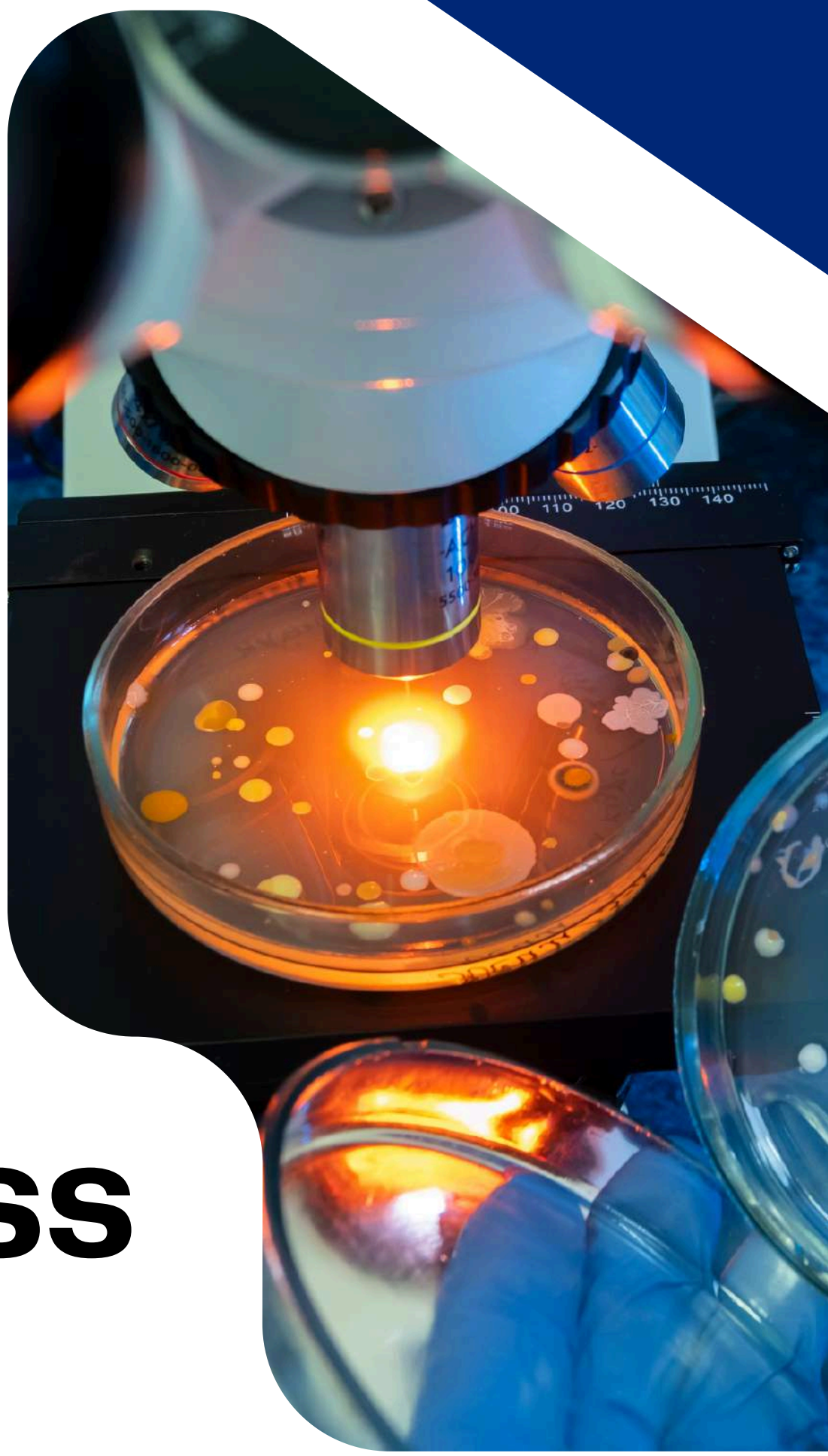
USP-BRAZIL



Business Plan

Glycosy-N-ation

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1. Executive Summary

The project aims to engineer two model microorganisms widely used in biotechnology, Escherichia coli (bacteria) and Saccharomyces cerevisiae (yeast), to produce glycoproteins with a sugar profile compatible with human forms. As a proof-of-concept, we sought to work with human beta-glucocerebrosidase, an enzyme used in the treatment of Gaucher disease. This protein, when expressed in other non-human biological systems such as E. coli and S. cerevisiae, requires the necessary glycosylations for its enzymatic activity.

In this context, the entire experimental design was developed in the following steps: construction of the recombinant gene; cloning and expression vector; transformation of the host strain; screening of producer clones; recombinant expression; modulation of glycosylation; extraction and purification; enzymatic activity testing; as well as characterization by mass spectrometry.

This will be the first β-glucocerebrosidase expression systems in bacteria and yeast adapted for human enzyme production. This could represent a much more affordable therapeutic alternative compared to commercially available drugs.

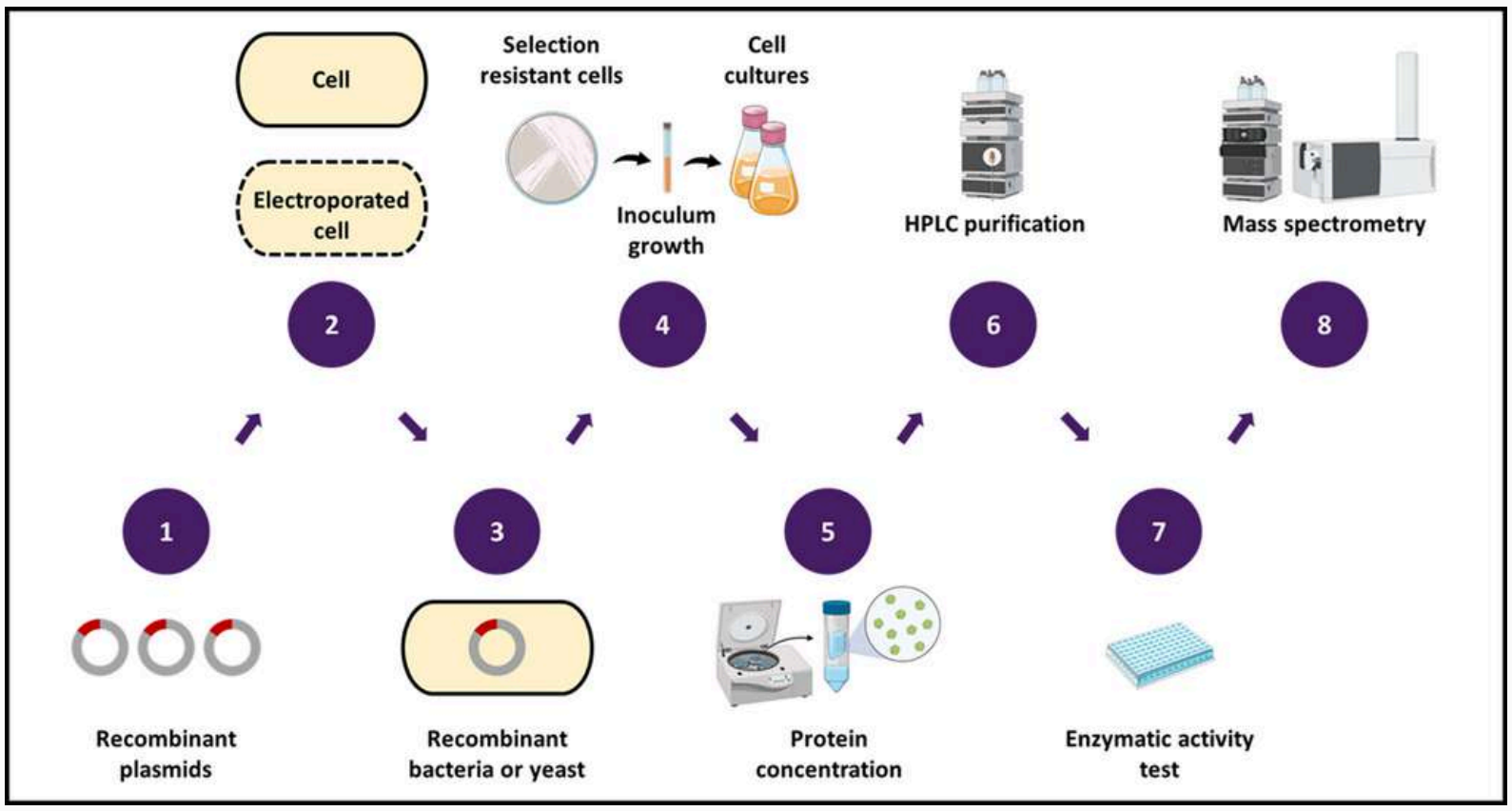


Figure 1. Experimental workflow. Expression enzymatic of human beta-glucocerebrosidase in recombinant models of microorganisms such as bacteria (E. coli) and yeast (S. cerevisiae). Source: obtained on our own.

2. Project Description

Sphingolipidoses are a group of inherited metabolic diseases caused by deficiencies in enzymes responsible for breaking down sphingolipids. These molecules form a class of lipids found in cell membranes, particularly abundant in nerve cells, playing crucial roles in cellular structure and function, including cell signaling and the regulation of processes related to nervous system development and myelination. However, the accumulation of sphingolipids in organs and tissues can lead to neurological, bone, joint, respiratory, and cardiac problems, as well as enlargement of the liver and spleen. Each sphingolipidosis is associated with a deficiency in a specific enzyme and the accumulation of different sphingolipids.

The treatment of sphingolipidoses depends on the type and severity of the disease. In some cases, enzyme replacement therapy is used to substitute the deficient enzyme. Substrate reduction therapy is an alternative approach, particularly when enzyme replacement is not suitable, and involves the use of drugs to decrease the production of sphingolipids accumulated in the body. In addition, other treatment options such as bone marrow transplantation and gene therapy exist, though these procedures are highly complex and costly. It is important to note that there is no definitive cure for sphingolipidoses; however, when detected early, effective treatments can significantly increase patients' life expectancy and quality of life.

Gaucher disease is a sphingolipidosis characterized by the accumulation of glucocerebrosides in organs such as the spleen, liver, and bone marrow due to a deficiency in the production of glucocerebrosidase. This enzyme breaks down glucocerebrosides within lysosomes — organelles responsible for intracellular digestion and recycling of cellular components. Glucocerebrosides are glycosphingolipids, also known as glycolipids, consisting of a sphingosine backbone linked to one or more sugar residues. These lipids play important roles in biological processes such as signal transduction, modulation of the immune response, and cell adhesion.

Since rare diseases such as Gaucher disease have a low annual incidence in the population, it is estimated that only about 1 in 60,000 people worldwide are affected. In Brazil, approximately 700 patients are currently being treated through the Unified Health System (SUS), although this figure is only an approximation, as the number of undiagnosed cases is unknown. Clinical diagnosis is made by measuring decreased beta-glucocerebrosidase enzyme activity and through genetic testing to identify mutations in the GBA1 gene. Imaging exams such as abdominal ultrasound or magnetic resonance imaging (MRI) of the abdomen and bones are used to assess the extent of systemic organ involvement.

Gaucher disease can be clinically classified into three main types. Type 1 is the non-neuropathic or chronic non-neuropathic adult form, which may be asymptomatic or present varying degrees of liver and spleen enlargement, hematologic manifestations, and bone involvement. Type 2 is the acute neuropathic or infantile neuropathic form, usually appearing within the first two years of life and associated with simultaneous enlargement of the liver and spleen, severe neurological alterations, and early death. Finally, Type 3 is the subacute neuropathic or juvenile neuronopathic form, which manifests in childhood and is considered more severe than Type 1. It is associated with slow and progressive neurological dysfunction, with death typically occurring between 10–19 or 30–39 years of age. Studies indicate that the non-neuropathic form is the most prevalent, whereas the neuropathic forms are rarer among individuals affected by Gaucher disease.

Only a few biological drugs are currently available for the treatment of Type 1 Gaucher disease through enzyme replacement therapy. The first was Taliglucerase alfa, produced using genetically modified carrot root cells by the Israeli company *Protalix BioTherapeutics*, which established a technology transfer and local production agreement with Brazil's Fiocruz. Another option is Imiglucerase, produced in Chinese hamster ovary cells by the French company *Sanofi*, and Velaglucerase alfa, produced in a human fibroblast cell line by the Japanese company *Takeda Pharmaceutical Company Limited*. The major advantage of these drugs lies in their glycosylation pattern, which closely resembles that of the endogenous enzyme, reducing the risk of immune reactions.

There are also several technological initiatives from startups and emerging companies with clinical-stage projects aimed at developing new gene and enzyme replacement therapies for Gaucher disease. For instance, the British companies *Spur Therapeutics* and *Freeline Therapeutics* focus on inducing endogenous enzyme production directly in the liver, while *M6P Therapeutics* in the United States and *BioArctic* in Sweden are dedicated to treating the neuropathic forms of the disease.

	Scientific name	Taliglucerase alfa	
	Trading name	Elelyso / Uplyso	
	Treatment	Gaucher disease type 1	
	Therapeutic class	Enzyme replacement therapy	
	Production	Genetically modified carrot root cells	**It was the first biological medicine produced in plant cells**
	Administration	Intravenous infusion	
	Enterprise	Protalix BioTherapeutics	**Protalix has signed an agreement with Fiocruz for technology transfer and local production of Ulypso in Brazil**
1	Country	Israel	
	Scientific name	Imiglucerase	
	Trading name	Cerezyme	
	Treatment	Gaucher disease type 1	
	Therapeutic class	Enzyme replacement therapy	
	Production	Chinese hamster ovary cells	**Imiglucerase undergoes controlled glycolytic modifications, which are essential for the enzyme to be effective in treating the disease**
	Administration	Intravenous infusion	
	Enterprise	Sanofi	**Originally developed by Genzyme Corporation (United States)**
2	Country	France	
	Scientific name	Velaglucerase alfa	
	Trading name	Vpriv	
	Treatment	Gaucher disease type 1	
	Therapeutic class	Enzyme replacement therapy	
	Production	Human fibroblast cell line	**Since these cells are human, theyv produce a glycosylation (sugar modification) of the enzyme that is closest to the natural enzyme**
	Administration	Intravenous infusion	**This reduces the risk of immune reactions**
	Enterprise	Takeda Pharmaceutical Company Limited	**Technology was originally developed by Shire plc (United Kingdom)**

	Startups and Emerging Companies	
1	**Spur Therapeutics**	Development of gene therapies for rare diseases, including Gaucher disease type 1
	(United Kingdom)	Uses an adeno-associated viral vector (AAV) to deliver a modified version of the GCase enzyme (GCase85) directly into the liver
		Aims to have an endogenous and sustained productiojn of the enzyme
		Status: clinical phase
2	**M6P Therapeutics**	Development of gene and enzyme replacement therapies for lysosomal storage diseases
	(United States)	Employs an S1S3 co-expression platform to increase the mannose-6-phosphate content of enzymes, improving their uptake by target tissues
		Positive preclinical data for candidate AAV-GBA-S1S3, also targeting neuronopathic forms of Gaucher disease
		Status: clinical phase
3	**Freeline Therapeutics**	Development of gene therapies for rare diseases, including Gaucher disease type 1
	(United Kingdom)	Utilizes an AAVS3 vector to deliver a midified version of the GCase enzyme (GCase_var85) to the liver, promoting sustained endogenous production
		Clinical phase 1/2 data indicates reduction in substrate load and improvements in symptoms with a single intravenous treatment
		Status: clinical phase
4	**BioArctic**	Development of therapies for rare neurological diseases, including Gaucher disease type 3
	(Sweden)	Combines enzyme replacement therapy with its brain transporter technology to improve enzyme delivery to the central nervous system
		Started a project focused on neuropathic forms of Gaucher disease
		Status: clinical phase

3. Problem

Sphingolipidoses, including Gaucher disease, are rare inherited metabolic disorders caused by deficiencies in enzymes that break down sphingolipids, leading to their harmful accumulation in organs and tissues. This can result in severe neurological, bone, joint, respiratory, and cardiac complications, as well as organ enlargement. Gaucher disease, specifically, is caused by a lack of glucocerebrosidase, resulting in the buildup of glucocerebrosides.

Current treatments, primarily enzyme replacement therapies (e.g., imiglucerase, taliglucerase alfa, velaglucerase alfa), are limited in availability, expensive, and rely on complex eukaryotic production systems. Alternative approaches, such as substrate reduction therapy, bone marrow transplantation, and gene therapy, are either limited in efficacy, highly complex, or costly. The rarity of the disease further complicates diagnosis and treatment, with only a few hundred patients in Brazil currently receiving care through the public health system.

In summary, the key problems are: limited treatment options for Gaucher disease, especially for rare neuropathic forms; high cost and complex production of enzyme replacement therapies, restricting patient access; no definitive cure, making early diagnosis and effective management essential; as well as the need for innovative therapies that are more accessible, scalable, and effective.

4. Market

4.1 SWOT Analysis

The SWOT analysis is a strategic planning tool used to evaluate a project's internal and external factors by identifying its Strengths, Weaknesses, Opportunities, and Threats. This framework helps guide decision-making by revealing the project's advantages and limitations, as well as external conditions that can influence its success. For scientific and technological initiatives, such as the development of biotherapeutic production systems, the SWOT analysis is particularly valuable because it enables a comprehensive understanding of both technical feasibility and market positioning, supporting strategic choices and partnership development.

Strengths (S)

- Drastic cost reduction: The proposed technology significantly lowers production expenses compared to conventional eukaryotic systems, making therapies more affordable and accessible.
- Global market potential: The innovation can be applied to a broad range of biopharmaceuticals, expanding its relevance beyond national boundaries and increasing its competitiveness internationally.
- Public interest (SUS): The technology directly benefits public healthcare systems like Brazil's SUS by reducing governmental expenditure on high-cost treatments.

Weaknesses (W)

- Non-native glycosylation: As microbial systems do not naturally perform human-like glycosylation, this poses a technical challenge that may affect the efficacy or acceptance of the final product.
- Downstream process complexity: The purification and post-production stages can be technically demanding, requiring optimization to ensure product quality and scalability.
- Blocking patents: Existing patents in the field may restrict the use of certain enzymes or pathways, potentially delaying or complicating the development and commercialization process.

Opportunities (O)

- Licensing with local companies: Collaboration with domestic pharmaceutical or biotech firms could facilitate technology transfer, accelerate product deployment, and strengthen the national biotech sector.
- Public funding programs: Governmental and institutional grants can support research and development, reducing financial barriers and stimulating innovation.
- Partnerships with CDMOs and universities: Strategic alliances with contract development organizations and academic institutions can enhance technical expertise, accelerate innovation, and expand the project's reach.

Threats (T)

- Competition with already approved biopharmaceuticals: Established therapies with proven efficacy and regulatory approval may hinder the market entry of new alternatives.
- Regulatory barriers: Biopharmaceutical products must comply with strict safety and efficacy standards, which can delay approval and commercialization.
- Clinical skepticism: Healthcare professionals and patients may initially hesitate to adopt a new production technology until it proves its reliability and safety through clinical validation.

4.2 Costs

The treatment of rare diseases, such as Gaucher Disease, relies heavily on enzyme replacement therapies based on glycoproteins, such as imiglucerase. Currently, the production of these glycoproteins depends on complex eukaryotic expression systems (including Chinese hamster ovary, carrot, or human fibroblast cells), which result in extremely high production costs and, consequently, limited patient accessibility.

For an average patient weighing 70 kg, requiring a dosage of 60 U/kg every two weeks, the annual cost of treatment with imiglucerase (commercially known as Cerezyme) is approximately R$1,107,618.96, based on a cost of R$4,057.52 per 400 U vial. With 825 patients currently receiving treatment through the Brazilian Unified Health System (SUS) — a public healthcare system providing universal and free medical access funded by taxes — this scenario represents an annual public expenditure of nearly R$1 billion. This highlights a clear and urgent need for more accessible and efficient biotherapeutic production solutions to improve affordability and expand access.

Regarding our project's application potential, glycosi-N-ation aims to overcome the current production limitations by developing innovative microbial platforms in Escherichia coli and Saccharomyces cerevisiae for the production of recombinant glycoproteins with human-like glycosylation patterns. As a proof of concept, our focus is on the β-glucocerebrosidase (GCase) enzyme, used in Gaucher Disease treatment.

However, the true innovation of our strain lies in its theoretical ability to produce the universal glycan precursor $Man_3GlcNAc_2$. This precursor can either be directly applied in therapies such as GCase or used modularly, allowing the same strain to be adapted for the production of any desired human glycoprotein — ranging from vaccines and diagnostic tools to other therapeutic proteins — simply by introducing additional complementary enzymes. This modularity opens a broad range of applications and represents a disruptive market potential.

Ultimately, mutual benefit is achieved through strategic partnerships aimed at advancing innovation and leadership in the biopharmaceutical sector. For pharmaceutical, biotechnological, or diagnostic companies, collaboration represents a unique opportunity to gain access to a disruptive technology, positioning themselves at the forefront of affordable glycoprotein production. Such a partnership enables: significant cost reduction, through scalable and efficient microbial systems capable of dramatically lowering current and future therapy prices, thus expanding markets and patient access; accelerated innovation and R&D, via a versatile and modular platform for developing new commercially valuable glycoproteins; enhanced corporate reputation, through alignment with a high-impact social project developed by a leading research team from the University of São Paulo (USP) committed to healthcare accessibility; as well as strong return on investment (ROI), as leadership in this niche market and the creation of more competitive and affordable biotherapeutics promise substantial financial and reputational returns.

4.3 Benchmarking (TAM–SAM–SOM)

Total Addressable Market (TAM)

In our case, the TAM represents the global market potential for enzyme replacement therapies (ERTs) and recombinant glycoproteins that could benefit from cost-efficient microbial glycosylation technologies.

According to market reports, the global enzyme replacement therapy market is valued at approximately USD 10–12 billion annually, with an expected growth rate of ~7% CAGR due to increasing diagnoses of rare diseases and expanding therapeutic applications. Additionally, the global recombinant glycoprotein market, encompassing monoclonal antibodies, vaccines, and therapeutic enzymes, exceeds USD 250 billion, representing the full potential addressable through scalable and affordable glycoprotein production technologies.

The estimated USD 250 billion TAM represents the total potential market for recombinant glycoproteins, encompassing all biopharmaceutical applications that depend on glycosylated proteins. This figure extends beyond the enzyme replacement therapy (ERT) segment, valued at approximately USD 10–12 billion annually, and includes major categories such as monoclonal antibodies (mAbs)—the largest share of the biopharmaceutical market, exceeding USD 180 billion—along with recombinant and glycoprotein-based vaccines (over USD 70 billion) and other therapeutic enzymes and recombinant proteins.

Together, these segments form a global market exceeding USD 250 billion, which defines the total addressable opportunity for scalable, cost-effective glycoprotein production platforms like the proposed microbial technology. This estimation is supported by consolidated biopharmaceutical market analyses that indicate global biopharmaceutical revenues surpassing USD 350 billion, with more than 70% derived from recombinant glycoproteins (GRAND VIEW RESEARCH, 2024; FORTUNE BUSINESS INSIGHTS, 2024).

Serviceable Available Market (SAM)

The SAM narrows the focus to markets directly related to enzyme replacement therapies for lysosomal storage disorders (LSDs) — particularly Gaucher Disease, the proof-of-concept target for this project.

Gaucher Disease affects roughly 1 in 50,000–100,000 individuals worldwide, translating to an estimated 100,000 patients globally, though underdiagnosis remains an issue (BRASIL, 2014; WALSH, 2018). The cost of treatment with imiglucerase (Cerezyme) or similar drugs ranges from USD 200,000–400,000 per patient per year, generating an annual market value of approximately USD 2–4 billion exclusively for Gaucher Disease (GRAND VIEW RESEARCH, 2024; FORTUNE BUSINESS INSIGHTS, 2024; BRAUN et al., 2018).

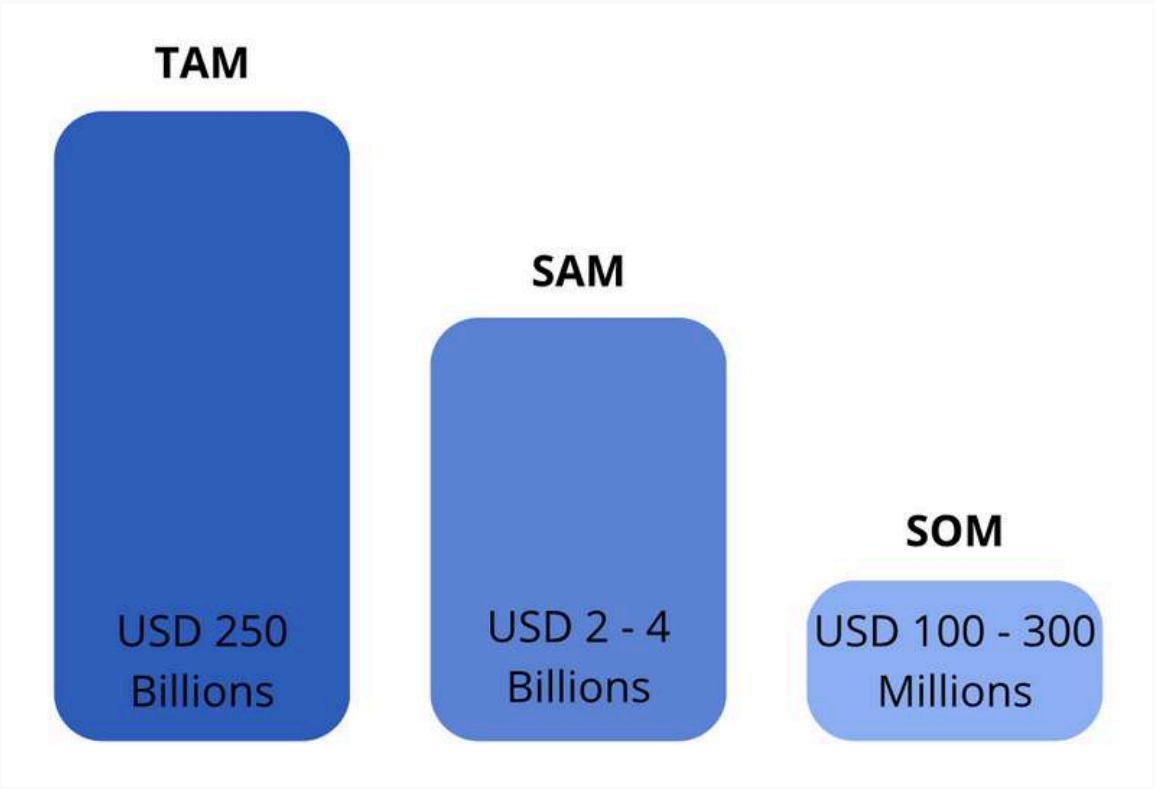
In Brazil, where 825 patients currently receive imiglucerase via the Unified Health System (SUS) at an annual cost of around R$1 billion (~USD 200 million), the SAM represents a significant national opportunity for cost reduction and domestic biotechnological independence (BRASIL, 2014).

Serviceable Obtainable Market (SOM)

For our project, the SOM identifies the realistically achievable portion of the SAM that the project could capture within its first commercialization phase.

Given that the proposed microbial platform could reduce production costs by up to 80–90% compared to mammalian or plant-based systems (Walsh, 2018; Ahmad et al., 2014; Nielsen, 2013), the technology has strong potential for adoption by public health systems and local pharmaceutical partners. Considering regulatory timelines, partnerships, and market penetration barriers, it is reasonable to project an initial market capture of 5–10% of the Gaucher therapy segment within 5 years of deployment.

This translates to a SOM of approximately USD 100–300 million globally, or around USD 10–20 million within the Brazilian market — a feasible early-stage benchmark supported by local licensing and public-sector interest (SUS).



5. Our Solution

5.1 Project Technoloy

The Glycosi-N-ation project aims to engineer two model microorganisms, Escherichia coli and Saccharomyces cerevisiae, to produce glycoproteins with human-like glycosylation patterns, addressing a major limitation in current biopharmaceutical production. Traditional systems for producing therapeutic glycoproteins, such as CHO cells, human fibroblasts, or plants, are costly, slow, and resource-intensive, while prokaryotic systems like E. coli grow rapidly and cheaply but cannot perform human-like post-translational modifications.

The project's innovative approach lies in enabling microorganisms to assemble and transfer the $Man_3GlcNAc_2$ glycan, a central, universally conserved human glycan precursor, onto target proteins. This glycan serves as a modular platform, allowing future extension into hybrid or complex human glycosylation patterns by adding complementary enzymes.

For S. cerevisiae, the team focused on adapting the existing glycosylation machinery to prevent excessive hypermannosylation. For E. coli, the approach involved in rebuilding the glycan assembly and transfer system from scratch, mimicking eukaryotic mechanisms. The glycan is assembled on the cytoplasmic face of the inner membrane, flipped to the periplasmic side, and transferred to asparagine residues of the protein by an oligosaccharyltransferase.

5.2 Strategy

As a proof of concept, the project focused on human β-glucocerebrosidase (GCase), the enzyme used in Gaucher disease enzyme replacement therapy. This choice is based on its clinical relevance as a commercially produced glycoprotein; insolubility in E. coli and dependence on glycosylation for proper folding and stability; the need for exposed mannose residues for macrophage recognition and lysosomal targeting; and the potential to significantly reduce public healthcare costs in Brazil, where annual GCase therapy expenses range from R$300–500 million.

By successfully producing $Man_3GlcNAc_2$-modified GCase in microorganisms, Glycosi-N-ation represents a novel, cost-effective, and scalable platform for producing therapeutic glycoproteins, with broad future applications in vaccines, diagnostics, and other biologics. The project combines microbial engineering, synthetic biology, and modular glycoengineering, positioning it as a disruptive innovation in biotechnology.

6. Communication Plan

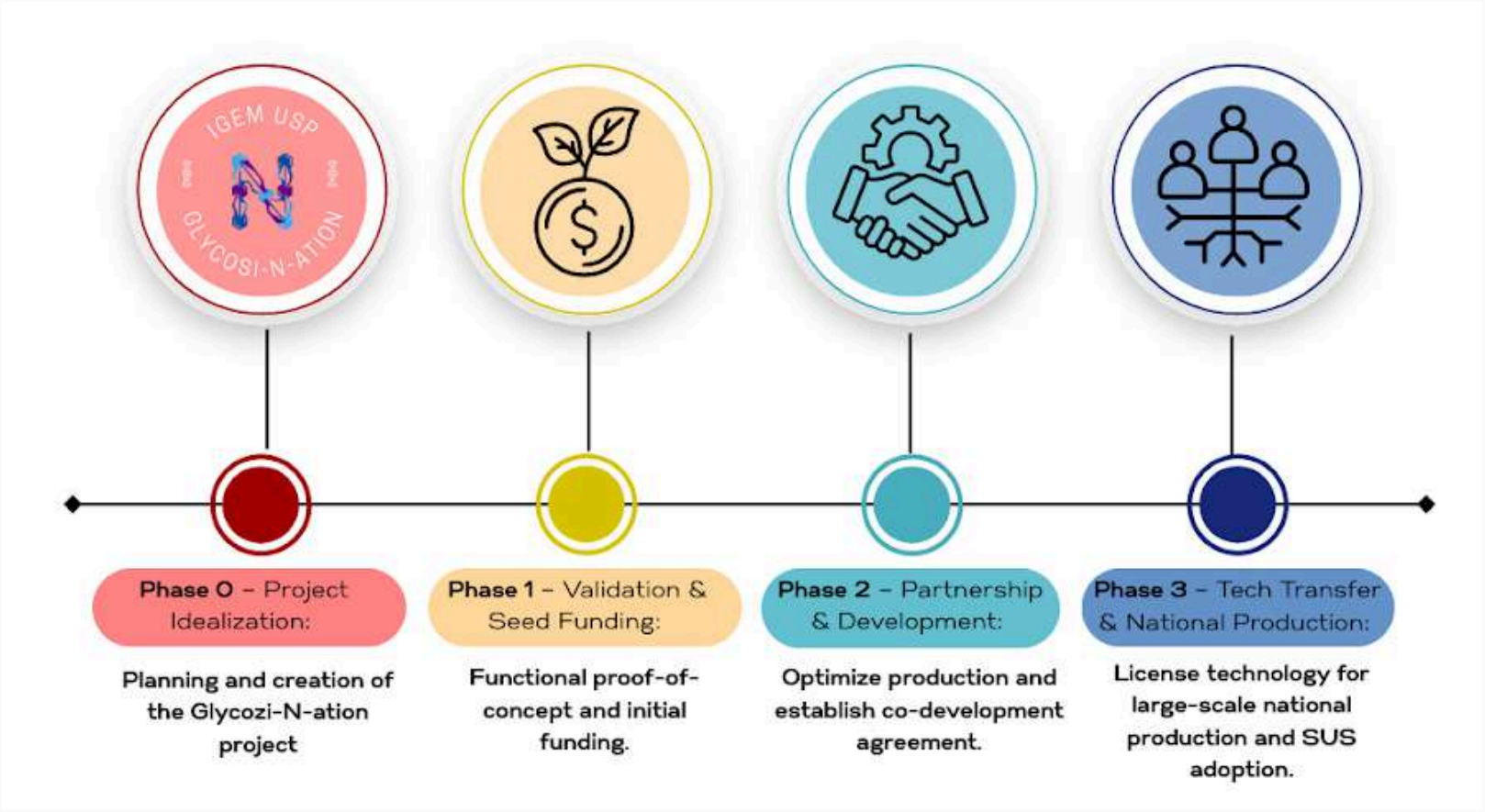
The high cost of enzymatic replacement therapies, such as the one for Gaucher disease, places a significant financial burden on public health systems. In Brazil, this cost can reach R$500 million annually, challenging the sustainability of treatment. Our project, Glycosi-N-ation, directly addresses this issue by creating a microbial platform for the low-cost, high-yield production of the GCase enzyme, positioning our innovation as a strategic solution for national public health through a business-to-government strategy in order to reach an impact to society.

We have adopted a Business-to-Government (B2G) model, as the Brazilian Federal Government is the primary purchaser and distributor of this therapy through the Unified Health System (SUS). Our goal is not to compete in the traditional pharmaceutical market, but to forge a strategic partnership for technology transfer with a public institution, such as the Fiocruz Foundation, enabling a B2G partnership for public good.

The key advantages of this model include: maximum social impact, by reaching all patients within the public system, ensuring equitable access through our solution; alignment with national interests whereas we directly address the government's need to reduce healthcare costs and promote national biotechnological autonomy; as well as streamlined implementation insofar as, partnering with an established public entity like Fiocruz, facilitates regulatory pathways with ANVISA and integration into the SUS supply chain.

Regarding our implementation roadmap, our path from the lab to the patient is structured in three key phases: phase 1 - validation & seed funding objective by achieving a functional proof-of-concept for GCase production and secure initial non-dilutive funding for R&D, reaching key stakeholders through the iGEM competition, such as the scientific community (via publications), and funding agencies like FAPESP (specifically the PIPE program for innovative research); phase 2 - strategic partnership & development, with the objective of optimizing the enzyme production process and formalizing a co-development agreement with a strategic partner, focusing in Fiocruz (as the industrial partner), the Ministry of Health (to validate demand), and ANVISA (for initial regulatory guidance) as the key stakeholders; phase 3 - technology transfer & national production, focusing in licensing our technology to the partner, enabling large-scale national production and official incorporation into the SUS, pursuing the ministry of health's technology incorporation committee (CONITEC) and patient advocacy groups, whose support will be crucial for adoption.

By successfully implementing this plan, Glycosi-N-ation will not only provide a more accessible treatment for Gaucher disease but also establish a versatile platform for producing other essential biopharmaceuticals, strengthening Brazil's capacity to respond to its own public health challenges.

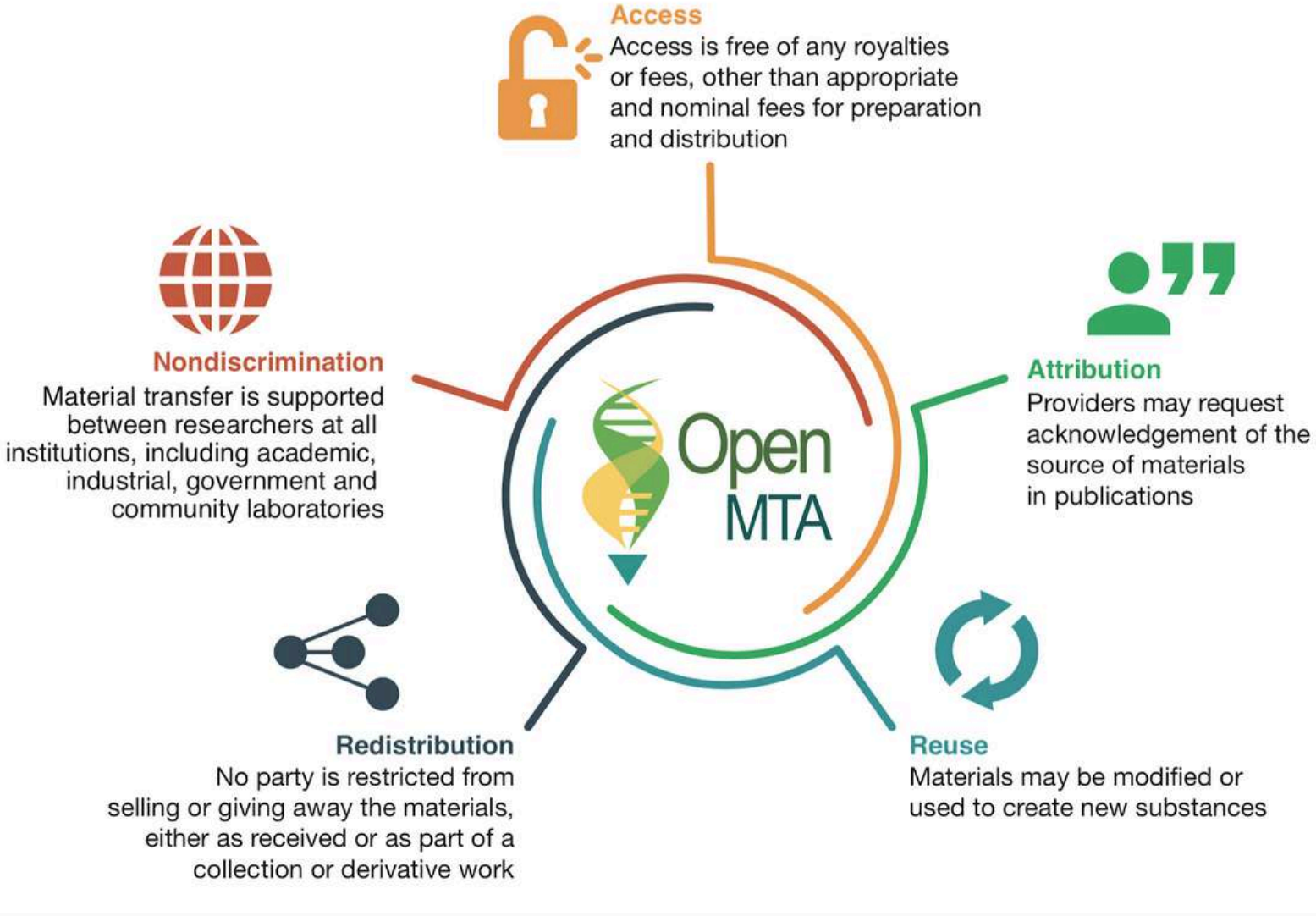


7. Sustainability and Future

Glycosy-N-ation has the potential to revolutionize the pharmaceutical industry. With our proof-of-concept - the production of recombinant GCase - we can substantially decrease the costs of a rare disease that has an annual cost of nearly $150 million in Brazil, funded by public healthcare systems. Expanding on the case of GCase, if we consider other healthcare systems, we could expand to all interested countries that work with the purchase of GCase analogues.

This is just a first step, using one application of our glycosylation models. However, we have innumerable uses in the fields of diagnostics, therapeutics, and vaccine production. Because our models will be able to produce glycosylated proteins with a universal humanized glycan pattern, and our model will be modular to produce any glycan adapted to the specific needs of the target protein, we offer strains that are applicable and valuable not only to scientists whose work involves the study of glycoproteins, but also to the broader glycoprotein market.

With the aim of ensuring our model's longevity beyond the iGEM competition - and following feedback from stakeholders (see more information in the Integrated HP section) - we decided to register our strain or plasmids through the Open Material Transfer Agreement (OpenMTA), a simple, standardized legal tool that enables individuals and organizations to share their materials on an open basis.



BUSINESS EXPANSION ROADMAP

Proof-of-concept

2025
iGEM Grand Jamboree

Scientific Dissemination

2026
Publish our work in a peer-reviewed journal to contribute to the global scientific community

Knowledge Democratization

2026
Promote access to our technology by distributing our engineered plasmids and protocols through iGEM and OpenMTA agreements, fostering future research and innovation.

Sustainable Impact

2027
Form B2G collaborations to scale our platform for real-world application, creating a sustainable and cost-effective solution that significantly reduces public healthcare spending on rare disease therapies.

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