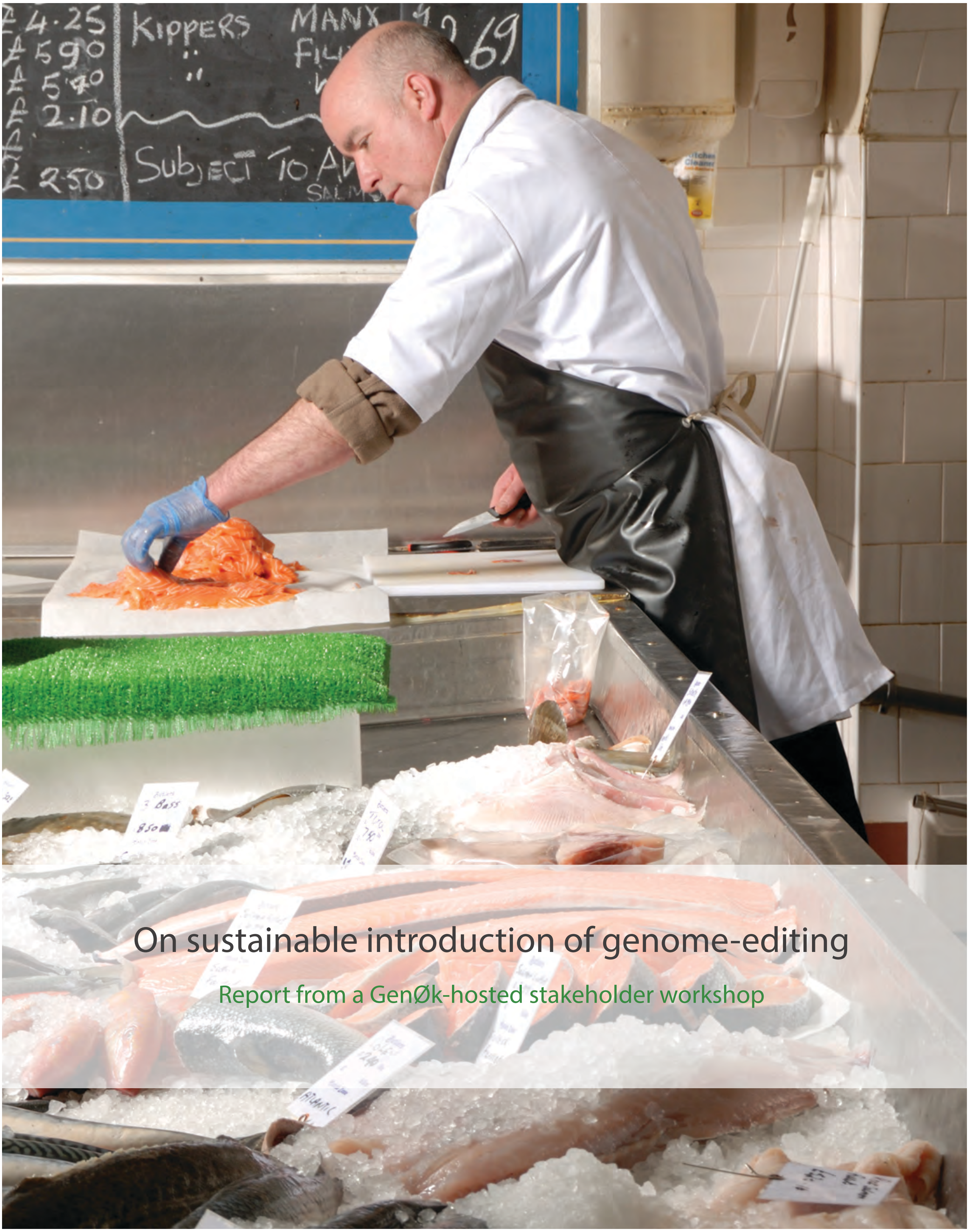

On sustainable introduction of genome-editing

Report from a GenØk-hosted stakeholder workshop

September 2019

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On sustainable introduction of genome-editing in Norwegian salmon aquaculture

– Report from a GenØk-hosted stakeholder workshop

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Norsk sammendrag

Akvakulturnæringen opplever betydelige tap grunnet fiskedød og har høye kostnader relatert til medikamenter for bedret fiskehelse. Det etterspørres stadig mer potente, presise og effektive løsninger for økt bærekraft i norsk Atlantisk lakseoppdrett. Her kan moderne bioteknologi, særlig med CRISPR/Cas-metoden som hovedredskap, potensielt benyttes til å enten forbedre egenskaper eller introdusere sykdomsresistens i oppdrettslaks i en prosess som kalles genredigering.

Sammenlignet med andre typer genmodifisering, er genredigering med CRISPR/Cas9 billigere, effektiv og mer presis til bruk i genredigering. Siden genredigeringen kan endre DNAet, må mulige sosiale, miljømessige og økonomiske konsekvenser evalueres og debatteres, for eksempel i tråd med prinsippene for Ansvarlig forskning og innovasjon (Responsible Research and Innovation, RRI). Ved å inkludere 18 representanter fra ulike norske forskningsinstitusjoner, statlige departementer, offentlige råd og ideelle organisasjoner i en workshop holdt av GenØk – Senter for biosikkerhet, satte vi oss følgende mål for prosjektet:

- Identifisere hvordan bruk av CRISPR/Cas9 kan øke bærekraften i fiskeindustrien og, i tråd med prinsippene for Ansvarlig forskning og innovasjon (RRI), kartlegge i hvilken grad den offentlige mottakelsen av en slik prosess vil kreve ytterligere debatt og inkludering av ulike perspektiver;
- Diskutere og planlegge hvordan nye problemer som identifiseres, sammen med eksisterende problemer, kan undersøkes gjennom feltundersøkelser og eksperimentell forskning relatert til bruk av CRISPR/Cas9 i norsk akvakultur;
- Basert på økosystemet og miljøet, identifisere parametere som kan påvirkes negativt eller positivt ved bruk av CRISPR/Cas9 i norsk akvakultur.

Det ble utformet syv oppgaver basert på nevnte mål. Deltakere diskuterte oppgavene i mindre grupper og oppsummerte utfallene i plenum. Her kom gode ideer og anbefalinger fram, der blant annet følgende hovedanbefalinger kan trekkes basert på hele workshopen:

- CRISPR/Cas9 kan brukes til å forbedre lakseoppdrettens bærekraft, men burde benyttes sammen med andre tiltak som gode alvsmål og utvikling av effektive vaksiner. I åpne produksjonsanlegg er steril laks anbefalt;
- Offisielle retningslinjer for bruk av genredigeringsteknikker i laks burde utvikles, og offentlige tiltak mot monopolisering av teknologien burde iverksettes for å øke åpenhet og bidra til vitenskapelig demokratisering;
- For å unngå misforståelser, øke åpenhet og bidra til inkludering, burde utdanningsinitiativer rettet mot den generelle befolkningen styrkes;
- For fremtidige workshoper burde ideelle miljø-og konsumentorganisasjoner inkluderes samt representanter fra fiskeoppdrettsselskaper;
- I tillegg burde miljø- og forbrukerorganisasjoner involveres i enda sterkere grad i det videre arbeidet.

Executive summary

With tremendous financial losses to fish health in Norwegian Atlantic salmon (A. salmon) farms, e.g. the cost of drugs and fish mortality, more potent, precise and effective solutions are sought in order to improve sustainability in Norwegian A. salmon farming. This is where modern biotechnology, especially with the advent of CRISPR/Cas-systems, can potentially be applied to enhance positive traits or introduce disease resistance in farmed salmon in a process called genome editing (GE).

The CRISPR/Cas-system is, relative to similar GE technologies, cheaper, effective and more precise. However, due to the invasive nature of GE, and the iconic value of salmon in Norway, its societal, environmental and economic implications as well as adherence to the principle Responsible Research and Innovation (RRI) need to be assessed and thoroughly debated. By engaging 18 representatives from different Norwegian research institutions, government departments, official advisory bodies and NGOs in a workshop hosted by GenØk – Centre for Biosafety, we aimed to highlight the importance of adhering to those principles and achieve the following:

- Identify how the application of CRISPR/Cas9 may increase the sustainability of the fish industry and to anticipate what the public perception may be that needs further investigation to ensure responsible innovation and research;
- Discuss and plan how the identified issues (together with other known issues) can be translated into practical experimental and field research in the application of CRISPR/Cas9 in Norwegian aquaculture;
- Identify parameters based on the ecosystem and environment that can be inadvertently impacted by the application of CRISPR/Cas9 in Norwegian aquaculture.

Based on these aims, seven tasks were made. The participants discussed the tasks in smaller groups, which was followed by a sum-up session in plenum. Several good ideas and suggestions were made, of which the main recommendations for the whole workshop can be presented as follows:

- CRISPR/Cas9 can be used to improve sustainability of salmon farming, but should be used alongside other measures such as long-term breeding programs and development of effective vaccines. For open production of GE salmon, sterile salmon is recommended;
- Official guidelines for utilisation of genome editing techniques in salmon should be developed, and anti-monopolisation policies of the technology should be in place in order to increase transparency and to aid scientific democratisation;
- To avoid misunderstanding and increase transparency and inclusion, educational incentives toward the general public are emphasised;
- For future workshops, more environmental and consumer-based NGOs should be included. Additionally, it is recommended to include representatives from fish farming companies.

1. Background

This report presents the outcomes of a stakeholder workshop held in Tromsø, Norway, which was hosted by GenØk – Centre for Biosafety and funded by Regionale forskningsfond Nord-Norge (RFF Nord-Norge). The workshop is a part of a preliminary project which will serve as a pilot study that will provide much-needed preliminary data, enhancing the success of grant applications for the main project. The primary purpose of this workshop was to bring together relevant stakeholders in the Norwegian aquaculture industry to discuss pertinent issues related to sustainability and perception of the use of CRISPR/Cas9 in Norwegian aquaculture helping to manage Infectious Salmon Anaemia Virus infections.

The report will encompass a brief comment on the status of knowledge regarding salmon disease control and the potential benefits of using genome editing in aquaculture. Secondly, the workshop structure and design as well as aims will be presented. Next, the main outcomes will be summarised and discussed. Lastly, concluding recommendations based on workshop discussions will be itemized.

1.1 Status of the knowledge – Salmon disease control

In Norway, management of diseases that plaque farmed A. salmon is one of the areas where modern biotechnology can potentially be applied. Infectious diseases continually threaten the Norwegian aquaculture, and the salmon industry is plagued with several diseases of viral, parasitic and bacterial aetiology (Hjeltnes; et al., 2019). Management of these infections is hitherto by vaccination and good farm practices, but these approaches are not entirely efficient relative to the technologies that have become available, especially for viral and parasitic diseases. The economic burden of parasitic, viral and bacterial diseases on the salmon fish industry runs into billions of Norwegian kroner annually, and resistance against different pharmaceuticals (e.g. anti-sea lice chemicals) is a growing problem (Aaen et al., 2015; Abolofia et al., 2017; Groner et al., 2016). Likewise, the introduction of non-chemical alternative treatments has resulted in new health challenges for the fish (Hjeltnes; et al., 2019). The potential to apply CRISPR/Cas9 in managing the disease problems of Norwegian fish farming is new and innovative given the growing problem inherent in the use of pharmaceuticals and chemicals. The simplicity, effectiveness, low cost and robustness of CRISPR/Cas9, which has made it adaptable to editing the genomes of virtually any organism including salmon, viruses and protozoa (Soares Medeiros et al., 2017; Ura et al., 2014; Wargelius et al., 2016), can potentially be applied to manage the disease burden of Norwegian fish aquaculture.

Modern genome editing (GE) techniques such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR associated protein 9 (Cas9), Transcription Activator-Like Effector Nucleases (TALENS), and Zinc Finger Nucleases (ZFN) are revolutionising how the genomes are edited. The techniques have the potentials to provide far-reaching solutions to myriad challenges and provide new opportunities in different sectors including aquaculture, human health, agriculture and veterinary medicine. Our focus lays with CRISPR/Cas9, which was derived from the *Streptococcus pyogenes* Type II CRISPR/Cas system (Jinek et al., 2012), and uses the gRNA (guide RNA)-guided cas9 gene to target and cut specific DNA sequences (Heler et al., 2015). The cut stimulates the cell´s DNA repair mechanisms that result in mutations such as, insertions, substitutions, deletions and/or rearrangements at the target site (Heler et al., 2015). Off-target mutations occur when changes are induced at sites other than the target site. In Norway, the EU and other regions, the current discussion is whether and how products arising from modern GE techniques, especially CRISPR/Cas9, should be regulated. Given the enormous importance of the subject, decisions regarding regulations should be based on scientific knowledge.

1.2 Workshop structure and design

The workshop had a span of two days from the 5th of February to the 6th of February 2019. Some of the invited stakeholder representatives held presentations about their opinions and observations around the topic, after which group discussions commenced followed by a quick sum-up. For details, see Annex 1. In these group discussions, the 18 participants (Annex 2) were divided into three groups and were given the same questions to discuss during each session. In total seven tasks were given to the participants. Each group elected a presenter that presented their group's findings after each session. For simplicity, the seven tasks are summarised as questions in Annex 3.

1.3 Objectives of the workshop

The principal objective of the workshop was to articulate, together with relevant stakeholders, aspects where CRISPR/Cas9 technology can be responsibly applied to ameliorate or solve the infectious diseases burden of farmed A. salmon in Norway.

The sub-objectives were to:

- Identify how applying CRISPR/Cas9 as a solution A. salmon infectious disease may increase the sustainability of the fish industry and to anticipate what the public perception may be that needs further investigation to ensure responsible innovation and research.
- Discuss and plan how the identified issues (together with other known issues) can be translated into practical experimental and field research in the application of CRISPR/Cas9 as a solution to the infectious diseases of farmed A. salmon in the Norwegian aquaculture.
- Identify parameters based on the ecosystem and environment that can be inadvertently impacted by the application of CRISPR/Cas9 in Norwegian aquaculture.

2. Outcomes from the workshop

As Annex 3 specifies, seven main tasks were provided. The outcomes and activities will now be summarised for each day, with a short sentence explaining the rationale behind each task. The specific outcomes in each group session are outlined in Annex 4.

2.1 Presentation summaries

2.1.1 Challenging diseases in Norwegian aquaculture

In this presentation, participants were presented with the current challenges in terms of different bacterial, viral and parasitic diseases in the Norwegian aquaculture. Eight diseases were mentioned and briefly presented, among which Infectious Salmon Anaemia (ISA, caused by the ISA virus) and Salmon louse infection (caused by *Lepeophteirus salmonis*) were given particular attention.

2.1.2 A new method of increasing vaccine effectiveness against salmon viruses

This presentation gave a brief introduction to fish vaccinology, commercial availability, and status of the knowledge. Current vaccines, the presenter mentioned, are all based on inactivated pathogens, which are emulsified in mineral oils with stabilisers. Fish are vaccinated in systems developed for high-throughput injection, which can inject up to 20 000 fishes/hour, and vaccines are presented as viable alternatives to the problem of viral diseases.

2.1.3 CRISPR – opportunities for sustainable aquaculture

The presenter made clear that current salmon farming production needs to be more sustainable and mentioned disease, gene mixing and access to feed as some of the significant hinderances to this. The presenter highlighted the sterile salmon which was created with CRISPR/Cas9, and the process leading up to that point. Further, to emphasise that viral infections can be tackled with CRISPR, the procedure of making a porcine reproductive and respiratory syndrome virus (PRRSV)-resistant pig was used as an example where a CRISPR/Cas9-induced inactivation of a particular receptor-gene made it sterile to PRRSV. Lastly, if genetic causality is proven, the salmon louse resistant humpback salmon may be used to introduce traits, likewise in farmed salmon using GE. Also, there was made a clear point of the fact that a proof of concept regarding CRISPR/Cas9 applications in salmon now exists. However, security measurements such as closed research facilities were emphasised.

2.1.4 Consumer and environmental interests attached to GE in aquaculture

The "Network of GMO-free food and feed" first made a general presentation of its organisation, specifying the consumer and organisational groups it represents. Throughout the presentation, it became apparent that the network is interested in modern gene technology and its application in the creation of new GMO's. However, they require further knowledge generation around potential risk factors in addition to labelled and transparent commercial use of an approved GMO. The current restrictive mode by the Norwegian government in considering GMO-applications is preferred by the network.

2.1.5 New suggestions regarding the regulation of gene technology by the Norwegian Biotechnology Advisory Board

The Norwegian Biotechnology Advisory Board (NBAB) has recently suggested a softening of the current Norwegian regulation of GMO in Norway. The presentation gave an international perspective of how this matter is being evaluated, where it described the current debate on the definition of GMOs. After showcasing the complexity surrounding the definition, regulation and labelling of GMO/GE products, the process which led to the current suggestion was clarified. The suggestion, backed by 11 of 14 NBAB participating members, outlines four levels of increasing regulation complexity, in which the three highest levels require the GMOs to contribute to sustainability, societal utility and ethics during consideration of an application.

2.1.6 Contributions to sustainability and relevance of RRI in the use of gene technology on salmon

The presenter started with the introduction of the Gene Technology Act (1993) and its potential implications For GE application. The main take-home from the Act is that commercial approval of GM organisms needs to be based on an assessment of contribution to sustainability, be it of societal utility, and that relevant ethical aspects are considered. In addition, any decision needs to adhere to the precautionary principle, and lastly, GMOs must have no harmful environmental or health-related trait. Moreover, sustainability needs to be evaluated globally and includes the following three dimensions: environment, social factors and economy. Lastly, Responsible Research and Innovation (RRI) was briefly introduced.

2.2 Group discussions

2.2.1 What are the most important challenges for the Norwegian salmon industry today?

In the first group work the participants were given the task of outlining the challenges Norwegian aquaculture is facing, their suggestions on how to solve them, and of these, which challenge did they found to have the greatest limiting effect on future expansion of the industry.

All challenges and those that limit the expansion of the industry

Many of the challenges presented by the groups were intertwined and had shared causality. For example, two of the main challenges outlined for salmon aquaculture were disease and pathogens, which again affects fish welfare and mortality, and as a result, may also introduce a negative burden on the environment, industry's economy, and its reputation. Primary pathogens/diseases mentioned were the salmon lice and ISA. The environmental effectors mentioned were mainly pollutants resulting from the farming facilities, for example, organic waste (fish faeces, uneaten feed) and pesticides. Another environmental factor is the escapee farmed salmon, as it is capable of crossing with wild salmon and hence pose a risk to the genetic integrity of wild salmon. Besides, even if the salmon is sterile, a point was made that farmed escaped salmon still might be able to ecologically disrupt wild salmon by, for example, competing for resources in a river in which wild salmon might breed. Another challenge is access to nutritional and reasonably priced feed to maintain the nutritional integrity of the fish – a key marketing point often utilised when salmon is sold. In a more holistic suggestion, climate change was also mentioned. As water temperatures increase, more species south of the Barents Sea are adapting to life in northern regions, thus increase in the interspecific competition among local species, including wild salmon, is being experienced. Lastly, the lack of knowledge of fish health and immunology and corporate secrecy was mentioned as an expansion-inhibiting challenge.

The solution

Considering the challenge posed by corporate secrecy, one solution proposed by a participant was the development of precise requirements of information transparency with open access, much in line with current RRI frameworks. Different suggestions regarding the feed and its ingredients were proposed to solve several of the mentioned challenges (e.g. disease, nutritional value and feed accessibility). For example, one could turn the GE farmed species vulnerable to particular nutrients, and hence biologically control the farmed fish by giving it specially modified feed for its survival. Hence, if a farmed salmon escapes, it would eventually die due to lack of that particular substance in the feed. Other suggestions were to introduce different raw materials for feed, i.e. microalgae in order to introduce a natural source of nutrients, especially omega-3 fatty acids. It was also proposed to introduce genes from the louse tolerant humpback salmon into the farmed Atlantic salmon to increase tolerance to the salmon louse, though there have been minimal developments to determine whether particular genes are the leading causes for this tolerance. Amongst more obvious solutions, closed farming facilities to lessen the burden of environmental impacts and illnesses, more effective vaccine development, and increased social dialogue was also proposed as solutions. It became apparent during the discussions that the focus needs to shift from a quantity-based production to a more quality-based production. Lastly, long-term breeding goals promoting fish health and robustness was considered important in the future among several of the participants.

2.2.2 What is a healthy fish, and what are the most important factors that contribute towards making a healthy fish?

The participants outlined their points regarding what they consider to be a healthy fish and the essential factors contributing to creating one.

Healthy fish

One interesting point highlighted by some participants is the consumer perception of what a healthy fish is, and what healthy fish de facto is. For example, some of the participants pointed out that the resemblance to wild salmon does not necessarily imply better fish health, as wild salmon, for example, hold higher concentrations of heavy metals. Continuing with the consumer's perspective, a healthy fish can be described as fish that is healthy for the consumer. This does not necessarily consider fish health itself, but rather the nutritional benefits of fish consumption in humans. Hence, a healthy fish is healthy and nutritious for the consumer. Considering fish health only, a healthy fish can be defined as a robust fish able to withstand disease and harsh environments, as some participants pointed out, and one that eats and grows well. Furthermore, advantageous breeding abilities in ancestral fish was also suggested to promote healthy fish production. The latter point, a healthy fish production based on the above suggestions may even add to healthy farming and thus, sustainability.

Factors contributing to the making of a healthy fish

Participants pointed out that there needs to be an enhanced emphasis and focus on good living conditions, disease control, fish welfare and health in general to maintain healthy fish. Making robust fish through carefully planned breeding programs and high-quality feed was presented as a better alternative relative to the use of drugs and antibiotics, which can biomagnify in the system and result in pathogenic antibiotic resistance. Throughout the workshop, the lesser use of antibiotics in Norway relative to its past use was seen as a good practice. However, the importance of vaccine development was also communicated. If these factors are left poorly regulated, as they are in Chile, for example, in terms of battling disease and the use of antibiotics, this might cause a detrimental effect on fish welfare and thus, fish health. Hence, clear regulations and their enforcement are vital to produce healthy farmed fish.

2.2.3 What are the desirable and undesirable outcomes of genome editing VS current methodology on their potential use in Norwegian aquaculture?

The participants compared the desirable and undesirable potential outcomes of GE with current methods of solving challenges faced by the Norwegian salmon farming industry.

Desirables

A potential disease resistant fish resulting from GE procedures can, according to the participants, lead to a more effective, precise and less expensive solution than other current methods (i.e. vaccines, drugs and breeding programs). It may lead to less environmental impact, as drugs, antibiotics and pesticides will have reduced relevance if diseases can be avoided using CRISPR/Cas9. Furthermore, it was argued that this procedure might free the farmed salmon from mechanical stress and provide better health as some treatment methods involve pressure or stress which can be deleterious to the fish. Coupled with sterility (to prevent interbreeding with wild salmon), increased precision and control, and reduced costs and time-consumption, there were plenty of take-home in terms of desirable outcomes in the workshop.

Undesirables

The main points highlighted here were the cultural value of salmon, unknown long-term impact and unforeseen off-target effects of GE. The technology might be seen as a quick-fix, such that other viable incentives and approaches may be left out. Also, making the salmon resistant to one specific disease or parasite may cause the creation of a vacuum to be filled by other infectious diseases. Further, if the requirement of sterility is not present, the salmon might introduce the newly acquired traits to wild species, which can affect salmonid genetic diversity. A CRISPR/Cas9 procedure on salmon also presents a value-based and demand-affecting debate: Do we want to eat genome-edited salmon and edit the genes of an iconic marine species for the Norwegian culture and economy?

2.2.4 CRISPR/Cas9 and its potential use in aquaculture, what is the trending research focus? What is the future of the technology in the Norwegian aquaculture?

The stakeholders outlined their perception of the current research focus and future regarding CRISPR/Cas9 and its potential in Norwegian aquaculture.

Trending research focus

Some of the most successful research on the matter has been CRISPR/Cas9-introduced sterility in farmed salmon, so that escapees are not able to interbreed with wild salmon. The topic of sterility and anti-interbreeding had thus been a trending research focus. Additionally, as participants again pointed out, research in treatment of virus and parasites, vaccine development, enhanced nutritional value in fish (either through feed or other mechanisms such as CRISPR/Cas9), disease resistance mechanism in the fish are increasingly relevant topics worth mentioning. As highlighted above, the ways of approaching these topics, as participants have laid out, are GE, breeding programs and specific feed composition.

Future of the GE technology in Norwegian aquaculture
In this question, participants focused on factors that will steer the technology in the future.

Public perception of a product created with such technology was emphasised during the workshop, and potential impacts on reputation was thus highlighted as an essential factor by several stakeholders since the use of GE is linked to public concern and scepticism. Also, the future depends on the extent to which the technology is utilised, both in terms of the areas it is applied and the size of the editing. Lastly, the future of the technology depends on laws regulating such technologies and the level of knowledge gathered before such technologies can be put in use. The participants predicted that CRISPR/Cas9 will be an important tool in future aquaculture and has, therefore, come to stay. Furthermore, some participants predicted that it would be in particular used for disease resistance -the technology has already been used to avoid porcine virus infection.

2.2.5 What are the most important components of the Norwegian environment and ecosystem that can be impacted if CRISPR/Cas9 is used to modify salmon?

Components and impacts
All participants highlighted wild salmon to be one component. The introduced genetic change in the farmed salmon may be introduced in the wild salmon via interbreeding. As stated above, a strategy to prevent this is the development of the sterile salmon. The introduction of sterile salmon ahs increased the positive impact of the use of CRISPR/Cas9 in the Norwegian Aquaculture, i.e. by ensuring that the genetic integrity of wild salmon is protected. However, if a CRISPR/Cas9 edit is introduced without the introduction of sterility, the wild salmon genetic composition is further threatened both in terms of its genetic composition and population composition (due to both competition and interbreeding). According to some participants, an ecological component which may be affected is the farmed salmon's ability to compete in the environment in case of escape. If an increased ability to compete is acquired, i.e. resourcefulness, it may add to the competitional stress of the wild species environment.

CRISPR/Cas9-introduced disease-resistance was identified by the groups as a positive outcome due to the increased sustainability of production by decreased fish loss, improved animal welfare, and reduced chemicals used for treating the diseases. Also, as a result, the disease will spread to a lesser extent. However, if such resistance is acquired by using genetic elements from other salmonid species, as the concept was presented in the presentation under section 2.1.3, the disease may be able to overcome the resistance and thus threaten even more salmon species, as was pointed out by one participant. The problem may have been thus only displaced, rather than solved.

2.2.6 In terms of consumers' perception regarding the potential application of CRISPR/Cas9 in salmon, what benefits are there? What risks are there?

The aim of this task was to stimulate discussion on consumer perception of a GM salmon, and what benefits vs risks exist with a GM salmon.

Benefits
Introducing sterility in farmed salmon will, according to participants, aid in wild salmon protection. The wild salmon is iconic for the Norwegian blue economy and culture, and the consumers will thus

perceive the salmon farming industry as more responsible. Furthermore, coupled with sterility, gene-editing developed disease resistance and enhanced nutritional value in salmon implies healthier fish and thus gives the impression that fish farming facilities care about animal welfare. This is in line with many consumer groups and NGOs with a particular interest in animal welfare. Also, a disease-resistant farmed salmon, as has been mentioned by participants on several occasions, will reduce the need for drugs and other chemicals used in treatment. This will limit the biomagnification effects on the environment and ecosystem, thus preserving the interests of those consumers that may utilise the unaffected ecosystem services. Additionally, the limitation of a footprint can be and is used as a marketing function to attract ethical consumers. The rising consumer demand of marine fatty acids, especially EPA and DHA, can also be met by involving CRISPR/Cas9 in the process of making a salmon with a higher fatty acid composition (either in the feed or in the salmon itself if genetic causality is identified).

The participants also speculated in potential future outcomes if a CRISPR/Cas9 edit has a successful outcome. Firstly, the aspect of use will broaden. Secondly, if used for disease resistance, less salmon would die, leading to more economically sustainable production. A more economically viable production may, in turn, lead to a cheaper product price. However, as was pointed out by the group that suggested this idea, this is not necessarily good given current Norwegian status of food waste.

Risks
One of the most crucial risk factors suggested by the participants was lack of transparency in the industry and corporate monopolism of the technology, causing mistrust amongst consumers. In terms of monopolism parallels to Monsanto’s (Now Bayer) world-renowned crises were drawn, highlighting the danger of monopoly in the industry. Hence, open-access and transparent knowledge generation were emphasized by many participants as reducing risks of negative consumer perception and aiding the democratisation of science. Also, the underlying potential threat to salmon diversity, fish-welfare and unintended editing effects, and a lack of safe-use history may further amplify consumer fear.

Also, as mentioned in the discussions, the salmon farming industry is often both rightfully and unrightfully under pressure, which may make it easier to misunderstand or misinterpret farming practices and relevant scientific knowledge. Hence, educational incentives, in addition to transparency towards the general public, are of interest. Also, social factors such as maintaining jobs and values like the iconic value of wild salmon were mentioned as relevant points for positive consumer responses.

2.2.7 Matrix considering sustainability aspects of the whole production chain from development to consumption of GM salmon in the light of social utility, and ecological & economic factors

The last group exercise was presented and done in a different manner, where instead of a specific task, the participants were asked to fill out Matrix 1 in groups. We will present each level/part of the production chain separately, considering the ecological, economic and social factors for each level.

Matrix 1: An empty matrix showcasing how participants were asked to discuss sustainability aspects of the whole production chain from development to consumption of virus resistant GM salmon.

PART OF THE PRODUCTION CHAIN	**ECOLOGICAL** (ATMOSPHERE, WATER, DIVERSITY, ENERGY AND INPUTS)	**ECONOMICAL** (INVESTMENTS, VULNERABILITY, PRODUCT QUALITY, INFORMATION AND LOCAL VALUE-GENERATION)	**SOCIAL/CULTURAL** LIVING STANDARD, HUMAN HEALTH, CULTURAL DIVERSITY AND PARTICIPATION

DEVELOPMENT	
GROWTH	
STORAGE, PACKAGING, TRANSPORT, AND PROCESSING	
CONSUME	

Development

One of the first points made by participants is that development of such GE and GM salmon needs to follow the principle of Responsible Research & Innovation (RRI), due to all the known and unknown risks and threats such technology could pose. The consensus was that it is crucial to limit field exercises to enclosed facilities and experiments should be based on salmon nature and the natural environment in which the fish normally exists. In terms of economic factors, CRISPR/Cas9, due to its effectiveness and low price, has the potential of having a democratising function as even small institutions and companies can afford it. This function is perceived by some participants to be more socioeconomically more beneficial to research compared to the very expensive older techniques of genetic modification, which inhibits the pace of knowledge creation. One of the main questions asked here was: "Who reaps the benefits on this, and who is conducting the research?". These opinions overlap with the discussions around social and cultural aspects where, again, the interrelation between transparency, thus an active engagement of RRI, and trust was mentioned. Moreover, the importance of educating and creating awareness of the technology to the general public was emphasised. An educated general public may lead to a more fruitful conversation about the effective development of the technology.

Growth

Some participants pointed out that despite disease resistance, and thus no spreading of virus, there might still be a risk of spreading other unintended effects such as other diseases like salmon louse, or if sterility is "lost" as well as off-target genetic edits. Hence, constant monitoring of the GM effect was suggested, and the process should align with novel, appropriate policies and animal welfare guidelines. Economically speaking, the cheaper CRISPR/Cas9 procedures can be used to develop disease resistant fish which will lead to reduced disease-related cost such as specialised fish health employees, drugs, food wastage and chemicals. This reduces the risk for small-scale farmers who are not able to sustain major losses. Additionally, productivity of the farm facility will be improved given that a healthy salmon grows faster with better quality in, e.g. muscle.

Storage, packaging, processing and transporting
In this section, the participants were of the opinion that GE does not solve environmental problems such as long-distance transportation of fish and carbon emission. The emphasis needs to be more focused on sustainability rather than short term profit. Economical aspects highlighted under discussion was the reduced loss due to reduced fish deaths and associated costs. Additionally, it was suggested that labelling the fish may increase productivity. If the salmon is genome edited for a better muscle quality, that may ease the filleting process, thus saving time and improving productivity. Lastly, in the social context, it is important to realise that the fish farming industry currently employs many specific competencies for increased productivity and waste reduction. While the development of such technology and product inevitably requires the acquisition of new specialised competencies, job losses may occur. This may or may not reduce competence locally.

Consumption
The main focus here became the consumer, rather than the consumption itself, although "consumers" were not mentioned explicitly. This way of understanding the section was the same for all three groups. Other than the focus on consumers, there were few contributions on ecology, indicating participants´ interests in the environment and corporate social responsibility. Economically, as participants pointed out, the price of the GM salmon is also important, and it may become cheaper if monopolisation is avoided. Since a GM procedure may add to the sustainability and nutritious value of farming facilities, it may also become a sales argument and increase the demand for farmed salmon. However, as with many products, safety and the right of choice may challenge the GM salmon as they have challenged other GM products.

3. Recommendations based on the workshop

The main recommendations of the workshop are:

- CRISPR/Cas9 can be used to improve sustainability of salmon farming but should be used alongside other measures such as long-term breeding programs and development of effective vaccines. For production in an open facility (i.e. non-contained or closed system) use of sterile salmon is recommended.
- Official guidelines for utilisation of genome editing techniques in salmon breeding should be developed, and anti-monopolisation policies of the technology should be in place in order to increase transparency and aid scientific democratisation.
- To avoid misunderstanding and increase transparency and inclusion, educating and creating awareness in the general public are emphasised.

4. Acknowledgements

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5. Annexes

5.1 Annex 1: Program

Date/Time	*Activities*
Day 1: 5th February	
12:00-12:45	Lunch
12:45-13:45	Welcome, introduction, workshop rules
13:45-14:15	**Presentation 1:** Challenging diseases in Norwegian aquaculture
14:15-14:45	**Presentation 2:** New method of increasing vaccine effectiveness against salmon viruses
14:45-15:00	Coffee break
15:00-15:30	Group discussion 1
15:30-15:50	Group presentations based on discussions
15:50-16:20	**Presentation 3:** CRISPR – opportunities for sustainable aquaculture
16:20-17:10	Group discussions 2
17:10-17:30	Group presentations based on discussions
19:30	Dinner
Day 2: 6th of February	
09:00-09:10	Small introduction
09:10-09:40	**Presentation 1:** Consumer-and environmental interests attached to genome editing in aquaculture
09:40-10:10	Group discussions 1
10:10-10:30	Group presentations based on discussions
10:30-11:00	**Presentation 2:** New suggestions regarding regulation of gene technology by the Norwegian Biotechnology Advisory Board
11:00-12:00	Lunch
12:00-12:30	**Presentation 3:** Contributions to sustainability and relevance of RRI in the use of gene technology on salmon.
12:30-13:00	Group discussions 2
13:00-13:10	Group presentations based on discussions
13:10-13:30	Coffee break
13:30-14:30	Future project suggestions
14:30-15:00	Thank you and conclusions

5.2 Annex 2: Stakeholder Representatives

Institution Represented	**Number of Representatives**	**Backgrounds**
NOFIMA	2	Molecular Biology/Fish Health
KLD	1	Policy/Bureaucrat
Network for GMO-free food and feed	1	Farmer/Pressure group
UiT – The Arctic University of Norway: Faculty of Health, and Faculty for Biosciences Fisheries and Economics	4	Molecular Biology/Fish Health
SINTEF Ocean: Environment and New Resources	1	Ecology/Fish Health

Institute for Marine Research	2	Molecular Biology/Fish Health
Norwegian Biotechnology Advisory Board	1	Humanities/Philosophy
GenØk – Centre for Biosafety	4	Microbiology/Molecular Biology/Biotechnology/Ethics/Food Science
N/A	2	Undergraduate Marine Biotechnology Students

5.3 Annex 3: Questions asked for group work

<table>
<tr><td colspan="2">Day 1</td></tr>
<tr><td colspan="2">1. What are the most important challenges for the Norwegian industry today?</td></tr>
<tr><td colspan="2">2. What</td></tr>
<tr><td>… is a healthy fish?</td><td>… are the most important factors that contribute to making a healthy fish?</td></tr>
<tr><td colspan="2">3. What are the desirable and undesirable outcomes of genome editing VS current methodology on their potential use on Norwegian aquaculture?</td></tr>
<tr><td colspan="2">4. In terms of CRISPR/Cas9 and its potential use in aquaculture, what is</td></tr>
<tr><td>… the trending research focus?</td><td>… the future of the technology in Norwegian aquaculture?</td></tr>
<tr><td colspan="2">Day 2</td></tr>
<tr><td colspan="2">5. What are the most important components of the Norwegian environment and ecosystem that can be impacted if CRISPR/Cas9 is used to modify salmon?</td></tr>
<tr><td colspan="2">Components of the environment & ecosystem</td></tr>
<tr><td>Positive impacts?</td><td>Negative impacts?</td></tr>
<tr><td colspan="2">6. In terms of consumers' perception regarding potential application of CRISPR/Cas9 in salmon, what</td></tr>
<tr><td>… benefits are there?</td><td>… risks are there?</td></tr>
<tr><td colspan="2">7. Considering societal utility, ecological and economic factors, can you identify relevant sustainability aspects regarding virus resistant salmon throughout the production chain (Development → Consumption)?</td></tr>
</table>

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