

AQUADVANTAGE[®]

SALMON:

A CASE STUDY IN THE DEVELOPMENT AND APPROVAL OF TRANSGENIC AQUATIC ORGANISMS



One approach to the genetic improvement of aquatic organisms that has emerged as a discipline in its own right over the past two decades is transgenesis, the transfer of foreign genes into new hosts.

C. Greg Lutz

Transgenic fishes (or molluscs or crustaceans) can be defined as possessing within their chromosomal DNA, either directly or through inheritance, genetic constructs which have artificial origins. The key word for researchers, producers and even consumers here is within the chromosomal DNA: introduced constructs are incorporated into the target organism in such a way as to be expressed and passed along to subsequent generations.

The potential pay-offs for utilizing this type of technology in aquaculture are high: rapid, almost

instantaneous gains in many types of important production traits such as growth, cold tolerance, or disease resistance may be possible. The potential problems, however, are also impressive: labor- and capital-intensive methodologies and consumer distrust of genetically engineered products in many nations. Another major constraint to the widespread adoption of transgenic stocks in aquaculture involves regulatory restrictions on stocking and culture of genetically modified organisms. Due to a lack of performance data, it is usually quite difficult to assess (or even speculate on) the potential im-

pacts of genetically modified aquatic organisms on natural systems. As a result, resource managers, politicians and bureaucrats are reluctant to even attempt to develop protocols for the use of these organisms in situations where inadvertent releases could occur.

One (and probably the only) case study of transgenic organisms in aquaculture involves the company AquaBounty Technologies. In a press release dated November 19, the company announced that the FDA had approved the production, sale and consumption of its transgenic salmon. This approval was the

result of many years of diligence and perseverance, and at many times in the process it seemed virtually unattainable. Jack A. Bobo, Senior Vice President and Chief Communications Officer at Intrexon, a US-based biotechnology company and AquaBounty's main shareholder, stated "The U.S. Dietary Guidelines Advisory Committee encourages Americans to eat a wide variety of seafood—including wild caught and farmed—as part of a healthy diet rich in healthy fatty acids. However, this must occur in an environmentally friendly and sustainable manner. FDA's approval of the AquAd-

vantage Salmon is an important step in this direction."

In 1989, AquaBounty developed *AquAdvantage*[®] salmon, a genetically modified Atlantic salmon (*Salmo salar*), by inserting a gene from the Chinook (King) salmon (*Oncorhynchus tshawytscha*), coupled to DNA fragments from the coldwater marine fish Ocean Pout (*Zoarces americanus*). This modification allows specimens to reach smolt size and commercial size in half the time required by traditionally farmed salmon. For many years, AquaBounty has fought to bring their genetically modified (GM) salmon to the marketplace.

Since this would be the first GM animal suitable for human consumption to be submitted for FDA approval, the company initially faced an uphill battle in terms of generating scientific data required to meet regulatory concerns, and subsequently to encourage opponents to accept the science in the decision-making process. For some time now, the U.S. Food and Drug Administration has been in 'the final stages' of reviewing AquaBounty's dossier and application for approval of the *AquAdvantage*[®] salmon.

In anticipation of an FDA approval, some groups have expressed

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concerns about commercialization of the product in spite of company assurances that its salmon will comply with the sterility levels required by the FDA. The regulatory application for *AquAdvantage*[®] salmon production includes a manufacturing site for egg production in Canada, and a grow-out site in Panama. The agency's approval would allow *AquaBounty* to send eggs to Panama, and products harvested there could then be imported and marketed in the USA. The company assures they have taken all the necessary precautions in the design and production process to ensure a safe, healthy and environmental risk-free product.

In 2013, Environment Canada determined that the company's salmon would pose no significant threat to the environment or human health when produced in contained facilities, clearing the way for the egg production component of the company's plans. The agency reached this conclusion following a risk assessment conducted by the Department of Fisheries and Oceans Canada, involving a panel of independent scientific experts in the fields of transgenics and fish containment

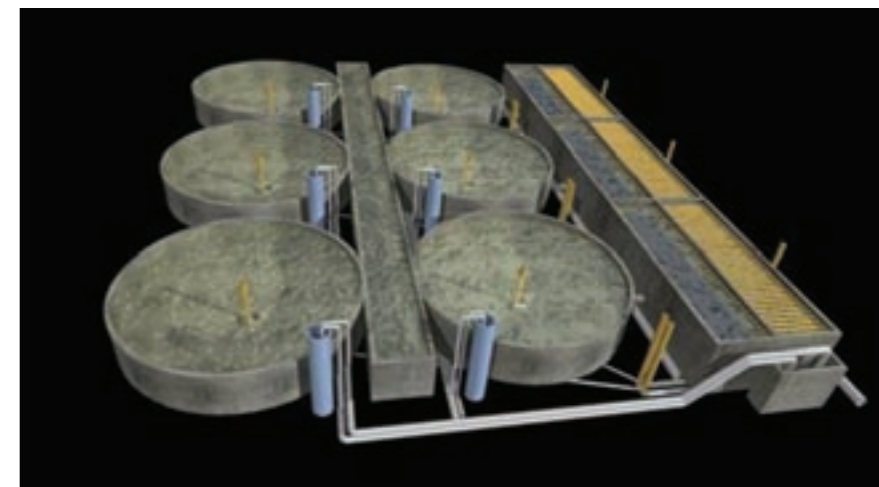
technologies. In the U.S., one final step before the FDA could issue a formal approval was the public comment process for the draft Environmental Assessment and preliminary Finding of No Significant Impact. This was also completed in 2013. After compiling all the responses, it was expected that an FDA approval or rejection would be released at some point in 2014.

Politics, and opponents unwilling to allow the scientific review process to follow its proper course, put the status of *AquAdvantage*[®] salmon in limbo for several years. Due to the delays in the regulatory approval of the product, the company almost depleted its initial capital. The company reported net losses of \$4.7 million for 2013, following losses of \$4.4 million in 2012. Losses reported for 2011 and 2010 were \$2.7 million and \$5.3 million, respectively. Nonetheless, financial prospects have improved since Intrexon became *AquaBounty*'s main shareholder. Intrexon has a broad portfolio of technology and bio-molecular applications, and funded a short-term bridge loan to support operations through mid-2015.

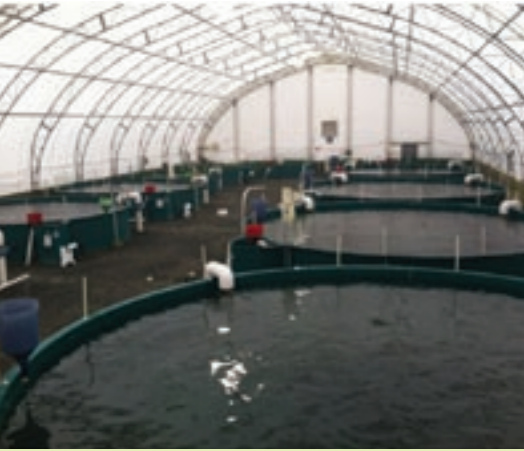
The company is banking on economic and environmental incentives



AquAdvantage[®] fish will pose no genetic threat to wild salmon. Photo courtesy NOAA.



Closed containment design. Courtesy of DFO Canada.



Land-based production in Naimo Canada.

to use GM salmon, due to its improved growth and feed conversion ratio (FCR) characteristics. Studies carried out by the company suggest that producers may obtain a lower FCR (20-25%), and more efficient utilization of dietary protein. Both would have direct environmental benefits. The company has also cited a number of other potential improvements to sustainability. Because *AquaAdvantage*[®] salmon will be raised only on land-based systems, this will hopefully contribute to increase the adoption of closed systems such as RAS. Additionally, scientific applications incorporated into the product, as triploid, monosexed populations, may be more easily transferred to conventional aquaculture species, in order to protect both the environment and the intellectual property of genetic improvement companies. The use of a more efficient, high-turnover fish such as *AquaAdvantage* salmon might be the key to making land-based salmon culture economically sustainable.

According to the company, virtually all *AquaAdvantage*[®] salmon are triploids. The percentage efficiency of triploid induction in general has been reported to exceed 99%. In the validation study submitted to the

FDA, 7,000 eggs from 20 families were individually analyzed, using flow cytometry. Of those 20 crossings 14 were found to be 100% triploid, and the overall average was 99.85%. In addition, 100% of *AquaAdvantage*[®] salmon are mono-sex (all female), so that they cannot establish reproductively active, self-sustaining populations. In many salmonid species, females are considered superior (and more efficient from a bio-economic perspective) in most production traits. Since sex in salmonids is based on female homogamety (as is the case with humans), which we can refer to here as an XX state, it is possible to produce all-female stocks by mating normal female salmon with XX 'males' produced through hormonal masculinization of normal XX fry.

Like all Atlantic Salmon, *AquaAdvantage*[®] salmon cannot breed with any of the five species of Pacific salmon, including Coho Salmon. Therefore, the combination of triploidy, monosex populations and natural reproductive incompatibility, as well as multiple containment barriers built into culture centers, mean that the reproductive interaction between *AquaAdvantage*[®] salmon and wild salmon stocks would be essentially zero. No accidents like we saw in Jurassic Park.

AquaAdvantage[®] eggs will be labeled as genetically engineered Atlantic Salmon; this label will be implemented on each batch to be marketed. However, the company has no power to control how customers and distributors will label their final products. Opponents have focused on this aspect of the market chain as a means to prevent the commercialization of fish like *AquaAdvantage*[®]. For example, although voters in Washington rejected mandatory labelling of genetically modified organisms in 2013, Rep. Cary Condit introduced a bill the following year that would require genetically engineered salmon

to be clearly marked at the point of sale. Similarly, the U.S. Senate Appropriations Committee adopted an amendment sponsored by Senator Lisa Murkowski of Alaska, requiring mandatory labelling of GM salmon.

A number of arguments against *AquaAdvantage*[®] salmon were publicized in the resulting discussion, none of which were scientifically sound. At the time *AquaBounty's* CEO, Dr. Ronald Stotish, stated that "The amendment appears to be an attempt to usurp legal authority for food labelling from the FDA where it has resided historically. More importantly, it appears to be an attempt to utilize labelling as a weapon for protection of economic interest." Murkowski was widely considered to be acting to protect the interests of wild salmon fisheries in her home state.

The relationship between price, sustainability and consumer acceptance presents a complicated balance in the case of *AquaAdvantage*[®] salmon. When one considers the overall environmental impacts in terms of containment and conversion efficiency, many of those criticizing these GM fish apparently have not considered that they may be "cutting off their nose to spite their face." However, those producers who want to work with a salmonid with accelerated growth and reduced FCR will have

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PEI-Hatchery-Fish-Tanks. Courtesy of AquaBounty.

to deal with resistance in the marketplace, at least initially. Presumably, *AquaAdvantage*[®] salmon will have a lower production cost than traditional farmed salmon. By using land-

based RAS systems that are specially designed for *AquaAdvantage*[®] salmon culture, the company estimates that producers could save up to \$1-1.50/kg. For end users, *AquaAdvantage*[®]

salmon will hold the same nutritional and biochemical properties as conventional farmed salmon, so apart from any stigma associated with a genetically enhanced product, they may accept it and enjoy it like any other farmed salmon.

As has been shown in the case of *AquaAdvantage*[®] salmon, sound science is only a part of the regulatory process when it comes to GM organisms. Future GMO applications submitted to the FDA will be handled on a case by case basis, and it is impossible to predict their outcomes, but now that *AquaBounty's* application is finally approved it could give hope to other GMO producers. ^{EM}

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