ID Cover Page

Summary of WP Student Team

DECA PHARMACEUTICALS: FIGHTING FUNGAL INFECTIONS WITH ORGANOMETALLIC COMPOUNDS, FROM BREAKTHROUGH TO APPROVAL.

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DECA PHARMACEUTICALS: FIGHTING FUNGAL INFECTIONS WITH METALLOORGANIC COMPOUNDS

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Abstract

Deca Pharmaceuticals is a company working on an exciting innovation that can revitalize the anti-fungal market.

From a well-defined pain that consists of the lack of a new class of antifungals, the team behind the company planned what needs to be done in order to get a new treatment capable of circumventing the occurring drug resistance mechanisms from inception to reality.

A set of key players are directly involved in making Deca Pharmaceuticals grow, in which we underline the need for funding from investors, due to the cash-burning nature of biotech startups.

Given the attractivity of our solution, the main objective is to get acquired by a major, well-established pharmaceutical company, resulting in maximum ROI for our investors and enhanced value for every stakeholder involved. In any case, as a contingency plan, a go-to-market strategy is also a contemplated scenario.

Keywords

Adjuvant, Antifungal, C. glabrata, Caffeine, Candidemia, Clinical trials, Compound, Corporate Investor, CRO, ESG, Exit, Funding, Innovation, Invasive Fungal Infection, Intellectual property, Mode of Action, Nickel, Patient, R&D, Stakeholder, Venture Capital

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

Humankind has always tried to stay ahead of disease-causing agents by creating new solutions that interfere with their proliferation, thus avoiding illness or death to infected individuals. Fungal pathogens are a good example of this adaptative fight, continuous and sometimes negligent use of existent measures to eradicate fungal infections, such as the likes of anti-fungal medications, have created resistant isolates, responsible for more deaths *per annum* than Malaria or Tuberculosis. That is a death toll of 1.7 million lives lost to invasive fungal infections.

About 70% of nosocomial invasive fungal infections, responsible for the above-mentioned deaths, are caused by the *Candida* species, being *C. albicans* and *C. glabrata* the main contenders of that percentage.

Despite all efforts, these molds and yeasts are becoming ever more resistant to known means of treatment. Presently, despite the need, no new classes of antifungals have been in the market since 2006, due to the large investment needed and low returns.

Facing this concern, our recently formed company - Deca Pharmaceuticals was created, pursuing novel ways, aside from the traditional classes of antifungals, to deal with the growing number of resistant fungal infections.

To relieve patients of these infections, and governments of costly health burdens that can top up to billions, we present a breakthrough that has already been proved to have fungistatic capabilities. By leveraging on complex organometallic chemistry as an innovation to circumvent resistant fungal pathways, our researchers are synthetizing caffeine (a xanthine derivative) with nickel, as raw materials to produce a batch of molecules, in which our first compound, Xaniglucan, will emerge.

Our product can effectively eradicate *C. glabrata* resistant isolates, while maintaining a high safety index for human cells. Current projections show that the compound will be fairly cheap to produce due to its raw materials (caffeine and nickel), benefitting as well from a low minimal inhibitory concentration (or dosage), and therapy combination synergies with other drugs.

The pool of molecules is still being tested and more data is being acquired to enable the compound, or compounds, to finish pre-clinical trials and reveal whether a greater scope of fungal pathogens are encompassed, amidst other potentialities.

While the pharmaceutical industry is known for its innovations' cash-burning efforts, development milestones for phases I, II, III, were planned. The team aims to raise up to $39 million mainly from VC funds and corporate investors to face our capital needs until the end of phase II in 2026, where we expect to be an interesting prospect to be acquire by a large pharmaceutical company. As a contingency plan, if no opportunities at the end of stage II appear, we forecast funding needs of at least $100 million, to complete phase III with little to no setbacks.

To be able to maximize ROI, we present a few exit scenario alternatives to our investors, with the ideal goal of being acquired by a major pharmaceutical firm, such as Pfizer. In case we need to go to market by 2030, going public through an IPO is a suitable option to get funded and to ensure our investors profit from their shares. Concerning ROI, selling royalties on drug sales also suits as a part of the contingency plan.

Several players and key partners were identified for us to understand the ecosystem and who can help us grow throughout our development stages. Value is generated for every stakeholder, either being monetary, moral, or both, resulting on mutual interest.

Regardless of the heavy presence of centurial pharmaceutical companies, which focus lies greatly on profits, today more than ever small bio-tech companies such as ours can play an important and revitalizing role in supplying new ideas to the pipeline of these market giants.

THE PROBLEM

Problem statement

Pathogens like viruses, fungus and bacteria are no novelty. In fact, some of these pathogens can have symbiotic relationships with other living creatures. However, developments have been made throughout history to detect and treat the harmful impact that some of these germs have in one's life. Antifungal medications, for instance, cure fungus infections by eliminating or halting the development of harmful *fungi* in the body. Unfortunately, similarly to how bacteria can become resistant to antibiotics, *fungi* can also acquire resistance to antifungal medications. Resistance occurs when the pathogen, being bacteria, virus or fungus learn to adapt to the medications that are intended to kill them, resulting in the development of dangerous stains of these pathogens.

Since there are now only a few different antifungal medication types, resistance may drastically reduce the range of available treatments. Some fungus, including *C. auris*, have the potential to develop resistance to every antifungal medication typically used to treat these infections. For patients who have invasive fungal infections—severe infections that involve the blood, heart, brain, eyes, or other parts of the body—resistance can be particularly troubling.

Certain fungus species natively resist some antifungal medications. For instance, Fluconazole (the most commonly used antifungal) is ineffective in treating infections brought on by *Aspergillus*, a form of mold that is commonly present in most environments. Additionally, when *fungi* are

exposed to antifungal medications over time, resistance might form. When antifungals are used to treat sick people, especially if the medications are utilized incorrectly, this resistance may develop even stronger if the dosages and duration of the treatment are inadequate

Fungicide use in agriculture for the prevention and treatment of *fungi* induced diseases in crops can also lead to pathogen resistance in humans. *Aspergillus* in the environment, for instance, may develop a resistance to medications used to treat human illnesses if it is exposed to fungicides, which are chemical compounds related to antifungal medications used in agriculture. The result is that people can get sick by breathing in the environment resistant *Aspergillus* spores. (CDC 2020-a)

Antimicrobial resistance, a global concern

Our capability to cure common diseases is still endangered due to the creation and spread of bacteria that are resistant to drugs and have developed new resistance mechanisms. The increasing global development of multi- and pan-resistant bacteria, commonly referred to as "superbugs," which cause diseases that cannot be treated with current antimicrobial medications like antibiotics, is particularly concerning.

There are hardly any promising antimicrobials in the clinical pipeline. Only six of the 32 antibiotics that tackle the World Health Organization list of priority pathogens that were identified as being in clinical development in 2019 were considered novel. Access to high-quality antimicrobials also continues to be a big problem. All countries, regardless of their state of development, are being impacted by antibiotic shortages, particularly in the health care systems.

As drug-resistance increases on a global scale, antibiotics are becoming less and less effective which leads to diseases becoming harder to cure and ultimately to increased mortality. According to the World Health Organization priority pathogen list, new antibiotics are urgently needed, for instance, to treat carbapenem-resistant gram-negative bacterial infections. However, these novel treatments will experience the same fate as the present antibiotics and become useless if the way of using them remains unchanged throughout the years.

Antimicrobial resistance has a substantial financial impact on national economies and health systems because it reduces patient or caregiver productivity by causing longer hospital stays and more expensive and intensive treatment.

All in all, the number of individuals who see their treatment fail or who pass away from illnesses will rise in the absence of efficient methods for the prevention and sufficient treatment of drug-resistant diseases. This will be aggravated without improving the access to current and novel antimicrobials. Surgeries, cancer chemotherapy, and organ transplants are examples of medical procedures that will inevitably become significantly more dangerous (WHO 2021).

But how does this problem materialize in terms of numbers? Well, if we look at bacteria, for instance, in 2019 the estimation of deaths attributed to bacterial antimicrobial resistant infections was around 4.95 M across the globe. However, as stated before, the problem is expected to increase its impact aggravating the number of yearly deaths to around 10 M by 2050. This combined with fungi and has been considered to be one of the greatest threats to modern day society.

The need

Facing the challenge of antimicrobial resistance is complex and requires various entities and players from various fields to come together in a multisectoral strategy that must be used in unison.

The One Health approach brings together various stakeholders from different fields involved in the design and implementation of programs, policies, legislation, and research to improve public health outcomes for people, animals, plants, food production, and the environment.

Operational research, as well as the development of novel antimicrobial drugs, vaccines, and diagnostic tools, needs more innovation and funding, particularly for those that target dangerous gram-negative bacteria. The introduction of the Global Antibiotic Research & Development Partnership (GARDP), the Antimicrobial Resistance Multi Partner Trust Fund (AMR MPTF), the AMR Action Fund, and other funds and efforts may close a significant financing shortfall. Many governments are testing payment approaches. However, to come up with long-term fixes, more initiatives are required.

After analyzing the previous context, we could derive that, regardless of other factors, there will always be **an underlying need:** the urgency to find alternative, cost-efficient, and easily scalable ways to fight the rising resistant streams of fungus and other pathogens that are presenting a threat to public health worldwide (WHO 2021).

THE SOLUTION

Call-to-action

Considering this situation, the priority of developing effective antifungals is quite overlooked, with a fairly disseminated interest in developing drugs for other fields, such as oncology drugs. This happens because the anti-infectants market is seen as a less profitable businesses than the others. Being difficult to produce, some antibiotics can cost more than a billion, while the yearly revenues averages at $46 million, making it less relevant for big investments (Plackett 2020). As could we

also conclude form Filipe Assoreira, MBA, interview (See Interview notes section, in the Appendix – "Any insights on product distribution and marketing of these products?").

New drugs were still developed nonetheless; however, they fall on the existent categories of modes of action (MOA) or classes (i.e.: Isavuconazole), meaning these new compounds act on already documented inner-cell mechanisms, thus grouping them into categories with the main ones being Azoles, Polyenes, Allylamines, and Echinocandins.

Tackling the urgency of developing new antifungals under these tough conditions, Deca Pharmaceuticals was born. This is our call-to-action, we are working to anticipate a growing concern of the number of ailments and deaths caused by resistant fungus strains, by proposing a new class of antifungals that circumvent resistance mechanisms, while being easily affordable, in contrast with other new anti-infectants that are usually expensive as per our interviewees: Dr. Cristina Toscano and Dr. Ana Rita Domingues (See Interview notes section, in the Appendix).

By not leveraging on already known mechanisms of action, we took a step back and created a new class of antifungals that interfere with the pathogen's oxygen intake. The solution is supported by the therapeutic qualities of metals as anti-infectant. Metal complexes have unique geometric features, electronic properties, and reactivity that, when combined with organic molecules, can display new MOAs that are not usually found in organic molecules alone (Karges, Stokes, and Cohen 2021, 523).

We explore complex organometallic chemistry to create molecules with antifungal properties. As some metals are quite expensive, by recognizing the need for a cheap solution, our first line of products uses nickel, which is cheap to obtain.

Yet, far from solving the issue on all invasive fungal infections, our company makes its first step into the potential of what an innovation can bring. Showing effectiveness on a few species of

fungal pathogens acts as our proof-of-concept for future developments and increasing scope to deal with more pathogens.

ESG compliance

Our innovation is aligned with the UN Sustainable Development Goals (SGD). By tackling fungal microorganisms that can create bloodstream infections in particular situations; where an estimate of 1 billion people per year suffers from any form of fungal infection, and among those around 1.5 million die as a result (Bongomin et al. 2017, 1), our solution plays an active role in diminishing the said statistics.

Our first product already shows selectivity for *C. glabrata*, known to be quickly adapting to known means of treatment and the second most prevalent pathogen responsible for Candidemia. This blood infection comprises of 1.05 million cases of the universe of 1.5 million. Depending on the country *C. glabrata* incidence can vary, going from 8% to almost 30% (Guinea 2014, 6). For the sake of this example, assuming that only 15% of lethal Candidemia cases are caused by *C. glabrata*, at least 157.5 thousand people could be saved every year.

Deca Pharmaceutical's innovation falls within the SDG goal number 3 – "Ensure healthy lives and promote well-being for all at all ages", more precisely the target 3.d, the reinforcement of the capacity for all countries, especially under development ones, to improve their health risk management. The indicator used by the UN to measure this goal is the 3.d.2, that gives respect to bloodstream infections causes by resistant microorganisms.

It also falls in the framework of the target 3.b that, in short, reinforces the support of R&D of new medicines accessible for developing countries at an affordable price. The indicator used by the UN

to measure this goal is the 3.b.3, that gives respect to healthcare facilities having a sustainable and recurrent stock of affordable medicines to treat their patients.

THE MARKET

Description, dimension, and development prospective

Over the years fungal infections have been considered a rising health problem across the globe. This is due to 2 main factors: rising in pathologies (and their treatment) affecting the immune system and lowering immune defenses, and an increasing resistance of the existing *fungi* to the current medications. These factors boosted the effort of pharma companies and start-ups to introduce into the market new solutions to the problem, but none has been introduced over the past decades, it has been almost 20 years since the last class of anti fungal-infections drugs introduced in the market in 2006.

Although this market has some common features across the globe, it has different dimensions among regions: North America is the biggest in terms of money spent for this family of drugs, Europe follows, and China right after showing the highest expected CAGR) for the next years (Grand View Research 2022-a); the developing countries show a rising awareness of the issue and an increase of the cases, but a lack of budget reduces their economic potential.

This is a fairly concentrated market where big pharma companies are investing billions every year to renew their research and the budget at their disposal makes almost impossible to enter as an outsider in this market, but on the other hand, the main factor of growth for these players is related to M&A activities: most of the times they buy small companies with prominent ongoing research,

either to enrich their drug portfolio or as a defensive move avoiding the entrance of a new player in the market.

The global antifungal drugs market size has been valued at around $14.8 billion in 2021 and has been projected a compound annual growth rate (CAGR) of 3.7% from 2022 to 2030; this will bring a future potential valuation of $20.5 billion globally (Grand View Research 2022-b).

These estimations refer to the whole antifungal drugs industry but to have a clearer idea about our potential market valuation we need to make some drill down from this numbers.

In the market right now, there are 4 main antifungal classes to treat fungal infections, differentiating from each other because of their different molecules and MOAs: Azoles, Echinocandins, Polyenes and Allylamines.

Candidiasis is the leading infection in terms of people infected and it is projected to keep the lead in the forecasted period.

Having only these categories of compounds treating such a spread disease as fungal infections means that, overtime, there will be an increasing resistance of the infections to these drugs mechanism, making them less effective and "entering in a vicious circle where the patient need to take a higher dose of the drug to fight the infection", as an internal medicine doctor we interviewed stated to us; but most of the time, the drug is not able to target exclusively the infected cells, and it will also attack the healthy ones, making a higher dose of it more harmful for the body and, at the same time, less effective overtime to fight the infection.

Development prospective: as previously said, the market is boosting up the research for new compound to treat the rising numbers of fungal infections in the last years, and another way to tackle this issue is the immunotherapy, which is a new promising strategy to strengthen the host immune system in order to fight more aggressively fungal infections.

Currently there are 2 fungus antibodies in clinical development; one additional layer of research in this area is related to radio-immunotherapy, this approach is showing promising results on a specific infection (*Cryptococcus neoformans*).

Another field of research is represented by the research of potential target that are exclusive to *fungi* and cannot be found in human cells, in order to reduce potential drugs toxicity to a minimum, in this field of research Novartis dark matter or sphingolipid synthesis pathway are showing promising progresses (Bouz and Doležal 2021, 1).

Marketed drugs being repositioned as antifungals

Drug repositioning consists in applying drugs that have been approved already or that are undergoing clinical trials to treat other diseases rather than the ones they were supposed to target. The repositioning of previously approved drugs is a way to reduce the time and money required to develop novel antifungal treatments to front the urgent and unmet clinical need against invasive fungal infections (Cui et al. 2022). The great advantage is that drugs that have been already approved for human use can be transposed into clinical use for other diseases relatively fast. Among the drugs that have been studied for repurposing, there are:

- Auranofin: This compound is an anti-inflammatory and anti-rheumatic gold thiol compound. It is currently an FDA-approved drug to treat rheumatoid arthritis but has been investigated for therapeutic application against several other diseases (Roder and Thomson 2015). Among those diseases, there are also *Candida* infections. In fact, the drug showed

that it can significantly reduce the metabolic activity of *Candida* cells encased in a biofilm. The studies already conducted demonstrated that auranofin has good promises to be repurposed as a novel antifungal agent. Experiments showed effectiveness towards Fluconazole-resistant *C. albicans* strains (Cui et al. 2022) (Thangamani et al. 2017);

- Sertraline: It is a modern, relatively safe, and very selective serotonin reuptake inhibitor mainly used as an antidepressant and to treat panic attacks, obsessive-compulsive disorder, and post-traumatic stress disorder (NHS 2022). Recently it has been tested *in vitro* showing a good antifungal effect against *Candida* infections. Specifically, sertraline has been screened against three isolates of *C. auris* (Gowri et al. 2020). The antifungal activity of the drug was then further confirmed by kinetics assay (kinetics assays are laboratory methods to assess the enzymatic inhibition). Sertraline inhibits the mycelial transformation of *C. auris* with an inhibition rate of 71% after treatment, which makes it a potential new approach to treat diseases caused by *Candida* but also *Aspergillus* and *Cryptococcus* (Cui et al. 2022);

- Tamoxifen: This drug is a selective estrogen receptor modulator used in medicine to manage and treat breast cancer. It has been discovered it has antifungal activity, even though its mechanism of action is still unknown. *In vitro*, tamoxifen showed effectiveness against different yeasts such as *C. albicans* and *Cryptococcus neoformans*, and it has also been tested *in vivo* on mice checking its activity against candidiasis. Moreover, the studies conducted demonstrated how the drug can augment the antifungal actions of azoles, suggesting its potential synergic action to this kind of drug class (Cui et al. 2022).

In general, all the previously mentioned drugs that are trying to be repositioned are valid potential options for combination therapies. Drug combination therapies are particularly relevant because they could help slow down or arrest the current phenomena of drug resistance for *fungal* infections, which occurred after the abuse of antifungal drugs used alone. Through a variety of mechanisms, drug combinations may result in a greater killing/inhibitive effect, may reduce the size of the whole pathogen population, and consequently reduce the possibility for drug-resistant mutations to be generated. By selecting precisely specific combinations, the effect of these therapies may be not only to hinder and neutralize the microbial resistance but even reverse this occurrence through a process known as selection inversion. For instance, studies already conducted showed how the combined application of different stress response inhibitors (such as calcineurin inhibitors and TOR signal inhibitors) and already marketed antifungals led to increased efficiency of the antifungal drug, with remarkable therapeutic effects. Other studies have identified already other interesting inhibitory drug combinations effective against *C. albicans* and *Cryptococcus* strains (Cui et al. 2022).

The relevance of drug combination therapies is particularly important for us and our specific case. In fact, some of the studies conducted *in vitro* in the laboratory showed some interesting results in terms of future purposes of our compound. Our molecule can potentially become an effective adjuvant for Fluconazole, the most common antifungal currently present in the market for which most strains of *fungi* (including some of the most dangerous ones) have already developed a resistance. Our molecule, if the future tests that will be run will confirm that, could be able to boost the effectiveness of Fluconazole and improve its activity against the resistant strains, making our

compound a remarkable product and a great added value for the companies that are currently marketing Fluconazole as their main antifungal. Therefore, this pathway will be further explored, and it has already been considered as a potential option to evolve our product, giving it a precise specialization and targeting.

Competition mapping, points of difference, and opportunity identification

It was possible for us to draw graphics in order to have an immediate visualization of the competitive environment, with the aim of highlighting what is our current situation and identifying opportunities for our further development. Moreover, understanding the dynamics of the environment and where our under-development competitors are placed helps build hypothetical scenarios and gives directions in terms of what to technically aim to develop in the laboratory.

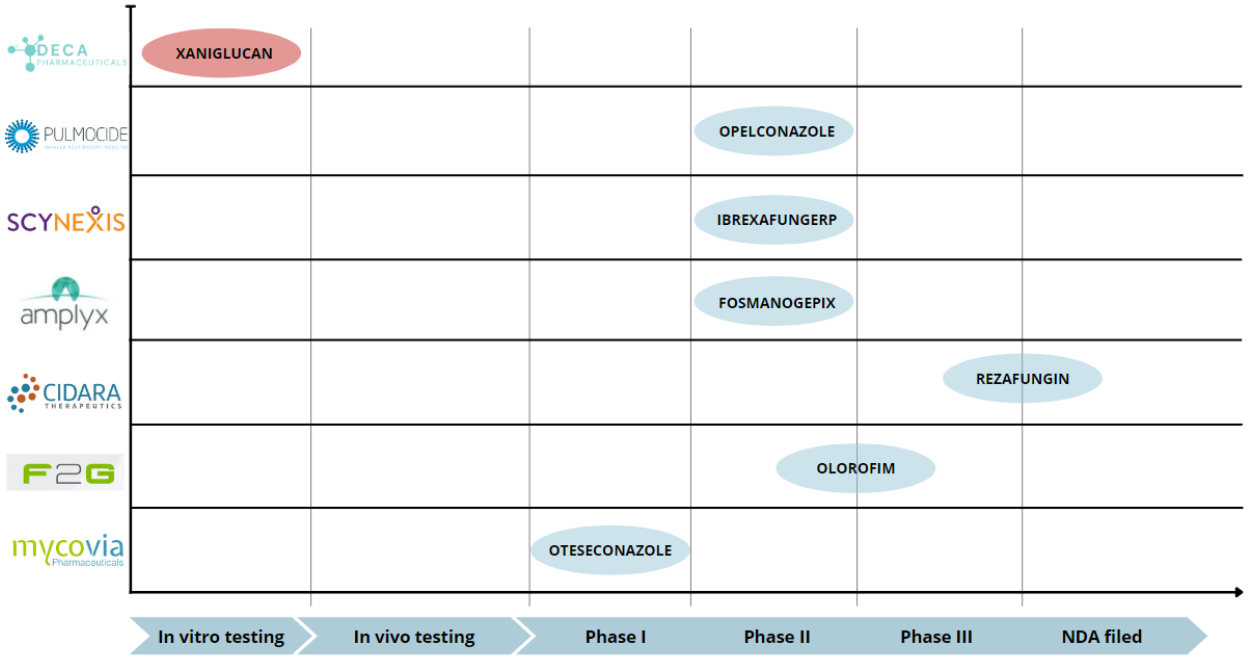

Figure 1 - Cartesian plane competitor map by phase of clinical trial (x axis) and upcoming players (y axis)

Figure 1 shows where the main identified development-stage players are positioned within the development procedure. All of them have managed to already get into the clinical trials phase. They are all ahead of us, and that's exactly what makes them extremely valuable role models. Since our goal is to reach successfully the clinical trials stage, learning from their pathway will certainly give us good hints on how to manage to get there. It must be underlined again that even if these players have been called competitors by us, and in effect, they are our competitors and that is the reason why we also looked for competitive advantages against them and points of differentiation that would make our molecule a better choice, they have been actually considered mainly as benchmarks. Our ultimate, direct competitors are the current antifungals already available on the market. The compounds that are currently marketed as universally recognized antifungals are the obsolete, non-effective technologies that we aim to substitute. Our future

product point of differences and added value against these drugs is so evident that we decided not to broadly discuss nor analyze the big pharma companies as competitors. In fact, a whole process of replacement of the already established drugs has already been started by the companies owning those solutions themselves, since the drugs are not functioning properly anymore. This clarification serves to explain that the early final approval of any of the above-mentioned under-development competitors prior to the approval of our molecule does not necessarily represent a downside for us. Actually, now that some big pharmaceutical companies have started to show their interest in such compounds by either partnering or acquiring the smaller companies that brought the molecules to the clinical trials, we anticipate they will be more incentivized in merging with some other small companies that are working on the development of different molecules under the same drug category, to diversify their investment risk and prevent their competitors to have the chance of getting a bigger share of the market. One new approved antifungal will not be enough either to solve the entirety of the issue we are aiming to tackle or to guarantee any dominance of the antifungal market.

Getting back to the under-development competitive environment, *Figure 13* below shows what are the key characteristics that justify the greater value that the future drugs that are being tested will bring to the market assuring them an advantage against already established drugs, while underlining a differentiation advantage that we will have against some of them. All the data taken was considered in comparison to traditional antifungals. The MIC levels are compared to the ones from Fluconazole, the most commonly prescribed and used antifungal. The choice was driven by the fact that the data regarding these attributes are hard to find in absolute values, and it was easier to find it compared to standard antifungals, which still makes a lot of sense since, again, the traditional drugs are what these pipelines aim to substitute. MIC levels in particular are complex

to compare since they vary accordingly to the specific pathogens taken into account when testing. Since it wasn't feasible to report all the levels for each possible pathogen, we made a rough average of the registered MICs. This table aims to summarize and show intuitively how, in general, the under-development compounds have shown to behave during the clinical trials, compared to how traditional antifungals behave in the host.

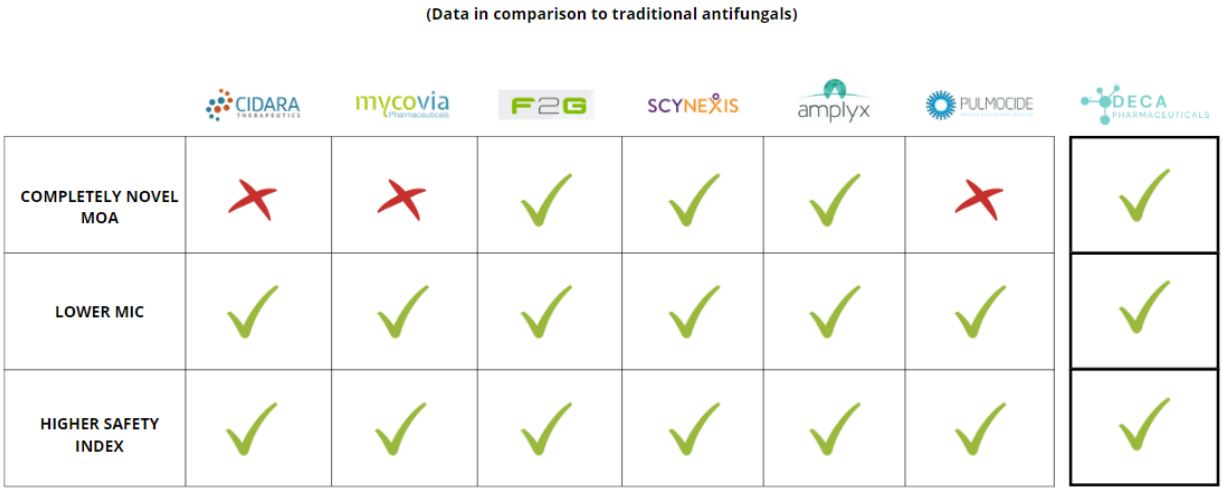

Figure 2 - Comparison table competitor map by interest variables (rows) and upcoming players (columns)

All the promising compounds taken into account have shown great results in terms of MICs and safety indexes when set side by side with traditional solutions. Antifungals are generally hard to produce since the mechanisms of action that serve to neutralize or kill the pathogen are often dangerous for the healthy cells of the human body as well. Therefore, it is obvious in which way is beneficial to have a higher safety index: it results in more secure drugs better tolerated by the hosts, reducing the chances of having collateral effects after assumption and any severe complications consequent to the administration of the drug, ensuring an safer experience for the patients. As what regards the MICs, having lower levels is a great benefit since it allows for a minor dosage in terms of quantity and/or frequency of the drug. Having a drug that requires a

lower dosage to be effective is a great value proposition, especially in this specific case of experienced drug resistance from the pathogens. In fact, part of the reason why the *fungi* population has been able to build its resistance is because of overexposure to the medical treatments. Adopting drugs with considerably lower MICs is a good starting point to fight back this tendency. These two key characteristics are the more important among the three. More than important, they are fundamental in order for the under-test molecules to be even considered as potential new solutions for the future. However, when looking at the MOAs, we do not see the same outcome for all the molecules. This is a different discussion, the MOA is related to the way the molecule tackles the pathogens and is effective against them, and it depends on the antifungal category in which the molecule falls into. All the molecules belonging to one of the already recognized antifungal categories will have more or less the same mechanism of action of the category with some specific adjustments and improvements, while the molecules that are creating a brand-new class of antifungals will consequently have a totally novel mechanism of action against the pathogens. Even if having a completely new MOA is not an essential feature to have, it can still provide, again, an added value against the resistance phenomena. For the sake of simplicity, we can imagine the *fungi*'s resistance mechanism to work, more or less, like our immune system. It is a memory-based defense; once a fungus is fought multiple times with the same modality, it then remembers such a modality and starts building resistance to it. Hence, brand new modalities will be able to better overcome their defense system. Moreover, since it takes time for these resistance mechanisms to be built, a different MOA can assure a longer life period for an antifungal drug in terms of effectiveness.

To sum up, the key takeaways from this table are that Xaniglucan, after testing, turns out to be in line with the fundamental features to have in order to become a valid substitute for the currently

available treatment options, being these features a lower MIC and a higher safety index. Also, being Xaniglucan a compound that does not fall into any of the already known antifungal categories (is the first of a novel category of antifungals), this gives it an advantage and a further point of differentiation against three out of the six most promising under-development compounds. Moreover, a unique MOA gives Xaniglucan a common link with the ones we consider to be the most interesting ones, being them Olorofim by F2G and Fosmanogepix by Amplyx.

With the following positioning map shown in *Figure 14* we want to give an immediate visualization of what kind of pipelines the biopharma companies analyzed are working on. We took into consideration the molecules' spectrum of action, checking how broad that is by looking at how many kinds of pathogens they showed activity against (Hoenigl et al. 2021). Then, we also gathered the standard drugs' dosages registered from the clinical trials (Hoenigl et al. 2021). This makes understanding the current situation and in what direction these companies are going with their products much easier. It also helps in making hypotheses about future scenarios that may occur for our company.

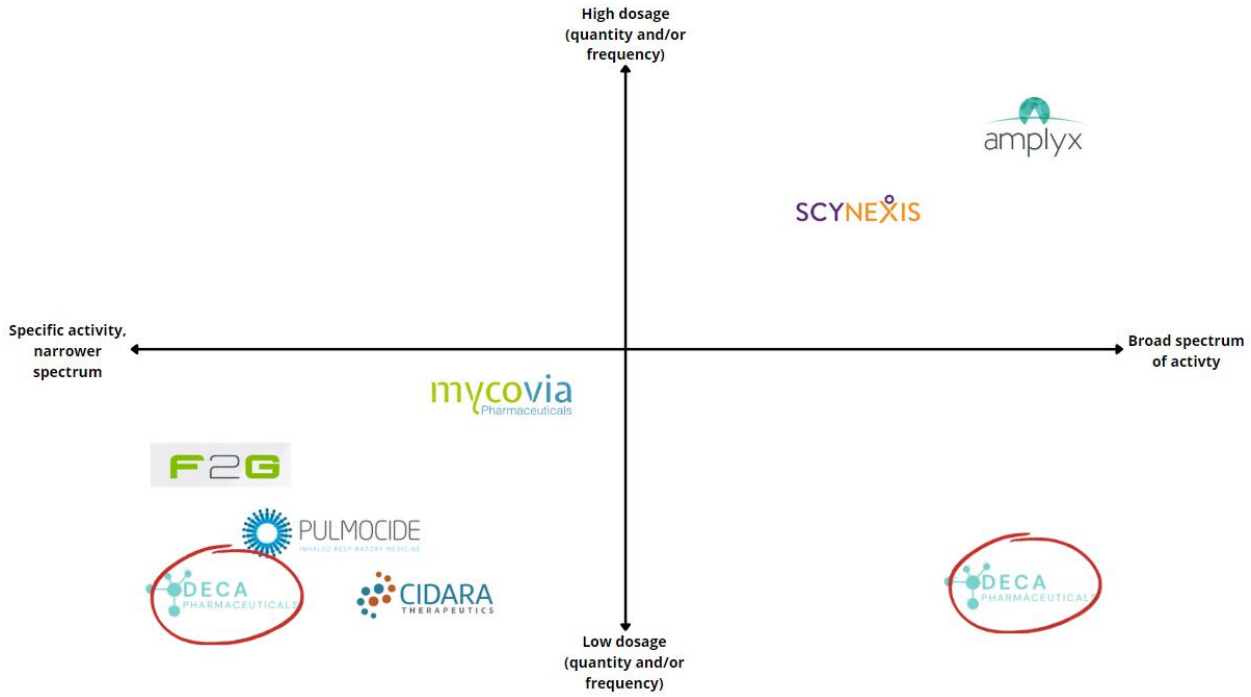

Figure 3 - Cartesian plane competitor map by spectrum of activity (x axis) and dosage (y axis) variables

As shown, most of the under-development competitors sit in the bottom-left quarter of the map. These companies are developing drugs with narrower spectrums of action, and therefore that are selective against specific types of pathogens. They also managed to construct a product that allows for a lower dosage, which is a good thing for all the reasons already mentioned previously in this chapter. On the other hand, in the top-right quarter, we find Amplyx, which still is certainly one of the most interesting cases since it has already managed to be acquired by Pfizer. That indicates that, probably, even if its required dosage to be effective is higher than the others, this is compensated by having the broadest spectrum of action among the pooled compounds, which leads potentially to a greater number of possible applications. Anyways, getting to our case, our scientific team is developing a drug that showed very promising MICs. However, the compound until now has only been tested against *C. glabrata* and *C. albicans* but showing remarkable

activity. It remains then to discover against how many pathogens the compound will be effective; potentially, our drug might have a broad spectrum of action and consequently many different potential applications.

Given the current results gathered through testing and the competitive landscape, we identified two possible positions in which we may end up being inside the map, and it is to achieve one of these two alternatives that we will center our technical efforts on. Regardless of the spectrum of activity, our scientific team will focus on developing a formulation that will have the lowest MIC possible, allowing for a low dosage administration. In fact, we believe this is the best strategic choice for the product development in both cases, and it will translate into a cost advantage as well. At this point, the two different scenarios open up.

In scenario number 1, we develop a compound that shows a broader spectrum of action. We will end up being in the bottom-right quarter, establishing a kind of blue ocean strategy and developing a very unique technology that benefits from strong differentiation points. Pfizer for example made a bet on a broad-spectrum molecule; it makes sense if it would be interested in another broad-spectrum product that differs in terms of required dosage.

In scenario number 2, we find out with further testing that our compound does not have a very broad spectrum of activity. With our compound being more selective against certain types of infectious organisms, we will end up sitting in the bottom-left quarter of the map, competing with the other compounds shown in the graph. However, even in this case, we will maintain a strong differentiation by positioning our drug to be specific for the treatment of candidiasis, especially for *C. glabrata* infections against which we already know for sure that our compound has selectivity. In fact, even if some of the other compounds in this positioning area have shown activity against *C. glabrata*, none of them is clearly or strongly positioned as a specific solution

against it except, in some ways, for Cidara's Rezafungin, and the market size for this specific strain justifies the positioning choice.

THE PRODUCT

Description

Fungal infections can have many forms, and they are caused by a variety Species, inside the Genus: *Candida*, *Aspergillus*, *Streptococcus*, among others.

Patients that suffer from nosocomial infections, opportunistic pathogens that invade the body, usually immunosuppressed, account for more deaths than Tuberculosis every year. In turn, nosocomial fungal infections reach mortality rates of 40%, as per our scientific team.

The proposed innovation results on the synthesis of nickel complexes based on xanthine. Out of this organometallic chemistry, one of the several molecules created (see figure 15) is capable of stopping the development of infections caused by *Candida* spp., precisely of *C. glabrata*, one of the main *Candida* spp. responsible for problems such as: UTI's, genital and mouth infections, and more seriously, bloodstream infections that cause systemic failure.

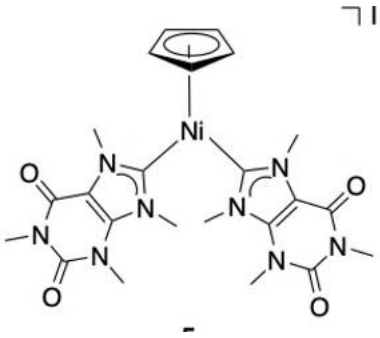

Figure 4 - Biscarbene complex 5[NiCp(NHC)2]+

It is [the molecule] synthesized out of purified caffeine and powdered nickel, both very cheap to obtain. Caffeine is a derivative of xanthine (a purine base/ or a heterocyclic aromatic organic compound, consisting of two rings, pyrimidine and imidazole), which part of its molecular structure comprises of an imidazole unit, azoles group, known for their highly therapeutical potential to treat fungal infections (Siwach and Verma 2021, 1-2). As for the nickel, being a metal, with the right synthesis and structure, it is known for antifungal properties as well (Chohan et al. 2006, 11).

The compound has high selectivity, which means it targets the pathogen without harming healthy human cells. This is very difficult to achieve since both cells [*fungi* and human], are eukaryotes and share many similarities.

The drugs' posology means of administration, and mode of action are still unknown since the innovation is on level 2 (out of 9) of technology readiness level. Nonetheless, knowing the mode of action, and therefore the class of antifungal this innovation would fit in, would not stop the drug from progressing to clinical trials. In fact, by being a new product that fulfills the need for decreasing the mortality rate in ICUs, improving the offer of healthcare systems, positive pressure can induce the pipeline into developing this solution faster than usual (as witnessed in development of the SARS-CoV-2 outbreak in 2019). Thus, the bigger the need, the more investment will be channeled.

Testing of the innovation shows synergetic effects with commonly prescribed antifungals such as Fluconazole – a fungistatic drug, member of the azoles class, that acts on the reproducing mechanism of the fungal cell, since it cannot make multiply itself, it will eventually die out.

Combining drugs to deal with resistance fungal infections is known as antifungal combination therapy and holds one of the best treatments available to circumvent drug resistant molds and yeasts in immunosuppressed patients.

Although the focus will be in on the above molecule, with selectivity to *C. glabrata,* other molecules are being tested, some show selectivity against *C. albicans* as well, however, they present high toxicity to human cells likewise. This development is imperative as *C. glabrata* infections are rising and becoming a reason for concern due to highly resistant isolates and *C. albicans* which constitutes around 70% of fungal infections around the world (Talapko et al. 2021).

Development roadmap

In order to reach the final outcome, it is essential to plan some key milestones of the research path and also of the potential production phase, in case it will be needed.

The first milestone is set after two years from the beginning of the research: by June 2023 the molecules must have completed their *in vitro* testing where the lab will assess molecules' toxicity, efficacy and other pharmacokinetics information; this phase is crucial to understand if the molecules studied are able to target mainly *fungi* cells without harming human ones (toxicity), moreover it will be assessed their efficacy in fighting the infection; especially here it will be fundamental to measure the "safety index" which measure the ratio between the maximum exposure that does not induce toxicity, to the exposure that exerts efficacy.

Here the goal is also to pick, within a pool of prominent molecules, a smaller group of 6-7 molecules that will move to the next stage of the research.

In this phase the risk of finding out that the molecule does not have the characteristics expected is high, but if it shows prominent results, the risk will decrease sharply, and the resources invested

at this stage do not represent a huge loss for the company in case the results do not meet the expectations.

The amount of money invested for this phase is quite low (€50 thousand) and it comes from a joint fund including ITQB, IGC and Oeiras Municipality as non-dilutive capital. Throughout this year the team will apply for international IP patents to protect the production mechanism of the compound and its application as antifungal; it will also get the approval from the Portuguese authority for its IP application, this will guarantee a legal protection in case the study will have a positive outcome within national borders avoiding the risk of "prior art".

The second milestone is set after 3 years from the beginning of the research: by 2024 the pool of molecules, which have been found to be the most promising candidates for the study, must have been tested in animals (I.e., *in vivo* testing).

This phase will observe and assess the interaction of the molecule with an organism (and not only with other cells), giving the chance of better evaluating its efficacy on the infection and, at the same time, its impact on the healthy cells surrounding the infected ones.

This phase, even if it can still be run into a lab without the need of outsourcing to an external facility, will be more expensive than the previous one because it will last longer and because using animals (e.g., rats, mice, zebrafishes, etc.) will be more expensive than just testing the compound *in vitro* with cells: the expected budget for this phase is of €500 thousand, taking into consideration to outsource to an external company the animals supply since its highly regulated.

The risk has already decreased sharply since we obtained positive results from *in vitro* tests of toxicity and efficacy.

According to a report on "Clinical Development success rate" published by Biotechnology Innovation Organization and pharma intelligence, that analysis date of clinical studies for the

period 2011-2020, the success rate of infectious diseases drugs passing from phase I to phase II is 57.8%, prom phase II to phase III 38.4% and from phase III to NDA 64%. The LOA (Likelihood of approval, from phase I to approval) is about 13.2%.

In this frame of time, it will be essential to obtain the approval of the international IP protection, for which was applied in phase one, in order to add a stronger layer of protection to the legal rights around the research and to protect the novelty of our production process.

The next milestone is set after 8 years from the beginning of the research: by 2029 the molecule, must have been completed clinical trial.

This chapter of the research will run a series of tests on the molecule that showed the most promising results in the previous phases, among the pool of 7 that was shortlisted in the beginning, with the purpose of evaluating if it will finally become a drug approved by competent authorities. Moreover, the molecules have been tested in preclinical stages both as stand-alone drug and as adjuvant of Fluconazole, since preliminary results showed a boosting effect of some molecules for the action of Fluconazole, one of the most prescribed drug for the treatment of fungal infections nowadays.

Before starting our clinical trials and testing the compound in humans, the scientific team will assess the results and decide whether the most promising molecule will have a stronger impact as stand-alone drug for candidiasis infections or it will be further tested only as a adjuvant of Fluconazole.

This decision needs to be taken primarily based on scientific evidence because from this will depend the output of the entire research, therefore needs to be solid and science based; however, if the results will be equivalent, compering the efficacy and toxicity of the molecule both as stand-alone and as adjuvant, the management team will pick a strategic decision, moving at the next step

of the research. Looking at potential demand estimate we project to have higher figures marketing the drug as a stand-alone but, following this path, won't exclude the possibility for Xaniglucan to be used also as an adjuvant if the infections are particularly resistant and severe, since scientific test showed equivalent result both in terms of safety.

It starts from phase I, where is generally tested the safety of the drug in a small group of healthy patients, assessing the presence of unforeseen side effects (this phase lasts ~10 months usually) and where is defined the right dose to administrate by testing it with an ascending method: in this phase the success rate of moving to phase II is 57.8%, according to 2021 report "Clinical development success rate and contributing factors 2011-2022", released by Biotechnology Innovation Organization and pharma intelligence.

Afterwards, if in phase I the compound shows an acceptable safety profile, in phase II tests are run on a slightly higher number of patients, some of whom have the infection, in order to start testing the effectiveness of the compound, this phase lasts ~18 months usually and has a success rate of 38.4%, the lowest among all the key steps of the research.

If the results are acceptable and promising in phase III the compound is tested on higher number of patients, always keeping a control group to assess the real effectiveness of the treatment and to monitor potential side effects, this phase lasts ~30 months usually and has a success rate of ~ 60%.

If also in phase III the results will be acceptable and promising, the drug will be submitted to competent authorities (e.g., FDA, SFDA, EMA, etc.) for approval, after ~5 years from the beginning of clinical trials.

Once the drug has been approved there might be some unanswered questions about the MOA or safety profile of the molecule, therefore it might require an additional phase, phase IV, where the

trial is projected to investigate those answers, but this phase can be completed while the drug is already on the market.

Overall we have the potential to be designated as an orphan drug, since this happened to many drugs in the development pipeline for this same therapeutic area (due to the urgent need for new drugs in the market), and this might fast track many bureaucratic steps of the research, reducing the time needed to get the approval and for the Competent Authorities to validate the results of the research at each stage (i.e., phase I, II, etc.).

This might reduce by ~1 year the overall time to get the drug on the market, reducing therefore the money needed to get the approval and representing a much more interesting opportunity for the investors

This chapter of the research will be entirely outsourced to a selected Contract Research Organization (CRO) since the faculty lab does not have the resources neither the authorizations to run this trial; this will allow the research group to oversee the progress of the trials without the need of developing an expertise on clinical trial management and without to raise a much higher level of funding.

A shortlist of potential CROs working for our research has been built thanks to an interview to some executive members of a pharma company, who has a 20+ years of experience in working with CROs for different studies across the globe:

- IQVIA: Premium company of the sector, extremely expensive and offers a pool of services and tools that are not necessary at our stage, however, is extremely efficient and reliable regarding patient enrolment and reporting of various Adverse Events or other results of the study and good structure for data management and data handling;

- ICON: Well-structured CRO with consolidated processes and a worldwide knowledge of the industry. Reliable on the output and slightly cheaper than IQVIA. However mainly focused on consulting and commercialization of products;
- Medpace: Worldwide company, mid-sized with a focus on phase I, II, III, IV clinical trials and a potential expertise in regulatory policies in 37 different countries;
- Parexel: Worldwide company, covering more than 50 countries with a strong expertise in clinical trial design, clinical trial management, decentralized clinical trials, regulatory affairs and medical writing.

Others might be added in future, but we already have a clear understanding of the market with multiple feedbacks from different pharma companies regarding CROs working with them.

This is the most time and money consuming phase among all, it will need an average of $39 million to reach conclusion of phase II taking the risk of failure to its minimum if all the steps will give successful results and an additional ~3 years and +$100 million to complete phase III of clinical trials and obtaining the approval from competent authorities.

Once the drug has been approved, it is ready to be launched in the market, therefore it starts a new phase of production and scale-up of the compound.

It is important to highlight that, opposite to any other market, in the drug development industry the "market risk" is extremely low, you have incredibly high development risks, but if the drug gets the approval, it will be almost certainly bought by the market, especially if is something needed in terms of efficacy and costs, compared to the current solutions in the market.

Taking into consideration that for the industry is rare to see a biotech startup starting from the research on a new compound and bringing it to the market including the production, scale-up and go-to market strategy in their strategic planning, we aim to structure a strategy that will represent a contingency plan in case we will not find a buyer or a partner to complete the clinical study.

The production of the compound will be fully outsourced to a Contract Manufacturing Organization (CMO) that is specialized in manufacturing and scale up of drugs for other pharma companies or start-ups, some potential partner could be:

- PCi pharma services;
- Patheon;
- Syngene;
- Tergus Pharma.

These companies, being specialized in manufacturing, offer an efficient and more economical way to produce our products compared to an internalization of the production process that would represent a huge obstacle for the company, creating the need to develop from scratch the infrastructure needed, to build the expertise needed to manage this new section of the company and, on top of that, the need to raise a huge amount of money.

This whole process would also postpone significantly the market entry for the company and this would represent the biggest negative aspect of this strategy for 2 reasons:

1. The patents cover the innovation for a limited amount of time; 20 years for the production process and innovative application (World Intellectual Property Organization 2022), therefore staying in the market “protected” by the patents as long as possible is key to maximize the return on investment for our investors,

2. The longer we take to entry the market the higher the chances will be of a new drug being developed and approved, reducing drastically our competitive advantage.

The outsourcing strategy gives us all these advantages in the medium-short time, on the other hand, it will produce smaller margins on the single unit if compared to an internalized production process.

Even taking into consideration this last aspect the outsourcing model remains the best option for the company for the reasons listed above. This strategy will not preclude the possibility of internalizing the manufacturing structure in the future, reinvesting the capital made with the drug in the market for several years.

This is the regular development roadmap to follow in case we pivot from our original idea, allowing us to bring pre-clinical *in vitro* research to and product market ready.

Following our initial strategy, we aim to follow this path up to end of clinical trial phase II, where we will have proved the efficacy of the compound and the development risk will be much lower, therefore we will target pharma companies to sell our company, including our research and all our patents, so that they can complete the process with their research infrastructures, and we can guarantee a remunerative exit strategy to our investors.

After passing phase II the compound will represent an interesting and much safer investment for potential buyers (I.e., pharma companies) since it has the smallest success rate.

This is showed to be a common practice within the industry and a strong incentive for potential investors in earlier stages of the research.

(Sertkaya Aylin, Anna Birkenbach, Ayesha Berlind, Jhon Eyraud, 2014) (IFOPA 2022).

IP protection

In the pharmaceutical domain, it is important to have intellectual property protected at the soonest, under the threat of the innovations being eventually replicated or becoming prior art. It is important to find the right balance between protecting the most out of the innovation without extensively writing claims, under the issue of infringing third-party rights or paying more than expected.

Being the only organization working on an innovation, the IP holder can assure a sustainable competitive advantage over other players, as well as security in disclosing ideas and internal processes of the innovation publicly without fearing of being copied or infringing other inventors, and generate profits from the laborious task of developing the idea from project to the market, or even other forms of profit generation such as licensing (Sammon 2022).

In the first half of the present year, Deca Pharmaceuticals has submitted a manuscript through NOVA university (the holder of the IP) with 2 claims: (1) the production of the compounds, (2) and their application as antifungals, with priority date as of 29th of March, 2022, as a provisional patent application, in Portugal. Up until now, no claims whatsoever exist for this patent.

After gathering more data on checkerboard assays to test our drug for combination therapy, which should fall within the time scope of the provisional patent in Portugal, a third claim will be added to the manuscript, protecting the unique synergetic interaction of Xaniglucan with other already existent classes of antifungals and their drugs - its usage as a drug adjuvant.

Further plans include filling a draft and submit a provisional PCT patent (which offers patent coverage internationally, if the countries are a part of Patent Cooperation Treaty), after 12 months has passed from the submission of the provisional patent in Portugal, that being 29th of March 2023. The provisional PCT patent will last for 18 months and the priority date that will be visible on the document, will be the one submitted in the Portuguese patent (29th of March 2022). Any

compound production process, or the aforementioned application of the raw materials hence, thereafter, will be considered prior art, since our innovation was registered first.

Applying for a patent is expensive, the cost varies with the complexity of what needs to be protected with a mean range between $6 and $12 thousand, plus up to $100 thousand for a PCT patent, and $200 to $400 per hour if a specialized attorney is needed to help on the process. As a strategy to manage the funds, Deca Pharmaceuticals submits provisional patents to protect our innovation early on, taking advantage of 2.5 years of exclusivity (after the Portuguese patent submission date) with minimal costs. Throughout this window, if needed, we can plan to add more claims as our innovation develops, while applying for funding to be able to pay for an international patent.

After the 29th of September 2024, before the PCT expires, we will pay the needed amount for the PCT patent to be active. From this point onwards, the patent will protect our innovation for the upcoming 20 years (World Intellectual Property Organization 2022), in the meanwhile, the process of producing Xaniglucan plus its application to treat fungal infections will be maintained, with proper fee submissions; 3.5, 7.5 and 11 years after the submission of the PCT patent (Thervo 2022).

After the 29th of September 2044, our patent will no longer be protected and a generic, cheaper version of our drug will appear on the market.

Potential development

To better explain how the innovation can reach its full potential, first we need to distinguish two different categories: (1) **Per definition**, (a) as a stand-alone drug, or (b) as a adjuvant. (1) per definition, (a) as a stand-alone drug, or (b) as a adjuvant. After climbing through the development

roadmap steps, considering the possibility that the molecule does not pose interest to possible partners, after phase III the management Team will submit an NDA to the Health Authority in order to be able reach the market in 2030. Long by then, the conclusive testing will show the best application for the molecule, either being a stand-alone drug, effectively treating one or more resistant isolate species, or a adjuvant, increasing the effectiveness of other antifungals by treating one or more resistant isolate species. We can discover in the short-term, for example, that the molecule boosts the effectiveness of other molecules, with a wider scope of *fungi* species. Which leads us to the other category: (2) **per action spectrum**, since we found ourselves in very early stage of development, as referred on the description section, other molecule configurations of the same raw ingredients will be tested, as well as the main contender, on other resistant isolates of the *Candida* spp.: *C. parapsilosis*, *C. krusei*, *C. lusitaniae* and other spp.: *Cryptococcus neoformans* and *Aspergillus fumigatus*.

In short, up until now, out of the tested molecules, only one shows selectivity against *C. glabrata* and at the same time, being non-toxic for human cells. Further studies are going to determine if this and the other molecules will act along strongly in one kind of fungal pathogen, or have a much greater scope, increasing our product's therapeutic availability.

Both dimensions will reach a conclusive state in the short-term. Optimal scenarios comprise of Xaniglucan being able to cover the gap where Fluconazole is rendered ineffective against azole resistant isolates, by using drug combination therapy. Since Fluconazole is still one of the most prescribed antifungals presently (as per Dr. Ana Rita Domingues, see Interview notes section, in the Appendix), a synergetic effect where increased value is created for both sides is an expected possibility. Another optimal scenario is one where the scope of Xaniglucan is rendered with high levels of effectiveness, that could spark the interest of financing parties in investing in a new way

of fighting fungal infections. More capital going to R&D enables the creation of better and improved products that can one day be used as one of the main choices of prescribing doctors to cure a myriad of fungal diseases.

THE TEAM

The team is composed by 2 core parts, one is the scientific team and the other one is the business team.

They both have the same goal but they look at it from two different angles, working synergically to reach it.

Management Team

The business team is composed of 4 key people, and it will be enlarged in the future accordingly to the company needs:

- **Pietro Bovio**, CEO: in charge of designing implementing and overseeing the strategic path of the company from the beginning until an exit. Create contingency plans to avoid any problem coming from unforeseen events, building and managing relationships with partners (I.e., pharma companies, CRO, legal offices, etc.), harmonize the work between the scientific team and the management one, aligning goals, efforts, and milestones in order to have both teams aware of what needs to be done, when it needs to be done and why, avoiding a silos structure and improving efficiency.

  Master graduate in international management at NOVA SBE after a bachelor's in management at Bocconi University, attended strategic investment management class at

London Business School and has working experience in a consultancy firm following relevant projects within the life science industry, strictly related to biotech research and development for pharma companies. Within his professional experience he deepened his pharmaceutical industry knowledge, and the understanding of clinical trials management, which are an essential part of a pharma company, taking part in multiple projects on these topics he had the chance to understand and solve some of the most common obstacles for the industry, to create a relationships network with some meaningful players of the industry, to understand the regulations and the requirements necessary for a clinical trial to be successful;

- **Miguel**, COO: ensures the laboratory has a steady pace of work development, with all the necessary equipment and consumables ready for usage, in an efficient manner, with the available funds. Also responsible for the project management, reassures future planning for each clinical stage to be fulfilled in the minimum reasonable time possible, being also a hub of communication with the stakeholders and the firm.

  Master graduate in Impact Entrepreneurship and Innovation at NOVA SBE, with background studies in Port Management at “Escola Náutica Infante D. Henrique”, counts with 6 years of experience in a multinational shipping company, managing cargo, container vessel services and connecting port authorities, brokers and other companies to the ship owner and ship manager, serving as a representative of the latter, defending their best interest. Extensive knowledge and experience in planning in of utmost importance to keep the firm development at a fast yet solid pace.

- **Manuel**, CMO: Responsible for understanding the market dynamics and characteristics, to then better implement the strategic vision defined by the board. Major functions of this position include: researching the market trends and dynamics, clustering the market in various segments, forecasting profitability of each segment and targeting the one that is most valuable for the stakeholders and defining a positioning strategy that best addresses the target segment's needs.

  Bachelor's degree at Católica Lisbon SBE, international exchange program at ESSEC Business School and a last year Master's student at NOVA SBE, has been working in retail for the past year as a Production Assistant (Assistant Buyer), for a Portuguese fashion start up;

- **Giovanni Dagnino**, CBDO: in charge of developing the company's vision and strategy from an operational point of view. Also responsible for identifying the best business opportunities and product-development pathways to follow by having a comprehensive view on the competitive dynamics and gaps to be filled. Heavily involved in operational day-to-day projects maintaining the company aligned with the overall strategy.

  Master graduate in Management at Nova SBE with a focus on innovation, marketing, and expansion. Has experience in startups as a digital marketer and brand supervisor offering services and delivering projects as a consultant.

Scientific Team

The scientific team is composed of:

- **Ana Petronillho**, CSO: Dr. Petronilho is the leader of the Bioorganometallic Chemistry group at ITQB-NOVA. Prior to her independent work at ITQB-NOVA, she completed her

PhD in 2010 (U. of Seville, E. Carmona). Later she worked as a postdoctoral fellow in the group of M. Albrecht (2011-2014), developing metal catalysts for artificial photosynthesis. At ITQB-NOVA her team developed a new methodology for the synthesis of N-Heterocyclic carbenes (NHCs) based on guanosine and adenosine, stabilized by platinum and palladium complexes. This methodology included a suitable deprotection methodology for the sugar, that is unprecedented and paramount for incorporation of metalated NHCs into DNA and RNA.

Her team was able to isolate a the first N-Heterocyclic carbene based on mRNA cap0, a molecule of great importance in transcription, by means of direct and unsupported C-H activation (Chem Commun 2020). In this work, it was possible to demonstrate that metalation imparts a higher stability to the nucleoside towards hydrolysis, which is particularly relevant for organometallic nucleosides based on RNA. In 2018 She was awarded the NOVA-Saude Grant to develop novel triazoles for HIV based on AZT derivatives. In collaboration with Dr. Soares, it was possible to demonstrate that these new compounds, synthesized via click chemistry, are active as prophylactic agents for HIV-1 since they are very effective in preventing healthy cells from being infected.

Since Ana joined ITBQ she was able to secure competitive funding (both salary and research), she has co-supervised one PhD thesis and she is currently supervising 3 PhD students. She has supervised one master thesis and one BSc thesis. She has established collaborations both in Portugal and abroad. She actively participates in national and international conferences (27 oral communications, of which 11 invited communications). In 2019 she was invited as a plenary speaker at the Inorganic Chemistry National Meeting of the Mexican Chemical Society;

- **Catarina Pimente**l, Head of R&D: is an Auxiliary Researcher at ITQB NOVA. She earned her Ph.D. in Molecular Biology from Universidade de Coimbra (2006), in the field of Plant Sciences, with Prof. Carlos Faro. Soon after, she shifted her scientific focus and did postdoctoral training at ITQB NOVA with Prof. Claudina Rodrigues-Pousada, where she began her studies on yeast (unicellular *fungi*). Her independent career started in 2017, after being awarded a competitive FCT Investigator Starting Career Grant. She is the Head the Yeast Molecular Biology Laboratory (2021), ITQB NOVA, and her group's research is centered on the development of novel antifungal drugs and sensitive diagnostic tests capable of detecting drug resistances in real-time; current research focuses on the opportunistic yeast *Candida* spp. CP regularly collaborates in outreach activities and communication with the media. She lectures in the ITQB PhD Program MolBioS and in the Masters in Biochemistry for Health. She is a member elected of the Institute Council, ITQB NOVA, and member of the Executive Committee of the PhD program, Biology at the Host-Microbe Interface;

- **Giulia Francescato**, R&D specialist: PHD student in Bioorganometallic Chemistry.

This team will be in charge of writing the protocol for the study, designing and carrying out the experiments in the preclinical phase of the research and overseeing all the clinical trial process and results, ensuring that the research is properly conducted and analyzing the results continuously during the process.

Their first milestone is to create a shortlist of 7 molecules that will move to the in-animal testing, based on their preliminary results; their second milestone is to select, among the shortlisted group, the best molecule to be tested in human after the results of in-animal testing and decide whether the selected drug has more potential as a stand alone drug or as a adjuvant of Fluconazole.

This team is also in charge of the medical writing and eventual publications regarding the research: this will be an essential part for the funds raising, both in the first part when the company will apply for public grants and when the money will be raised from pharma companies' foundations or VCs.

They will be in charge of being the scientific lieson with every stakeholder throughout all the research, both to communicate key results achieved, potential obstacles encountered or to answer stakeholders' question about the research.

The management team, mixing knowledge and expertise from different field and different industries has different responsibilities:

- In a preliminary phase, during *in vitro* tests, must set up a business plan for the venture, set the basis to found a company, organize the structure within the company in order to make it work smoothly throughout the entire research and study the topic, in order to be fully aware of the subject of the research and of the rationales behind it;
- Interact with the internal legal team or with external partner to design and implement the contracts' structure that will regulate the dynamics within the company, describing responsibilities, ownership and compensation for each member of the company;
- Oversee IP application process and the construction of an IP portfolio;
- Strategically select the sources of funds necessary to complete the preclinical research and put in place all the necessary procedures to reach the chosen target (i.e., be in contact with

external companies that will facilitate the process of applying for national and international grants, monitoring economic conditions of the grant and others);

- Build the strategy necessary to fund raise before the clinical tests, contact the potential investors targeted and build a proposition good enough to satisfy their requirements;
- Manage the collected funds between all the expenses, both variables and fixed;
- Build economic prospects and forecasting;
- Engage potential buyers during the clinical tests, follow an eventual negotiation on terms and clauses of a buyout or another form of deal, oversee the acquisition process;
- Study and create contingency plans for all the key decisions throughout the research;
- Identify eventual key profiles to be included in the team, structure an agile selection process and implement it, integrating their figure in the contract structure built before.

Advisory board

This mix of expertise and different backgrounds is completed by Professor Arantes-Oliveira as senior advisor of the company: a former professor at NOVA SBE in science based entrepreneurship, at NOVA SBE he also leads his field lab on the same topic for master students, he is a PHD in genetics at the University of California, he attended an executive course at Harvard and he is a multiple successful entrepreneur that founded/co-founded multiple successful startup in the science innovation field, he is an investor in multiple startups both as angel investor and as a founder of Clinical Research Ventures (CRV), that funds the early clinical development stages of pharmaceutical drugs, diagnostic tools, and medical technologies. Professor Arantes-Oliveira will be a key resource for the product both with his expertise and knowledge of the industry and with his network.

We are also planning to enlarge the advisory board including future investors or mentors that are in our professional and academic network, since this project is strongly linked to the academic environment of Lisbon, we plan to use this link strategically to build a diverse and structured advisory board that will be crucial for the company development.

To complete the team, we have a legal office supporting the project with regulations and IP applications which is internal to the faculty and coordinated by dr. Pedro Pedrosa, PHD, Innovation manager for multiple institutions over the past years and an experience of multiple years as head of technology transfer for LifeArc.

All the regulatory pathways of the clinical trial will be followed by the CRO selected to carry it out. This decision is made because the legal office of the faculty does not have an extensive expertise on clinical trials regulation and approvals, therefore they will support the team in the startup phase and in the process of building an IP portfolio to protect the research outcome.

Company features

Deca Pharmaceuticals has recently been founded, at the beginning of the *in vitro* testing phase.

It is legally established in **Sweden**.

This decision is strategic to the company's development for different reasons:

- Sweden is world famous for its contribution to the medical innovation landscape;
- It is one of the most efficient countries in Europe in terms of infrastructure, health system and bureaucracy processing time;
- Is the fifth country globally in terms of venture funds for start-ups, second European country after Estonia (Glasner Joanna 2021);

- Being a member of the European Union is a key success factor for our choice since it will be an essential criteria to assign the European grants that we will apply for before second phase of preclinical testing;
- The taxation is not one of the lowest within the European Union, but this is not a stringent requirement for us, since we do not forecast cashflows at least until approval is reached, but also in that case our strategy is to sell the company and/or the rights to another company, therefore the taxation will not have a strong impact on our balance sheet;
- From an investor point of view, it is also crucial the data transparency policy that the country applies, since it ensures a much more secure way of reading our research data and output; the strict policies applied by regulatory agencies regarding new hirings, corporate governance and environmental themes, all factors that institutional investors such as VC's, foundations and companies need to take into consideration when investing in a new venture.

The operative headquarter and all the operations, however, are based in Portugal, next to the research center, this is a strategic choice, since Portugal is a cheaper country compered to Sweden and USA in terms of rent and general expenses. We decided not to base our headquarter in the USA, where the biotech competitive arena stands and were most of the investors looks for opportunities at first, also because we want the company to be strongly linked with EU, both to take advantage of European grants, and because we have built a strong network of stakeholders (i.e., investors, advisors, partners and others); moreover Portugal is the best fit for our headquarter because we prioritize being close to the research in order to oversee the process more directly and,

therefore, reducing the risk of misconduct of the trials and any potential mistake, since this represent the biggest cause of failure of clinical trials.

FUNDING

The company has clear needs in terms of funds; indeed we have forecasted ~ €39 million in addition to €50 thousand already raised, in order to complete our clinical trial up to phase II. This estimate is based on the kind of clinical study we are carrying out and some standards of the market, considering that all the parts of the clinical trials (e.g., phase I & phase II) will be outsourced to a CRO.

Our strategy is to carry the research until phase II is completed, and then find a pool of companies interested in buying our company (i.e., also our research and our patents).

We chose the end of phase II as the best stage to sell because this represents a key inflection point of our study for 2 main reasons:

1) If the results are promising after phase II the risk that the drug will not be approved by competent authorities will significantly drop. Phase II is indeed the phase with the lowest success rate, therefore if the drug passes it there will be a cumulative high chance of it being approved;
2) Phase III is the most time and money consuming phase of the clinical trial and it would represent a significant effort in terms of fund raising to reach almost other €100 million or more to complete this phase, and at least 3 years more to have return on initial investment.

The first round of fund raising was successful and in the beginning of 2022 the team raised €50 thousands of non-dilutive capital from a joint fund from local entities (e.g., ITQB, IGC and Oeiras Municipality).

This capital will be used to complete *in vitro* testing during the first year and it will help us identify a pool of 7 molecules showing the most promising results that will move forward to the next phase.

To complete the pre-clinical trials with some in-animals testing we forecast to need €500 thousand over a period of 2 years; this budget will be used to develop in house preclinical trials, testing the compound on different animals, therefore the company will have to rent a bigger space to be used as a lab, to buy animals to test the compound on and to enlarge the team with a key scientific figure, who must have expertise in animal testing, to conduct and coordinate this phase of the research as an external consultant. Based on the amount of money raised with grants we will evaluate the possibility of outsourcing this phase of preclinical trial, if the budget will be enough to fully outsource it, it will be our first option, in order to simplify the process and obtain more qualitative results.

The animal selection and supply will be outsourced to companies specialized in this procedure since it is a highly regulated and sensitive stage.

To obtain this second round of funds we plan to apply for national and international grants such as: Horizon Europe 2022, MCSA (Marie Skłodowska-Curie Actions), European Commission, Institut National de la Santè et de la Research Mèdical, Wellcome Trust, Bill and Melinda Gates foundation, and others.

These grants usually work as loans, with favorable conditions for the applicant or as fund without obligation of restitution, therefore represent a huge opportunity to finance our research at a cheap price.

In particular, Horizon Europe 2022 has a budget of $95 billion to be spent until 2027 exclusively

dedicated to European players improving and innovating in various fields such as health, environment, culture, inclusivity and others.

Due to recent governmental commitments, projects improving the environment are one of the main targets of this program, but health gained priority one, and therefore, a big majority of this fund will be targeting health related initiatives such as ours.

Knowing that these grants are essentials for our research and that the application process is always technical and bureaucratic, we will evaluate the option of using the services of companies that will guide and consult us throughout the entire process, increasing our chances of getting the funds.

This strategy gives us the possibility of spending a small amount of the money raised as a commission for these kinds of services, but it increases significantly the chances of reaching our budget goal of €500 thousand, decreasing proportionally the need of a contingency plan involving Angels investors, that would represent a much more expensive way of raising funds.

As a matter of fact, if the money raised from these entities will not be enough to cover the cost of preclinical trials, we are in contact with some potential Angels Investors throughout the academic network of the project stakeholders that will provide the missing part of the budget. This scenario, however, needs to be considered as a contingency plan to be used just in case the public/private entities grants will not provide enough money for the research.

The rationale behind this strategy is not mainly economical since Angel Investors conditions usually are more expensive than the ones offered by the initiatives mentioned before, but also strategical since it is common that Angels Investors want some rights or future royalties in exchange for their funds, making the operation less appealing from a founder point of view and for potentials future buyers.

Once we have started our in-animal testing having the first results, we will start raising funds for the first 2 phases of the clinical trials.

In order to successfully start, conduct and finish phase I and phase II of the clinical trial we estimate to need ~€41 million, considering the size and the typology of our study.

We have different options to raise funds at this stage of the research:

- Corporate Venture Capital funds (e.g., Pfizer, Novo Nordisk, GlaxoSmithKline and others);
- Family office Venture Capital;
- Venture Capital targeting life science sector (e.g., Ra capital, OrbiMed, Sofinnova, Versant,5 AM Ventures and others);
- Corporate foundations (Novo Holdings, …);
- Advocacy groups foundations;
- Partnership with pharma companies.

Each one of these has different characteristics, considering that our "exit strategy" will led us to find a pharma company willing to buy our research, it is strategic to already build a partnership with one of them at this earlier stage for 2 reasons:

1) If the company that is building a partnership with us right now will see interesting results, it will have more interests in making an offer since it would have already invested in our research;
2) Other companies that have not invested in our research at this stage, will be more interested to make an offer after phase II in order to prevent a competitor from gaining a competitive advantage.

For these reasons our main target will be corporate foundations and Corporate VC, or also potentially building a partnership with one of them involving a potential strike price on a future

acquisition, royalties on drugs sales when it will be on the market or a percentage of a potential future acquisition from another company.

Another potential upside of partnering with a pharma company at this stage would be that, since our interests are aligned (we both want to conduct the clinical study successfully and bring a new drug to the market), we might receive strategic "mentorship" from company executives during key decisions of our research.

The main companies that can be interested in our research and that might have the capabilities to complete the research are:

- **Pfizer**, being the biggest player for infectious disease and with an already rich pipeline of drugs in this therapeutic area, moreover is one of the main producers of Fluconazole.
- **M**erk, being strongly focused on oncology and immune system disease, infections will be a focal problem of their patients, making our research appealing for them.
- **Roche**, being strongly focused on infectious diseases and also on multidrug-resistant infections and having an annual budget of almost $15 billion for R&D in 2021, representing a huge budget for investment in phase II research.

Moderna, Cidara and Synexis are other pharma companies with a focus in *fungal* infections treatment, committed to enlarge their pipeline in this therapeutic area and with the budget large enough to carry out meaningful M&A operations or impactful deals with early-stage research.

VC firms and Family office VCs have a lot of resources to put in place but the competition is really high: VCs usually have strict requirements and they invest money only when results show a safe outcome, when the risk is quite low; they usually put in place a strong analysis of the research results that, if not recorded properly or if not clear enough, will be an alarm ring for the firm that will not close any deal.

- **NOVO holdings**, is NOVO NORDISK holding, it invests almost €500 million in 2021 alone, split in 46 investments, it aims to invest in companies committed to develop new drugs, medical devices or services
- **RA capital**, with a fund of about €2 billion, is a VC fund actively investing both with public equity and private equity, it represents the second largest fund focusing on this industry
- **Orbimed**, is the biggest VC with a focus only on this industry, with a fund of around €18 billion invested both as private/public equity and as debt/loyalty it represents a huge opportunity not only of funds for the company but also of network and guidance for the future stages of the research.
- **AMR action** fund is the world largest private-public partnership investing in small mid-sized companies, developing antimicrobial therapeutics, it has a focus on the same problem as Deca pharmaceuticals and therefore, it would represent a good fit for our funding strategy.

These are 4 of the main targets to get our first round of private investment but we are aware of the presence of a huge ecosystem of funds focusing on this industry.

Patient advocacy foundations (e.g., Fungal infection Trust, GAFFI and others) are a much less reliable source of funds, since their main objective is not strictly economic, but the resources at their disposal is often very limited; on the other hand, they are always at the center of a stakeholder network that might create value for the company, both as funds sources and mentors or promoter of our research.

In order to define at which valuation, we should aim to sell our company, it will depend on the results we will obtain during the previous phase, in terms of efficacy shown by the molecule and

also in terms of safety levels. In fact, to have a clear understanding of what kind of investment our company requires, we need to discriminate all the costs, from rent to patents, that we might incur in the meantime. The total money raised should be enough to cover the following costs:

EXIT STRATEGY

If the results are going to be as good as expected, we will proceed to find a buyer for the research setting the price in between this range €250 – €350 million.

This range is based on comparable acquisitions that happened in the recent years, it takes into consideration that most of the acquisitions happened at stage II and that anti-infective drugs are not the most valued drugs on the market. Considering a potential designation as orphan drugs we can expect an evaluation higher than the upper limit of the range.

Considering that the amount invested is €39 million the multiple for the investor would be 6x-9x; it will be higher for early investors, but for the ones investing at the end of preclinical stage, the time period will be short, indeed potentially a fund investing in 2024 will see a 6x-9x return in 2-3 years, aligned with VC funds expectations for these kind of deals within this therapeutic area.

If we will not be able to find an adequate offer for our research, we have other options to guarantee an exit to our investors:

- **VC investment**: round of investment from previous investors that are already committed to the project and from new investors, at a higher evaluation compared to the one made after pre-clinical testing. This option would mean giving up more equity, having to outsource and oversee phase III of clinical trials, postponing the exit of our previous investors but not necessary up to the end of phase III, since, if results keep being as good

as expected, we will keep looking for a buy-out from a pharma company throughout the entire phase III;

- **IPO**: it is an option to go public as a newborn company, and opening to the market would give the chance to our investors to exit their investment in a profitable way; this practice is common in this industry but is mainly used by companies with a revenue stream that allows them to be more interesting for an investor point of view, however, nowadays evaluations for this sector could be based only on future expectation and on current research results;
- **Other deals**: another way of raising money at this stage would be to sell royalties on future drug sales, for an investment in the company today. This would make a future acquisition less appealing for pharma industries because it would reduce the future revenue stream of their investment.

The 3 options previously described need to be considered as a contingency plan in case no pharma company will be interested in buying the company out.

The IPO is the riskier among them since it exposes the company to the market, which might be highly irrational and would make the company not "controlled" anymore by the founders; furthermore, it is highly regulated and would expose the company and the research to stricter procedures and every decision would cause a reaction of the market (I.e., the choice of the CRO, some irregularities in the animal supply during previous phases, a potential side effect of a patient, and others).

For these reasons a new VC round would represent a better option for our company to raise money compared to an IPO, reducing the exposure to the public market and its volatility and gaining some mentorship to conduct and conclude the research successfully.

From our previous investors point of view this might represent a delay on their return on the investment period, however it would increase the expected return significantly, since VCs funds invest only with the expectations of certain multiple and a certain level of risk, moreover they bring expertise and network that will help to successfully finish the research.

FINANCIAL PROJECTIONS

Our company, being a biotech startup, focusing on research and development of a new drug to be launched into the market has the same financial needs and prospective of all the other companies of the same kind.

In particular, this kind of venture, burns cash for at least 8-10 years before seeing a return on the investment.

In fact, to have a clear understanding of what kind of investment our company requires, we need to discriminate all the costs, from rent to patents, that we might incur in the meantime. The total money raised should be enough to cover the following costs:

- **Estimated Cost per Researcher in Portugal:** In Portugal, the salary of a scientific researcher is on average 2.725€ per month ("Glassdoor," n.d.). However, our company will have incremental costs regarding the labor of these people. Such costs are the mandatory Portuguese social security tax that is paid by both the company and the employee (the company contribution is: 23,75%) in addition to the estimated cost of the employee's insurance against accidents at work, that is, on average around 1% of the salary. According to our computations and considering that we are hiring two researchers, the expected yearly cost with researchers is **95.184€.** We expect a salary increase of 7% per year.

- **Estimated Cost per Internal Consultant in Portugal (Management Team):** At Deca Pharmaceuticals, we also need to consider the management consultants that are working. Consulting jobs often are trickier when it comes to the application of social security rates and insurance. This is because the consultant's salary has two dimensions to it, the fixed dimension and the variable dimension. On average, the fixed part of the salary is around 1.270€, while the variable dimension takes up the bigger portion of the total salary at around 3.107€ ("Glassdoor," n.d.). In Portugal, legislation states that the social security rate only needs to be applied to the fixed part of the salary, rather than the total compensation. This means that, from the company standpoint, the social security costs are lower. However, since we are the founders of the company, our variable bonus is not going to be monetary but rather paid in shares, if the managerial objectives are fulfilled. All in all, our expectation of costs with management consultants is going to have a yearly impact of around **104.790€** (since we are four people for this position). The same salary growth rate of 7% per year is applied.
- **Fund Raising Bonus:** In order to give an incentive to internal staff, Deca Pharmaceuticals is planning on attributing as a total budget for bonuses a 3% fraction of the money raised. This bonus will be distributed by all of the internal members, scientists and managers.
- **Costs with Contract Research Organizations:** As talked before, we are going to outsource the development of clinical trials to a Contract Research Organization that will handle this process. The development of these research and trials are most certainly the largest expense the biotech companies have. However, the cost of the research will not only depend directly on the phase of the development, but also on the field of the development. In other words, clinical trials for cancer will have a different cost than for anti-infectives. According to report submitted to the U.S. department of Health and Human Services, Phase

1 of clinical trials will take several months (we are assuming a year) and will cost around **€4 million** for the case of anti-infective drugs (Ledesma 2020). As expected, the second phase of clinical trials will take longer and will be more investment intensive as a whole. In fact, for the whole study a company would pay around **€13,5 million**. However, this value will be distributed by the two years we will be spending on this phase. Therefore, the yearly investment on CROs will be **€6,75 million** from the middle of 2024 to 2026 (end of clinical phase 2). However, since these values are from 2014, around 10 years ago and before a pandemic, crisis and war situation, we believe that these prices have increased significantly, in other words, for our financial projections, we will assume that our costs with CROs are going to be double the value provided by these reports, as presented in the table further down this section;

- **Estimated Cost per External Consultant in Portugal:** Even with internal consultants managing the company, we need to have a budget for other external consultants to advise us on some fields that none of the in-house employees are experts at. However, since we are hiring a service, no social security taxes need to be paid by us. Therefore, the salary of the consultant will be the expense of having them working for us, considering both the variable and fixed dimension. As stated before, on average, the fixed part of the salary is around 1.270€, while the variable goes up to 3.107€, making the total cost of the external consultant around **4.376€** per month. This is equivalent to, on average, **61.264€** per year. In 2023 and 2024, this value will increase by 50%.
- **Rent Costs:** From the report we got from the scientists already working on this compound, the amount attributed to rent of the laboratory was about **5.000€.** We are assuming this is the value of the rent per month, therefore, we computed its yearly equivalent, which is 60.000€. The laboratory is currently located at the university in Lisbon;

- **Consumables:** In this category, we are considering several (chemicals, growth media, kits for molecular biology purposes, plastic and glass material plates, pipettes, Eppendorf's, tubes, tips, gloves, lab coats, and other necessary laboratory materials. The value estimated from the researchers was 35.000€ for the preclinical trials. We are assuming that this value will double when moving to phase two of clinical trials, assuming a yearly cost of **70.000€**;
- **Patents:** To make sure our investigation is safe, and we move away from the possibility of getting our discovery stolen by a more investment heavy juggernaut, we will have to buy several patents over the years whose costs need to be covered. We are planning on having two provisional Patents (PT 29th March 2022 and PCT 29th March 2023) which will cost around 4.000$ combined, Search fees (29th March 2022) that have a cost of 475$, Examination fees (29th March 2022) that account for sensibly 450$ and, finally, Non-provisional PCT patent (international, 29th Sep 2024) which will be the most expensive one priced at 100.000$. It is important to note that more patents will be purchased, however in these projections we are only going to display the costs incurred up until the moment of selling the company (2027);
- **General Expenses:** In this category we are considering the scenarios where the team must travel abroad for business meetings or other business activities. In fact, we believe this is a section to invest some money in, since our company will be running in several areas of the world, namely the United Sates, and for everything to run smoothly, there needs to be budget for such activities. The general expenses account will include hotel rooms, plane tickets, dinners with investors, other meals, … and we plan to save around **50 000€** per year for these tasks.

Baseline scenario	2023	2024	2025	2026	2027
Money Raised	€ 500 000	€ 10 000 000	€ 15 000 000	€ 13 200 000	€ -
Available Cash	€ 500 000	€ 10 008 451	€ 16 094 918	€ 19 396 554	€ 9 544 562
Researcher's Costs	€ 95 184	€ 101 847	€ 108 976	€ 116 605	€ 124 767
Management Team Costs	€ 104 790	€ 104 790	€ 104 790	€ 104 790	€ 104 790
Bonus	€ 15 000	€ 300 000	€ 450 000	€ 396 000	€ -
Rent	€ 120 000	€ 120 000	€ 60 000	€ 60 000	€ 60 000
Consumables	€ 35 000	€ 70 000	€ 70 000	€ 70 000	€ 70 000
Patents	€ 4 679	€ 95 000	€ -	€ -	
General Expenses	€ 25 000	€ 50 000	€ 50 000	€ 50 000	€ 50 000
Operating Expenses	€ 399 653	€ 841 637	€ 843 766	€ 797 395	€ 409 557
External Consultant Cost	€ 91 896	€ 91 896	€ 61 264	€ 61 264	€ 61 264
CRO Outsourcing	€ -	€ 7 980 000	€ 8 993 333	€ 8 993 333	€ 8 993 333
Outosurcing Expenses	€ 91 896	€ 8 071 896	€ 9 054 597	€ 9 054 597	€ 9 054 597
Total Expenses	€ 491 549	€ 8 913 533	€ 9 898 364	€ 9 851 992	€ 9 464 154
Remaining money	€ 8 451	€ 1 094 918	€ 6 196 554	€ 9 544 562	€ 80 407

Figure 1 - Financial Projections

Contingency Plan:

Unfortunately, we know that not everything goes according to plan. Therefore, we must be prepared for the mere possibility of not being able to raise all the money necessary to get our initial plan off the ground. Therefore, we came up with a cost structure adjustment to face a 30% decrease in the fund-raising strategy. These measures will be more significant in the CROs we'll be looking at to outsource, where we expect to reduce to 70% of our previous budget. This will happen since we're going to look at less costly entities to reduce our largest cost-driver. We'll also reduce the research team to one and decrease 20% of the salaries of the management team. General costs and rent will also see some reductions. Patents will remain unchanged, in order to protect our intellectual property, and our investors' interests. The new projections can be shown below.

Worst case scenário	2023	2024	2025	2026	2027
Money Raised	€ 500 000	€ 10 000 000	€ 15 000 000	€ 1 533 715	€ -
Available Cash	€ 500 000	€ 10 182 070	€ 18 851 119	€ 13 331 148	€ 6 670 918
Researcher's Costs	€ 47 592	€ 50 924	€ 54 488	€ 58 302	€ 62 384
Management Team Costs	€ 83 832	€ 89 700	€ 95 979	€ 102 698	€ 109 887
Bonus	€ 15 000	€ 300 000	€ 450 000	€ 46 011	€ -
Rent	€ 60 000	€ 60 000	€ 30 000	€ 30 000	€ 30 000
Consumables	€ 35 000	€ 70 000	€ 70 000	€ 70 000	€ 70 000
Patents	€ 4 679	€ 95 000	€ -	€ -	€ -
General Expenses	€ 7 500	€ 15 000	€ 15 000	€ 15 000	€ 15 000
Operating Expenses	€ 253 603	€ 680 624	€ 715 467	€ 322 012	€ 287 270
External Consultant Cost	€ 64 327	€ 64 327	€ 42 885	€ 42 885	€ 42 885
CRO Outsourcing	€ -	€ 5 586 000	€ 6 295 333	€ 6 295 333	€ 6 295 333
Outosurcing Expenses	€ 64 327	€ 5 650 327	€ 6 338 218	€ 6 338 218	€ 6 338 218
Total Expenses	€ 317 930	€ 6 330 951	€ 7 053 686	€ 6 660 230	€ 6 625 488
Remaining money	€ 182 070	€ 3 851 119	€ 11 797 433	€ 6 670 918	€ 45 430

Figure 2 - Conservative Financial Projections

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APPENDIX

Abbreviation Index

AIFA – Italian Medicines Agency

AMR MPTF – Antimicrobial Resistance Multi Partner Trust Fund

BfArM – The Federal Institute for Drugs and Medical Devices

C. – *Candida*

CAGR – Compound Anual Growth Rate

CDC – Centers for Disease Control and Prevention

CMO – Contract Manufacturing Organization

CRO – Contract Research Organization

EMA – European Medicines Agency

EU – European Union

FDA – US Food and Drug Administration

GAP – Global Action Plan on Antimicrobial Resistance

GARDP – Global Antibiotic Research & Development Partnership

ICU – Intensive Care Unit

IDSA – Infectious Diseases Society of America

IFI – Invasive Fungal Infection

IPO – Initial Public Offering

IV – Intervenus

M&A – Mergers and Acquisitions

MCSA – Marie Skłodowska-Curie Actions

MIC – Minimal Inhibitory Concentration

MOA – Mode of Action

NDA – Non-Disclosure Agreement

OOPD – Office of Orphan Products Development

PCT – Patent Cooperation Treaty

PoD – Point of Difference

R&D – Research and Development

ROI – Return on Investment

SDG – Sustainable Development Goals

SFDA – Saudi Food and Drug Authority

Spp – Species

TOR – Target of Rapamycin

UN – United Nations

VC – Venture Capital

Table of Figures

Interview notes

Filipe Assoreira, MBA – Biotech Entrepreneur and Consultant

In your point of view, since we are very early stage, what follows next?

New drug application to get to clinical stages

Considering our project and the early stage, what would be more appealing to pitch to investors?

Unique selling point, our competitive advantages

Strong points – low cost and unique in terms of *fungi* resistance

How should we get funded, and in what stages? Do you know ideal venture capital firms that would be suitable to our project?

EU Grants, VC or Business Angels.

VC, if they believe in the results, they'll only enter in Phase I.

There are Private Equity firms that invest in Pre-Clinical, if the patent is robust, followed with a need in the market.

Investival (https://www.lsxleaders.com/investival-showcase/our-story)

Depending on the innovation, you may have fast-track approval (cancer, orphan drug designation - big deals)

Antifungals and Antibiotic are not very attractive at the moment

Welcome foundation, Bill and Linda Gates foundation – for low-income countries

Given the nature and stage of our investigation, from your experience, what would you say could be the best? Continue to the market or sell the company at the end of 2nd stage?

Crunchbase and pitchbook for public information on exits

Regarding the Business model? Should we have different mock-ups along the phases? More alternative for each phase of development? Is it to early to draw a business model canvas?

Characterize the patient journey, how does the patient reach this point, and how he's treated. Then assume a percentage of the money, by simulating how many patients will be cured, how much money will come back in

What are the needs of Big Pharma? How should we get visibility to sell to Pfizer, or how should we approach? or should we focus small?

Needs proof that is adjuvant of Fluconazole.

Instead of Pfizer, since it is generic already, why not test the molecule to Fluconazole solely, to be defined a path after the Pre-Clinical

Other notes from the interview:

EIC it is a good set of money that would fit our situation. These grants you apply for them, and then if the project is good enough and there is market, they will give the grant à these grants will cover like 70% of the cash needed, the resting 30% should be private (VC or angel investors)

VC (check investivalia) might decide to enter already in Phase 1 if they are convinced about the results. Also, they would need the patent to be really robust and if there is a clear need. Orphan drug classifications is game changing (fast track (in some), longer time in the market, … other info that I had found already).

Antibiotics and anti-infectives are not very attractive currently.

Pharma directly or pharma VC (also other than VC, other foundations have programs we can apply to à but geographical distribution of the diseases? Crucial question in order to understand to which foundation applying).

How to be more appealing at this stage? Finding the USP

It is going to be cheaper (discuss the cost, not the price. It is also important in order to understand if low-medium countries could afford it), hopefully it will be more efficient.

CrunchBase and PitchBook databases

Testing the molecule already as a complementary molecule to Fluconazole might be a good move, to have a proven value proposition for Pfizer in case it works.

1. Product for ambulatory (e.g.: aspirin)
2. Product exclusively sold in hospitals (e.g.: injectable paracetamol, many antibiotics) à these ones have generally a premium price

Business Model: probably unnecessary at this stage (in my opinion might be worth to show some business model canvas as we were planning to propose more than one way to develop this innovation and company)

Talking to doctors to have details about the patient journeys and see if it would makes sense to bundling with Fluconazole.

Demand Estimations (Extra Calculations)

Stand Alone

Percentage of fungal infections that are candidiasis	76,3%
Indicence of fungal infections/ Year	2,7%
Incidence of Candidiasis	2,1%
Percentage of candidiasis caused by Cand. Gal.	22,0%
Incidence of Candidiasis (Cand. Gal.)	0,5%

	Population 2021	Exp. Population 2030	idiasis cases/ year (2030)	C.G. Candidiasis cases/ Year (2030)
United States	331 900 000,00	340 969 591,75	7 054 649,55	1 552 022,90
Europe	747 747 396,00	768 180 549,39	15 893 630,11	3 496 598,62

Penetration Rate	10%
Population Growth Rate	0,30%
Penetration rate increase / 4 years	5,00%

	Demand Y1
United States	155 202,29
Europe	349 659,86
Total	**504 862,15**

	Business Year			
	1	2	3	4
Demand Projection	506 376,74	533 290,66	561 635,06	591 485,96

Adjuvant

Fluconazol perscriptions	3 308 929,00
Candidemia cases/ year	25 000,00

	Population 2021	% of American population	Fluconazol perscriptions	Cases of Candidiasis / year (2021)	Cases of Candidemia a year	% Candidemia cases over candidiasis	onazol Perscriptions due to candidemia 2021	onazol Perscriptions due to candidemia 2031
United States	331 900 000,00	100%	3 308 929,00	6 867 000,00	25 000,00	0,364%	12 046,49	12 375,67
Europe	747 747 396,00	225%	7 454 784,70	15 470 868,84	56 323,24		27 139,89	27 881,52

Penetration rate:	40%
Pop. Growth Rate:	0,30%
Penetration rate increase / 4 y	5,00%

	Demand Y1
United States	4 950,27
Portugal	11 152,61
Total	16 102,88

	Business Year			
	1	2	3	4
Demand Projection	16 151,19	17 009,62	17 913,68	18 865,80

Financial Projection Cost Structure

Cost Description			
Researcher Salary (month)	€	2 725,00	
TSU		23,75%	
Work Insurance		1%	
Total Yearly Cost per Researcher	**€**	**47 592,13**	
Consultant Salary (month)	€	1 500,00	
TSU		23,75%	
Work Insurance		1%	
	€	-	
Total Yearly Cost per Internal Consultant	**€**	**26 197,50**	
CRO (phase 1)	$	8 400 000,00	€ 7 980 000,00
CRO (phase 2)	$	28 400 000,00	€ 26 980 000,00
Dollar to Euro		0,95	
Provisional Patents	$	4 000,00	€ 3 800,00
Search Fees	$	475,00	€ 451,25
Examination Fees	$	450,00	€ 427,50
Non-provisional PCT patent	$	100 000,00	€ 95 000,00
Maintenance Fees	$	980,00	€ 931,00
General External Consultant	€	61 264,00	
Rent 23-24	€	120 000,00	
Rent 25-27	€	60 000,00	
genral expenses	€	50 000,00	
Consumables	€	35 000,00	
Overall yearly % bonus		3%	

Limitations

Within every project, there are always mishaps. Agendas that once idealized, upon realization, everything would be perfect. Unfortunately, in reality, that is not the case. Several companies from other stakeholders were contacted via LinkedIn, Web-site email and friends' referrals, but regretfully, denials and no replies limited our validation of assumptions, despite several tries. Nontheless, all our efforts were channeled, as best we could, to come with the most solid case, with the resources that we possess.

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