

## ➤ Human Milk Fat Globule and its membrane

Claire Bourlieu<sup>1,4\*</sup>, Mathilde Cancalon<sup>1,4</sup>, Nathalie Barouh<sup>3</sup>, M. Robert<sup>1</sup>,  
 Véronique Vié<sup>2</sup>, Olivia Ménard<sup>4</sup>, Didier Dupont<sup>4</sup>, Amélie Deglaire<sup>4</sup>

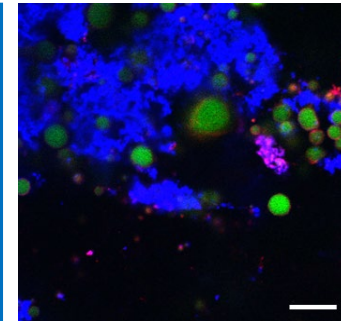
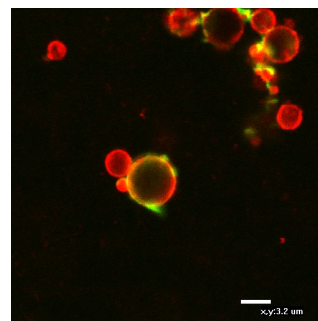
claire.bourlieu-lacanal@inrae.fr

<sup>1</sup>UMR 1208 IATE, INRAE, Univ Montpellier, Institut Agro, Montpellier, France;

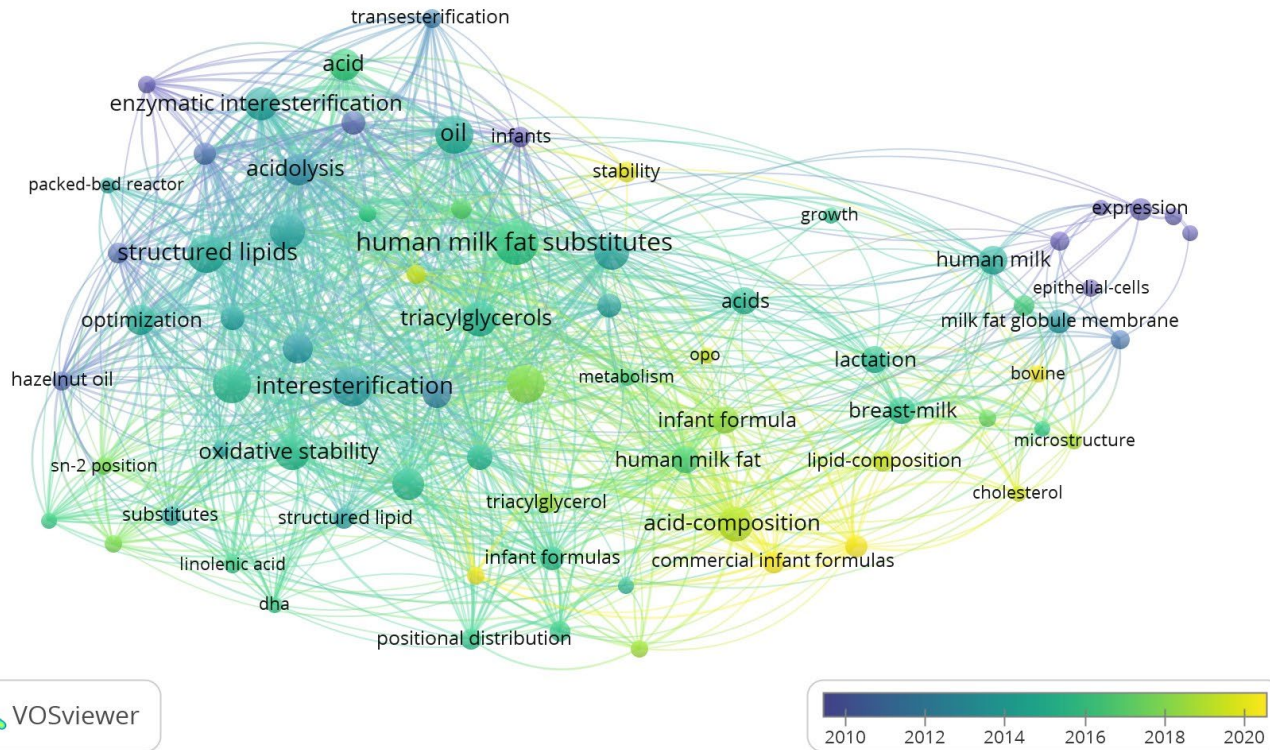
<sup>2</sup>IPR Institute of Physics, Rennes University 1, Rennes, France;

<sup>3</sup>UMR QUALISUD, CIRAD, Univ Montpellier, Univ Avignon, Univ Réunion, IRD;

<sup>4</sup>UMR 1253 STLO, INRAE, Agrocampus Ouest, Rennes, France;



# ➤ Human Milk Fat Globule and its membrane on WOS



Query = Titles : « HMFG, HMM, HMF, BMF, BMFM, HMFM » – OR => 294 papers

<https://www.webofscience.com/wos/woscc/summary/fe5409c8-3a41-45d5-a8b3-a4d7afa16e49-010d64a41f/date-descending/1>



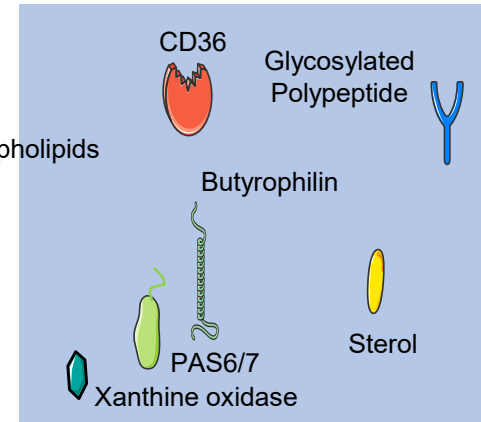
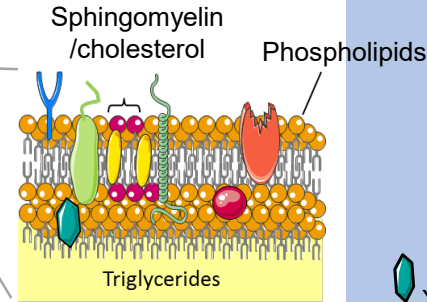
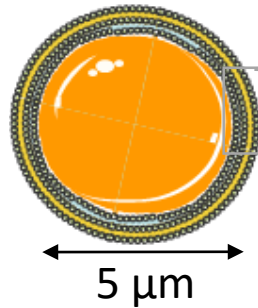
INRAE

Human milk fat globule and milk membrane

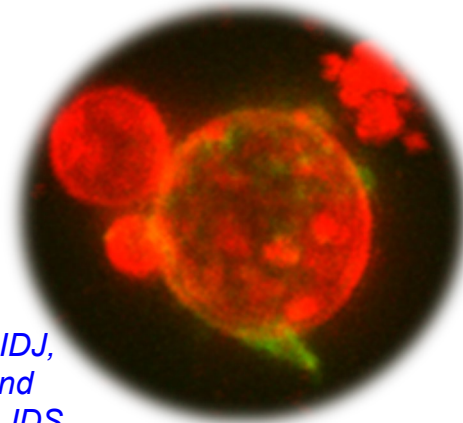
October 03-04, 2024 #pediatrics-conference/ C. Bourliou-Lacanal

# CONTEXT

## Milk Fat Globule



High specificity of structure with similarities between mammals



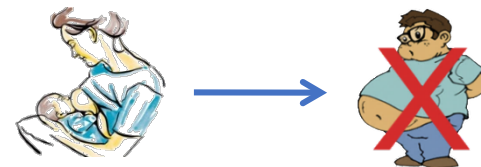
## Milk Fat Membrane

Support infant growth (45-55% total calories under the form of triglycerides)



(Armand et al., *Ped. Res*, 1996; Delplanque, Gibson et al., *J. Pediatr. Gastroenterol. Nutr.*, 2015; Jensen, *Lipids*, 1999; Roman et al., *Ped. Res.* 2007; Lindquist and Hernell, *Curr. Opinion Clin. Nutr. Met.Care*, 2010, Guesnet et al., *OCL*, 2013)

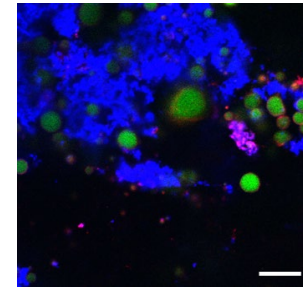
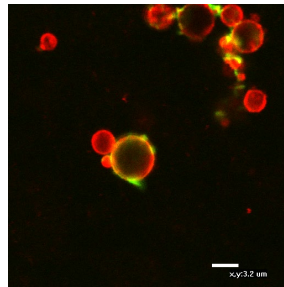
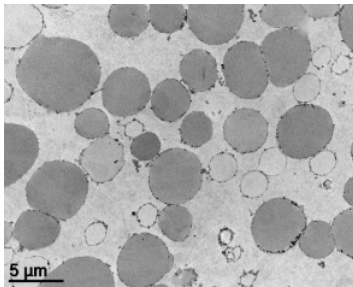
Milk fat structure is involved in infant development and programming



(Oosting et al. *Translational Inv.*, 2012; Baars et al. *BJN* 2016; Bourlieu and Deglaire et al., *OCL*, 2017)

# OUTLINE

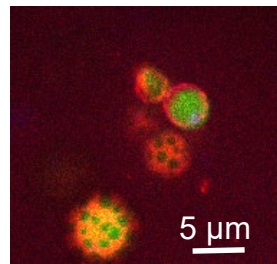
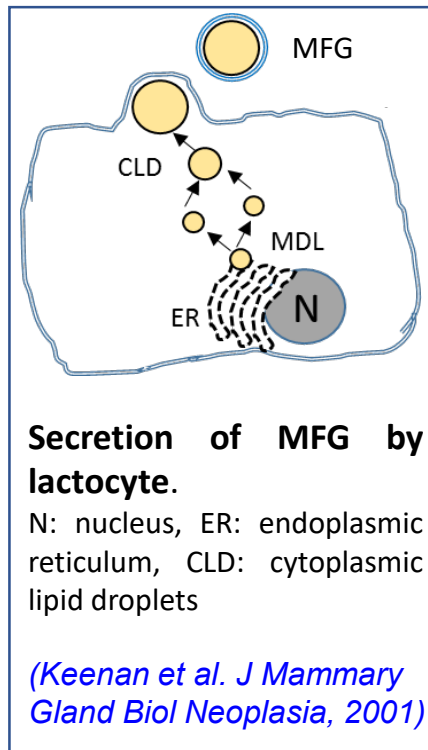
- ✓ Human milk lipids vary but have consistent structure : Human milk fat globule (HMFG)
- ✓ Part played by core constituents to deliver rapidly energy and key (micro)nutrients
- ✓ Evolution of HMFG with lactation / during digestion
- ✓ Human milk fat globule membrane, an element of resistance key in the programming effect ?



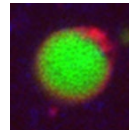


# ✓ Human milk lipids vary but have consistent structure : HMFG

## MILK FAT GLOBULE MEMBRANE



■ Apolar lipids ■ Amphiphiles ■ Proteins



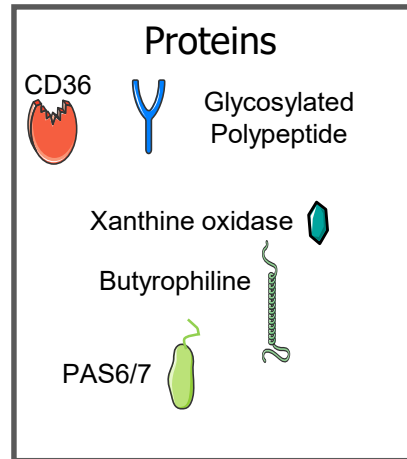
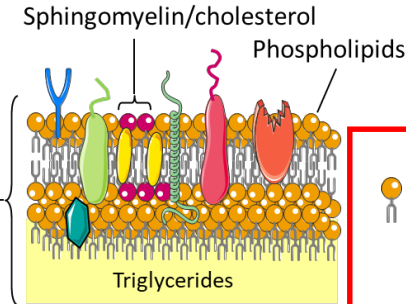
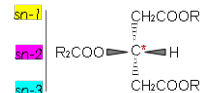
**MILK FAT GLOBULE (MFG)**  
 (3-5 μm, range 0.1-15 μm)

Bilayer →

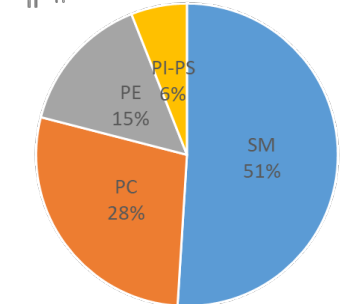
Primary membrane

**Cytoplasmic crescent**  
 (RNA and miRNA)

**TG CORE**



0.6 (0.39 – 0.97) %  
 Total lipids



Global composition in MPL

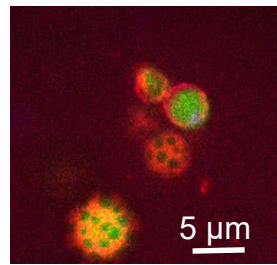
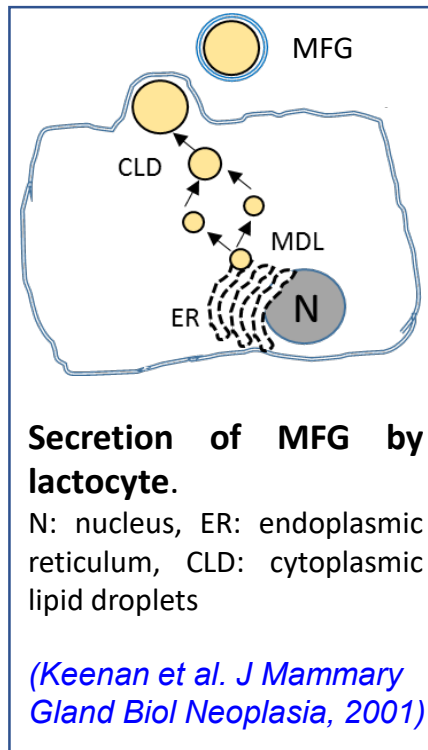
**Sterols = 0.5 (0.3-1.3) % total lipids totaux, minor sterols**

+ Complex lipids other than PL : gangliosides, cerebrosides, sulfatides...

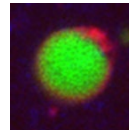
*(Bourlieu and Michalski, COCNM, 2015; Bourlieu et al., CND, 2018; Bourlieu et al., EJSLT, 2015; Jensen, Lipids, 1992)*

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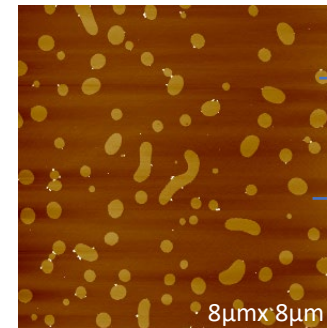
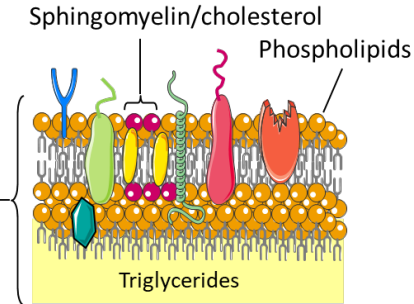
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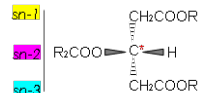
**TG CORE**



Digestion resistant:  
 condensed phase:  
 immunitary and  
 microbiota education

Fluid phase:  
 enzymes can get  
 inserted

AFM image indicating an heterogeneous physical state



*(Bourlieu and Michalski, COCNM, 2015; Bourlieu et al., CND, 2018; Bourlieu et al., EJSLT, 2015; Jensen, Lipids, 1992)*

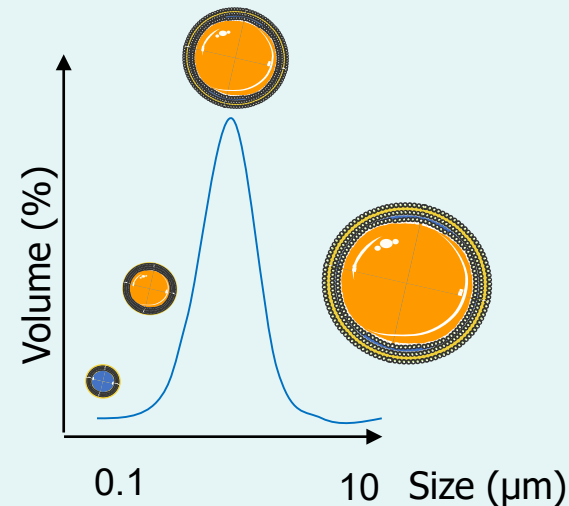
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## HM MFG NATURAL VARIATIONS OF SIZE impacts on chemical composition and metabolization

Concept of submicronic droplets or lactosomes without TG core  
d~plasma HDL, enriched in immunomodulatory prot, specific lipidome/proteome



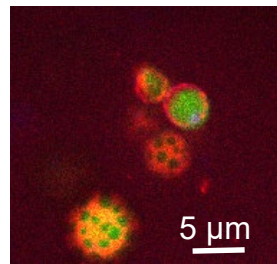
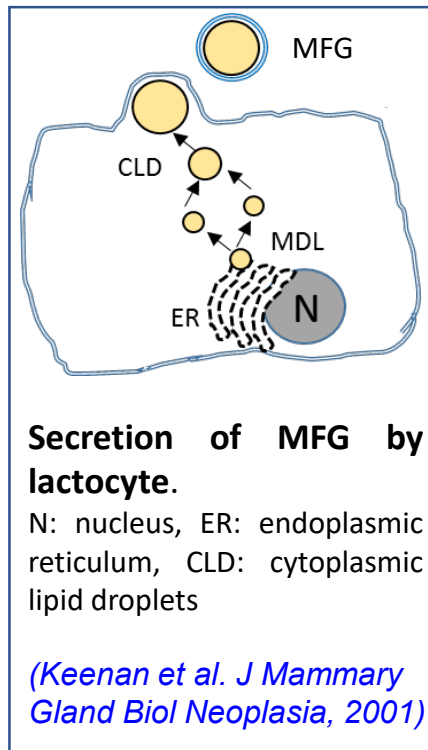
Small milk fat globules with increase medium chains (C8-C12) and decrease in C18:0



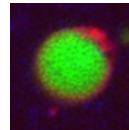
(Argov-Argaman, et al., J. Agric. Food Chem. 2010)

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## MILK FAT GLOBULE MEMBRANE



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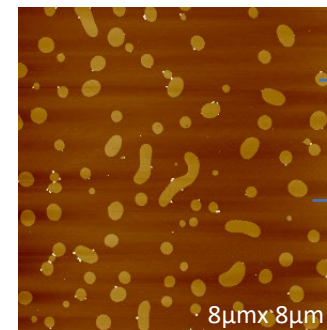
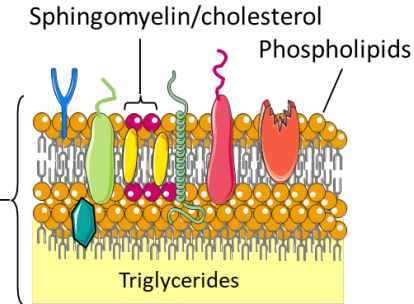
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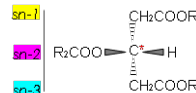
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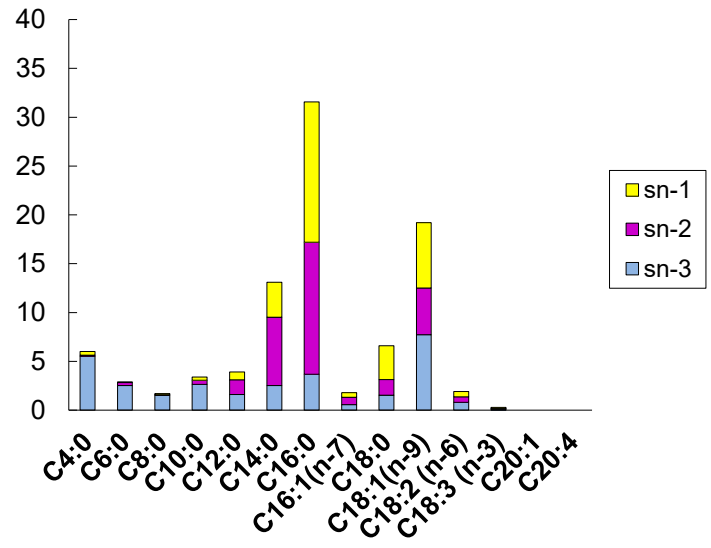
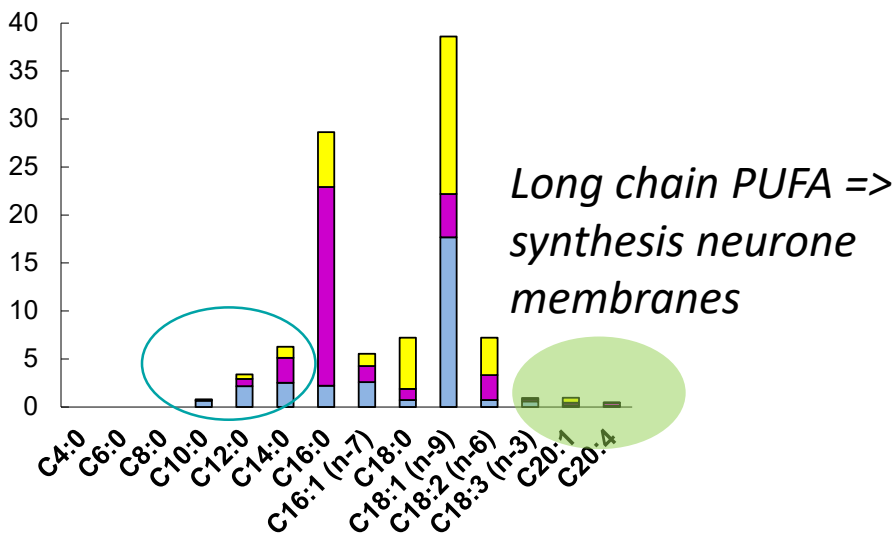
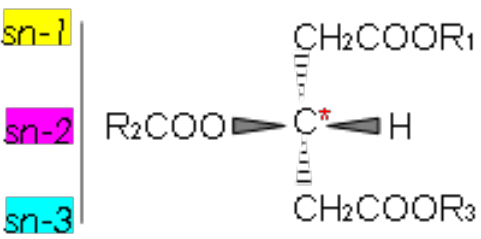


*(Bourlieu and Michalski, COCNM, 2015; Bourlieu et al., CND, 2018; Bourlieu et al., EJSLT, 2015; Jensen, Lipids, 1992)*



# 70's : specific triacylglycerol (TAG) structure in HM results in improved fatty acids absorption (Tomarelli et al., 1968).

**NON RANDOM** Distribution of fatty acids ( $R_1, R_2, R_3$ ) on the glycerol backbone



Comparison of the composition and regiodistribution of FA in human and bovine milks (% mol main FA > 0.5 % total)



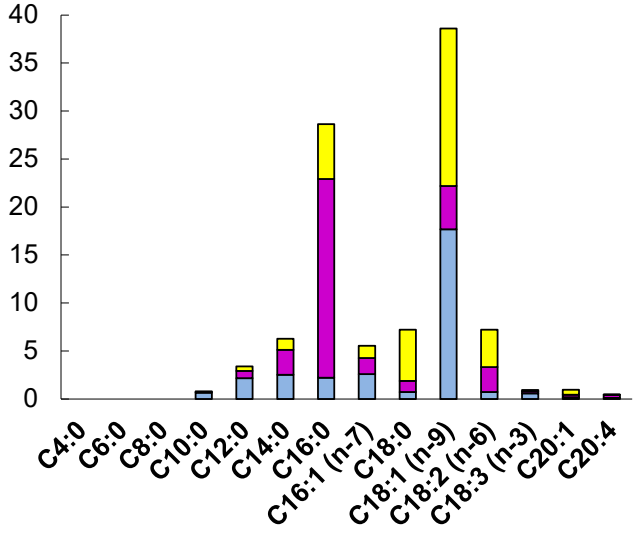
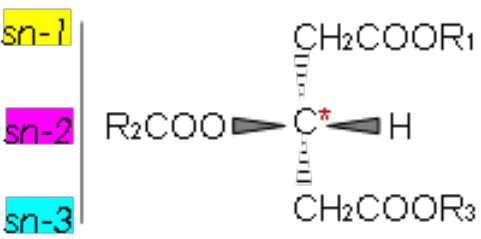
**INRAE**

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(Blasi et al., J Food Comp. & Anal, 2008; Bourlieu et al., TFST, 2009; Innis, Adv. In Nutr., 2011; Strandvik, EJLST, 2015)

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**NON RANDOM** Distribution of fatty acids ( $R_1, R_2, R_3$ ) on the glycerol backbone



- C16:0 main saturated FA in human milk (20–25% of milk's total FA) => 60% in *sn*-2 position
- C18:1 major monounsaturated FA (28– 46% of milk's total FA) ++ esterified in external positions (*sn*-1,3)
- Medium chain saturated FA C6:0 to C12:0 in *sn*-3 positions

Comparison of the composition and regiodistribution of FA in human and bovine milks (% mol main FA > 0.5 % total)



**INRAE**

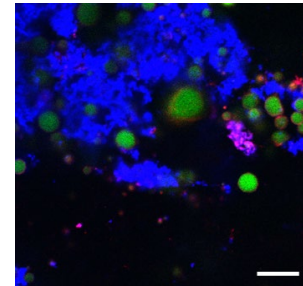
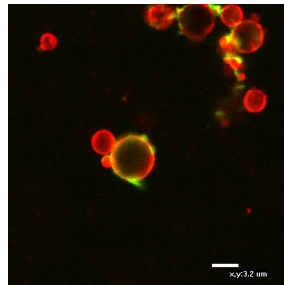
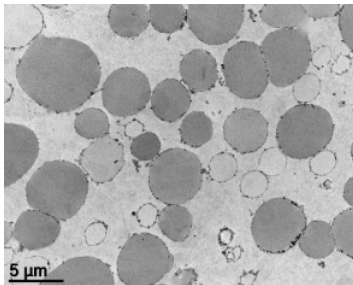
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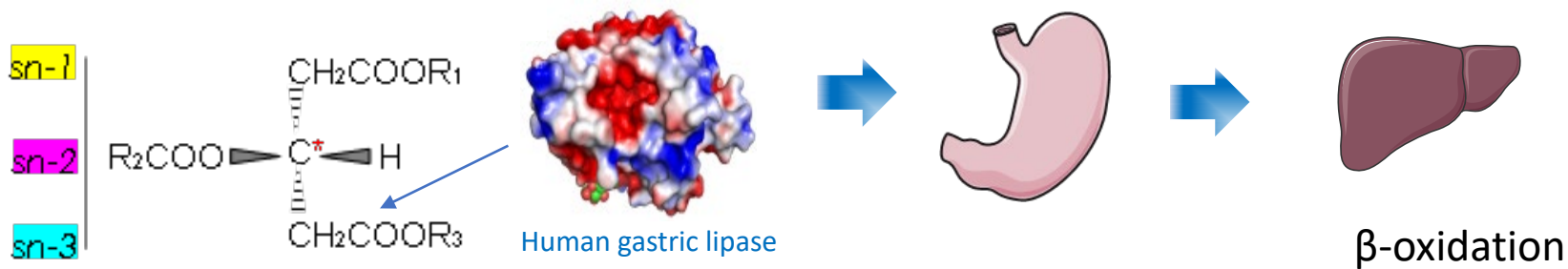
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# OUTLINE

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✓ Part played by core constituents to deliver rapidly energy & key nutrients

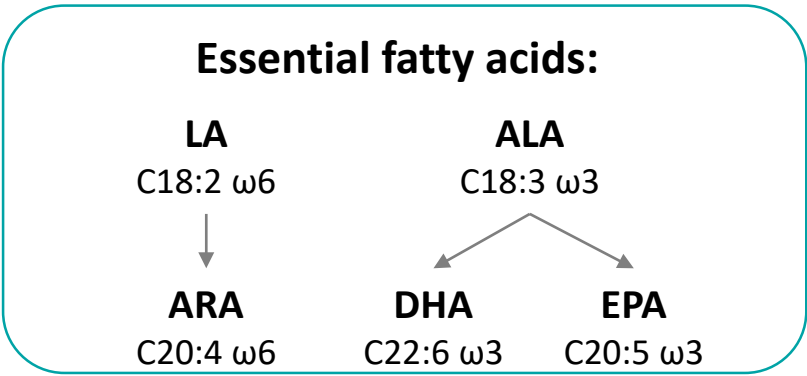


➤ sn-3 esterified 6:0–12:0 => absorbed in the stomach => transported to the liver and oxidized in decreasing amounts as the molecular weight increases. Quantities in milk dependent on amount of carbohydrate in diet



➤ Reintroduction of cow's milk TAG favours DHA accumulation in brain

*(Delplanque et al. Prostaglandins Leukot. Essent. Fatty Acids, 2013)*

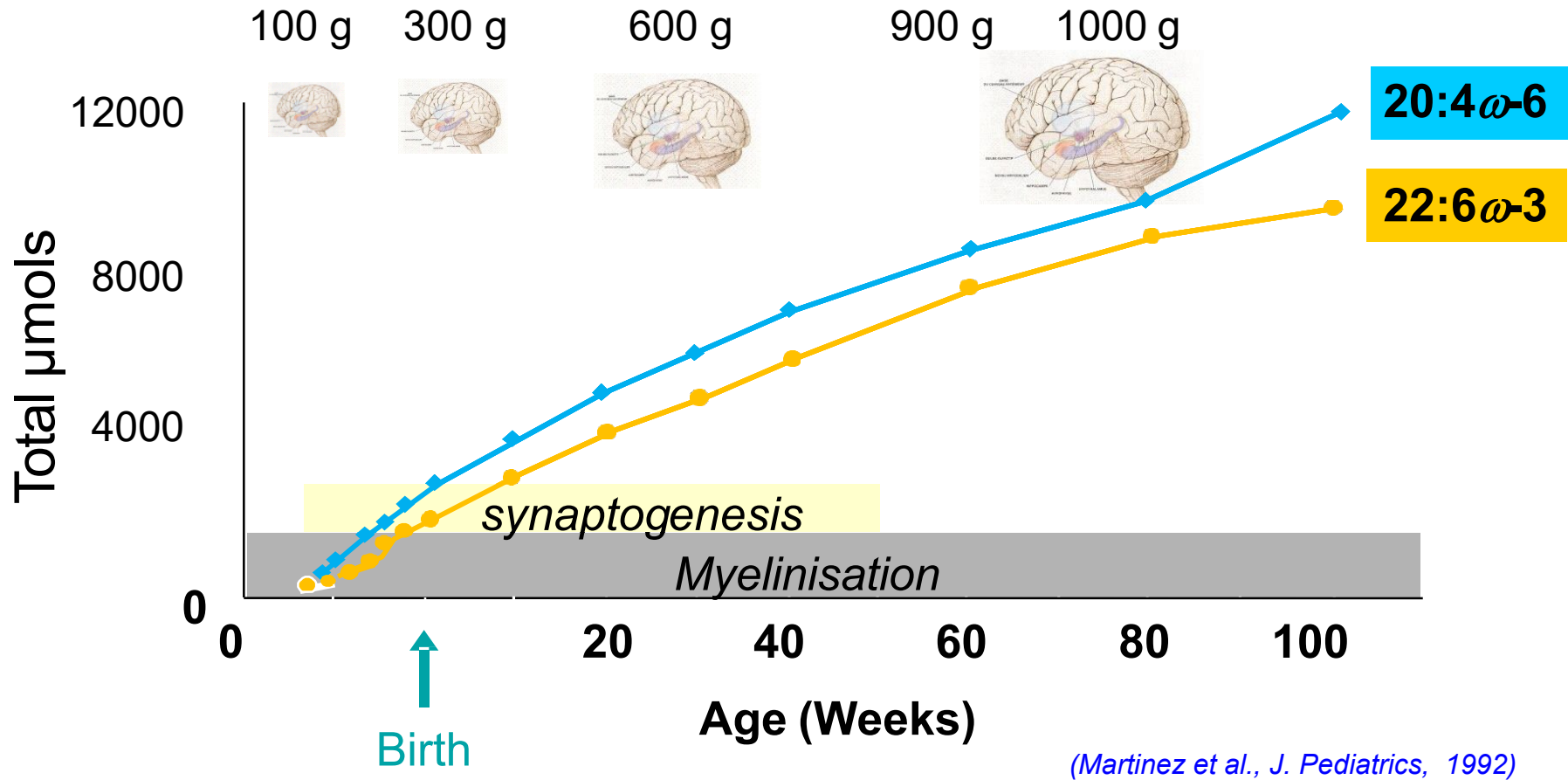


Protection of essential FA against  $\beta$ -oxidation

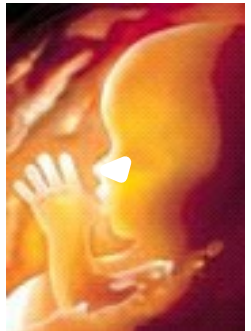


**INRAE**

✓ Part played by core constituents to deliver rapidly energy & key nutrients



Placenta transfer during development



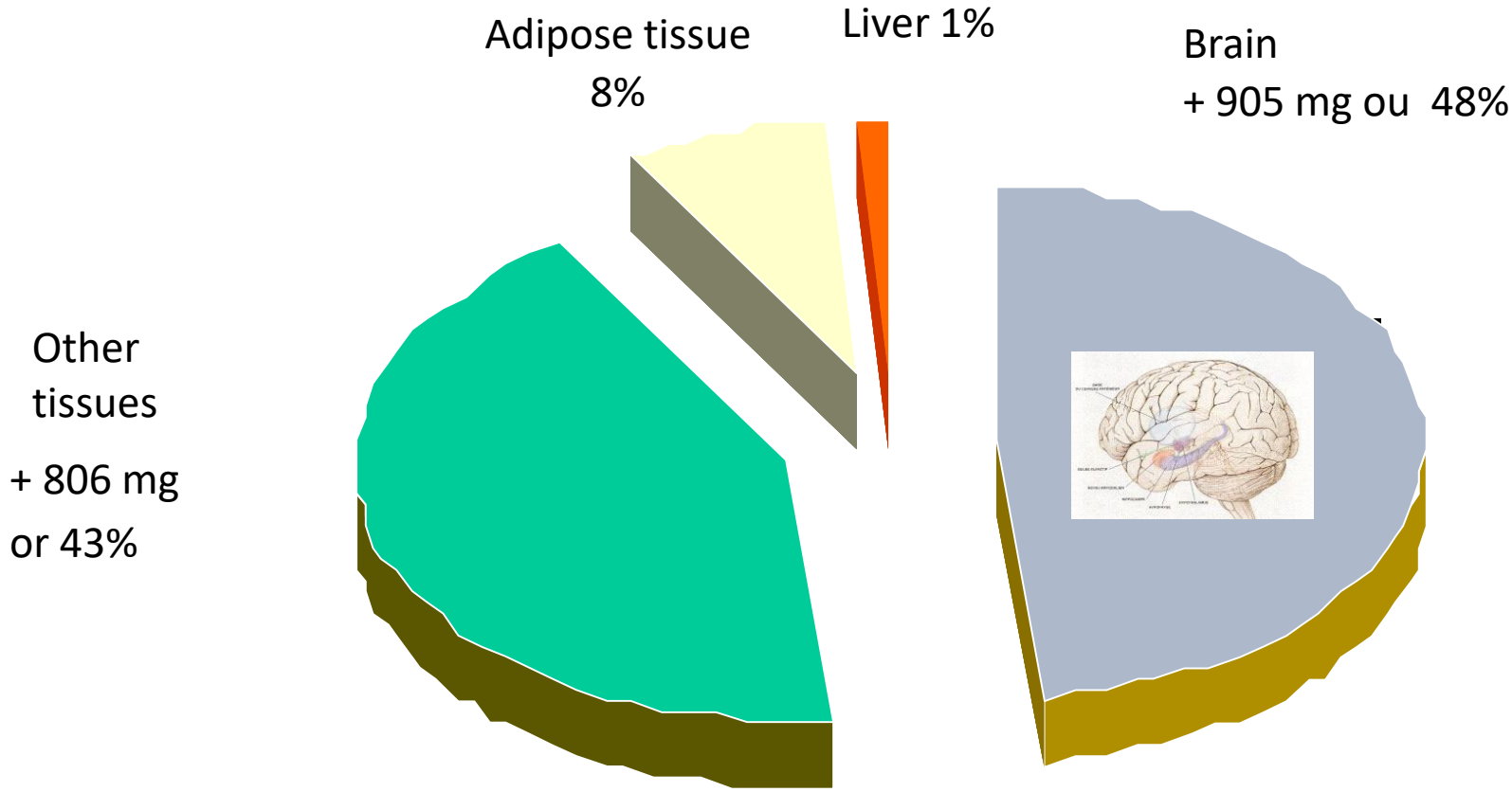
Intake by breast milk



✓ Part played by core constituents to deliver rapidly energy & key nutrients

➤ HM supports DHA accumulation in brain / other part of organism during lactation

*(Cunnane et al., 2000)*



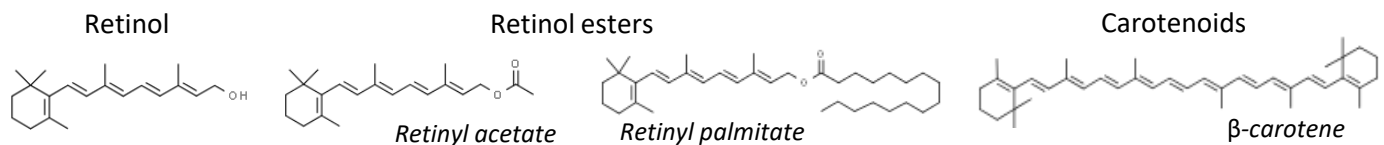
➤ Variation of DHA levels worldwide =  $0.32 \pm 0.22$  and a range of 0.06–1.4%

*(Brenna et al., Am J Clin Nutr., 2007)*

✓ Part played by core constituents to deliver rapidly energy & key nutrients



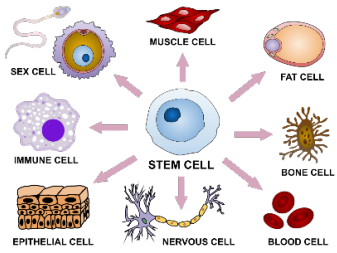
➤ vitamin A content of breast milk ↘ as lactation progressed, range: **300-800 µg/L for mature breast milk** (Zhang, Ren et al. 2022; Jensen et al., Annu. Rev. Nutr, 1992); Beta-carotene, lutein and lycopene ~50-200 µg/L



key functions in various biological processes



Visual



Cell differentiation



Immune system



Limited liver store capacity in newborn

(Dror and Allen, Adv Nutr 2018)



## ✓ Part played by core constituents to deliver rapidly energy & key nutrients



- Provide about 15 mg (10-25 mg) of cholesterol/dL
- Precursor of steroid hormones and other derivatives in humans
- Not affected by changes in maternal diet nor plasma levels
- H: Predispose the infant to efficiently metabolize dietary cholesterol as an adult.

*(Reiser, et al. Nutr. Rep. Int. 1979)*

- Breastfed infant have higher circulating cholesterol during infancy, lower in adulthood in breast-fed infants compared to formula fed infants

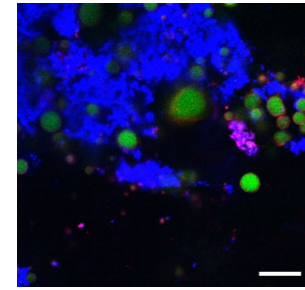
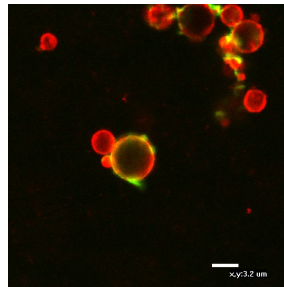
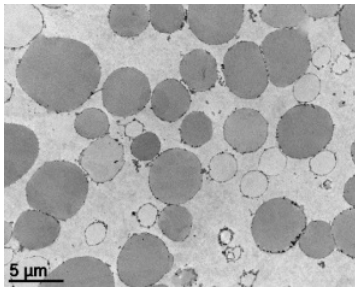
*(Owen et al., Pediatrics, 2002)*

- RDB-CT (n=160 infants, 2–12 months of age) ↑ cholesterol intake between 2-6 months via the supplementation of an experimental infant formula with bovine MFGM => higher total serum cholesterol [ ] = [ ] observed in breast-fed infants (∅ modification of LDL/HDL ratio). Experimental IF reduced in energy and protein content compared to the standard formula

*(Timby et al., Pediatr. Res. 2014)*

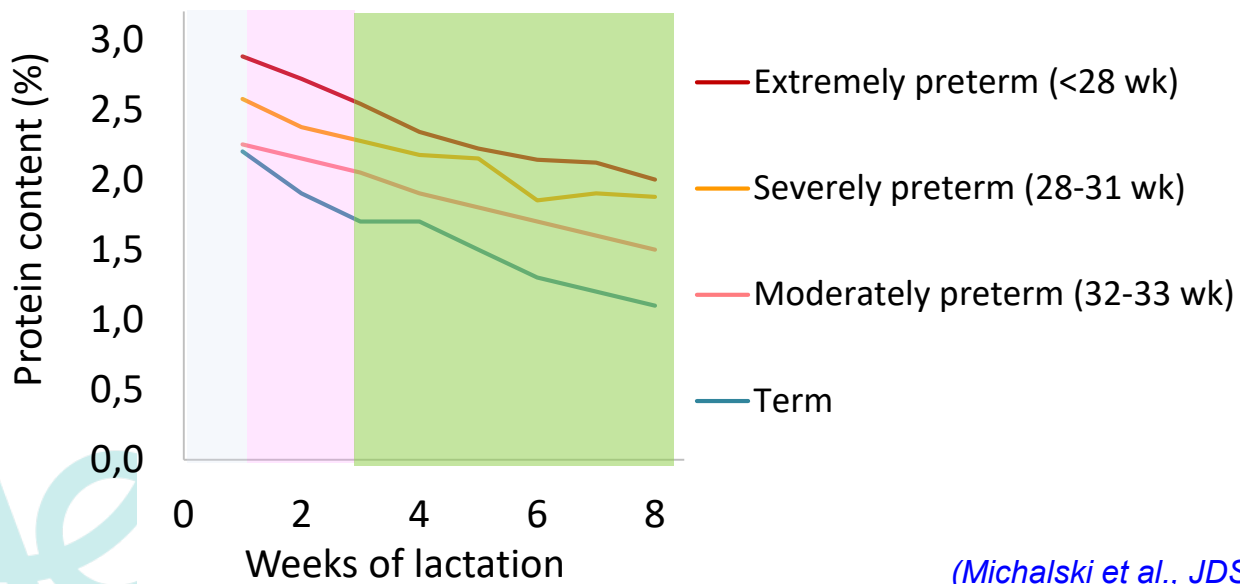
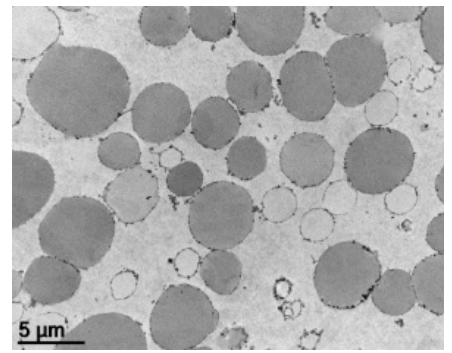
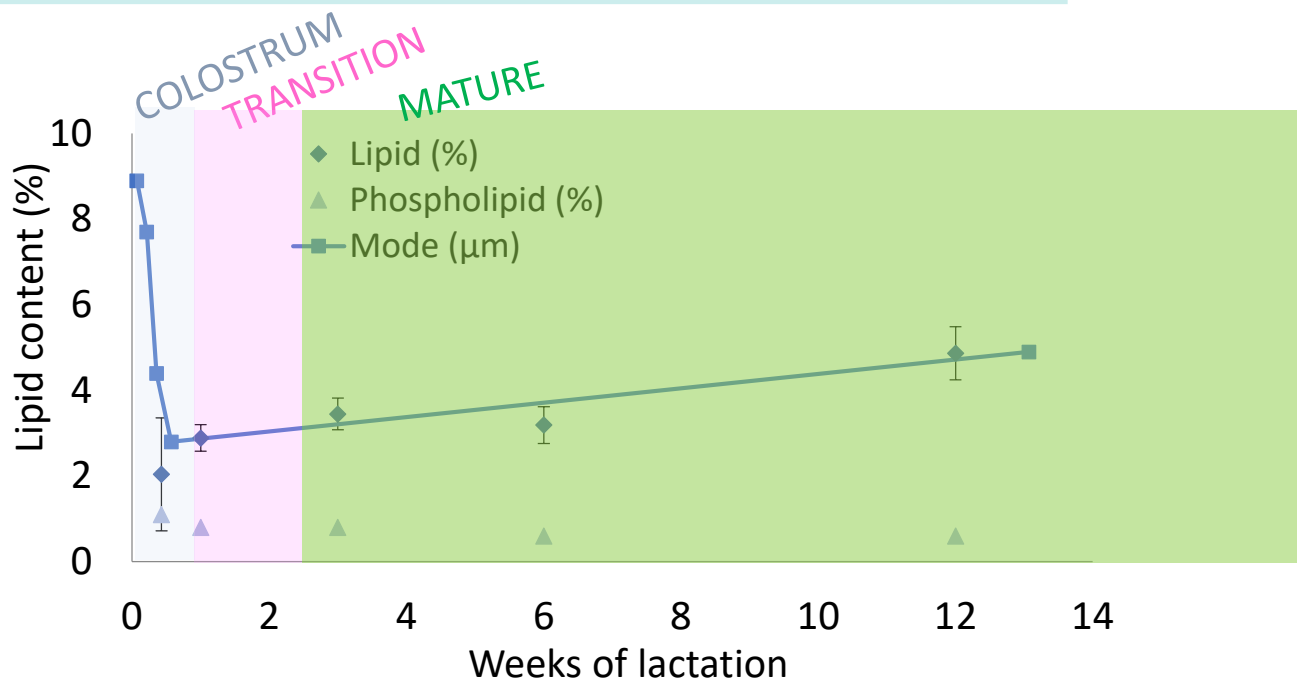
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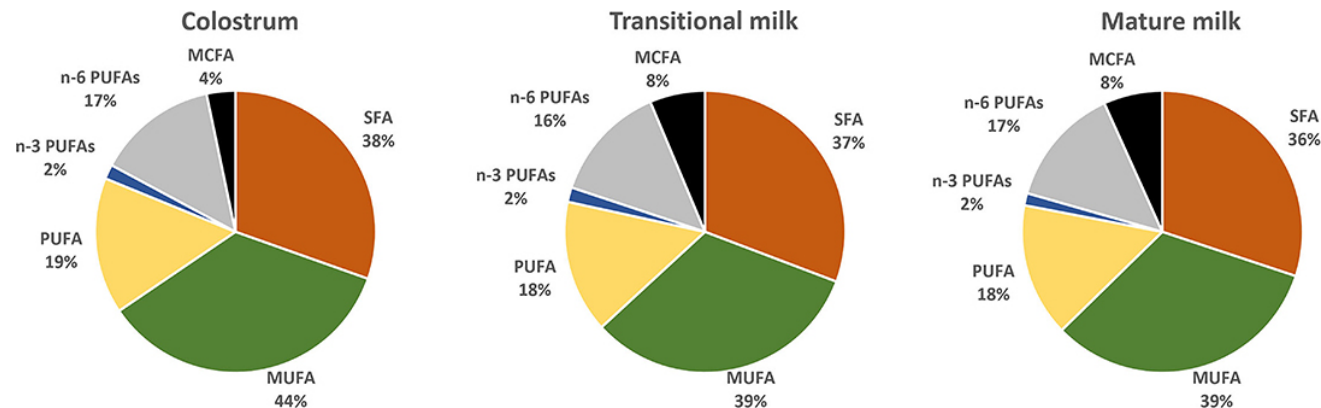


# ✓ Evolution of HMFG with lactation / during digestion



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- Systematic review (n=55 studies; n=4,374 term milk samples reported analysis for the variation of 36 main FA across lactation):
  - Most abundant SFA : palmitic (C16:0), stearic (C18:0) and myristic (C14:0) and MUFA oleic acid (C18:1 n-9) STABLE
  - Gondoic (C20:1 n-9), erucic (C22:1 n-9) and nervonic (C24:1 n-9) ↘
  - MCFAs, specially the most abundant, lauric acid (C12:0), ↗ X 2 from C to TM
  - Long-chain PUFAs : LA, eicosapentaenoic (EPA; C20:5 n-3) and ALA, STABLE
  - Arachidonic acid (ARA; C20:4 n-6), docosahexaenoic acid (DHA, C22:6 n-3) and docosapentaenoic acid (DPA; C22:5 n-3) ↘



INRAE

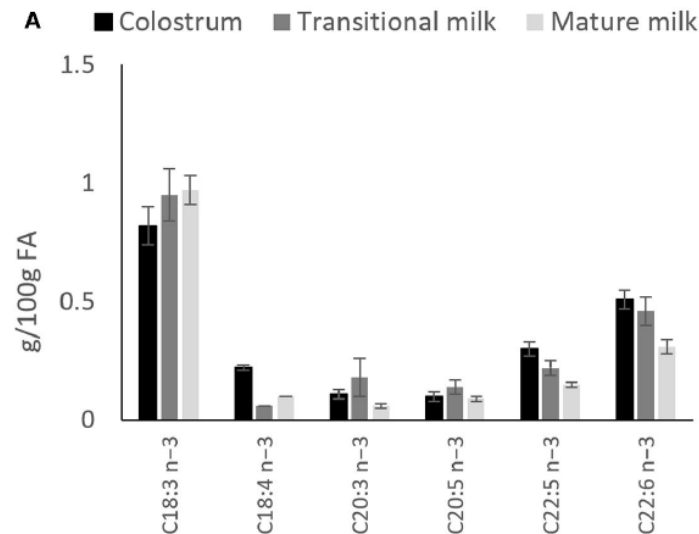
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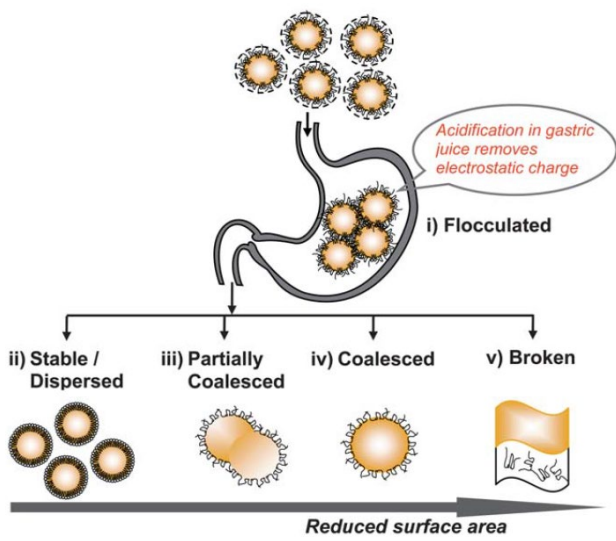
(Floris et al. PLEFA. 2020)

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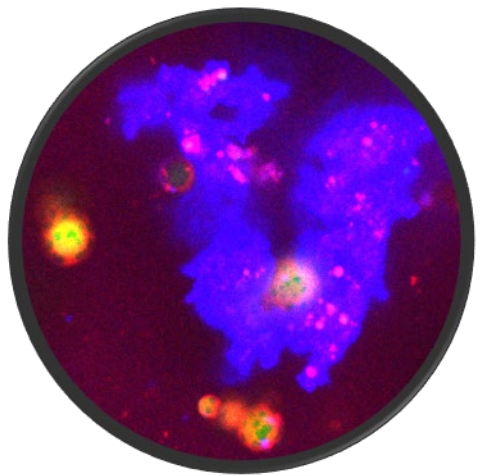
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(Armand et al., *Am J Clin Nutr*, 1999; Couëdelo et al. *Food and Function*, 2015; Golding et al., *Soft Matter*, 2011; Vors et al., *Am J Clin Nutr*, 2013)



Thèse S. Cassia de Oliveira 2013-3016



INRAE



## DIGESTION OF HM IN PRETERM INFANTS

NCT02112331 (ClinicalTrials.gov)

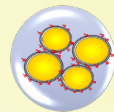
- Randomized controlled trial
- Hospitalized tube-fed preterm infants (GA < 32 wks)
- Alimentation  $\geq 120$  mL/kg/jour every 3 h
- 6-day experimental period; 2 independent groups

### GROUP A

HM from their own mother



Raw HM



Past HM

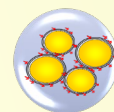
→ collected < 24h  
before feeding

→ 1 pool aliquoted in  
6 bottles

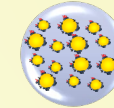
n=12, GA  $30.0 \pm 1.1$  wk, age at first day  $27 \pm 12$  d,  
Body weight at first day  $1.83 \pm 0.41$  kg

### GROUP B

HM from anonymous donor



Past HM

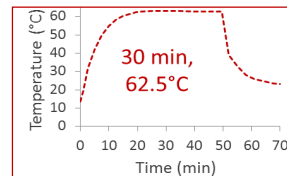


P+Homog HM

→ The same pool from one donor was  
used for the two types of milk  
n=8, GA  $29.5 \pm 1.5$  wk, age at first day  $32 \pm 21$  d,  
Body weight at first day  $1.73 \pm 0.48$  kg

### HM bank

Holder pasteurization



Indirect homogenization by ultrasonication



→ 595 W, 3 periods of 5  
min interrupted by 30s  
of pause

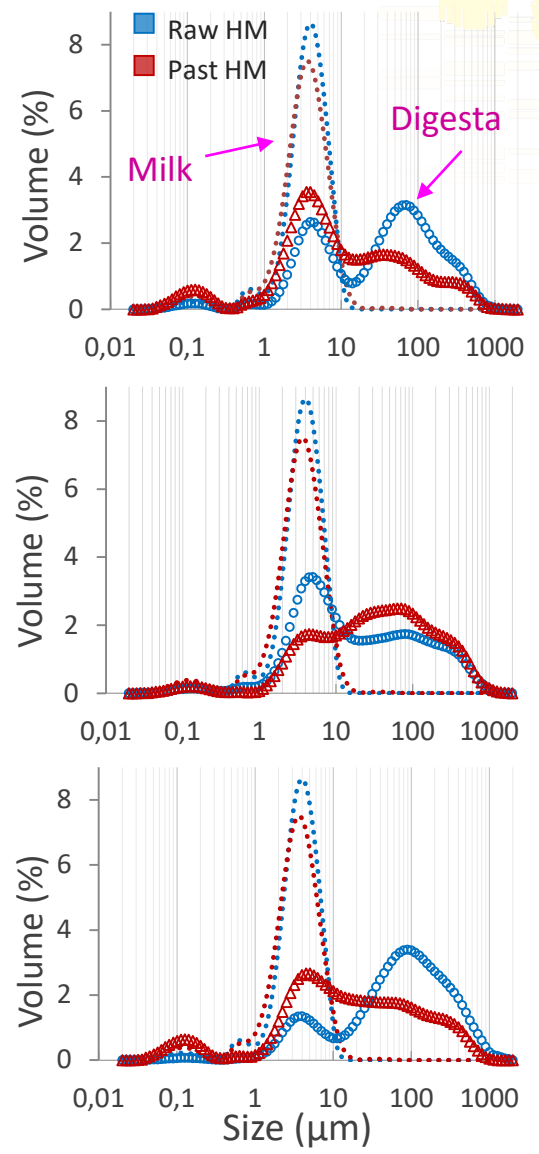
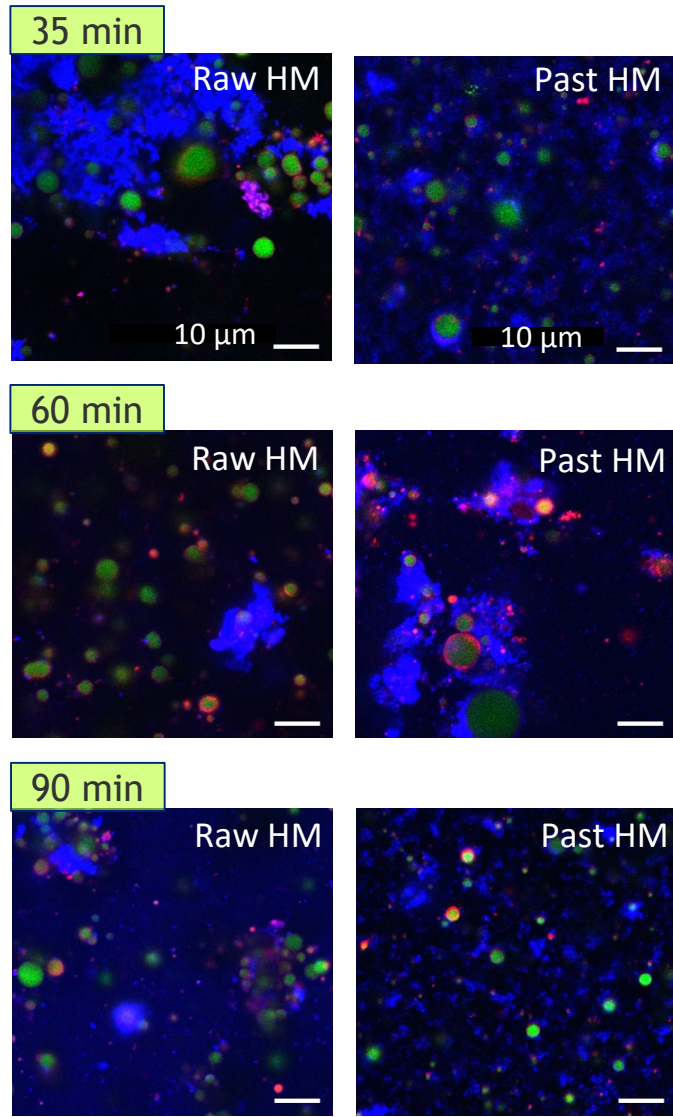
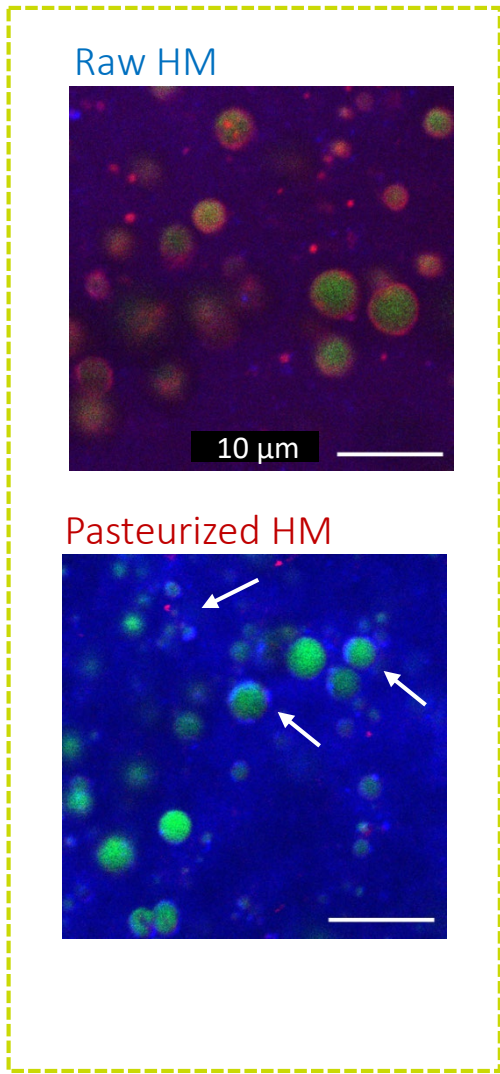
INRAE

Human milk fat globule and milk membrane

October 03-04, 2024 #pediatrics-conference/ C. Bourliou-Lacanal



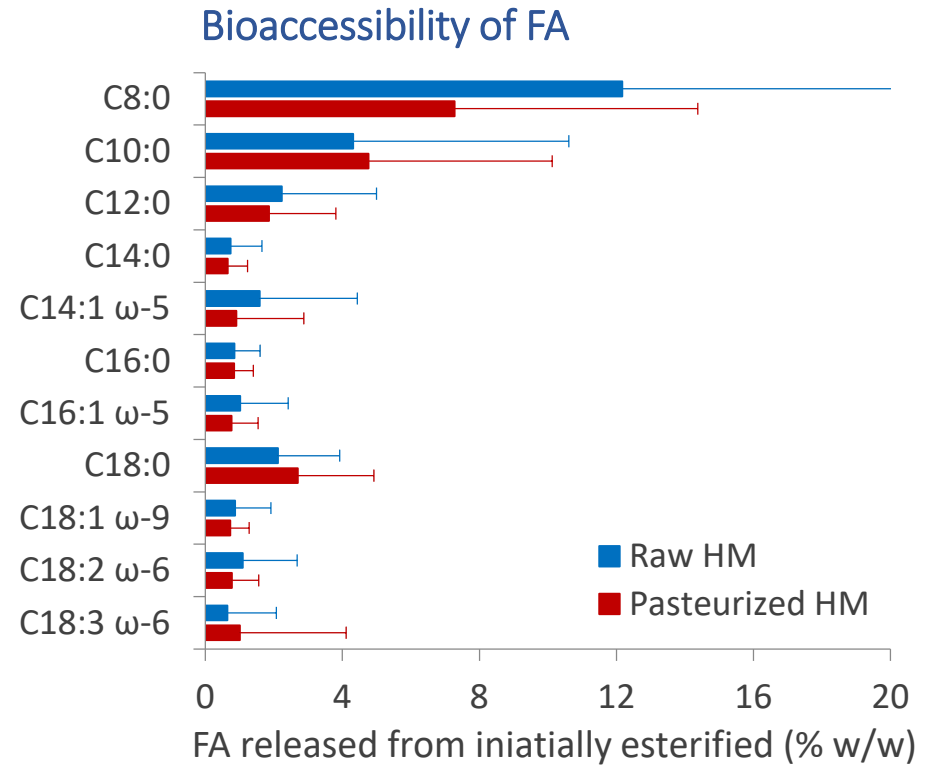
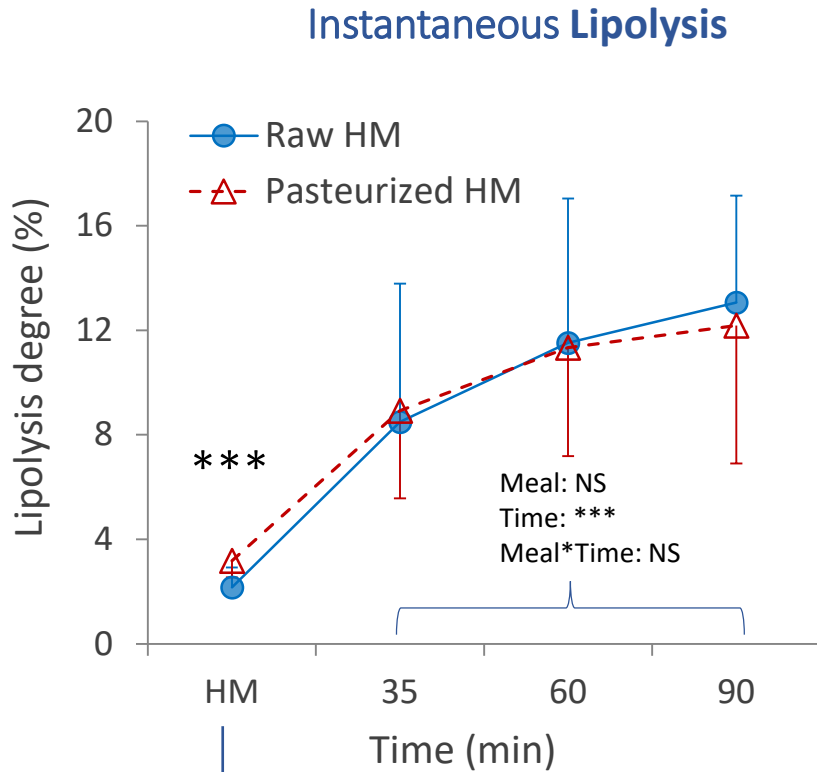
# GROUP A GASTRIC BEHAVIOUR OF HM IS DOMINATED BY AGREGATION AROUND MILK FAT GLOBULE AND INFLUENCED BY PASTEURIZATION



■ Apolar lipids 
 ■ Amphiphiles 
 ■ Proteins

(De Oliveira et al., AJCN, 2017)

# GROUP A PASTEURIZATION DID NOT LOWER LIPOLYSIS NOR BIOACCESSIBILITY BUT MODULATED PROTEOLYSIS



Pre-lipolysis: n = 4 infants

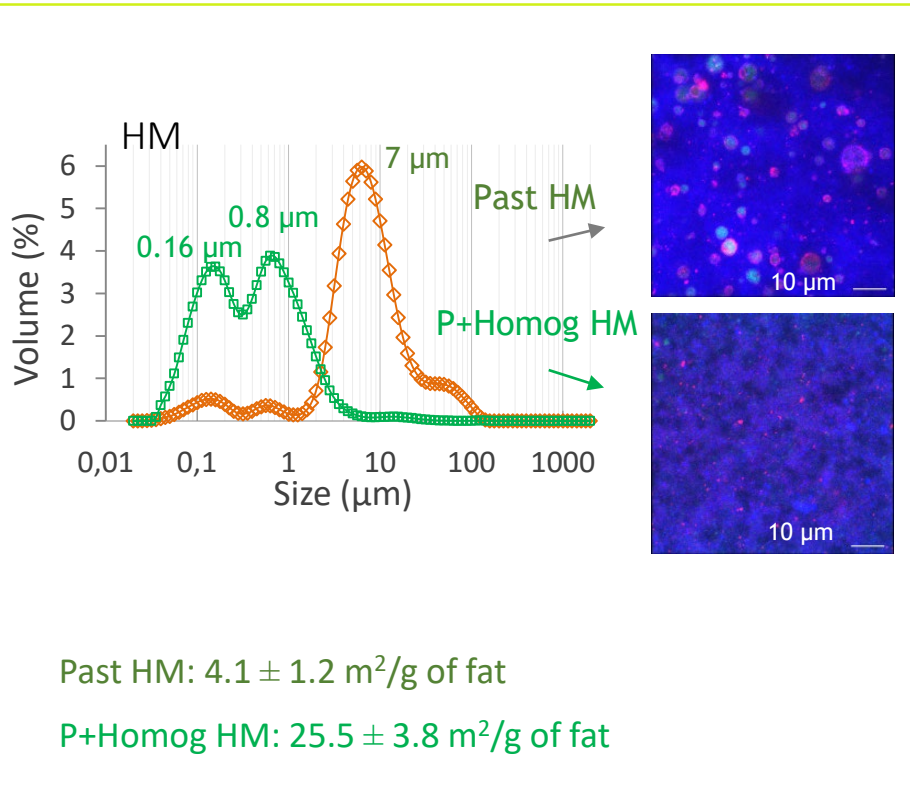
Raw HM =  $2.2 \pm 0.8\%$

Past HM =  $3.2 \pm 0.6\%$

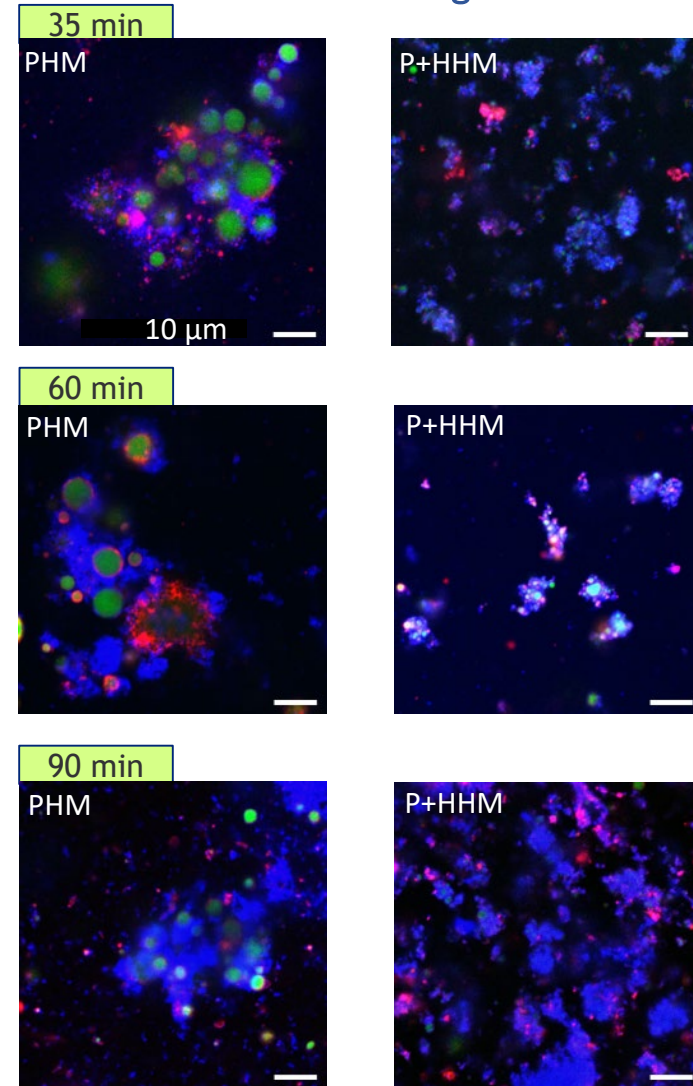
(De Oliveira et al., AJCN, 2017)

# GROUP B HOMOGENIZATION AFFECTED THE INITIAL STRUCTURE AND THE EMULSION DISINTEGRATION OF HM

Initial structure



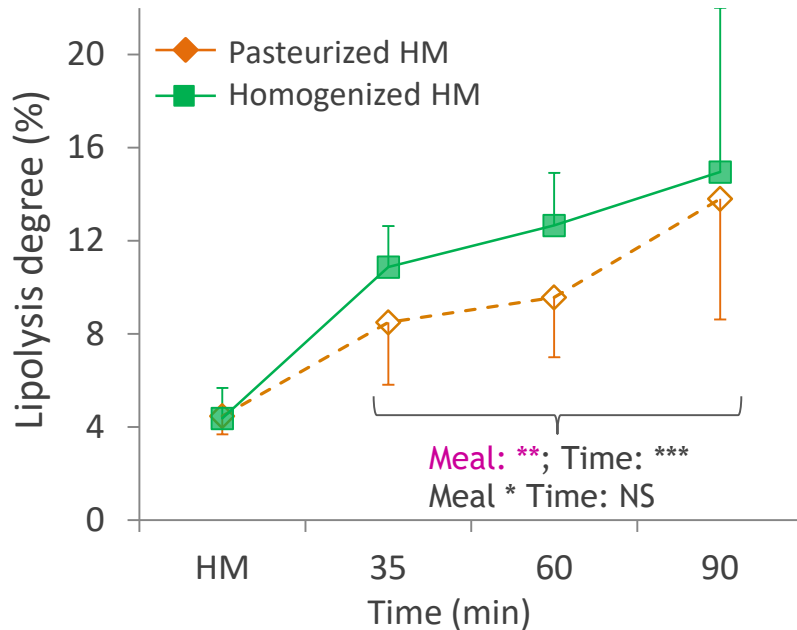
Gastric disintegration



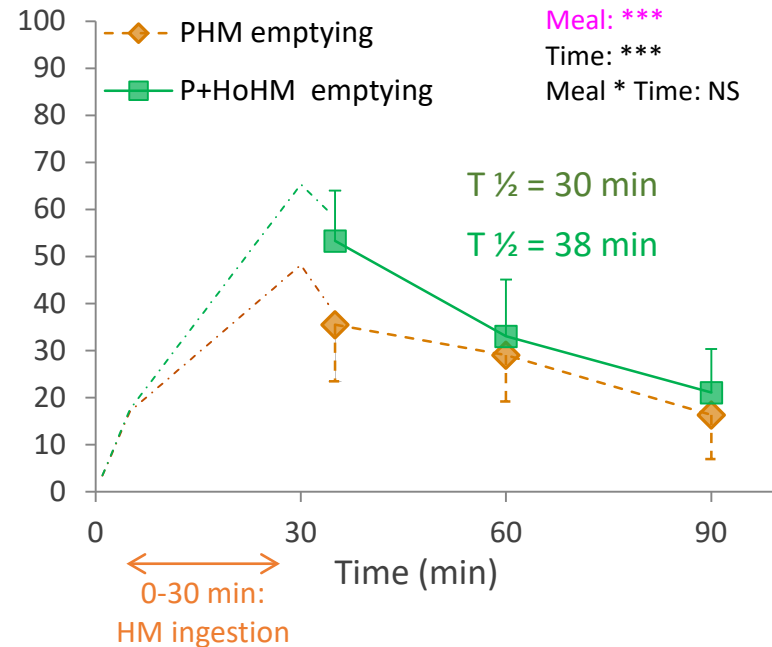
(De Oliveira et al., Clinical Nutrition ESPEN, 2017)

# GROUP B HOMOGENIZATION IMPACTED GASTRIC LIPOLYSIS AND EMPTYING

## Instantaneous lipolysis level



## Gastric emptying



■ Hormonal feedback triggered by higher lipolysis level

↗ Free fatty acids in the duodenum → ↗ cholecystinin secretion → ↘ pylorus contractions and gastric emptying  
(Grider, 1994; Yamagishi & Debas, 1978)

■ Difference of colloidal behavior between the native MFG and submicronic droplets

Half gastric emptying times reported in preterms

30 38

↗ Infant formula

PP Time (min)

# ✓ Evolution of HMFGM with lactation / during digestion



➤ HMFGM => more favorable to boost digestive lipolysis after a lag

(Armand et al. 1996, *Pediatr Res*; Fondaco et al., 2015. *Food Biophys*)



➤ MFGM => sharper sharper postprandial lipemia peak (+ 1 hr et - 4 hr)



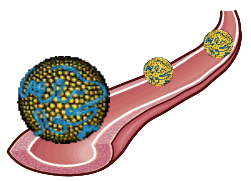
Milk polar lipids(MPL)



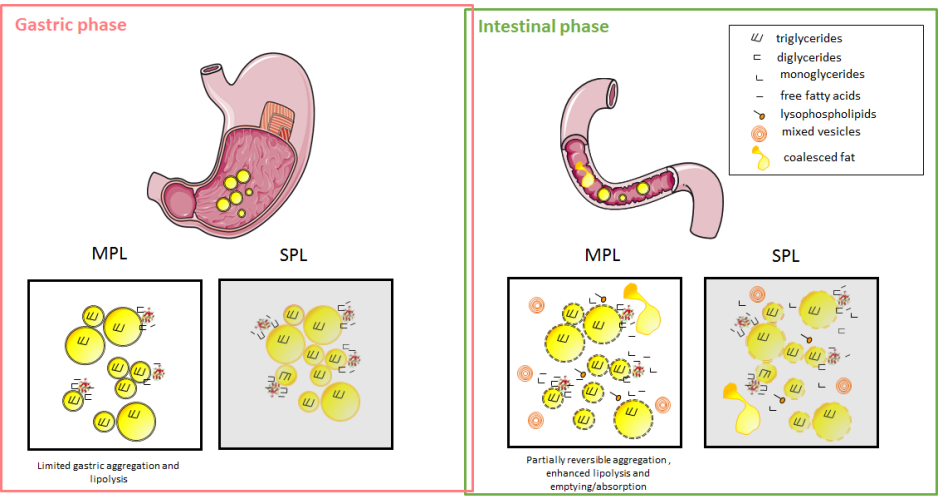
Soy lecithin (SPL)



Postprandial kinetics



(Lecomte et al., *The Journal of Nutrition*, 2015)

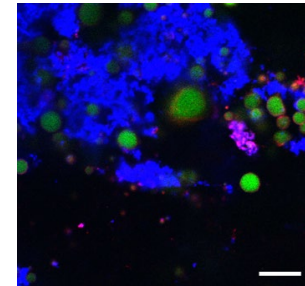
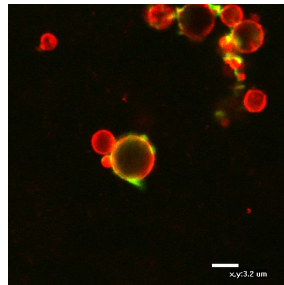
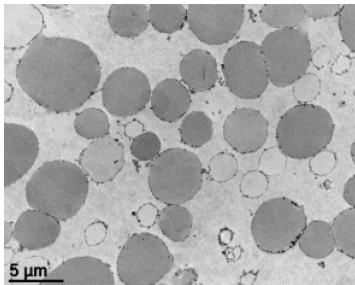


INRAE

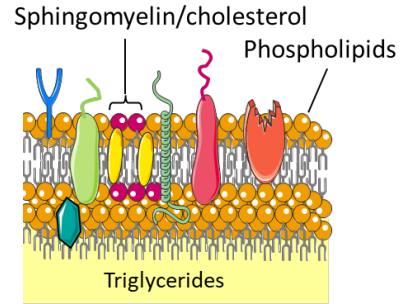


# OUTLINE

- ✓ Human milk lipids vary but have consistent structure : Human milk fat globule (HMFG)
- ✓ Part played by core constituents to deliver rapidly energy and key (micro)nutrients
- ✓ Evolution of HMFG with lactation / during digestion
- ➔ ✓ Human milk fat globule membrane, an element of resistance key in the programming effect ?



✓ Human milk fat globule membrane, an element of resistance key in the programming effect ?

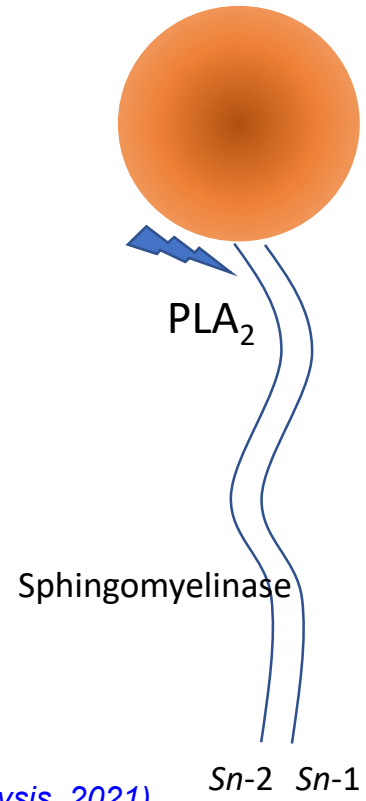
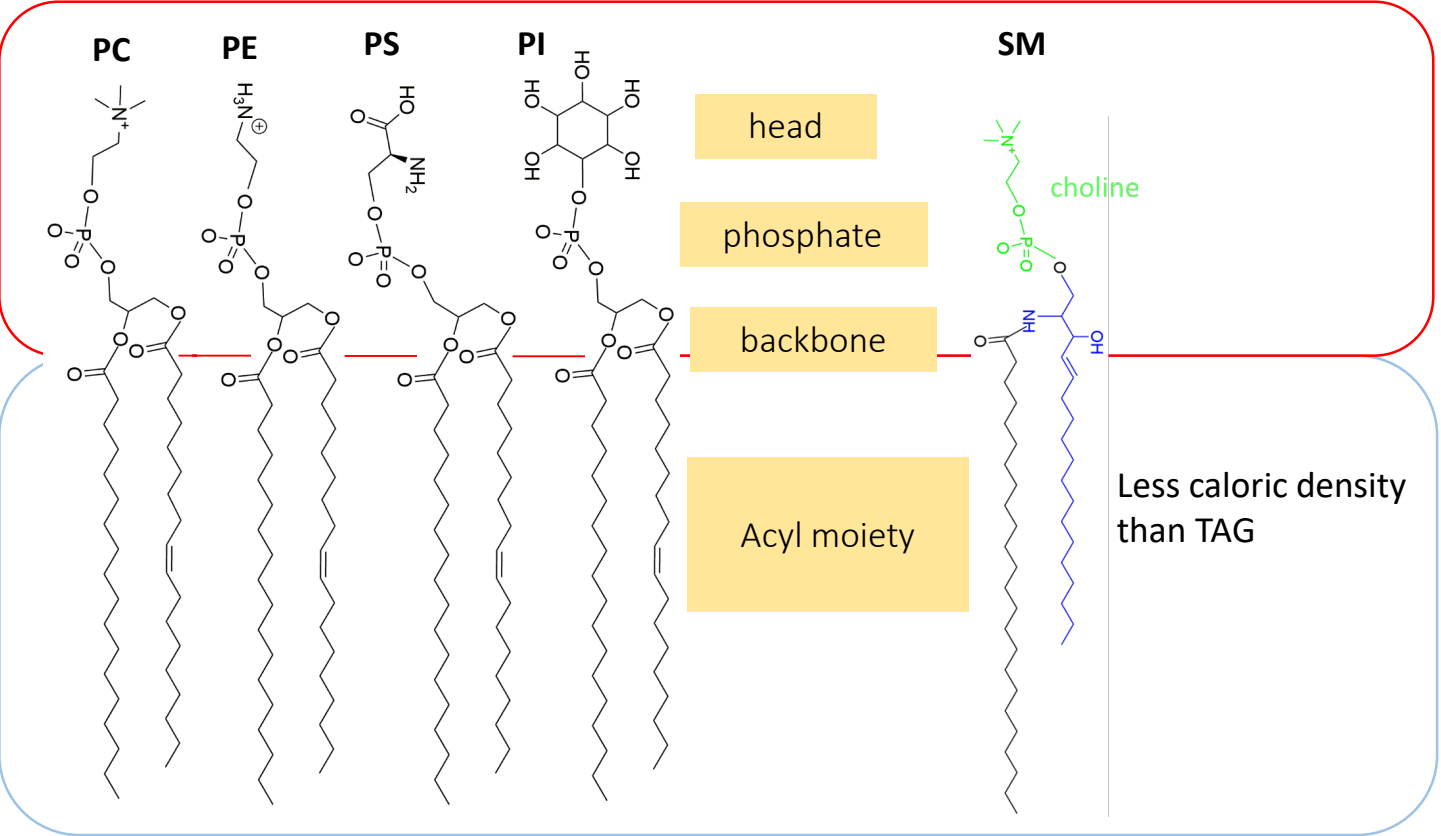


**Glycerophospholipides**

**Sphingolipids**

choline ethanolamine serine inositol

sphingomyeline



(Bourlieu et al., Chapter 9, Handbook Dairy analysis, 2021)



**INRAE**

Human milk fat globule and milk membrane  
 October 03-04, 2024 #pediatrics-conference/ C. Bourlieu-Lacanal

- lipase

+ lipase

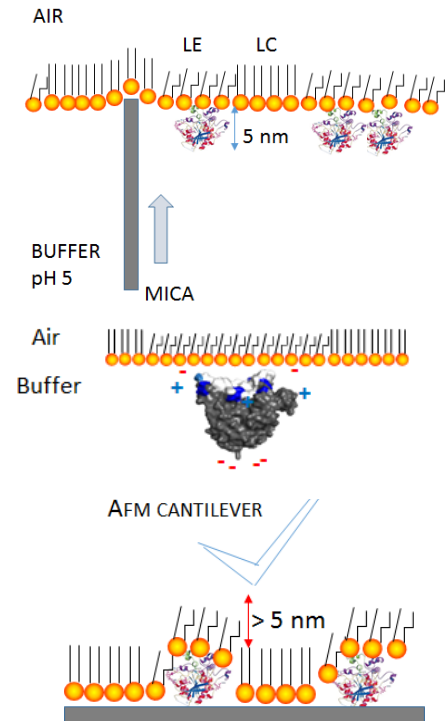


(rDGL analog of HGL)

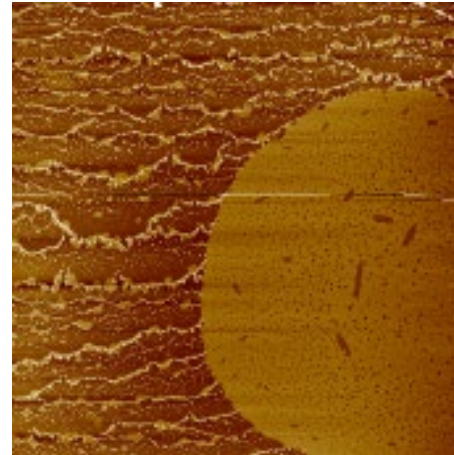
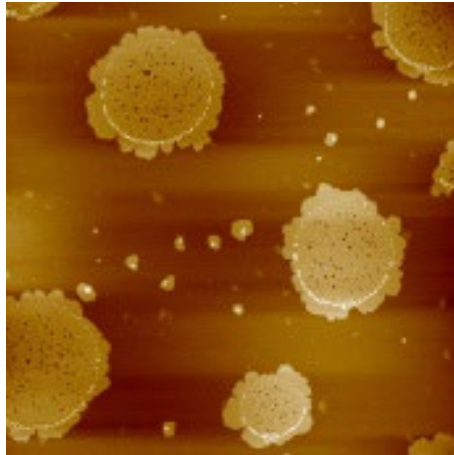
AFM images  
(8 × 8 μm<sup>2</sup>)



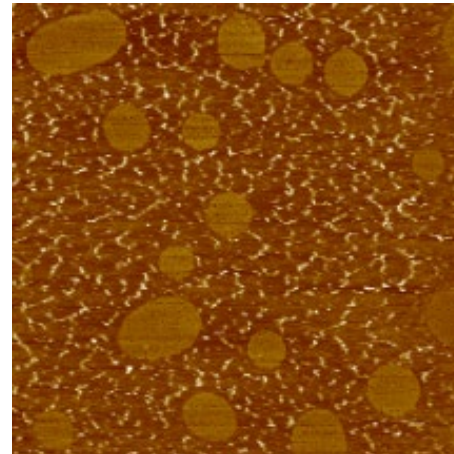
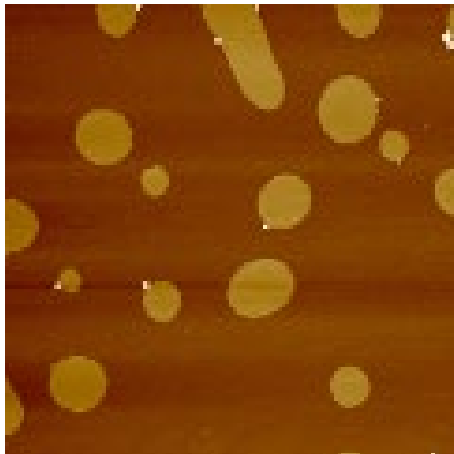
AFM imaging and topography



BMM

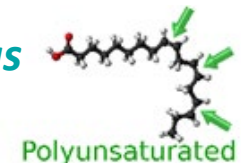


HMM



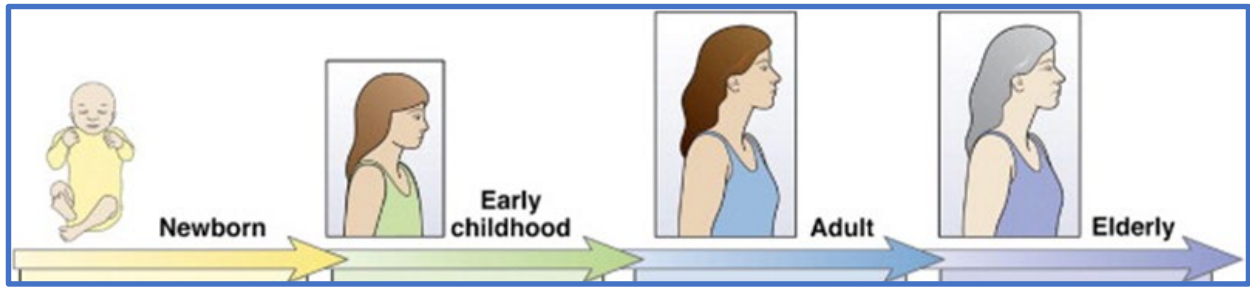
- **Global similarities** (insertion in LE phase and at phase boundaries, ↗ small LC nanodomains)
- **Higher compressibility of HMM and one level of insertion versus 3 levels in bovine membrane** (H: molecular cooperation)

(Bourlieu et al., Col. Interface B, 2016; Bourlieu et al., Biochimie, 2019)



# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect ?

➤ Beneficial health effects of MPL at key physiological stages



Cognitive, behavioural, gut health and immunity benefits (*Zavaleta et al., J Pediatr Gastroenterol Nutr, 2011; Gurnida et al. Early human development, 2012; Billeaud et al., Clin Med Insights Pediatr, 2014; Poppitt et al., JPGN, Timby et al., J Am Clin Nutr, 2014; Timby et al., J Pediatr Gastroenterol Nutr, 2015*)

↘ Febrile episodes (*Veereman-auters et al., Nutrition, 2012*)

Positive outcome on walk (*Kim et al., Arch Gerontol Geriatr, 2019; Kim et al. PLOS ONE, 2015; Minegishi et al., J Nutr Sci Vitaminol 2016*) - PLICAR

6 Double blind RCT: safety and effectiveness of formulas supplemented with MPL (*Hernell, Timby et al., J Pediatrics, 2016; Ortega-Anaya and Jimenez-Flores, J Dairy Sci, 2019*)

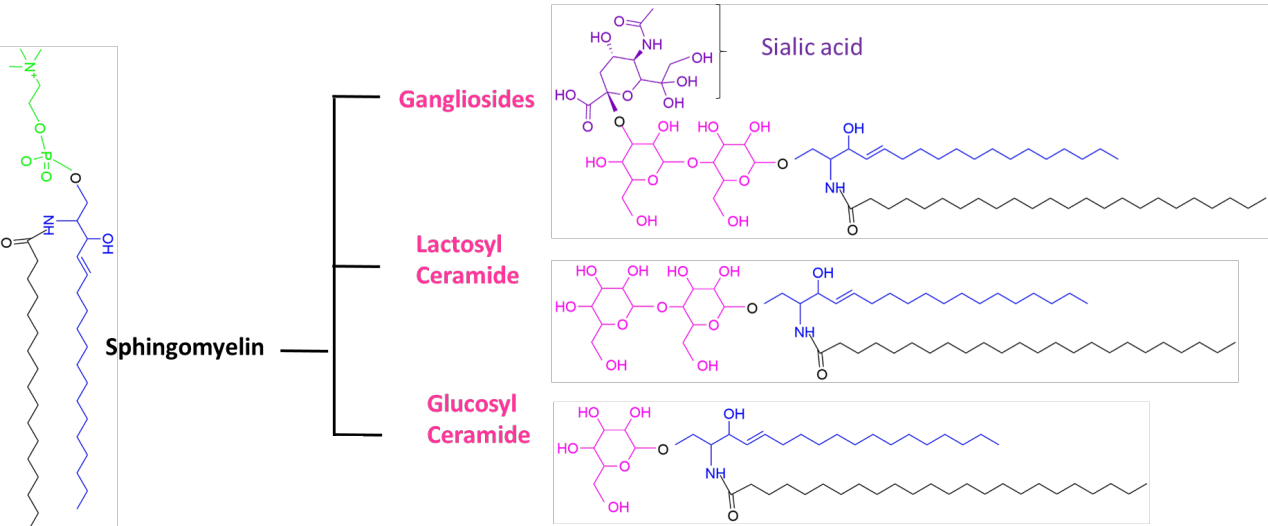
Combination of MPL + probiotic *Lactobacillus paracasei* ssp. *paracasei* strain F19 (*Li et al., Front Pediatr, 2019*)



**INRAE**

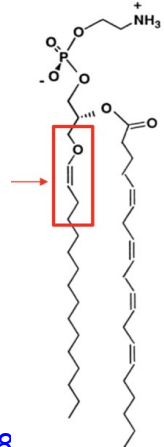
# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

- How can we explain these health effects? Sphingolipids bioactivity
- Metabolites from sphingolipids: secondary messengers that regulate cell growth, differentiation and apoptosis (*Spiegel, FASEB J, 1996*)



## ACTION PARADIGM

Complex sphingolipids ⇔ growth factor receptors, extracellular matrix and neighboring cells



Gangliosides and plasmalogens : rapid accumulation during gestation and infant development ; associated with essential processes (synaptic development and myelination) for appropriate growth and development of the brain.

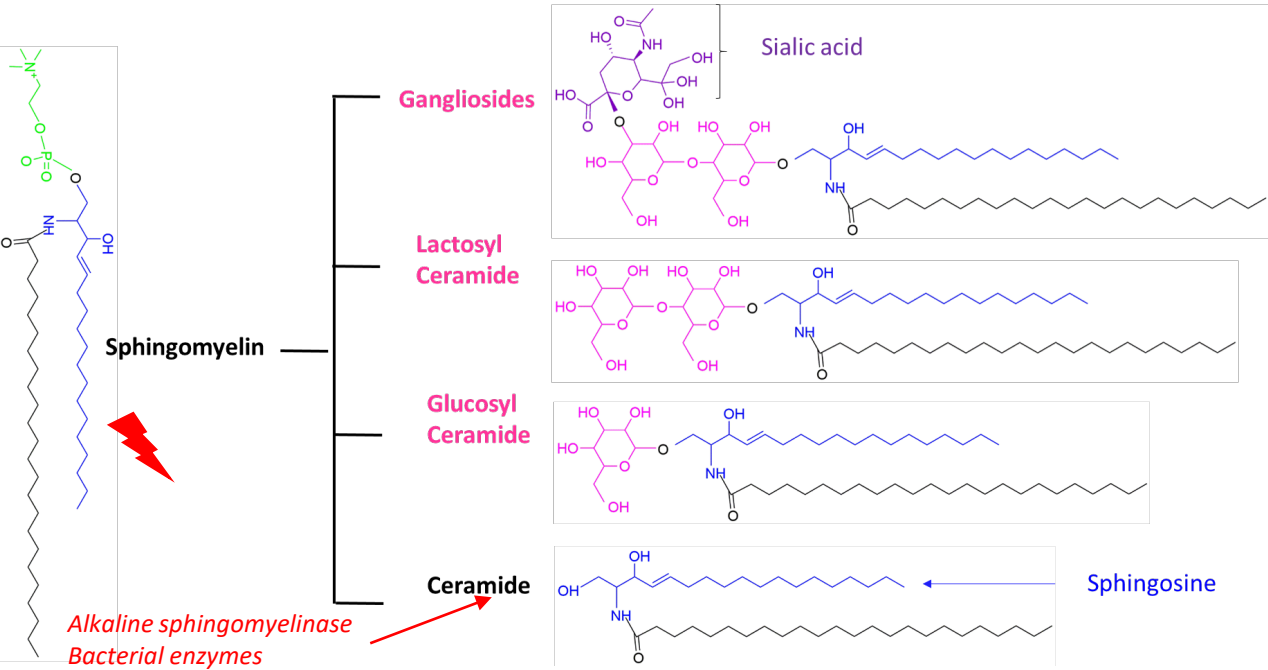
(*Martinez and Ballabriga, Gang. Plasmalogens Brain Res., 1978,*



**INRAE**

# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

- How can we explain these health effects? Sphingolipids bioactivity
- Metabolites from sphingolipids: secondary messengers that regulate cell growth, differentiation and apoptosis (*Spiegel, FASEB J, 1996*)



## ACTION PARADIGM

Complex sphingolipids ⇔ growth factor receptors, extracellular matrix and neighboring cells

Backbone molecules sphingosine / ceramides regulate kinases, phosphatases, ions carriers... => APOPTOSIS

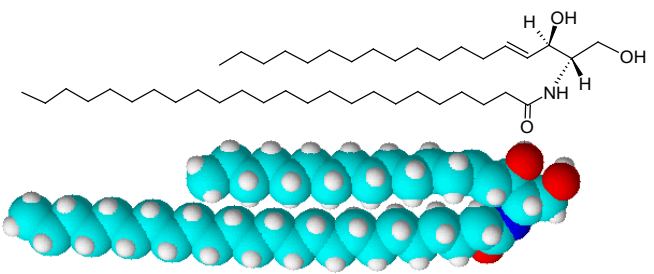




# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

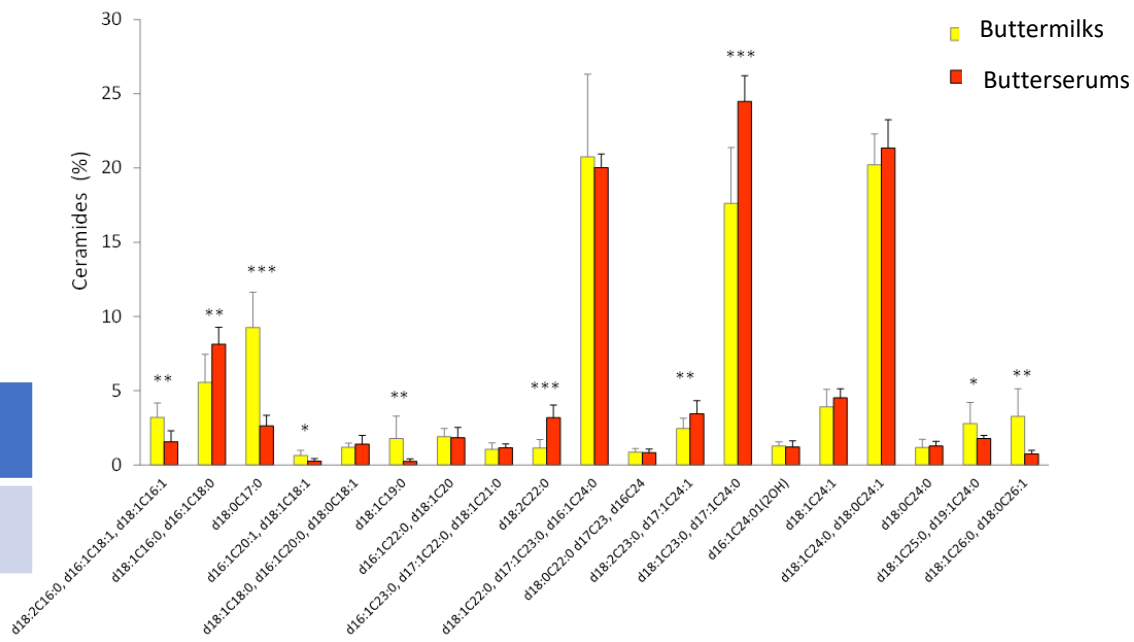
- How can we explain these health effects? Sphingolipids bioactivity
- Metabolites from sphingolipids: secondary messengers that regulate cell growth, differentiation and apoptosis (*Spiegel, FASEB J, 1996*)

*Ceramide d18:1C22:0*



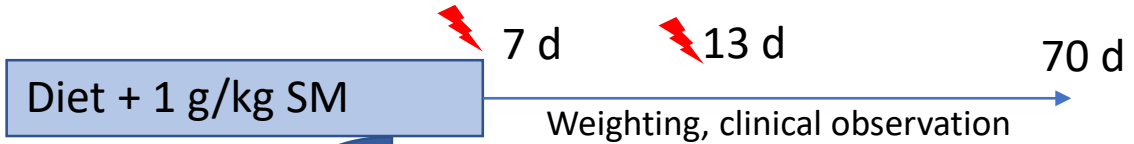
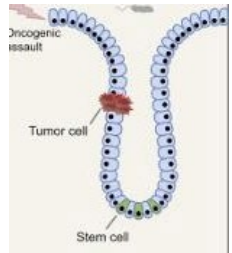
| Ratios ceramides /sphingomyelin (% mol/mol) | Buttermilk | Butterserum |
|---|------------|-------------|
|   | 1/5        | 1/10        |

(*Bourlieu, Cheillan, et al. Food Chem 2018*)



**INRAE**

# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?



Normal / Ko PPAR- $\gamma$   
 Induced Colitis / dextran sodium sulfate induced cancer / azoxymethane

↘ inflammatory lesions with SM, stronger survival PPAR- $\gamma^{+/+}$   
 but ↘ not related to PPAR- $\gamma$  (Mazzei et al. J Nutr Biochem, 2011)

7 d Sprague-Dawley rat pups

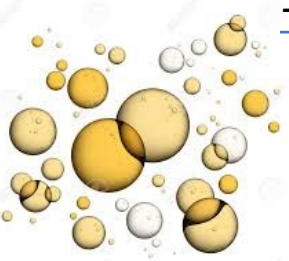
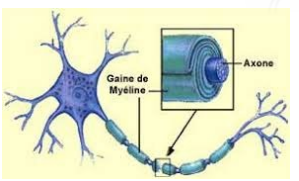


cannulated intragastrically / reared artificially on milk with 0.5 % SM or 0.5 % PC



SM plays an important part in gut maturation

(Motouri et al., J Pediatr Gastroenterol Nutr, 2003)



Diet + 810 mg/100 g of SM derived from bovine buttermilk

Dietary SM contributes to CNS myelinisation during development (Oshida et al., Ped Res, 2003)

⚡ Treated with I-Cycloserine inhibiting sphingolipid biosynthesis

# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

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## Impact on microbiota ?

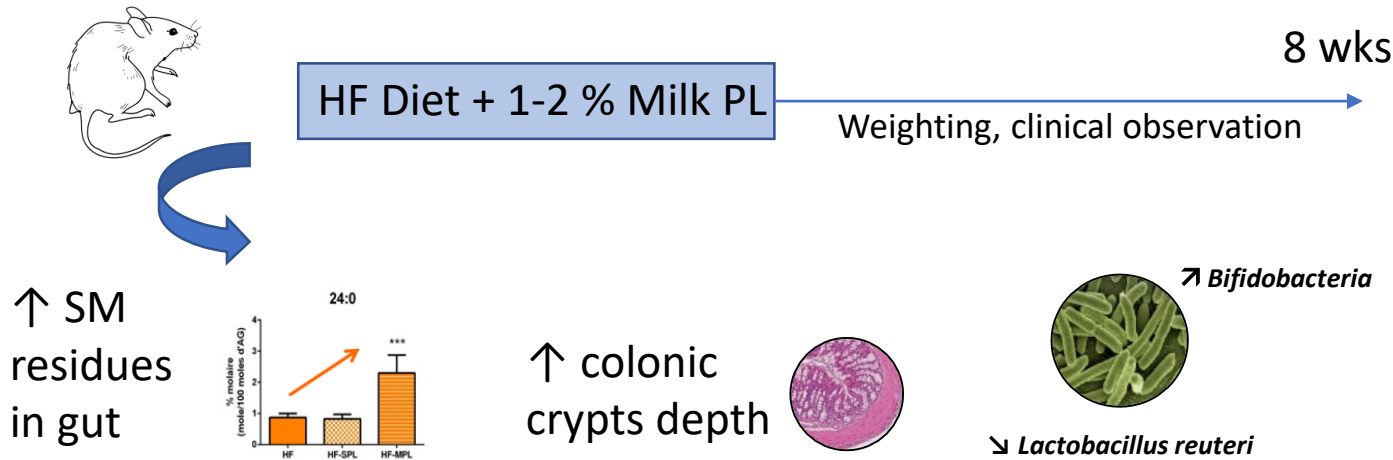
- milk sphingolipids => protective effect against bacterial toxins /development via competition for bacteria binding sites as many bacteria binds to epithelial cell via glycosphingolipids
- ⇒ Decrease pathogens adherence to mucosa
  
- Reinforced bactericidal effect of lysosphingomyelin

*(El-Loly , Pol J Food Nutr Sci, 2011; Sprong et al., 2001. Antimicrob Agents Chemother)*



# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

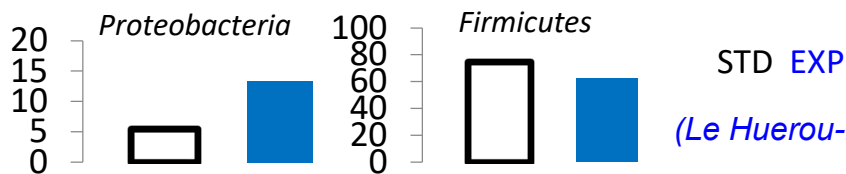
Impact on microbiota ?



(Milard et al., Mol Nutr Food Res, 2019)



➤ Piglet model => dairy fat + MPL => promotes intestinal and immune development and positively influenced the intestinal microbiota



(Le Huerou-Luron et al., Eur. J. Nutr., 2016)



INRAE

# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

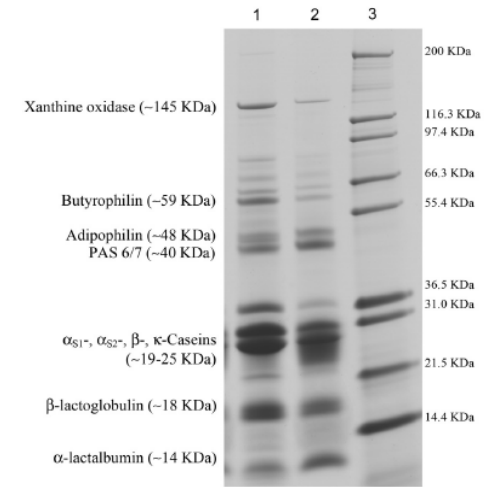
- Membranes fragments: anti-bacterial/viral, anti-inflammatory, immune modulation

(Zanabria et al. *Food Func.*, 2013; Zanabria et al. *JDS*, 2014; Bourlieu and Michalski, *COCN* 2015; Bourlieu et al., *CND*, 2017)

Anti-proliferative effect modulated by heat treatment (Zanabria et al. *J Dairy Sci.*, 2013)

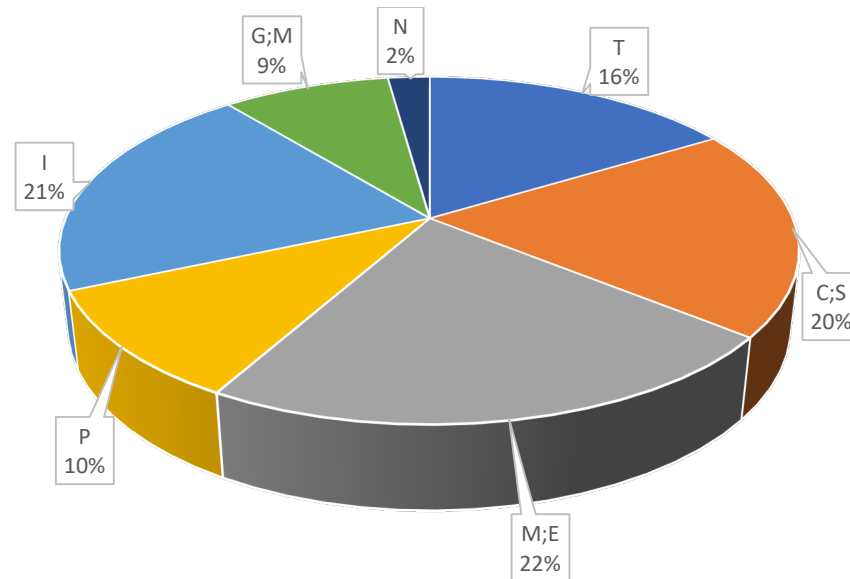
## ✓ Complementary constituents

- Residual proteins (Gassi et al. *Int Dairy J.*, 2016)
- Minerals



# ✓ Human milk fat globule membrane, an element of resistance key in the programming effect?

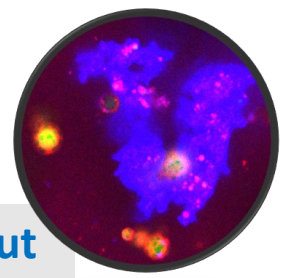
- Proteins of HMFGM : 1 % total mass MFG, 1-4 % total milk protein, very bioactive fraction
- Proteome over lactation : 191 proteins included glycosylated proteins



Functional characteristics of HMFGM proteins. With : C;S cell communication; signal transduction; N nucleobase, nucleoside, nucleotide and nucleic acid regulation; I immune response; G;M cell growth and/or maintenance; T transport; P (protein metabolism); M;E metabolism;energy pathways; M multiple.



# ✓ TAKE Home messages

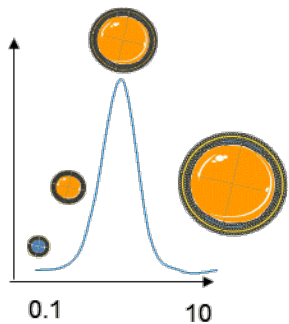


Complexity of HMFG and HMFGM ... well addressed by high high throughput screening tools and meta-analyses – towards an assembly effect far beyond the nutritional part played by each individual compounds

Digestive behaviour of HMFG is specific

## - Size of droplets in emulsion /quality of interface

- Directly determines surface available for lipase adsorption and lipolysis kinetics
- Influences gastric aggregates size and emptying
- Impact subsequent PP plasma kinetics : higher TG



## - Regiodistribution of FA on TAG

- Induces specific release of FA and favours PUFA absorption

## - MFGM

- Persistent elements (sphingolipids, glycosphingolipids, glycosylated proteins...) => gut maturation and microbiota education



For your kind  
attention and  
invitation

To colleagues and collaborators of  
projects VALOBAB, ARCHILACT-LACTA...