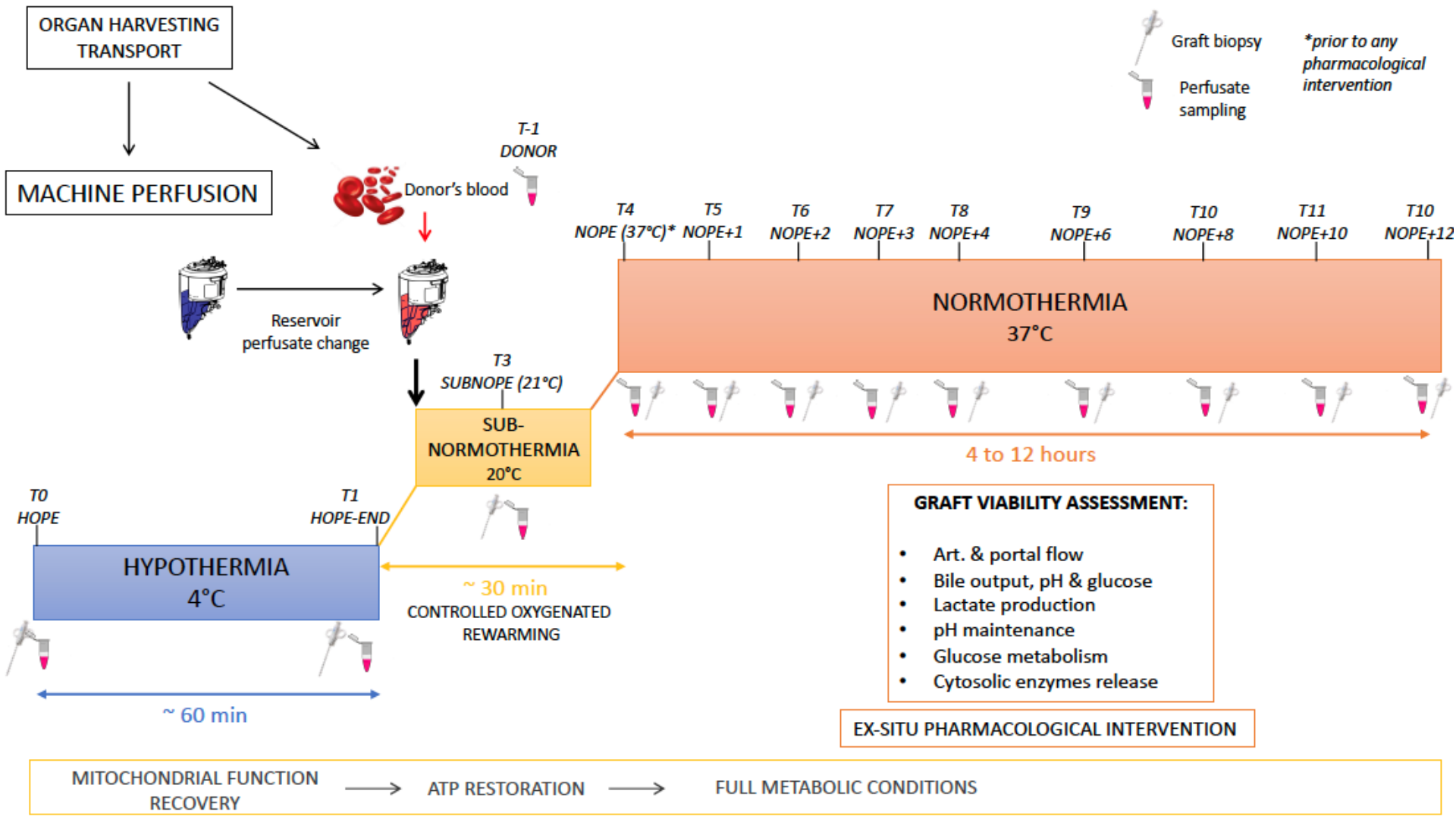
Combiner perfusion et défatting ex vivo





10 foies rejetés : 5 vs 5 réduction steatose 40%, TG 38%. Normothermie 12h

Boteon et al; Liver Transplantation 2019 et Plos 2020


ORGAN HARVESTING TRANSPORT
MACHINE PERFUSION
T-1 DONOR
Donor's blood
Reservoir perfusate change
T3 SUBNOPE (21°C)
SUB-NORMOTHERMIA 20°C
T0 HOPE
T1 HOPE-END
HYPOTHERMIA 4°C
~ 60 min
~ 30 min
CONTROLLED OXYGENATED REWARMING
T4 NOPE (37°C)*
T5 NOPE+1
T6 NOPE+2
T7 NOPE+3
T8 NOPE+4
T9 NOPE+6
T10 NOPE+8
T11 NOPE+10
T10 NOPE+12
NORMOTHERMIA 37°C
4 to 12 hours
Graft biopsy
Perfusate sampling
*prior to any pharmacological intervention
GRAFT VIABILITY ASSESSMENT:
Art. & portal flow
Bile output, pH & glucose
Lactate production
pH maintenance
Glucose metabolism
Cytosolic enzymes release
EX-SITU PHARMACOLOGICAL INTERVENTION
MITOCHONDRIAL FUNCTION RECOVERY
ATP RESTORATION
FULL METABOLIC CONDITIONS

Expérience Pitié humain protocole D FAT

Variable	DFAT 1	DFAT 2	DFAT 3	DFAT 4	DFAT 5	DFAT 6	DFAT 7
Donor characteristics							
Age, years	63	60	44	69	67	64	63
Gender	male	female	female	female	female	male	female
BMI, kg/m²	32	29	25	39	42	23	34
Type of donation after death	BDD	CDD	CDD	BDD	BDD	CDD	BDD
Cause of death	Cerebrovascular accident	Cerebrovascular accident	Anoxia	Anoxia	Cerebrovascular accident	Trauma	Anoxia
Co-morbidities	Hypertension	Hypertension, CVA	fragile X syndrome, epilepsy	Drinker, hypertension, diabetes, smoker, COPD	0	Drinker, smoker	0
Donor risk index	1.883	3.469	2.187	1.931	2.277	1.887	2.219
Peak ALT, IU/L	38	70	701	289	56	156	260
Peak GGT, IU/L	53	527	408	279	36	264	79
Liver characteristics							
Liver weight, g	2090	1462	1413	1420	2126	2100	1380
CIT, minutes	630	600	480	780	540	420	780
Steatosis at retrieval, %	90	<5	<5	60	80	40	70
Machine perfusion parameters							
Lactate, mmol/L							
Lowest	3.4	2.2	8	7	ND	ND	3.9
Highest	10.5	NA	11	31	ND	ND	ND
Total bile production, ml	150	2	0	0	0	0	10
Arterial flow, ml/min	500	600	460	350	525	525	345
PV flow, ml/min	700	1000	1250	1000	1575	1575	1035

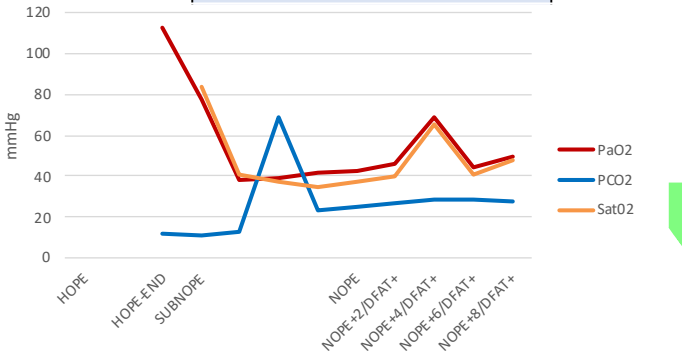
DFAT 1

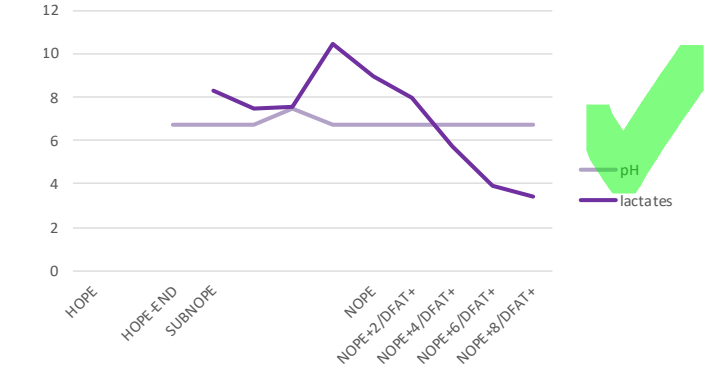
Graft weight : 2090 –> 2090g
CIT : 10h30
HOPE : 4h
NOPE : 8h

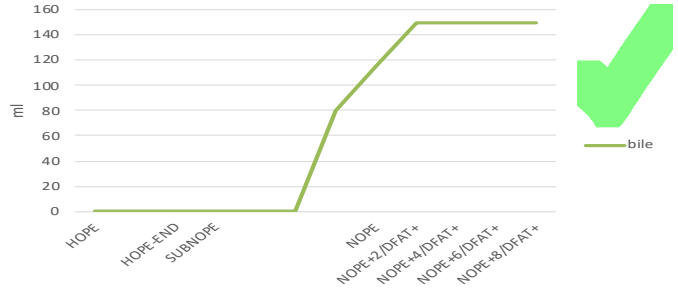
Perfusion parameters:
- Arterial flow = 500 ml/min
- Portal flow = 700 ml/min

Histology : **steatosis = 90%** (no change)

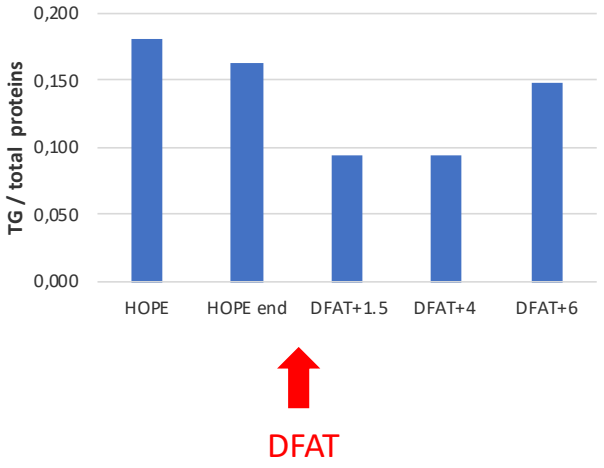
Viabilité: OUI







Defatting



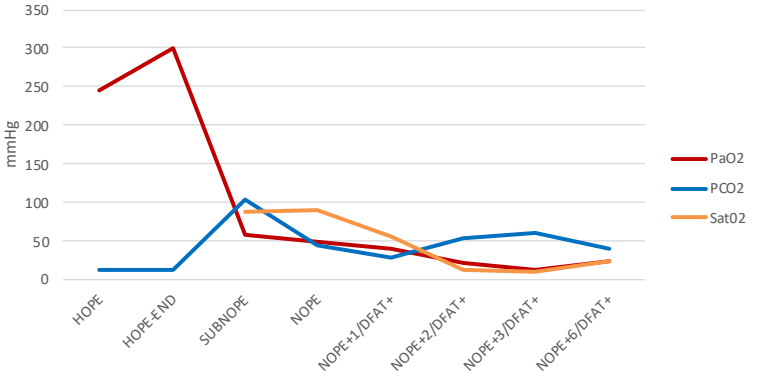
DFAT 4

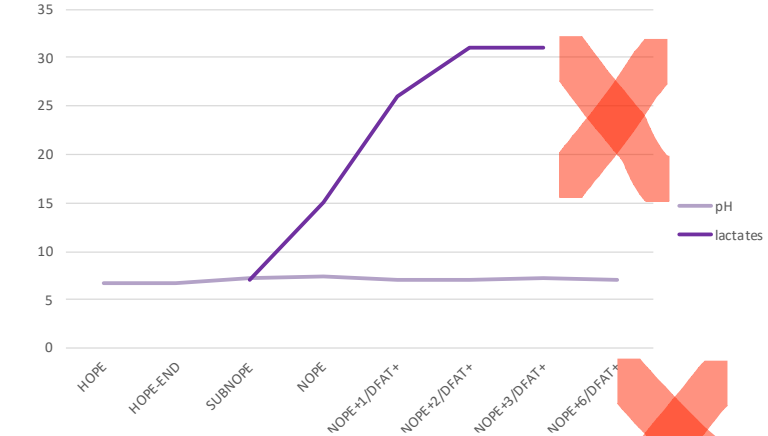
Viabilité : NON

Graft weight : 1420 –> 2500g
CIT : 13h00
HOPE : 3h
NOPE : 6h00

Perfusion parameters:
- arterial flow = 350 ml/min
- portal flow = 1000 ml/min

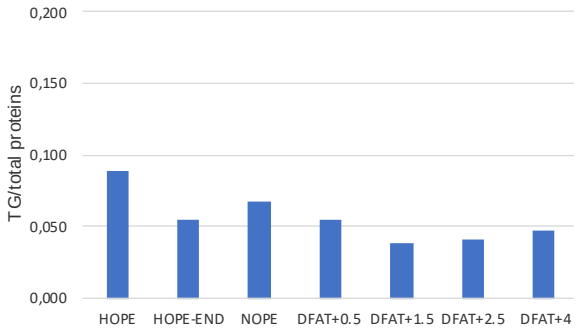
Histology : **steatosis 60%**
S2A1F1





Bile production = 0 ml

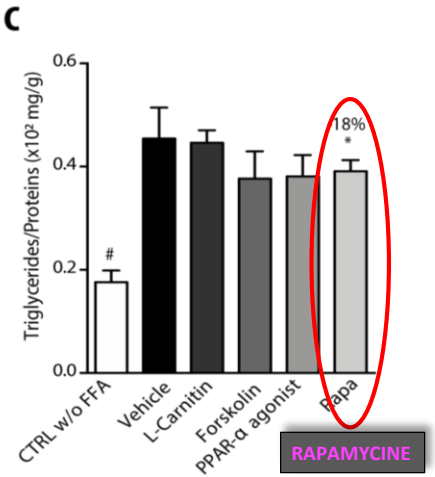
Defatting



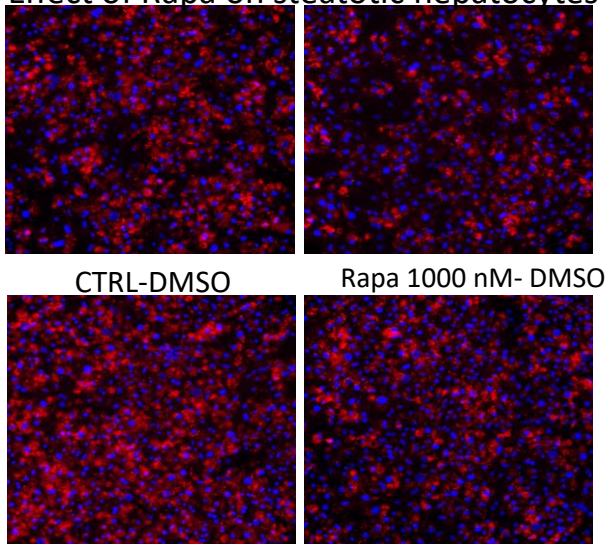
DFAT

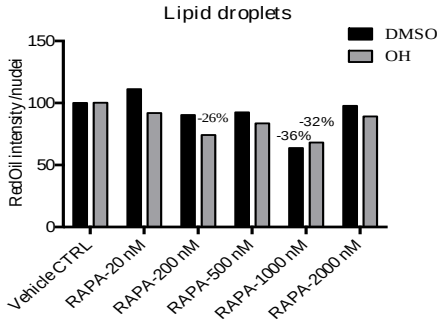
DÉVELOPPEMENT D'UNE SOLUTION DE RAPAMYCINE POUR LE TRAITEMENT PAR DES GREFFONS HÉPATIQUES STÉATOSIQUES PAR PERFUSION *EX VIVO* SUR MACHINE AVANT TRANSPLANTATION

RAPAPERF



Effect of Rapa on steatotic hepatocytes





-> Etudier l'administration de rapamycine par perfusion ex vivo normothermique sur machine comme traitement curatif de la stéatose des greffons hépatiques non transplantables.

OBJECTIFS: AMICAP: AGEPS-Pitié Sorbonne

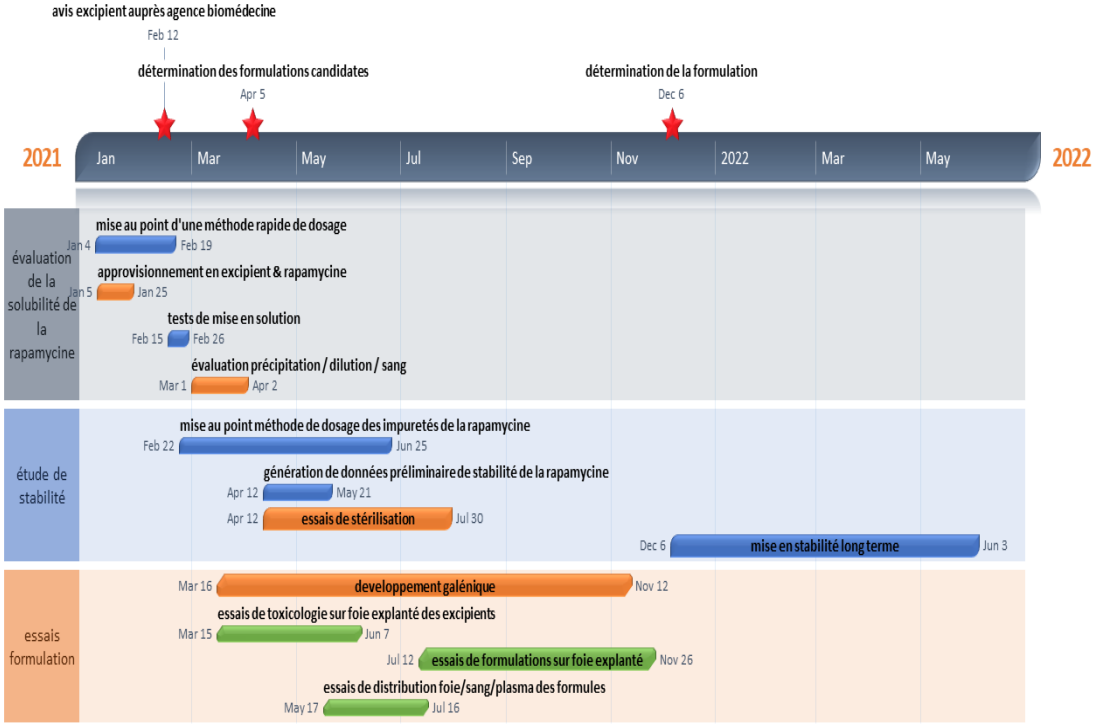
1/ Concevoir et optimiser une formulation contenant de la rapamycine sous forme de solution à administrer par injection ex vivo

- solubilité (étude de solvant)
- stabilité dans le temps et conservation
- tolérance et toxicité
- dose

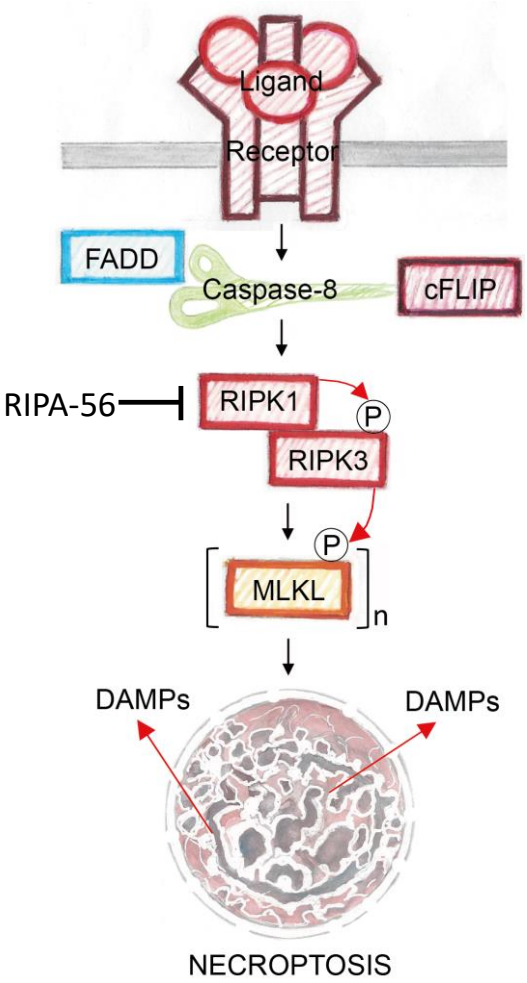
2) Etude de l'effet de la rapamycine sur le "defatting"

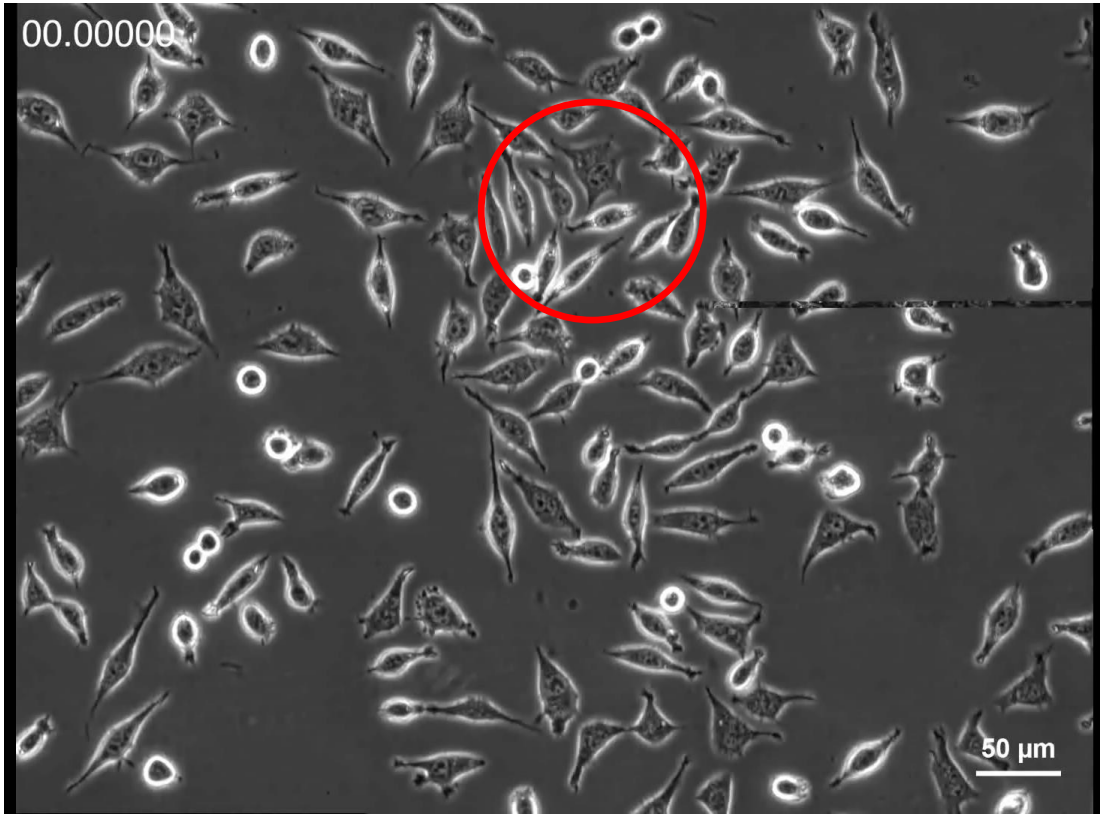
3) Etude immunologique :

- **immunosuppression**
- **immunotolérance**



Necroptosis : RIPA 56…



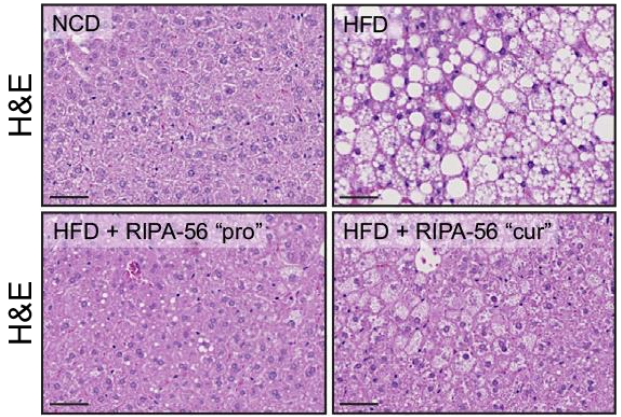


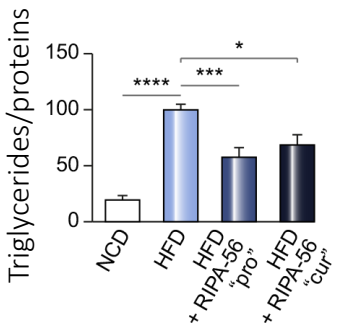
ANR (2022– 2025) + Projet SATT LUTECH : Modulating activity of the necroptosis pathway to rescue steatotic liver grafts

1) RIPA-56 améliore les lesions d'ischémie-reperfusion chez la souris

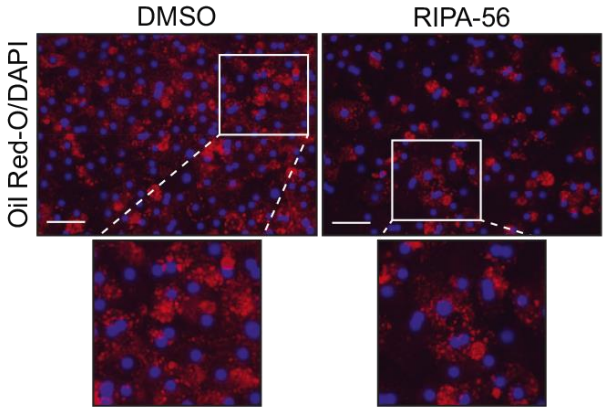
2) RIPA-56 améliore la stéatose

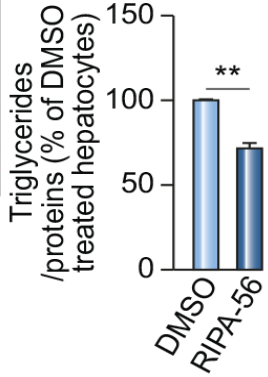
Souris





Homme





Majdi et al, 2020 Journal of Hepatology
Baidya et al, 2021 J Clin Med

Conclusion

- Apport dynamique d'oxygène améliore la tolérance à l'ischémie reperfusion (hypothermie) ou l'évite (normothermie)
- La perfusion peut "améliorer" et sélection des greffons marginaux
- La manipulation pharmacologique ex vivo du foie est une voie d'avenir potentielle