WORLD CONGRESS
ON OILS & FATS AND
ISF LECTURESHIP SERIES

Rosario, Argentina - Salón Metropolitano
September 15-19, 2025

Expanding lipid sciences and industries by analysis and development of novel microbial functions

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Fermentation:

Transformation of compounds by activities of microorganisms.

For examples in wine brewing, glucose in the grape juice is transformed into ethanol by metabolisms of microorganisms.

Fermentation supports our good health and life, better society, and maintain good environments of the earth.

The first description of brewing was found in
The ***Epic of Gilgamesh*** is written in **Mesopotamia** in B.C. 2000.

Figures of wine brewing on the wall of pyramid in ancient Egypt

In Europe, in 6th century, monasteries started brewing using their well-organized infrastructure.

Japanese sake was reported from about 2,000 years after establishment of rice cultivation.
Modern sake manufacturing was established around 16th to 17th century.

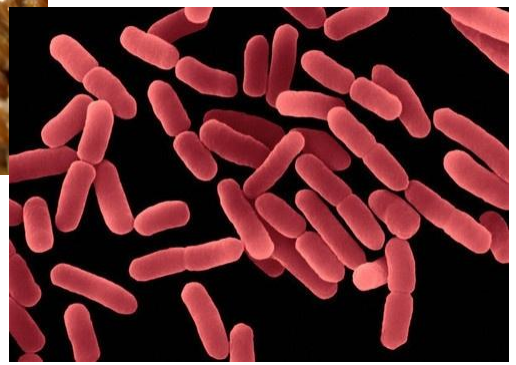
秋里籬島「摂津名所図会」1798年
“Figures of famous places in Osaka” by Ritou Akishima in 1798

Mold (*Aspergillus oryzae*)

Yeast
(*Saccharomyces sereviciae*)

Lactic acid bacteria

Mold (*Aspergillus oryzae*)



Bacillus subtilis var. *natto*

History of industrial fermentation

Ancient brewing

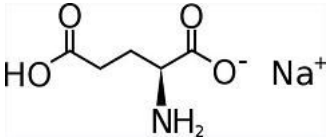
Alcohol fermentation

Acetone butanol ethanol fermentation

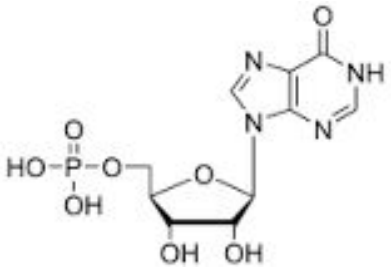
Organic acid fermentation

Antibiotics fermentation

Amino acid fermentation



1955~ Dr. Shukuo Kinoshita & Dr. Shigezo Udaka



Nucleoside / nucleotide fermentation

1957~ Dr. Akira Kuninaka

Lipid fermentation
(Single cell oil)

1985~ Prof. Hideaki Yamada & Prof. Sakayu Shimizu

Natural isolates

↓

Mutant breeding

↓

Molecular breeding

↓

Metabolic engineering

↓

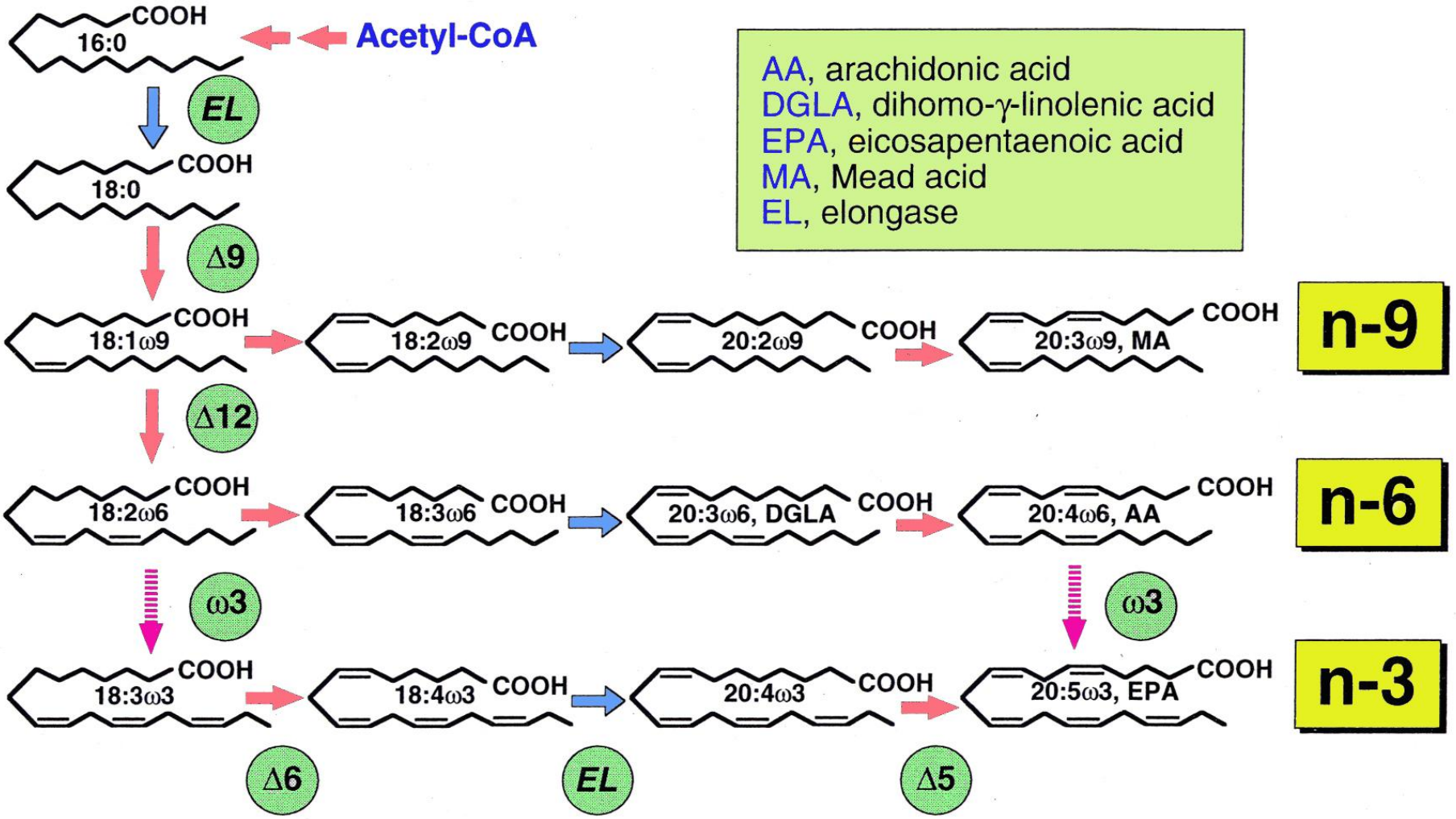
Synthetic biology

Expanding lipid sciences and industries by analysis and development of novel microbial functions

1) Polyunsaturated fatty acid production and modification

2) Gut microbial fatty acid metabolism

Fatty acids in animals and plants



1) Polyunsaturated fatty acid production and modification

Various physiological activity

- Cardiovascular fitness
- Cerebral function development
- Anticancer
- Lipid metabolism control
- Immune and inflammation control

Precursor of active metabolites

- prostaglandin, leukotriene, thromboxane
- Anti-inflammatory mediators: resolvins etc.

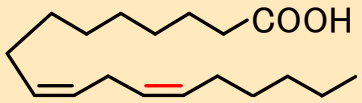
Current source… fish oil, plant oil

- unstable supply
- low purity
- contamination of unhealthy compounds

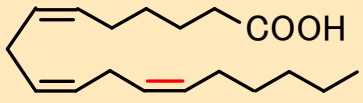
Microbial oil

as alternative source

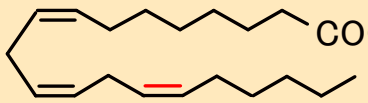
ω6 (n-6) PUFAs



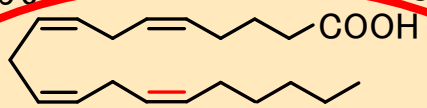
Linoleic acid
LA, 18:2ω6



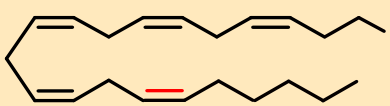
γ-Linolenic acid
GLA, 18:3ω6



Dihomo-γ-linolenic acid
DGLA, 20:3ω6

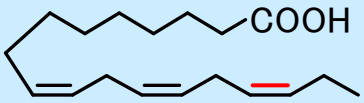


Arachidonic acid
AA, 20:4ω6

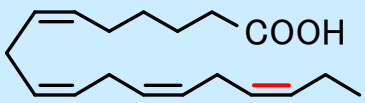


n-6 Docosapentaenoic acid
n-6 DPA, 22:5ω6

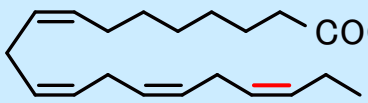
ω3 (n-3) PUFAs



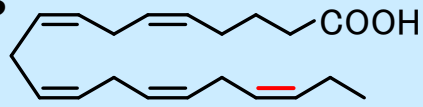
α-Linolenic acid
ALA, 18:3ω3



Stearidonic acid
SDA, 18:4ω3



Eicosatetraenoic acid
ETA, 20:4ω3



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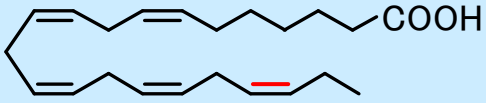
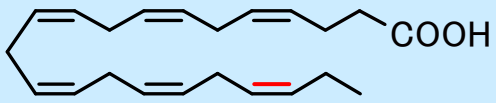
EPA, 20:5ω3

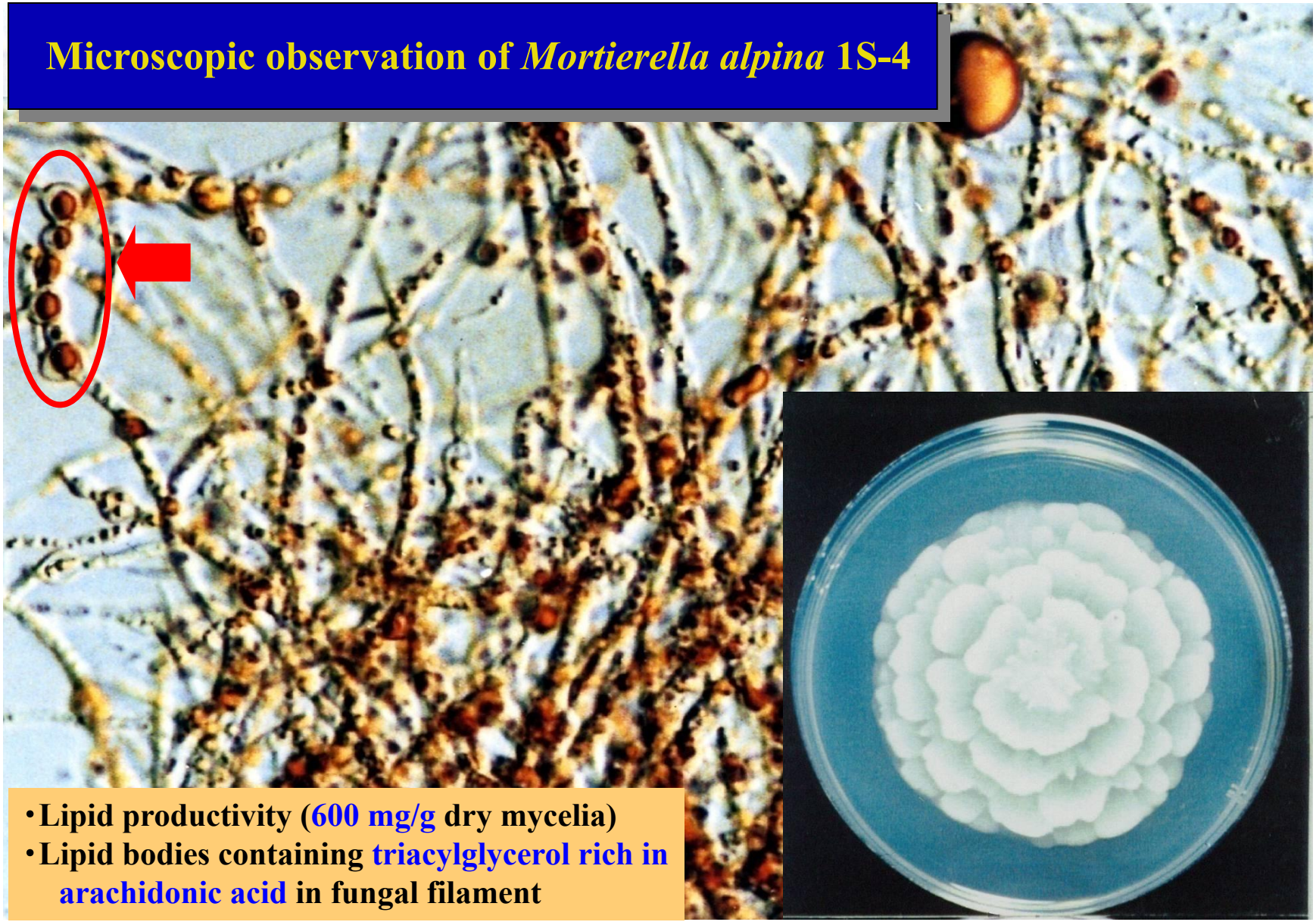


n-3 Docosapentaenoic acid
n-3 DPA, 22:5ω3

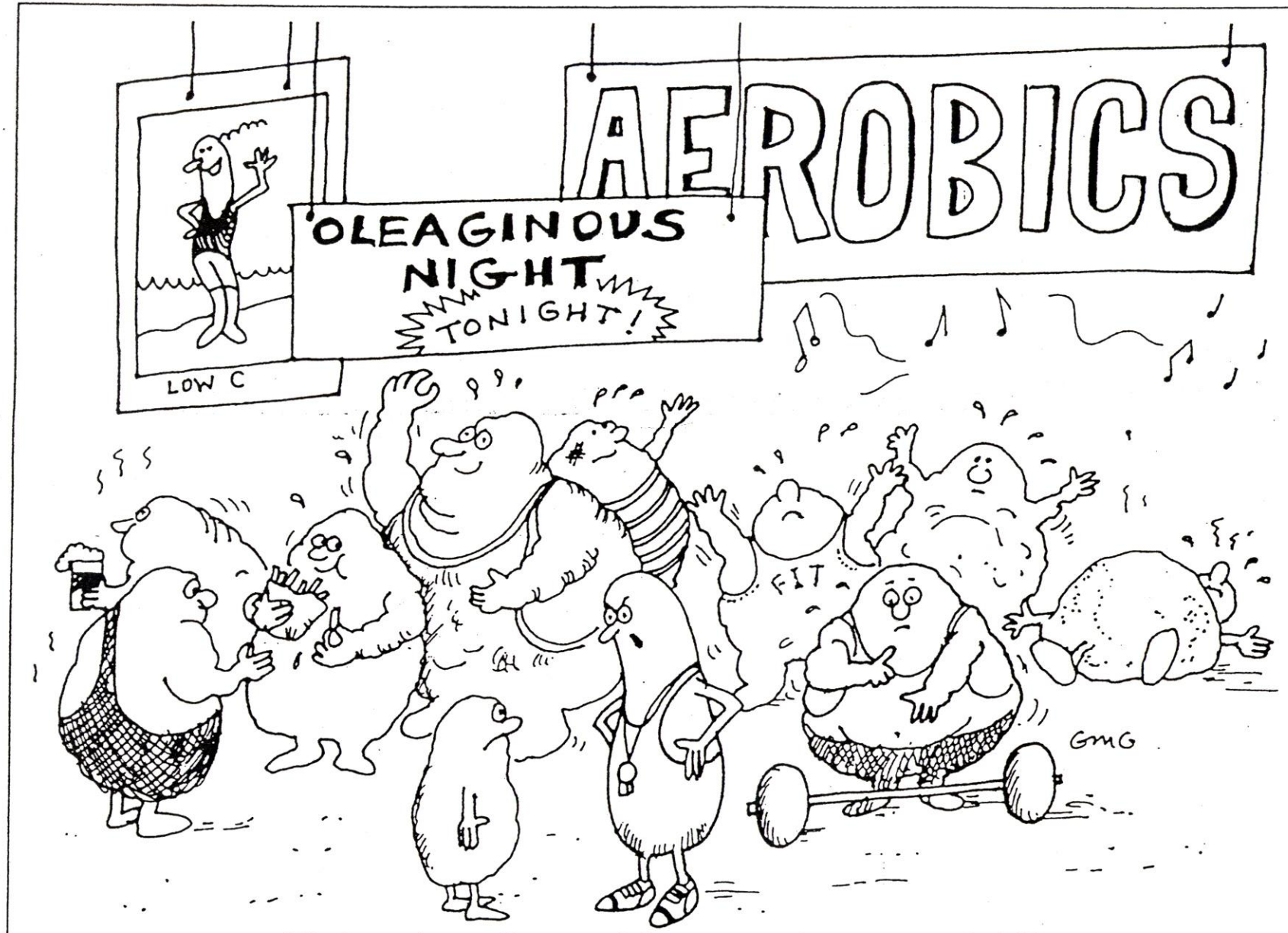


Docosahexaenoic acid
DHA, 22:6ω3

Microscopic observation of *Mortierella alpina* 1S-4

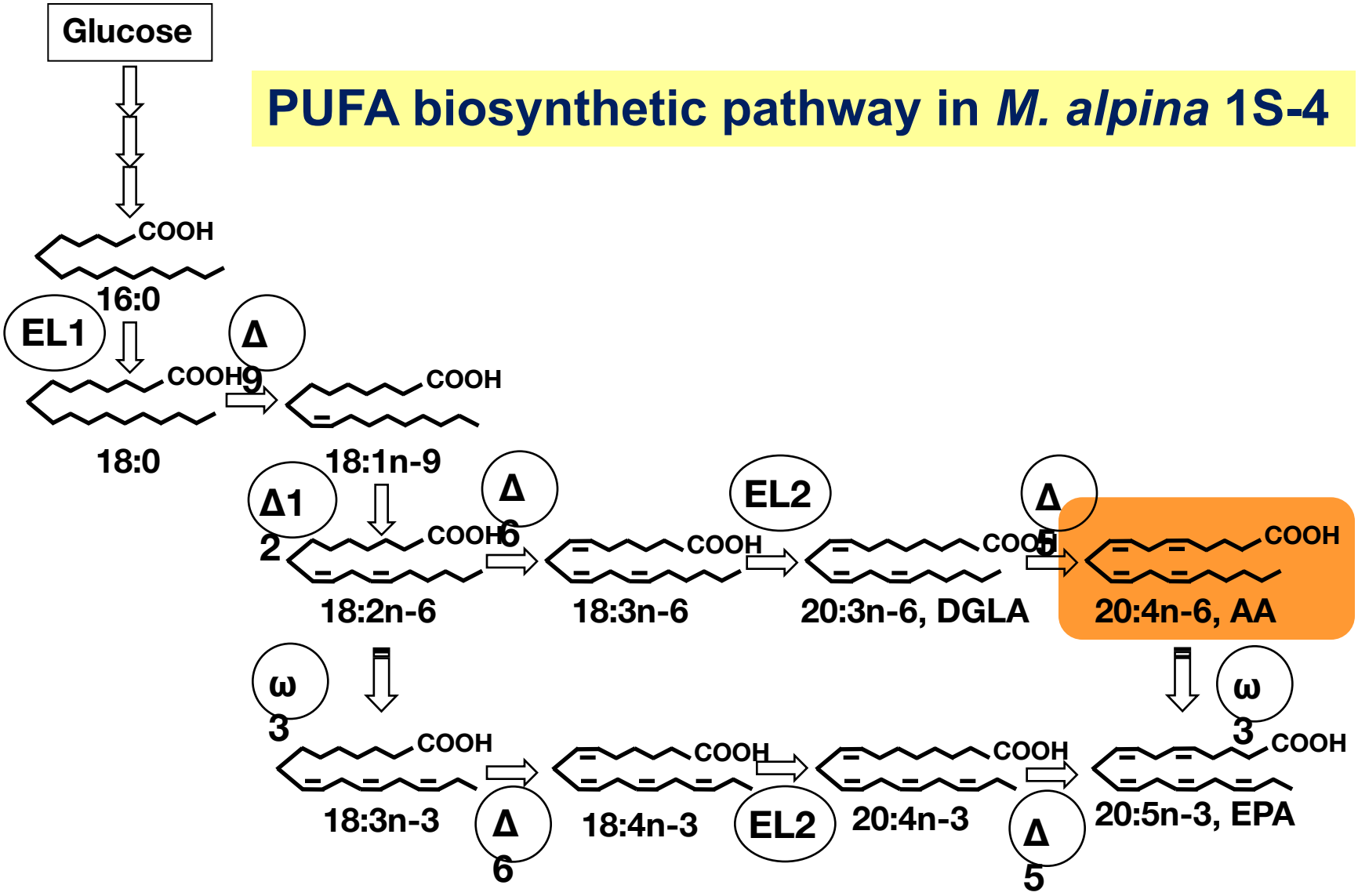


- Lipid productivity (600 mg/g dry mycelia)
- Lipid bodies containing triacylglycerol rich in arachidonic acid in fungal filament

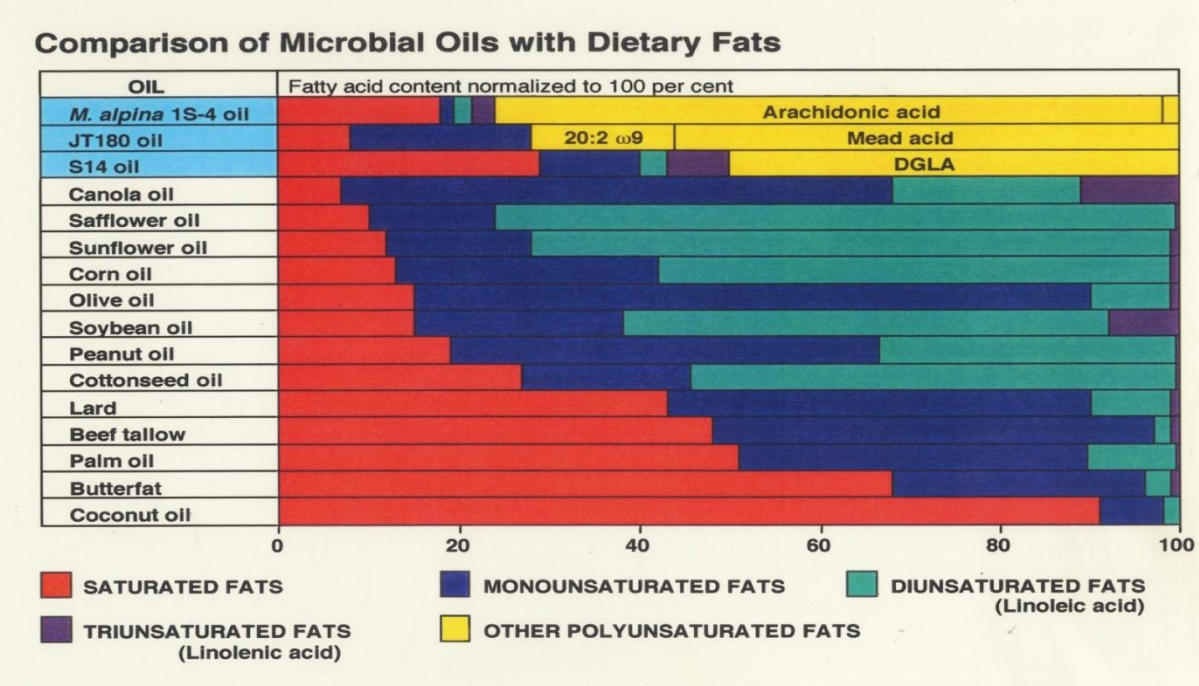


'It's hopeless. Some of them are almost 80% lipid!'

PUFA biosynthetic pathway in *M. alpina* 1S-4

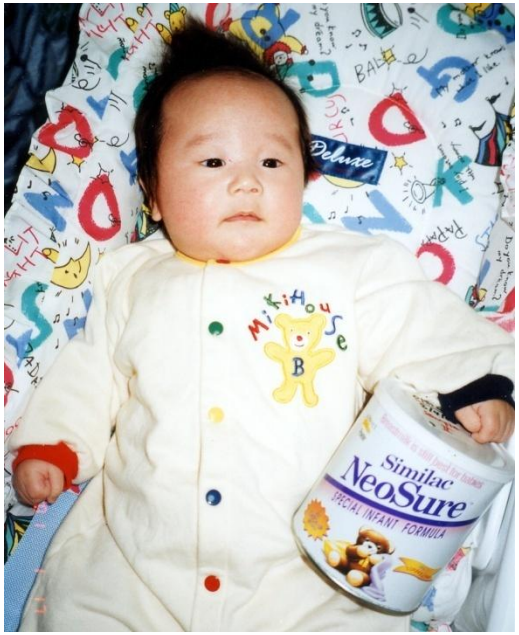


Fatty acid profile of "Single Cell Oil" produced by *M. alpina* is quite different from common edible oils and is used as an ingredient for infant formula in the world.

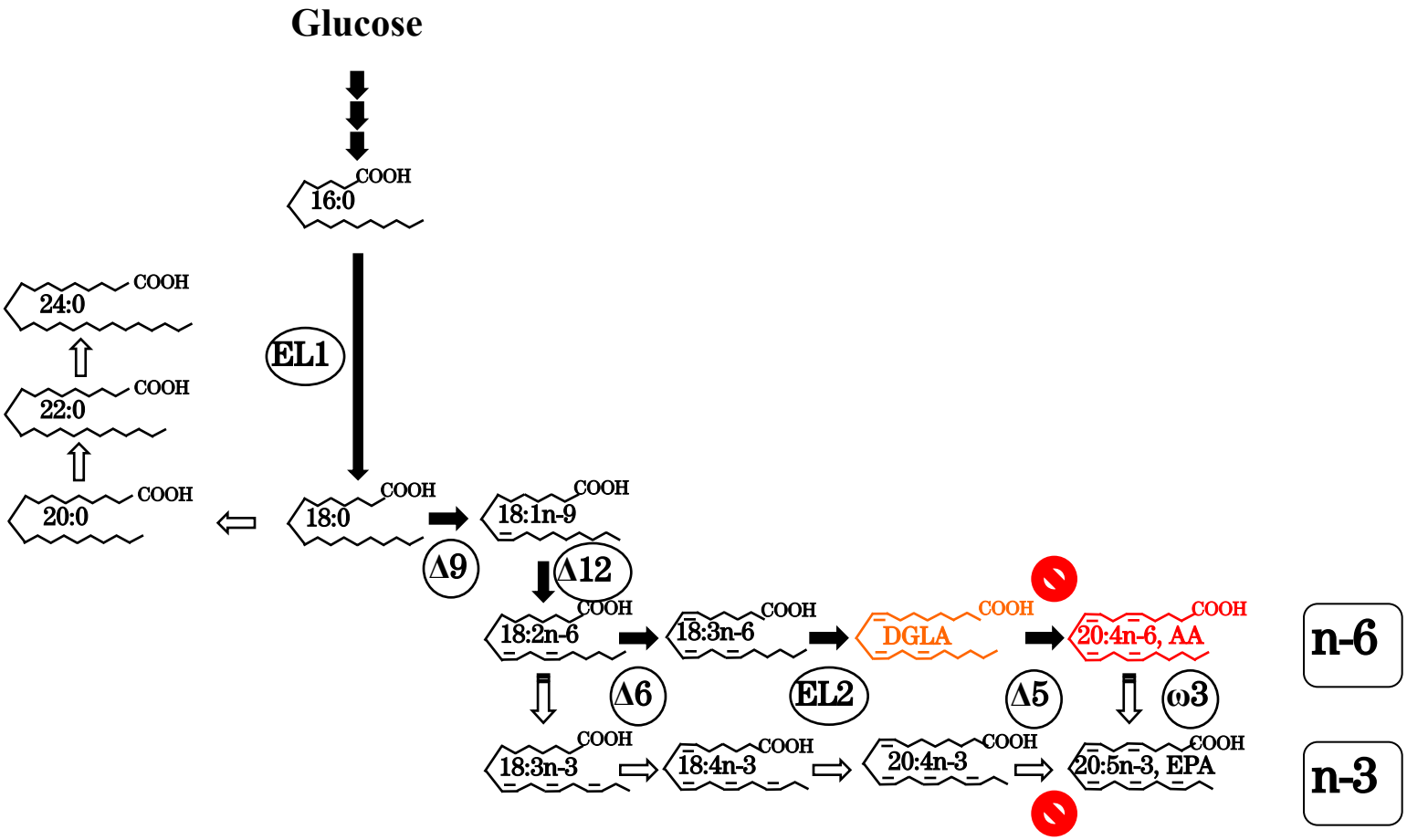


Used for Infant milk ingredients

Looks like plant oils for diet, but the fatty acid profile is quite different and rich C20 n-6 PUFA



Various PUFA biosynthetic pathways in *M. alpina* and its mutants



Sakuradani, E. et al, *Appl. Microbiol. Biotechnol.*, 84, 1-10 (2009).

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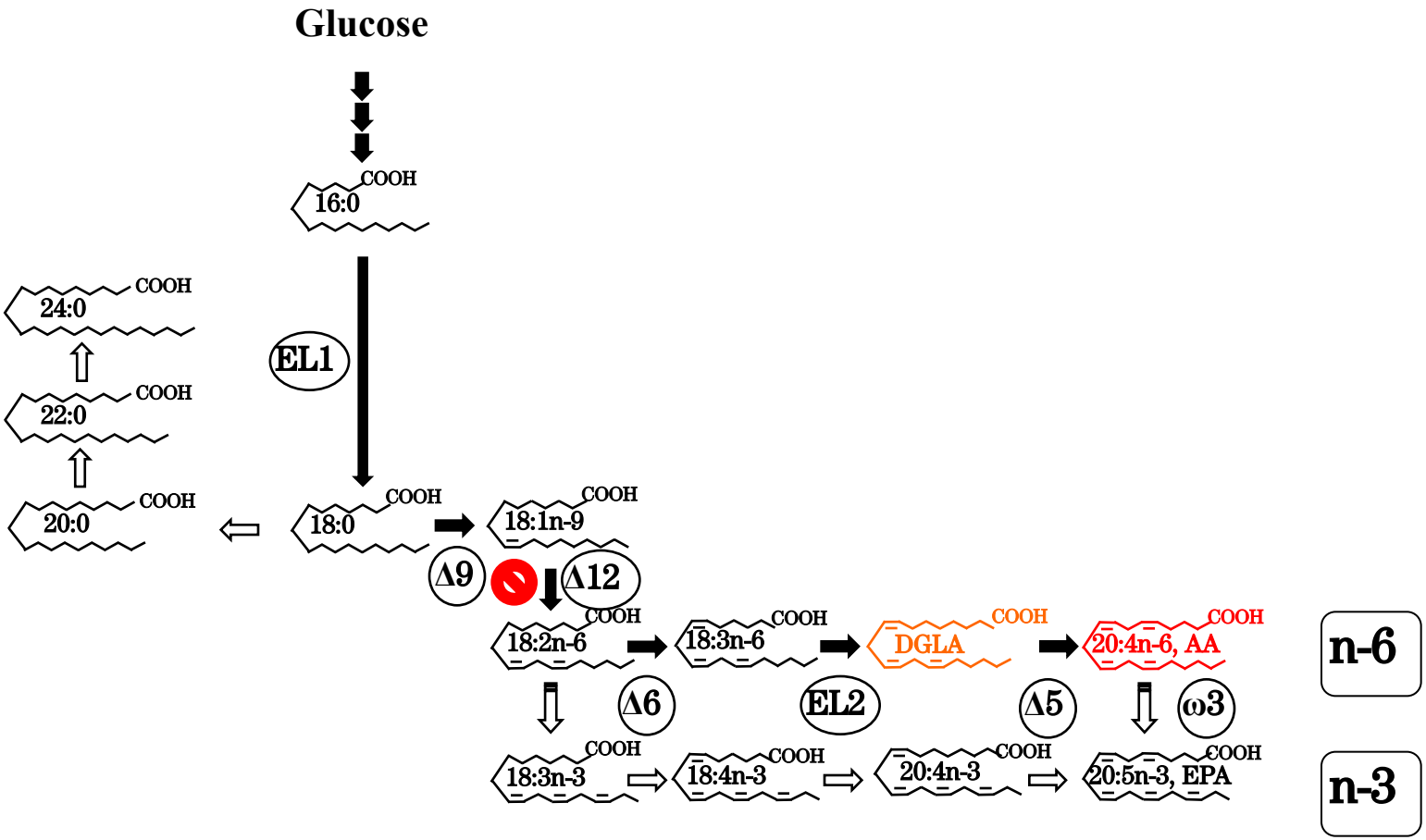

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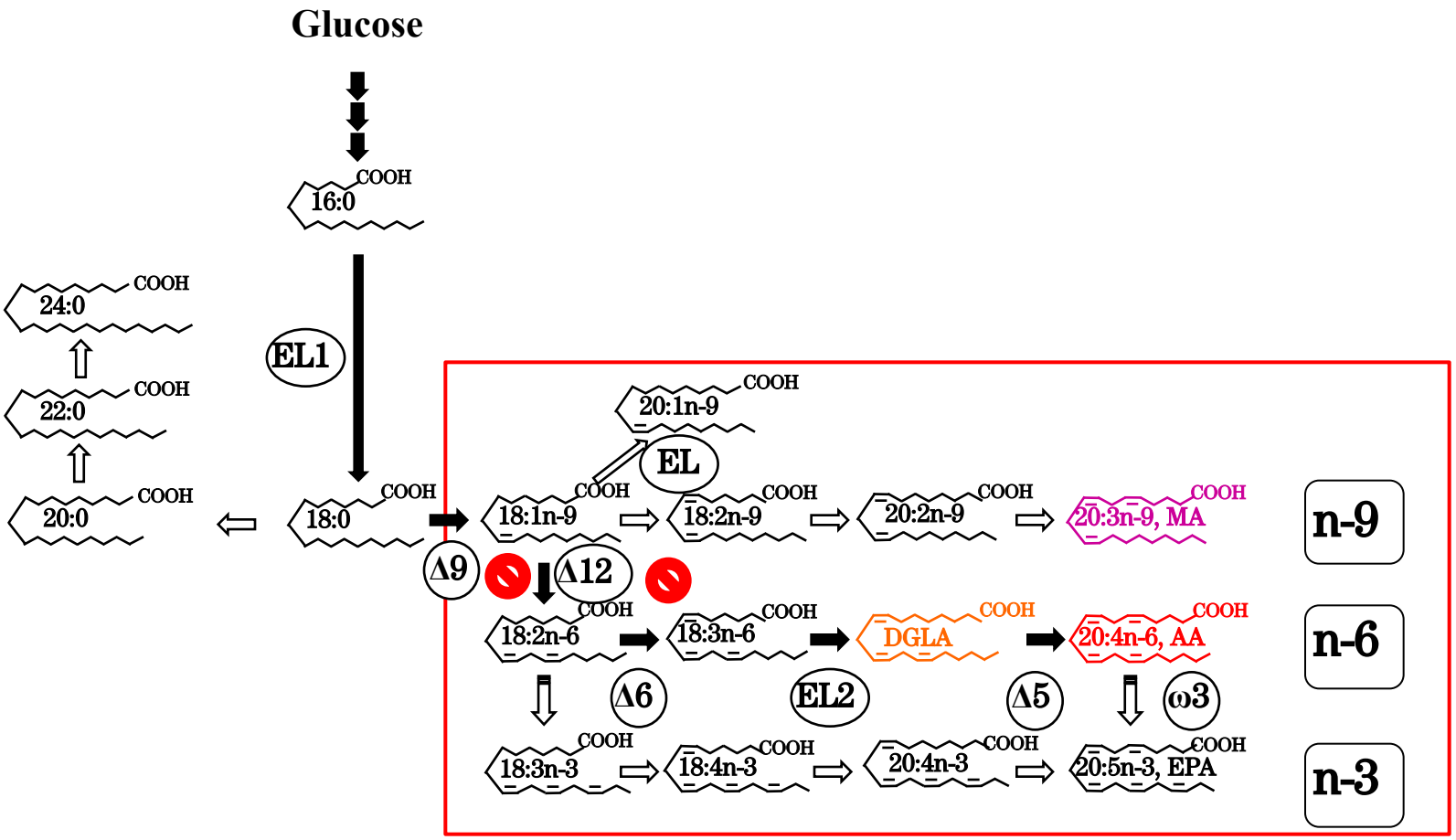

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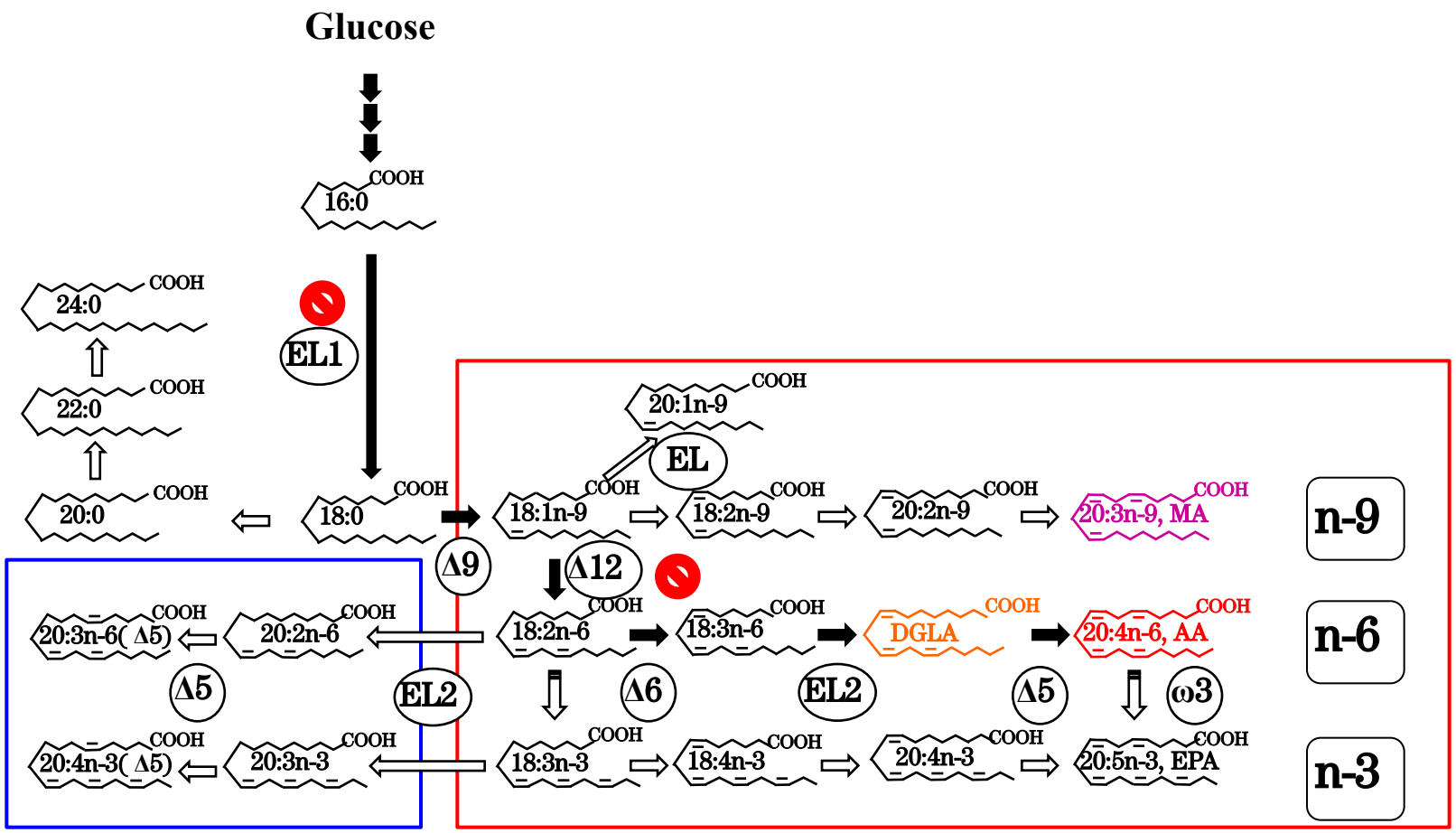

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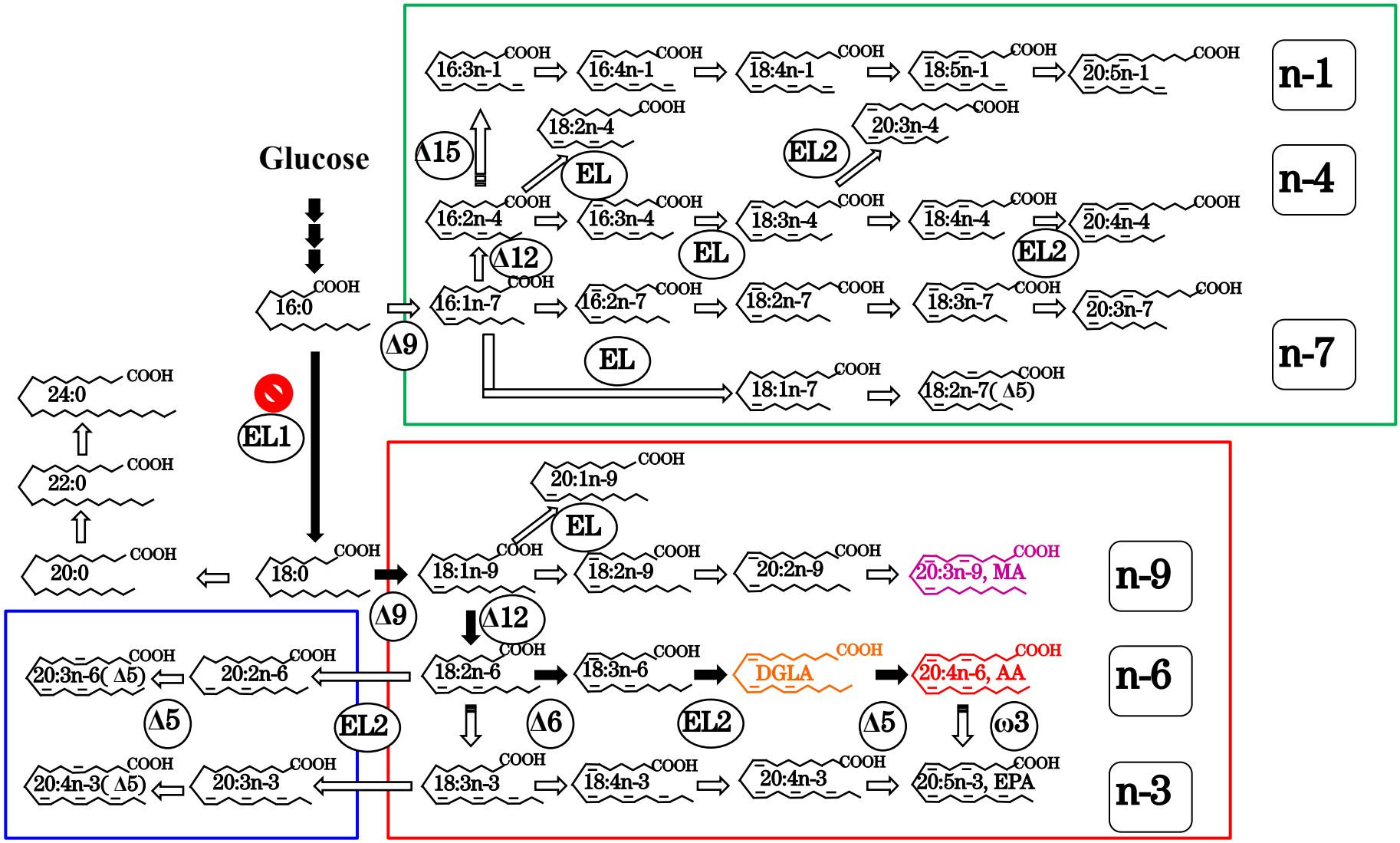

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1) Polyunsaturated fatty acid production and modification

Various physiological activity

- Cardiovascular fitness **(Medical use)**
- Cerebral function development
- Anticancer
- Lipid metabolism control
- Immune and inflammation control

Precursor of active metabolites

- prostaglandin, leukotriene, thromboxane
- Anti-inflammatory mediators: resolvins etc.

Current source… fish oil, plant oil

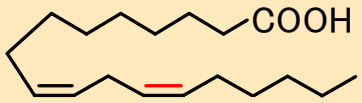
- unstable supply
- low purity
- contamination of unhealthy compounds

Microbial oil

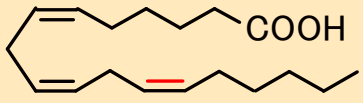
as alternative source

Molecular breeding for efficient production

ω6 (n-6) PUFAs



Linoleic acid
LA, 18:2ω6



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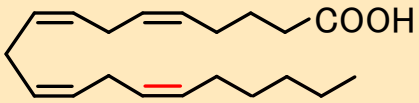
DGLA, 20:3ω6



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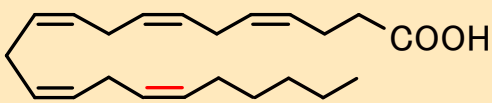
AA, 20:4ω6



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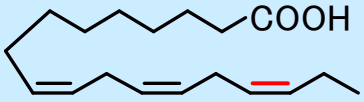
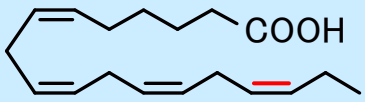
n-6 DPA, 22:5ω6

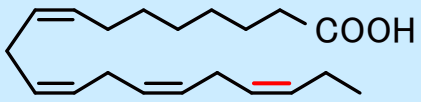
ω3 (n-3) PUFAs



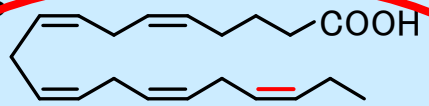
α-Linolenic acid
ALA, 18:3ω3



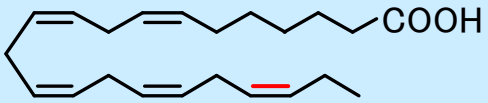
Stearidonic acid
SDA, 18:4ω3



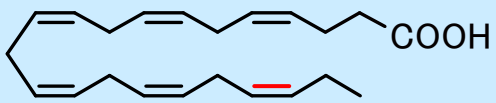
Eicosatetraenoic acid
ETA, 20:4ω3



Eicosapentaenoic acid
EPA, 20:5ω3



n-3 Docosapentaenoic acid
n-3 DPA, 22:5ω3



Docosahexaenoic acid
DHA, 22:6ω3

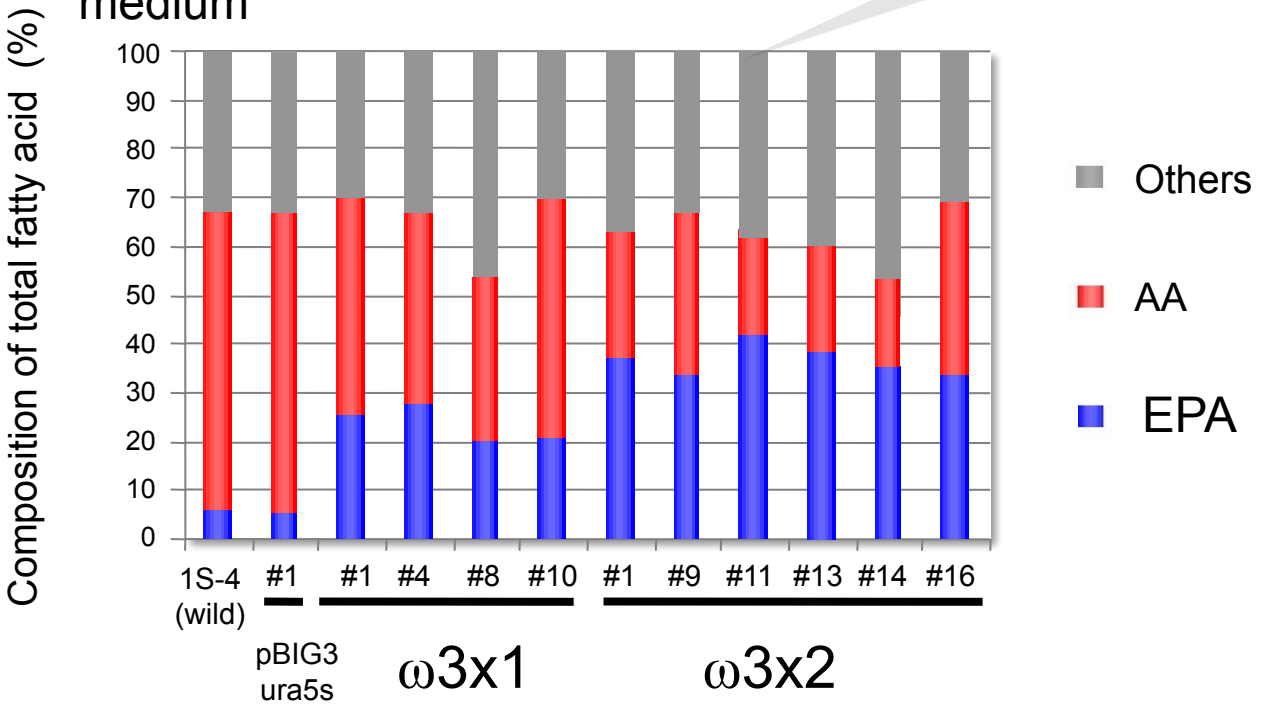
The homologous ω3-desaturase gene was overexpressed in *M. alpina* 1S-4 and succeeded in raising EPA production, but only under low cultivation temperature.

28ºC 、2 days and 12ºC、12 days cultivation

2% glucose
1% yeast extract

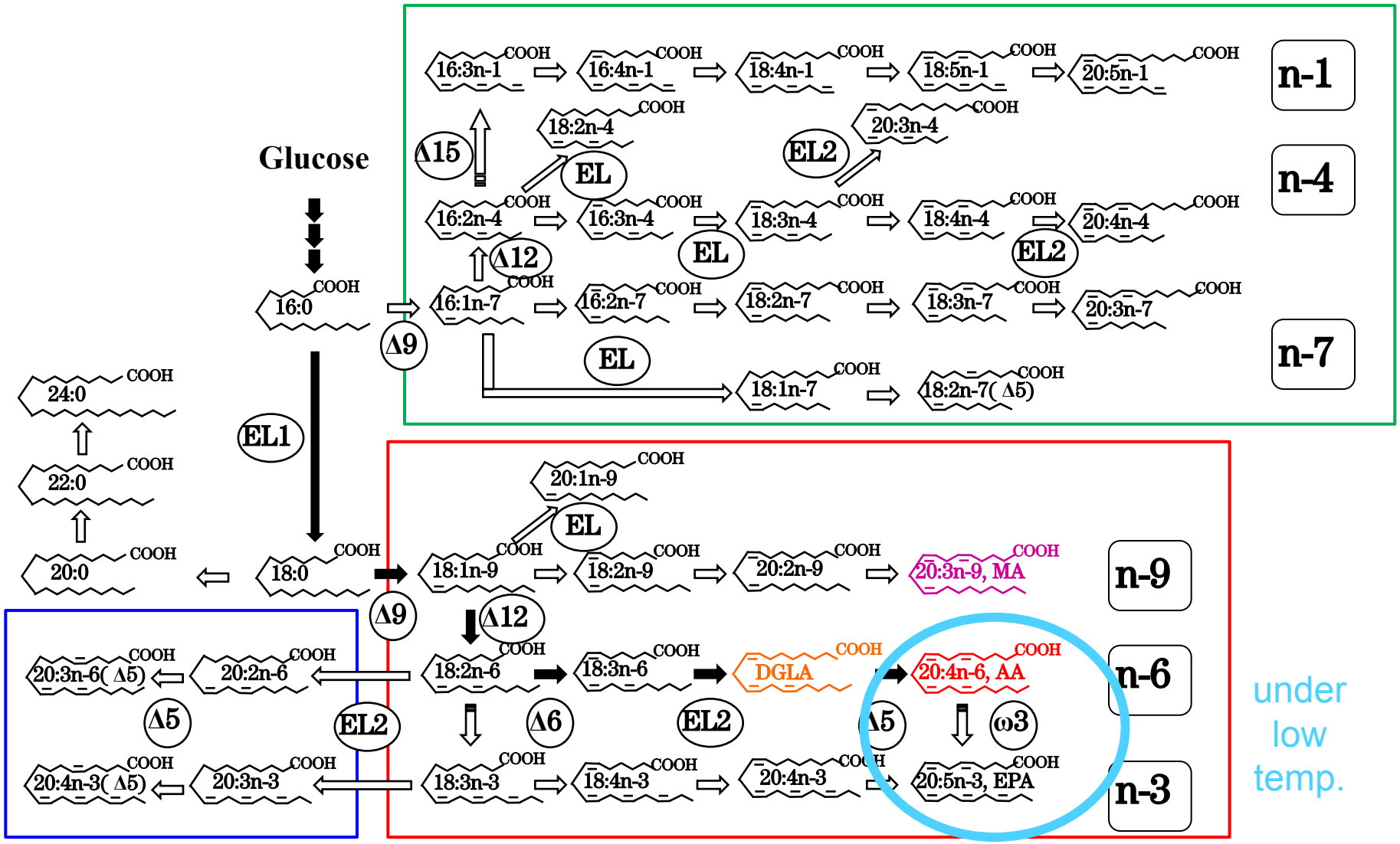
4 ml GY medium

pBIG3ura5sω3x2 No. 11
EPA composition (42.2%)



Ando, A. et al, *Appl. Environ. Microbiol.*, 75, 5529-5535 (2009).

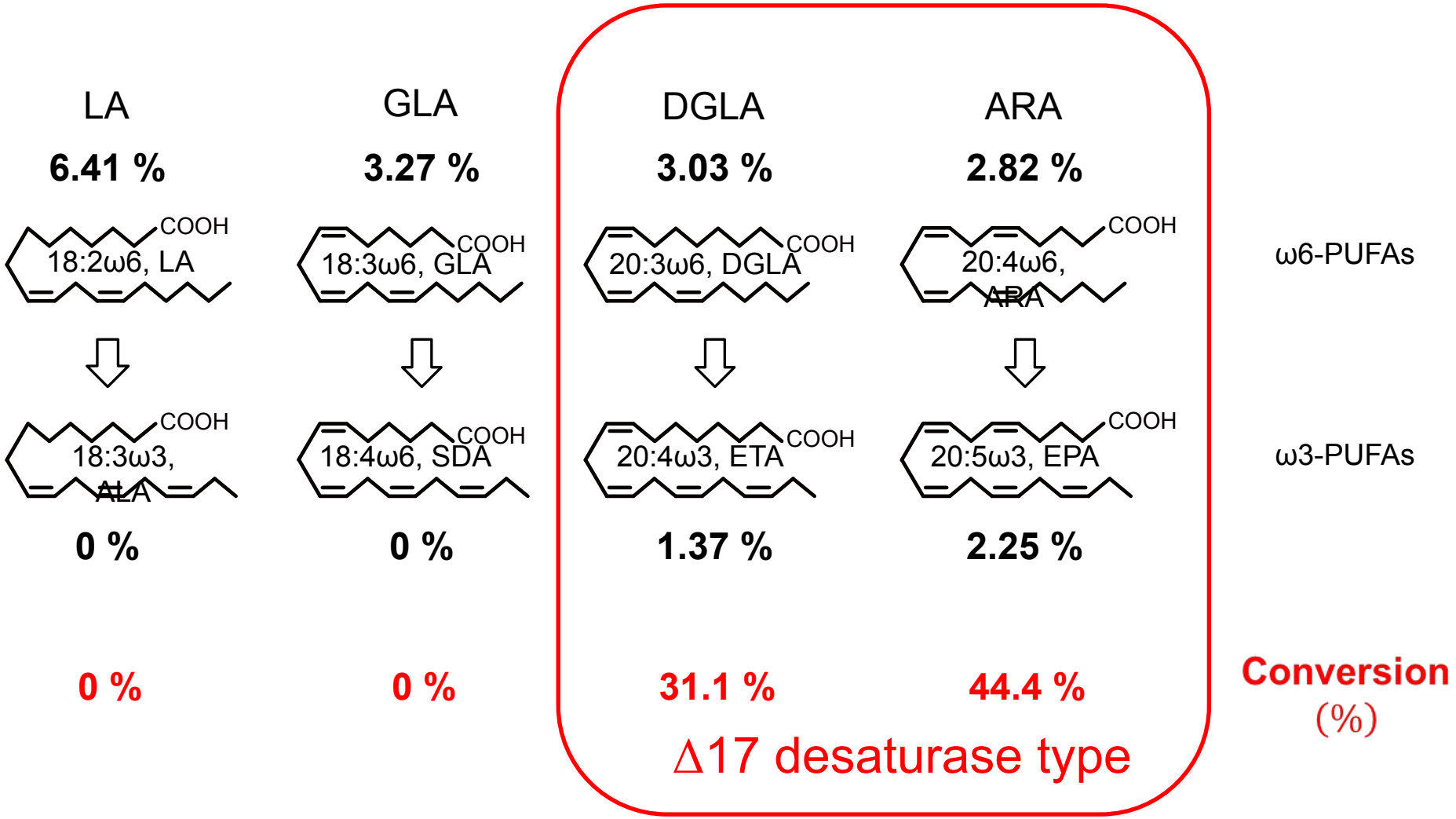
Various PUFA biosynthetic pathways in *M. alpina* and its mutants



EPA production by expression of heterologous desaturase genes in *M. alpina* 1S-4 under **ordinary temperature**

Characterization of *PmΔ17* desaturase from *Plectospira myriandra*

$$\text{Conversion}(\%) = \frac{\text{Product}}{\text{Substrate+Product}} \times 100$$



Mo, B. K H. et al, *Biosci Biotechnol Biochem.*, 85, 1252–1265 (2021).

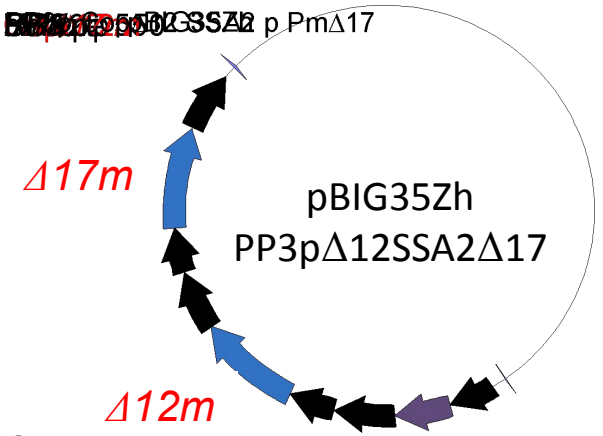
EPA production by expression of heterologous desaturase genes in *M. alpina* 1S-4 under ordinary temperature

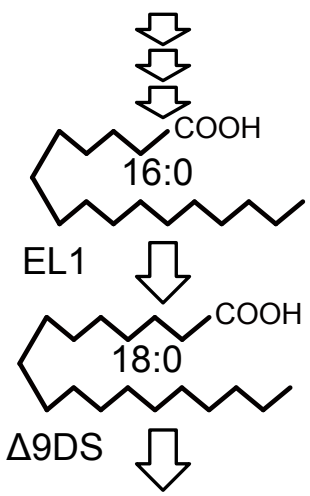
Glucose

gene: Δ17 desaturase (*Δ17m*) gene and Δ12 desaturase gene (*Δ12m*)

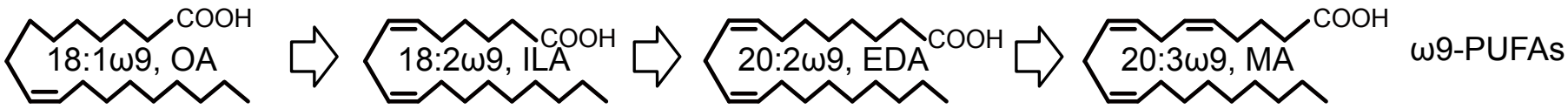
promoter: SSA2 promoter and PP3 promoter

host: *Mortierella alpina*（uracil auxotroph）



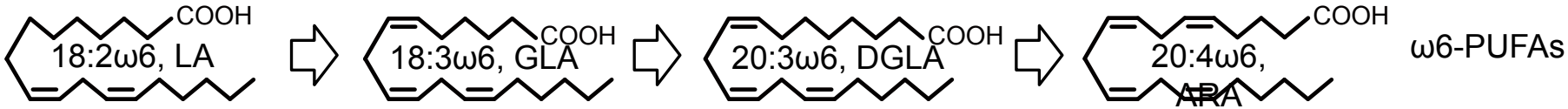


Δ6DS　　EL2　　Δ5DS



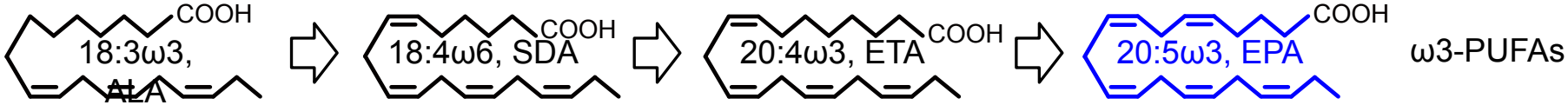
ω9-PUFAs

⇩ Δ12 desaturase *Δ12m*



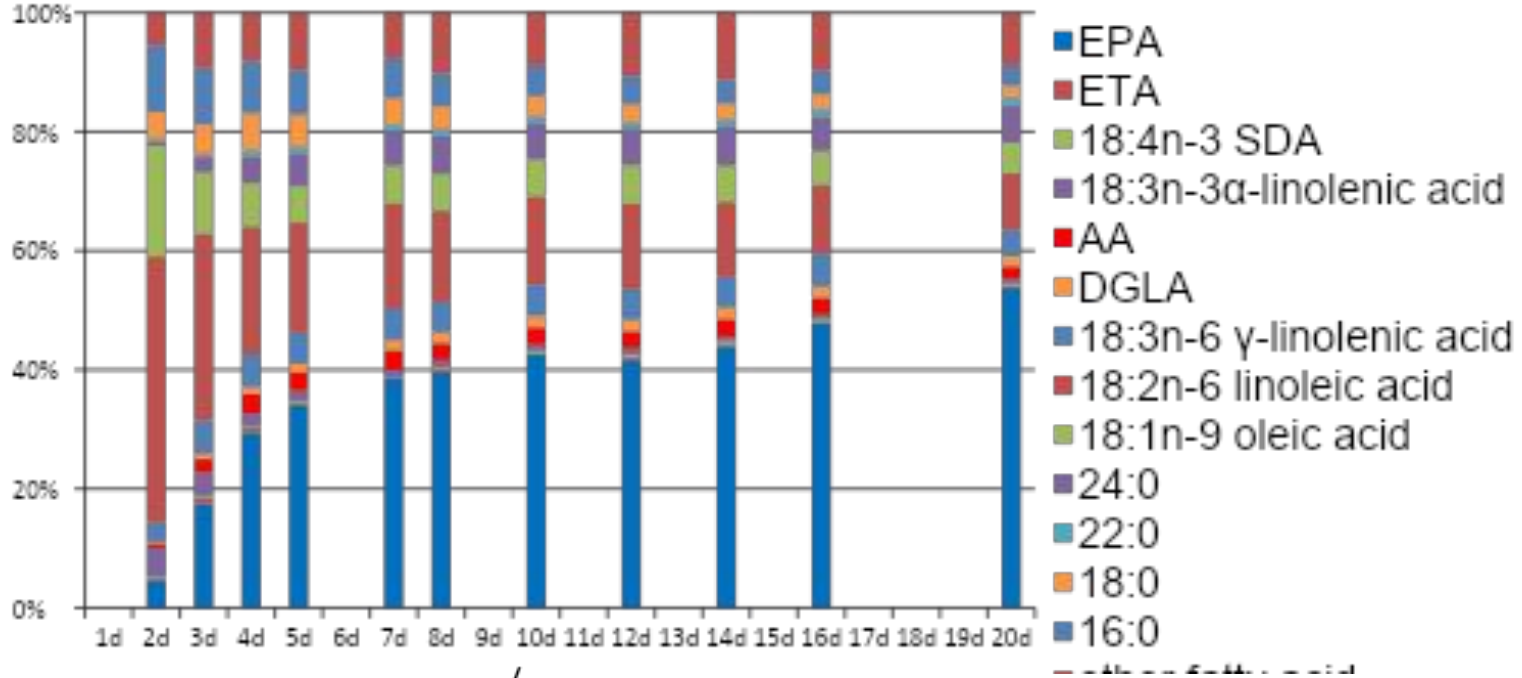
ω6-PUFAs

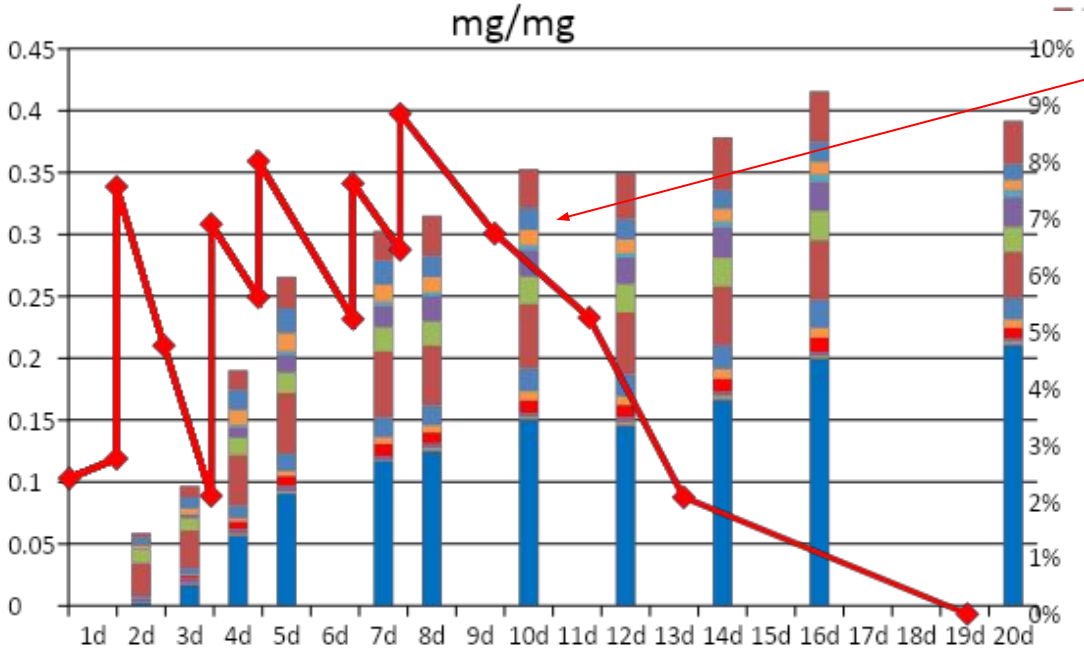
⇩ Δ17 desaturase ⇩ *Δ17m*



ω3-PUFAs

5L jar fermentor scale EPA production (26ºC, 20 days cultivation)

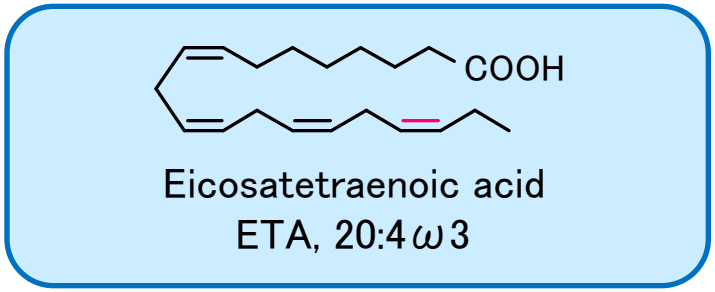


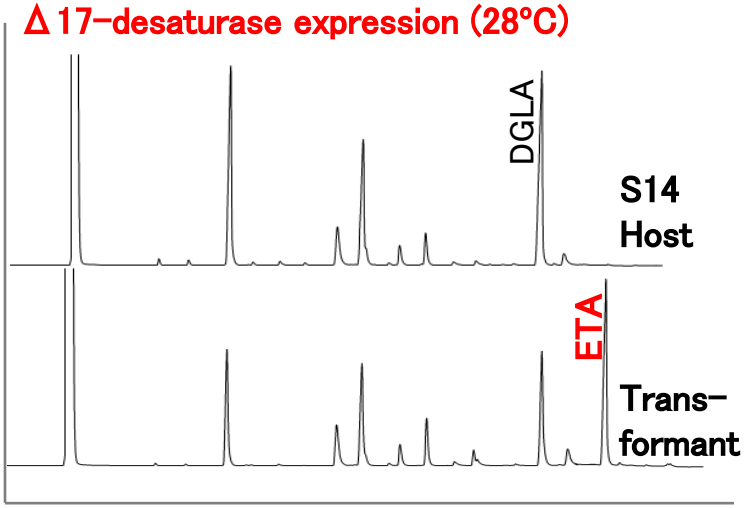


Glucose (%)

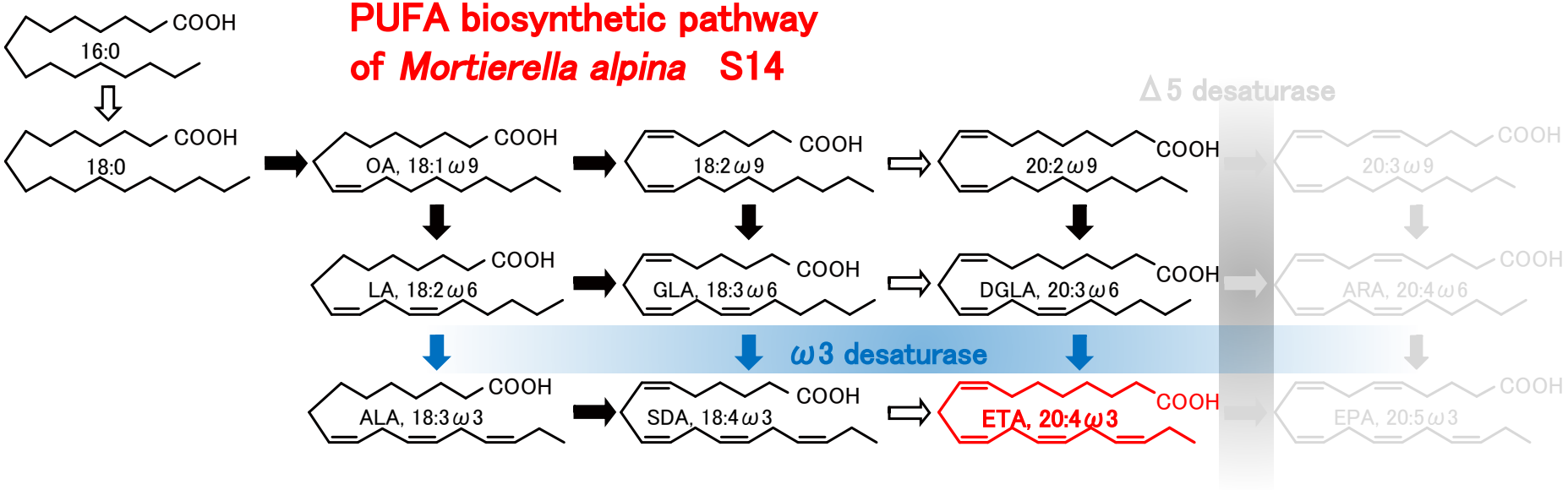
- dry cell weight 70 g/L
- lipids production 28 g/L
- EPA production 52 % 14.4g/L

ETA production by expression of heterologous desaturase genes in *M. alpina* S-14 (Δ5-desaturase-defective mutant) under ordinary temperature





PUFA biosynthetic pathway of *Mortierella alpina* S14



OA, oleic acid; LA, linoleic acid; GLA, γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; ARA, arachidonic acid; ALA, α-linolenic acid; SDA, stearidonic acid; ETA, ω3 eicosatetraenoic acid; EPA, eicosapentaenoic acid.

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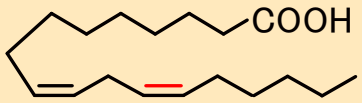
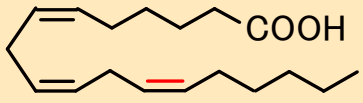
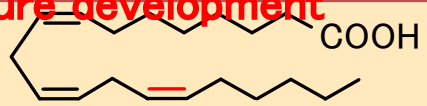
ω6 (n-6) PUFAs



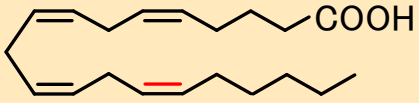
Linoleic acid
LA, 18:2ω6



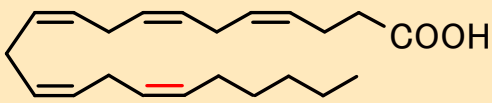
γ-Linolenic acid
GLA, 18:3ω6



Dihomo-γ-linolenic acid
DGLA, 20:3ω6

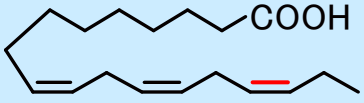


Arachidonic acid
AA, 20:4ω6

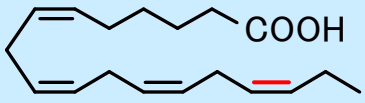


n-6 Docosapentaenoic acid
n-6 DPA, 22:5ω6

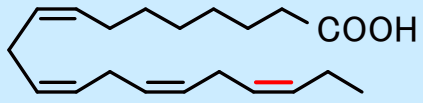
ω3 (n-3) PUFAs



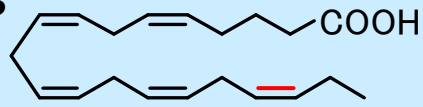
α-Linolenic acid
ALA, 18:3ω3



Stearidonic acid
SDA, 18:4ω3



Eicosatetraenoic acid
ETA, 20:4ω3



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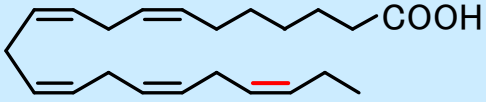
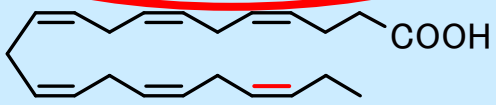


n-3 Docosapentaenoic acid
n-3 DPA, 22:5ω3



Docosahexaenoic acid
DHA, 22:6ω3

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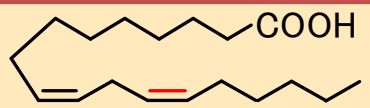
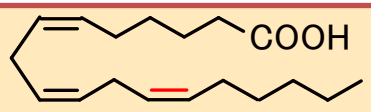
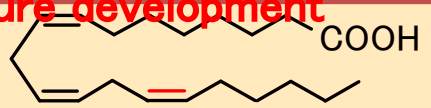


Linoleic acid
LA, 18:2ω6



γ-Linolenic acid
GLA, 18:3ω6



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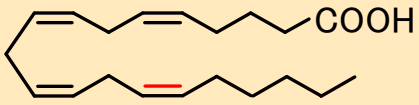
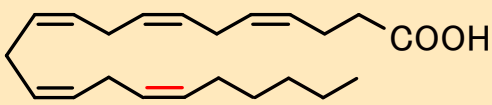
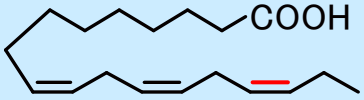


Arachidonic acid
AA, 20:4ω6



n-6 Docosapentaenoic acid
n-6 DPA, 22:5ω6

ω3 (n-3) PUFAs



α-Linolenic acid
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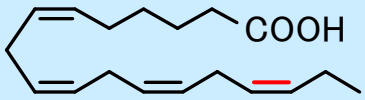

Stearidonic acid
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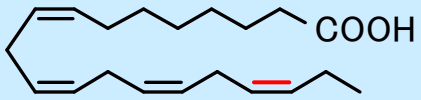

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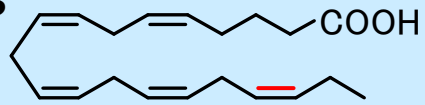

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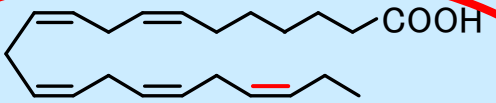
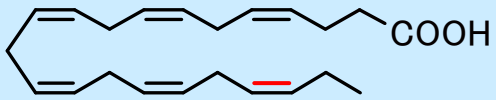


n-3 Docosapentaenoic acid
n-3 DPA, 22:5ω3

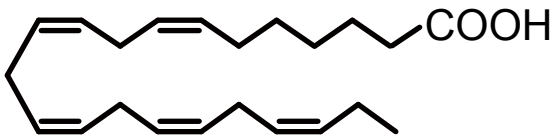


Docosahexaenoic acid
DHA, 22:6ω3

Introduction

n-3 DPA (n-3 docosapentaenoic acid)

- Preventive effect of arteriosclerosis (~10 times more effective than EPA)
- Inhibitory effect of angiogenesis



n-3 DPA
(22:5n-3)

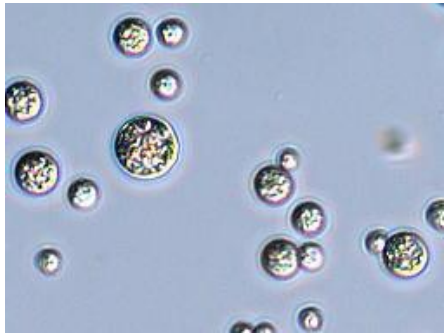
Current n-3 DPA source : **harp seal oil**

- Low DPA content (< 5%)
- difficulty of stable and large supply

Alternative source such as microorganisms is required.

Labyrinthulomycetes

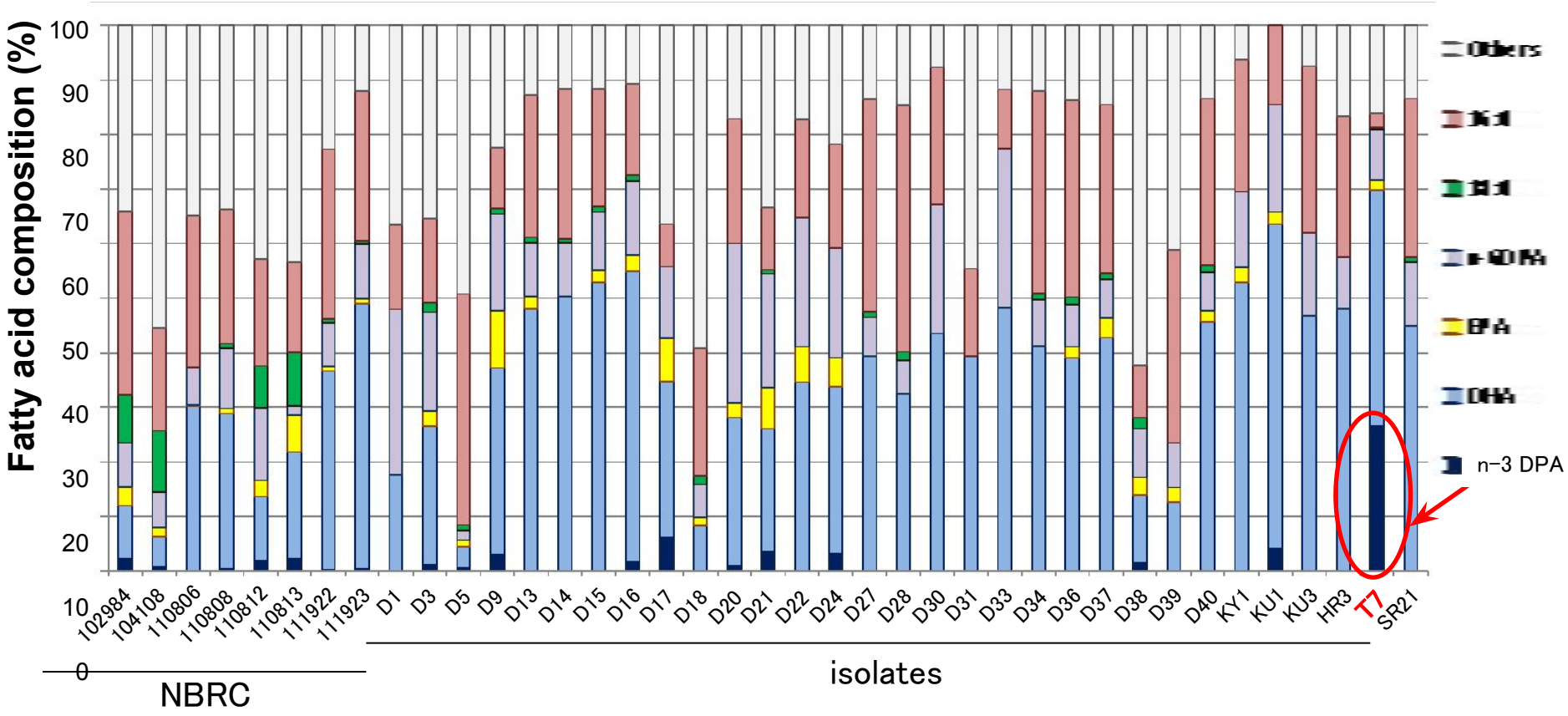
- marine eucaryotic microorganism
- highly accumulate PUFA (including DHA and EPA), astaxanthin, etc.



Isolation of n−3 DPA producing microorganism

—— fatty acid compositions of isolates and NBRC strains

31 isolates and 8 NBRC strains were analyzed of fatty acid profiles.



Isolated strain T7 highly accumulated n−3 DPA (26% of total fatty acids).
The strain T7 was identified as *Aurantiochytrium* sp.

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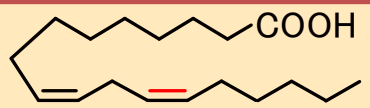
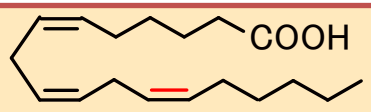


Linoleic acid
LA, 18:2ω6



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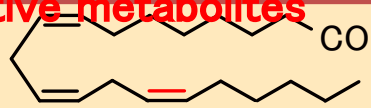

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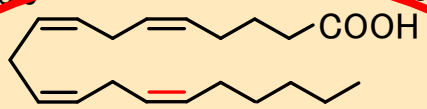

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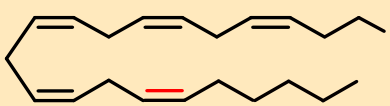

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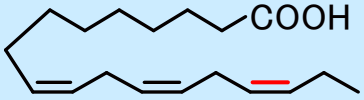

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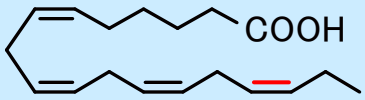

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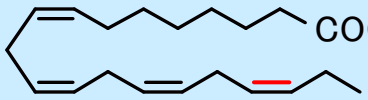

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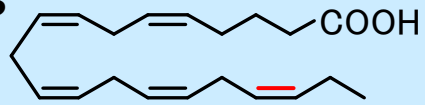

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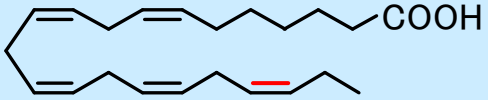

n-3 Docosapentaenoic acid
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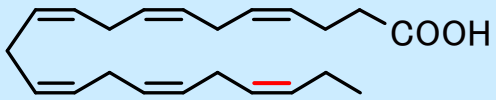

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Prostaglandins (PG)

Bioactive substance

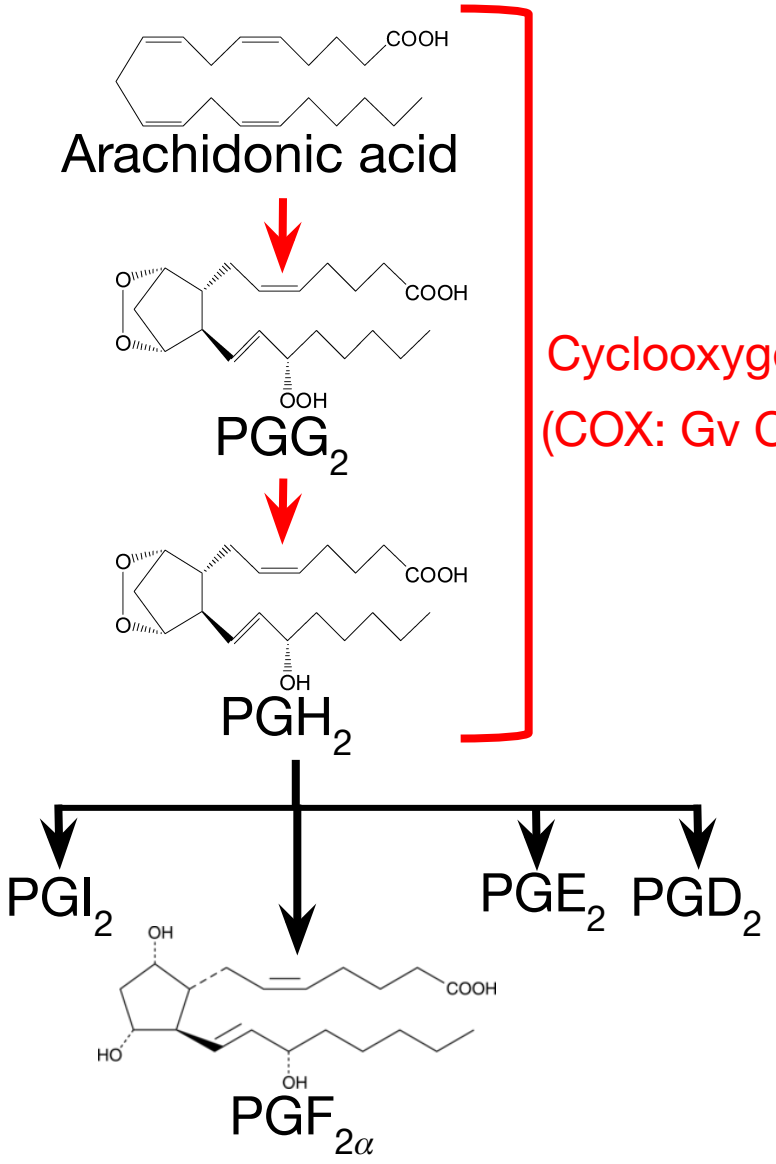
PGE_2, $PGF_{2\alpha}$ etc.

- ✔ Vasodilation
- ✔ Inhibition of platelet aggregation
- ✔ Constriction of smooth muscle

↓

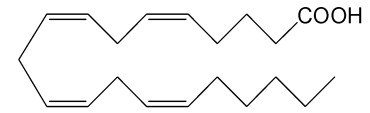
Pharmaceuticals

Biosynthesis pathway of PGs



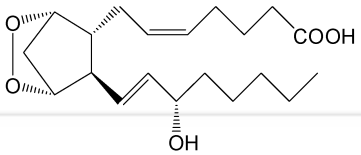
Mohd Fazli, F.A. et al, *Biosci. Biotechnol. Biochem.*, 83, 774-780 (2019).

Time course Analysis of PGF2α Production by *Mortierella alpina* 1S-4 transformants



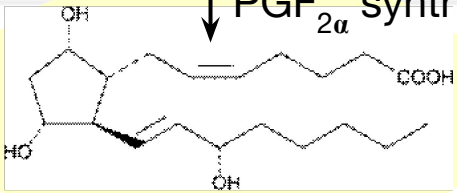
Arachidonic acid

↓ GvCOXm

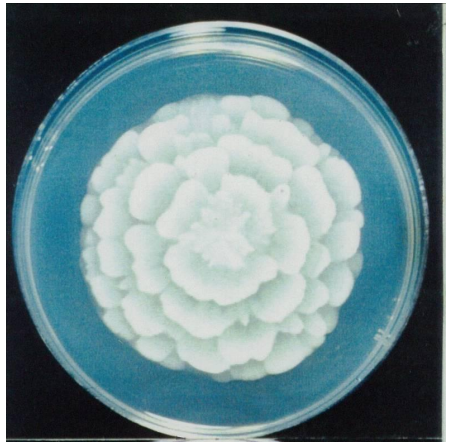


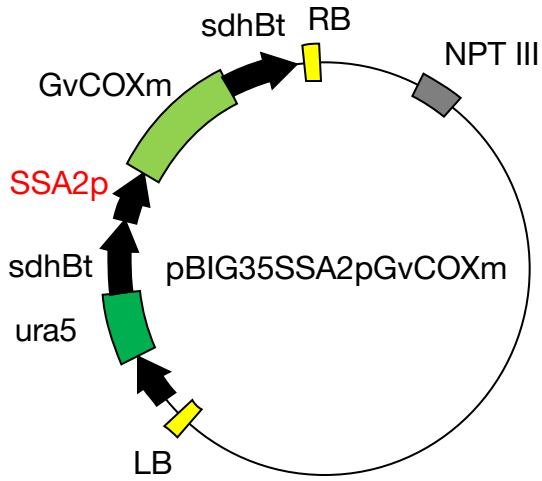
PGH_2

↓ $PGF_{2\alpha}$ synthetase



$PGF_{2\alpha}$





GY Medium (glucose 2%, YE 1%) , 28℃, 12 days

Mohd Fazli, F.A. et al, *Biosci. Biotechnol. Biochem.*, 83, 774-780 (2019).

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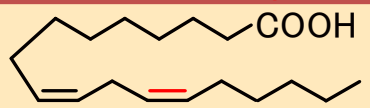

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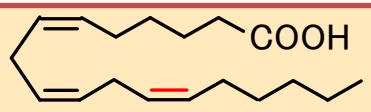
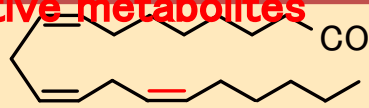
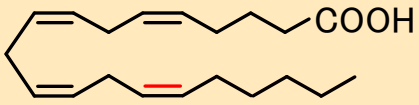


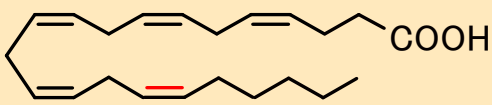
γ-Linolenic acid
GLA, 18:3ω6



Dihomo-γ-linolenic acid
DGLA, 20:3ω6

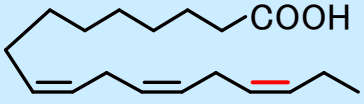


Arachidonic acid
AA, 20:4ω6

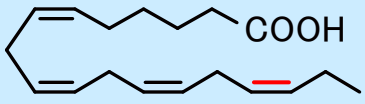


n-6 Docosapentaenoic acid
n-6 DPA, 22:5ω6

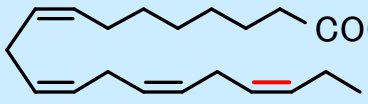
ω3 (n-3) PUFAs



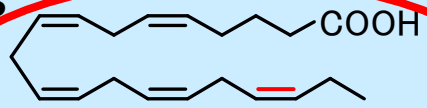
α-Linolenic acid
ALA, 18:3ω3



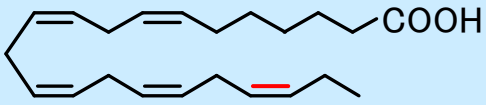
Stearidonic acid
SDA, 18:4ω3



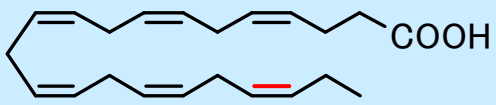
Eicosatetraenoic acid
ETA, 20:4ω3



Eicosapentaenoic acid
EPA, 20:5ω3

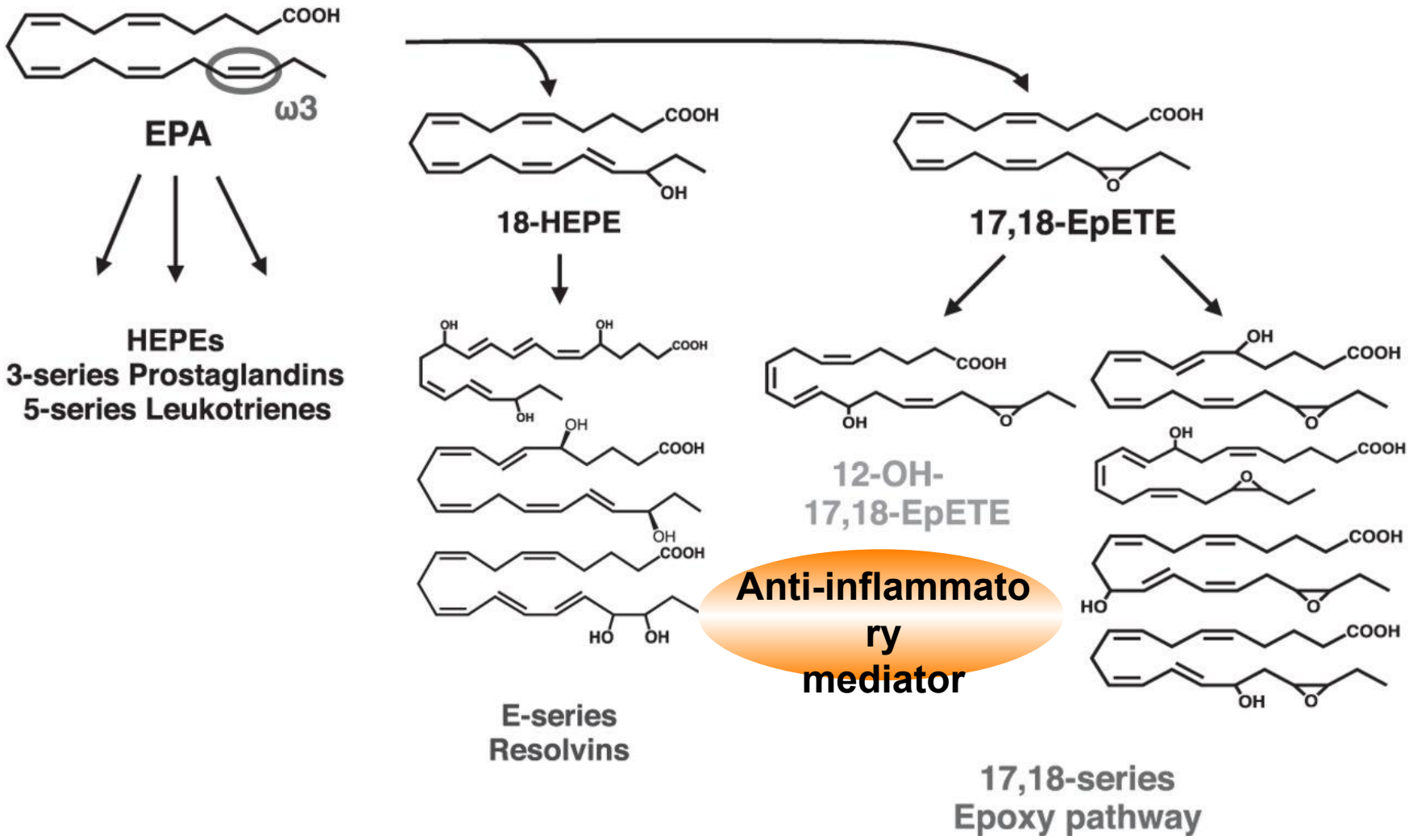


n-3 Docosapentaenoic acid
n-3 DPA, 22:5ω3

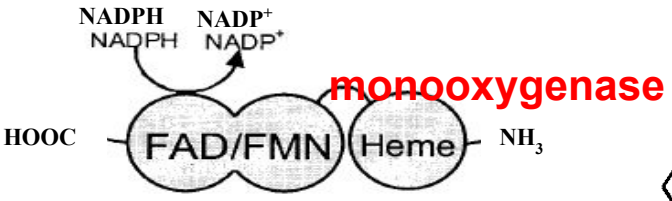


Docosahexaenoic acid
DHA, 22:6ω3

EPA metabolome in the body

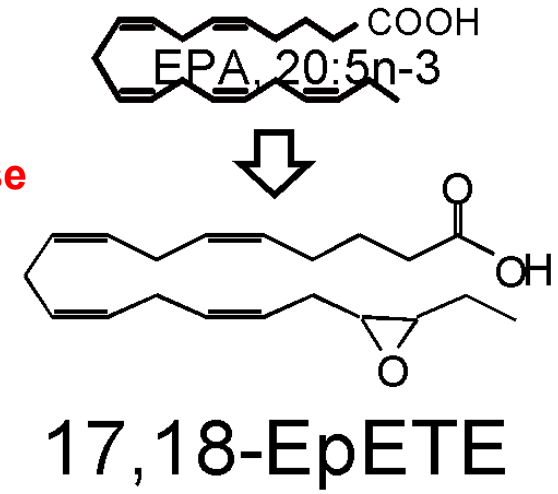


Kubota T et al. FASEB J
2014;28:586-593

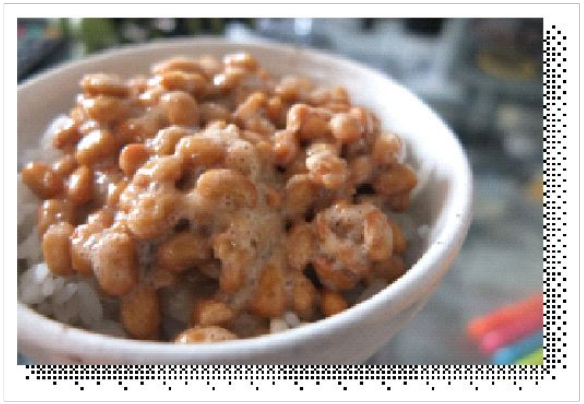


P450

monooxygenase



17,18-EpETE



Developing new Natto (soy been fermentaion)
containing anti-inflammatory lipids
using *Bacillus* sp. showing P450 monooxygenase activity

Summary

1) Polyunsaturated fatty acid production and modification

Various physiological activity

- Cardiovascular fitness
- Cerebral function development
- Anticancer
- Lipid metabolism control
- Immune and inflammation control

Precursor of active metabolites

- PGF_{2a} (6 mg/ L) by *M. alpina* transformant
- 17,18-EpETE (0.4 mg/mL) by *Bacillus* P450 MO

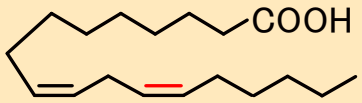
Current source… fish oil, plant oil

- unstable supply
- low purity
- contamination of unhealthy compounds

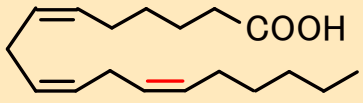
EPA: 52 % 14.4 g/L, ETA: 27%, 0.6 g/L
(*M. alpina* transformant)

n-3 DPA: 165 mg/L
(*Aurantiochytrium* sp. T7)

ω6 (n-6) PUFAs



Linoleic acid
LA, 18:2ω6



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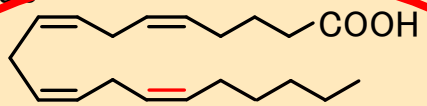
DGLA, 20:3ω6



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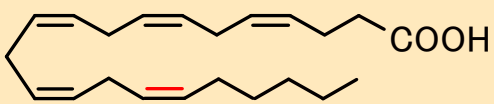
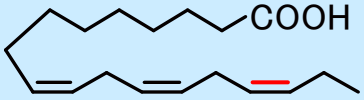
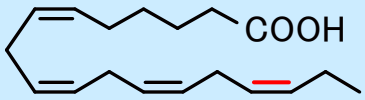


n-6 Docosapentaenoic acid
n-6 DPA, 22:5ω6

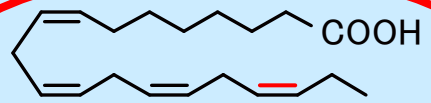
ω3 (n-3) PUFAs



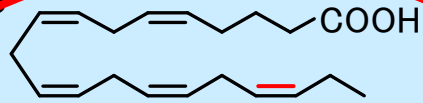
α-Linolenic acid
ALA, 18:3ω3



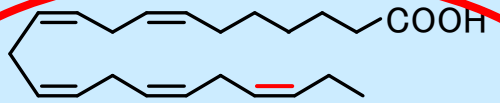
Stearidonic acid
SDA, 18:4ω3



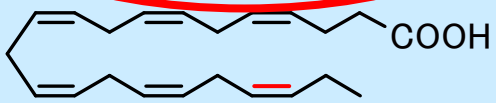
Eicosatetraenoic acid
ETA, 20:4ω3



Eicosapentaenoic acid
EPA, 20:5ω3



n-3 Docosapentaenoic acid
n-3 DPA, 22:5ω3



Docosahexaenoic acid
DHA, 22:6ω3

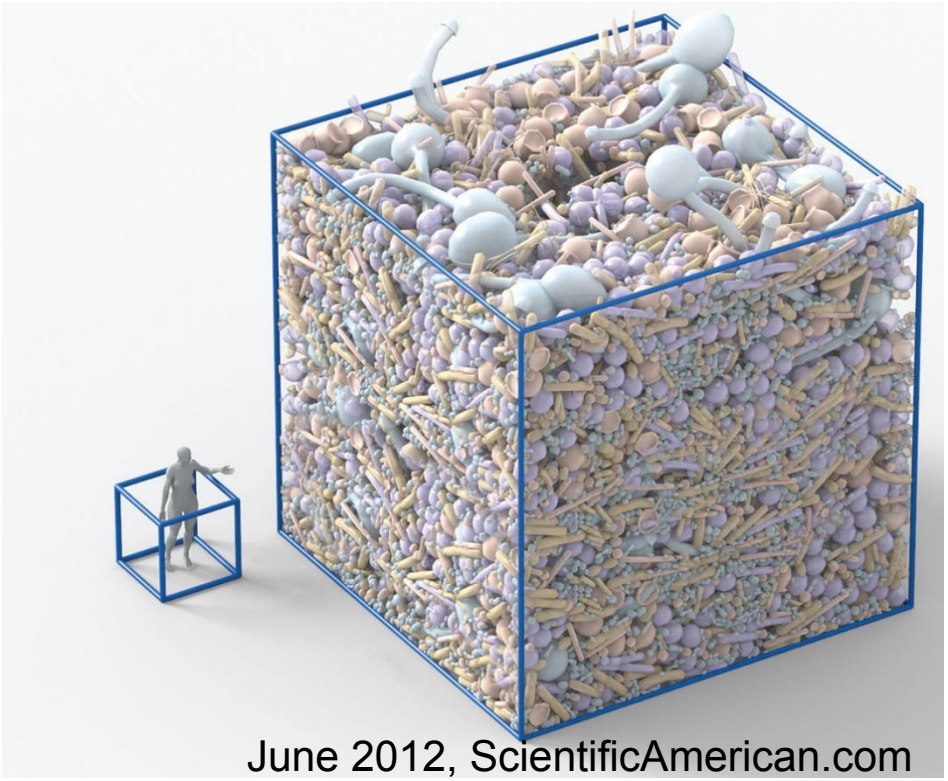
Expanding lipid sciences and industries by analysis and development of novel microbial functions

1) Polyunsaturated fatty acid production and modification

2) Gut microbial fatty acid metabolism

2) Gut microbial fatty acid metabolism

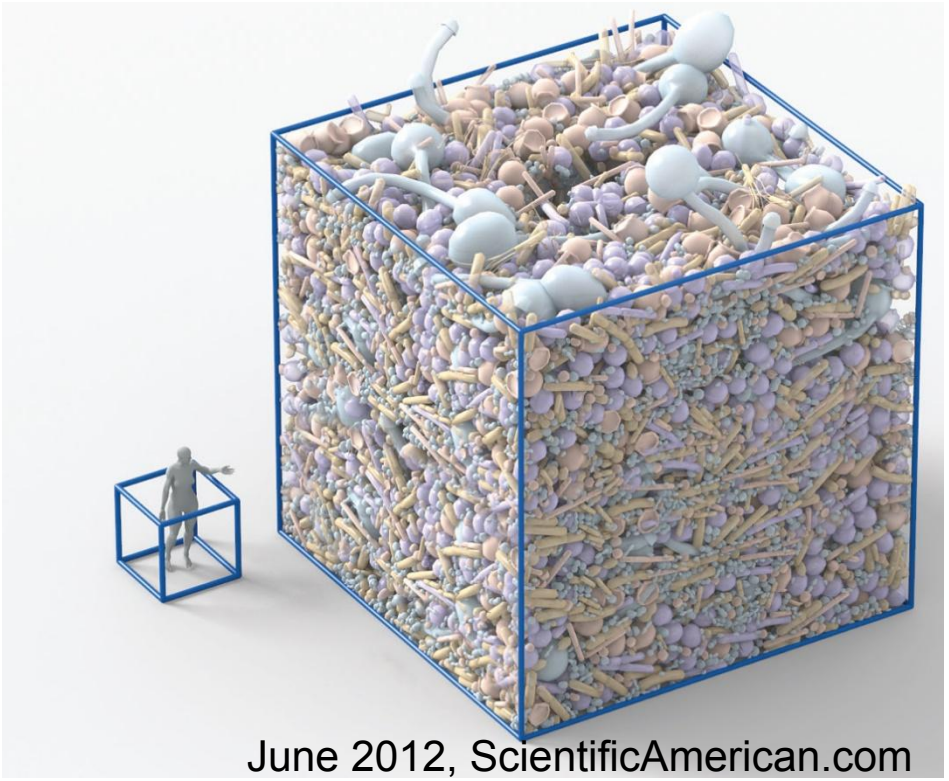
New lipid science in our inner ecosystem



June 2012, ScientificAmerican.com

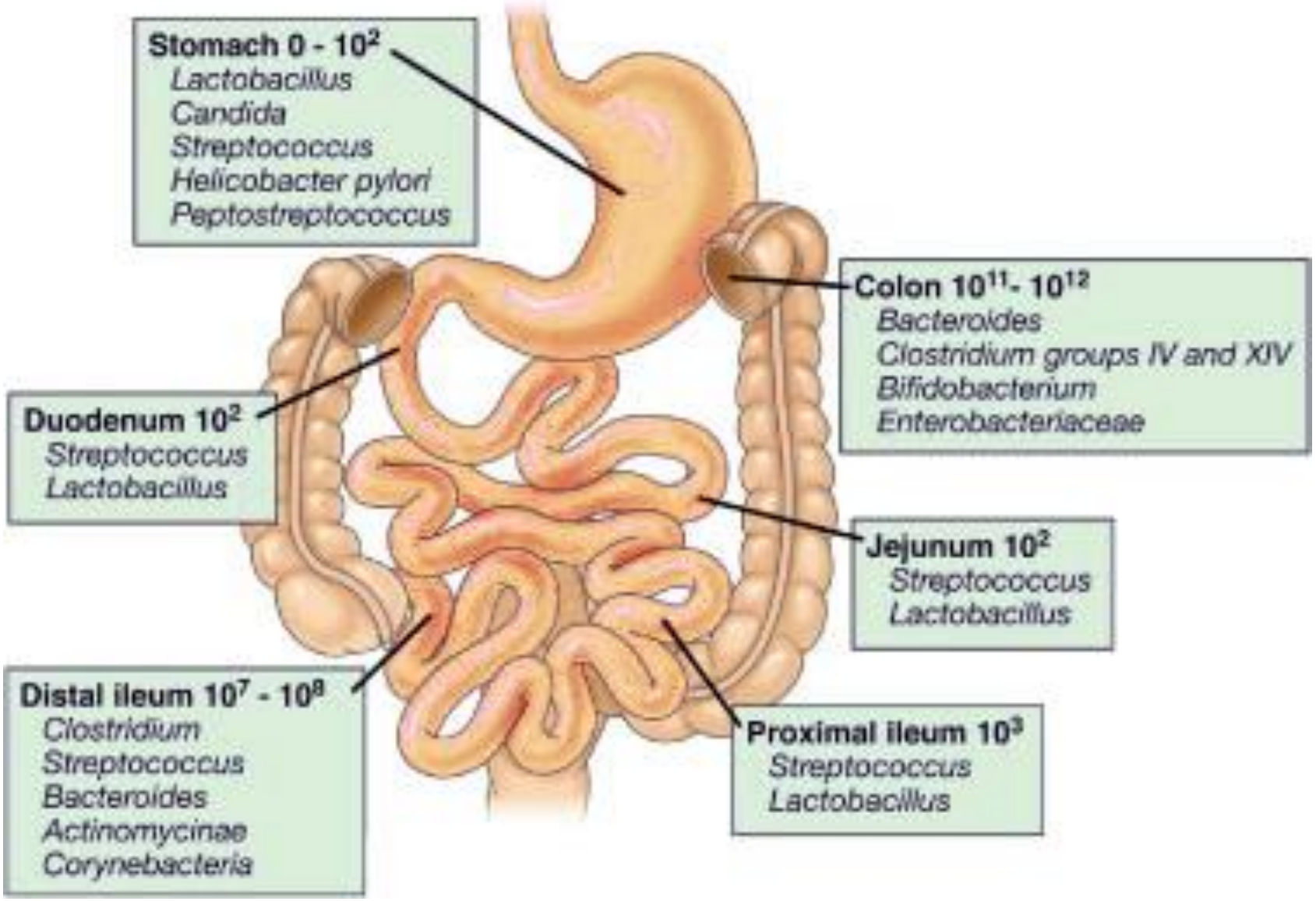
The gut microbiota

The gut microbiota consists of approximately 100 trillion cells, greater than the human somatic cell count of 37 trillion, with the number of species ranging from 500 to 1000.



June 2012, ScientificAmerican.com

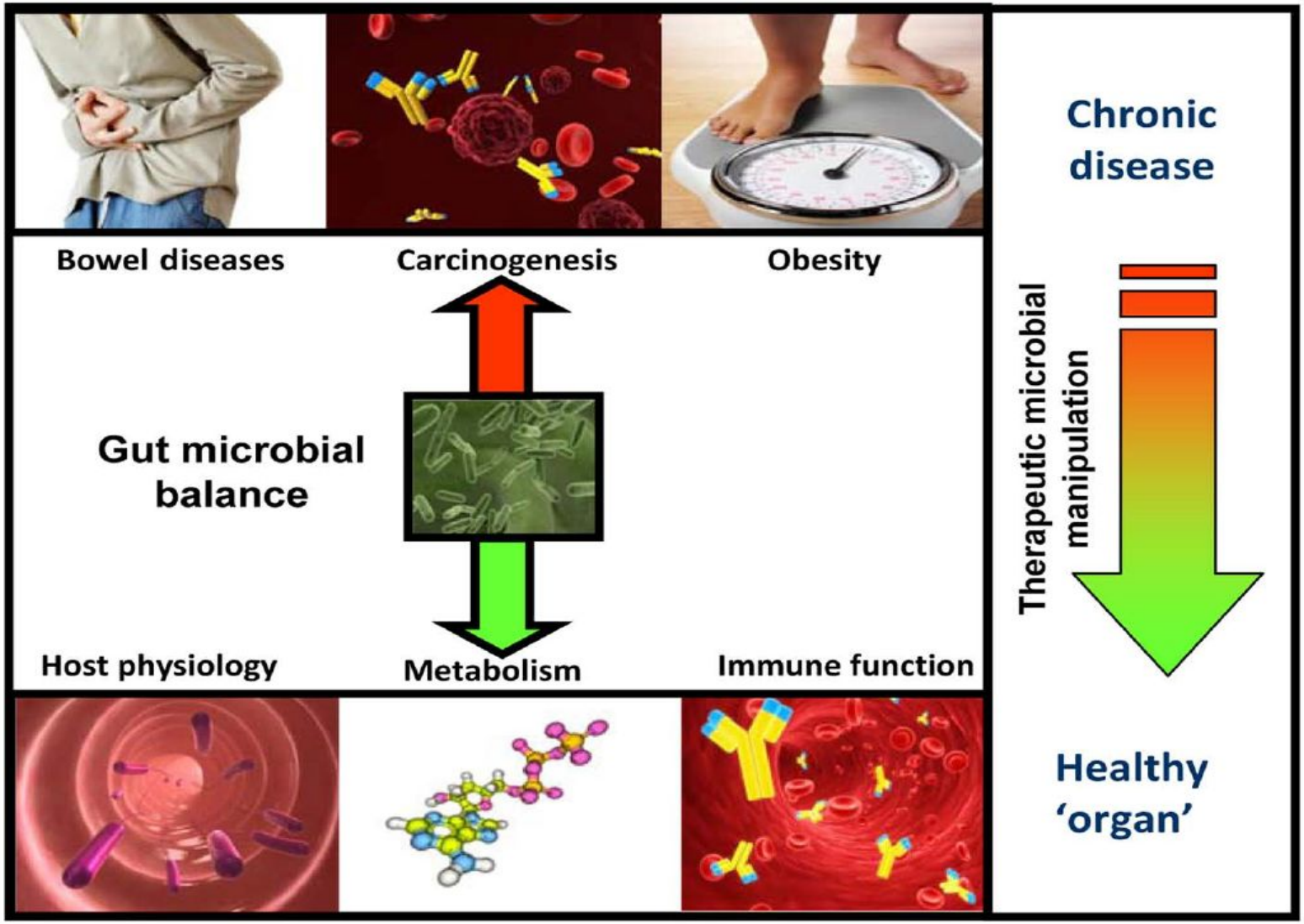
The gut microbiota



Distribution and abundance of bacteria in human gastrointestinal tract.

[Figure modified from B. Sartor Gastroenterology 2008]

The gut microbiota in health and intestinal disease

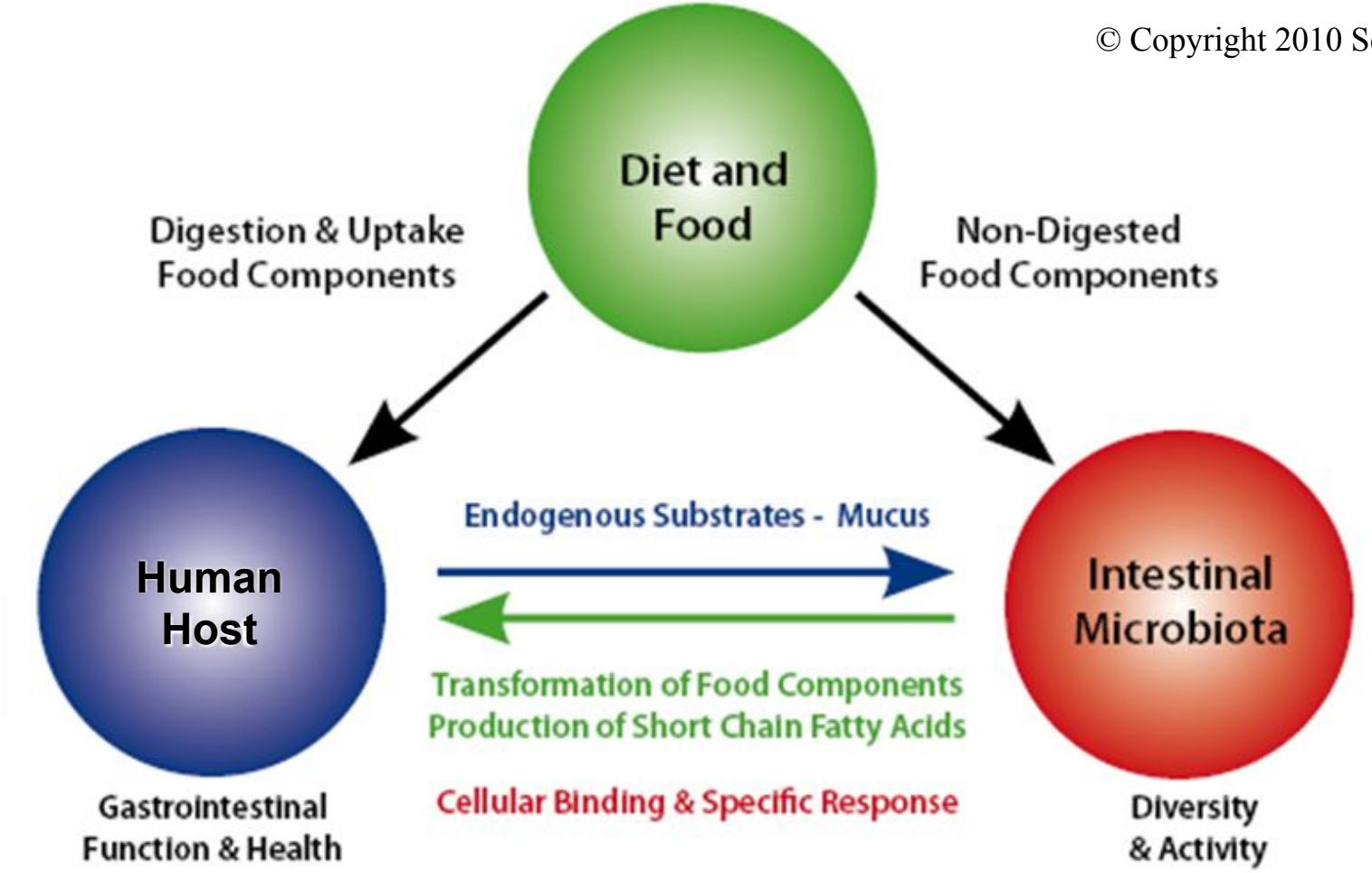


*Therap Adv Gastroenterol **6**, 295 (2013)

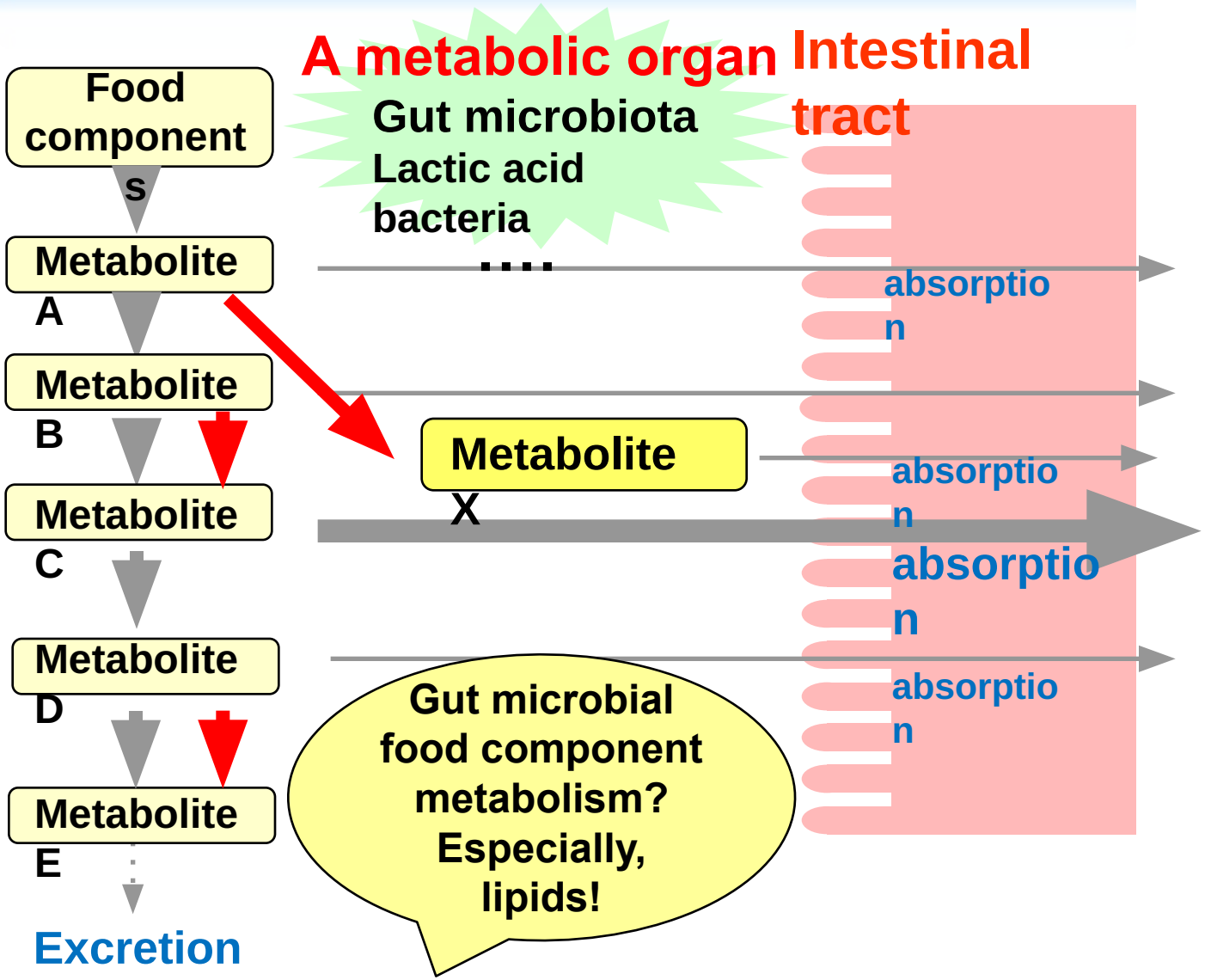
The microbiota also provides many effects to the host that influence the host's metabolism, immune and organ development, and behavior.

The gut microbial metabolism

" The microbiota can be viewed as **a metabolic organ** exquisitely tuned to our physiology that performs function we have not had to evolve on our own " (Bäckhed F *et al*. *Proc Natl Acad Sci USA*. **101**, 15718 (2004))



2) Gut microbial fatty acid metabolism



What kind molecular species of fat, especially bioactive PUFAs, are generated by our gut microbes and what kind of function they have in relation with our health?

Polyunsaturated Fatty Acid Saturation Metabolism of Gut Microbiota (Lactic Acid bacteria) Affecting Host Health via Bio-active Fatty Acid Generation

- Gut microbial PUFA saturation metabolism
- Distribution of gut microbial PUFA metabolites in the host
- Physiological activities of gut microbial PUFA metabolites
- Preparation of gut microbial PUFA metabolites
- Prebiotic, probiotic, and postbiotic applications

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Novel PUFA-saturation metabolism found in *Lactobacillus plantarum*

HOOC 9 12 **LA**

HOOC 10 12 ***t*10, *c*12-CLA**

HOOC 9 11 ***c*9, *t*11-CLA**

HOOC 9 11 ***t*9, *t*11-CLA**

HOOC 9 oleic acid

HOOC 10 **10(*E*)-octadecenoic acid**

CLA-HY

CLA-HY

CLA-HY

HOOC OH 12 10 10-hydroxy-12(*Z*)-octadecenoic acid (HYA)

HYA

HOOC OH 10 11 10-hydroxy-11(*E*)-octadecenoic acid

HYC

HOOC OH 10 10-hydroxy octadecanoic acid

HYB

CLA-DH

CLA-DH

CLA-DH

HOOC O 12 10 10-oxo-12(*Z*)-octadecenoic acid

KetoA

CLA-DC

HOOC O 10 11 10-oxo-11(*E*)-octadecenoic acid

KetoC

CLA-ER

HOOC O 10 10-oxo-octadecanoic acid

KetoB

cla-dh, Short-chain dehydrogenase/oxidreductase (861 bp)
cla-dc, Acetoacetate decarboxylase (846 bp)
cla-er, Nitroreductase (645 bp)

Kishino, S. et al, *Proc. Natl. Acad. Sci. USA,* 110, 17808-17813 (2013)

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CLA-HY

CLA-HY

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HOOC OH 10 10-hydroxy octadecanoic acid **HYB**

CLA-DH

CLA-DH

CLA-DH

HOOC O 12 10 10-oxo-12(*Z*)-octadecenoic acid **KetoA**

CLA-DC

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CLA-ER

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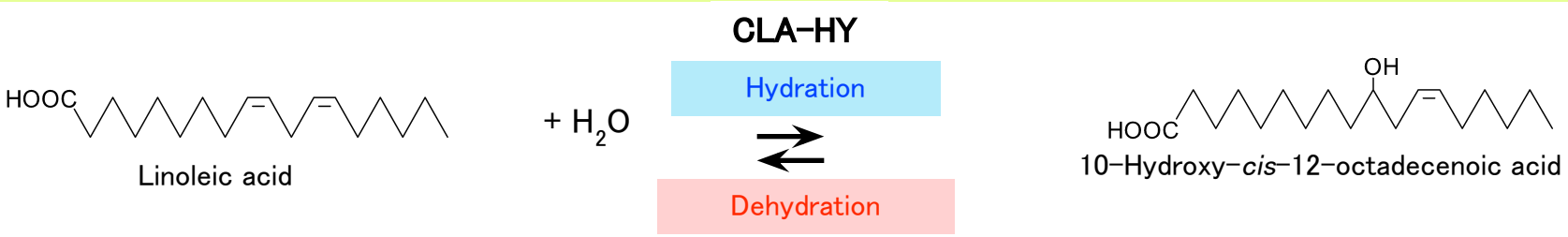
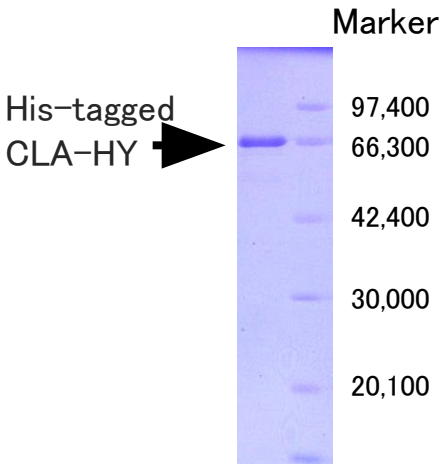
1. CLA-HY -Summary-



Native M_r	52	kDa
Number of subunit	1	
Cofactor	FAD	
Activator	NADH	
Optimal reaction temperature	40℃	
Optimal reaction pH	5.5	
Thermal stability	~28℃	
pH stability	5~7	

(For hydration and dehydration)



(For linoleic acid)

$appK_m$	92	μM
k_{cat}	2.6×10^{-2}	sec^{-1}
$k_{cat}/appK_m$	2.8×10^{-4}	$sec^{-1} \cdot \mu M^{-1}$
Hill coefficient	3.3	
V_{max}	3.1×10^{-2}	$\mu mol \cdot sec^{-1} \cdot mg^{-1}$

*Sodium succinate buffer pH 5.5, 20 mM;
FAD, 0.1 mM; without NADH; reaction temperature, 37°C

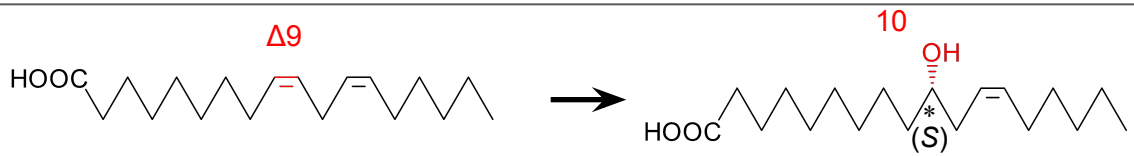
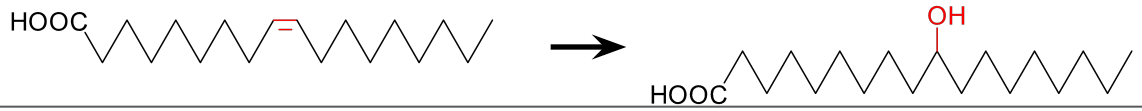
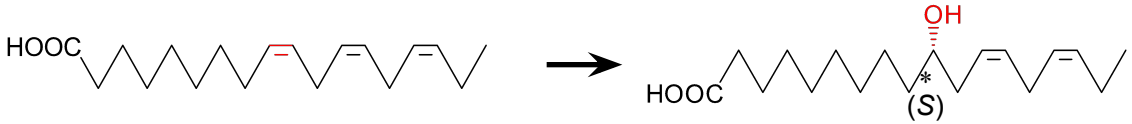
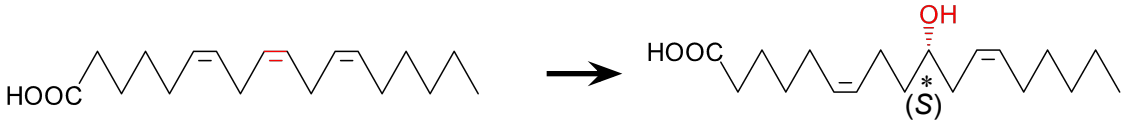
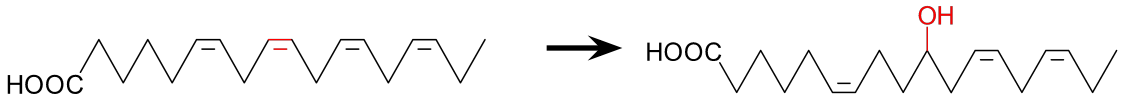
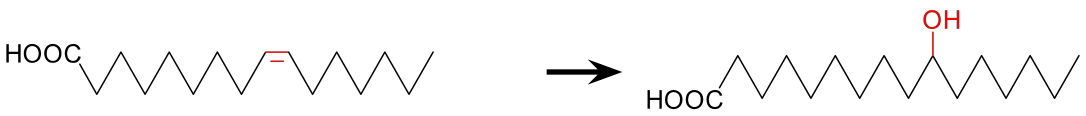
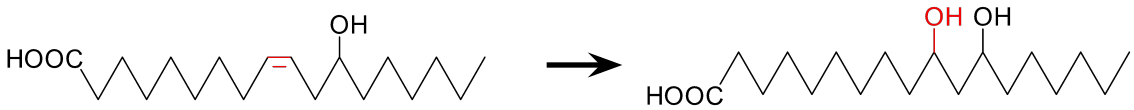
(For 10-hydroxy-*cis*-12-octadecenoic acid)

K_m	98	μM
k_{cat}	1.2×10^{-3}	sec^{-1}
k_{cat}/K_m	1.2×10^{-5}	$sec^{-1} \cdot \mu M^{-1}$
V_{max}	1.4×10^{-3}	$\mu mol \cdot sec^{-1} \cdot mg^{-1}$

*Sodium succinate buffer pH 5.5, 20 mM;
FAD, 0.1 mM; without NADH; reaction temperature, 37°C

Takeuchi, M. et al, *J. Biosci. Bioeng.* 119, 636-641

1. CLA-HY -Substrate specificity-

Substrates (for hydration)		Relative activity (%)
Linoleic acid (18:2)		100
Oleic acid (18:1)		335
α-Linolenic acid (18:3)		29
γ-Linolenic acid (18:3)		43
Stearidonic acid (18:4)		43
Palmitoleic acid (16:1)		44
Ricinoleic acid (12-OH 18:1)		0.5
cis-Vaccenic acid (*cis*-11-Octadecenoic acid) (18:1)		—
Elaidic acid (*trans*-9-Octadecenoic acid) (18:1)		—
Methyl linoleate (18:1 methyl ester)		—

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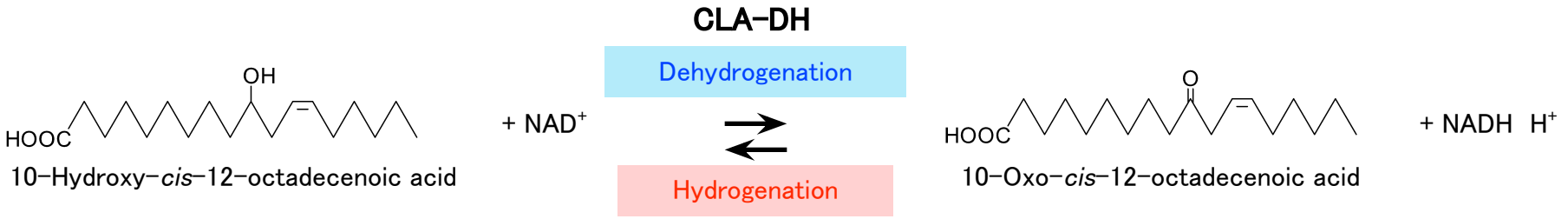
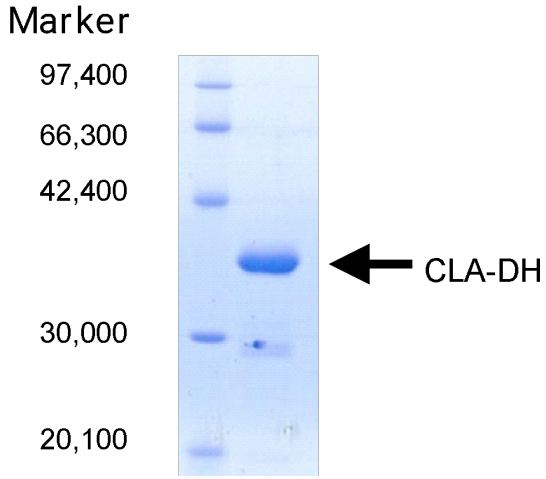
2. CLA-DH -Summary-





Native M_r	32 kDa
Number of subunit	1
Cofactor	NAD^+/NADH
Optimal reaction temeprature	52° C
Optimal reaction pH	4.5
Thermal stability	~28° C
pH stability	4.5~7.5

For 10-hydroxy-*cis*-12-octadecenoic acid

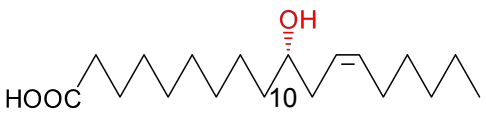
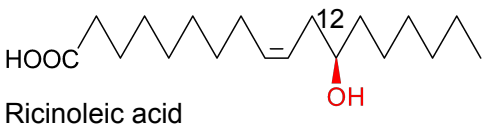
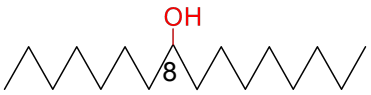
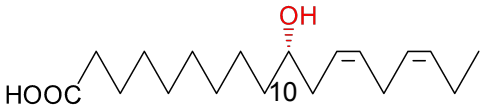
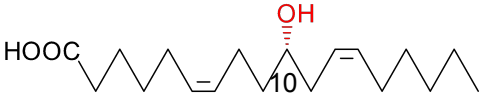
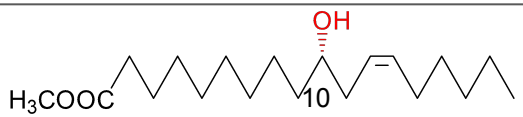
K_m	38	μM
k_{cat}	7.6×10^{-3}	sec^{-1}
k_{cat}/K_m	2.0×10^{-4}	$sec^{-1} \cdot \mu M^{-1}$
V_{max}	2.4×10^{-4}	$\mu mol \cdot sec^{-1} \cdot mg^{-1}$

For 10-oxo-*cis*-12-octadecenoic acid

K_m	1.8	μM
k_{cat}	5.7×10^{-1}	sec^{-1}
k_{cat}/K_m	3.1×10^{-1}	$sec^{-1} \cdot \mu M^{-1}$
V_{max}	1.9×10^{-2}	$\mu mol \cdot sec^{-1} \cdot mg^{-1}$

Takeuchi, M. et al, *J. Mol. Catal., B Enzym.* 117, 7-12

2. CLA-DH -Substrate specificity-

OH position		Substrate	Relative activity (%)	OH position		Substrate	Relative activity (%)
10	18:1	 (*S*)-10-Hydroxy-*cis*-12-octadecenoic acid	100	12	18:1	 Ricinoleic acid ((*R*)-12-Hydroxy-*cis*-9-octadecenoic acid)	62
10	18:0	 10-Hydroxyoctadecanoic acid	25	13	18:1	 13-Hydroxy-*cis*-9-octadecenoic acid	142
10	18:1	 10-Hydroxy-*trans*-11-octadecenoic acid	69	8	C16	 8-Hexadecanol	24
10	18:2	 (*S*)-10-Hydroxy-*cis*-12,*cis*-15-octadecadienoic acid	75	2	18:0	 2-Hydroxyeicosanoic acid (C20)	-
10	18:2	 (*S*)-10-Hydroxy-*cis*-6,*cis*-12-octadecadienoic acid	54	3	18:0	 3-Hydroxyoctadecanoic acid (C18)	-
10	18:1 methyl ester	 Methyl (*S*)-10-Hydroxy-*cis*-12-octadecenoate	127	3	18:0	 3-Hydroxytetradecanoic acid (C14)	-

Takeuchi, M. et al, *J. Mol. Catal., B Enzym.* 117, 7-12

Novel PUFA-saturation metabolism found in *Lactobacillus plantarum*

HOOC 9 12 **LA**

HOOC 10 12 ***t*10, *c*12-CLA**

HOOC 9 11 ***c*9, *t*11-CLA**

HOOC 9 11 ***t*9, *t*11-CLA**

HOOC 9 oleic acid

HOOC 10 **10(*E*)-octadecenoic acid**

CLA-HY

CLA-HY

CLA-HY

HOOC OH 12 10 10-hydroxy-12(*Z*)-octadecenoic acid (HYA) **HYA**

HOOC OH 10 11 10-hydroxy-11(*E*)-octadecenoic acid **HYC**

HOOC OH 10 10-hydroxy octadecanoic acid **HYB**

CLA-DH

CLA-DH

CLA-DH

HOOC O 12 10 10-oxo-12(*Z*)-octadecenoic acid

KetoA

CLA-DC

HOOC O 10 11 10-oxo-11(*E*)-octadecenoic acid

KetoC

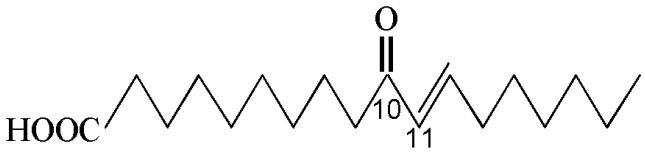
CLA-ER

HOOC O 10 10-oxo-octadecanoic acid **KetoB**

cla-dh, Short-chain dehydrogenase/oxidreductase (861 bp)
cla-dc, Acetoacetate decarboxylase (846 bp)
cla-er, Nitroreductase (645 bp)

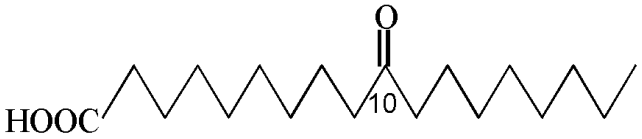
Kishino, S. et al, *Proc. Natl. Acad. Sci. USA,* 110, 17808-17813 (2013)

3. CLA-ER

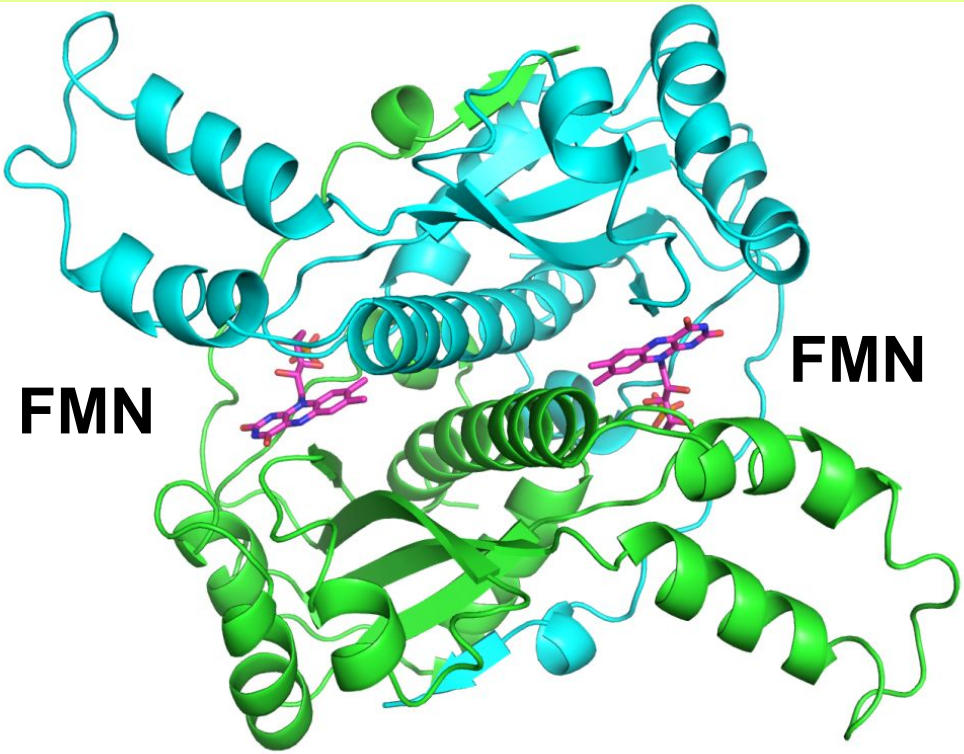


10-oxo-11(*E*)-octadecenoic acid

CLA-ER



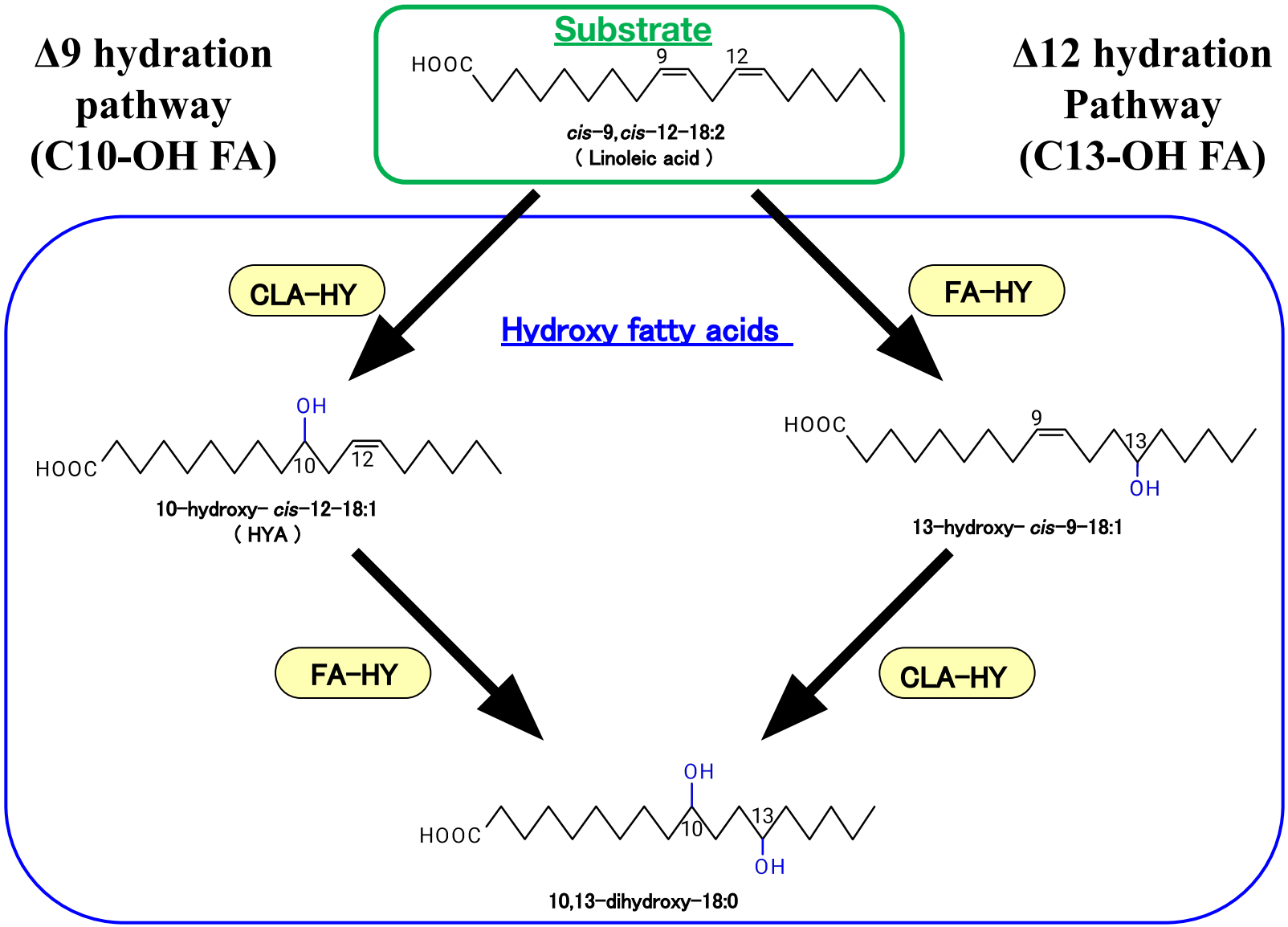
10-oxo-octadecanoic acid



CLA-ER was identified as an enone reductase that can saturate the C=C bond in the 10-oxo-*trans*-11-octadecenoic acid (KetoB) to produce 10-oxo-octadecanoic acid (KetoC).
This enzyme is the sole member of the NADH oxidase/flavin reductase family that has been identified to exert an enone reduction activity toward free enone fatty acids.

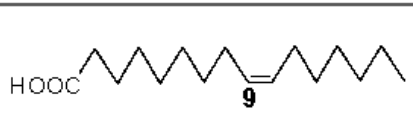
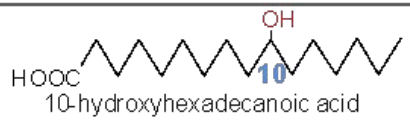
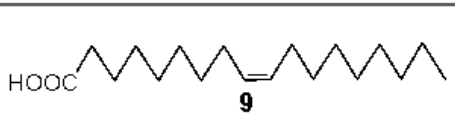
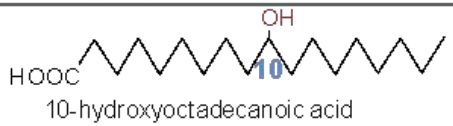
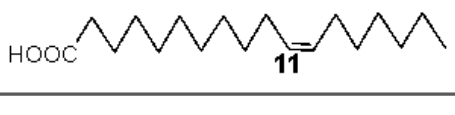
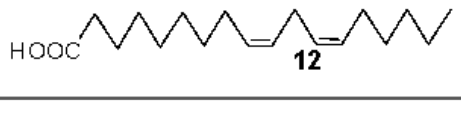
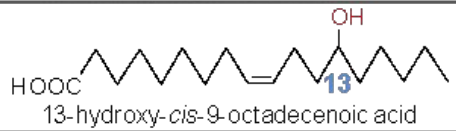
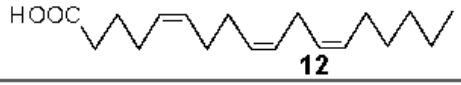
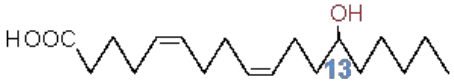
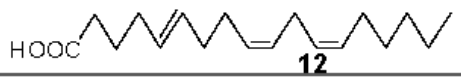
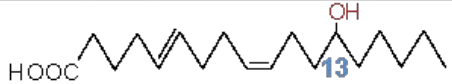
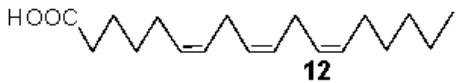
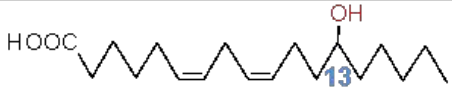
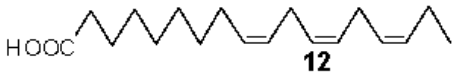
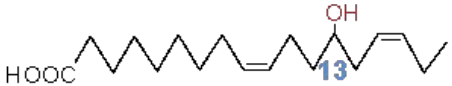
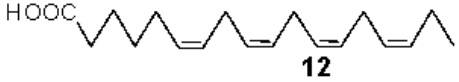
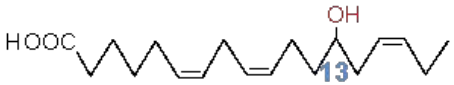
Feng, H. et al, *FEBS Journal,* 282 , 1526-1537 (2015)

Linoleic acid metabolism by *Pediococcus* sp. AKU 1080



Takeuchi, M. et al, *Eur. J. Lipid Sci. Technol.*, 115, 386-393 (2013)

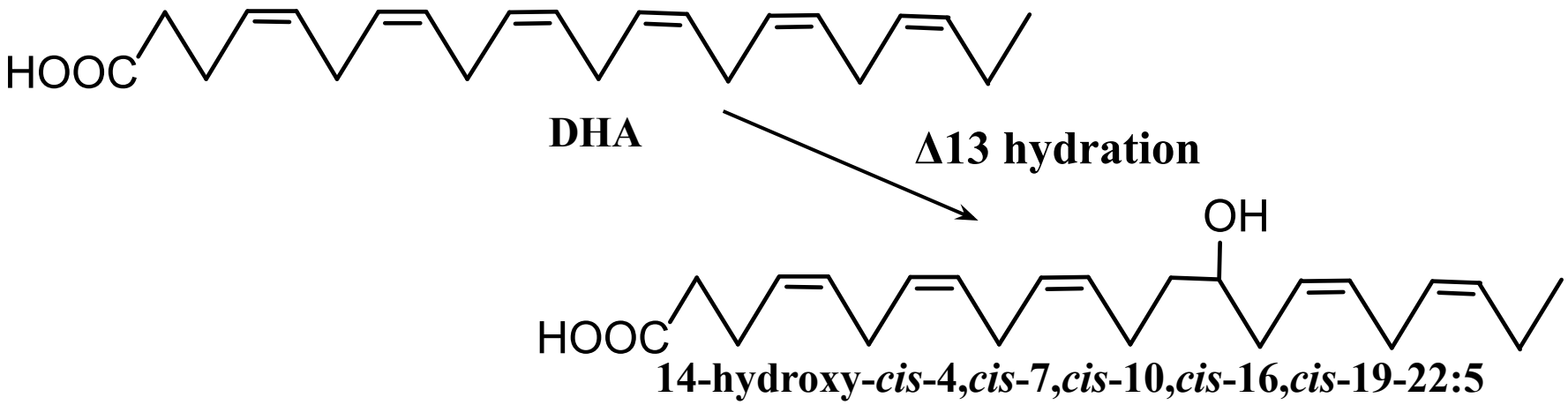
Hydration reactions catalyzed by *L. acidophilus* hydratase (FA-HY1)

Substrate (10 mM)	Product	Yield (%) in 16 h reaction
Palmitoleic acid C16:1$^{\Delta 9 cis}$		 10-hydroxyhexadecanoic acid	2
Oleic acid C18:1$^{\Delta 9 cis}$		 10-hydroxyoctadecanoic acid	1
cis-Vaccenic acid C18:1$^{\Delta 11 cis}$		 12-hydroxyoctadecanoic acid	59
Linoleic acid C18:2$^{\Delta 9 cis, \Delta 12 cis}$		 13-hydroxy-*cis*-9-octadecenoic acid	48
C18:2$^{\Delta 9 trans, \Delta 12 trans}$		Not hydrated	
Pinolenic acid C18:3$^{\Delta 5 cis, \Delta 9 cis, \Delta 12 cis}$		 13-hydroxy-*cis*-5,*cis*-9-octadecadienoic acid	57
Columbinic acid C18:3$^{\Delta 5 trans, \Delta 9 cis, \Delta 12 cis}$		 13-hydroxy-*trans*-5,*cis*-9-octadecadienoic acid	46
γ-Linolenic acid C18:3$^{\Delta 6 cis, \Delta 9 cis, \Delta 12 cis}$		 13-hydroxy-*cis*-6,*cis*-9-octadecadienoic acid	57
α -Linolenic acid C18:3$^{\Delta 9 cis, \Delta 12 cis, \Delta 15 cis}$		 13-hydroxy-*cis*-9,*cis*-15-octadecadienoic acid	54
Stearidonic acid C18:4$^{\Delta 6 cis, \Delta 9 cis, \Delta 12 cis, \Delta 15 cis}$		 13-hydroxy-*cis*-6,*cis*-9,cis-15-octadecatrienoic acid	12

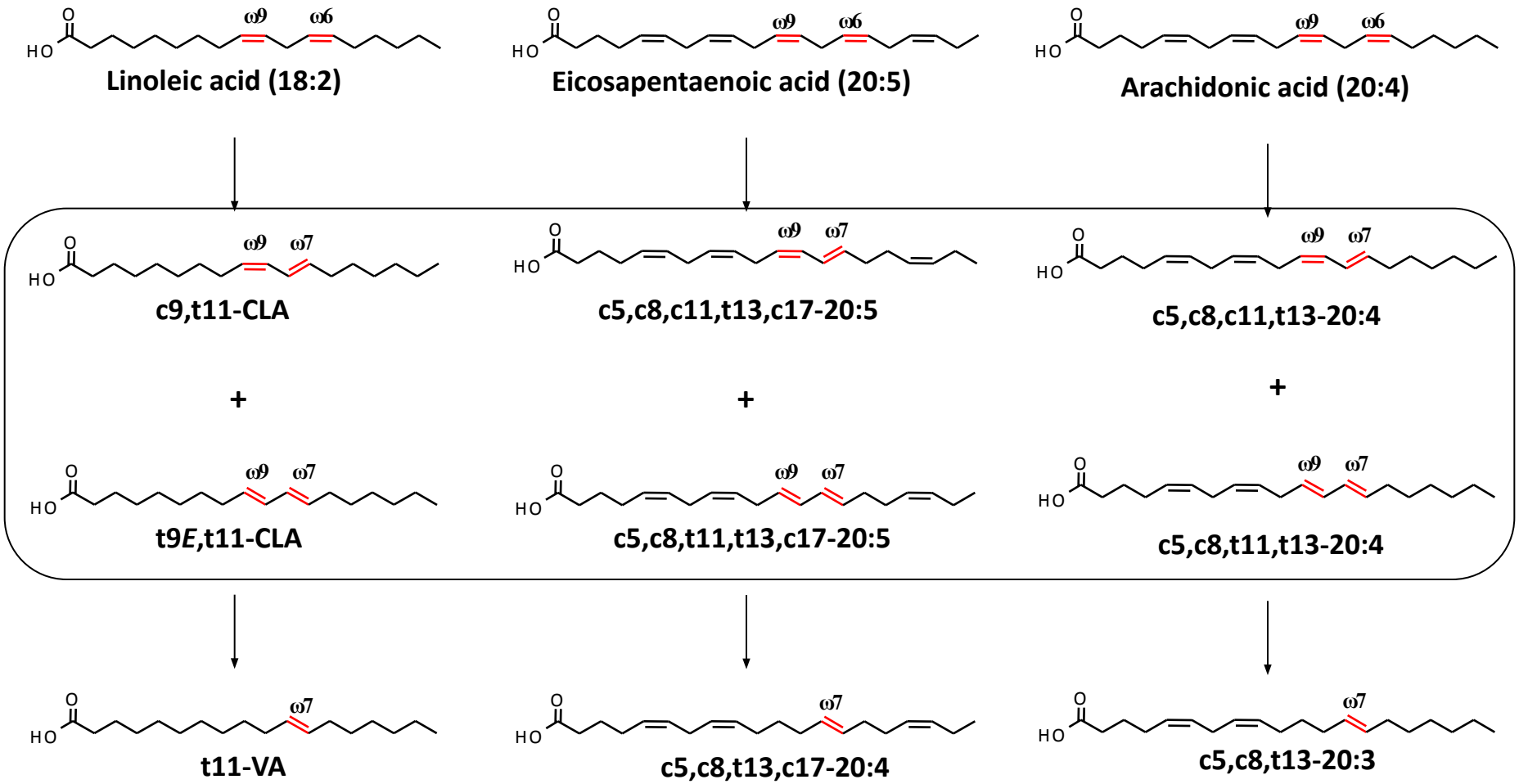
Hirata, A. et al, *J. Lipid Res.*, 56, 1340-1350 (2015)

Substrate specificity of fatty acid hydratase (FA-HY1) from *Lactobacillus acidophilus* NTV001

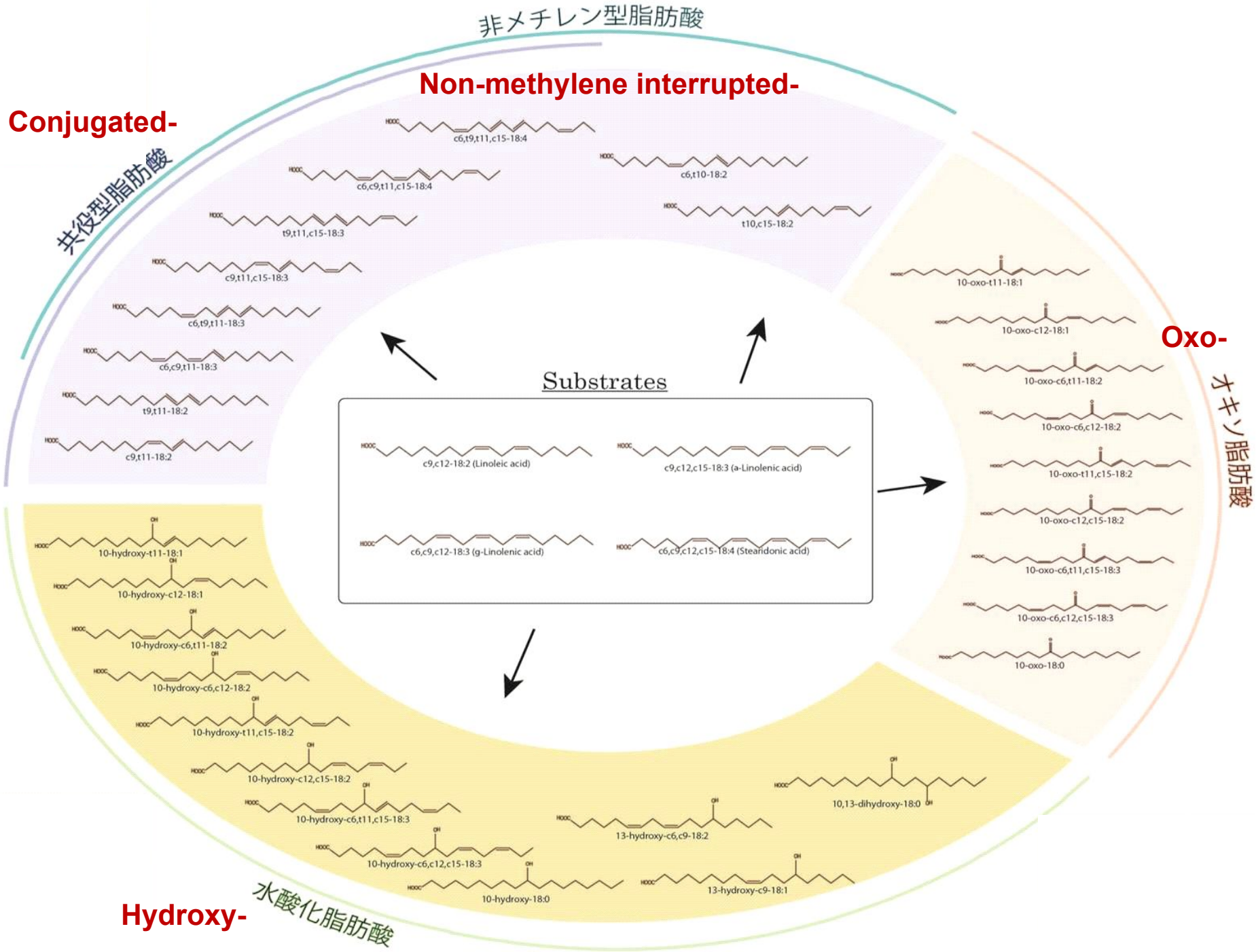
Substrate	Product
20:2$^{\Delta 11cis,\ \Delta 14cis}$	15-hydroxy-*cis*-11-20:1
20:3$^{\Delta 5cis,\ \Delta 8cis,\ \Delta 11cis}$	12-hydroxy-*cis*-5,*cis*-8-20:2
20:3$^{\Delta 5cis,\ \Delta 11cis,\ \Delta 14cis}$	15-hydroxy-*cis*-5,*cis*-11-20:2
20:3$^{\Delta 8cis,\ \Delta 11cis,\ \Delta 14cis}$ (DGLA)	15-hydroxy-*cis*-8,*cis*-11-20:2 12-hydroxy-*cis*-8,*cis*-14-20:2
20:3$^{\Delta 11cis,\ \Delta 14cis,\ \Delta 17cis}$	12-hydroxy-*cis*-14,*cis*-17-20:2 15-hydroxy-*cis*-11,*cis*-17-20:2
20:4$^{\Delta 5cis,\ \Delta 8cis,\ \Delta 11cis,\ \Delta 14cis}$ (AA)	15-hydroxy-*cis*-5,*cis*-8,*cis*-11-20:3
20:4$^{\Delta 8cis,\ \Delta 11cis,\ \Delta 14cis,\ \Delta 17cis}$	12-hydroxy-*cis*-8,*cis*-14,*cis*-17-20:3
EPA	–
DHA	**14-hydroxy-*cis*-4,*cis*-7,*cis*-10,*cis*-16,*cis*-19-22:5**



Putative pathway of biohydrogenation of polyunsaturated fatty acid by *Clostridium bifermentans* JCM1386



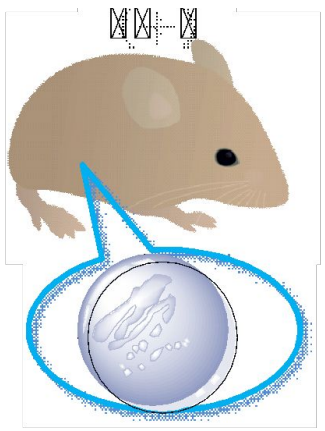
Sakurama, H. et al, *J. Lipid Res.*, 55, 1855-1863 (2014).


非メチレン型脂肪酸
Non-methylene interrupted-
Conjugated-
共役型脂肪酸
c6,t9,t11,c15-18:4
c6,c9,t11,c15-18:4
t9,t11,c15-18:3
c9,t11,c15-18:3
c6,t9,t11-18:3
c6,c9,t11-18:3
t9,t11-18:2
c9,t11-18:2
c6,t10-18:2
t10,c15-18:2
Substrates
c9,c12-18:2 (Linoleic acid)
c9,c12,c15-18:3 (a-Linolenic acid)
c6,c9,c12-18:3 (g-Linolenic acid)
c6,c9,c12,c15-18:4 (Stearidonic acid)
Oxo-
オキソ脂肪酸
10-oxo-t11-18:1
10-oxo-c12-18:1
10-oxo-c6,t11-18:2
10-oxo-c6,c12-18:2
10-oxo-t11,c15-18:2
10-oxo-c12,c15-18:2
10-oxo-c6,t11,c15-18:3
10-oxo-c6,c12,c15-18:3
10-oxo-18:0
Hydroxy-
水酸化脂肪酸
10-hydroxy-t11-18:1
10-hydroxy-c12-18:1
10-hydroxy-c6,t11-18:2
10-hydroxy-c6,c12-18:2
10-hydroxy-t11,c15-18:2
10-hydroxy-c12,c15-18:2
10-hydroxy-c6,t11,c15-18:3
10-hydroxy-c6,c12,c15-18:3
10-hydroxy-18:0
13-hydroxy-c6,c9-18:2
10,13-dihydroxy-18:0
13-hydroxy-c9-18:1

Polyunsaturated Fatty Acid Saturation Metabolism of Gut Microbiota (Lactic Acid bacteria) Affecting Host Health via Bio-active Fatty Acid Generation

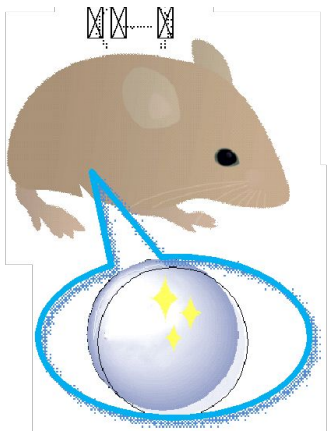
- Gut microbial PUFA saturation metabolism
- Distribution of gut microbial PUFA metabolites in the host
- Physiological activities of gut microbial PUFA metabolites
- Preparation of gut microbial PUFA metabolites
- Prebiotic, probiotic, and postbiotic applications

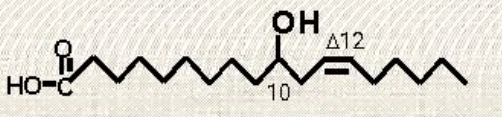
With gut microbes
(specific pathogen-free)

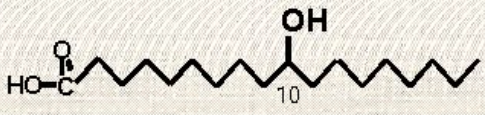


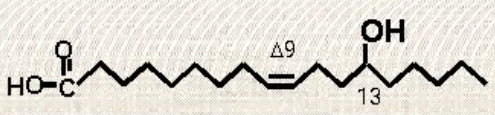
VS

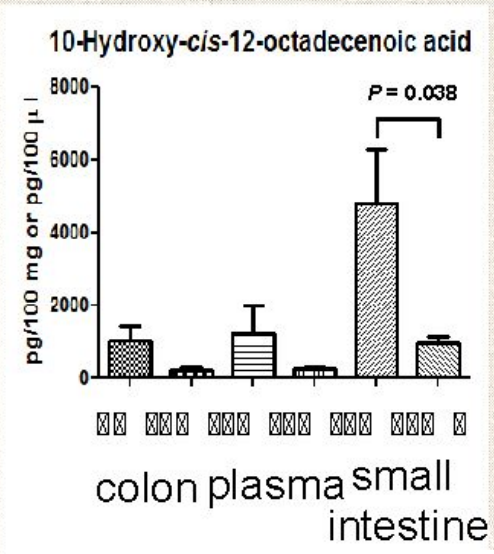
Without gut microbes
(germ-free)

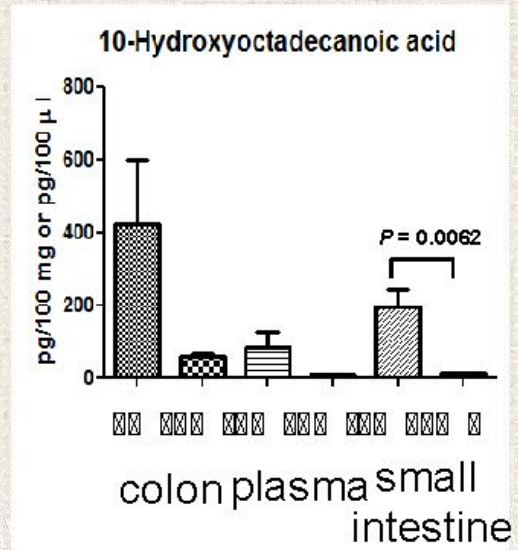


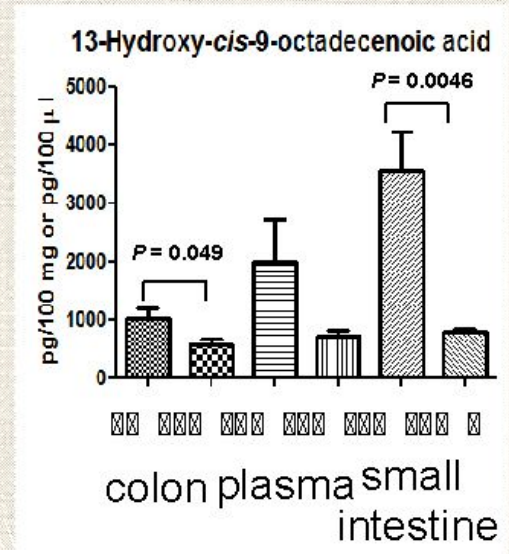












The concentrations are 0.01 to 0.1μ M

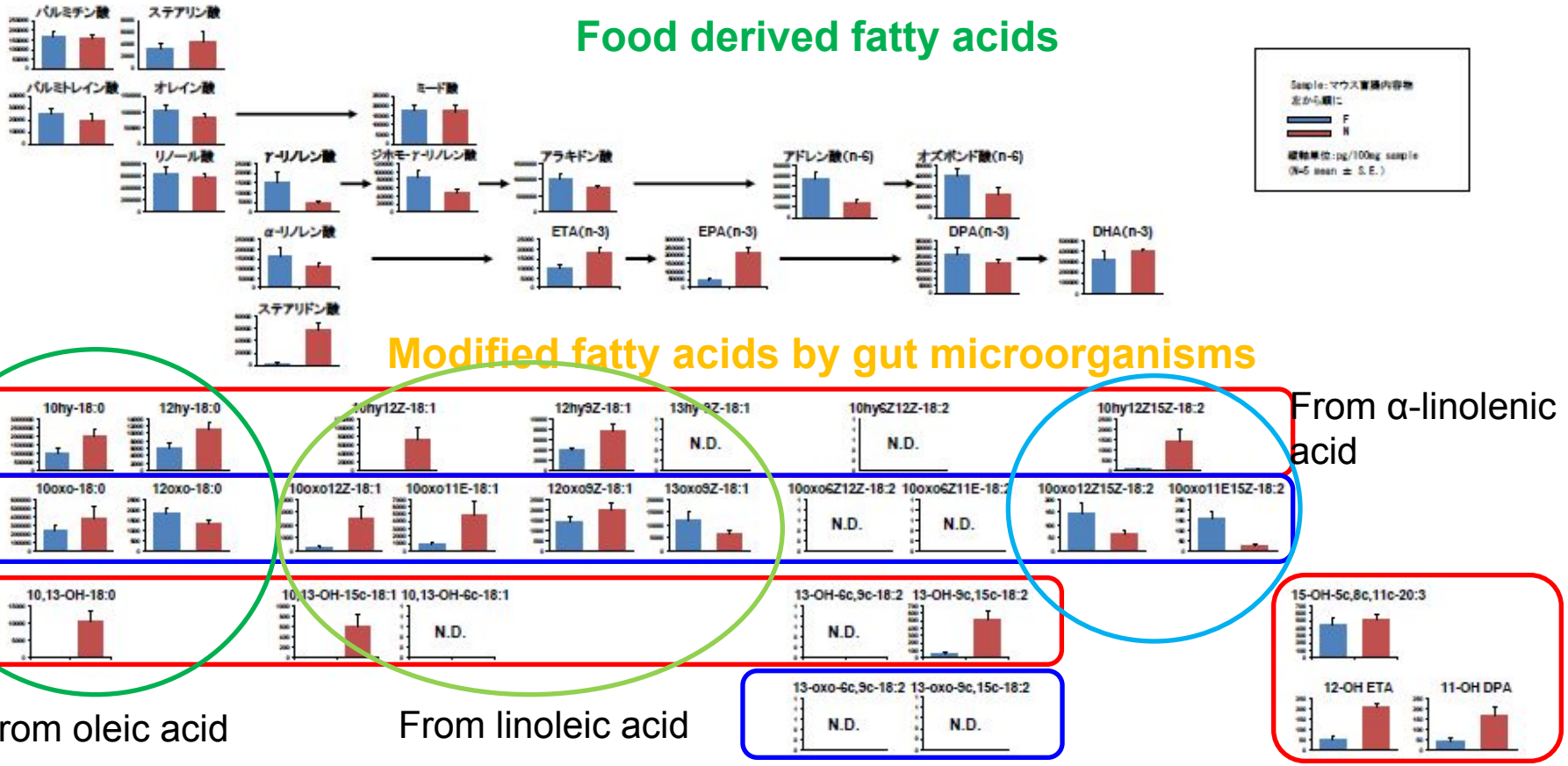
Kishino, S. et al, *Proc. Natl. Acad. Sci. USA,* 110, 17808-17813

In gut ingredients (feces), there are various kinds of modified fatty acids by gut microorganisms (hydroxy, oxo, enone fatty acids).

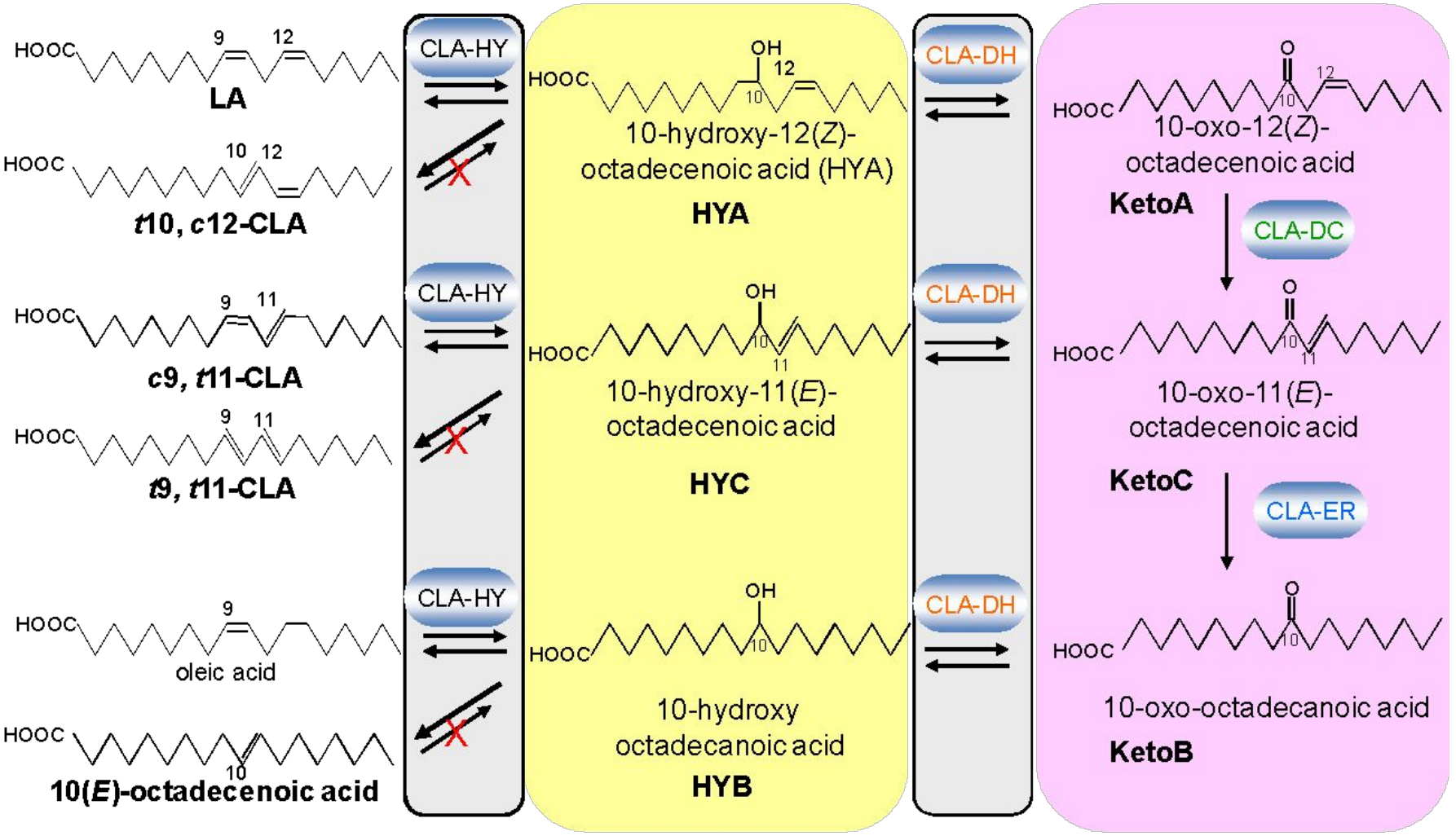
Concentrations: 1 μM ~ 100 μM

Mocelular species: from oleic acid, linoleic acid, α-linolenic acid, etc

Ratio of food derived / modified : 10 / 1 ~ 1 / 10



Novel and Beneficial function!!!?



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Anti-oxidative effects

α-Linolenic acid-derived metabolites from gut lactic acid bacteria induce differentiation of anti-inflammatory M2 macrophages through G protein-coupled receptor 40 (GPR40) and PPARγ

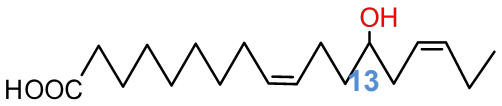
α-linolenic acid (ALA)

↓

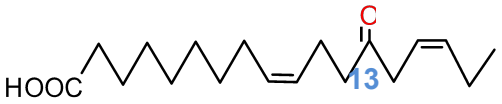
A lactic acid bacterium

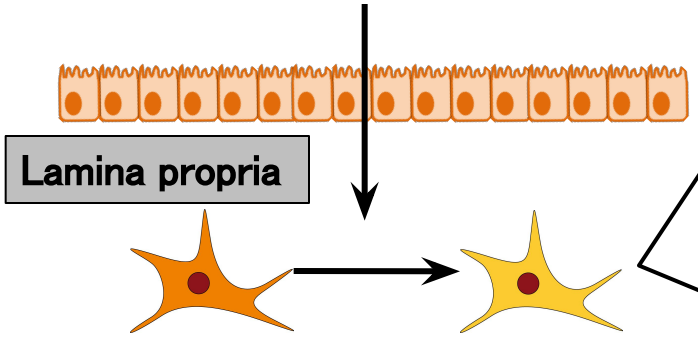
↓

13-OH- *c*9,*c*15-18:2 (13-OH)

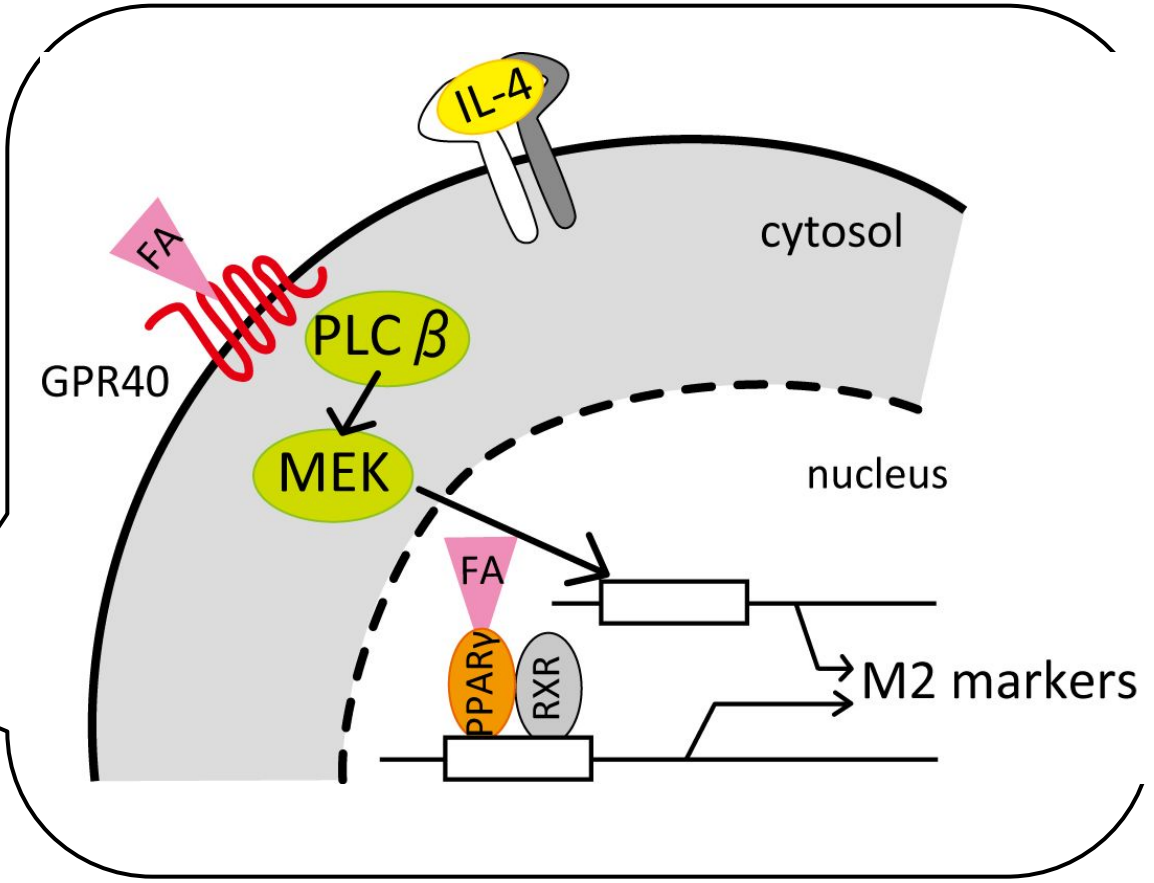


13-oxo- *c*9,*c*15-18:2 (13-oxo)





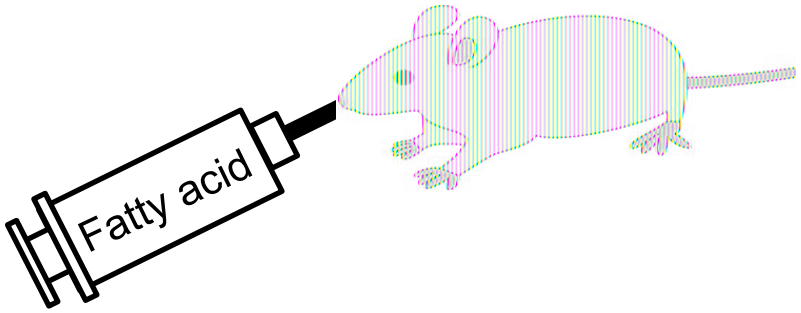
M2 type Mϕ

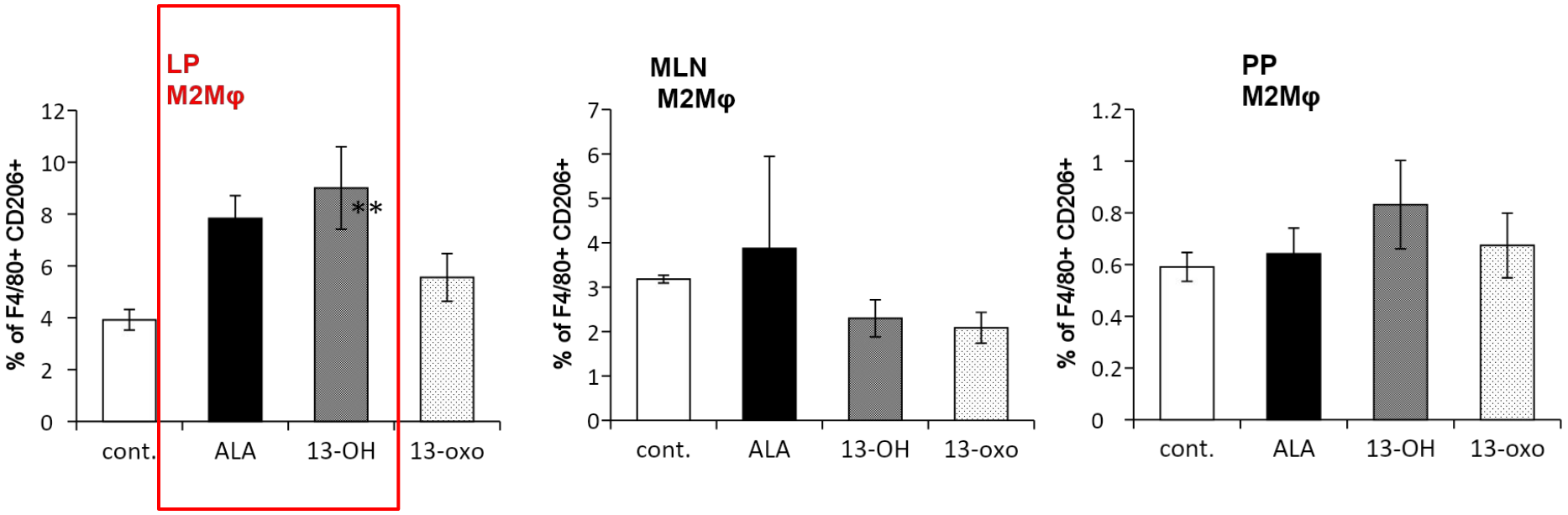


Ohue-Kitano, R. et al., *FASEB J.*, 32, 304-318 (2018)

α-Linolenic acid-derived metabolites from gut lactic acid bacteria induce differentiation of anti-inflammatory M2 macrophages and accumulate M2 macrophage in lamina propria

C57BL/6 ♂
1g/kg BW/day
3 days oral addministration.





LP; lamina propria, MLN; mesenteric lymph node, PP; peyer's patch.

*p<0.05, **p<0.01 compared with cont.(n=2–6).

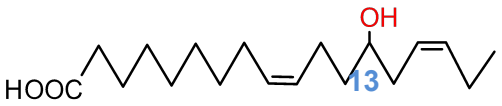
Ohue-Kitano, R. FASEB J., 32(1), 304-318 (2018)

α-Linolenic acid-derived metabolites from gut lactic acid bacteria accumulate M2 macrophage in adipose tissue and repress inflammation

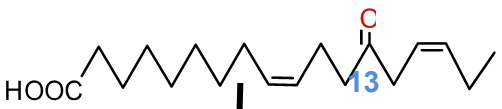
α−linolenic acid (ALA)

A lactic acid bacterium

13−OH− *c*9,*c*15−18:2 (13−OH)



13−oxo− *c*9,*c*15−18:2 (13−oxo)

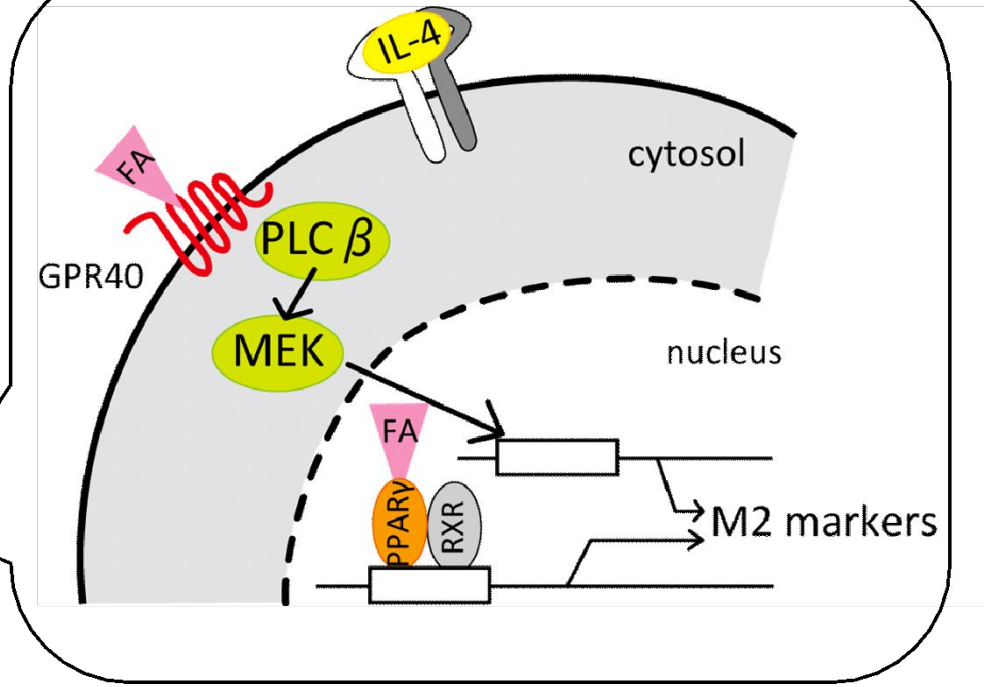


Intestine

M2 type Mϕ

Adipose tissue

M1type Mϕ



Mϕ; macrophage, PPARγ; peroxisome proliferator−activated receptor−, RXR; retinoid X receptor, FA; fatty acid.

Ohue-Kitano, R. FASEB J., 32(1), 304-318 (2018)

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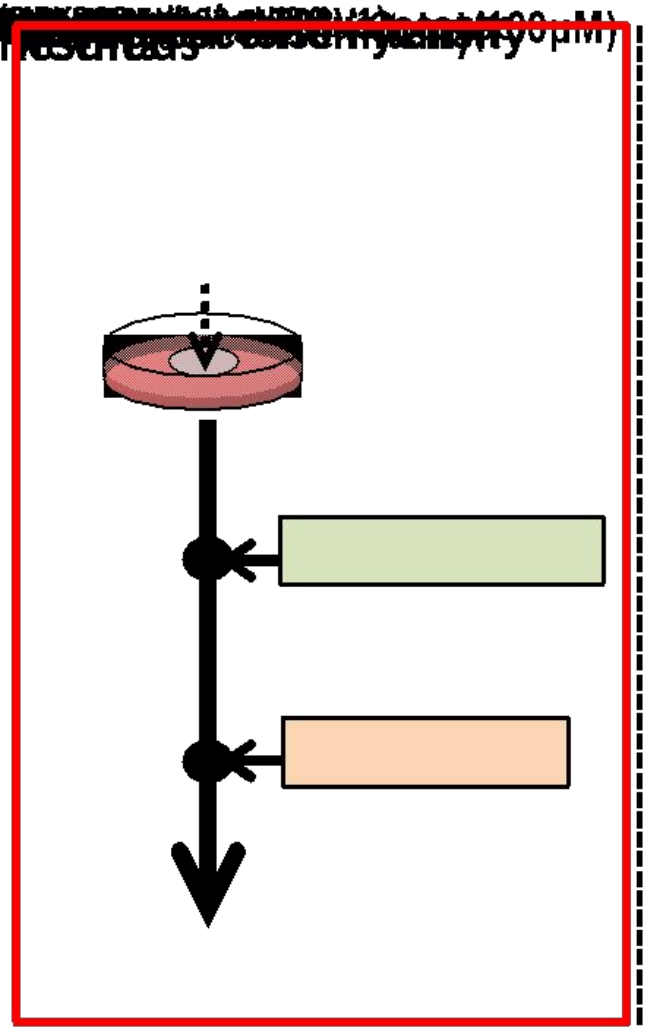
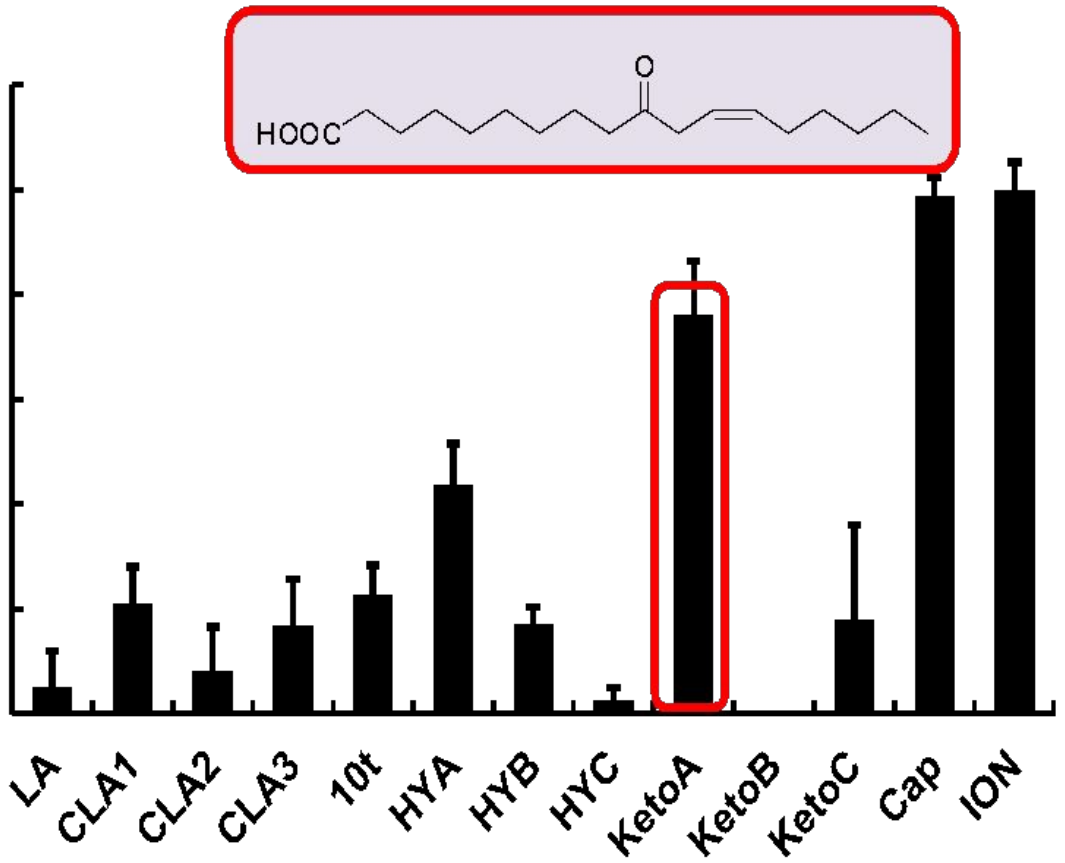
KetoA induced TRPV1-mediated Ca^{2+} influx



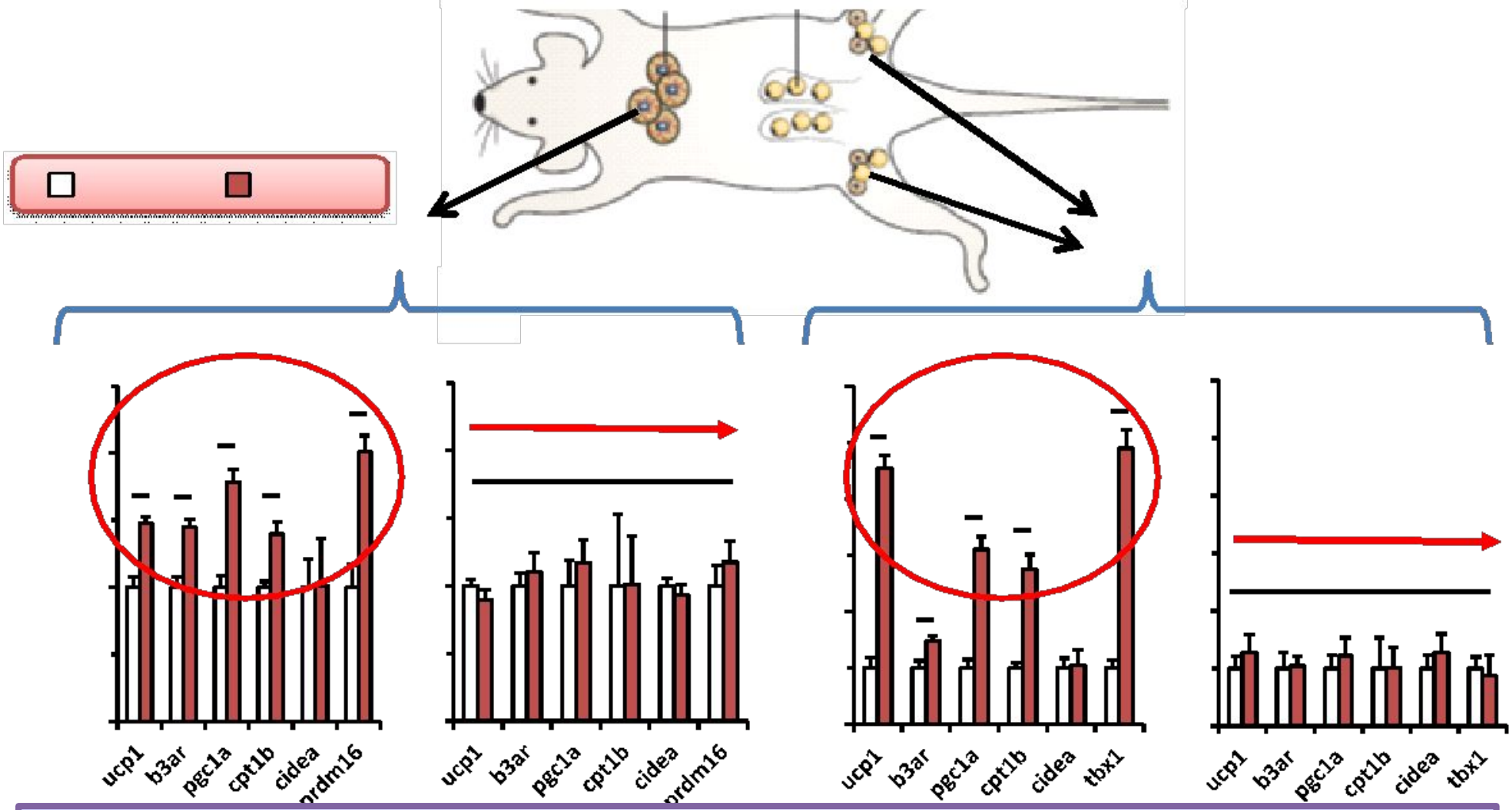


KetoA most potently induced TRPV1-mediated Ca^{2+} influx among the LA-derived various fatty acids.

Kim, M. et al, *FASEB J.*, 31(11),5036-5048 (2017)

KetoA up-regulated genes expression related to BAT function

Gene expression in iBAT and iWAT of WT or TRPV1 KO mice treated with KetoA



KetoA treatment up-regulated BAT function in iBAT and iWAT and this function was dependent on TRPV1 activation.

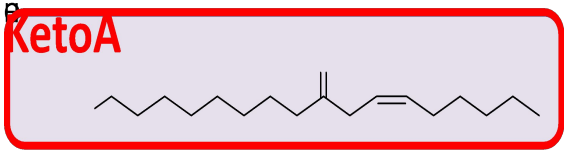
Kim, M. et al, *FASEB J.*, 31(11),5036-5048 (2017)

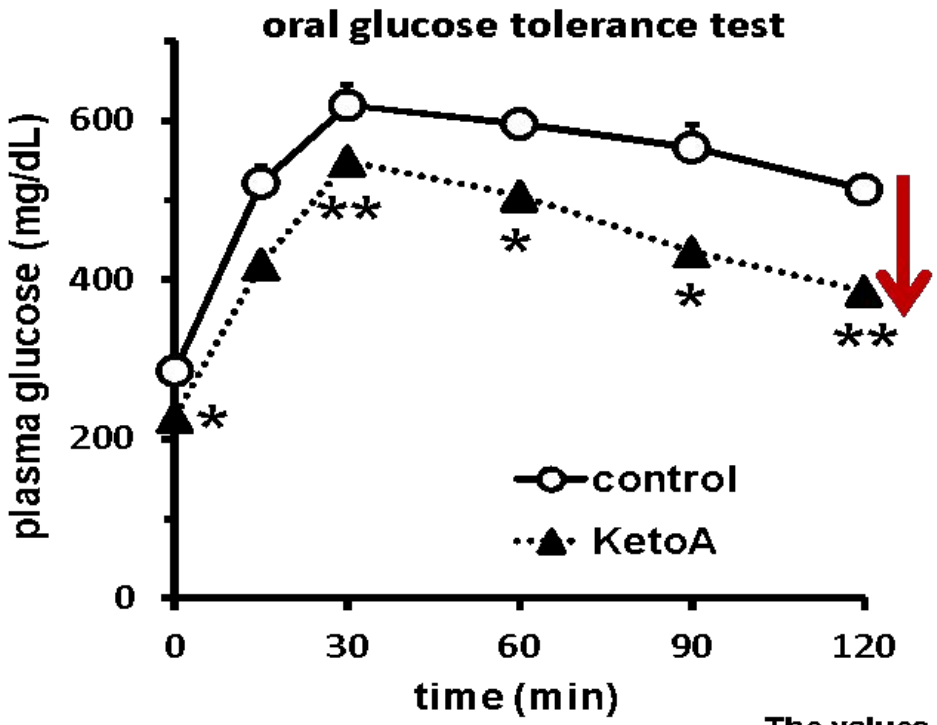
KetoA, a linoleic acid metabolites of gut microbiota, has anti-diabetic and anti-hypolipidemic effects

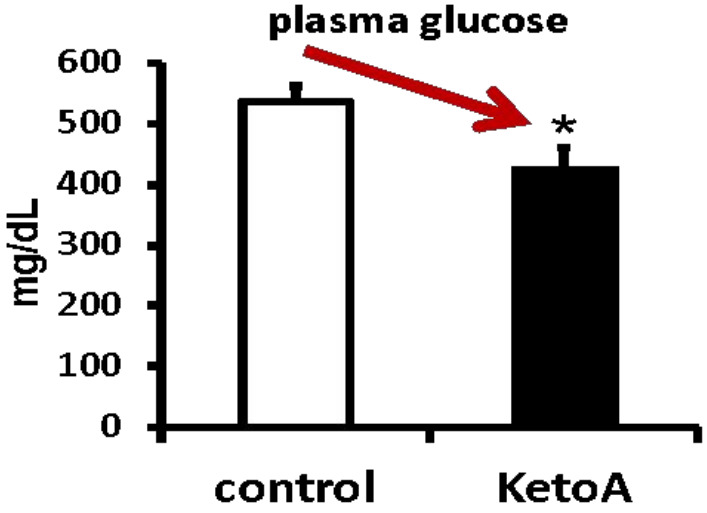
KK-Ay obese mice
(5-wks-old)

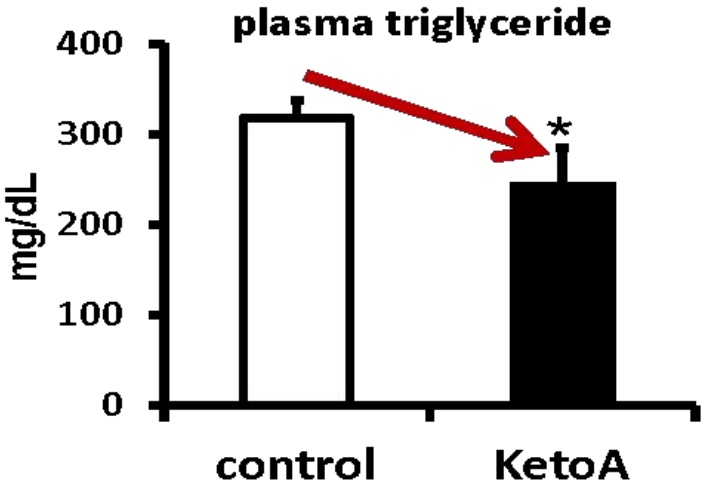
4 wks

0.1% KetoA
/ high fat diet (HFD)









The values are mean ± S.E.M. *$p<0.05$, **$p<0.01$ compared with contro

Dietary KetoA intake improved obesity-associated metabolic disorders via up-regulation of adipose tissue function by TRIPVI activation.

Kim, M. et al, *FASEB J.*, 31(11),5036-5048 (2017)

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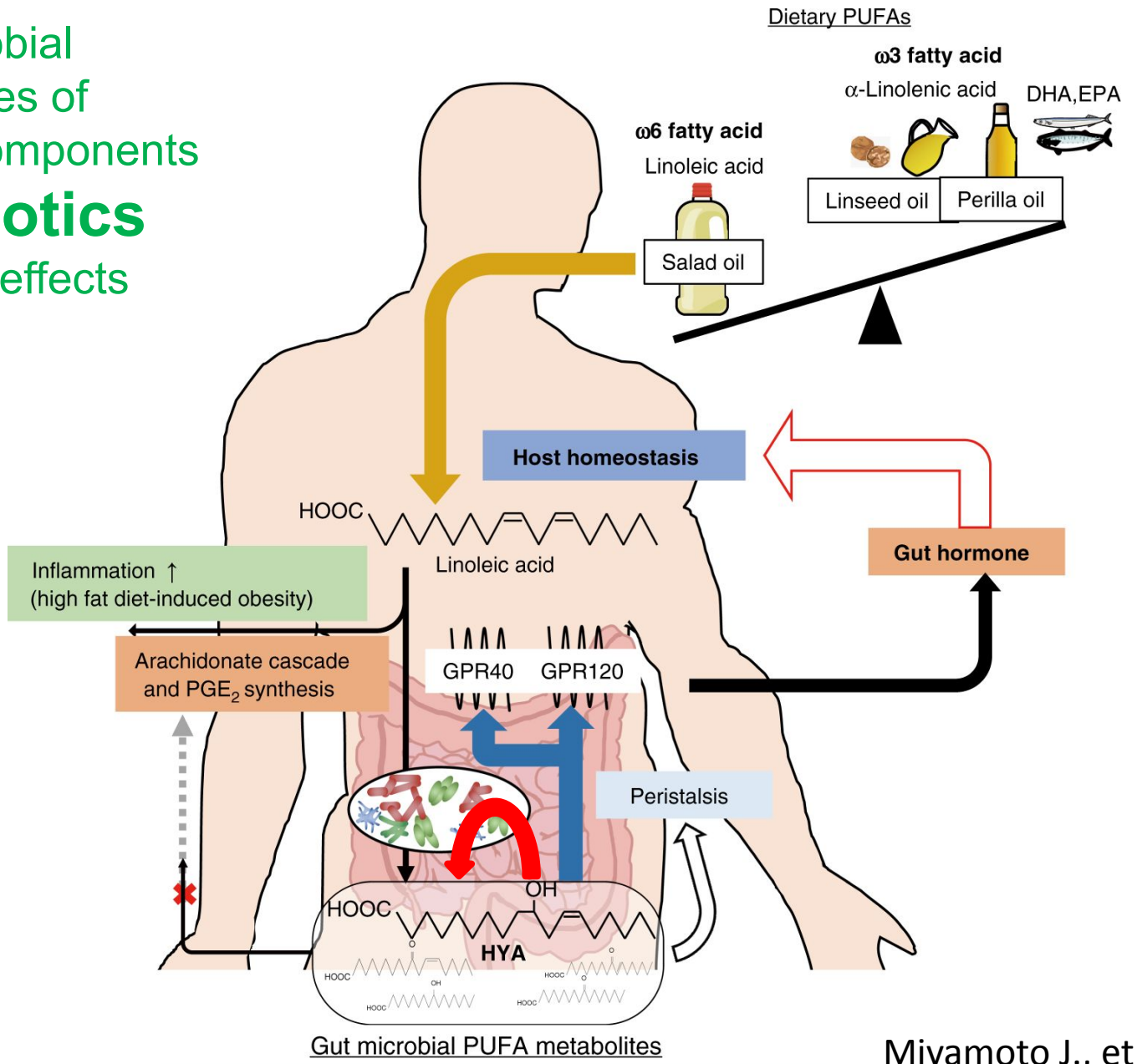
Anti-oxidative effects

Gut microbial metabolites of dietary components

Postbiotics

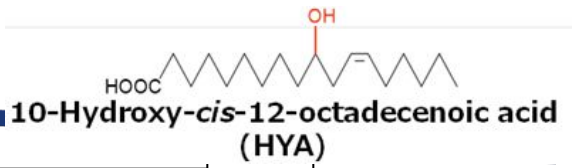
with dual effects



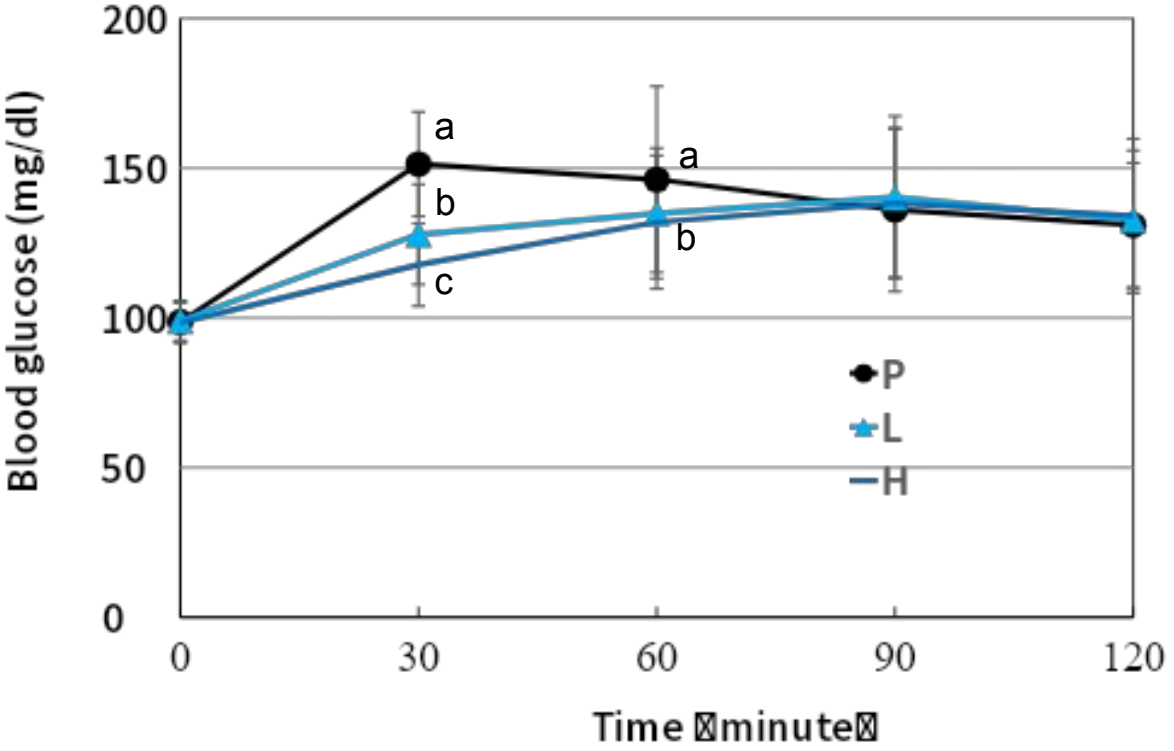
Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids

Miyamoto J., et al,
NATURE COMMUNICATIONS
10:4007, 2019

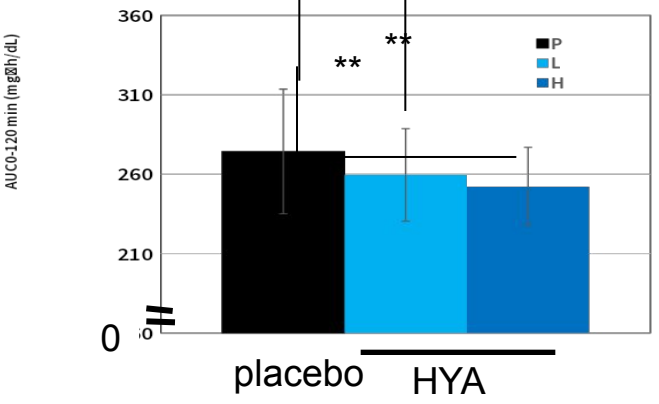
Clinical trial results



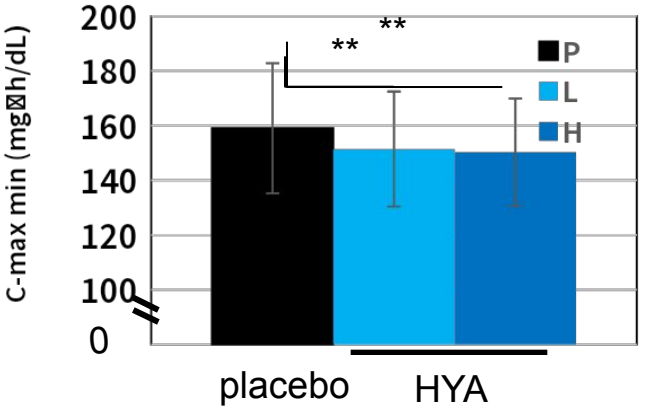
Changes in blood glucose after ingestion



AUC$_{0\text{-}120\ min}$



C-max$_{min}$



P: ingesting a placebo
L : ingesting low dose HYA (1000mg)
H : ingesting high dose HYA (2000mg)

Yonejima Y., et al, ***Prog. Med.***, 37, 1105-1111 (2017)

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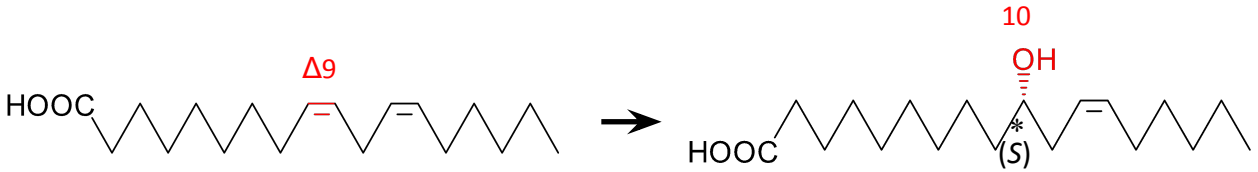
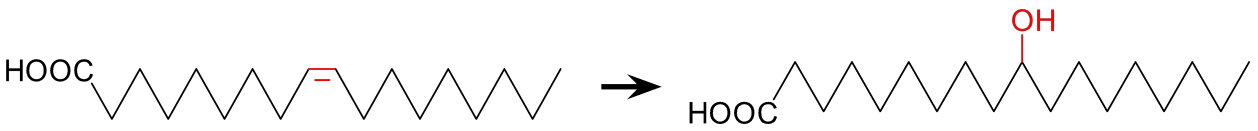
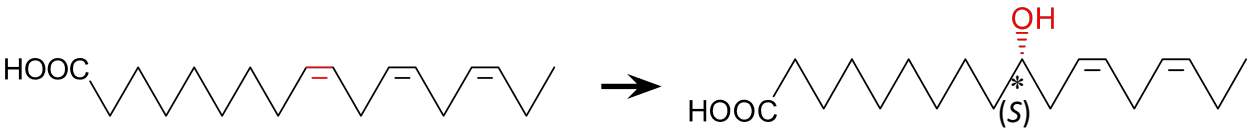
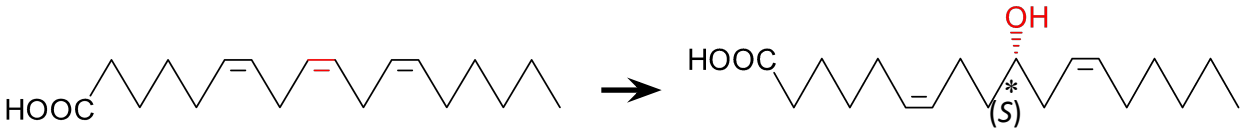
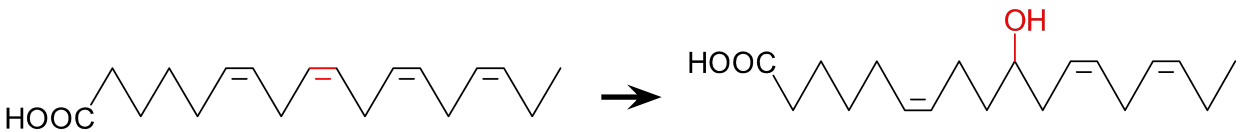
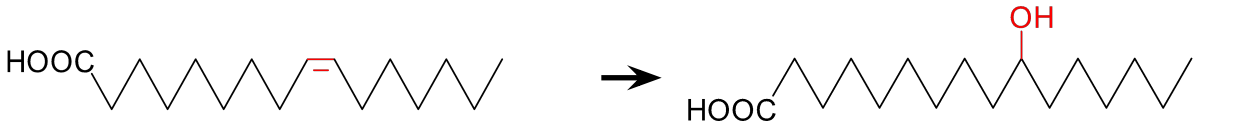
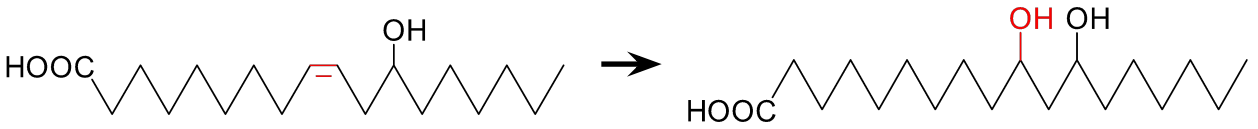
- Preparation of gut microbial PUFA metabolites
- Prebiotic, probiotic, and postbiotic applications

Hydroxy fatty acid production using CLA-HY expressed in *E. coli*

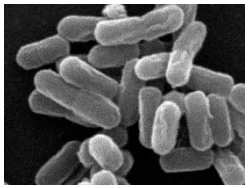
Substrates (280 g/L)		Yield [%]
Linoleic acid (18:2)		98% (292 g/L)
Oleic acid (18:1)		96% (286 g/L)
α-Linolenic acid (18:3)		96% (286 g/L)
γ-Linolenic acid (18:3)		95% (283 g/L)
Stearidonic acid (18:4)		96% (286 g/L)
Palmitoleic acid (16:1)		98% (294 g/L)
Ricinoleic acid (12-OH 18:1)		99% (294 g/L)

Takeuchi, M. et al, *J. Appl. Microbiol.*, 120, 1282-1288 (2016).

HYA production from edible plant oils using lactic acid bacteria

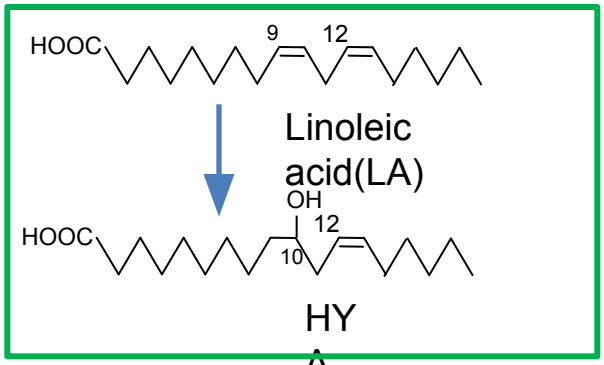
Oil

Lipase

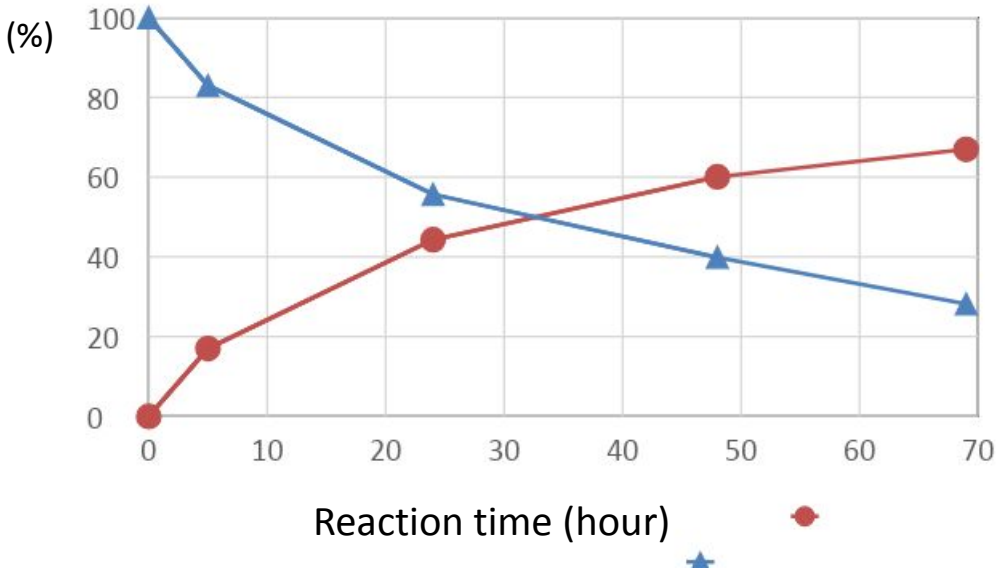


Lactic acid bacteria (LAB)

HYA



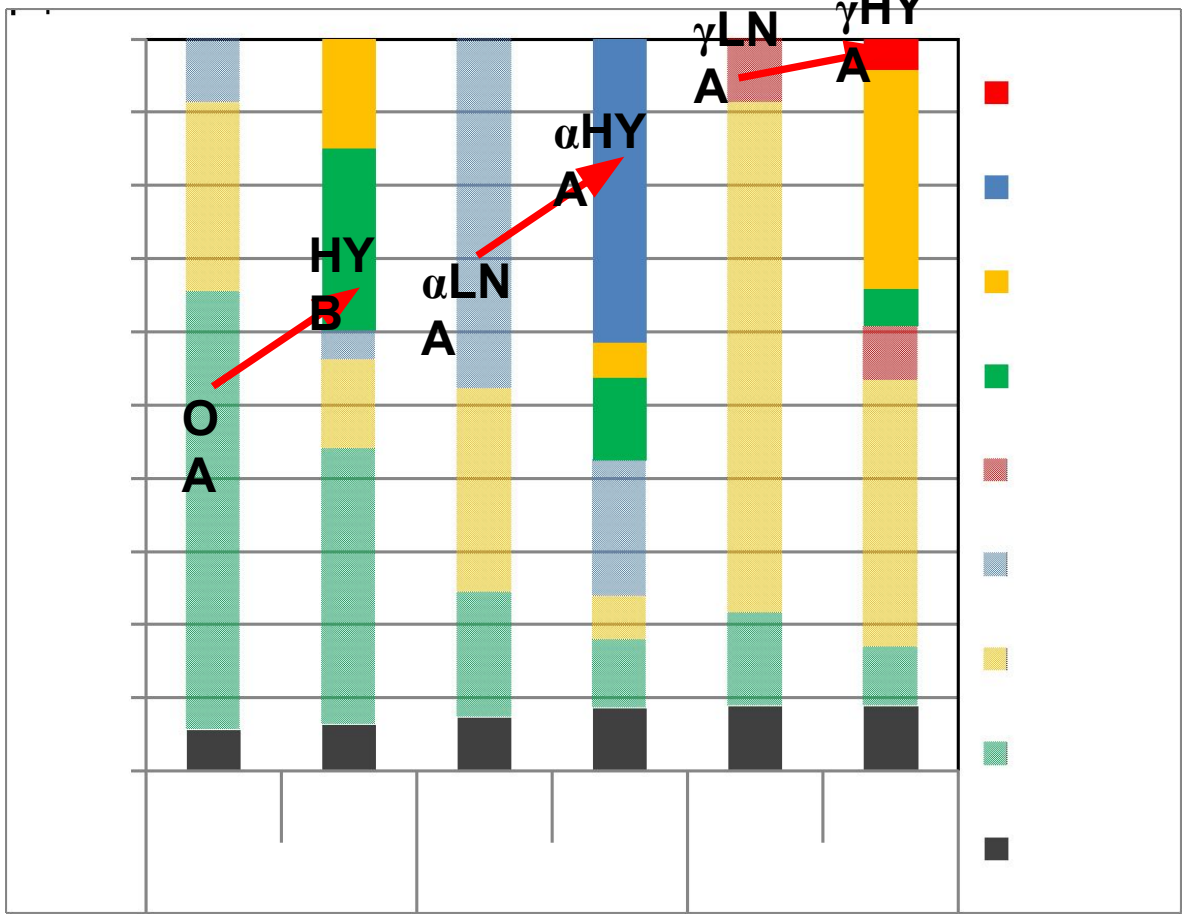
Time course of HYA production

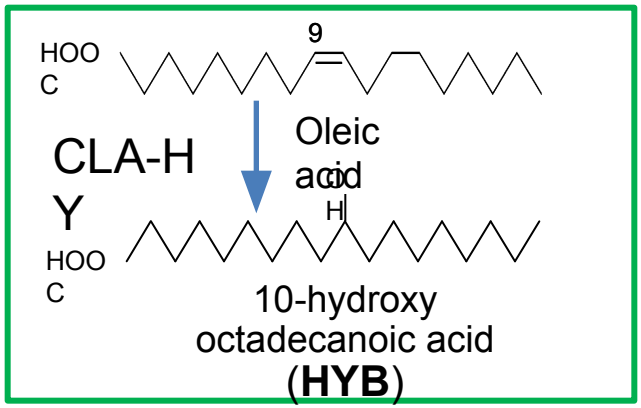


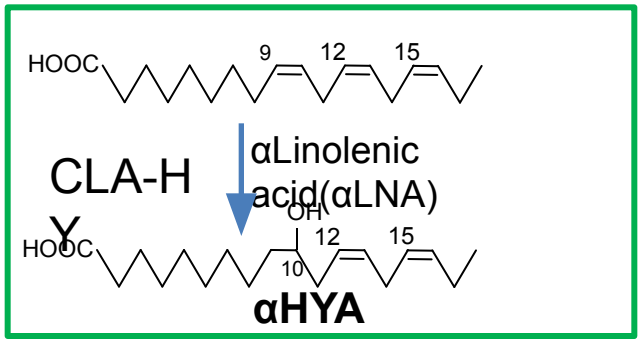
reac

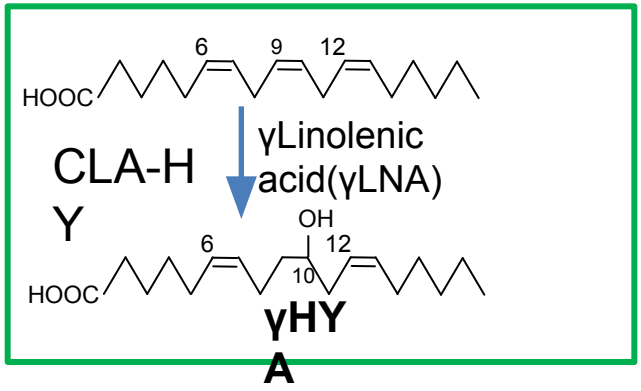
Postbiotics

Production of various hydroxy fatty acids through hydration from edible plant oils using lactic acid bacteria



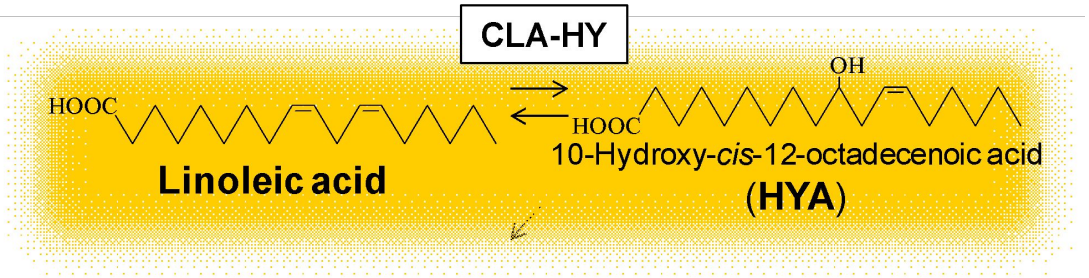






Polyunsaturated Fatty Acid Saturation Metabolism of Gut Microbiota (Lactic Acid bacteria) Affecting Host Health via Bio-active Fatty Acid Generation

- Gut microbial PUFA saturation metabolism
- Distribution of gut microbial PUFA metabolites in the host
- Physiological activities of gut microbial PUFA metabolites
- Preparation of gut microbial PUFA metabolites
- Prebiotic, probiotic, and postbiotic applications



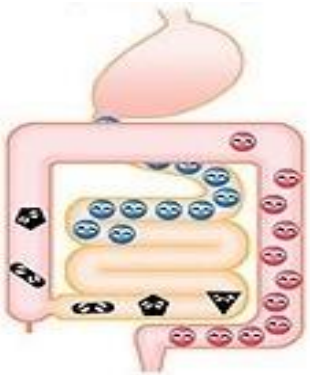
Enhanced HYA-production by probiotic cells.

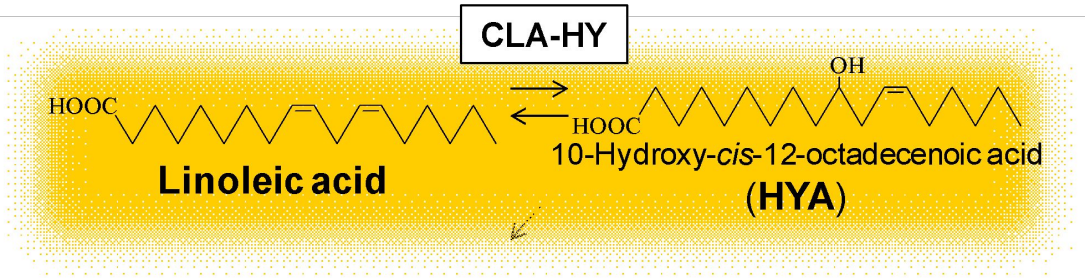
Lactobacillus plantarum
Lactobacillus brevis
Lactobacillus curvatus
Lactobacillus sakei

Intestinal probiotics and nutrient uptake

Probiotics
HYA-producing microorganisms

Dietary fat
Linoleic acid





Enhanced HYA-production by probiotic cells with prebiotics in the intestine.

Intestinal probiotics and nutrient uptake

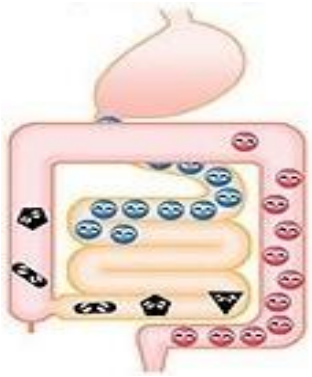
Lactobacillus plantarum
Lactobacillus brevis
Lactobacillus curvatus
Lactobacillus sakei

Probiotics
HYA-producing microorganisms

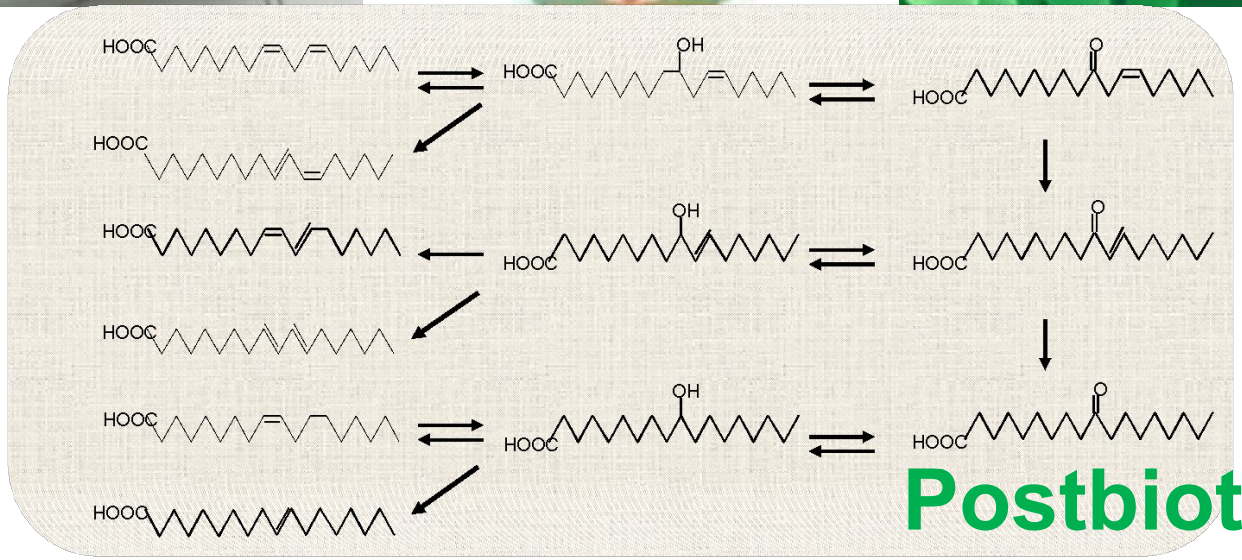
Dietary fat
Linoleic acid

Prebiotics

Vitamin (niacin)



The combination of fatty acid composition in the dietary fat and the fatty acid-metabolizing activity in gut microbe would regulate the intestinal disorders and lipid metabolisms of the host.

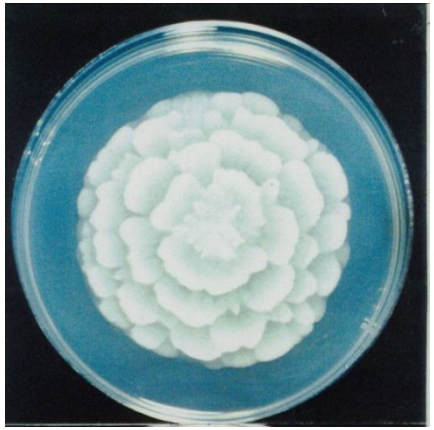


Summary

Functional lipid production by microbial metabolisms and enzymes:

beyond common polyunsaturated fatty acids

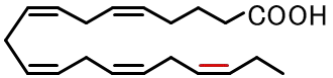
Fermentative production of PUFAs

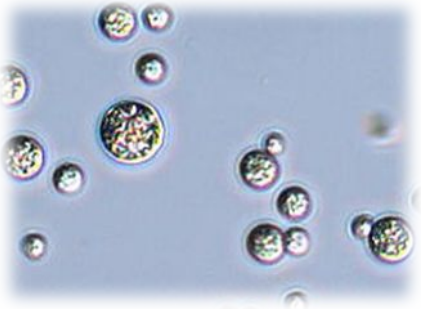


EPA: 52 % 14.4g/L

M. alpina transformant expressing

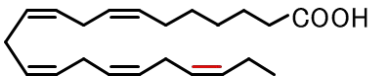
Δ12, Δ17 desaturases





n−3 DPA: 165 mg/L

Aurantiochytrium sp. T7

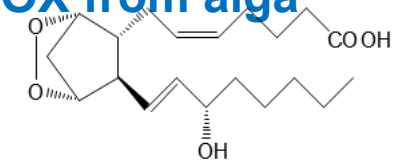


Biotransformation of PUFAs

$PGF_{2\alpha}$: 6 mg/L

M. alpina transformant expressing

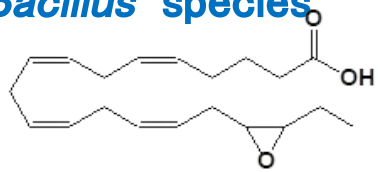
COX from alga

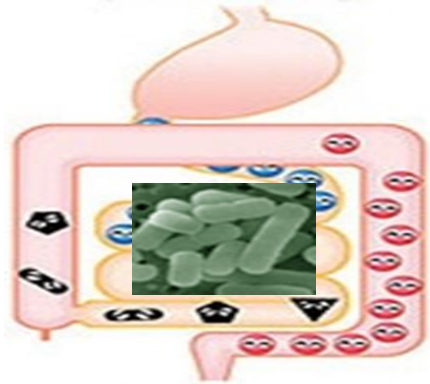


17,18−EpETe:

0.38 mg /mL

P450 MO from Bacillus species

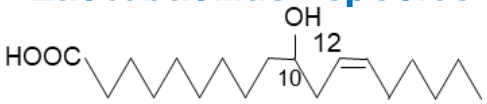




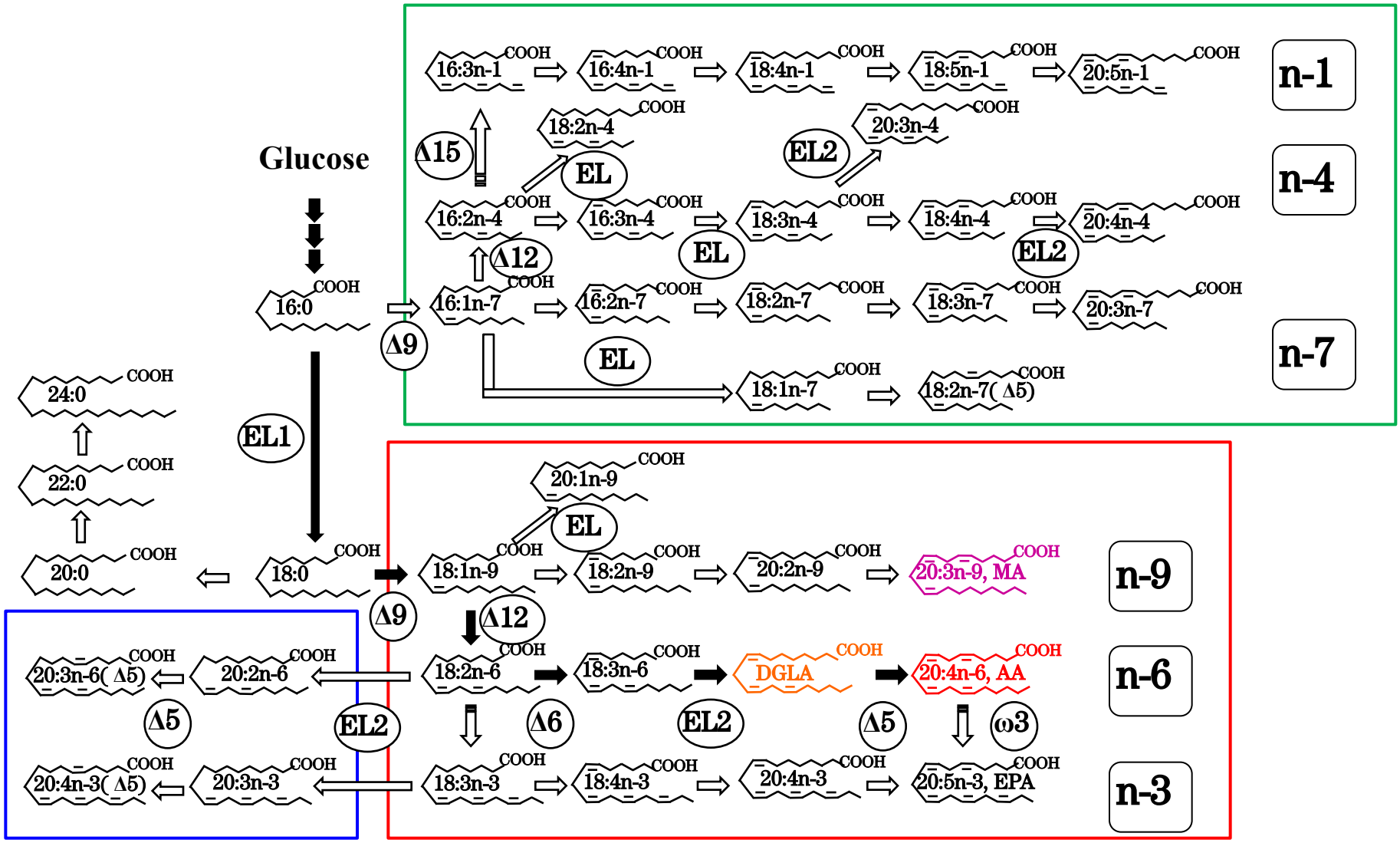
HYA: 292 g /L

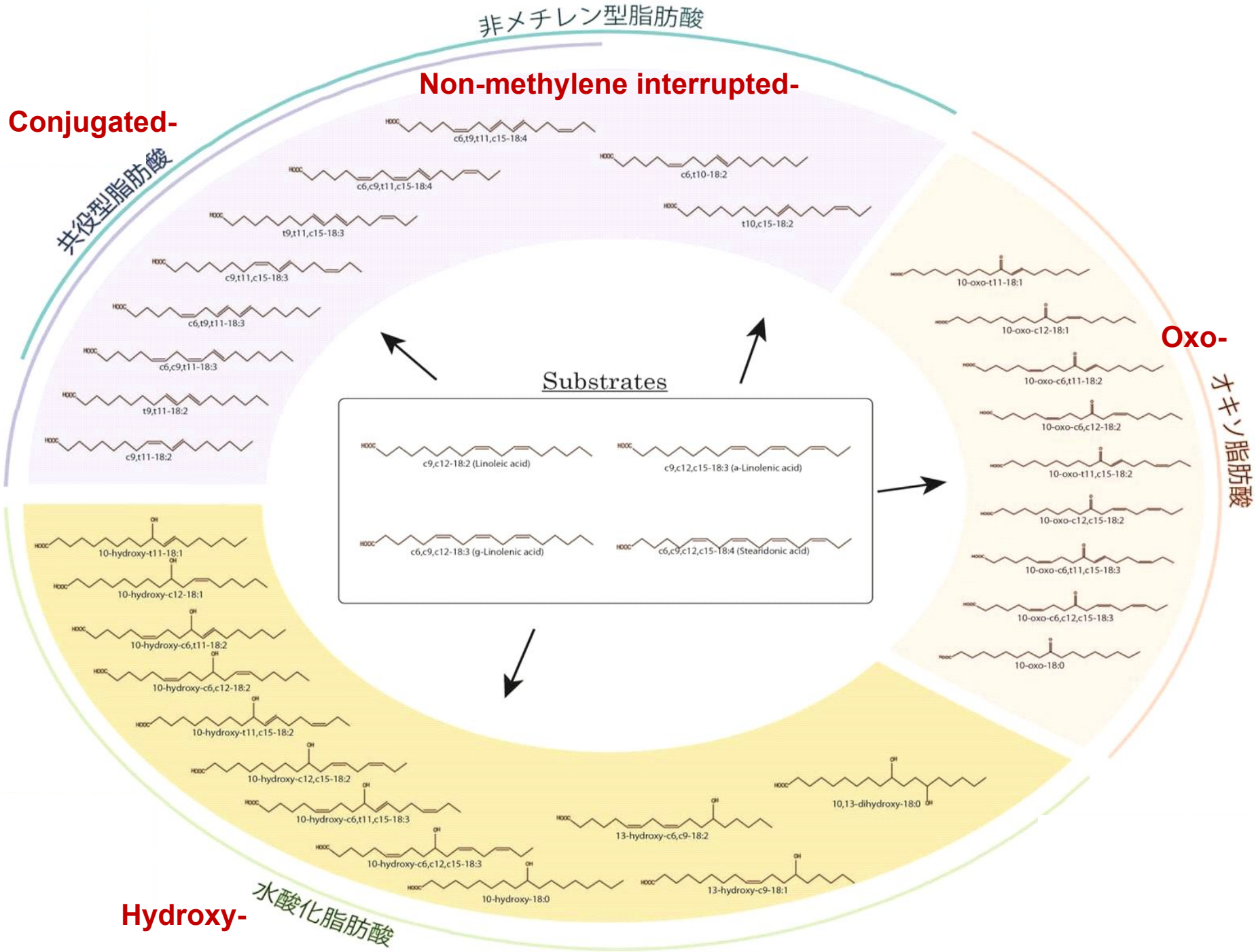
Other hydroxy FAs, Oxo−FAs, enone FAs

Lactobacillus species



Various PUFA biosynthetic pathways in *M. alpina* and its mutants




非メチレン型脂肪酸
Non-methylene interrupted-
Conjugated-
共役型脂肪酸
c6,t9,t11,c15-18:4
c6,c9,t11,c15-18:4
t9,t11,c15-18:3
c9,t11,c15-18:3
c6,t9,t11-18:3
c6,c9,t11-18:3
t9,t11-18:2
c9,t11-18:2
c6,t10-18:2
t10,c15-18:2
Substrates
c9,c12-18:2 (Linoleic acid)
c9,c12,c15-18:3 (a-Linolenic acid)
c6,c9,c12-18:3 (g-Linolenic acid)
c6,c9,c12,c15-18:4 (Stearidonic acid)
Oxo-
オキソ脂肪酸
10-oxo-t11-18:1
10-oxo-c12-18:1
10-oxo-c6,t11-18:2
10-oxo-c6,c12-18:2
10-oxo-t11,c15-18:2
10-oxo-c12,c15-18:2
10-oxo-c6,t11,c15-18:3
10-oxo-c6,c12,c15-18:3
10-oxo-18:0
Hydroxy-
水酸化脂肪酸
10-hydroxy-t11-18:1
10-hydroxy-c12-18:1
10-hydroxy-c6,t11-18:2
10-hydroxy-c6,c12-18:2
10-hydroxy-t11,c15-18:2
10-hydroxy-c12,c15-18:2
10-hydroxy-c6,t11,c15-18:3
10-hydroxy-c6,c12,c15-18:3
10-hydroxy-18:0
13-hydroxy-c6,c9-18:2
10,13-dihydroxy-18:0
13-hydroxy-c9-18:1

Conclusion

Through analysis of microbial metabolisms, we developed technologies to provide rare lipid compounds that became starting points of new lipid sciences.

The examples are:

- rare polyunsaturated fatty acid fermentation and transformation through oxidative microbial metabolisms.
- reductive fatty acid metabolisms generating novel fatty acid metabolites.

These researches:

- stemmed from the ***screening*** of novel microbial function.
- expanded by the ***observation*** of newly found microbial function.
- contributed to the society through ***application*** of unique microbial function.

These are based on the nature of microorganism……

The earth is a closed space.
Materials are cycling on the earth
just changing their chemical forms.

Microorganisms are the most important players of this geochemical material cycle.
They decompose, transform, and produce various kinds of compounds though their unique metabolisms supported by vast genetic diversity.

Appreciation for Microorganisms

Microbe Monument

(Manshuin temple, Kyoto, Japan)

To the innumerable souls of microbes who have dedicated and sacrificed for the existence of humans, we pay our deepest respect.

Here, we hold a memorial service for their soul's rest and condolence, build a microbe monument.

Acknowledgments

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Thank you for your attention