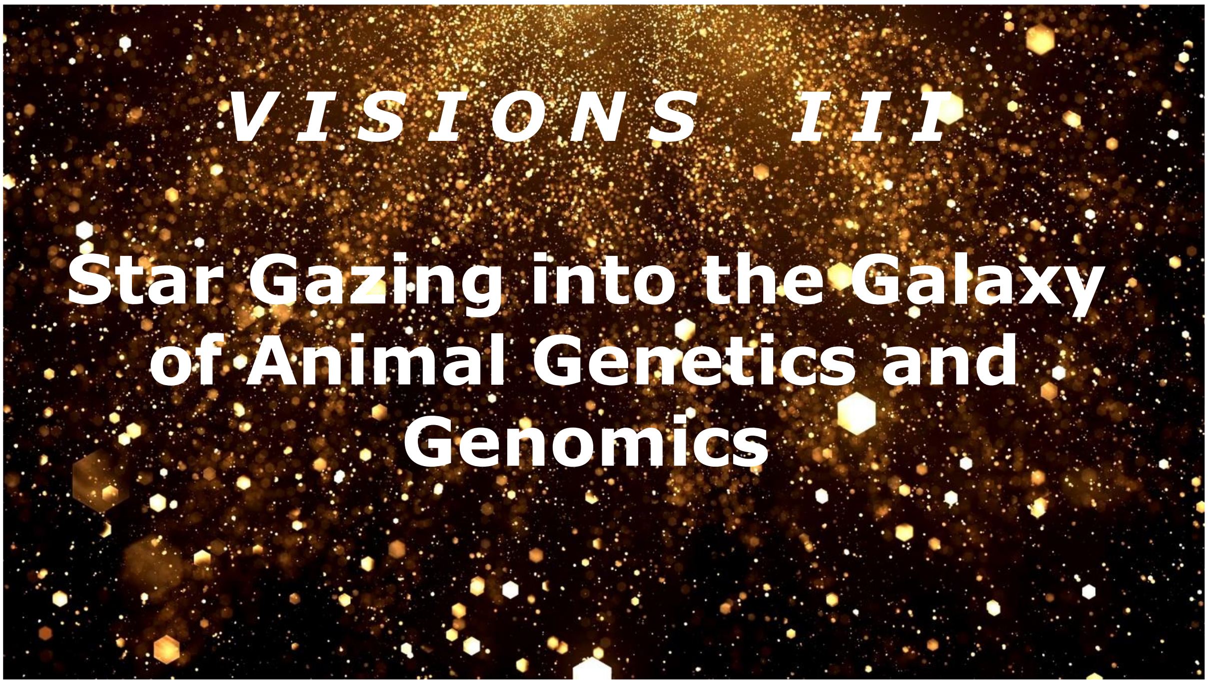

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Max Rothschild and Susan J. Lamont
Co-Organizers

Symposium Proceedings

Keynote Address

A galaxy of possibilities: the role of genomics and other technologies in future animal improvement

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Introduction

Agriculture is at an interesting time in its long and impactful history. Over the next 30 years, as we respond to population, demographic and resource changes, we as a society will ask more from agriculture than we ever have in the past or ever will again in the future. By 2050 we need to produce 70% more food, with less resources, in a changing climate, without destroying the planet. Animal improvement seeks to improve agricultural productivity and sustainability by altering the genetics of our animal populations so that they can be healthier, more sustainable and more productive. Historically about 50% of improvement in animal performance has been directly attributable to breeding. Faced with the societal need over the next 30 years, what could animal improvement do?

Animal improvement is also at an interesting time in its long and impactful history. It is emerging from a 20-year cycle in which a technology was discovered, was adopted, and completely disrupted the field. This technology was genomic selection. Genomic selection has transformed almost all aspects of animal improvement over the past two decades. Cast in the framework of the breeder's equation which embodies the concept of genetic improvement, genomic selection has driven increased rates of genetic gain by directly addressing three of the four parameters of this equation. Generation intervals were shortened. Selection accuracies and selection intensities were increased. For researchers, students, and practitioners of animal improvement this technology was a boon. We had to rethink our understanding of breeding program design, open our minds to new technology, learn new skills, invent and innovate. It was exciting, but for those of us who surfed this wave, what now?

Faced with these two challenges, the societal need and the maturation of a technology cycle, Max Rothschild and Sue Lamont, who over many years have made seminal contributions to the field of animal improvement, have brought us together to ask: What are the big opportunities and open questions in animal improvement for the next 30 years?

Technology landscape

Retrospectively, the route of immediate implementation and application of the technology landscape at the inception of genomic selection was far more obvious than what I see in front of us today. Variants and precursors of genomic selection were alluded to at various times in the previous 80 years (e.g., Sax, 1917, Smith 1967), marker assisted selection was intensively researched in the 1980's and 1990's (including seminal work by Rothschild), cheap easy to use genome wide genotyping technology was on its way as a consequence of developments in the burgeoning human genomics field, and the route to implementation was remarkably straightforward needing limited mindset change (i.e., change the relationship matrix in Henderson's much loved mixed model equations from $\mathbf{A}^{-1}$ to $\mathbf{G}^{-1}$) and then modify the breeding program at a rate that each individual manager was comfortable with. Of all of these factors, perhaps the most important was the mindset. In my view genomic selection did not challenge the collective mindset of the animal improvement community in a significant way. Arguably, and potentially unfortunately in the fullness of time, it validated our long-standing belief in quantitative genetics, the breeder's equation and BLUP, etc.

What are the technologies that are in front of us today and which will continue to emerge over the next 30 years? Will the "*Maslow's hammer*" that comprises quantitative genetics, the breeder's equation and BLUP continue to be the tool through which the animal breeder will seek to implement?

Some of the technology that will emerge includes abilities: (i) to precisely control key biological processes (e.g., recombination, reproduction, and the expression of individual genes in individual tissues); (ii) to edit and write genomes in somatic and germ cells, (iii) to precisely measure physiology at the cellular, tissue, organism and population level across time; (iv) to precisely measure, predict and control the lifetime environments in which our animals will live; and (v) to analyse data on an unprecedented scale, using models with unimaginable complexity, using quantum computers (perhaps it would be unwise to entirely discard "*Maslaw's hammer*", but we may want to consider dumping "*Occams razor*").

What should we do with these technologies?

Innovate. Innovation is the serendipitous force that drives economic development. How do we innovate? Matt Ridley argues in his excellent book "How Innovation Works", that innovation *"is an incremental, bottom-up, fortuitous process that happens as a direct result of the human habit of exchange……… it is always a collective, collaborative phenomenon, involving trial and error, not a matter of a lonely genius"*. Innovation is a team sport and it requires an ecosystem. Ridley makes three additional points that are pertinent for the coming epoch in animal improvement:

- Innovation needs a purpose – societies need over the next 30 years means animal improvement has a purpose like never before.

- Innovation needs freedom – perhaps not complete freedom in the classic sense of academic freedom but rather complete freedom within the guard rails of the purpose – we seek to innovate for the purpose of transforming animal improvement.

- Innovation needs resources – society needs to invest and to patiently wait.

I think the field of animal breeding needs to ask itself if it can do more to create an open minded, sharing ecosystem that is well resourced and certain of its purpose so that innovation has the best possible opportunity to occur.

Big questions

The field of animal improvement is still faced by some of the same big questions that have been around since its inception.

How does genetic variance work?

We still don't clearly know how genetic variation is generated, operates, and is maintained, lost or utilised from our livestock populations. To address this we need huge amounts of data from a diverse set of sources, at many layers, made possible by legacy, new, emerging and yet to emerge technologies. To make real progress here the community we need to figure out how to bring together the public and private sector, to assemble sufficient resources and to tackle this. Does the current approach in which relatively closed networks create consortia, with their intricate webs and politics, have the objectivity to create the scale, openness and freedom to make meaningful progress on the biggest of questions? Should we identify a single model biological process in one species (e.g., muscle in pigs, mammary function in dairy cows, bone in chickens) and answer this question with sufficient focus and scale.

Which technologies should we go after?

A beautiful feature of innovation is that it is almost entirely unpredictable. We don't know, where, when or why the next game changing innovation will emerge for animal improvement. Therefore, we need to pursue all technologies but with the intention to be ready to abandon any one of them at the right time. If we use the control of recombination as one example. Recombination creates genetic variation within our population. Based on what we know today, precise control of recombination would enable us shuffle our genomes more quickly, enabling us to explore more permutations, giving us greater insight into the genetic variation in our populations and given us greater access to this variation to enable greater ability to make more sustainable genetic gain. Precise control of recombination is a very promising technology that needs to be pursued. However, I think it would be immediately trumped by an ability to edit genomes at scale, which itself would be trumped by an ability to write whole genomes at scale, if we precisely knew how genetic variation is generated, operates, and is maintained, lost or utilised from our livestock populations. Consequently we need to go after all these technologies.

In going after all technologies we need that the community balances its emphasis. Over the past 15 years we have seen a huge emphasis on statistical models to extract accuracy from our genomic data. In contrast we saw much less emphasis on breeding program design. Based on this trend many people would predict that the field place a huge emphasis on statistical models to extract accuracy from phenomic data (probably using deep learning or what follows it in the hype cycle). Within the realm of phenomic data I think it would be prudent to ensure that we place sufficient emphasis on how breeding programs need to be modified, how selection indices could be modified, how mechanistic biological models (i.e., the equivalent of crop growth models) could be integrated, etc. But more importantly, we need to ensure that we place sufficient emphasis on the opportunities out width the realm of phenomics.

How do we leverage expertise, activities and the mindset of other fields?

The animal improvement community is small and like many fields (big and small) somewhat endogamic. It is a very natural human characteristic to be tribal, factional or even insecure with respect to our field or to components of that field. Rather than focussing energy on molecular versus quantitative, dairy versus aqua, plant versus animal, Bayesian versus frequentist, human versus animal, etc and wondering which one is ahead, more impactful, had the idea first, etc we need to think how we can leverage the combined resources and brainpower of all fields to help us with our purpose. Innovation happens most frequently at the interface. Lets expand out interfaces.

What about the Global South?

Animal improvement is a slow cumulative process. Breeding programs require sustained and long-term investments, infrastructure and governance. Such situations are prevalent in the Global North and consequently animal improvement has been hugely impactful in that region. The absence of such situations in the Global South has meant animal improvement programs are still to have the huge impacts that they could, despite the tireless, ingenious and heroic work of many animal breeders who operate in that region. However, the possibilities demanded by the purpose and presented by the new technologies harbour much room for optimism. The confluence of genotypes, mobile phones, advances in artificial insemination and scalable peer to peer market places could enable accurate animal evaluation, dissemination of improved germplasm and the business model to sustain this. I hope I am not holding Diax's rake in my hand!

What does this mean for our training programs?

Training programs for the next generation of animal breeders could be more interesting, broader and more impactful than ever before. We need that these programs equip the next generation with: (i) the context; (ii) the technical pillars of the core sciences (quantitative genetics, molecular biology, genomics, statistics, computer programming, reproductive biology, and animal physiology and husbandry; (iii) exposure to technical skills, culture, and questions of other fields (e.g., computer vision, engineering, plant breeding, evolution, human genetics); and (iv) with the soft skills needed to have the right mindset and operate effectively. The list of required soft skills is long and all are important. In the context of this article I want to highlight one, the ability to be open minded so that innovation can happen.

Conclusion

We are at an incredibly interesting and important time in the development of the field of animal improvement. Over the last 20 years we have had the luxury of surfing the wave of a transformational technology. That wave is beginning to peter out. Over the next 30 years we will ask more from agriculture, and therefore animal improvement than ever before. There is a vast array of new technologies spawning around us. It is not clear which one will be transformational. We need to prepare our collective mindset to be let innovation happen and leverage its resulting potential.

*John M Hickey is currently an employee of Bayer Crop Science. His participation in this meeting was agreed prior to his employment at Bayer Crop Science. Therefore, he is participating in this meeting in an entirely personal capacity.

Plenary 1

Big data, statistical inference and use of artificial intelligence in the future of animal genomics

Molly Jahn
DARPA

The past two years have shown us that any future vision based on linear extensions of today's patterns is certainly questionable. Over the past 60 years, under the lash of efficiency and productivity, we have created highly consolidated, narrowly based plant and animal-based food production systems that are indeed, highly efficient and "productive," (as we have defined productivity), but brittle and fragile, loaded with uncharacterized or poorly characterized dependencies and contingencies. Amidst i) compound global pandemics affecting animal agriculture and human health; ii) major dietary shifts both toward (due to increasing affluence among the world's poorer populations) and away (due to concern about adverse health effects from over-consumption) from animal protein in human diets; iii) unprecedented effects of climate change; and iv) ongoing evidence of damage done by unsustainable production practices, the future may be driven by some very different constraints and goals than the present and recent past. Arguably, animal agriculture is an original big data application, going back to the 1950s and 60s with a big jolt when artificial insemination entered the picture and coops began keeping detailed records connecting animals' genetics to their production. If "big data" is nothing new to animal breeding, what is new that sits on this foundation, and where are we going?

The first important question when looking into the future is, "What will our targets be for genetic shifts in animal production/performance?" Big data, the ability to make fine-grained inferences based on vast troves of data and automated approaches to processing data into information act to facilitate our ability to hit targets set otherwise. I am now a civilian employee of the Department of Defense so my metaphors and examples will be drawn from my current environment. The analogy that comes to mind is that these techniques I've been asked to discuss are the rocket boosters on the juggernaut of animal breeding, but they don't necessarily intersect directly with the guidance system.

Tomorrow's targets for animal breeding

Since the U.S. Civil War, today's production practices in livestock agriculture have evolved to prioritize cheap food for urban consumers with only relatively recent interest in objectives for animal breeding that address waste, air and water pollution including GHG, degradation of soil, reduction of widespread use of antibiotics, biosecurity and animal welfare. Some believe animal agriculture is facing existential threat from the potential loss of the implicit political and social licenses that allow certain consequences and costs of contemporary animal production systems such as pollution, climate change and animal welfare concerns to be radically discounted or omitted entirely. Such shifts in public opinion often seem impossibly far-fetched before the shift (for example, the public attitude immediately preceding the decline of smoking acceptance or a requirement that every public facility be handicap-accessible) and are generally highly contentious before during and after a shift in public policy, but they do occur with profound consequences for those affected. I think it is increasingly unlikely that animal agriculture will continue to get the pass it has largely received to date. This means there are a host of breeding targets, many of which are already being aggressively addressed, that collectively mean animal agriculture does less environmental damage to air, climate, water and soil resources, that certain practices viewed as inconsistent with optimal animal welfare are no longer generally accepted, and that meat products take their place in healthier diets. Implications of these observations for animal breeding are that the days of a laser focus on maximizing production at the expense of system impacts are over.

New targets for animal breeding in an era with new power in large scale approaches

In the developed world, we will probably see continued dominance of the handful of species that have been the focus of intensive investment throughout the 20th century, cattle, swine, poultry (chicken/turkey) and to a much lesser extent sheep. In these mainstream species in the developed world, the intensive vertical integration will remain the dominant force in shaping and controlling the targets for improvement. Implications of big data and the application of automated approaches to building and testing inferences, will probably center on maintaining productivity and efficiency within current production systems that will in due course likely lose the right to pollute and degrade resources to the same extent as today, lose access to antibiotics to quell routine inflammation and that will be held to more and more stringent standards for health of products and animal welfare. It's possible that meat will continue to undergo the same types of "de-commodification" as has been observed for some fruits and vegetables that has resulted in a proliferation of "heritage" breeds, products distinguished by absence of substances or practices considered objectionable by consumers (e.g., fat content, antibiotics, cages, farrowing pens) or presence of substances or practices (Ω-3 fatty acids, grass-fed, wagyu beef). Meanwhile the meteoric rise of meat alternatives and interest in vegetarian, vegan, pescatarian diets would likely have been impossible to predict 30 years ago. From my experience as a vegetable breeder over the past 30 years, it is important not to under-estimate the potential of these trends to knock the familiar species and types off their pedestals. Of the mainstream species, cattle production, whether for meat or dairy, has moved to a central target for those concerned about health and negative environmental impacts.

Worldwide, the number of animal species (excluding insects) regularly eaten by local populations number in the hundreds that are cultivated intentionally, of the tens of thousands edible animal species. North American consumers would not recognize the vast majority of these species, nor would they be likely to accept them. Any of these species that have local markets and much less intensive production requirements may be brought forward for use as they often occupy important multifunctional niches in integrated food production systems tailored for local conditions. Many of these species, though by no means all (e.g., rabbits, rodents), are at risk, due to loss of habitat and over-harvest. It may be that if carbon/methane/air/water pollution becomes the new human slavery and is banished, some of these species may snap to the fore for domestication, leveraging the jump start that large scale genomic sequencing and artificial intelligence could provide toward animals more suitable for large scale, organized production in a world where we are less bound by idiosyncratic chance e.g., focus on only the handful of species today. It is important to note that it is possible to apply the techniques of big data, statistical inference and artificial intelligence to the genomes used in "cellular" cultivation, effectively applying these techniques to animal genomes at the cellular level via techniques such as cultured meat, without the animal *per se*.

A revolution just starting to crest in terms of applied implications focuses on microbe-plant and -animal interactions. Where we once saw one corn plant or one heifer, we now see billions of organisms both inside and out of the plant or animal on which we have focused on and bred. Obviously, we have been indirectly selecting within these interactions, but the next several decades may bring new opportunities to break open and optimize with intention the microbial interactions within microbiomes and between microbiomes and their hosts and environments to reduce the need for various inputs, improve health and wellness of both animals and people, and reduce environmental consequences of animal production. We know these microbial interactions and communities are immensely consequential but are still in the earliest days of learning how to "steer" them effectively or even appreciate the many dimensions of their significance. This is nothing short of a massive paradigm shift from the post-war view that germs were bad, and better living would be achieved through chemicals that were often introduced into complex systems with little or no appreciation for the collateral effects put into motion on the relevant microbiota and beyond. Widespread use of antibiotics in animal agriculture has been challenged intensively, with the loss of antibiotic efficacy increasingly attributed to animal production practices. With the rise of genome editing approaches and synthetic biology, microbes may be early targets for genetic shifts that advantage the animal, animal cell, or the production system in some way. Interactions between animals and their internal and external microbiota may have very significant opportunity to be optimized, given recent estimates that there are a trillion bacterial species, only 30,000 of which or thereabouts have been named. The technique of sequencing an environment will yield breakthrough insights with regard to these interactions and how they may be harnessed to improve productivity and safety of production systems.

Big data, statistical inference, AI, "surveillance culture," power and information in the 21st century

A very consequential implication of the rise of artificial intelligence applied to "surveillance" data, whether that be human facial recognition coupled with fintech and social credit schemes as in one notable near-peer country to control human behavior, or daily milk yields per cow coupled to ration intake in a coop, is that more data is more power. In contrast to the U.S., China has undertaken a highly strategic set of investments to generate and curate vast troves of genetic, performance and other types of data through collaborations and investment largely channelled through the Beijing Genome Institute (BGI). The asymmetry that this investment creates between the U.S. and China is profound with regard to the ability to make and test inferences and test strategies to steer complex biological systems, such as those that underlie livestock production for food, as desired. The U.S. has recently sent a high level mission to many allied countries highlighting the potential implications of sharing human, animal, plant and microbial sequences so freely. Seemingly unconnected data, if curated in a system with sufficient meta-data for each data resource, can be very powerful in addressing not just the questions we think of today, but questions in the future, notably questions that focus on leveraging interactions that our old-fashioned views did not appreciate (such as between microbiomes or between microbiomes and higher organisms such as livestock, plants and/or humans). U.S. public data storage and curation resources and mandatory policies for curation of research and operational data for the scientific/technical and business communities fall woefully far behind those of China, meaning that a vast proportion of the world's technical community generating sequence data use Chinese data assets which have been publicly offered both to enhance the resources available to the global scientific and technical communities and ensure ongoing Chinese dominance in a contemporary and future world where big data and power are inextricably connected.

Provocateur's Responses

Pandemic visions and illusions

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Professor Jahn's (PJM) essay takes a broad view of animal agriculture, seemingly arguing for a systems approach. Her holistic perspective transcends my narrow background as a specialist in livestock improvement via quantitative genetics. I will follow an even narrower pathway here, attempting to relate current and future roles of machine learning (ML) and artificial intelligence (AI) to animal breeding.

Defining breeding objectives (the classical Smith-Hazel problem) is crucial. The task must be done in a careful manner, stating what needs to be improved and avoiding measuring irrelevant features. "Systems biology" (their AI counterpart is network analysis) does not seems to give much guidance because many and loosely defined variables often intervene, for which causal relationships and unknown rate coefficients must be available. The systems theory of von Bertallanffy has not shined in economics (Prebisch), anthropology (Levi-Strauss), it sounds absurd in psychology and literary critique (Lacan, Althusser), went out of fashion in animal production (Dent, Fitzhugh, Joandet) and it failed in planning the Afghanistan invasion. Referring to the system proposed by the military, General McCrystal stated: "by the time I understand the slide the war will be over"; the system crashed about a decade after the statement. Until buzz terms such as eco-system, robustness, resilience, sustainability, animal welfare, interactome, and metagenome, say, are defined precisely and unambiguous metrics are developed, researchers will navigate in an Orwellian world of vagueness. Intelligence informs AI but the opposite may not hold true. PJM implicitly suggests that a high degree of inter-disciplinarity is needed, and I agree. Our current academic system rewards hyper-specialization and self-reproduction, apart from being inefficient. A university professor spends much time writing grants and articles with a microscopic impact, instead of thinking and creating science, transmitting new ideas and engaging in interactions that broaden perspectives. AI will not generate fertile interactions if the various compartments do not overlap. Breeding objectives will not be delineated properly by intellectually consanguineous specialists.

The rate of change due to selection (given assumptions) is proportional to the correlation between predictand and predictors. Animal breeders developed and adapted prediction procedures beyond Galton's regression and Fisher's infinitesimal model, invented "simple" methods such as BLUP and tailored Bayesian machines (an entire aisle in the supermarket), bagging, boosting, reproducing kernel Hilbert spaces regression, and deep neural networks (DNN). So far, DNN have not been better for trait prediction than simpler linear Bayesian regressions or BLUP. There is now massive genotypying, epigenotying, proteomics, metabolomics, enviromics and (fine) phenotypying. Also, there is a field called "prediction analytics" that drives entirely on observational data from, e.g., infrared, sensor, drones, spectroscopy images, etc. PJM refers to "surveillance": we are capable of monitoring whether a pig is happier if its pen mate is a turkey instead of a sheep (no pig polygraphs yet, so pig happiness is yet to be defined). Last week, "The Economist" argued that big data in economics provides a panopticon that may allow instant effective intervention, but also asks how far we can see into the future. Breeders may get inebriated with the wapatuli of measurements, apps and tweets, and drown in a technology-big data-induced Maelstrom. On a positive side, Coffey stated: “at the time of genomics, phenotype is king”. AI, ML and DNN may lead to the discovery of more relevant phenotypes, e.g., by advances in visualization that allow to identify crop diseases or tumors (animals and plants) from shapes or images. A salutary impact of ML and AI has been to help us view the mechanistically naïve theory of quantitative genetics less seriously. In ML, heritability and genetic correlations cease to have an existential meaning, with these parameters (entelechies) becoming transitional tools that help us go from past and current phenotypes to expected phenotypes.

Current emphasis on "big data", "massive computing" and "visualization" perhaps will diminish basic science education. Thesis students start crunching data before they know genomics or understand the meaning of a probability distribution, attain an elementary knowledge of experimental design, randomization or causality, or even of the algorithms employed (downloading is easy), that somebody else (perhaps a robot) has written. Foundational theory and strong basic biology must continue being taught if animal breeding wishes to maintain a status as a science and not as a technology. Otherwise, new critical and visionary perspectives may end up playing roles that are secondary to that of a visualization or, even worse, of an AI-driven robot. It has been said that the dairy farm of the future may be handled by a dog and by a human. The dog will protect the robots and the human will feed the dog. What about if the robot and the big data end-up driven by a fake algorithm? Perhaps the dog will have the last word.

Artificial Intelligence in the Future of Animal Genetics

Benny Mote
University of Nebraska

Animal agriculture has been painted in a negative light on many controversial topics, some undeservingly so while others are justified knowing what we know today. Gone are the days of simply selecting for the “est” (biggest, smallest, etc) of a few production traits without a thorough systems analysis of how those traits interact with the world around it, perhaps to the extent of “sequencing the environment” for a truly holistic approach. Poultry lines have been started that do not grow as fast as many of the traditional broiler lines. Sow lines have shifted focus away from maximizing the number of total born per litter to sows that have lower preweaning mortality. Cattle producers are matching the size and production outputs of cows to their environment. Animal breeding has always and will always strive to improve the accuracy of selection to enhance genetic progress. Data, big and small, have constantly been added to the tool kit for animal breeders to utilize in those selection decisions evolving alongside the ever-increasing computing power. The reality is that phenotyping in production livestock hasn’t evolved as fast as genotyping or quantitative genetics with the bulk of the phenotypes in today’s selection indices being eerily similar to those of the 1950’s. The rapidly accelerating use of Artificial Intelligence in agriculture will allow the pendulum to swing back to the advancement of novel, advanced, and more accurate phenotyping of livestock for holistic and sustainable production.

In many cases, the “simple” production traits have either reached optimum levels or are at the point of diminishing returns. Geneticists are on a never-ending quest for a more thorough understanding of genotype by environment interactions needed to maximize production. Computer vision advancements have shown great promise in facial and body recognition to allow for individual animal identification in commercial group settings. Data such as this is the precursor to even bigger data sets needed to fully analyze the genetics of animal health and animal behavior. Current computer vision work is elucidating heritabilities to many of the daily activities such as distance traveled, time standing, and time lying, etc. Not only are these traits interesting in their own right, but they are expounding on components of feed efficiency, once simply lumped into residual feed intake. Furthermore, computer vision technology can be applied closer to the animal of interest, the commercial herds, versus simply the nucleus facilities and on a far greater number of animals. Utilizing nucleus animals in highly controlled environments offers a correlated response to selection, though for many traits that correlation is not 1. In swine, it is now common to hear production companies use the talking point of a carbon neutral pig and the trait with the largest impact on carbon neutrality being feed efficiency.

It is widely known and accepted that the environment of the pen dynamics can affect animal production. Therefore, adjusting for the pen effect of group raised animals is commonplace in genetic evaluations. Common environmental impacts are heat, humidity, and wind chill even within climate-controlled barns of livestock. We are also aware that some livestock bully other animals causing them to either not spend as much time at the feeder or perhaps change the time when they go to feed and water. Computer vision technology along with neural networks can identify these events that lead to a change in animal behavior.

Identifying animals that are able to excel in group pens in a host of varying environments versus a single highly controlled environment will pay dividends to selection of more robust animals.

Artificial Intelligence can also be utilized 24/7 within the commercial pens to identify precursors to events such as tail biting thus allowing the environment to be changed to reduce the risk of the adverse event or to identify and remove the bully pig from the environment.

Modern livestock production must produce more with less all while being environmental conscious, welfare friendly, and with more nutritious focus than ever before due to consumer preference/demand, government regulation, and because it is simply the right thing to do. Through the use of Artificial Intelligence to produce and analyze big data, animal breeders will be more equipped than ever to solve the challenges ahead of us.

Plenary 2

Public Acceptance of Animal Genomics and Biotechnology

Alison Van Eenennaam
University of California, Davis

Animal **biotechnology** is the application of recombinant DNA techniques to animals. Genetic engineering and cloning are two older forms of animal biotechnology (Thompson, 2020), and genome editing is a more recent entrant. Animal **genomics** is the scientific study of structure, function and interrelationships of both individual genes and the genome in its entirety. Utilization of genomic information in breeding is often referred to as genomic selection (GS). In my view these two fields – biotechnology and genomics - face entirely different public acceptance issues. In the following paper I review the literature associated with public acceptance of these two fields, and then discuss some of my own (perhaps controversial) thoughts regarding these topics based on my experience and observations.

Genetic Engineering

Genetic engineering (GE), sometimes less precisely referred to as genetic modification, has historically involved the introduction of a novel recombinant DNA (rDNA) transgene into the genome of an organism to give it a desired characteristic such as fast growth. GE animal applications are as diverse as the species involved, and each comes with its own specific set of risks, benefits, concerns and considerations. To date the vast majority of GE animals, primarily mice, rats, rabbits and pigs, have been developed for research purposes in private or university laboratory settings. A small number of applications have been successfully commercialized including GE animals as pets (GloFish®) and GE animals that produce pharmaceutical products in their milk or eggs. Despite the fact that arguments for or against GE crops are largely applicable to GE animals, with some modifications (Figure 1), only a single GE food animal, the fast-growing AquAdvantage salmon, has ever been sold to consumers, and even then, in only two countries, Canada and USA. This has been in part due to regulatory gridlock (Van Eenennaam and Muir, 2011), but also due to the politicization of issues associated with GE food.

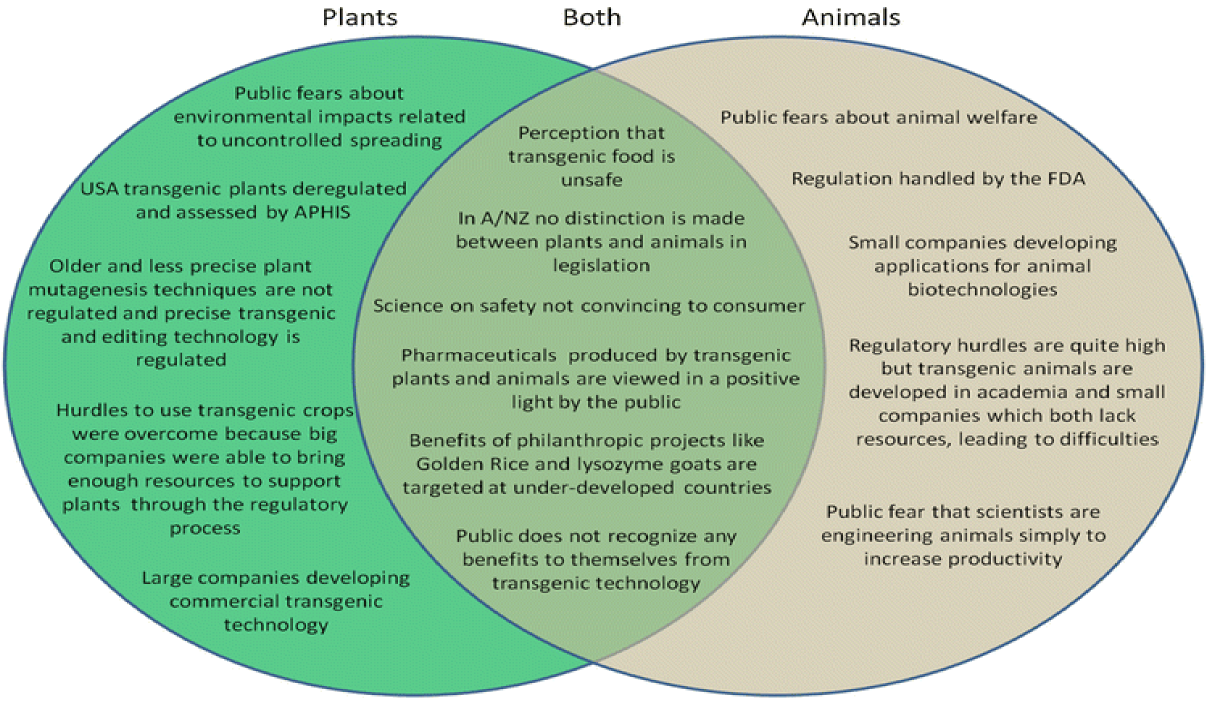

Figure 1. Public perception issues posed by plant and animal genetic engineering (Tizard et al., 2016).

Opposition to GE animals frequently goes hand in hand with opposition to research involving animals or even use of animals more generally, echoing fundamental disagreements about what our attitudes and behavior towards animals should be. Pets are considered as members of the family by many in modern society and this, coupled with the increased advocacy of animal rights and welfare groups, makes the topic of GE animals of particular interest to the mainstream public. Oftentimes, public attitudes regarding GE of animals are not specific to the use of GE per se, but rather are more generally around the production methods associated with intensive animal agriculture (Van Eenennaam and Young, 2018). Some traits generated through genetic engineering, such as faster growth, have also been spectacularly achieved through traditional selective breeding, in the absence of extensive public scrutiny or consultation. One global study reported that 62% of respondents did not approve of biotechnological applications focused on increasing farm animal productivity (Mora et al., 2012).

Activist organizations have been vocal in condeming GE animal applications starting with Jeremy Rifkin's infamous campaign against recombinant bovine somatotropin (rBST). Perhaps one of the best examples of the effect of anti-GE rallying of the public to halt a GE animal application is the case of the Enviropig. Scientists in Canada genetically engineered pigs that produced phytase in their saliva resulting in manure with reduced levels of phosphorus. This GE animal was intended to be an environmentally-friendly alternative to traditionally-bred animals as excessive phosphorus produced by swine facilities is known to contaminate groundwater and lead to algal growth, which in turn has negative effects on fish populations. Despite years of research and positive progress within the regulatory review system in the US and Canada in the late 2000s, anti-GE activists vigorously condemned the project as a "technofix" and an excuse to farm pigs more intensively. This caused the long-time funder of the project to withdraw their support. In the absence of other funding sources, the project was halted, withdrawn from regulatory review, and the animals were euthanized.

The case of the Enviropig highlights the intuitive appeal of opposition to GE. People often reject GE plants and animals based on disgust and absolute opposition to genetic engineering irrespective of any potential benefits that might be associated with the application. People who are genuinely concerned about the environment often reject GE applications that have been demonstrated to address environmental problems (Blancke et al., 2015). This outright rejection of GE is often associated with concern that it is unnatural and "violates species boundaries" or is equivocal to "playing God". It has been argued that these concerns are spurious from both scientific and ethical standpoints as species are not fixed nor unchanging, and that when we domesticated animals we effectively changed their genetics in an unnatural way as evoked by the term "artificial", as distinct from "natural", selection (Rollin, 2014).

The year 2020 marked 35 years since the first GE livestock were reported. To obtain FDA approval for the AquAdvantage salmon first reported in 1992 (Du et al., 1992), AquaBounty estimated it has spent $8.8 million on regulatory activities including $6.0 million in regulatory approval costs through approval in 2015, $1.6 million (and continuing) in legal fees in defense of the regulatory approval, $0.5 million in legal fees in defense of congressional actions, and $0.7 million in regulatory compliance costs (~$200,000/year for ongoing monitoring and reporting, including the testing of every batch of eggs), not to mention the $20 million spent on maintaining the fish while the regulatory process was ongoing from 1995 through 2015 (David Frank, AquaBounty; personal commmunication, January 2020). It is not obvious that any actual risk reduction benefit resulted from this incredibly expensive regulatory outlay. There are considerable opportunity costs associated with delaying the adoption of useful GE livestock applications in animal agriculture (Van Eenennaam et al., 2021). At this time genetic engineering is effectively absent, if not entirely verboden, from livestock genetic improvement programs globally.

Cloning

Cloning through embryo splitting has been used in livestock improvement programs since the early 1990s, however it was not until 1996 that researchers succeeded in cloning the first mammal from a mature (somatic) cell (SCNT) taken from an adult animal to produce the infamous Dolly. Many species have been cloned since then, and this technique is used by several companies that specialize in cloning farm animals (van der Berg et al., 2019). Both the FDA in 2008, and the European Food Safety Authority (EFSA) in 2012, concluded that products derived from animal clones are not different from those of non-cloned animals. In North America, South America and New Zealand, cloning for agricultural purposes is not restricted (Table 1). However, in the European Union (EU), food derived from animal clones falls under the 'Novel Foods Regulation' as food derived from animals obtained by non-traditional breeding practices. Current regulation in the EU has placed a ban on food products from animal clones, given, amongst others ethical considerations regarding animal welfare. This ban does not cover products from their progeny, which are considered to be indistinguishable from traditionally bred livestock (van der Berg et al., 2019). Currently no company in Europe is contemplating bringing products derived from animal clones, or their offspring, to market (Galli and Lazzari, 2021). A Supply Chain Management Program to identify cloned livestock in the US was set up by Viagen and Trans Ova companies in 2007. According to them, although the program was run from 2008 until 2012, no other cloning companies showed interest in participating in the program, and it was never accessed by industry. It is unclear how cloned animals produced in countries that allow cloning are kept out of products exported to the EU.

The literature around public perception of cloning is mostly from the early 2000s, in the years immediately following the arrival of Dolly. In a 2005 International Food Information Council survey of the US public regarding the cloning of animals, 74% were not in favor, 15% were in favor, with the remaining respondents unsure. In a follow-up question, respondents were asked how likely they were to buy food products from cloned animals if the Food and Drug Administration (FDA) decided that they were safe to eat. Two-thirds (64%) stated that they were unlikely to buy such products, and one-third (34%) said that they would be likely to do so. In that same year, a Eurobarometer Survey on Social Values, Science and Technology found that found 31% of respondents would never approve of cloning animals, 22% only in exceptional circumstances, 35% only if it was highly regulated and control, 8% were supportive in all circumstances, with 2% undecided.

Genome Editing

Genome editing is a relatively new player in the animal biotechnology field, having been around since the early 2000s (Bishop and Van Eenennaam, 2020). Genome editing involves the use of molecular 'scissors' to introduce changes into existing DNA, as opposed to classical GE which often involved moving genes from one species to another. Genome editing also enables a much wider-range of changes, for example, gene knock-outs, base pair substitutions, targeted insertion/deletion of larger genomic regions, and modulation of gene expression. Genome editing may produce changes that are not known to exist naturally in that species. But if these could reasonably have occurred naturally, even if they remained unrecognized by livestock breeders, it could be argued that these changes are also 'natural' (Bruce, 2017). The regulatory picture for this technology is mixed (Table 1). In the EU, New Zealand and the US, it is being treated as equivalent to GE, whereas in other jurisdictions if no foreign DNA is introduced (i.e. knockout, base pair or intraspecies allele substitution) the resulting animals are being regulated in the same way as those resulting from conventional breeding. I, and other scientists https://www.gopetition.com/petitions/harmonize-us-gene-edited-food-regulations.html, consider that the proposed US regulatory approach for animals is not fit-for purpose (Van Eenennaam et al., 2019).

Table 1. Regulation of animal cloning, transgenesis and genome editing in livestock in selected countries Modified from van der Berg et al. (2020).

Country	Animal cloning	Transgenic livestock	Gene-edited livestock
EU member states	Prohibited, until specific regulations on animal cloning are in place	Requires approval according to EU Directive 2001/18/EC and Regulation (EC) No. 1829/2003, safety assessment performed by EFSA GMO Panel	Requires approval according to EU Directive 2001/18/EC and Regulation (EC) No. 1829/2003, safety assessment performed by EFSA GMO Panel
USA	Allowed, a risk management plan and guidance for industry have been issued by the FDA	Requires approval according to Federal FD&C Act, regulations for new animal drugs as stated in 2009 FDA Guidance for industry #187 (Draft guidance) and NEPA	Requires approval according to Federal FD&C Act, regulations for new animal drugs as stated in 2017 FDA Guidance for industry #187 (Draft guidance) and NEPA
Canada	Allowed, food products of cloned animals and clone progeny are considered "novel foods" and require pre-market safety assessments according to the regulations in Division 28, Part B, of the Food and Drug Regulations (Novel Foods)	Requires approval according to the Canadian Environmental Protection Act, 1999, the New Substances Notification Regulations (Organisms) and Food and Drugs Act	No specific policy on gene editing, may be considered "novel" and require case-by-case safety assessment by Health Canada
Argentina	Allowed	Requires approval according to animal biotechnology regulation, case-by-case assessment by CONABIA	Requires approval according to animal biotechnology regulation, case-by-case assessment by CONABIA
Brazil	Allowed, commercial animal cloning mostly in partnership with EMBRAPA, registration of cloned cattle at ABCZ	Requires approval according to animal biotechnology regulation, case-by-case assessment by CTNBio	Requires approval according to animal biotechnology regulation, case-by-case assessment by CTNBio, gene-edited animals lacking recombinant DNA are regarded non-GM according to

			Normative Resolution #16
Australia	Allowed, generally in confined research environment	Requires approval according to Gene Technology Act 2000, by OGTR	Requires approval according to Gene Technology Act 2000, by OGTR, gene editing techniques that do not introduce new genetic material are not regulated as GMOs
Uruguay	No specific legislation on animal cloning, animal biotechnology performed in research institutes such as Institut Pasteur in Montevideo and the Animal Reproduction Institute of Uruguay	No specific legislation on animal biotechnology, environmental release of GMOs and biosecurity is subject to prior authorization by competent authorities, as stated in article 23 of law No. 17283 on the protection of the environment	No specific legislation on gene editing in animals, during a meeting of the CAS the minister of agriculture signed a declaration in favor of gene editing. Gene-edited animals may be subject to prior authorization according to law No. 17283

Note: EFSA, European Food Safety Authority; FD&C Act, Food, Drug and Cosmetic Act; NEPA, National Environmental Policy Act; FDA, Food and Drug Administration; CONABIA, National Advisory Commission on Agricultural Biotechnology; EMBRAPA, Brazilian Agriculture and Livestock Research Enterprise; ABCZ, Brazilian Zebu Cattle Association; CTNBio, National Technical Biosafety Commission; OGTR, Office of the Gene Technology Regulator; CAS, Southern Agricultural Council.

Genome editing in animals is likely to receive a range of public acceptance responses depending upon the application (Bruce, 2016). The lead application at the current time is a knockout pig that is resistant to porcine reproductive and respiratory syndrome (PRRS) virus. In general attitudes are likely to be influenced by the particular reason given for the application, how beneficial or risky it is considered to be, and specific context of application and the alternatives available. Bruce (2017) argues "*Public support for genome edited livestock is essential for the promised products to gain wide market penetration. Frivolous, or controversial applications raising public disquiet have the potential to make it very difficult for future genome edited livestock applications to be socially accepted*."

On January 18, 2017, the U.S. Food and Drug Administration released for public comment their Draft Guidance 187 on the Regulation of Intentionally Altered Genomic DNA in Animals. The draft guidance recommends that genome edited animals should be regulated in a manner similar to that used by the agency to regulate GM animals. Although this was followed by a public comment period, the FDA has yet to respond to any of these comments. This decision by the FDA to regulate genome edited animals – or more correctly the intentional alterations in the genome of animals - as new animal drugs irrespective of product risk was done in the absence of public discourse. Similarly, the decision by the European Court of Justice that these genome edited organisms were to be considered as subject to the full range of testing and regulation according to the EC Directive, as if they were transgenic, but that the early untested products of random mutagenesis were de facto considered to have been immune from such risks was made without an engagement with publics. The decision by the European Court of Justice effectively side-stepped any processes of wider societal engagement (Bruce and Bruce, 2019). These authors wrote, "*Regulation sets bounds to what can be done, who can do it and under what conditions can things be done. But if there has been no discussion with the public, this could be argued to be a case where regulation has been socially premature, and not done on behalf of the society*."

While a highly precautionary regulatory approach may be of little consequence in food-secure developed regions like North America and the EU, such an approach is likely to hinder the adoption of animal biotechnology in some developing regions that could most benefit from targeted applications such as disease-resistant livestock. In Africa, 60% of all citizens are still farmers and they are not highly productive. Yet the debates around GE crops have been dominated by a few elite scientists or largely international NGOs leading to a polarization that by-passes those most directly affected by decisions. For resource-poor Africa, responding to the promises and challenges of animal biotechnology is likely to be complex, not least because most lack the capacity for regulatory oversight. Hopefully these countries can adopt a risk-based and product-focused approach. Evidence from Mora et al. (2012) suggested that if geographic differences are considered, consumers' acceptance is higher in developing countries where the requirement for enhanced food production might be met by application of this technology.

In wealthy countries where food security is not a priority, consumer acceptance of genome edited animals is expected to be lower, especially for those applications offering economic advantages mainly to the livestock producer. Bruce and Bruce (2019) considered two examples of genome editing in livestock; hornless cattle and disease resistant pigs, from the perspective of Responsible Research and Innovation (RRI). They suggested that the knowledge gap of publics of current practices in livestock agriculture, could lead to unexpected outcomes from public consultations. For example, if an argument is made regarding genome editing to introduce the polled allele is the advantage of polled cattle, this might not be immediately obvious to those not versed in agricultural practice, and more generally "the need for dehorning may be considered shocking by some publics" (Bruce and Bruce, 2019). Applications for reduced antibiotic use, greenhouse gas emissions, and reduced possibility of transmitting zoonotic diseases were all deemed acceptable in a consultation performed by the UK Royal Society (Van Mil et al., 2017). Although it should be noted that a major pre-occupation of these participants was to ensure genome editing was used to address inequality. The participants were particularly concerned about who owns the technology, who gets rich from its use, and whether it could be used to unfairly obtain monopoly power. This raises interesting questions regarding the fit-for-purpose of the regulatory approaches that have been proposed in the US and EU which advantage large companies and incentivize intellectual property (IP) protection. Meeting the requirements of IP regimes allied to genome edited animals may prove to be disruptive to the breeding industry (Bruce, 2017).

Genomic Selection

Genomic selection was first implemented in the dairy industry in 2009, following the sequencing of the bovine genome. Based on tools to better assess the inheritance of naturally occurring genetic variation, implementation of this technology required no regulatory review or approval, and it was rapidly adopted by global dairy breeders. Other livestock industries soon followed (Van Eenennaam et al., 2014). And although its implementation has been associated with some concerns regarding increased rates of inbreeding (Misztal et al., 2021), I am unaware of a targeted campaign to prohibit or limit the use of this technology. A non-scientific google search of "opposition to genomic selection" returned only academic literature. Genomic technologies currently have no regulatory requirements for labelling or other identification or acknowledgement of use of this technology in the production of food, whether plant or animal.

Coles et al. (2015) noted that there are few studies carried out on stakeholder attitudes regarding the application of genomics that do not involve genetic modification to animal production in the human food chain. These authors considered the range of ethical issues and potential stakeholder priorities associated with the application of genomic technologies applied to animal production systems, in particular those which utilized genomic technologies in accelerated breeding. They reported that genomics, because it avoids many of the disadvantages and consumer perceptions associated with GM, is likely to prove a more publicly acceptable route than is GM for the development of healthier and more productive animals. They did caution that the use of GS should be communicated to the consumers if "*the process involved any form of disenhancement* [i.e. removing something from an animal] *or other animal welfare issue or indeed results in the use of any practices or processes that might be damaging to the environment such as increased use of pesticides, hormones, non-veterinary use of antibiotics, or other pharmaceutical products, or to the genetic diversity of domesticated animals*."

A recent paper looked at the uncertainties associated with GS in forestry (Blue and Davidson, 2021). They interviewed a group of forest research professionals working in this field in Canada, and noted that the respondents. The wrote "*public acceptance of technology was identified as a key site of uncertainty that needs to be addressed and managed by those developing genomic technologies. Although public engagement was deemed important, we encountered repeated emphasis on the need to educate and inform the public to align with scientific views, and for most respondents, these objectives appeared to merge. Many qualified their enthusiasm for public engagement with concerns that lay publics do not know enough about GS to participate in its development and governance. Most respondents expressed concern about the capacity of lay publics to distinguish genomic selection from genetic engineering. Even those who acknowledged that public responses to emerging technologies are varied assumed that public rejection of genetic engineering is rooted in emotion and financial interests rather than reason, and thus reactions to GS would likely be the same.*" These authors criticized the forest research professionals for relying on assumptions and in some cases stereotypes to inform their understanding of public perception, saying "*that only one person referenced published research, and only a few provided actual details to substantiate claims"* regarding public perception.

These authors further argued that "*failure on the part of scientists and decision-makers to communicate uncertainties can cause problems. Notably, the prevalence of statistical, risk-based approaches to the uncertainties associated with genetically modified crops in* *agriculture and forestry in the 1990s provoked public alienation and fomented controversy*". They concluded with a recommendation that "*we call for acknowledgment and communication of the range of uncertainties that pervade all biotechnology research efforts, particularly those that are promoted as potential adaptation measures for climate change. Scientists should be upfront about the limitations of knowledge with due humility, without assuming that all uncertainties could or should be presented mathematically and statistically. In turn, scientists and decision-makers need to be cognizant that the potential responses of various publics to emerging technologies are uncertain, much in the same way that the effects of implementation of new technologies are unknown from the outset. This acknowledgment of uncertainty about existing states of public knowledge can enable a more flexible and adaptive relationship between science and its varied publics. In turn, engaging social scientists in assessing and communicating uncertainty can broaden the scope of issues and values for public discussion."*

My thoughts

There exists a considerable literature castigating "scientists" (typically meaning research professionals and bench practitioners) for poor communication with the public on the topic of genetic engineering and cloning, and more recently genome editing and GS. The contention seems to be that this failure to communicate uncertainty is what historically "*provoked public alienation and fomented controversy"* around these technologies, and that this will likely cause problems for genome editing and GS. I beg to differ. Unless these later two topics become politicized, or perhaps more importantly competing business interests develop an approach to monetize fear around these technologies by inflating public perceptions of risks and arousing opposition in an attempt to trigger a spiral of silence (Scheufele, 2014), they will be integrated into livestock breeding programs largely without public scrutiny in the same way as other breeding advancements have been. Artificial insemination has not been recently communicated to the public, and yet its use is routine. However, if they become targeted, both bench and social scientists will have a hard time being heard above the drone of misinformation on social media where science and politics are inextricably linked, similar to what we observed with communications around uncertainties and relative risks associated with COVID vaccines and treatments.

I use the following evidence and observations to support these assertions. There is no money to be made opposing GS. There is no "Non-GS Project" label. There are no large multinational companies controlling its use that can be used as a proxy for evil (e.g. Monsanto). I do not foresee a targeted campaign to preclude the use of GS in genetic improvement programs, in part because it is founded on naturally-occurring genetic variations, and in part because it is hard to problematize into a clean, dichotomous framing i.e. genomic bulls are "bad", and conventionally-selected bulls are "good". And while many of the same criticisms leveled against GE and cloning can be equally associated with GS (e.g. increasing the rates of inbreeding), these concerns are likewise associated with conventional selection programs. Artificial insemination reduces genetic diversity, and conventional selection programs include traits like docility which could be considered a behavioral disenhancement. Layers are selected to not exhibit broody behavior. I am unaware of any campaigns to preclude the incorporation of temperament traits into breeding goals for ethical reasons, despite the fact this clearly alters the telos of the animal. Additionally, there are glaring disparities when it comes to the implementation of GS in the developing world, and even in small breeds; it is expensive to develop large populations of genotyped, phenotyped animals. It is not a scale-neutral technology, advantaging large breeds and genetic providers over small ones. Such inequality concerns would be problematic for a GE application, yet these concerns are rarely even discussed as it relates to GS, and they have not precluded the adoption of this technology.

Genomic selection is not a perfect science, there are uncertainties and emerging issues (Misztal et al., 2021), but it is the most accurate tool we have to select the future performance of the offspring of an individual. The absence of an additional regulatory layer to the use of genomic testing has allowed the unfettered, uncontested and rapid adoption of GS in livestock breeding programs globally.

Cloning is clearly unnatural, well at least SCNT is unnatural in that it takes place in a laboratory. Cloning is actually rather common in nature, as evidenced by identical twins. Cloning elite animals has no obvious benefit to the consumer, and really is not that useful in breeding programs as it replicates the current generation rather than the next generation. It has had limited application in serving as a genetic insurance policy, and at times enabling the production of elite sires using less resources (Kasinathan et al., 2015). By these metrics it would appear cloning is destined for market failure. And it has been effectively banned in the EU. In the Netherlands, the Dutch Animal Health and Welfare Act and Animal Biotechnology Decree prohibited the application of biotechnology to animals without a specific license. Criteria for being given a license included: the goal serves a public interest, has no unacceptable impacts on health and welfare of animals and does not raise any overriding ethical objections. It is characterized as a 'No Unless' policy – no application of biotechnology to animals unless there is a very good reason for doing so. Since 2005, Denmark has required special licensing for animal biotechnology through the Act on Cloning and Genetic Modification of Animals. This legislation came about in large part due to ethical concerns surrounding the impact of biotechnological applications on animal integrity. This Act effectively limits the commercial use of animal cloning and genetic engineering to "creating and breeding animals producing substances essentially benefitting health and the environment". However, in countries where it is allowed (Table 1), opposition to cloning has slowly faded, and it is being adopted where it is cost-effective – mostly in high-value recreational animals like bucking bulls and polo ponies.

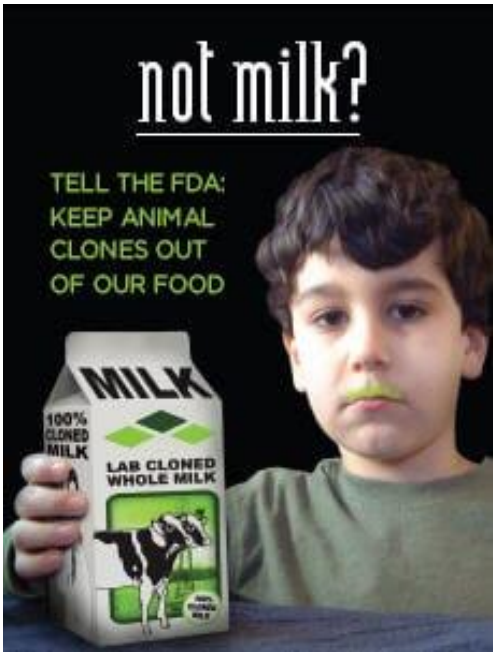

Figure 2. The Center for Food Safety depiction of cloned milk from their 2007 campaign against animal clones.

I would argue in countries where clones are not regulated differently to conventional breeding, and products from clones are not labeled as they are in fact impossible to differentiate from products from non-cloned animals – (despite the apparent green milk moustache in Figure 2!), there has been no way to effectively monetize fear around clones. The Center for Food Safety, Consumers Union, Food and Water Watch, The Humane Society of the United States, the American Anti-Vivisection Society, the Consumer Federation of America and the Organic Consumers Association tried hard in the early days of cloning, but at the end of the day it is hard to create a convincing argument that a cloned product is somehow more dangerous than its identical progenitor. And in the absence of tracking or labelling requirements, it was just not possible to create a cost-effective "absence-labelling" campaign as was done with rBST and GMOs. It is worth noting that a lucrative pet cloning industry has emerged in the absence of regulatory oversight of non-food applications of cloning. In fact, Barbara Streisand recently took on two puppies cloned from her dead dog for the fee of $50,000. If there is a direct benefit, at least in the mind of the person cloning their pet dog or bucking bull, then people are willing to overcome their hesitations regarding cloning. And as to the entry of these clones into the food supply, it is mostly a moot point. Undoubtedly products from cloned livestock – elite breeding stock at the end of their productive life, and even bucking bulls at the end of their bucking career have entered the food supply on a limited scale. And considering that the US exported 190 million dollars' worth of bovine semen in 2018, it is more than likely that there are offspring of clones running around globally.

And so we come to genome editing, the new kid on the block. And its fate is currently uncertain. Public perception is still forming around this technology, but I have a sinking feeling that genome editing will suffer the same fate as GE animals for the following reasons. Firstly, competing market forces have already started to conflate the two technologies. The Non-GMO project has come out with the following announcement "*GMOs are now being created with newer genetic engineering techniques, some of which do not involve transgenic technologies. The Non-GMO Project is committed to preventing these new GMOs from entering the non-GMO supply chain*." The National Organic Standards Board voted to exclude all genetic modification and manipulation from organic production in 2016, including genome editing. And Greenpeace in their 2021 position paper entitled "Danger Ahead. Why genome editing is not the answer to the EU's environmental challenges", *warns that the use of so-called gene (or genome) editing techniques like CRISPR-Cas could not only exacerbate the negative effects of industrial farming on nature, animals and people, but it could effectively turn both nature and ourselves (through the food we eat) into a gigantic genetic engineering experiment with unknown, potentially irrevocable outcomes.*" And so we again have a situation where activist groups and the natural and organic food industry will monetize fear and run a campaign of misinformation to suggest that genome edited animals are "unsafe", whilst animals with naturally occurring genetic variants are "pure" (and also more expensive!).

Secondly, irrespective of the nature of the genome edit, the proposed regulatory approach to genome edited animals is the same as for GE animals, in both the EU and the United States. Even SNPs and deletions are being treated as drugs in the US. The absence of one intentionally altered base pair among 3 billion in the bovine genome thus results in an unsaleable new animal drug. By capitulating to this regulatory logic and tacitly agreeing that the emperor is wearing clothes, we replicate the situation where only large companies will be able to afford the regulatory and IP costs of bringing a genome edited animal product to market. Hitherto, the IP in livestock breeding has been primarily protected by secrecy and use of cross-breeding (Bruce, 2017). Small companies and academic laboratories will be unable to make use of a technology that originally resulted from public research funds. They will again be relegated to the side lines, unable to afford even experimental work in large animals as all milk, meat and eggs from all genome edited "investigational animals" are unsaleable, and the animals themselves have to be composted, buried, or incinerated. There is then little incentive for public sector scientists to stick their neck out doing public communication around a technology they cannot use. Especially when doing so will likely result in hostile freedom-of-information act requests, and reputational defamation by front groups financed by the natural and organic food industry such as U.S. Right To Know (Kloor, 2015).

At the end of the day, I am not convinced widespread public opposition is what is preventing the adoption of new animal biotechnologies. The prevailing narrative repeated verbatim is that the public outright rejects GMOs. But that is not observed in actual purchasing behavior when GMO products are available. For example, GloFish® (Figure 3) are marketed to aquarists in the US, where they are now sold in every state in the nation, as well as throughout Canada. Sales represent approximately 15% of US aquarium fish sales. Although some authors raised early environmental and ethical concerns about GloFish (Rao, 2005), these concerns have waned over time. GloFish is subject to enforcement discretion in the US. This is not a determination of "safety" under the Federal Food, Drug, and Cosmetic Act but is instead a determination that, based on risk, FDA does not believe it would be a good use of its limited resources to act against sponsors for the marketing and distribution of these unapproved products. Its sale is prohibited in other jurisdictions, including Europe, Australia, and Singapore. The success of this product suggests that consumers are willing to purchase GE animals, at least as aquarium pets. Alan Blake, CEO of the company marketing GloFish, wrote regarding public acceptance that consumers will purchase a product that they desire, irrespective of the breeding method that was used to produce it. In his words, "*It is not about the process* [of genetic engineering], *it is about the product*" (Blake, 2016).

Figure 3. There is a total of four species of transgenic fluorescent GloFish® available in six colors.

Similarly, the Impossible Burger, a soy-based food product is proudly GMO with it recombinantly produced, bleeding leghemoglobin, has been a market success. Ironically the same anti-GMO groups that targeted GE in agriculture; GMO Watch, Consumer Reports, and the Center for Food Safety, went after Impossible Burger for using GMO heme and soy. They perpetuated the same fearmongering around GMO in Impossible Burgers as they had used around GMO in corn - claiming it hurt rats in a feeding study. And Impossible Food fought back, Rachel Conrad, Chief Communications officer wrote, "*Finally, we'd like to request that Consumer Reports disclose its anti-GMO agenda in full transparency, and the biases of its activist employees. For years Consumers Reports, and fellow anti-GMO ideologues have been waging a PR war against GMOs — whether in vaccines, insulin, cheese or more recently the Impossible Burger*." And likewise, the PinkGlow GE pineapple that contains lycopene, a pigment that gives some produce its red color has been success, fetching a premium of as high as $50 per pineapple.

These GE applications might be considered frivolous, after all we can live without fluorescent aquarium fish and pink pineapples. But they are market successes because 1) they were allowed to come to market, and 2) they are products that the customer wanted with at least a perceived benefit. One thing is for sure – if products are not commercially available because it is cost-prohibitive, or even impossible to get regulatory approval, then the public will not be able to indicate their acceptance by purchasing them. That has essentially been the situation for GE food animals for the past 35 years. And for GE food in Europe more generally, although there is of course a glaring incongruity there. In 2018 alone, the EU imported more than 30 million metric tons (MT) of soybean products, 10 to 15 million MT of corn products, and 2.5 to 4.5 million MT of rapeseed products, mainly for livestock feed. The EU's main suppliers are Argentina, Brazil and the United States. The share of GE products of total imports is estimated at 90-95 percent for soybean products, 20-25 percent for corn, and less than 20 percent for rapeseed (USDA Foreign Agricultural Service, 2018), suggesting GMOs are a resounding market success!

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Provocateur's Responses

Public Acceptance of Animal Genomics and Biotechnology.

Elena Rice
Genus PLC.

1. Breeding overall.

Today, public lacks basic knowledge about breeding, which is a huge challenge for Animal Ag today. Recently, we conducted research with a group of Food eVangelists, people who eat chicken, pork, and beef at least occasionally, do not feel extremely positively or negatively about traditional agriculture, aged 18-64, and influence others about food and agriculture. The research shows that even Food eVangelists, who tend to be more knowledgeable about food production, are confused about animal agriculture. While 53% responded that they are highly knowledgeable about the science and technology behind food production, only 40-60% could correctly identify technologies that are in use today: genomic selection, artificial insemination, semen sorting, big data, and artificial intelligence. And only 20-30% correctly answered about the current use of cloning, genetic modification, and gene editing. It is difficult to expect the public to think positively about new technologies when they are mostly unaware of science and technologies that have been successfully used for many years and brought significant benefits to animal productivity, health, taste, well-fare. This lack of knowledge is a huge challenge. It allows for technologies to be demonized and could threaten animal agriculture in general.

2. Gene Editing.

The situation we see today with Gene Editing is quite different from where GMO was several years ago. There is a strong movement from academia, industries including crops, animal, and human applications. Many countries are developing reasonable approaches to the regulation of gene editing. And, what is more important, we started to see a shift in consumers' sentiments. Despite skepticism of individual methods, a majority feel positive or neutral about "new breeding methods". In our research, 81% of participants felt neutral or comfortable eating pork with a gene-edited heritage after being exposed to detailed information about gene editing and the explanation that the heritage is produced through conventional breeding. These animals will enter the food system just as any other animals will, through traditional breeding. One-fifth of participants said COVID-19 has made them feel more positively towards the idea of gene editing for at least disease-resistant traits. Importantly, approval from gov't organizations, followed by safety and testing is seen as the most significant factor to increase acceptance of the technology such as Gene editing. Consumers also see some benefits as more ethical and acceptable than others – public health, animal health, and planet health are top of their concern.

3. Path forward.

As we think about the path forward, there are three takeaways:

- **Lean into the benefits.** As retailers and processors receive pressure on what products make it to consumers' plates, we need to be open to more dialogue about public health, animal health, and planet health benefits that come with the use of technology. There is category acceptance when speaking about benefits of breeding animals versus the technology itself. We must lean into the "why" if we want to make progress. If these technologies are dismissed, they remove huge solutions for improving the sustainability of our food system and meeting the food industry's stated goals.
- **Responsible use of technology.** We are transparent and clearly show the rigorous safety testing and ethical commitments we live by when using technology. Genus has

adopted a series of ethical commitments to guide our use of new breeding approaches. These commitments range from transparency, regulatory compliance, focus on disease, environmental stewardship, and monitoring for unintended consequences. We are not using technology for entertainment or to harm animals.

- **Accessibility of technology.** We are focused on making new technology solutions available to farmers of all sizes.

Today, we need to do the right things if we want gene editing in animals to have a real opportunity to thrive:

1. We need to engage diligently with regulators to build trust and avoid trade interruption.
2. We need to be diligent in ensuring we do the science to incredibly high standards. For instance, we go to great lengths to validate we get precisely the edit we want and only that edit without untended consequences.
3. It is important to explain that the animals that come to the market for meat and milk would not be gene-edited. Instead, we need to lean into the idea of a 'gene-edited heritage' to bring to life that their ancestor/great great grandparent was the animal that had the gene-edited trait, and they have inherited it through the traditional breeding process. Right now, we have an opportunity window, but the window can close faster than we can act on it.

4. What can go wrong?

Almost everything. While the current regulatory process in the US is not fit for its purpose, it does not stop the approval of gene-editing animals. However, the time it currently takes to achieve approval status is long and expansive. Without changes, it will prevent small start-ups and academia from engaging.

Other countries (e.g. Japan, China) will take the lead, and the US will fall behind with developing innovation for animal ag. As a result, scientific progress will derail, scientists will choose other areas to engage where opportunities are growing and easier to implement.

If unintended modifications are identified post-approval, it will close the door for subsequent product approval. I have no doubt there will be numerous studies done in an attempt to "uncover" unintended changes, and many "findings" will be misleading.

The competing interests (organic foods, sustainability of animal ag, etc) can influence public opinion, especially in a vacuum of positive, science-based information. Retailers will refuse to sell products containing gene-edited heritage.

The trade will be disrupted without a coordinated global regulatory framework, making gene-editing products not profitable from producers' perspectives.

Companies will stop investing in gene-editing technologies if the products fail to be successful on the market.

We have an opportunity to join all our forces and align on the best path forward. If we don't, everything can go wrong.

Public acceptance of animal genomics and biotechnology – who is going to eat ChickieNobs?

Graham Plastow
University of Alberta

"This is the latest," said Crake.

What they were looking at was a large bulblike object that seemed to be covered with stippled whitish-yellow skin. Out of it came twenty thick fleshy tubes, and at the end of each tube another bulb was growing.

"What the hell is it?" said Jimmy.

"Those are chickens," said Crake. "Chicken parts. Just the breasts, on this one. They've got ones that specialize in drumsticks too, twelve to a growth unit."

"But there aren't any heads," said Jimmy. He grasped the concept – he'd grown up with sus multiorganifer, after all – but this thing was going too far. At least the pigoons of his childhood hadn't lacked heads.

"That's the head in the middle," said the woman. "There's a mouth opening at the top, they dump nutrients in there. No eyes or beak or anything, they don't need those."

Margaret Attwood, "Oryx and Crake" p202, 2003 McClelland & Stewart Ltd. Toronto.

From the late 80s to the mid 90s I was part of a large multinational agri-food company spanning everything from seeds to branded food products. My role was to identify where biotechnology could impact our businesses. I looked at where gene cloning or genetic modification (GM) could improve existing processes or create new products, worked with researchers creating transgenic plants, visited plant biotechnology companies in Europe and the US, and sat on committees trying to decide how to introduce genetically modified products to the UK. These included farmer groups, ingredient manufacturers and grocery retailers. I should also say that before this I had been part of a project looking to use GM to introduce novel variation into pig populations. I closed that project down at the beginning of the period I am describing (late 80s and mid 90s). However, all of these groups were trying to ensure the technology remained available for research and indeed product development. After all we had seen food irradiation confined to the dustbin as a far as mainstream food use was concerned. We set about providing workshops and training materials for our own staff (25,000) to learn about the technology and its benefits as well as taking the message to producer meetings. The first GM food was on the shelves of UK supermarkets labelled as such and it sold out. That was unfortunately over in the blink of an eyelid when our "slow and steady" approach to building support was derailed by investments that needed a faster return. Labelling did not work for commodities, or so those spearheading the GM revolution said, their ubiquity meant that producers and consumers would have no choice but to accept them. GM soya marched on, but not without creating a push back that we still see today – think of Golden Rice and the time for AquaAdvantage (GM) salmon to find its way onto N. American shelves. Unfortunately, I do not think the lessons we learnt from Flavr Savr (GM) tomatoes and Roundup Ready (GM) soya have been understood as we try to embrace the potential of gene-editing.

Animal applications have been more limited and have faced many obstacles set out for us by our plenary speaker. To briefly comment on two of the examples, which began in Canada: Enviropig – "A Bioengineered Pig That Excretes Fewer Pollutants" and AquaAdvantage salmon "Pioneering the Future of Seafood". Why did Enviropig fail? Undoubtedly for a number of the reasons identified but also because there are non-GM animal alternatives – the

ick-factor of engineering an animal is not required for the proposed benefit, and in my view it was a technology first approach – it seemed like a great idea but was not tested with the public. In the case of AquaBounty's salmon it still seems it is being sold without any labelling. If the product is so great – fresh, safe, environmentally friendly or "Always Free of Antibiotics and Other Contaminants", "bringing Atlantic salmon closer to seafoodies throughout the U.S. and Canada, without the high carbon footprint" and "helping save the planet" - then I would be shouting the benefits from the rooftops especially when supplies are sold-out. Would I still have a job, perhaps not with such an approach? However, I would be providing consumers with a choice to determine if the advantages worked for them.
Taking the opportunity to star gaze then I would start by asking what will a liveable future look like? For me it includes animals, both as companions and as part of sustaining a healthy planet and healthy humans. As we look at Grand Challenges of global warming, antimicrobial resistance, and pandemics of animal origin how is it possible to consider that as a viable future? Especially as we can easily lose out to those providing conspiracy theories at our fingertips. Well, as you would expect, I am optimistic about the role of technology to address some of these challenges, although not necessarily about the ability of democracy to survive in the face of a torrent of social media disinformation. These futures for animal agriculture, may or may not include gene-editing, but they will see an evolution of how we go about providing high quality nutrition to everyone across the world. To do this we will need to do much more than focus on cost of production, most importantly we will need to listen to what the public is saying about a wide range of topics from animal welfare, sustainability, waste, poverty, and all of the other things included in the UN's Sustainable Development Goals. We will need to find the places where our values are shared by the people we aim to serve and to stay there even when it apparently slows down our definition of progress. There will be no place for "shell games" or sleight of hand, as once the high ground is lost then so are all the potential benefits that could accrue from a technology.

The opportunities for new technologies in animal genetics and breeding are not derived from the precision of the technology, the nutritional equivalence of the products, or whether such products can be distinguished from conventional products. They come from the benefits they bring to consumers and why scientists and businesses want to provide them. Shared value takes into account a broader set of societal needs and not just economics. Taking this approach can help companies to look at potential problems that will create barriers or "hidden" costs for taking technologies to market. Giving consumers the choice to determine how they benefit from these opportunities can help create markets rather than approaches that push technology first and create hurdles and objections and make regulators nervous. Making those connections with consumers is very powerful and I regularly use the really excellent examples from our speaker to help teach students how to do this successfully. These are all part of (re)building societal acceptance for food animals in the future. Unfortunately, I continue to see defensive attitudes in the breeding industry even about revealing current tools and procedures. They see the importance of engaging with publics to try to gain social license for new technologies but would prefer not to open the barn door on technologies they rely on, such as genomic selection or advanced artificial reproduction. They need to be committed to this process, as breeders they should know better than anyone that an animal cannot be "half-pregnant". We should also choose the models and exemplars very carefully. Using gene editing to remove the need to dehorn dairy cows may sound like a winner in terms of improving animal welfare and demonstrating shared values around caring for animals. However, it looks like another Enviropig to me. One of the arguments goes along these lines, we cannot introduce the polled gene from other breeds as consumers will not want to pay more for their milk. Yet, I would argue that consumers already think that dairy cows are "tortured monstrosities" who suffer from their skeletal appearance and huge udders etc. Using another icky-lab technology to solve the problem does not sound animal friendly to those consumers. As an aside, Meriam Webster says "any monstrosities born to the farm animals were sent to the agricultural college for study".

Hopefully there will be many futures with different approaches to these challenges with each finding their own markets whether they are plant-based milks, "*in vitro*" meat, or other successful alternatives. These will include those providing "circular food systems" where man and animals combine successfully together to nourish humans across the world and simultaneously reduce the footprint left behind. These options will be different for different geographies and needs. Perhaps we should look much more widely, and beyond just our own disciplines, to explore some of these futures, after all many are already described as "science fictions" from ChickieNobs, pigoons, wolvogs and other Attwood creations to GloFish and the like -

> *"The display that had caught their attention was of genetically moulded pets. […] the bushbaby's colour almost exactly matched the hair of the one in the radio-dresslet."* John Brunner, "*Stand on Zanzibar"* p48, 1968 Doubleday & Company, Garden City, NY

- and perhaps some of them may also suggest other solutions to the challenges we face. As an aside the Scanalyzer in Brunner's novel is an all pervasive chopped up flow of information that is used to manipulate its users.

Goals may be much more about utilisation of non-human feedstuffs and how animals are raised including all aspects of their welfare especially affective states. Consumers will demand that livestock have a life worth living and that an increasing proportion should have a good life (as suggested by the UK Farm Animal Welfare Council in 2009). Some of the needs may be different in the developing world (we will hear later), where providing sufficient high quality protein may well require different approaches. This could include making better use of the genetic resources *in situ* rather than those developed by international breeding companies. In all cases collecting and using phenotypic data to make better selection decisions for the production system will continue to increase in importance. Indeed, this may be the most exciting frontier for animal genetics and genomics rather than creating new variation via gene editing. I can imagine a future where the convenience of fast food will be increasingly satisfied by plant-based options and that animal protein returns to the high days and holidays as it was 60 years ago (at least where I grew up). We will all need to join together to find better and different ways forward if we are going to address our Grand Challenges and at the same time build the trust required for them to be applied and adopted in the world's array of futures.

Plenary 3

Alternative proteins and high-tech frontier food

Kate Krueger with Thea Burke
Helikon Consulting

It's amazing that only seven years ago, the field of high-tech food was mostly contained to a handful of people with a dream - the dream of applying the world of biotechnology to comestibles and other traditionally derived materials. The idea of making foods using cell culture, custom-bred insects, CRISPR technology in animal husbandry, or even making foods from cell culture, was considered crazy at best. Now, all of these technologies are in active development, and some can even be found on supermarket shelves.
What happened between then and now?

It's hard to say for certain, but it is possible that a number of factors came together to make high-tech food possible:

- Early biofuel technologies demonstrated our ability to manipulate genetic pathways to generate high value products.
- With falling gas prices the biofuel industry fell, leaving the biotech industry ripe for innovation in the food sector.
- The continuance of green investing, no longer justifiable in biofuels, but very much so in food pushed the trend forward.
- Rising vegan and vegetarian movement, and added understanding of how diet affects health and the planet furthered the push behind high tech food.
- Many scientific and technical achievements that left a lot of low-hanging fruit in the food space
- Industrial biotechnology paved the way for a more straightforward regulatory approval process

At Helikon Consulting, the frontier biotech consulting firm that I lead, we are experts in the disciplines that produced the high-tech food space - metabolic engineering, protein biochemistry, chemical engineering, microbiology, bioengineering and more. These backgrounds have allowed us to contribute to the field and watch its development from the inside and out. As technology, and the field, have matured, we have contributed to the technical validation and development in the field. By providing consultation in cutting edge biotech, which expands beyond the food sector into synthetic biology such as cosmetics. Our team holds deep expertise and work experience in both high tech food and synbio. We work with highly trained scientists to deliver quality consultation to investors in the biotechnology industry, namely the high tech food space, so we have seen many innovations enter the sector firsthand. To give the smallest glance at some of the innovations that have transformed science and that are at the very cutting edge of food technology, I will talk about the science behind CRISPR and about its potential to change how we produce our food, particularly high tech foods and alternative proteins.

CRISPR/Cas9 are, in a simple form, genetic scissors. Recipient of the 2020 Nobel Prize in Chemistry, these genetic scissors have the ability to edit genome sequencing. It can cut and paste different DNA units, effectively eliminating errors or correcting predisposed medical conditions through deletions and insertions. This has enormous implications for genetically predisposed conditions and genetically modified foods and animals. We have the ability to eliminate certain medical conditions and create food that is less susceptible to climate change, pests, and so on. CRISPR also gives us the ability to detect precancerous genetic markers and has more recently been used to curb malaria by genetically altering mosquitos.

In this brave new world, we will have new considerations, and we will need to eat. Whether this food is sourced through traditional means or through scientific innovation, tools like CRISPR will become all the more necessary. Biotechnology in animal husbandry could quickly transform the field. In fact, CRISPR has been shown to reduce heat stress in cows by lightening their spots, thus reducing heat stress, which is expected to increase due to climate change. In order for traditional husbandry to remain sustainable in the next 30 years as the climate continues to warm, using biotechnology like this could become essential.

Biotechnology has taken off in the food space within the last seven years, creating a promising future for a hybrid industry (between traditional methods like regenerative agriculture, and more modern ones like modifying food with CRISPR, growing proteins in yeast, or culturing cells in a laboratory). Feeding ourselves in the future will be no mean feat, either on earth, in space travel, or on other planets. As bombastic as it may sound to some, conversations around how we will feed our population, whether they stay on Earth or eventually move into a greater galaxy, means reaching beyond the traditional. A practice like animal husbandry will not easily transfer to an extraterrestrial environment, let alone feed our growing population on Earth (which is expected to reach 9 billion plus by 2050, and with the added challenge of climate change). What kinds of proteins would allow us to be ready for either of these scenarios? Would insect protein be a possibility? Insect protein powders have become a popular source of protein, and the global narrative around eating bugs has begun to shift. Hans Kelstrup's work shows us that artificial selection of certain genes over time yields a larger organism, increasing the protein mass of the yellow mealworm. This has implications for both human consumption and animal feed (feed being another area that biotechnology can help us become sustainable). How will we take what we already have, and make it more sustainable? How can we increase nature's yield in a way that's healthy for the planet, and enough to sustain our population? How do we ensure we have mass quantities, and who has access to what?

As we think about how we can — and must — feed the world, we begin to realize the magnitude of the challenge. There is no silver bullet solution. Perhaps we can think about the future not as an and/or situation, where technology and traditional agriculture vie for the market, but as an and/and situation. We need innovative ways that will work in tandem to effectively reach various types of consumers.

Provocateur’s Responses

Mealworm genomics: one bug’s journey from the underground to outer space

Hans Kelstrup
Beta Hatch

Selective breeding for desirable traits in animals and plants has led to a dizzying number of varieties that we take for granted today. It’s easy to lose sight that such within-species diversity simply did not exist before humans started meddling. For example, our forebearers turned a little weed specialized for life on limestone cliffs into cabbage, brussels sprouts, kohlrabi, kale, broccoli, and cauliflower through the conscious selection of specific desirable traits. Intense artificial selection for desirable traits is also evident in birds, from Charles Darwin’s observations of fancy pigeon breeds to the gigantic strides made in broiler performance over the last few decades. For example, FCR values have dropped by 35% and breast meat yields have been doubled in a span of just 25 years. And up to 90% of this change is attributed to changes in genetics instead of improvement in feeding.

At Beta Hatch, we are entering a new frontier with insect breeding and industrial farming, but we will be standing on the shoulder of giants whose hard work and experimentations with classical livestock yielded much of our understanding of selective breeding today. Insects have the advantage being extremely malleable in terms of evolution and phenotypic plasticity. Within just a few years, for example, we have produced larvae that are double the size of their ancestor, and the adult females from this large strain lay more eggs. At the same time, we are using CRISPR-Cas technology to accelerate larval growth rates, boost mycotoxin detoxification and, more recently, to hitch antigen production to our mass rearing system to facilitate the rapid amplification of vaccines. And this is just the beginning, not just for Beta Hatch, but for the entire industry. There is a reason *Drosophila melanogaster* became the preeminent model organism for research in genetics: they are easy to rear and are very fecund. With clear economic and environmental incentives, we should expect mealworms, black soldier flies and other feed insects to follow in the technological footsteps of *Drosophila*.

Right now, the mealworm is like the little weed on the cliff, but in the Next Generation there will be bioengineered strains for a diversity of applications, from customized augmented feed ingredients to pharmaceuticals and biomaterials to waste management. The only known way to biodegrade Styrofoam is in the gut of a mealworm – perhaps this humble beetle holds a vital key in reducing plastic waste. Dr. Kate Krueger also touched on space travel, and indeed, the mealworm is a prime candidate: with an adaptive metabolism they can thrive in dry and low light (and perhaps in zero G) environments, are able modulate their resource use and survive in suboptimal conditions and can turn inedible parts of spacecraft-grown plants into nutritious protein and fat. We have also shown that their excrement or “frass” works as a fertilizer for plants in Mars soil analogs. Why not use CRISPR to create mealworms with lower oxygen requirements and a microbiome specialized for Martian waste conversion? Indeed, the lava tunnels of Mars could serve as suitable habitats. After all, the sandworms of Dune got started somewhere.

Back on Earth, one of the more appealing aspects of insect farming is that it is sustainable. Climate change and the increasing demand for animal protein will place stress on our food system, and so we need to be efficient and mindful of greenhouse gases. Many of Dr. Krueger’s questions boil down to efficiency: we need to improve yields while simultaneously reducing industrial waste that harms the planet. In the future, zero-waste insect farms will be co-located with food production facilities to upcycle waste into valuable secondary products that could feed back into the system. Land use for conventional protein crops like soy and traditional agriculture will continue to be essential, but we need to reduce the footprint in agriculture, and there will be an explosion of fully or semi-automated energy-efficient vertical farms for both plants and insects. Picture conjoined skyscrapers full of plants and insects, where a standard processing step is to pass plant waste to insects which then convert the inputs into i) frass fertilizer for the source plants; ii) CO_2 is captured and metered for plant intake; and iii) water removed from the drying of insects is recirculated into the hydroponic system.

Finally, let's not lose sight that there are 30 million species of insects on Earth, and only a handful are farmed by humans. In fact, 1 out of every 6 animals is a species of beetle. How can we both feed the future and do so in a way that maximizes preservation of this natural diversity? Start with a good foundation of naturally derived variation, build on the meticulousness of traditional breeding and apply some next generation genomic tools. This is the future of farming.

Exploring Brave New Worlds: Some Thoughts on Alternative Protein Sources

John B. Cole
PEAK

Advocates of cultured meat, encouraged by recent life cycle and techno-economic assessments published by the Good Food Institute (GFI), have argued that it can outperform all forms of conventional meat production, reduce air pollution, make land available for climate mitigation and biodiversity, and be cost-competitive with some conventional meats by 2030. That certainly sounds very appealing, particularly for consumers who want to make environmentally responsible food choices or add more animal protein to their diets as their income grows. However, independent analyses by Humbird (2020) and Hughes (2021) suggest that the GFI results make assumptions that can't be justified based on current knowledge of cell-culture and industrial biotechnology. In fact, Hughes notes that 1 kg of cell culture product for consumption is likely to cost ~$8,500 per kg, while the wholesale price of trimmed chicken meat in the US is $3.11. A recent peer-reviewed study by Risner et al. (2021) supports this conclusion about costs, with manufacturing performance needing to approach technical limits for cultivated meat to achieve profitably as a commodity. An economic argument based on fanciful assumptions isn't much of an argument at all, particularly when it's used to suggest that the public should invest billions in research so that the private sector can reap the profits. If cellular agriculture is so obviously a game-changer then why can't it pay its own bills?

This conversation concerns me greatly because we're really talking about replacing food with engineering. We already have tools that can reduce the environmental impact and increase the productivity of our animal systems. Do we want to surrender control of our food supply to the private sector when we're facing a climate crisis because of unchecked corporate behavior? What people need today, and will need even more of in the future, is food, not a license to temporarily access someone's intellectual property. They need food that is locally sourced, provides a living for farmers, and is culturally respectful. I argue that the best use of our scientific resources and talent is not the replacement of proven systems with promises, but in the continued improvement of animal agriculture.

It's no surprise that Krueger and Burke choose to take a stand on more solid ground. Gene editing isn't a new technology – zinc finger nucleases and TALENs have been used for many years – but the development of CRISPR-based tools is a major step forward because of their precision. It's also the least-surprising idea discussed, even if it's sometimes misrepresented. For example, gene-editing by itself doesn't ameliorate effects of heat stress on cattle. Once you've got a gene-edited embryo, what do you do with it? A whole system is needed to translate that product of technology into an actual solution to a problem. When we combine gene-editing with modern animal breeding programs we can make meaningful long-term changes to populations. But this awareness of the system is lacking in the vision presented, and I wonder if the authors are interested in the technology for its own sake rather than as a tool for change.

The idea of using insects as an alternative protein source is interesting in an academic sense, one supposes. It's certainly more appealing as a thought exercise than an aspiration for the future. I've not seen a life-cycle analysis that convinces me this is any more scalable or sustainable than plant- and animal-source proteins, and I certainly don't know of anyone volunteering to give up beef in favor of cricket powder. Bugs have to eat and drink something, and their environments also must be maintained. I'm more optimistic about feeding insect protein meal to livestock than to humans but it must be cost-competitive with plant proteins, and it has to be affordable sooner than later. Nobody's making enough money that they can absorb notable feed cost increases. I'm even more in favor of feeding insects to aquaculture species because I don't generally include either in my diet. Generations of science fiction authors have speculated about what we'll eat as humanity spreads beyond the surface of the Earth, including food pills, yeast derivatives, soy products, and – for the wealthy – perhaps modest portions of fish or chicken. "Star Trek" solved the problem with replicators that are almost, but not entirely, unlike 3-D printers for food. The Klingon delicacy *gagh* is famously made from serpent worms, ideally eaten live. The question is: do humans have strength enough to eat like true warriors? Are we Will Rikers, or Wesley Crushers? Personally, I'm as likely to eat a bug as I am to go to the Moon.

The challenge of spreading human life throughout the Solar System is so intimidating that it's hard to really get one's mind around it. The Saturn V rocket that sent people to the Moon was the largest ever launched. Its first stage was powered by five F-1 engines which produced 1.5 million foot-pounds of force each, marvels of modern engineering. The ideal rocket equation lays out in stark terms the limits that we face going to space and it may never make sense to send livestock into orbit. But we animal breeders also have mathematical truths that constrain our field. Jay Lush helped to formalize the Breeder's Equation that is the foundation of our craft. We can't change the laws of physics, but we can change animals. The challenge to us as scientists is to solve the problems that advance the interests of society, not just those that make the prosperous feel virtuous. The demand for animal protein in human diets is only going to increase as economic prosperity increases around the world, but telling people to instead eat insects and artificial "meat" is an astonishing act of hubris. We already have the technology at hand to efficiently produce animal protein while reducing its impact on the environment – why are we so reluctant to do that?

Plenary 4

Future contributions of animal genetics and genomics in the developing world

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Alfred de Vries
Bill and Melinda Gates Foundation

Introduction

Within the next half century, the world population will reach approximately 10.5 billion and it is anticipated that close to 80% of the total number of people on earth will be residing in regions that are currently known as the developing world. Africa will witness the most significant population growth. This growth and the anticipated expansion of the urban population is projected to continue up to the year 2100 and probably beyond. A direct and major consequence for the global population growth and urban expansion is the need to produce much more food to meet nutritional needs while addressing numerous environmental sustainability challenges. In the developed world, the remarkable achievements that are driving today's livestock production have largely resulted from technological innovations, especially in animal genetics and genomics. This paper will look at the potential impact of current and new genetic and genomic technologies on the transformation of livestock production systems in developing countries

Production systems in the developing world

In most developing countries, there has been a slow uptake of the available innovations in animal genetics and genomics. As a result, their livestock production systems are very low in productivity, profitability and efficiency, and very high in greenhouse gases (GHG) emission intensity. Therefore, there is a growing pressure for fast transformation and transition out of the current production systems.

Current genetic and genomic technologies

Over the past decade and particularly with the launch of the UN sustainable development goals, there are already promising success stories that lay the foundation for the transformation of the livestock systems in the developing world. Some highlights of innovations in animal genetics, genomics and associated disciplines in the developing world include: genomics-enhanced breeding programmes focusing on the identification of the most appropriate livestock breed or cross-breed types suitable for specific livestock production systems, the use of genomic approaches in the development of new breed types, genomic characterisation of indigenous livestock as resource population for discovery of genetic variants of economic, nutritional and ecological importance. As an example, African livestock display unique adaptive traits including enhanced disease resistance, superior innate immunity and greater ability to thrive, produce and reproduce in unfavourable environments which is consistent with the anticipated changes in production systems imposed by the ongoing climate crisis.

Transformative scenarios and technologies

The transformation of the current livestock systems in the developing world (with a main focus on Africa) over the next century will be enabled by ground-breaking innovations in genomics, reproduction and digital technologies, and will be accompanied by significant changes in the livestock sector. The main developments are listed below.

Livestock sector development: Like in western countries, the livestock sector in the developing countries will grow and shift to larger farms with more intensive production. The rate of change

Nigeria has 18 mln heads of cattle, of which 82% are kept extensive (pastoral), 17% semi-intensive (agro-pastoral) and 1% intensive. Only 2.2 mln cattle are considered as dairy animals. Most of them are dual-purpose indigenous breeds with very low productivity (~200 liter/year). Current milk demand is 1.3 MT/year, of which only 0.5 MT is produced domestically. To keep up with the growing demand and become self-sufficient, Nigeria needs to produce 11 MT/yr in 2050. FAO/USAID ("The future of livestock in Nigeria", 2019) explored 4 possible scenarios for developing the livestock sector. In their "inclusive scenario", the total cattle herd will double to 37 mln head. The number of animals in the extensive sector will hardly change (16 mln; 42%), the semi-intensive sector will triple in size (9 mln head; 25%) and produce more milk (0.8 MT/year), while the intensive sector will have a tremendous growth (12 mln head; 33%) and will produce the majority of the milk (9.8 MT/year).
Nigeria has 180 mln chicken, of which 83 mln are kept extensive, 59 mln semi-intensive and 38 mln intensive. Most of these extensive animals are from local breeds and have low productivity. To keep up with demand (and avoid illegal imports of poultry meat; currently 1.2 MT/yr), productivity needs to improve and the number of poultry will need to grow to 900 mln birds in 2050 (FAO/USAID (2019). In the studied "inclusive scenario", all sectors (extensive, semi-intensive, intensive) will grow, with the extensive sector growing to 90 mln birds, while semi-intensive and intensive will grow to 270 and 540 mln birds. Poultry meat production will grow from 0.3 to 3.1 MT and egg production will grow from 0.65 to 4.9 MT per year.

will depend on the local economic conditions and government policies. Nigeria could be used as an example for how the African livestock sector could develop in the next decades (See Insert). It shows that even with the most favourable development conditions, most dairy animals and a large proportion of poultry will be kept on small extensive or semi-intensive family farms in 2050.

<u>Precision animal breeding technologies</u>: Genome re-writing and animal cell reprogramming will become routine to enable ultrafast genetic development and dissemination of bespoke animal genetics adapted to the prevailing conditions. Genetic inputs will be regularly updated, comparable to what we see with software development and improvement today. In vitro animal breeding will build on (i) routine creation of distinct and differentiated cells derived from stem cells for in vitro fertilisation and embryo transfer and, ii) on cell-based genomic evaluation, prediction and testing of key performance parameters. Genomic selection, genome re-writing and dissemination of robust animal genetics will all be combined and performed routinely to respond to biotic and abiotic challenges. Fully tested genetics will be maintained in vitro as part of a pipeline for fast delivery of desired animal genetics products.

<u>Reproductive technologies</u>: In cattle, artificial insemination will be replaced with embryo transfer to produce hybrid commercial animals. All beef calves will be produced on dairy farms. The supply chain in poultry will benefit from a new technology that enables long-term storage of fertilized eggs.

<u>Animal genomics</u>: Genomic predictions will be replaced by machine learning systems that continuously optimize selection and mating decisions based on field performances of animals (with purposely planned genetic diversity), predicted changes in environmental conditions and market demand of specific commodities and specific consumers' needs.

<u>Breeding programmes</u>: Animal breeding programmes will evolve and undergo a full transformation into comparable operating entities with greater connectivity across the globe regardless of developed and developing countries. Prototypes of breeding programmes will remain commodity-dependent and will operate as sub-units of a global operational business providing bespoke animal genetics, the decision support tools ensuring common approaches that meet global standards for efficiency, emission and welfare.

<u>Evolution of commercial breeding companies</u>: Pharma companies will replace traditional breeding companies. They will develop and provide the genetic inputs, the required

microbiomes ("implanted" in live animals and/or as probiotics to be administered), the health management products, the data capture systems for optimum performance, adaptation, welfare and resilience under defined conditions. Feed companies will remain as separate businesses.

Provocateur's Responses

Development of new livestock breeds that design new civilizations.

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Thousands of years ago, animal and plant species adapted to human use were distributed intensively in the places of ancient civilization and contributed to agriculture and urbanization. Over the past 200 years, the success of the Industrial Revolution (chemical fertilizers, tractors, seeds etc) from solar energy-dependent agriculture to fossil fuel-based modern technologies has led to an explosive increase in food production and human population. However, we are now facing the limitations and challenges of the fossil fuel-based developments due to the climate crisis and global pandemic such as COVID-19.

Although records of agriculture and livestock use have been found for a long time ago in Korea, most of the indigenous livestock resources were recently disappeared or replaced with breeds introduced from the western countries due to low productivities or poor-quality values. Therefore, quality improvement that can enhance taste and nutrients was supported with genetic research and biotechnology in Korea. With this support, I have had the opportunity to study the genetic diversity of livestock in different environments and climatic conditions, especially developing countries in Asia and Africa over the past years.

Similarly, livestock resources in these developing countries were disappearing due to lack of interest or poor economic value to rapidly changing social demands. This is often expressed as low productivity. Therefore, livestock improvement in developing countries needs to focus value creation as well as conservation. To accomplish that, we should more actively create hybrids through genetic exchange of native livestock resources in developing countries. In the past, the Chinese native pigs in the late 18th or 19th century were introduced into the European pig breeds, contributing greatly to the production of modern pork around the world. It is noteworthy that Indian cattle were also introduced in the 19th century and created new beef cattle varieties like Brahman and Nellore, which are contributed to the creation of additional value in the beef industry. The basic method was to fix the beneficial alleles through selection and mating skills.

Companies and organizations with cutting-edge genomics and breeding technologies should be more interested in conducting joint research to create genetically enhanced hybrids using the livestock resources available in developing world. For example, through cooperative research, I am interested in bringing the semen of the Boran cattle from Ethiopia and use them to Korean cows, or produce embryos to create future generations with new genetic combinations, and increase genetic diversity. The resultant progeny will be tested for adaptability and performance in different environments.

This may sound like nothing new, genetic diversity in developing countries has declined as a result of a marked decline in population size. In the past, new varieties or breeds were created slowly through natural selection based on the performance under limited combinations, but it is now necessary to create varieties quickly and effectively through systematic breeding using genomic information or genetic modification. It is important to maximize genetic diversity and characterize genetic combination for the higher value of livestock resources in developing countries. In this way, I believe that we will be able to solve the problems we are facing and secure genetic diversity that can adapt to challenging environments that are difficult to improve with currently given livestock resources.

Provocateur response - future contributions of animal genetics and genomics in the developing world

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Overview

Introduction and adoption of new technologies in developing countries is a complex issue associated with production systems, limitations in management, environment, societal beliefs, and culture. Nonetheless, future adoptions of genetics and genomics are essential for sustainable production of animal protein in a world that continues to see increases in population growth. Adoption of genetic and genomic technologies will not be successful without the careful incorporation of necessary management, infrastructure, cultural, and political support, coupled with the associated adoption of technologies such as reproductive and sensor technologies or the parallel adoption of artificial intelligence and machine learning.

Data demonstrates that a significant portion of world population growth will occur in Africa, where adoption of new technologies in animal agriculture is essential. However, with my experience working in countries such as Ethiopia, Kenya, Malawi, South Africa, Zambia, and Zimbabwe, key considerations need to be incorporated for success.

Subsistence vs. Commercial Operations. In most African countries there is a dichotomy in productions systems that may be categorized as subsistence and commercial operations. Commercial operations are typical of western operations in terms of adoption of technology and generally provide a larger portion of the animal protein to population in urban areas. Alternatively, subsistence operations have few animals that may be comingled with multiple owners and are expected to provide meat, milk, wool or hair, and sometimes drafting on farmland. As a result of the differing production systems, genetics and management systems vastly differ between these two systems and need to be considered.

Cultural Considerations. Culturally, livestock are a measure of value among populations of people. For example, populations of indigenous Africans still practice 'lobola', the practice of paying for a bride in cattle. Any adoption of technology should account for the perceived value of livestock from a cultural standpoint.

Considerations for adoption of genetic and genomic technology

1) Genetic and genomic improvements will only be implemented with successful adoption of applied reproductive technologies. Use of these technologies will allow for systems that use transfer of embryos rather than artificial insemination to avoid negative impacts of heat stress. Improvements in in vitro derived embryos will allow for embryos to be produced at a central location/s; thereby, tailoring each embryo for a specific need. The technologies used could be through traditional mating of indigenous breeds or future utilization of gene editing or sexing technologies. Generating herds of single sex offspring or offspring that are produced to be resistant to disease or enhanced production has a significant benefit in developing countries.
2) Populations in developing countries have an unusually high value to cell phone technology. Developing breeding systems that incorporate sensor technology for detecting estrus or ovulation that can be transmitted through cell towers or satellites will enhance opportunities for adoptions of genomic technologies. Future use of machine learning or artificial intelligence will enhance these opportunities.
3) Establishment of cooperatives, networks, or government funded infrastructure to incentivize adoption of technologies will vastly enhance the upscaling of new genetic

or genomic technology. For example, experts at embryo transfer can be deployed to service a region, rather than training individual livestock owners. Offspring can be parent verified with incentives for meat or milk products from offspring derived from the new technology.

4) Indigenous breeds of livestock have been developed over generations and hundreds of years to resistant internal or external parasites and to be disease resistant. New genomic tests can be developed to identify specific genetics that reduce the use of parasiticide's and antibiotics. These traits, through genomic selection and/or gene editing can be broadly infused throughout a region. For example, the Malawi Zebu is a breed of cattle that was developed through selection to be resistant to heartwater, a tick-borne disease. Western genetics of *Bos taurus* cattle simply have not been able to be productive in the Malawi environment. However, western genetics and management have demonstrated to produce more beef or milk at a higher quality. Using future genomic or gene editing technologies, incorporation of disease resistance will enhance productivity and reduce management inputs (i.e., dipping or parasiticides).
5) For comingled or large extensive herds of cattle or flocks of small ruminants, use of stem cell transfer of sperm cells of superior donor males to allow environmentally adapted recipient males to mate females where adoption of reproductive technologies are not practical.
6) A significant shift will need to occur in genetics and pharmaceutical companies. An evolution in genetic companies will need to occur to tailor genetics for specific climate, production/management system, and desired end-products, where IVF embryos are delivered to remote regions of the world. Pharmaceutical companies (perhaps in relationship with genetic companies) will need to incentivize the reduction in external agents, such as parasiticides or antibiotics, and incentivize the adoption of new medical advances associated with vaccinations and treatments of livestock.

Abstracts

Using MAGIC and PGCs to Select Animals for Space

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Human colonization of other planets requires the development of livestock breeds adapted for novel environments. Using traditional breeding to generate the genetic variation necessary for these novel environments is currently limited by the slow generation time and net reproductive rate of animals. To remedy this limitation, I propose to use directed differentiation techniques on primordial germ cells (PGCs) to produce a Multi-parent Advanced Generation Inter-Crosses (MAGIC) population. We can use directed differentiation techniques on PGCs to initiate sperm and ova development followed by in-vitro fertilization to decrease the generation time from multiple months to a few days and increase the number of offspring. This PGC approach will make MAGIC feasible, resulting in a large, diverse population from which we can generate inbred lines and develop extraterrestrial phenotypes. Ultimately, developing livestock species for space exploration requires radical high-throughput reproduction and screening platforms to create bespoke breeds.

Genetic Analysis of Antibody Response to Porcine enzootic pneumonia and Mycoplasma Hyopneunomia in Commercial Pigs

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Infectious diseases primarily take a toll on the swine industry every year through increased mortality and reduced productivity. Diseases like Porcine reproductive and respiratory syndrome (PRRS) & Mycoplasma Hyopneunomia (MHYO) are some of the most common diseases that affect the swine industry, leading to huge annual losses for PRRS alone. Such diseases disrupt pig production goals that focus on meat quality, feed efficiency and much more. In recent years, the goal has expanded to include health traits such as disease resilience, and, through several collaborations, we have developed a natural challenge model that mimics a commercial environment with severe disease pressure to maximize expression of differences in disease resilience. During the challenge, blood samples are taken from each pig to measure the level of antibodies against PRRS & MHYO, and these data were analyzed in this study using various genetic models to estimate heritability and genetic correlation of the antibody production with multiple other phenotypes such as feed intake, growth rate, and mortality rate. This investigation aims to successfully predict various phenotypic and genetic models that affect the disease resilience of pigs and how infectious disease pathogens can be limited to obtain a better production performance and animal welfare.

BreedinAid: The ultimate recipe book for successful livestock production

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Significant undergoing efforts are focused on understanding the roles of genome structure and modifications (FAANG, AG2PI) on phenotypic diversity as well as cataloguing genomic diversity within a species (Cattle Pangenome). With these efforts, the scientific community expects to jump into the era of predictive biology. As with all technological and methodology developments, important steps are needed to translate knowledge to production. When coupled with the genetic diversity of the different breeds within a species, predictive biology could have paradigm-shifting effects in agriculture and the way food production is adapted to fulfil the demands of consumers. Imagine the composite recipe book: a single database with information regarding all breeds of a species. Contained within is a breed-wise EBV similar to what is seen in sire catalogues regarding performance under specific pathogenic and environmental stressors, productive potential (i.e. marbling score) under various management styles along with breed complementarity values. With this tool, each producer could tailor their germplasm to tackle the specific needs and desired goals of production, maximizing efficiency in production and differentiation of the final product by mating the specific individuals needed from the appropriate breeds to produce a specialized terminal hybrid.

CATTACA

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The 1997 Columbia Pictures film "GATTACA" introduced pre-implantation genetic diagnosis (PGD) and whole genome DNA profiling to produce children that are the genetic "best of you". A single finger prick of blood instantaneously confirmed identity. While eugenics is taboo for *Homo sapiens*, what about our companion animals? Animal breeding itself is a form of eugenics. How far can we take current technologies in pet cats? Is CATTACA feasible? Reproductive technologies are well developed and efficient in many of our domesticated animals, such as cats and many livestock species, thus, pre-implantation genetic diagnoses can be performed. While technologies are advancing to use single cell DNA sources, whole genome amplification can currently amplify the DNA to test panels of DNA variants for identity, desirable and undesirable traits and health conditions. Once the entire genome sequence of an individual cell can be produced, will we have a matrix of variant combinations and an algorithm that can accurately predict not only single gene conditions but the also the variation in presentations and the complex interactions of multigenic traits, including behaviors? Will be able to select the right queen and the right tom to make the "best kitten" for the best of you?

A genome-wide scan to identify signatures of selection of fat tail deposition in sheep

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Reducing or removing the tail fat in the sheep is one of the breeding objectives in this industry. Having causal SNPs (effective on fat storage in sheep tail) in the sheep SNP chips can help the future breeders to select against this trait. My finding in this study can help to identify important SNPs that are involved in this trait. Whole-genome sequencing data of two groups of animals (fat-tailed n= 5, thin-tailed, n= 5) were downloaded from the European Nucleotide Archive (www.ebi.ac.uk).The clean reads were aligned to the reference genome of sheep (Oar v.4.0).Overall 26 and 23 million SNPs were detected in fat-and thin-tailed, respectively. The FST was calculated for fat tailed and thin tailed using the sliding window approach (100 kb with) in VCF tool. A total number of 505 windows including 357 genes were detected in the top 1% of Z(FST) values. We could identify 4 genes in the top 1% of Z(FST) values that had been previously reported as candidate genes for fat deposition. These candidate genes are BMP2R, PID1, HOXA11 and HOXA13. The candidate genes in this study are responsible for developing the tail size and fat deposition. Our findings provided new insights into the genetic mechanisms of fat deposition in sheep.

Adding genomically discovered maternal grandsires and maternal great grandsires to the US evaluation system

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Based upon haplotype matching, missing maternal male ancestors can be discovered with > 90% accuracy. The Council on Dairy Cattle Breeding (**CDCB**) has already added over 370,000 discovered maternal grandsires (**MGS**) to dams with unknown sire where no pedigree was submitted for the dam. CDCB intends to extend this to maternal great grandsires (**MGGS**) where no pedigree was submitted for the maternal granddam (**MGD**). To add MGS or MGGS to the pedigree, where the dam or MGD is unknown, requires CDCB to create an ID for the dam or granddam. These constructed IDs consist of the breed of the discovered MGS or MGGS as the best guess of the unknown dam breed, the 'USA' code, the letters' DAM' or' MGD' followed by the genotyped animal internal sequence number. For about 30,000 cases, a dam can be discovered by finding a cow whose sire is the discovered MGS and has a calving date in the herd of the genotyped animal that matches its birth date. After further testing and a staged implementation, > 1 million discovered ancestors linked to genotyped descendants by constructed IDs will be added to the pedigree used in evaluations. A more complete pedigree is expected to improve evaluation accuracy.

Application of artificial intelligence to identify novel phenotypes and suggest optimal mating and selection strategies

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Automated phenotyping is now possible using sensing and imaging technologies that measure behavior traits and other unknown phenotypic measurements. Computer vision and Artificial Intelligence (**AI**) methods could be combined to identify novel phenotypes or indicator traits useful in selection. Such a methodology could identify and correct problems quicker than a human by identifying and tracking trends in new traits previously not considered by breeders, such as those impacting fitness. Given a breeding objective, an AI method could be developed to learn and decide which of these new traits should be added to a selection index, develop breeding goals, and provide options to breeders on the weights for new traits to optimize selection. This approach could quickly develop customized selection indexes for different environment and management scenarios. Additionally, given genotype data, optimal genetic markers could be rapidly identified for use in mate pair selection to enhance both additive genetic gain and gene combination effects. Such an algorithm would require breeders to make final assessments and decisions but could automatically provide several selection options to increase the nimbleness in making modifications to breeding plans.

The future for Animal Genetics: Pan-genomics, Pan-epigenomics and High-throughput Phenotyping

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Comprehending the underlying genetic and epigenetic mechanisms driving phenotypic variation and determining a means of exploiting this knowledge for implementation of precision agriculture is the future of animal genetics and breeding. Towards this end, the Cattle Genome to Herd Phenotyping for Precision Ag (CG2HP) initiative has been established to exploit new high-throughput phenotyping, genomics and epigenomics technologies to improve US cattle productivity and profitability. The emergence of pangenomes and pan-epigenomes are advancing our molecular understanding of how different genomes, epigenomes, and gene products from diverse breeds of livestock affect a variety of important biological phenotypes. The combination of this insightful information with the advances in high throughput phenotyping and data acquisition will increase the accuracy of trait predictions and dramatically improve animal breeding strategies to meet the needs of society. To accomplish this lofty goal, it is critical to identify and overcome the hurdles inhibiting the use of high-throughput data for precision animal agriculture. The intent of the Cattle Genome to Herd Phenotyping for Precision Ag (CG2HP) initiative is to do just that; create a vision and develop an executable strategy for precision animal agriculture in the US.

Fine Mapping of Complex Traits Through Whole Genome Resequencing

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Whole Genome Resequencing (WGR) provides a cost-effective method to fine map the genetics of virtually any complex trait for which a phenotype can be scored. We have used the technique to map the underlying genetics for ascites and bacterial chondronecrosis with osteomyelitis (BCO) leading to lameness. Currently we are also working on susceptibility to Infectious Bronchitis Virus. Regions identified through WGR consist of hundreds to thousands of SNPs spanning 10-200 kbp for which the case and control differ for Minor Allele Frequency (MAF). For ascites and BCO we have applied WGR to 3 or more different lines, breeds, resource populations and identified 10-30 regions in each, with very few regions being shared between lines. Thus, these complex traits have a very strong dependence on the specific genetic background. Never-the-less, with current methods for high-throughput purification of DNAs, production of pooled bar-coded library, and Illumina NovaSeq paired-end sequencing, the cost of fine mapping a complex trait is less than $10,000 in reagents, and supplies, and involves only 4-5 hours of lab bench time. Marker assisted selection for ascites using WGR regions successfully bred for ascites resistance and no loss in production traits.

Enabling precision beef cattle management through phenotypic prediction

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Genomic selection has generated unprecedented genetic gain across the beef industry and continues to improve. In the future, we anticipate that the decreasing cost of generating multiple types of "-omic" data will enable phenotypic prediction, even in terminal animals. While whole genomes, transcriptomes, metabolomes, and epigenomes on each feeder calf are impractical, targeted approaches and novel sequencing strategies might provide sufficient information to predict individual performance with adequate accuracy. These efforts will require extensive investments in identifying the highest-information functional networks. Our community will also have to develop novel strategies and algorithms to perform phenotypic prediction at scale. Further, we see opportunities to integrate these phenotypic predictions with sensors and other individual animal monitoring technologies for use in precision management contexts. By understanding phenotypic potential (beyond additive genetics), we can tailor management strategies to maximize animal performance and efficiency. Phenotypic predictions might be used to sort animals into management groups based on disease risk, growth potential, and docility. Precision feeding systems could then deliver each animal a uniquely formulated diet while sensors monitor at-risk animals for signs of subclinical disease. This idea is only one vision of integrating genomics and precisions management to increase sustainability and productivity across livestock species.

On the future of 'economically relevant' traits in livestock

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Selection schemes generally place pressure on traits that improve net profit by forming economically optimal selection indexes; yet the weighting of traits deemed important by society is problematic without direct economic signals to livestock enterprises. A potential solution is to re-frame the effort of going from genome to phenome by defining the phenome as the health and satisfaction of the consumer and the genome as that of the agricultural product. The heritability of such traits can be interpreted as the proportion of variation in human health and/or satisfaction with meat products that can be attributed to genetic differences among the animals that produced it. Similarly, animal growth and performance could be a phenotype attributed to the genetics of the plant products they consume. In essence this becomes an extension of 'embedded' or 'indirect' genetic effects whereby the genetics of one animal impacts the phenotype of another. Preliminary examples exist in the form of Microbiome Active Traits (MATs) showing relationships between crop genotypes and human gut microbial features. The desire to further refine genetics of food producing species to the personalized wants and needs of consumers could eventually lead to Microbiome Active Transgenic Traits (MATTs).

Resolving the disparity in genomic advancement of livestock

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Genomic technology has enabled significant production increases in the dairy and poultry industries but has been less widely adopted by other livestock species. A centralized repository of genetic information and has greatly benefited the dairy industry, however this resource is not available to the same extent for all breeds of beef cattle, and particularly sheep and goats. Additional challenges with collecting data on livestock managed predominantly in range-based environments presents further challenge. Important to the advancement of range-based livestock will be the development of technology for capturing data in more challenging production settings. Recently improved genomes for these species hold significant promise for more accurate selection tools but further expanding scientific understanding of gene regulation and expression through epigenetics, transcriptomics, and genotype by environment interactions will be critical. Moreover, maintaining breed variability to allow for adaptability to different production settings will be important, yet too will require a deeper understanding of genomic diversity within species. Elucidating the interaction between genetics and the broad environments in which livestock are produced within the United States will ultimately be foundational for the agriculture sector to provide a nutritious food supply for the future of society.

A Vision for Resources in Agricultural Genomics by 2030

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The USDA-NIFA is developing a vision for agricultural genomics and phenomics through the Agricultural Genome to Phenome Initiative (AG2PI). As part of AG2PI, we have been funded to take the pulse of the crop and livestock genomics communities for the future. A priority is identifying critical needs, as well as solutions, on how best to inform and accelerate genetic improvement across kingdoms. AG2PI is collecting ideas from both plant and animal groups to craft research programs for creating the technical, computational, and human infrastructure to accomplish this goal. One important component of this complex topic: how can we develop resources to effectively collect, describe, store, share, and analyze molecular genomics data across agricultural species? We predict that, by 2030, efforts supported by AG2PI will facilitate integrated tools to study genome structure, function, and genetic variation for important agricultural species. These resources will be available for researchers interested in interpreting results from genome-wide association studies and other studies that link variation to function. These resources, covering many important livestock breeds and crop cultivars, will be maintained by publicly resourced and supported groups that offer training to staff and students in government, academia, and allied industry.

The Chicken Genotype-Tissue Expression (GTEx): An atlas of genetic regulatory variants in chicken transcriptome

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Although thousands of genetic variants have been reported to be associated with phenotypic traits of economic importance in chickens, the identification of causal variants remains a huge challenge. Variation in gene expression is one of major factors accounting for phenotypic variation associated with complex traits. The main aim of the chicken GTEx (Genotype-Tissue Expression) was to identify genetic variants that regulate gene expression, i.e. expression quantitative trait locus (eQTL), which thus bridges the gap of genetic variants, gene expression and phenotypic variations. We collected 9,230 publicly available RNA sequences from 8,015 unique samples representing 79 tissues in chicken. After applying for a uniform and stringent pipeline, 6,930 samples were used for downstream analyses, e.g. SNP calling and expression quantification. In addition, a panel of 2,884 whole genome sequences were used to impute SNPs called from RNA-seq samples. The associations of imputed variants and gene expression were identified in 32 tissues with a sample size $\geq$ 40 per tissue. The analysis revealed that the number of eGenes ranged from 31 in blastula to 8,874 in liver, and the number of eVariants ranged from 51,860 in lung to 1,206,795 in liver. The results obtained in this study provide a useful source for dissecting genetic basis of phenotypic variation of economically important traits in chickens.