

Making fish oils in plants – how GM can help make crops more nutritious



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SUSTAINABLE DEVELOPMENT GOALS



We need solutions to problems now*

'Blah, blah, blah': Greta Thunberg lambasts leaders over climate crisis

Exclusive: Activist says there are many fine words but the science does not lie - CO2 emissions are still rising



■ 'All we hear is blah blah blah': Greta Thunberg takes aim at climate platitudes - video

Greta Thunberg has excoriated global leaders over their promises to address the climate emergency, dismissing them as “blah, blah, blah”.

“**Build back better.** Blah, blah, blah. Green economy. Blah blah blah. Net zero by 2050. Blah, blah, blah,” she said in a speech to the Youth4Climate summit in Milan, Italy, on Tuesday. “This is all we hear from our so-called leaders. Words that sound great but so far have not led to action. Our hopes and ambitions drown in their empty promises.”

****Solutions, not potential solutions***

Omega-3 Long Chain Polyunsaturated Fatty Acids

- Beneficial for human health
- A limited natural resource
- No known plant sources available
- Vital for aquaculture

“Omega-3 fish oils” and “omega-3 LC-PUFAs” are synonymous and used interchangeably. In general, these terms refer to eicosapentaenoic acid (20:5n-3; EPA) and docosahexaenoic acid (22:6n-3; DHA)

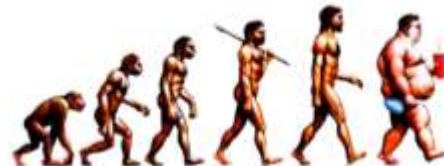


Omega-3 LC-PUFAs (“Fish oils”) are well-known to be health-protective



Obesity is now prevalent throughout much of the Western world. This and associated diseases such as CVD and type 2 diabetes represent an imminent public health crisis.

Moderate consumption (0.5-2g/day) of omega-3 long chain polyunsaturated fatty acids found in fish oils can help avert this problem



Not all omega-3 (n-3) fatty acids are the same

Fish oils vs Vegetable oils

Typical fatty acid composition of some commercial fish oils

	Anchovy	Cod Liver	Sardine	Salmon (Farmed)	Tuna
Saturated					
14:0	9	4	8	5	3
16:0	17	10	18	12	22
Monounsaturated					
16:1	13	8	10	6	3
18:1	10	25	13	20	21
20:1	1	10	4	9	1
22:1	1	7	3		3
VLCPUFAs					
20:5	22	10	16	7	6
22:5	2	1	2	3	2
22:6	9	10	9	11	22
Other					
	16	15	17	17	17

Omega-3
LC-PUFAs



Typical fatty acid composition of some commercial vegetable oils

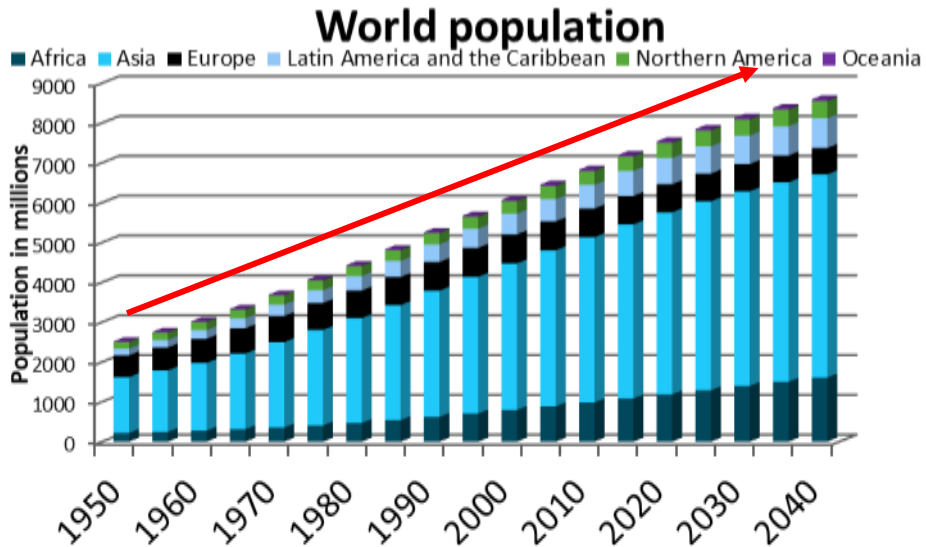
	Soya	Palm	Rape	Sunflower	Linseed
Saturated					
14:0	-	0-15	-	-	-
16:0	8-13	22-46	3-4	5-7	4-10
Monounsaturated					
16:1	-	0-2.5	-	<0.5	<0.5
18:1	17-26	36-68	9-16	15-25	10-20
20:1	<0.4	-	7-13	<0.5	<0.5
22:1	-	-	41-52	-	-
PUFAs					
18:2(n-6)	50-62	2-20	11-16	62-70	12-24
18:3(n-3)	4-10	<1	7-12	-	45-70
VLCPUFAs					
20:5	-	-	-	-	-
22:5	-	-	-	-	-
22:6	-	-	-	-	-

Omega-3
but not
long
chain



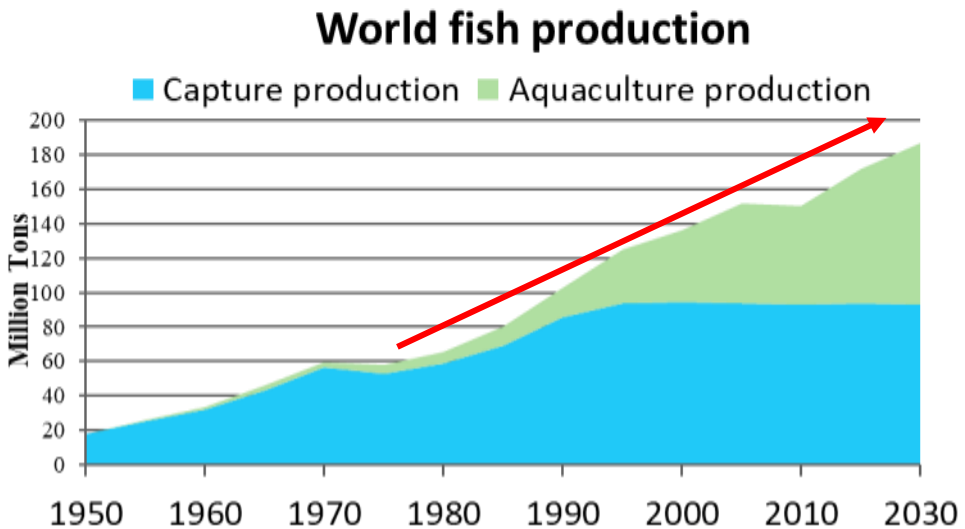
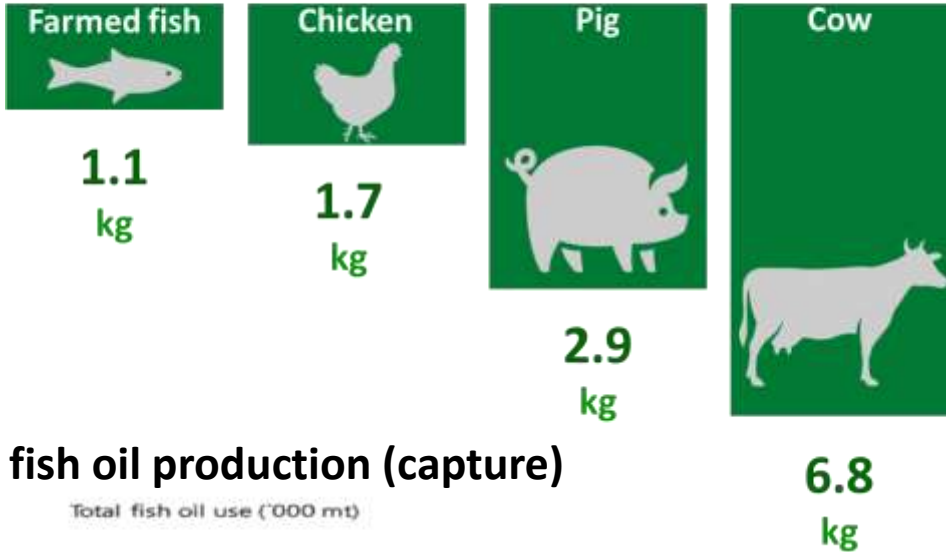


Aquaculture – vital for feeding the world now and in the future

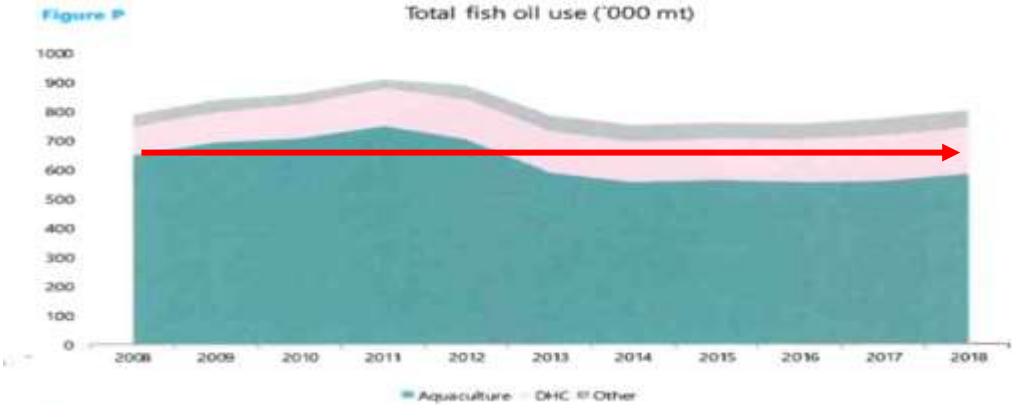


Feed conversion ratio

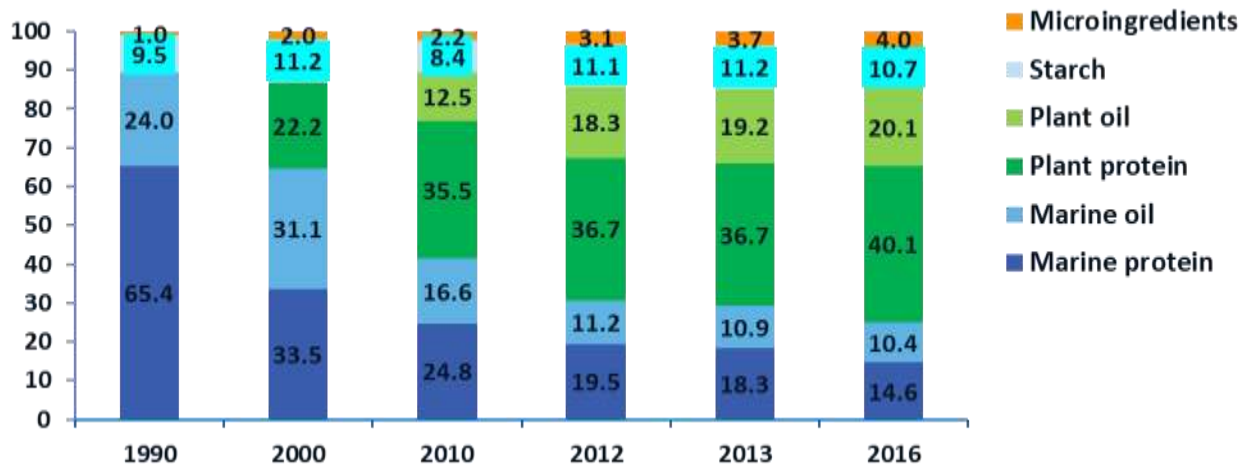
Estimated feed required to gain one kg of body mass



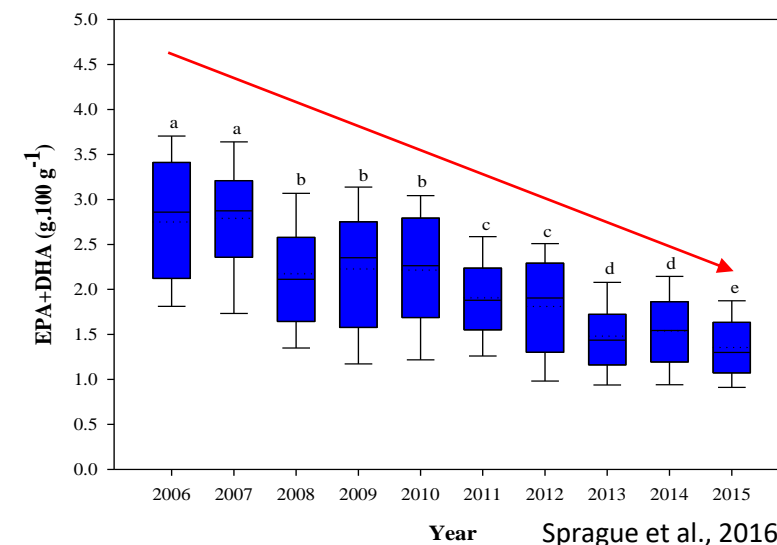
World fish oil production (capture)



Growth of aquaculture is “sustainable” but at the cost of nutritional value

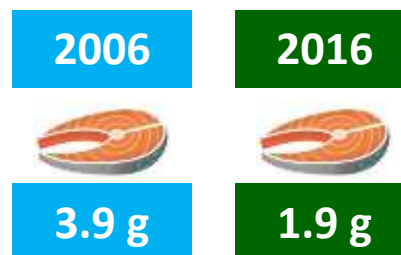


EPA+DHA Scottish farmed salmon fillet



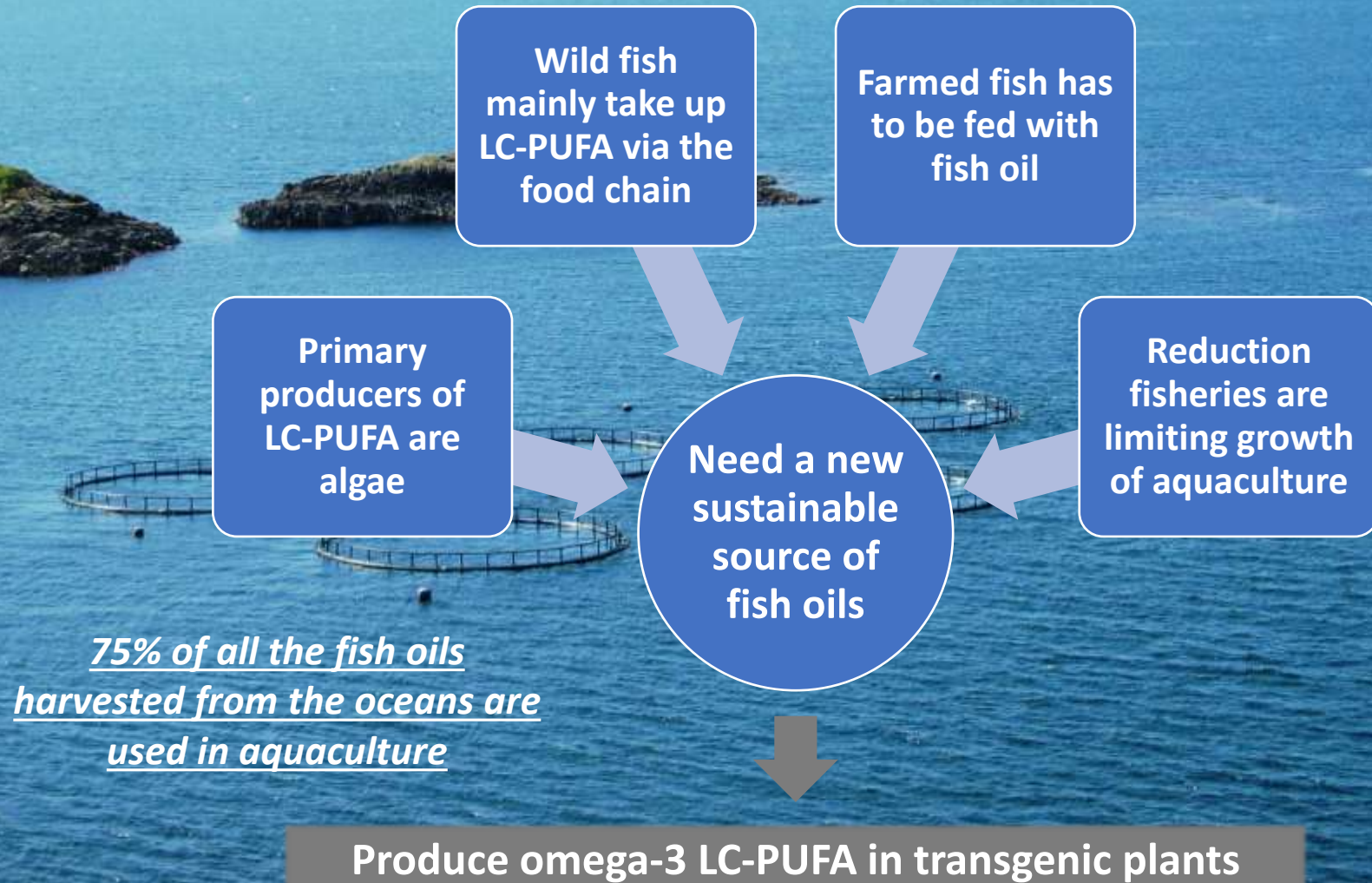
All marine and salmonid species require diets containing omega-3 fish oils. As the industry expanded, the finite & expensive fish oil was diluted with cheaper plant oils. Although this keep the costs low, it reduced the EPA & DHA levels in the fillet, meaning **the consumer got reduced nutrition**

ISSFAL  **3.5 g**
EPA+DHA/week



The USP of salmon

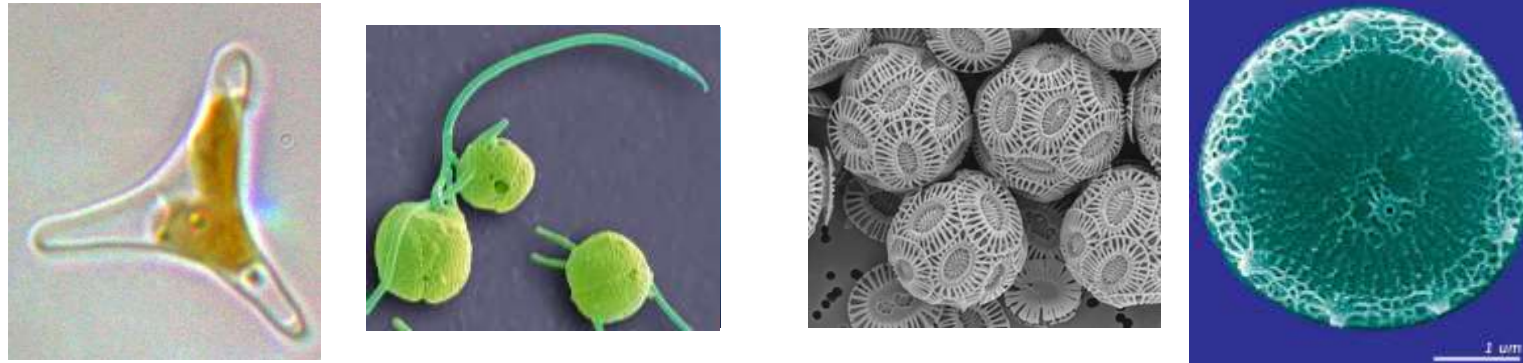
Aquaculture is the major consumer of fish oils



The Vision –to make omega-3 fish oils in a GM plant

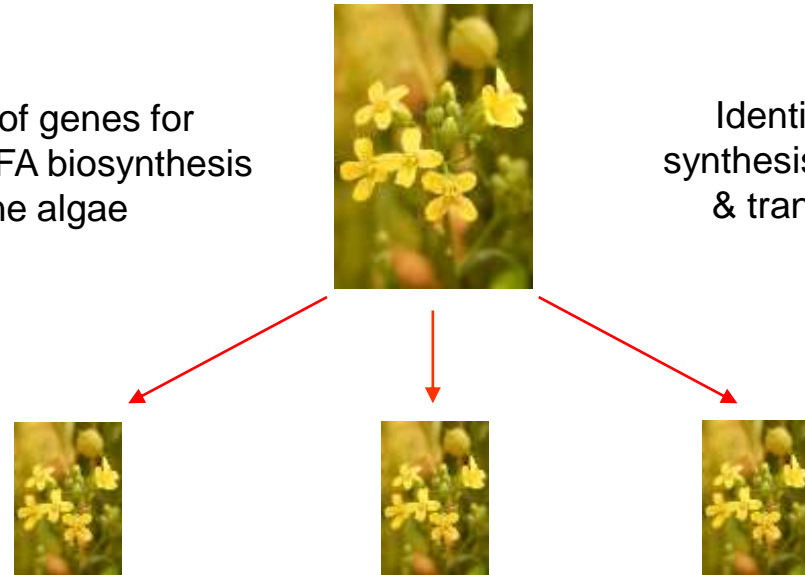


Making omega-3 LC-PUFAs in a GM Plant



The sources of genes for
omega-3 LC-PUFA biosynthesis
are marine algae

Identify algal genes for the
synthesis of omega-3 LC-PUFAs
& transfer them to oilseeds

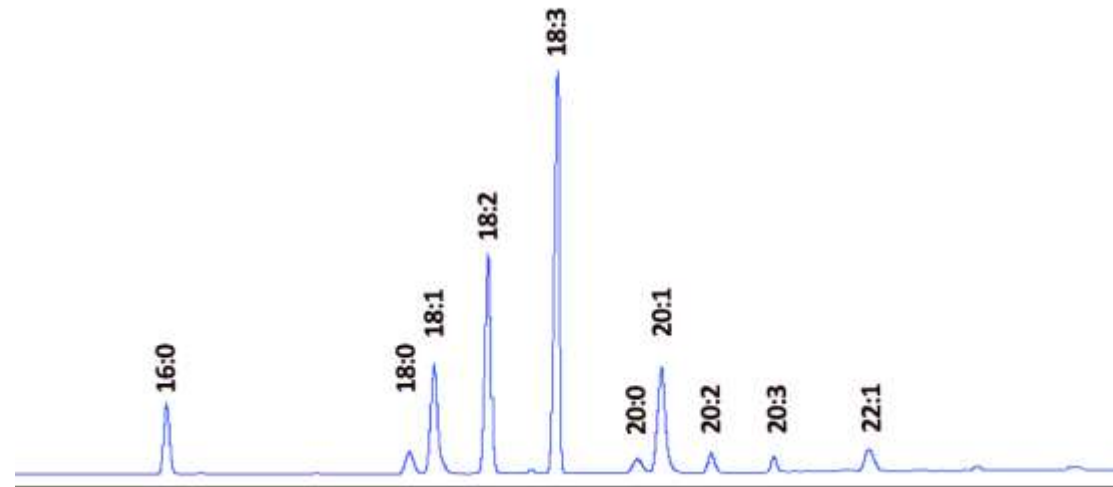


Regenerate transgenic plants with novel fatty acid traits

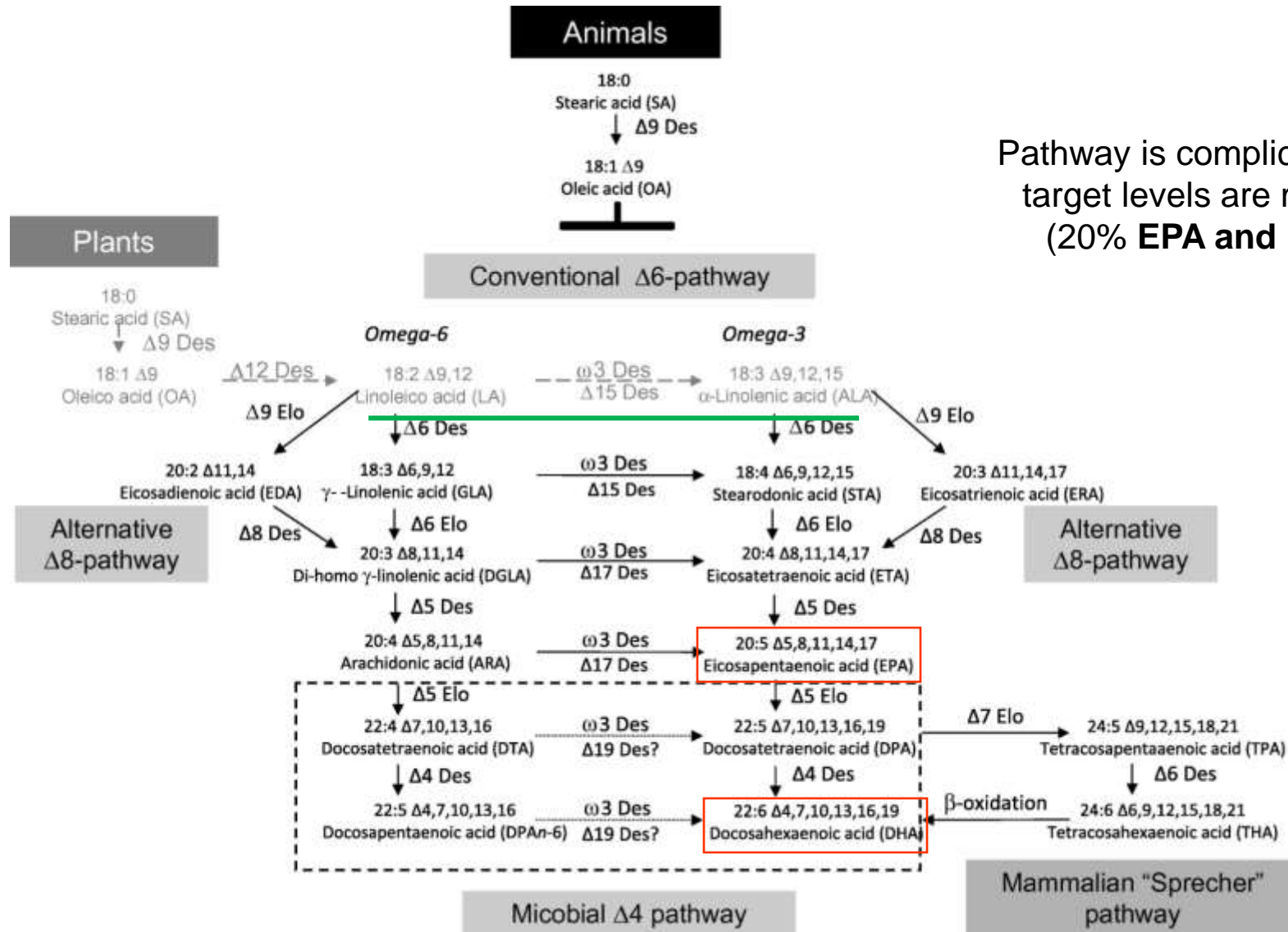
Camelina is an ideal host for making omega-3 fish oils



Easy to transform with *Agrobacterium*
Short growth season, 3-4 months
High ALA (omega-3 18:3) substrate
Not a Commodity Crop

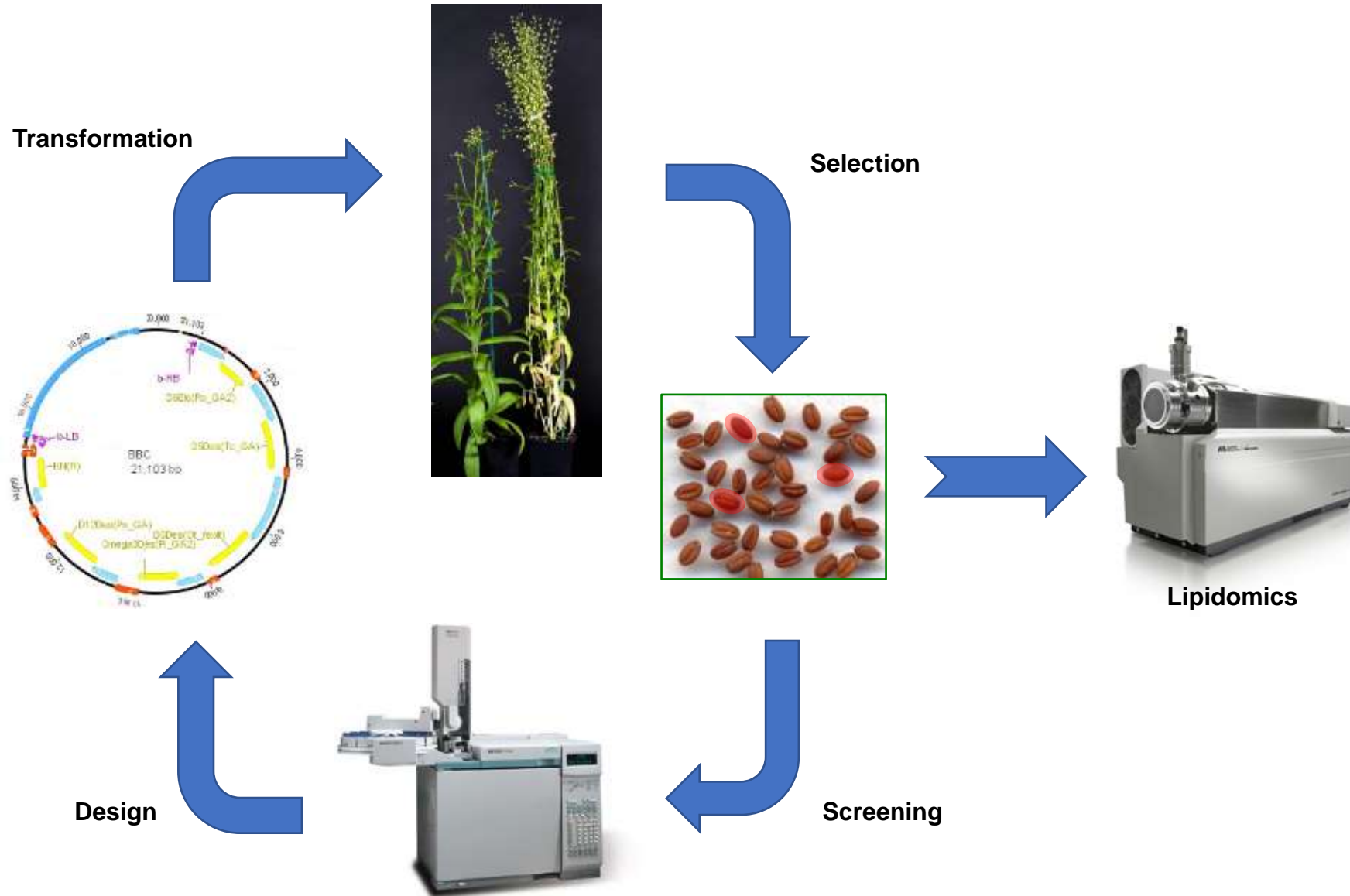


LC-PUFA Biosynthetic pathway



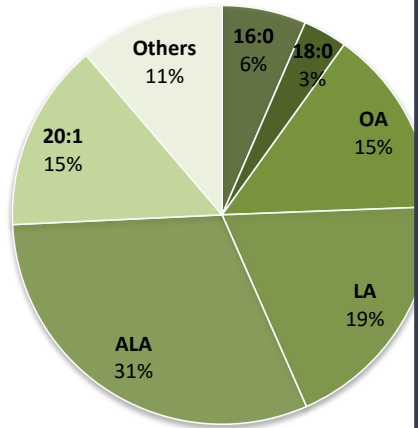
Pathway is complicated but target levels are modest (20% EPA and DHA)

Optimising the omega-3 trait in *Camelina* via metabolic engineering

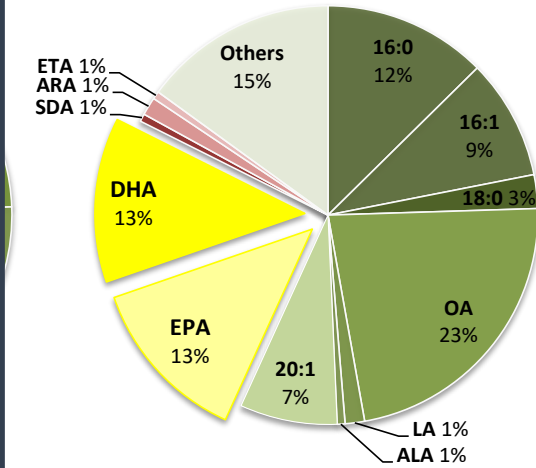


GM Camelina lines producing EPA+DHA: 2012/13 iterations

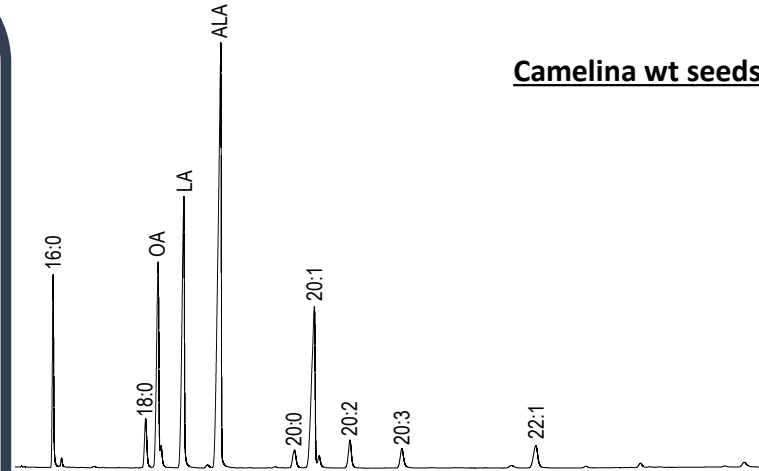
wt



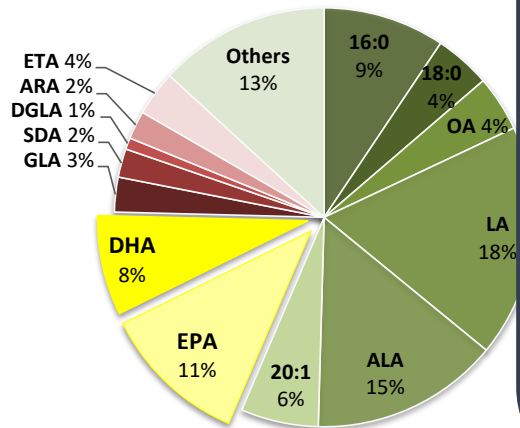
Bulk fish oil



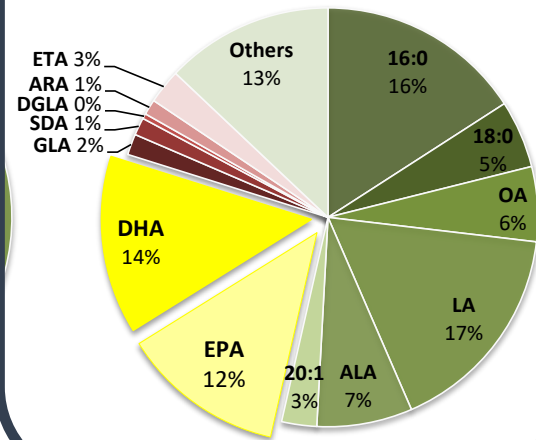
Camelina wt seeds



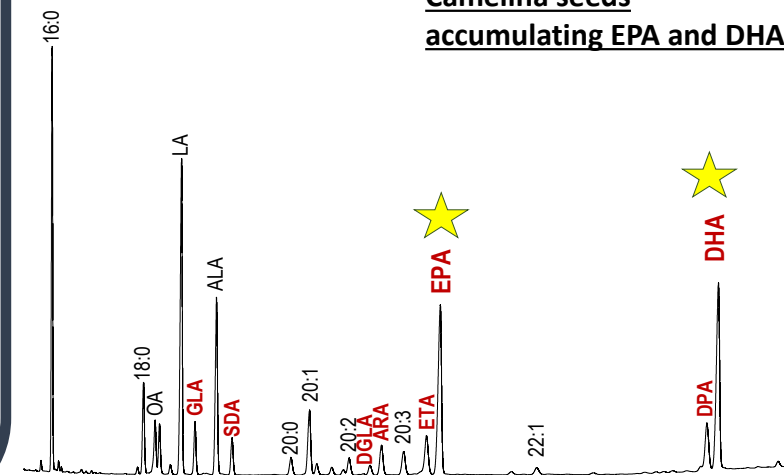
DHA line



Highest DHA seed



Camelina seeds
accumulating EPA and DHA



GM Camelina Field Trials at Rothamsted- 2014 onwards



The UK's most comprehensive GM field trials – and all that entails..

Positive press coverage of GM field trials



Fish oil made from GM plant to be saviour of the oceans

Ben Webster Environment Editor

Fish oil has been grown successfully on a British farm in a scientific breakthrough that could reduce the plundering of the oceans.

A field trial in Hertfordshire has demonstrated that plants can be genetically modified to reproduce the nutrients found in oily fish that protect against heart disease and help infant brain development.

Scientists genetically modified camelina, an oilseed plant known as "false flax", to produce seeds containing the omega-3 fatty acids present in salmon, mackerel and herring.

The trial at Rothamsted Research in Harpenden showed that the plants were able to produce useful amounts of fish oil without affecting their yield. If the results are confirmed in further trials, the camelina plants could be grown on millions of acres around the world to supply fish farms with fish oil.

Fish farms consume huge quantities of fish oil from small wild fish such as anchovies. The expansion of these farms is a major reason why fish stocks are declining. In 2011, about 80 per cent of the one million tonnes of fish oil produced globally from the seas went to fish farms. It takes up to 5kg of wild fish to produce 1kg of farmed salmon.

Professor Johnathan Napier, who is leading the publicly funded trial, said that the high cost of fish oil meant that fish farms had halved their use of it, so the fish they produced had lower levels

Finding a sustainable source of fish oils

Existing unsustainable route



New route



of omega-3 fatty acids. He said that humans would be unlikely to consume GM camelina seeds directly but would eat farmed fish fed on them.

Professor Napier said: "Fish farming is an expanding industry which, when combined with the increased global population, has an ever-increasing demand for fish oils. So there is great interest and need in finding an alternative source of these important fatty acids."

Chile, Canada and the northern states of the US are among the places where GM camelina is most likely to be grown commercially, but five to seven years of research is required first.

The next stage of the research will involve testing different strains at loca-

tions around the world and comparing them with conventional camelina.

Although some plants, such as flax, produce omega-3 oils these are of a "short-chain" strain that do not have the same properties as the long-chain omega-3 fatty acids in fish oil, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

The Rothamsted scientists modified the camelina plants by adding synthetic genes based on those found in marine algae that are involved in the production of long-chain omega-3 fatty acids.

Only the seeds of the camelina plant contain EPA and DHA. Other parts of the plant, including the stem and leaves, are unaffected.

Crop trial is a triumph

Analysis

Hot on the heels of admitting failure in one genetically modified crop trial, Rothamsted Research has triumphed in another which has profound implications for the way the world feeds itself (Ben Webster writes).

Last month, the research institute said that its £3 million publicly funded field trial of genetically modified wheat had failed after it was shown to be no better at repelling pests than conventional wheat.

Now it has announced that a further £3 million spent trying to produce fish oil from plants has had promising results from the first field trial.

The genetic engineering of camelina is being done very much with an environmental objective in mind. Fishing fleets are threatening the bottom of the marine food chain by catching billions of small fish, which are ground up and fed to larger fish in fish farms. GM camelina offers an opportunity to produce an alternative source of fish oil.

In Britain, we already eat pork, beef and poultry from animals reared on imported feed made from GM crops. In future, the farmed fish we eat may have been fattened on a vegetarian diet, offering guilt-free meals that do not harm the oceans.



Expand your horizons

Field trial in Manitoba, 2017

To provide 0.5 ton of Camelina oil for salmon feeding trial in Scotland



CAMELINA: THE QUEST FOR OMEGA-3

See our short film being
shown at the
India International
Science film festival

Validating the efficacy of our novel oil in aquaculture



SCIENTIFIC REPORTS

OPEN A nutritionally-enhanced oil from transgenic *Camelina sativa* effectively replaces fish oil as a source of eicosapentaenoic acid for fish

SUBJECT AREAS:
MOLECULAR ENGINEERING IN PLANTS
NUTRITION
FATTY ACIDS

Received 28 September 2014
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DOI: 10.1038/srep01191

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Evaluation of a high-EPA oil from transgenic *Camelina sativa* in feeds for Atlantic salmon (*Salmo salar* L.): Effects on tissue fatty acid composition, histology and gene expression

M.B. Betancor^{1,*}, M. Sprague¹, O. Sayanova², S. Usher³, P.J. Campbell³, J.A. Napier⁴, M.J. Caballero⁴, D.R. Tocher⁵

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⁴ Aquaculture Research Group, University of San Pablo de Cebu, Cebu, Philippines; ⁵ IZCM, Instituto Universitario de Investigación en Acuicultura, Universidad de Murcia, Murcia, Spain

PLOS ONE

RESEARCH ARTICLE

An oil containing EPA and DHA from transgenic *Camelina sativa* to replace marine fish oil in feeds for Atlantic salmon (*Salmo salar* L.): Effects on intestinal transcriptome, histology, tissue fatty acid profiles and plasma biochemistry

Mónica B. Betancor^{1,*}, Keshuai Li², Matthew Sprague¹, Tori Bardsley¹, Olga Sayanova², Sarah Usher³, Lihua Han⁴, Kjell Måsefjord⁵, Ole Tontissen⁶, Johnathan A. Napier⁷, Douglas R. Tocher⁸, Rolf Erik Olsen⁹

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PLOS ONE

RESEARCH ARTICLE

Nutritional Evaluation of an EPA-DHA Oil from Transgenic *Camelina sativa* in Feeds for Post-Smolt Atlantic Salmon (*Salmo salar* L.)

Mónica B. Betancor^{1,*}, Matthew Sprague¹, Olga Sayanova², Sarah Usher³, Christoforos Metochis⁴, Patrick J. Campbell⁵, Johnathan A. Napier⁶, Douglas R. Tocher⁷

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Lipids (2016) 51:1171–1191
DOI: 10.1007/s11745-016-4191-4

ORIGINAL ARTICLE

Replacement of Marine Fish Oil with *de novo* Omega-3 Oils from Transgenic *Camelina sativa* in Feeds for Gilthead Sea Bream (*Sparus aurata* L.)

Mónica B. Betancor¹, M. Sprague¹, D. Montero², S. Usher³, O. Sayanova⁴, P. J. Campbell⁵, J. A. Napier⁶, M. J. Caballero⁷, M. Izquierdo⁸, D. R. Tocher⁹



British Journal of Nutrition (2019), 121, 1235–1246

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Postprandial incorporation of EPA and DHA from transgenic *Camelina sativa* oil into blood lipids is equivalent to that from fish oil in healthy humans

Annette L. West¹, Elizabeth A. Miles¹, Karen A. Lillycrop², Lihua Han³, Olga Sayanova³,
Johnathan A. Napier³, Philip C. Calder^{1,4} and Graham C. Burdge^{1*}

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British Journal of Nutrition, page 1 of 9

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Dietary supplementation with seed oil from transgenic *Camelina sativa* induces similar increments in plasma and erythrocyte DHA and EPA to fish oil in healthy humans

Annette L. West¹, Elizabeth A. Miles¹, Karen A. Lillycrop², Lihua Han³, Johnathan A. Napier³,
Philip C. Calder^{1,4} and Graham C. Burdge^{1*}

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ELSEVIER

Biochimica et Biophysica Acta (BBA) - Molecular
and Cell Biology of Lipids

Volume 1865, Issue 8, August 2020, 158710



Differential postprandial incorporation of 20:5n-3 and 22:6n-3 into individual plasma triacylglycerol and phosphatidylcholine molecular species in humans

Annette L. West^{a, 1}, Louise V. Michaelson^{b, 1}, Elizabeth A. Miles^a, Richard P. Haslam^b, Karen A. Lillycrop^c, Ramona Georgescu^a, Lihua Han^b, Olga Sayanova^b, Johnathan A. Napier^b, Philip C. Calder^{a, d}, Graham C. Burdge^{a, e}

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<https://doi.org/10.1016/j.bbali.2020.158710>

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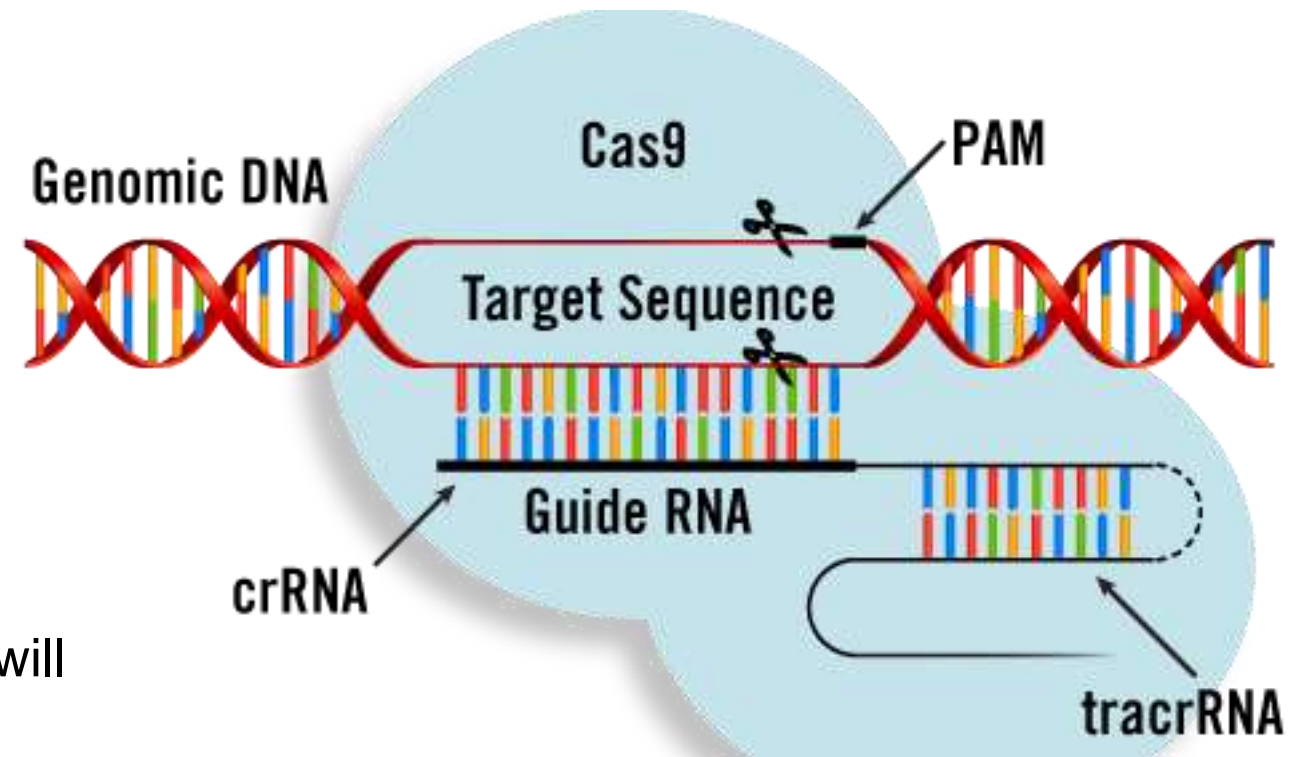
In collaboration with University of
Southampton (Philip Calder & Graham Burdge)

Gene-editing is transforming how we do life sciences

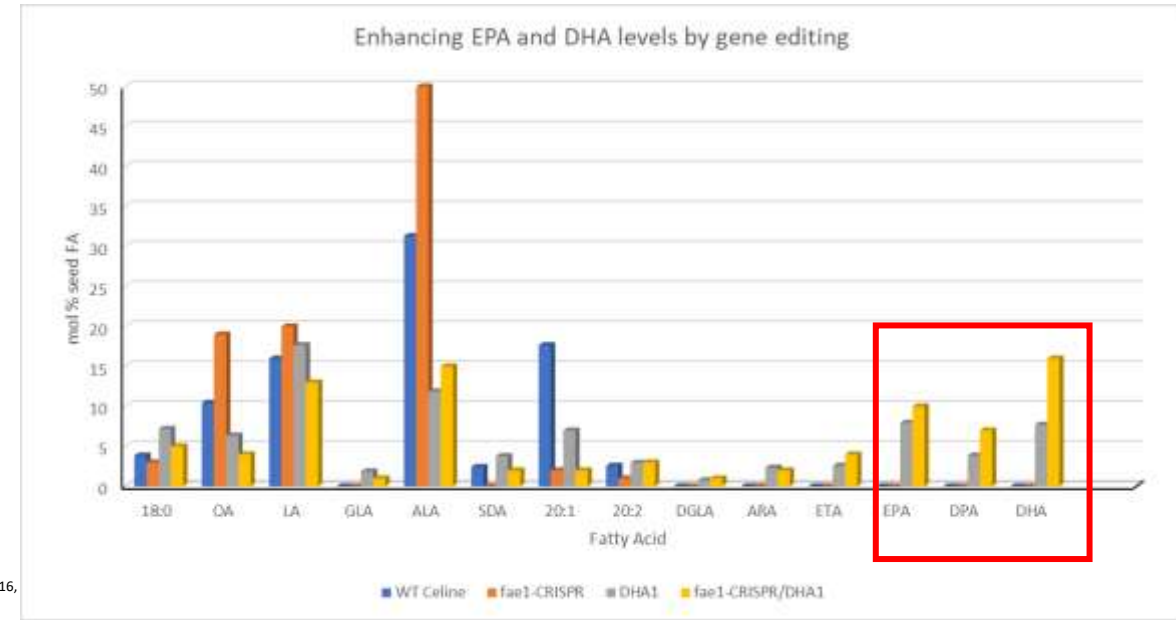
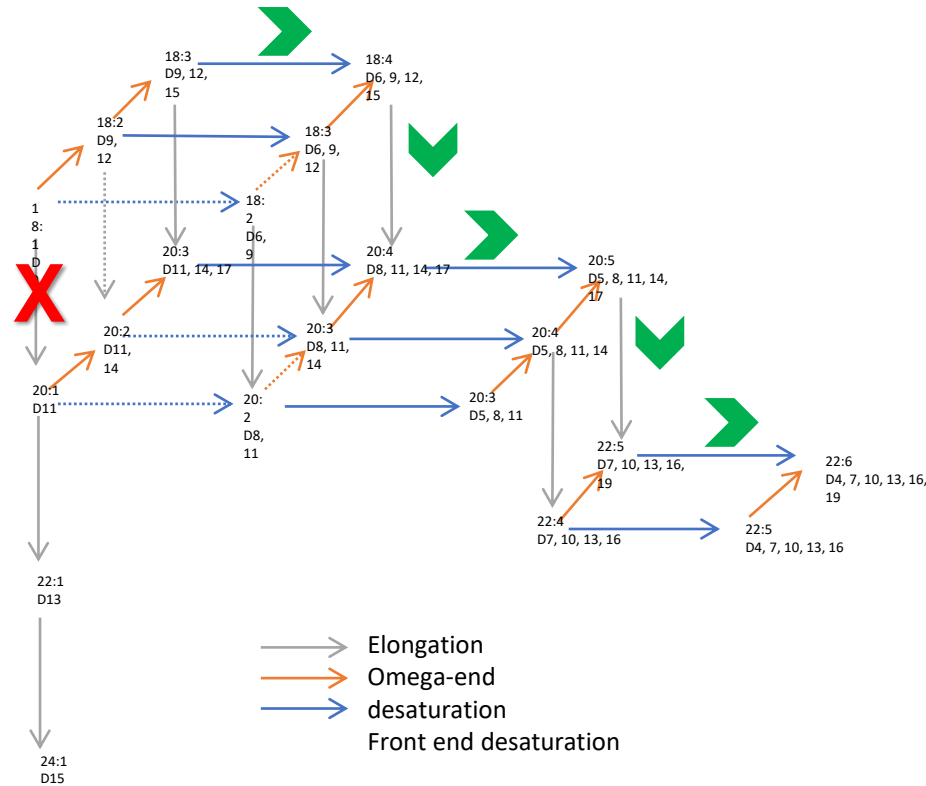
- CRISPR-Cas9 and related tools are a disruptive tool with which to edit DNA
- Incredibly precise, easy to use, “democratising” research.
- BUT – Use in EU has effectively been blocked by ECJ ruling of July 2018 (GE \equiv GM)
- Commercial use is covered by patents
- New technology largely untested at scale

Irrespective of that, it is widely expected that GE will transform plant and animal breeding, decreasing susceptibility to diseases, enhancing nutrition and decreasing environmental impact.

BUT – somethings can only be achieved by GM



Stacking GE and GM to enhance the accumulation of omega-3 LC-PUFAs



Research article
Mutagenesis of the *FAE1* genes significantly changes fatty acid composition in seeds of *Camelina sativa*
 Mehmet E. Ozseyhan^a, Jinling Kang^a, Xiaopeng Mu^{b,1}, Chaofu Lu^{a,2*}
^a Department of Plant Science and Plant Pathology, Maine State University, Bangor, ME 05717, USA
^b College of Horticulture, Shenyang Agricultural University, Tsing, Shenyang 110861, China

Using the CRISPR-Cas9 *fae1* mutant background enhances the accumulation of EPA & DHA

BUT... GE alone cannot create the omega-3 fish oils trait

The conversion of an idea into a product takes time and money



From field to fjord to fork

Creating a value chain which delivers better nutrition to the consumer and helps aquaculture to reduce its reliance on oceanic sources of fish oils

Hurdles: GM Regulation, IP/FTO, Business development, Commercialisation

Innovation in Agriculture – Time is not on your side



Slow magic: Agricultural R&D a century after Mendel (2000)
Persistence pays: US agricultural productivity growth and the benefits from public R&D spending (2009) *Professor Philip Pardey (Department of Applied Economics, University of Minnesota)*

Social license and consumer acceptance



A key question for the public: Who is paying and who is benefiting?

Don't assume that the brilliance of your idea will carry the day

Rothamsted Omega-3 Flagship – key messages

- *Camelina is a robust platform capable of producing superior levels of EPA and DHA compared with other plant systems*
- *Positive data from GM field trials in UK and N. America*
- *Significant positive data from feeding studies with salmon, sea bream and sea bass, also mouse & human studies – peer reviewed and open access*
- *An established network of expert collaborators in both aquaculture and human nutrition sectors, also Camelina biotechnology and agronomy*
- *Regular contributor to public dialogue and engagement in discussions on GM and GE – informing policy and perception*



Acknowledgments



Lihua Han

Richard Haslam

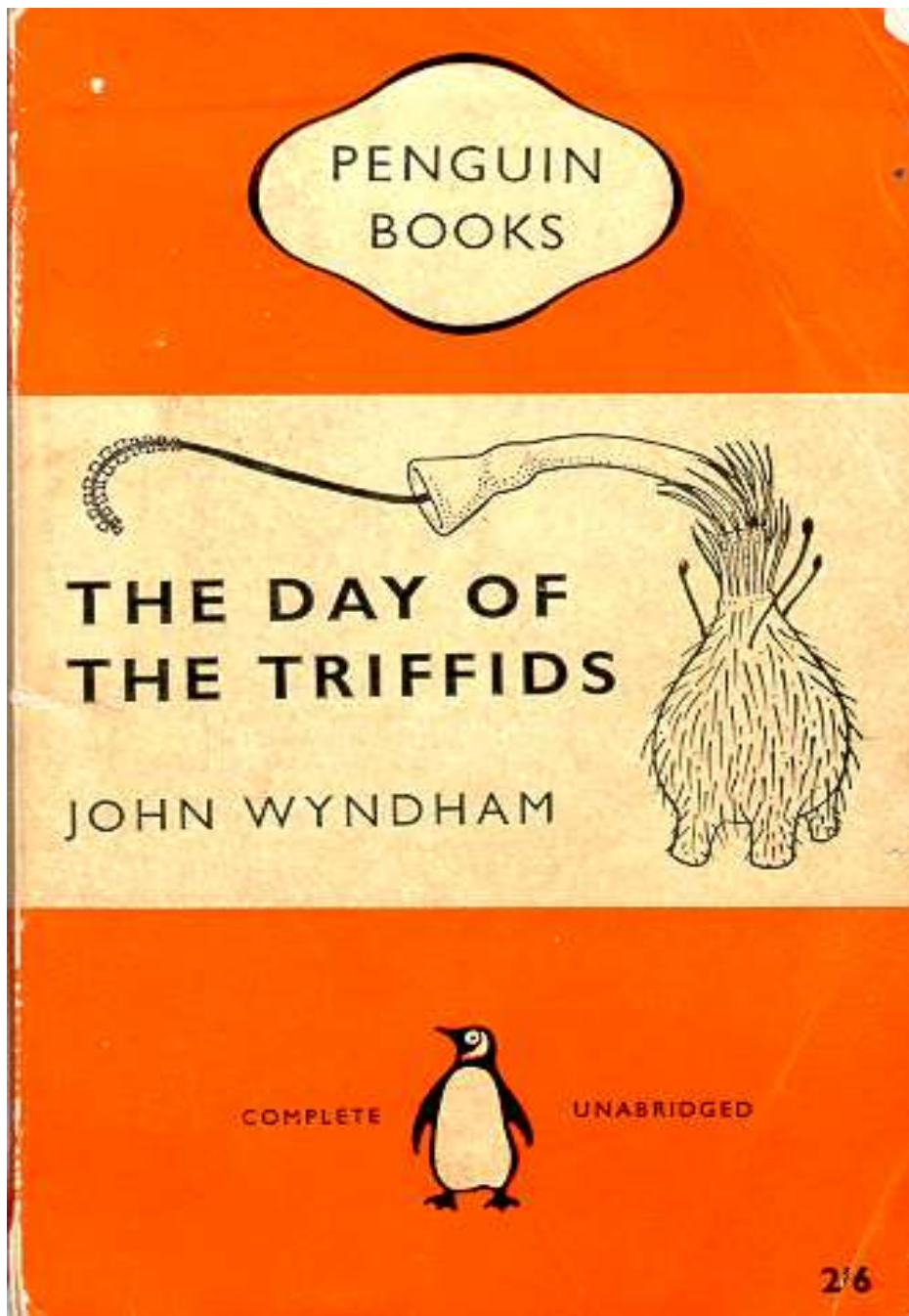
Olga Sayanova

**Noemi Ruiz-Lopez
Sarah Usher**

**Douglas Tocher (Stirling)
Monica Betancor**

Thanks for your attention – Questions?





“The triffids are grotesque and dangerous plants, over seven feet tall, originally cultivated for their yield of **high-grade oil**. So long as conditions give the mastery to their human directors, they are a valuable asset to mankind.

But when a sudden universal disaster turns these conditions upside down, the triffids become an active and dreadful menace.”

John Wyndham

Penguin Books 1951

(Fiction)

