Precision Fermentation and Cell-Based Meat: are they Viable Alternatives?

The Societal Role of Meat

Dublin 19/20th October 2022:

World population growth to 2100

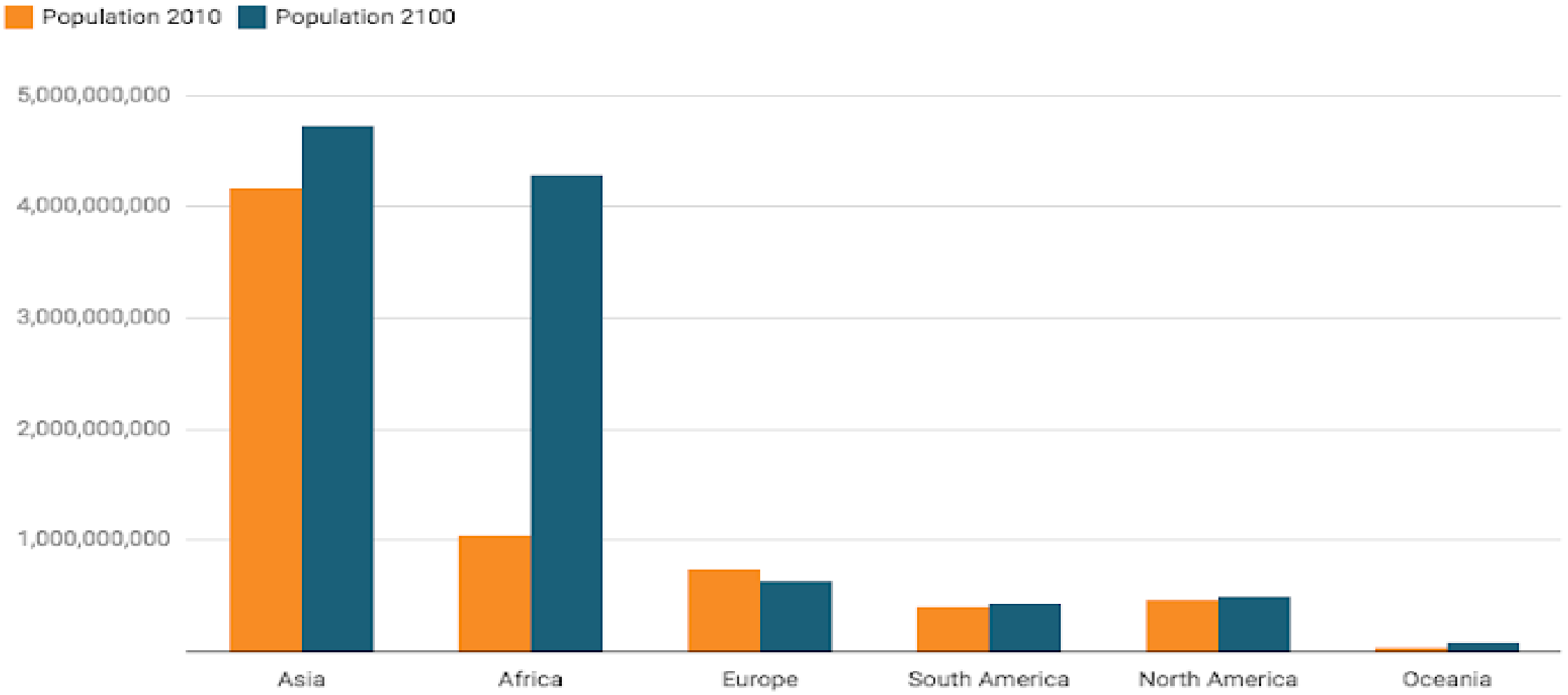
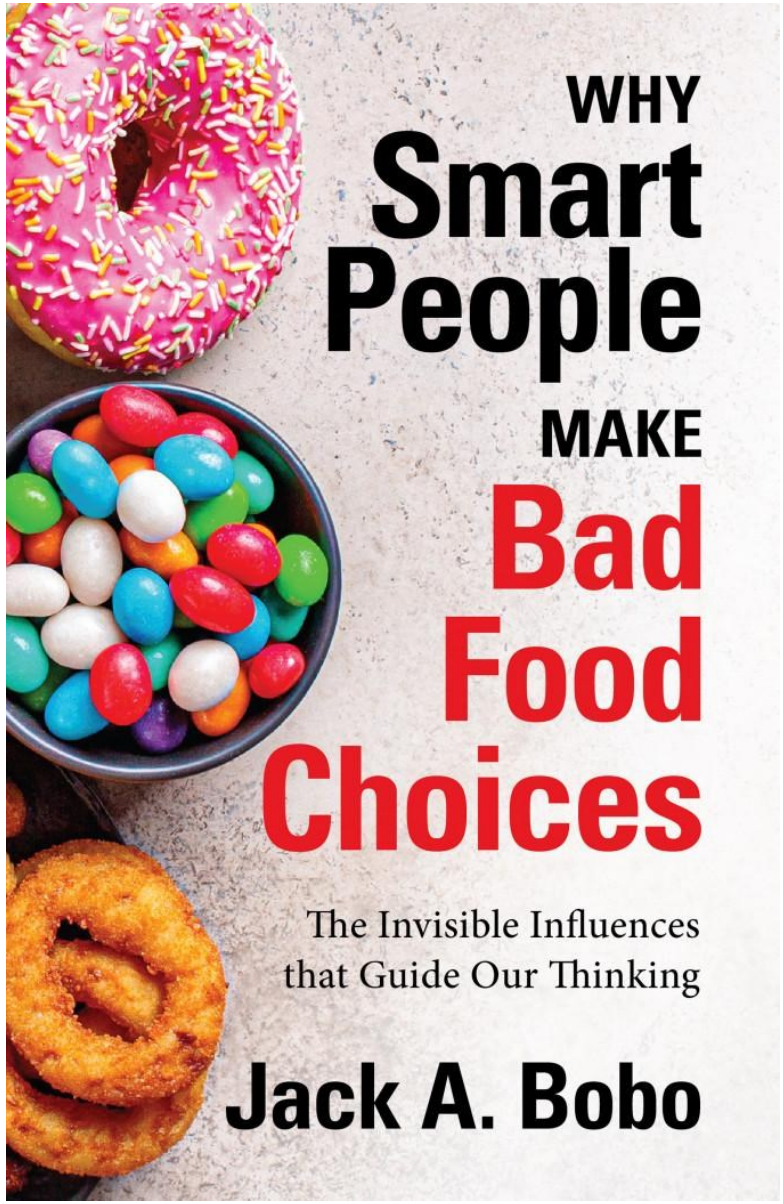


Chart: The Conversation • Get the data

There are currently over 800 million people subsisting on less than 1200 calories per day.



There are 2 Billion people who are over-weight.

Alternative or Complimentary Proteins

- Plant based –Meat (Impossible, Beyond, V2)
- Plant based-Dairy (Oats, Soy, Almond, Coconut, Rice)
- Fungi (Quorn, Enough, Meati)
- Algae (Spirulina,Sophie's Bionutrients,Algaecore)
- Insects (Protix, Enterra, Goterra, Viridian)
- Cell-based Meat (Upside, Just Eats, Mosa Meat, Aleph Farms, Vow)
- Precision Fermentation (Perfect Day, Motif, Clara, Remilk, All G, Eden Brew)

- **Over 1300 start-ups in this space, with the big food companies aggressively moving into the field (Cargill, JBS, Conagra, Tysons , Kellogg's, Nestle)**

Major issues for Growth of Alternative Protein market.

- Matching the taste and texture of animal-based products.
- Matching the nutritional profiles for meat and milk. While plant-based milk can be formulated to match dairy, this does not deal with the problem of bioavailability. Concerns with highly processed products.
- Growth in the market has stagnated. New products are taking market share from existing plant-based products.
- Nervous capital markets. Beyond and Oatly both lost 80% of their share value in the last year. That is around $20 Billion in valuation.
- Demonstrating sustainability claims, no longer good enough to just make a claim.
- The emergence of sustainable animal-based branded products.

- **Plant-based meat accounts for 1.4% of the total USA meat category.**

Rethink X: Rethinking Food and Agriculture 2020-2030.

Their major conclusions were:

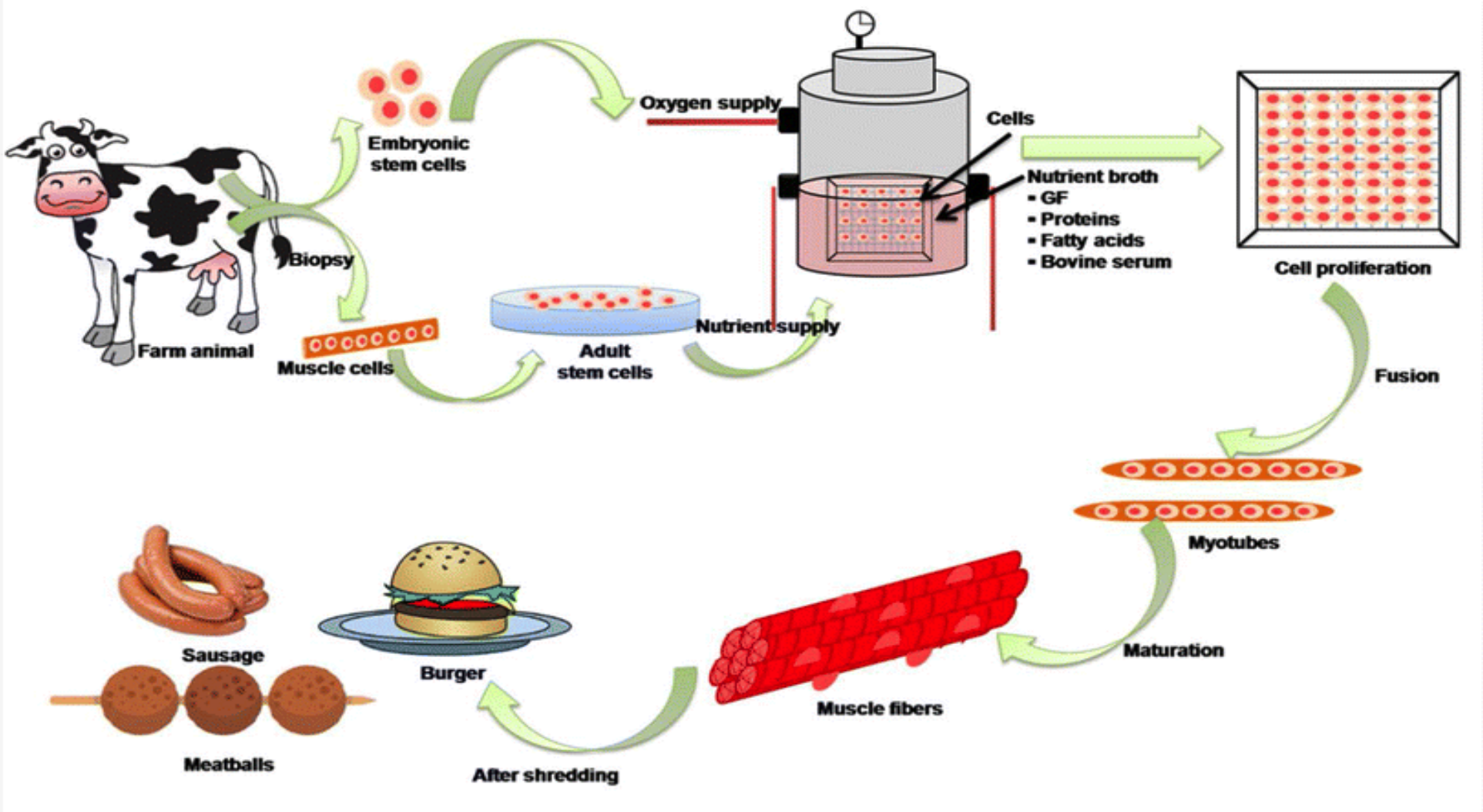
- By 2030 the number of cows in the USA will have fallen by 50% and the cattle farming industry will be all but bankrupt.
- These predictions were based on their view of advances in precision biology and that through precision fermentation this technology will allow for a totally new model of food production.
- The cost of proteins will be 5 times cheaper by 2030 and 10 times cheaper by 2035.
- Hence by 2030 modern food production will be higher quality and cost less than half as much to produce as animal-derived products.

The whole of the cow milk industry will start to collapse once these technologies are used to produce the individual proteins in milk and this industry will be bankrupt by 2030.

Tubb and Seba, 2019

Cell Based Meat

Cell-Based Meat



Some of the Key Players in this space

- Good Food Institute (GFI) Lobby group for Alternative products,80 companies in CB market.
- Upside Foods (USA, formerly Memphis Meats, facility with a capacity of 400K pounds/yr)
- Future Meat Technologies(Israel) $347M Series B funding
- Mosa Meat (Dutch company raised over $160M) Founded by Prof Post.
- Just Eats (raised $267M, first commercial product registered in Singapore)
- Aleph Farms (aim to produce a 3D steak)
- Mission Barns and Nourish (cultivated animal fats)
- Vow (Sydney based, focusing on Exotic meats)

- **Global Meat Market- $2308 Billion in value and 340 million tonnes in volume.**

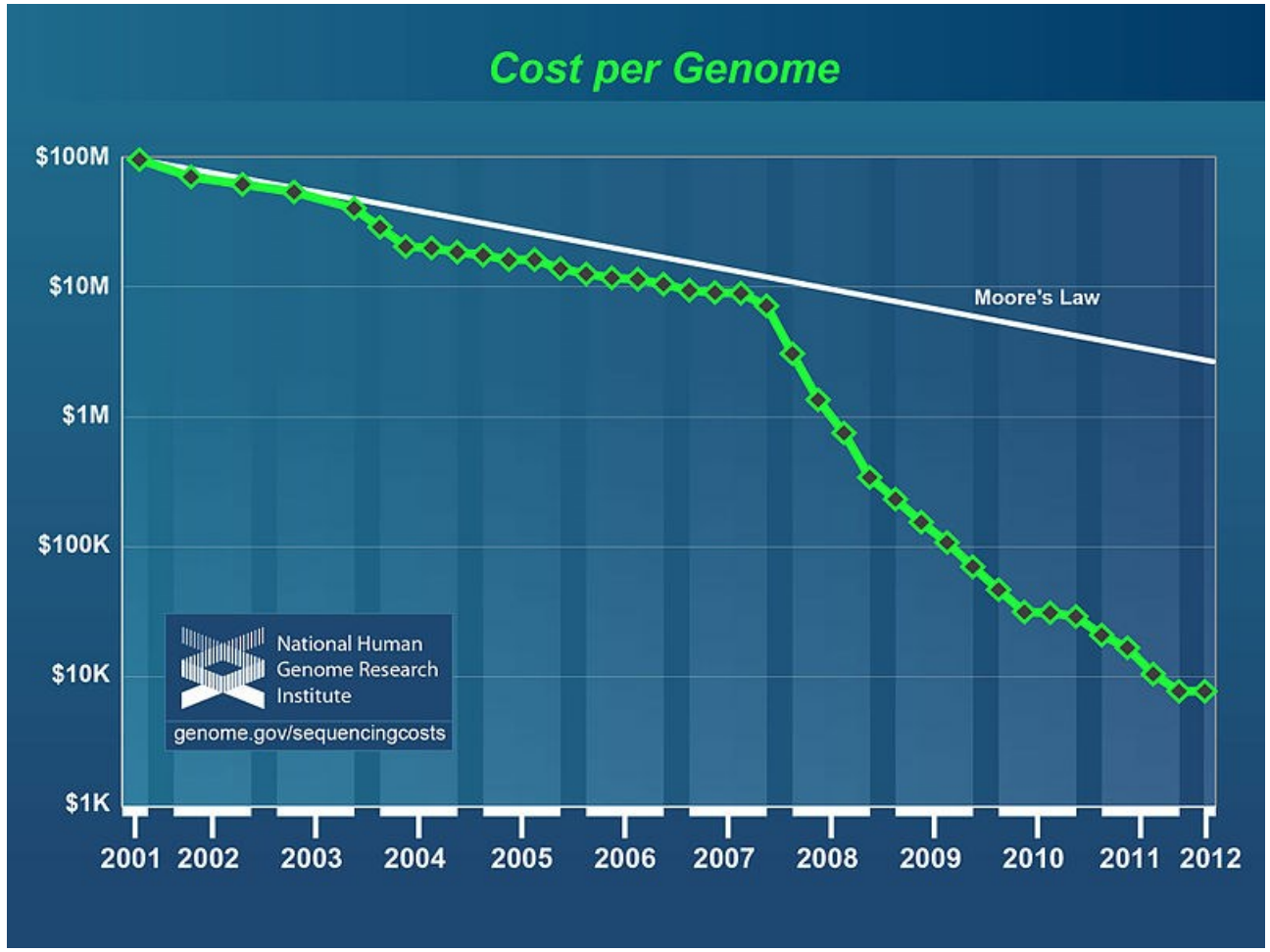
What are the Major Challenges?

- The Biology of Mammalian Cells
- The Cost of Culture Media and supplements
- The Capital Cost of a Facility
- Maintaining a Sterile Environment
- The Nature of the Consumer Products
- Regulatory and Consumer Acceptance
- Environmental impact
- The cost of manufacture has to come down over 1,000 fold.

The Biology of Mammalian Cells

- Primary cells like stems **cells are difficult to grow in continuous culture systems while maintaining phenotype**. There are limits to the density at which cells will survive.
- **Extraneous agents** may be present in freshly isolated stem cell cultures and could affect culture conditions. It will be difficult or impossible to extrapolate from one batch to another.
- **They require an amino-acid source; proteins** such as albumin, insulin, transferrin; hormones like TGF-beta and FGF-2, and buffers to maintain pH.
- **Scaling up of cells into large scale fermenters** has to be done gradually so the total culture time will be closer to 60 days.
- The **gains in productivity** that the Pharma industry have produced were **mostly by genetic manipulations of the cells.**
- **Mammalian cells grow more slowly** than bacteria, fungi or yeast and will be rapidly overgrown by any contaminant.
- **Biological systems have never heard of Moore's Law.**

Moore’s Law


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012

The Cost of Culture Media and Supplements

- The CE Delft report concluded that the **cost of media would need to be decreased by 100 to 10,000 -fold** based on their analysis of data from cultivated meat companies. Stem cells are the most fastidious cells to grow.
- The scenarios for decreasing these costs included growing cells to high cell densities, finding cheap sources of AA's and dramatically reducing the cost of the proteins and hormones required for cell growth.
- Currently the cost to produce these proteins and hormones as **recombinant proteins varied from $40/g to over $1million/g.**
- **The volumes of media required are likely to be higher** than estimated due to the longer culture phase and lower cell densities.
- Media is not 80% of the cost of cell production but only 20%.

The Scale and Capital Cost of a Facility

- CE Delft estimated the **cost of a facility** to produce 10Kton/year of cell-based meat **would be $450M US**.
- This facility did not include the cost of downstream processing , formulation of final product, packaging and QC.
- The **standard for manufacture assumed**, even if acceptable to regulatory authorities **would not be feasible due to the risks of contamination**.
- **The energy cost for these facilities would be high** and require all renewable energy sources to be more climate acceptable than conventional meat production.
- Scaling over 20K litres involves major technical and manufacturing risks. Just has announced plans to build 250K litre bioreactors.

Modern Biotechnology Facility

Maintaining a Sterile Environment

- To maintain an acceptable quality standard cell-based fermentation facilities will require.
- Positive pressure air handling systems with HEPA filtration.
- All of the water used for culture media would need to be distilled and sterilized.
- All incoming goods would need to be QC and sterilized before entering the clean rooms.
- Staff would need to wear full PPE and be highly trained.
- The final product would require some form of terminal sterilization or be stored and shipped frozen.
- First year microbiology quote : "JUST LIKE PREGNANCY, WHO CAN'T BE JUST A LITTLE BIT STERILE"

The Nature of the Consumer Products

- Insulin and other **pharmacologically active ingredients will have to be filtered out of the cell slurry** – this step was neither discussed nor costed in the Delft study (Downstream processing is (a) expensive and (b) often the most rate limiting step in production)
- **The final product of cell culture will mostly be a cell slurry** and as such cannot be frozen without the addition of other agents and preservatives.
- You will need to add a source of **fat for taste and texture**
- **Minerals and Vitamins** such as Calcium, Iron, B12 (Nutritional value?)
- What will the **self-life** be for these products (no preservatives?)
- Stored and shipped frozen
- **Not a Prime Steak** (talk of 3-D printing and edible cell scaffolds)
- How would you mimic the taste of an aged steak?

Aleph Farm 3-D Steak

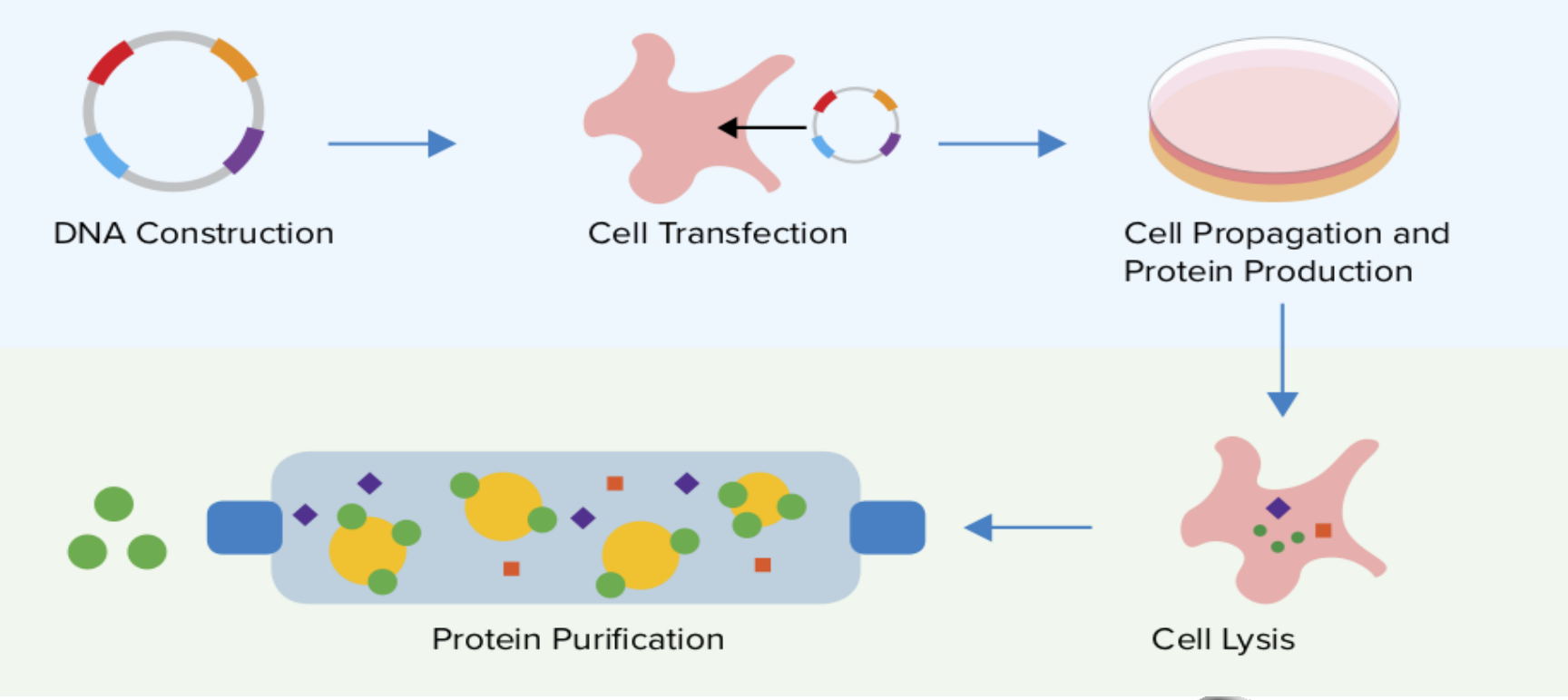
3D printed layers of cultured cells

Regulatory and Consumer Acceptance

- In the USA joint FDA/USDA regulatory control
- **In Europe questions around the use of recombinant proteins** in the manufacture of these products ?
- **Questions on labelling rules** (cultured meat) Several States in the US do not allow the word ‘meat’ to be used for anything other than animal products.
- **Taste** of the products ?
- **Nutritional Value** ?
- **Competition** from both plant-based and conventional meat
- **Cost** – no scientific evidence that the costs may be decreased by 1000-fold

Recombinant Protein Expression

OR PRECISION FERMENTATION



Use of Precision Fermentation in the Food Industry.

Protein produced	Expression system used	Type of food product	Company involved
Chymosin (rennin)	*Escherichia coli* *Aspergillus niger*	Enzyme for cheese production	Multiple manufacturers
Soy haemoglobin	*Pichia pastoris*	Ingredient in plant-based burger	Impossible Foods
Beta-lactoglobulin	*Trichoderma reesei*	Ice cream	Perfect Day
Casein proteins	Yeast	Protein powder	Fooditive group
			New Culture
		Yogurt	Remilk
		Milk	All G Foods
Myoglobin	*Pichia pastoris*	Plant-based meat	Motif FoodWorks
Egg white proteins	*Komagataella phaffi*	Sports drinks	Clara Foods (The Every Company)
Animal fats	Yeast	Multiple	Nourish Ingredients

Impossible Burger containing recombinant heme.

Using tobacco plants to produce cellular growth factors.

BioBetter-$10M raised to produce insulin,transferrin and TGF2

Regulatory

- **Rennet(chymosin)** an enzyme used in cheese production is a recombinant protein that has been used for many years (approved in 1990).
- In the USA, the **FDA and USDA** have agreed they will jointly regulate cell-based meat. FDA is using **GRAS** (generally recognized as safe) certification for recombinant food proteins.
- FDA has given perfect day approval for yeast produced **beta-lactoglobulin** for use in animal-free food except for infant formula. Requires the same allergy labeling as milk. Recombinant **Heme** is also approved for use in plant-based burgers.
- The **European marke**t has so far rejected the use of this technology in food.
- There is now an ideological rift between anti-GMO critics about the labelling of these products. New **USDA Bioengineered food label** introduced in 2016.

My Prediction for the Future of Food

- By 2030 all food will be marketed on the basis of: Nutrition Value vs Environmental Footprint.

- CBM and most PF products will service niche high-value markets.
- The inability to scale these technologies at reasonable costs is the major challenge.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