GREYSILO VENTURES
POSITION PAPER
02

REVOLUTIONIZING FOODTECH THROUGH MOLECULAR FARMING

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Introducing GSV Position Paper #2: Revolutionizing Foodtech Through Molecular Farming

Dear Readers,

In our ever-evolving world of food technology, innovation is the key to progress. GSV Position Paper #2 takes you on an exciting journey into the realm of molecular farming, where the future of food production is being reshaped by cutting-edge biotechnology. This document explores the fascinating applications of proteins produced in plants, a burgeoning field that promises to transform the way we nourish ourselves.

Within these pages, you'll find a comprehensive classification of some intriguing startups that have harnessed the power of molecular farming. But that's not all - we also take you on a deep dive into this groundbreaking technology with exclusive interviews featuring key players in the field. Their insights and experiences provide invaluable perspectives on the forefront of food innovation.

Moreover, we back our insights with concrete financial data from venture capital, shedding light on the investment landscape in this ever-expanding industry.
The fusion of technical and financial data in our GSV Position Papers is a unique approach to keep both critical aspects under the same roof. Our goal is to empower the foodtech community with the knowledge and tools needed for growth and success.

Join us in unraveling the potential of molecular farming, as we explore its transformational impact on the foodtech landscape. Get ready to embark on a journey that will shape the future of food and redefine the possibilities of biotechnology.

Welcome to GSV Position Paper #2 - your gateway to the future of food.

Sincerely,

The Authors.

GREYSILO VENTURES

POSITION PAPER 2

REVOLUTIONIZING FOODTECH THROUGH MOLECULAR FARMING

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From pharming to farming

Pharming is a term derived from the combination of 'pharmaceutical' and 'farming.' The concept, which began to take shape in the **early 2000s**, aimed to utilize genetically modified plants as bio factories for producing **therapeutic recombinant proteins**, spanning from antibodies to injectable enzymes for treating rare genetic diseases. The **first proof-of-concept** emerged in the 1990s, involving the production of **human serum albumin through transgenic tobacco and potato plants.** This pioneering effort aimed to address a significant challenge within the pharmaceutical industry: the high cost of therapeutics, particularly for chronic and orphan disease.

This issue persisted even after biotechnology had resolved key problems associated with the **initial hormonal treatments** that were already available, such as life-long **insulin injections** for diabetes through the engineering of human or mammalian cells. In 1923, Frederick Banting and John Macleod were jointly awarded the Nobel Prize in Medicine for their discovery that the absence of a small protein produced in the pancreas, insulin, was the cause of diabetes, and that its introduction into the bloodstream could effectively treat the disease. The pharmaceutical company Eli Lilly was the first to initiate **insulin extraction and production**, which involved extracting insulin from the pancreases of mammals like pigs and cows. This **process was costly**, dependent on the availability of source materials, and susceptible to **contamination from pathogens** that could be transmitted to humans.

Genetic engineering provided a solution by allowing the **expression of human insulin in a simple bacterium**, *Escherichia coli*, which eliminated the need for slaughterhouses and shifted the production to sterile GMP-compliant bioreactors. However, not all types of protein therapeutics can be produced using bacteria like *Escherichia coli*. Bacteria, as prokaryotes, lack the post-translational modification of proteins, which can significantly affect the reception and therapeutic effectiveness of the proteins in the human body. For example, proteins like glucore-brosidase and alpha-galactosidase A, used to treat Gaucher disease and Fabry disease, require cells to add the necessary post-translational modifications to the amino acid sequence, ensuring proper functionality in the human body.

To address this requirement, these proteins were typically produced by **genetically engineering human or mammalian cells.** However, the drawback of mammalian cell culture is the **high production cost**, which can result in the final price of therapeutic

proteins produced through these systems reaching thousands of euros per gram (and even exceeding this amount). On the other hand, plant cells can perform post-trans-lational modifications of proteins, some-what similarly (though not identically) to mammalian cells.

For these reasons, researchers began to explore the **potential of using plants** as bio factories to manufacture pharma-ceutical therapeutics. Plants, in fact, offer several advantages over mammalian cell systems. First, they do **not harbour pa-thogens** that could pose risks to human health. Second, as eukaryotes, they can perform crucial **post-translational mo-difications.** Third, they do **not require expensive bioreactors or growth media**, such as calf serum, making scalability a more feasible prospect by adjusting the amount of land used. This vision of the early 2000s ignited exci-tement and optimism around molecular pharming as the future production system for therapeutic proteins, including antibodies, recombinant enzymes, human and veterinary vaccines, and more.[1]

In pursuit of this vision, the European Union embarked on an ambitious international project in this field called **Pharma-Planta**, which brought together scientists from 12 countries, including South Africa.[2] However, within a few years, it became evident that major pharmaceutical com-panies weren't particularly interested in the **cost-effectiveness** of plant-based pharmaceutical production. This was because the primary expenses in drug development were associated with clinical trials. Additionally, **regulatory barriers emerged**, emphasizing the absence of a clear regulatory framework to ensure the safe introduction of plant-based pharmaceuticals into the market. The **reluctance to transition from traditional methods** to an **unproven and unregulated technology** partly accounts for why molecular pharming has remained a niche platform over the past two decades.

Moreover, the initial enthusiasm surrounding this new technology faced **significant setbacks** when it was revealed that genetically modified corn plants, created by the biotech company ProdiGene Inc., had mixed with a subsequent soybean crop in Nebraska. This incident prompted the U.S. Department of Agriculture (USDA) to fine the company and require them to purchase and destroy the contaminated soybeans. This controversy sparked a heated debate, with farmers and activists voicing their concerns and objections to the use of engineered plants for pharmaceutical production.[3]

The Resurgence of Molecular Pharming

Despite these earlier challenges, the outbreaks of **Ebola in 2014** and **COVID-19 in 2020** thrust this technology **back into the spotlight**. Its remarkable scalability, unburdened by the limitations of bioreactors, emerged as a potential solution to the global demand for vaccines. In 2014, researchers from the biotech company Mapp Biopharmaceuticals successfully produced **ZMapp4**, a cocktail of virus-neutralizing antibodies directed against three glycoprotein epitopes of the Ebola virus. These antibodies were manufactured using Australian tobacco plants (*Nicotiana benthamiana*) cultivated in dedicated greenhouses.

Although ZMapp's clinical trials did not yield the desired results, they did shed light on the incredible potential of plant-based drug production for **high-output** and **rapid scalability.**[4] On the other hand, the emergence of COVID-19 in 2020 has reignited interest in **innovative vaccine production methods**, reviving the concept of molecular pharming as a technology with significant scalability. This resurgence has sparked discussions about the possibility of implementing on-site vaccine production in regions where the need is most pressing.

Back to the "F": the Evolution of Molecular Farming

In contemporary times, the concept of molecular pharming is undergoing a transition from its original purpose of using genetically modified plants for therapeutic production to a **new paradigm: generating functional ingredients for human and animal nutrition directly from engineered plants.** This shift brings pharming back to the fields, with the aim of consistently enhancing agriculture and the food industry. Consequently, this area of biotechnology is returning to its roots, represented by the initial "F" in farming and, of course, food.

Genetically modified crops hold the potential to replace entire industrial sectors currently reliant on the exploitation of natural resources or unsustainable technologies. Many of the advantages observed in pharmaceutical production in plants, such as reduced production costs, enhanced scalability, and quicker market response that plague the pharmaceutical industry, can be extended to this new context. Furthermore, this approach offers **increased sustainability** and **reduced environmental impact**, harnessing the extraordinary chemical production capabilities of the most efficient systems on Earth: plants.[5]

02

Molecular Farming: Different Approaches, Same Momentum

ONE TERM, MULTIPLE TECHNOLOGIES

To make plants produce the same proteins as various organisms, different technologies and methods are required. Genetic transformation of plants can be either **stable or transient,** depending on whether the introduced genetic material is inherited by subsequent plant generations. This transformation can occur at the nucleus level or the chloroplast level and may be virus-induced or achieved through genetic modification. Let's delve into these methods in more detail.

Transient Transformation

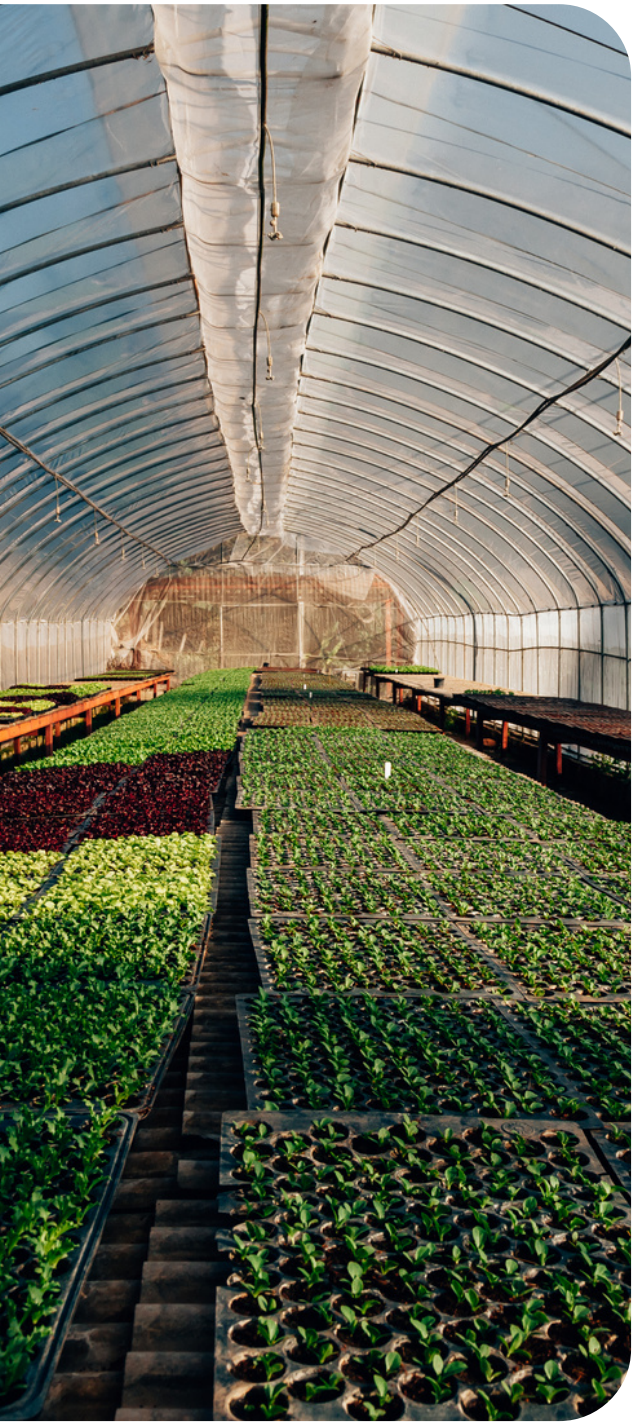
In this scenario, the **foreign gene(s) is not permanently integrated into the plant's genome,** preventing it from being passed on to the next generation upon reproduction. The advantage is that transient transformation can produce the desired molecules relatively quickly, typically within 1-8 weeks, depending on the plant species. This technique can be used to test whether the gene functions as intended before undertaking a stable transformation of the plant's genome.

Stable Transformation

In stable transformation, the new **genetic material is introduced into the plant's nuclear DNA, becoming a permanent part of its genetic makeup,** which is subsequently inherited by future generations. Similarly, stable transformation can be achieved by genetically manipulating chloroplasts, the small, organized structures in plant cells responsible for photosynthesis, which possess their own DNA. In this case, foreign DNA is introduced into the chloroplasts, becoming a permanent component of the plant's genetics, which can be passed on to subsequent generations. This method is sometimes preferred over modifying the nuclear plant DNA because it involves less complex procedures and results in more stable gene expression.

GMO vs. Virus-Induced

Viruses can be utilized to introduce foreign genes into plants and express relevant proteins. This technique **does not lead to a permanent modification of the plant's DNA,** which is why it is known as virus-mediated expression of proteins in non-GMO plants.



PRODUCTION SYSTEMS

Open Field

Open field agriculture is the **traditional method of farming** and can be applied to suitable crops, such as tobacco, corn, and soy, where stable genetic transformation is feasible. While it relies on **existing farming infrastructure** and has relatively **low capital expenditure (CAPEX)**, it comes with **regulatory risks** associated with open-field cultivation of GMOs. It also allows **flexibility in production** to meet demand.

Greenhouses

Greenhouse farming is suitable for **non-open field crops,** particularly vegetables like lettuce, tomatoes, hops, and even tobacco. Greenhouses can also be used for **transiently transformed plants.** They offer a **partially controlled environment,** enabling better control of plant nutrition and atmospheric conditions through CO2 injection. However, they are still **subject to seasonality,** and open greenhouses do not provide containment for GMOs.

Vertical Farming

Vertical farming is an evolution of greenhouse farming, involving **indoor cultivation under fully controlled conditions**, including lighting and atmosphere. These environments are contained by design, making them suitable for **GMO containment.**
Plants are typically grown on shelves, each illuminated by artificial lights to provide consistent inputs for growth throughout the year. Vertical farming is ideal for **transient expression systems** and allows for precise productivity measurement. Specific stress or signal induction for heterologous proteins, such as optogenetics tools, is more feasible in such systems. However, the limited space per plant may not accommodate larger tobacco cultivars, and the **high CAPEX and OPEX** make it more suitable for **high-value products** like pharmaceutical proteins.

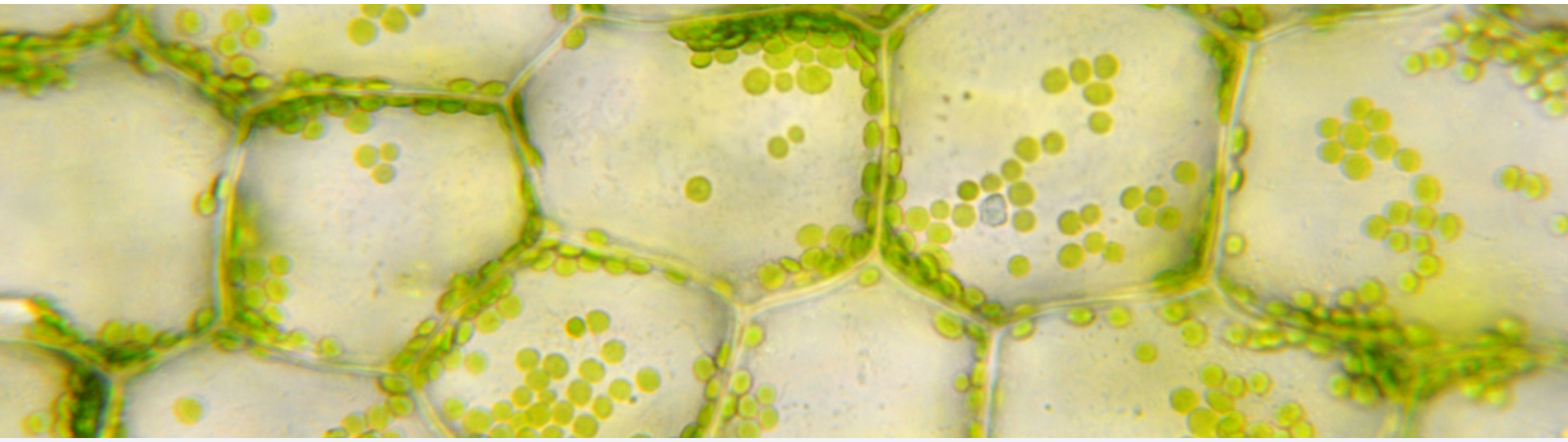
DOWNSTREAM PROCESSING

One of the primary challenges hindering the adoption of molecular farming is downstream processing. Although biomass production can be more scalable and cost-effective than bioreactors, downstream processing complexity and inefficiency can negate these advantages.

This is particularly relevant for **pharmaceutical-grade proteins**, which require **expensive purification systems** like high-affinity columns when the protein is randomly expressed in the cell's cytoplasm alongside millions or billions of other proteins.

To mitigate downstream processing costs and complexity, two strategies can be employed. First, **protein purification requirements can be reduced,** particularly when purity isn't critical, as is the case in some food applications. This approach involves using different and less expensive purification systems, like **isoelectric precipitation through wet separation.**

The second strategy involves **expressing the protein of interest in a less crowded cellular environment,** such as vacuoles. These two strategies can be combined. For instance, some of the first strategies involved expressing heterologous proteins in the seed oil bodies of *Brassica napus* by fusing the protein with an oleosin.[6] This approach can **capitalize on existing industrial processes**, like oil production from oilseeds, resulting in protein-rich by-products like defatted meal. Furthermore, protein content can be increased through wet separation and the use of membranes, which is a less costly alternative to high-affinity columns, although it may come with a trade-off in protein purity.



Why now?

The increasing global population, predicted to reach 10 billion by 2050, is driving a surge in meat demand. To address this growing demand sustainably, **new ingredients and technologies are required.** The current food system is a significant contributor to global greenhouse gas emissions, accounting for 26% of the total. Animal agriculture alone is responsible for 15% of these emissions. Most of the increased meat demand comes from emerging middle-income countries, where improved well-being has led to higher meat consumption. In response, innovations, and technologies such as **alternative proteins, biomass and precision fermentation,** and **cellular agriculture** have been considered as potential solutions to meet future protein demands.[7]

Even the seemingly distant field of **cellular agriculture,** involving the cultivation of real meat in a lab setting, could benefit from the development of plant molecular farming. One of the hurdles in cellular agriculture is the **growth media**, and essential animal proteins used in the growth media could be replaced by their heterologous counterparts produced in plants.
According to the Good Food Institute,[8] there are at least 12 companies currently enga-

ged in plant molecular farming to produce alternative food ingredients. We at **Grey Silo Ventures have identified 18,** differing from each other in terms of **molecular output** (chemical compound), **production process** and **geographic focus.**

This technology is now in the spotlight as it promises to be more cost-effective compared to existing technologies. It reduces the need for expensive bioreactors and eliminates the use of transgenic animals. Additionally, when GMO containment is necessary, the use of vertical farming can optimize production space.

The shift in focus from pharmaceutical proteins to food and industrial proteins is likely to allow for the use of **less expensive protein purification systems**. In this context, the purity of the protein itself is less critical than with pharmaceutical counterparts. Furthermore, the growing demand for plant proteins is paving the way for **multi-level production systems.** In these systems, most of the proteins are recovered to create a food protein concentrate or isolate, while the heterologous protein can be further separated from the process as a pure fraction. This potential separation allows for a more **economically viable process.**[9,10]

Investors are closely monitoring plant molecular farming as a cutting-edge avenue for fostering innovation within the alternative protein sector. This approach enables the cost-effective production of high-value functional ingredients. **In 2021,** investments in this field experienced a notable surge, reaching a total of **$118 million across 8 deals.**

According to GFI, **Moolec Science made history in early 2023 as the pioneer publicly traded company specializing in plant molecular farming,** joining the select group of publicly traded alternative protein firms. Moolec Science acquired LightJump Acquisition Corporation, a publicly traded special purpose acquisition company (SPAC), through a reverse merger valued at $138 million.

Subsequently, the amalgamated entity commenced trading on the NASDAQ under the ticker symbols MLEC and MLECW from January 3, 2023. As part of this transaction, **the company secured $10 million in development capital** from undisclosed investors on the same date through a private placement.

03

How many applications?

Given the extensive range of potential applications across various segments in both the **pharmaceutical** and **food markets**, the Molecular Farming total addressable market is extraordinarily vast. In addition to the well-known applications in the pharmaceutical industry, such as **antibodies, vaccines, and medical proteins,** plant molecular farming technology has made inroads into the food industry in recent years.

Several startup companies are now exploring this field to produce **food and industrial proteins,** which hold significant market potential. There's a strong focus on various **alternative proteins like dairy proteins (casein and whey), enzymes, heme** (a crucial ingredient in plant-based burgers like those from Impossible Meat, replicating the effect of meat-blood), **collagen, and egg proteins.**

Another promising area is the molecular farming production of **growth factors for cultivated meat.** This innovation not only has the potential to reduce their impact on pricing but also addresses ethical concerns related to the animal origin of current solutions. Furthermore, other markets that stand to benefit from plant molecular farming encompass **pigments, dyes, emulsifiers, fats, and metabolites.**

As a general observation, molecular farming unveils unexplored and extensive opportunities within the broader market of **nutraceuticals and functional foods.**

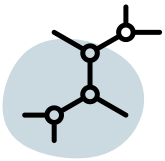
MARKET SEGMENT IN FOODS:

DAIRY PROTEINS

The **dairy ingredients market size** was valued at **USD 69 billion in 2022** and is expected to hit around **USD 132.59 billion by 2032**, growing at a CAGR of 6.8% during the forecast period from 2023 to 2032.[11]

Within this market category, the most interesting product category is **dairy proteins**: a market valued at **USD 13.93 billion in 2022** and is expected to expand at a CAGR of 5.95% during the forecast period, reaching **USD 19.71 billion by 2028.**[12] Two compounds that are being engingeered the most by companies in the space are (I) **whey protein** and (ii) **caseins**.

Respectively, the **global whey protein market size** was evaluated at **USD 8.25 billion in 2022** and is expected to attain around **USD 19.26 billion by 2032**, growing at a CAGR of 8.9% from 2023 to 2032.[13] The **global casein and caseinate market size** was evaluated at **$3.7 billion in 2022** and is slated to hit **$7.3 billion by the end of 2030** with a CAGR of nearly 5.8% between 2023 and 2030.[14]



ENZYMES

The **global food enzymes** (Carbohydrase, Lipase, Protease and others) **market size** accounted for **USD 2.06 billion in 2022** and it is expected to hit around **USD 3.92 billion by 2032**, expanding at a CAGR of 6.7% from 2023 to 2032.[15]

COLLAGEN

The **global collagen market size** was valued at **USD 9.12 billion in 2022** and is expected to grow at a compound annual growth rate (CAGR) of 10.2% from 2023 to 2030.[16]

However, if we consider the **food collagen market**, its size was valued at **USD 4.35 billion in 2021** and is expected to reach **USD 7.23 billion by 2030** with a CAGR of 5.1% from 2022 - 2030.

EGG PROTEIN

Different sources tried to amount the total market of egg proteins, and according to the number of coumpund that were included in the estimations the **global Egg Protein market size** is considered valued between **US$ 8.89 billion and USD 10.07 billion in 2022** and is expected to expand at a CAGR of 8.82% during the forecast period, reaching **USD 16.72 billion by 2028.**

GROWTH FACTORS

According to market research firm *Persistence*, the **global market for cellular ag growth factors** was valued at **$1.5 billion in 2019,** and is expected to grow 8% each year until **2029** when it will hit **$2.5 billion.**

04

Molecular farming: start-up companies

A Company operating in the field of molecular farming, producing **animal proteins leveraging plants** as hosts for production.

- **HQ:** Palo Alto (USA)
- **Date founded:** 2022
- **Stage:** Pre-seed
- **Funding:** Amount undisclosed
- **Investors:** Nucleus Capital, Tet Ventures, OneBio, Purple Orange Ventures, and ProVeg.

Bright Biotech developed a proprietary, light-driven, protein expression technology that uses **chloroplasts to make** extraordinarily high yields of **proteins in plants.**

- **HQ:** UK
- **Date founded:** 2019
- **Stage:** Seed
- **Funding:** 3,0 mln EUR
- **Investors:** FoodLabs, CPT Capital, Big Idea Ventures, FoodHack

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A Company working on **genetically engineered corn** (Zea mays) to express high levels of **bovine myoglobin** and other animal proteins.

- **HQ:** USA
- **Date founded:** 2022
- **Stage:** Seed
- **Funding:** Amount undisclosed
- **Investors:** ARCH Venture Partners, Open Prairie

A Company working on mass production of **recombinant human Type I collagen (rhCollagen)** for regenerative medicine.

- **HQ:** Israel
- **Date founded:** 2004
- **Stage:** Public Company
- **Funding:** 15.4 mln EUR
- **Investors:** Pontifax Funds, Mogdal Metal

Kyomei developed a **plant-based production system** producing animal proteins to power the next generation of meat alternatives, starting from **myoglobin.**

- **HQ:** UK
- **Date founded:** 2021
- **Stage:** Seed
- **Funding:** 2,0 mln EUR
- **Investors:** SOSV, Plug and Play

Molecular farming startup which operates in the dairy sector developing advanced **dairy proteins** through plant technologies.

- **HQ:** New Zealand
- **Date founded:** 2020
- **Stage:** Seed
- **Funding:** 2,1 mln EUR
- **Investors:** Movac, Better Bite Ventures, Ahimsa Investments, Aspire Fund

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PoLoPo is developing a plant bio-factory for high scale, custom-made production of proteins, with the first candidate being **egg protein (ovalbumin)** in an edible plant.

- **HQ:** Israel
- **Date founded:** 2022
- **Stage:** Pre-seed
- **Funding:** 1,5 mln EUR
- **Investors:** FoodLabs, CPT Capital, Siddhi Capital, Plug and Play, FoodHack, Milk & Honey Ventures

COMPANY NAME/ LOCATION	TECHNOLOGY	MOLECULAR OUTPUT/PRODUCT	STATUS
Aspyre Foods HQ: Palo Alto (USA)	*Not disclosed*	*Not disclosed*	Research phase
Bright Biotech HQ: UK	Stable expression in chloroplasts	Growth factors	Commercial phase
IngredientWerks HQ: USA	Stable expression in the corn (*Zea mays*) endosperm. Intended for wet method of protein extraction and purification. Open-field approach.	Heme, other animal proteins	Research phase
CollPlant biotechnologies HQ: Israel	Expression system Upstream growth Downstream processing	rhCollagen Multiprotein stable expression in vacuoles of Tobacco's leaves (*Nicotiana spp.*). Production in greenhouse.	Bioink for 3D bioprinted tissues – commercial phase Dermal/Soft Tissue Fillers – clinical phase 3D Bioprinted Breast Implants – preclinical phase
Kyomei HQ: United Kingdom	Stable expression in leafy greens	Bovine and porcine myoglobin and pigments	Pilot scale
Miruku HQ: New Zealand	Stable expression in Safflower	Dairy Proteins	Pilot scale
PoLoPo HQ: Israel	Stable/transient expression in potato's tuber (*Solanum tuberosum*)	Egg proteins first (Ovalbumin)	Research phase

05

In-Depth Exploration of Molecular Farming Startups

In this section, we present interviews with three pivotal startups in the molecular farming industry: **Aspyre Foods, Bright Biotech, IngredientWerks** and **PoLoPo**. These interviews offer valuable insights into the technology, covering its primary advantages and potential drawbacks, while also addressing regulatory challenges and opportunities within specific market segments.

Aspyre Foods is a stealth biotech start-up that utilizes biotechnology to produce animal proteins without exploiting animals. We interviewed **Thomas Bartleman, CEO and co-founder**, to gain insight into their decision to adopt molecular farming for protein production.

What motivated you to choose molecular farming for plant-based protein production?

"*There wasn't a single driving factor or moment that led to this decision. It was the culmination of a series of insights gained from extensive research on protein expression across various host organisms. These insights, combined with hypotheses regarding the potential of other technologies and industries, and a few 'aha moments' related to finer details, contributed to our choice. Once all these pieces fell into place, it became evident that molecular farming offered unique advantages compared to other technologies.*

It's important to note that ***molecular farming takes various forms****, including the* ***selection of specific plants, protein expression methods*** *(e.g., transient vs. transgenic), and the* ***choice of the growth environment*** *(e.g., contained vs. open field). Each of these choices presents its own set of advantages and challenges.*

*Arguably, the most challenging and promising combination is **transgenic protein production in field crops**. This approach has the potential to reduce humanity's reliance on animal-based agriculture, mitigate its negative environmental impacts, and do so at a price point that competes with animal-based proteins."*

In your view, what are the advantages of molecular farming technologies compared to well-known precision fermentation?

*"The advantages of transgenic protein production in field crops, when compared to precision fermentation, are particularly prominent in the production of low-cost, high-volume proteins. The primary advantage lies in the **overall production cost,** which comprises three components. The first is the cost of growing plants in open fields, mainly requiring sunlight and water, with additional nutrients, depending on the crop. The second and third components are infrastructure costs (CAPEX) and scaling capacity. The existing infrastructure for farming large crop volumes and processing already exists. When designing and building toward an at-scale solution, considering factors like the crop, the protein being produced, regulatory aspects, and other details, there's an **opportunity to utilize this existing infrastructure**, significantly reduce CAPEX, and enable substantial scaling capacity.*

*The secondary advantage, while not limited to transgenic field crops, is most pronounced in the transgenic field crops context. It involves leveraging the **existing revenue streams of selected field crops.** A good example is soybeans. When the protein of interest is produced transgenically in soybeans, the beans can be processed into oils, plant-based proteins, and the protein of interest. Stacking these revenue streams significantly increases the crop's value, allowing the protein of interest to be produced at a cost-competitive price compared to its animal-based counterpart.*

The advantages of transgenic protein production in field crops, [...] are particularly prominent in the production of low-cost, high-volume proteins.

Contamination risk can be both a significant advantage and a potential drawback of molecular farming. What is your perspective on this matter?

"*Molecular farming, when compared to fermentation, carries a* ***lower risk of contamination by harmful pathogens*** *in plants. In contrast, fermentation systems pose a much higher risk in this regard. This distinction has notable implications for operational costs and various aspects of food safety.*

However, it's essential to acknowledge that there are additional contamination risks to consider, extending beyond the presence of pathogens in plants. One concern relates to the ***potential contamination of product streams*** *from the selected crop with the desired protein when cultivated in open fields. Another consideration is the possibility of* ***gene flow,*** *where the specific genetic code for the desired protein spreads to other crops or plant lines.*
Mitigating these contamination risks necessitates a combination of rigorous testing, field trials, process optimization, and a comprehensive evaluation of the business model."

Despite choosing to keep their technological and scientific competitive advantages confidential for now, Thomas was able to share that they took the time to deeply understand the challenges of molecular farming and the associated processes, and to identify a set of solutions that address each pain point in an efficient and cost-effective manner. This aligns with the capacity of a company in this space to obtain regulatory clearance and commence sales.

How challenging is it to overcome regulatory barriers in the molecular farming field?

However, it's essential to acknowledge that there are additional contamination risks to consider, extending beyond the presence of pathogens in plants.

"*The challenges in overcoming regulatory barriers can vary significantly based on the jurisdiction. There are two distinct regulatory approval processes to consider.*
The first process involves regulatory approval for the protein of interest, known as Generally Recognized as ***Safe (GRAS)*** *status in the US, or its equivalent elsewhere. This process is well-established in the foodtech industry, and many precision fermentation ingredients have successfully navigated it. The level of difficulty and the timeline* ***depend on the jurisdiction****, with Singapore being perhaps the easiest, followed by*

the US, and the EU posing the most formidable challenge. We don't anticipate this to be a major hurdle.
*The second process, which applies to **transgenic field crops**, entails obtaining **approval for a genetically modified (GM) plant** variety capable of producing the protein of interest. This approval allows the crop to be commercially farmed in open fields.*"

Where does Aspyre plan to enter the market initially?

"*The US offers the **easiest path to market**, with a few other countries following closely. The regulatory barriers in other jurisdictions, such as the EU, will make it extremely **challenging to reach this stage** in the next decade, unless significant regulatory changes occur soon. This is, by far, the most substantial challenge. Even the most accessible path in the US will require a minimum of **three years of field trials**, with the potential for extension if the USDA and FDA, which jointly provide approval, deem it necessary or desirable.*

*As both regulatory pathways are currently **most favorable in the US**, we believe that's where we will initially enter the market. However, considering some indicators of regulatory framework shifts in other jurisdictions, and the fact that the USDA and FDA are still in the evaluation phases with other companies in this space, our perspective on this could change over the next 2-3 years.*"

> **The level of difficulty and the timeline depend on the jurisdiction, with Singapore being perhaps the easiest, followed by the US, and the EU posing the most formidable challenge.**

Bright Biotech, a Manchester-based biotech start-up founded at the end of 2019, employs chloroplasts as a biofactory to create animal-free growth factors from plants, specifically for the emerging field of cellular agriculture, with the goal of replacing animal-derived growth media, such as calf serum. Their mission is to reduce one of the major costs in cultivated meat production, which is represented by growth factors. By using chloroplasts to manufacture growth factors in plants, Bright Biotech aims to achieve price parity in the cultivated meat industry.

We spoke with **Mohammad El Hajj, CEO and co-founder** of Bright Biotech, to understand more about why he decided to focus his efforts on this technology.

What drove your interest in molecular farming technologies?

"*The interest in plant biotechnology and molecular farming was primarily driven by the* ***need for affordable proteins for medical*** *and* ***food applications****. The vast majority of recombinant protein manufacturers use fermentation-based technologies, which require expensive bioreactors and infrastructure, imposing constraints on cost-effective scalability and production capacity. In contrast, molecular farming* ***harnesses the inherent advantages of plants.*** *Plants can be grown on a large scale, significantly reducing production costs and offering remarkable scalability for protein production. This scalability allows for the rapid production of substantial quantities of proteins. Furthermore, plant-based production is intrinsically safer than using bacteria or mammalian cells due to its reduced risk of contamination with pathogens that can pose a threat to human health.*"

Bright Biotech's standout competitive advantage lies in its chloroplast-based expression technology, as well as the hyper-expression obtainable with plant leaves, which results in high yields. What can you tell us about your work?

"*Chloroplast-based expression technology capitalizes on the* ***stability and higher expression levels achievable in plant chloroplasts.*** *Unlike nuclear expression, which can diminish over time due to silencing effects and gene instability, chloroplast expression remains consistently robust. This reliability, combined with preci-*

sion-controlled farming for both yield and quality and the implementation of water recycling, underscores Bright Biotech's commitment to sustainability and cost-effectiveness.
Additionally, a ***plant leaf cell can contain up to 10,000 chloroplast DNA*** *that take in the gene of interest. The high gene copy number supports very high levels of recombinant protein production. Our yield is 2-5 grams per kilogram of leaf material. No gene silencing, position, and epigenetic effects in the chloroplast genetic system ensure unchanging levels of protein expression. Growth factors accumulate in our plants regardless of plant age, fluctuations in temperature, and light intensity.*

In terms of ***market entry,*** *Bright Biotech is strategically positioned to make a significant impact in the* ***cultivated meat technology sector,*** *possibly achieving a faster time-to-market thanks to a Generally Recognized as Safe (GRAS) system, as well as reducing the risk of contamination."*

What are the main advantages you see in using molecular farming technologies in the cultivated meat sector?

"*This burgeoning industry is actively shifting away from traditional components like Fetal Bovine Serum (FBS) for ethical reasons and to reduce variability in cell culture systems. Bright Biotech's plant-based technology offers a solution to this challenge by providing* ***growth factors at the necessary quantity, quality, and cost, aligning with the industry's scaling needs.*** *As the cultivated meat industry continues to evolve, Bright Biotech's high yield, lower-cost approach without the need for bioreactors or expensive infrastructure, ultra-scalability, and sustainability initiatives are poised to make a lasting impact on the future of protein production.* ***In terms of regulation****, unlike fermentation technologies,* ***our system does not harbor harmful microbial toxins or animal pathogens.*** *This advantage facilitates and reduces the cost of protein purification. The localization of foreign genes within chloroplast DNA eliminates transmission through pollen, addressing concerns related to the escape of foreign genes and antibiotic-resistant marker genes introduced into plants to the environment through pollen. This gives Bright Biotech a containment advantage compared to other plant technologies.*"

In terms of market entry, Bright Biotech is strategically positioned to make a significant impact in the cultivated meat technology sector.

IngredientWerks is a USA-based biotech start-up founded in 2022. They are developing a proprietary corn that expresses high levels of bovine myoglobin, a heme-binding protein used in meat alternatives to provide the taste, texture, and flavor of real meat.

Matt Plavan, CEO of IngredientWerks, addressed some key questions regarding molecular farming and explained why they believe it's the next big thing.

What led you to adopt molecular farming to develop proteins using corn?

"*Our team brings more than ten years of experience in transforming corn while at Agrivida to produce several protein enzymes for use in the animal feed market. Once the team demonstrated* ***the ability to transform corn to produce heme protein bioidentical to that found in animal meat,*** *they knew they had a breakthrough with significant commercial value. As for* ***corn as a host crop,*** *it possesses several properties that make it an ideal host for transformations:* ***efficient breeding, no toxins or anti-nutrients, and easy extraction.***"

What would you say is your biggest competitive advantage compared to other technologies?

The US heme protein market for meat analogues will be our first product to market. This will be our plant-based bovine myoglobin.

"*Clearly, the most significant advantage of our proteins as an ingredient for the meat or cheese analogue markets is the* ***low cost of production compared to precision fermentation.*** *This advantage is afforded by the ability to leverage the* ***existing corn cultivation and processing industry,*** *and to sell the vast majority of the grain (all but about 1% of the corn) components into the corn ingredient market. It's important to note that the carbon footprint is significantly less than precision fermentation and animal agriculture production.*"

Which market, both geographically and product-wise, do you believe you'll enter first?

"*The US **heme protein market** for meat analogues will be our first product to market. This will be our plant-based bovine myoglobin, which we hope will be in the market by 2026, serving as a scalable production source for the ingredient we believe is essential to **replicate that 'meaty' taste experience** with real animal meat.*"

PoLoPo is an Israel-based startup founded in 2022. The scope is to develop a plant bio-factory for high scale, custom-made production of proteins, with the first candidate being egg protein (ovalbumin) in an edible plant.

We had the opportunity to interview **Maya Sapir-Mir, the CEO and Co-founder** of PoloPo, to gain valuable insights into their technology and their approach to scaling up their processes.

What is (are) the target compound(s) (protein(s)) your company is working on?

*"At PoLoPo, we are focused on a plant-based platform that allows us to produce a wide range of animal-based proteins. Our initial target protein is **Ovalbumin,** a **functional egg protein** that enables the creation of egg-based products with identical properties."*

What is the host plant used to express it?

*"Our host plant is the **potato**, and the target protein accumulates specifically in the potato tuber. We refer to our host plant as "SuperAA," which serves as a versatile platform for animal-based protein production."*

What is the gene-induction method (transient/stable modification)?

*"Our approach involves bioengineering the potatoes through **stable plant modifications.** However, it's important to note that our finished product, a pure protein powder, is considered **non-GMO."***

> **Our downstream processing relies on existing potato processing technology, primarily used for starch extraction. We incorporate additional steps to extract the protein while preserving its functionality.**

Where do you plan to scale your production (open field / CEA)?

*"We are aiming to scale our production through **open field cultivation** to maintain **cost-effectiveness.** Potatoes are known for their **resilience and durability,** making them a favorable choice for our production. Additionally, we are exploring alternative growth techniques, such as **aeroponic cultivation**, which may offer more controlled growth conditions."*

What does your downstream processing entail?

*"Our downstream processing relies on existing potato processing technology, primarily used for **starch extraction**. We incorporate additional steps to extract the protein while preserving its functionality. This process is followed by a drying step, resulting in a **pure protein powder** that serves as a high-quality, functional ingredient."*

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References

[1] Journal: Pany, S; Mohanty, N; C. Koellhoffer, E; Osota, E; Shukla, S; P. Rybicki, E; K. Pokorski, J; F. Steinmetz, N; **Integrating plant molecular farming and materials research for next-generation vaccines**, Nature Reviews Materials, 7, 372–388. (2022) DOI: 10.1038/s41578-021-00399-5

[2] Journal: Pany, S; Mohanty, N; **Molecular Pharming: A Brief Overview.** Journal of Agricultural, Biological and Environmental Sciences, 2, 36-39. (2015)

[3] Journal: Kaiser, J; **Is the Drought Over for Pharming?**, Science, 320 n.5875, 473-475. (2008) DOI: 10.1126/science.320.5875.473

[4] Journal: Sainsbury, F; Lomonossoff, G.P; **Transient expressions of synthetic biology in plants**, Current Opinion in Plant Biology, 19, 1-7 (2014). DOI: 0.1016/j.pbi.2014.02.003

[5] Journal: Armstrong, E; Larson, E; Harper, H; Webb, C.R; Dohleman, F; Araya, Y; Meade, C; Feng, X; Mukoye, B; Levin; M.J; Lacombe, B; Bakirbas, A; Cardoso, A.A; Fleury, D; Gessler, A; Jaiswal, D; Onkokesung, N; Pathare, V.S; Phartyal, S.S; Sevanto, S.A; Wilson, I; Grierson; C.S; **One Hundred Important Questions Facing Plant Science: an international perspective**, New Phytologist, 238–2, 470–481 (2023). DOI: 10.1111/nph.18771

[6] Journal: Van Rooijen, G.J; Moloney, M.M; **Plant seed oil-bodies as carriers for foreign proteins**, Biotechnology (N Y), 1, 72-7 (1995). DOI: 10.1038/nbt0195-72. PMID: 9634752.

[7] Website: Kingstone Schweizer Ventures; **How will molecular farming shape the future of food production?**, Medium (2022).

[8] Website: Good Food Institute; **Plant molecular farming**, (2023).

[9] Website: Paradisi, L; **Unlocking the Potential of Plant Molecular Farming**, Forward Fooding, (2023).

[10] Online report: Carter, M; Cohen, M; Eastham, L; Gertner, D; Ignaszewski, E; Leman, A; Murray, S; O'Donnell, M; Pierce, B; Voss, S; **2022 State of Industry Report: Fermentation**, Good Food Institute, (2023).

[11] Online report: Precedence Research, **Dairy Ingredients Market** *(By Product: Milk Powder, Casein & Caseinate, Whey Ingredients, Lactose, Proteins; By Application: Pediatrics, Sports Nutrition, Medical Nutrition, Health Foods, Bakery, Dairy; By Livestock: Cows, Other livestock (Buffaloes, goats, sheep, and camels); By Form: Dry, Liquid; By Production Method: Traditional Method, Membrane Separation)* - **Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2023 - 2032**, (2023). Report code: 1718

[12] Online report: Industry Research, **Global Dairy Protein Industry Research Report 2023, Competitive landscape, Market size, Regional status and prospects,** (2023). SKU ID : Maia-22365920

[13] Online report: Precedence Research, **Whey Protein Market** *(By Type: Isolates, Concentrates, Demineralized, Hydrolysate; By Application: Nutritional, Personal Care, Food, Feed, Infant Formula, Sports and Performance Nutrition, Functional/Fortified Food; By Distribution Channel: Supermarkets/Hypermarkets, Convenience Stores, Specialty Stores, Online Stores, Other Distribution Channels; By End Users: Athletes, Bodybuilders, Lifestyle Users)* - **Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2023-2032,** (2023). Report code: 2530

[14] Online report: Zion Market Research, **Casein And Caseinate Market By Casein Type *(Rennet Casein And Acid Casein)*, By Caseinate Type** *(Calcium, Sodium, Potassium, And Others)*, **By Application** *(Food & Beverages, Pharmaceuticals, And Dietary Supplements)*, **And By Region - Global And Regional Industry Overview, Market Intelligence, Comprehensive Analysis, Historical Data, And Forecasts 2023 - 2030**, (2023). Report code: ZMR-7670

[15] Online report: Precedence Research, **Food Enzymes Market** *(By Source: Microorganism, Animal, Plant; By Type: Carbohydrase, Lipase, Protease, Others; By Application: Bakery Products, Beverages, Dairy Products, Nutraceuticals, Others)* - **Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2023-2032**, (2023). Report code: 2571

[16] Online report: Grand View Research, **Collagen Market Size, Share & Trends Analysis Report By Source** *(Bovine, Porcine)*, **By Product** *(Gelatin)*, **By Application** *(Food & Beverages, Healthcare)*, **By Region, And Segment Forecasts, 2023 - 2030**, (2023). Report ID: GVR-1-68038-835-0

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About the contributors

The mission of Grey Silo Ventures, the Corporate Venture Capital of Cereal Docks Group established to invest in the supply chain of non-animal-based ingredients and related innovative technologies, is to broaden horizons in the global food-tech sector while maintaining the original vocation as a processor of plant based sources and explorer of new opportunities for innovation and business diversification.
Grey Silo Ventures is committed to study the great potential of new fermentation processes and innovative green proteins, by using them to create novel ingredients. The ag-tech world and cellular agriculture represent other areas of interest that are part of the value chain in which Cereal Docks Group operates.

Cereal Docks is an Italian industrial group headquartered in Camisano Vicentino (Vi), active since 1983 in the first agro-food processing for the production of ingredients destined for applications in the feed, food, pharma, cosmetic and technical use sectors. Today, the Cereal Docks Group employs more than 410 people in eleven different facilities.
In addition to consolidation of its core business, the Cereal Docks Group is also committed to new development focused on transforming the concept of diet to that of nutrition. The development of solutions that guarantee the correct balance of nutritional principles in a context defined by quality, safety, standardization and environmental sustainability is central for offering better responses to health and wellness needs.

GREYSILO VENTURES

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