# How Meat Allergies Led to the Development of Bioengineered Pigs for Human Consumption

Written by Persephone Valentine, Undergraduate Science Writing Intern, Food Research Institute, University of Wisconsin-Madison

At the end of 2020, the FDA approved the first line of bioengineered pigs for potential therapeutic development and human consumption. The genetic alteration in these pigs halts their production of the sugar, galactose-α-1,3-galactose, also known as alpha-gal. This modification both minimizes allergic reactions to pork and decreases the likelihood of organ rejection of potential xenotransplants (pig to human). This line of pigs is called "GalSafe pigs," and they are produced by Revivicor Inc, a company researching safe, human-compatible alternatives in medicine.

Alpha-gal syndrome (AGS) is the name of the allergy to alpha-gal, which currently has no treatment besides avoiding red meats altogether. Hypersensitivity to alpha-gal went unnoticed until a new antibody (cetuximab) was in clinical trials in 2004 to treat colorectal cancer. Researchers observed that some participants developed adverse side effects and eventually identified the root cause to be alpha-gal, which was on the antibody protein. They also recognized that many participants who had reactions lived in regions where the Lone Star Tick is commonly found. Individuals bitten by Lone Star Ticks can develop AGS because they become exposed to, and subsequently develop immunological sensitivity to, alpha-gal found in the saliva of the ticks.

Before 2004 there was no explanation for the various reactions some people experienced after consuming red meat. Eventually, researchers recognized that some people bitten by Lone Star ticks developed an immune response to alpha-gal. AGS manifests differently from other allergies, making it difficult for people to realize they have an allergy to red meat. Although most other allergic reactions occur relatively soon after exposure to the allergen, AGS usually takes 2-6 hours and sometimes as long as 12-24 hours to become apparent. Common symptoms include rashes, nausea, vomiting, hives, difficulty breathing, decreased blood pressure, dizziness, faintness, and stomach pain.

Dr. Jeri Barak, Professor of Plant Pathology at the University of Wisconsin-Madison, is one of these people who developed AGS when its molecular cause was still unknown. Growing up on a cattle farm, Barak ate red meat as part of her diet. But as a teenager, she started noticing adverse symptoms after meals with red meat. Through trial and error, she slowly eliminated all meat, except for fish, from her diet. Fortunately, she grew vegetables on her farm near the Gulf Coast, so she was able to substitute red meat with fish and vegetables. Jokingly, Barak would tell others that she was a forced vegetarian, not a political vegetarian. However, Barak personally has no issue with having AGS now and says, "because of the wide availability of vegetables right now, it gives us so many choices that I don't consider it a hardship" and "it's been so long, that I don't even think about it." Even with the potential of adding pork back into her diet, Barak does not plan to purchase pork from GalSafe pigs.

GalSafe pigs are different from conventional pigs because the gene associated with alpha-gal production has been deleted from their cells. This change allows people with AGS to eat pork from GalSafe pigs without fear of exposure to alpha-gal. In addition, CD46, a human gene that may protect tissue from self-attack by the immune system, has been inserted. Beyond producing pigs for human consumption, Revivicor is actively partnering with the medical device industry to produce pigs that can serve as sources of medical products like Insulin and Heparin. Ultimately, Revivicor hopes to provide donor organs and tissue to address transplant organ shortages, which they have already started to achieve. In late 2021, scientists at NYU carried out the first successful kidney transplant from pig to human. The

kidney was from a GalSafe pig from Revivicor. However, there are still questions regarding whether the kidney will last over extended periods of time, as organ rejections can years after surgery.

If GalSafe pigs pave the way for further development and production of genetically modified animals for human consumption, it may spark more debate about the risks and benefits of genetically modified organisms (GMOs). It also raises additional questions about the wellbeing of the animals, their impact on the environment. and how safe they are to consume. Generally, consumers more favorably view "natural" foods that have not been genetically modified, assuming they are healthier and better for the environment. Although many also view GM foods as an opportunity to increase global food supply and decrease food prices, those most concerned with GM foods are likely to view them as potential detriments to the environment and public health. On the other hand, it could also be argued that genomic alterations occur naturally in organisms via mutations during DNA replication. The outcome in nature can be silent or cause positive or negative changes in the organism, but at least with GMOs, the genomic changes are planned and controlled.

Regarding the safety of consuming GM pigs, from reviewing the documents provided by Revivor, the FDA agreed with the Revivicor's assessment that they posed no safety concerns to humans. Nevertheless, it is ultimately up to consumers to determine whether they feel safe eating GM products. Interestingly, prior studies suggest people with food allergies are more likely to care about GM issues than people without allergies. People with AGS may see more benefits in GalSafe pigs because it would be the only source of pork they could eat.

With respect to the potential environmental impact of GalSafe Pigs, some may voice concern for the risk of GalSafe Pigs escaping and cross-breeding with wild pigs. According to the FDA environmental assessment, GalSafe Pigs would present no more danger to the environment than conventional pigs. Additionally, GalSafe Pigs are bred under much more controlled conditions and maintained with strict biosecurity, greatly reducing the likelihood of pigs escaping.

Another potential environmental impact of GM food like GalSafe Pigs that many people, including Dr. Barak, have pointed out is that the environmental impact of expanding red meat consumption. Livestock-based food production has been estimated to account for a significant proportion of greenhouse gas emissions globally, although this is largely from beef and not pork production. As Dr. Barack stated: "[GMOs] are super important to solving some of the problems that we have in agriculture, especially with the looming problem of climate change and food production" ... "with the question about the [GalSafe pigs], it's complicated; animal production has a higher cost to the planet than plant production." However, the number of individuals with AGS is very low, and it is not likely that the market for GalSafe pigs would significantly impact the total number of pigs raised in the U.S.

With the precedent now set for genetically modified meat animals to be approved for food consumption, there may be more interest in genetically modifying other food animals, which could affect their contribution to climate change. Pigs are not the first genetically modified animal approved for human consumption by the FDA. In 2018, a line of genetically modified Atlantic salmon, the AquaAdvantage salmon, was developed to be more nutritious and grow faster than conventional salmon. We may be entering a new era in which GMOs are designed for food production and medical purposes, as is the case for the GalSafe pig, which Revivicor hopes to use for eventual organ, tissue, and drug production. The development of GalSafe Pigs will spark further debate concerning the safety of GMOs that goes beyond food. For example, are people comfortable with receiving GMO pig xenotransplants? Conversely, xenograft products from GalSafe pigs could potentially save human lives. There is certain to be ongoing concerns and debate about the potential benefits, risks, and ethical concerns about the continued development of GMO animals for food and medicine.