Open Innovation in Life Science

Closing the Loop

An interdisciplinary perspective

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Abstract

To address the decline in the pharmaceutical industry, there has been proposals of developing the business model through adopting Open Innovation (Subramanian, 2014) approaches. I argue that engaging in co-funded conservation projects involving market-based bio-prospecting (rather than the current bio-prospecting-as-a-tool-of conservation pattern), might actually be the missing link to make the pharmaceutical cycle work more efficiently for the pharma entrepreneurs, and for the community. I argue that by adding conservation of biological and genetic resources to the holistic business model, it will become circular, dynamic and potentially more viable, as it allows the pharma entrepreneurs to have an input at the emergence point of discovery, and thus have significant control over the sustainability of the process, while they also contribute to the welfare of the community and get some public confidence back without compromising profit.

The first decade of the 21th century has been noted to witness a decline in the pharmaceutical innovation (Kaitin and DiMasi, 2011), with some recent signs of revival (Ward, 2014). According to the Centre for Medicines Research International in the USA, the average success rate of bringing a new drug to the market has declined, since the mid-nineties. Failure occurs predominantly in the later phases of clinical testing, which makes them even more expensive. The business witnessed only 24 new-drug approvals by the United States Food and Drug Administration during 1998 with a $27 billion Research and Development (R&D) cost. However, the industry in 2006 spent $64 billion, for only 13 new drugs, making it to the market (Kaitin and DiMasi, 2011). Some have proposed that the traditional linear model of bioinnovation, is no longer viable, concluding the need for a "fully integrated pharmaceutical networks," (FIPNets/FIPCO) or simply an "ecosystem". In this essay I explore reasons and practicalities of turning to Open Innovation. I also a potential enhancement in the quality of input into the earlier phases of drug production, with fungal conservation and bioprospecting as a case in point.

The traditional model consists, more or less, of seven steps:

1- Discovery ➔ 2- Preclinical development ➔ 3- Clinical development Phase I ➔ 4-Clinical Development phase II ➔ 5- Clinical Development Phase III ➔ 6-Approval ➔ 7-Market

(Kaitin and DiMasi, 2011).

The process, takes about 12-13 years on the average and was traditionally carried out - from the beginning to the end, by the pharmaceutical company, However, several factors have resulted in a radical transformation to the industry's ”landscape” over a decade; 2000-2009.

The observable change to the landscape was that it embraced less innovation, increasing turnover and serious near-future threats, in spite of the recent signs of revival (Ward, 2014)..

1- Change of the “innovation landscape”

1.1. Fear of terrorism

The concerns of terror attacks in the aftermath of the 11th of September 2001, in the United States – one of the leading nations in the pharmaceutical industry, caused a direction of resources towards the “initiation of prompt response to an anticipated bioterrorism” (Kaitin and DiMasi, 2011).

Moreover; **1.2.** the outbreak of new deadly diseases around the world such as the H1N1 and SARS urged the USA to issue new relevant regulations and roadmaps. The NIH's Roadmap, in the USA, as well as the Clinical and Translational Science Award (CTSA) program in 2006, led to the “expansion” of the translational medicine (ibid) to address knowledge transmission between basic science and clinical medication, and from the “clinical research to medical practitioners” then - in turn, to patients. The two initiatives “strengthened the role of academics in the pharmaceutical innovation”.

In addition to that, as Kaitin and DiMasi (2011) note, the US Food and Drug Administration initiated the Clinical Path Initiative 2004, to enhance the translation process of science so as to lead to safe medication applications. So has the European Union by its Innovative Medicines Initiative which aimed at “bringing together the respective capabilities of academia, industry, and government to identify new biomarkers and other tools to improve the selection of drug candidates and increase the likelihood of pipeline success”.

However, not all the regulatory interventions had such positive impact on bioinnovation. Some of them "raised the bar to the production of new drugs" (Scanell et al, 2012), upon the withdrawal of some "prominent drugs" from the market. The strict monitoring process on the business, to follow up on the distribution and use of drugs, had a deep impact on the innovation "ecosystem" (Pigott et al, 2014). It also had a negative impacts on the "credibility and transparency" of the pharmaceutical companies.

Finally, 1.3. the global economic crisis at the end of the decade, lead to vast acquisition or liquidation of smaller businesses (Kaitin and DiMasi, 2011). This has led to an increasing turnover to the remaining companies, but to less innovation and more future threats to the business as Munos (2009) notes. From 4,300 companies engaged in drug venture, only 261 of them – which are about 6%, have managed to register one or more new molecular entity (NME) since 1950. All the other 88% have failed; acquired, merged or liquidated. Less than half of the 6% exist today. Munos (2009) notes that the 35 small companies which managed to survive and thrive had found unique ways to do so, such as to focus on specific diseases or "sell (additional) products and services". Some others stayed local while others such as Boehringer–Ingelheim, Solvay, etc. are multinational, and some have focused on generics (Munos, 2009).

1.4. It has been also noted that a decline in the productivity of R&D "coincided with":

1.4.1. The shift away from natural compounds (Rausser and Small, 2000).

1.4.2. Target-based research. (Sam-Dodd, 2005)

Target based-research strategies, each, has advantages and limitations (Sam-Dodd, 2005; Schenone, 2013). Hence, no direct link has been made yet, nor a thorough analysis on the impact those two aspects on the declining productivity of R&D in pharma business.

2- Threats to the business

From the previous, the threats facing the success of pharma companies have been summarised as:

2.1. Patent expirations (Kaitin and DiMasi, 2011);

A number of intellectual property (IP) regulations have changed in the USA in the early 80s, which had a positive effect on biotech ventures. The *Bayh-Dole* Act of 1980 gave the universities and hospitals rights to register IP resulting from public –fund research. This facilitated the transfer of such knowledge and encouraged the creation of new biotech firms; as it allowed the utilisation of data which would, otherwise, stay confidential. In 1980, the Supreme Court decision in *Diamond vs. Chakrabarty* were also made, allowing the patenting of "genetically engineered life forms". Early in the 1990s, as part of the Human Genome Project, NIH, in the USA began patenting partial complementary DNA sequences as well. This was all granted on the grounds that such patent regulations would support the growth of the biotech business (Eisenberg, 1992 cited in William and Tulum, 2011).

In the 1980s such IP protection were a leading factor in luring people into investing in biotech start-ups by limiting competition. However, Orsenigo et al. (2006, p. 412 cited in William and Tulum, 2011) argued that; evidence that strong IP protection accelerates research efforts so as to develop new drugs is absent.

The issue of patents is extremely important for pharmaceutical industry where innovations are "build on each other". Geoffrey et al. (2011) argues that although patenting provided incentives and protection at the early stages of the biotechnological boom, there are good reasons why we should move on to a more open attitude in sharing knowledge for public health. Firstly, that technology facilitated quick and easy networking; and secondly that there is a "public interest" in open source scientific data exchange to advance scientific creativity for the welfare of humanity; and thirdly, that much of such knowledge were generated using public fund.

Open innovation and knowledge-sharing approach attitude are not without challenges, however, a good understanding of the dynamics of the industry should help us realise the incentives shaping a new era of Open Innovation in the life science (Lazonick and Tulum, 2011; Hashemi, 2011). There are signs that this has begun to occur and thrive already (Pigott et al, 2014).

2.2. “reimbursement pressures” (Kaitin and DiMasi, 2011),

It takes an average of 12-13 years to develop a new drug, with an average cost of $1.5 billion. This means that the drug price, protected by the patent, reimburses an investment set a decade earlier. (Pharmacology & Pharmacy, 2012). This has led to the “Pisano Puzzle” (cited in Lazonick and Tulum, 2011) which is that” despite the commercial success.. and the stunning growth in revenues for the industry as a whole, most biotechnology companies earn no profit.”

Of course the situation is not as simple as that - as will be explained later, however, such reimbursement pressures also influence the decision-making on target selection. When a drug has a good potential market, such as anti-cancer medications; or is extremely needed such as the schizophrenia’s, but have a high attrition probabilities or a longer developing time, it is considered as less likely to generate quick revenue for an adequate period to cover the reimbursement pressures so as to generate profit - taking the patent-period issue into consideration, and is thus less likely to be selected for production.

2.3. Increased regulatory requirements (Kaitin and DiMasi, 2011);

As previously explained;

> The ‘cautious regulator’ problem. Progressive lowering of the risk tolerance of drug regulatory agencies obviously raises the bar for the introduction of new drugs, and could substantially increase the associated costs of R&D52. Each real or perceived sin by the industry, or genuine drug misfortune, leads to a tightening of the regulatory ratchet, and the ratchet is rarely loosened, even if it seems as though this could be achieved without causing significant risk to drug safety. (Scanell et al, 2012)

2.4. Rising competition (Kaitin and DiMasi, 2011).

Due to patents coming to an end without new-drug-discovery replacement, to make up for the loss of such patents (an issue also related to the product rating), a drug faces competition,

if it only slightly (but adequately) advantageous over an old or current one; i.e. a “me too” drug (Scanell et al, 2012).

Historically, drugs from 1970 – 1990s were rated in three tiers for “prioritization for market approval” by the FDA: “1- a significant gain over existing therapy [A]; 2- a modest gain over existing therapy [B]; 3- little or no gain over existing therapy [C], but in 1992, the rating were briefed into “P (priority); S (standard).

What influences the drug position, as well, is the timing it enters the market, depending on such priority (Kaitin and DiMasi, 2011), If the drug is only adequately advantageous over an existing one, it has less chance to breakthrough. Scannel et al (2012) expresses this situation, analogously, as “the-better-than-the Beetles” problem!

2.5. “loss of public confidence” Not only due to the withdrawal (Pigott et al, 2014) of prominent drugs from the market - after years of consumption, for safety issues, but also due to the increasing (and often justifiable and unaddressed) concerns over the motivations and mechanisms driving the drug industry and controlling drug prices. Those concerns might not get expressed in peer-reviewed journals, but they are abundant on the media and social media (such as Facebook and Youtube) with a wide circularity and perhaps a greater impact on the public opinion than academic publishing.

2.6. The “relentless rise in research and development (R&D) costs” (Kaitin and DiMasi, 2011).

Pharmaceuticals are known to direct 20% of their turnover to fund R&D for new drugs. In a study on the American Pharmaceutical business model, however, William and Tulum (2011) explain that some aspects of such rise are not related directly to R&D but to “speculative investments” (stock-exchange) in Initial Public Offerings (IPOs), and secondary matters which might account for a great deal of the venture, public equity and R&D fund streaming into the business. Such “can enable financiers to reap returns on young biotech companies long before they have generated a commercial product”. In addition to that, there is the governmental support for the industry through funding basic science research; exploitable by pharmaceutical firms such as with the Bayh-Dole Act, and facilitating patenting through the strong provisions of IP protection and the Orphan Drug Act 1983, which gives the exclusive rights for commercialising an orphan drug - for seven years, with more than a

potential application (Botox, as an example of an orphan drug with multi-applications). This is where transparency and the shift to new collaborative businesses model have become a necessity to revive the industry and gain back the confidence of the public.

2.7. I finally propose a conflicting cultural considerations related to the need for more productive partnership between conservation scientists and pharmacologist for bioprospecting. Bioprospecting is "the search among living organisms for compounds that have commercial value as active ingredients in pharmaceuticals, pesticides, and other products" (Frisvold & Day-Rubenstein, 2008). However, this always involves a difficulty to *synergise* performance among partners due to the different cultures and motivations, which is one challenge of the open innovation

Where is the problem?

As Paul et al (2010) makes the point that, today's pharma is evidently unable to sustain adequate innovation to make up for the loss of revenues resulting from patent expirations for their "successful products". Without a significant increase in the waning R&D - in terms of efficiency and effectiveness, the industry is in decline. "The goal of a highly productive R&D system" as Paul et al note, is "to efficiently translate inputs into the most desired and valuable outputs"

He expresses productivity in the following formula:

$$Pa\ \frac{WIP\ x\ p(TS) x\ V}{CT x\ C}$$

(Paul et al., 2010)

> " Where productivity (P) can be viewed as a function of the elements comprising the numerator — (WIP) the amount of scientific and clinical research being conducted simultaneously, designated here as the work in process (WIP), the probability of technical success (p(TS)) and the value (V) which is related to a higher benefit-to-risk ratio. — divided by the elements in the denominator, the cycle time (CT) and cost (c)". (Paul et al., 2010)

By this formula, Paul et al (2010) assume that increasing the (WIP): i.e. “the amount of scientific and clinical research being conducted simultaneously” decreases the cycle time (CT) and cost of technology (C), provided that the probability of technological success [p (TS)] and drug value (V) remain constant.

Paul et al (2010) found that data on Phase I (WIP) have been recently indicating an overall increased investment in those stages, however, the number of NMEs, for most companies entering a later stage and to Phase II and III remain inadequate to reach two-five launches annually. Based on this model, Paul et al. suggest that, for most pharmaceuticals, the R&D operating expenses might not be well distributed through the different drug phases, and that unproportioned amount of resources is applied to the later stages with “relatively low p (TS) and/ or post-launch support of marketed products”. Paul et al. (2010) propose that this might be the main reason behind the contemporary decline in the industry, and conclude that the basic concern for the pharmaceutical industry is not the lack of productivity as much as it is a deficiency in the business model.

3- Open Innovation

Open innovation partnership aims at:
(to) “capitalise on and maximise the complementary expertise and resources within the life sciences ecosystem, various types of participants can contribute to them”. This entails sharing risk and profit in order, as Pigott et al (2014) articulates, to:

1. Develop and commercialise” new drug discoveries;
2. Develop tools, benchmarks, and development models
3. Create and maintain shared information databases
4. Establishing and maintaining networking platforms and portals to facilitate communication and information sharing as well as “accessing the crowd” for finance.

Four actions have been identified by Pigott et al. (2014), to reach open innovation, namely:

1. “Aligning objectives; That is that different objective of partners may potentially lead to the same target if coordinated and managed well.
2. Managing IP
3. Bridging cultures

4. Structuring for success and looking beyond the sector".

(Pigott, 2014)

This is further explained through the study case.

3.1 A study case: Partnership for bioprospecting

Interestingly, the current drop in the R&D productivity has coincided with target-based drug discovery (Sam-Dodd, 2005) and shifting away from Nature as a source of drug biochemicals (Rausser and Small (2000). More than 1/2 of the prominent drugs in the USA in the early twentieth century, as Grifo and Rosenthal notes (1997: cited in Scott, 2000) had at least one naturally-occurring active compound or has been "patterned after" a natural compound. This introduced a business model where big pharma partnered with some private companies specialised in screening natural product collections. However, there has been an extensive debate over the feasibility of partnership with private sector for bioprospecting. Biodiversity may be seen, in this context, as an immense, "unexplored library" with data possibly leading to "pharmaceutical breakthroughs". If that applies to all sort of natural entities, it applies specifically and above all to fungi. Historically, the owners/custodian of biological resources which have been exploited in several valuable research or discoveries, have not been compensated by any means or been positioned to share the benefits of the discoveries sourced from their samples (Scott, 2007), however, with the current laws and conventions (e.g. CBD) bioprospecting has become a complex situation where biological/genetic resources belong mainly to developing communities while the relevant biotechnology belongs to the pharmaceutical firms mainly in the USA and Europe, with an immense cultural gap to bridge. Previous discoveries and the current estimates suggest, for example, the existence of over three hundred undiscovered drugs in the tropical forests worth about $147 b. However, a massive portion of the tropical forests gets cleared each year for developmental activities (Scott, 2001). Rausser and Small (2000) implied the feasibility – for big pharma, of contributing to conservation (Scott, 2001) "as a tool of bioprospecting" and business growth – under certain conditions!

3.1.a. Proposed model of partnership

The traditional model, allows pharmaceutical firms to dig into a random collection of data in return of a "renting" fee, which gets directed to support conservation activities, economists

have been often sceptic about the feasibility of such business model for two reasons: That although biodiversity is extremely valuable – as a whole, only the value of some marginal species is what matters for pharmaceutical bioprospecting, and that would be, as estimated, low! Also due to the expected "redundancy" resulting from several species producing the same active compounds, the probability of finding a useful discovery or lead to a discovery would even be lower compared to the cost. Rausser and Small (2000), on the other hand, found that such marginal value could reach up to over $9,000/hectare under "plausible conditions". Under such conditions, the prospecting value of certain genetic resources would be adequate to sustain "market-based conservation of biodiversity" (Rausser and Small, 2000).

> A market in genetic resources will appear only if the expected benefit of conservation exceed the opportunity cost of holding these assets.
>
> (Rausser and Small, 2000)

Encouragingly, it has been reported for example that Novartis Pharmaceuticals spends millions of dollars in the attempt to discover "observable factors" correlating with the "biochemical creativity" of microorganism" as a molecular source for new drugs.

The key to a successful bioprospecting business model then would be "product differentiation" versus the traditional offered "Brute-force search" opportunity, where pharma companies pay to dig into a random large collection of scientific data, with no identification clue on what might be relevant to their target-based search, and with a high probability of redundancy. It is possible that pharmaceutical companies will prefer to pay premium rent to explore more target-specific data/ promising leads.

Also, it might be useful to consider compensating scientists/institutions cited in any patents with a tiny portion of the revenue, if their discovery or translation leads to drug development and production. As for indigenous information, they are as natural as the products themselves specially that they cannot be used without development and application of skills

(Heller, 1998). Compensation may be made to the whole community in the form of royalties, capacity building, job creation, investment, training/education or grants, as the parties agree.

However, and with fungi as a case in point, I propose that engaging in conservation leading to market-based bio-prospecting rather than bio-prospecting-as-a-tool-of conservation pattern, might actually be the missing link to make the pharmaceutical cycle work more efficiently for the pharma entrepreneurs and for the community, for two main reasons:

1- Conservation is of an interest to many parties, entities and authorities for its own sake; For the sustainability of life on earth. Therefore, with certain arrangements that would work for drug industry, it is multi-stakeholder and is likely to be effectively co-funded for a win-win situation to the private sector, public sector, NGOs and charities, the public and health sector and conservationists and even capital venture; each according to their motivation for engaging in the process. Some funding models proposed by Omidvar et al. (2014) might work well in closing this loop: Translation centres and/or bio-prospecting centres/parks; supported by the "philanthropic fund" which applies financial approaches to serve philanthropic goals, and "Biomedical mega funds" which use royalty incentives to get people who wouldn't normally invest in early stages, to strengthen the cash flow into the project from the early and most risky stages; Fundraising and grants also might work partly, since the project involves both conservation and public health. A process that may be coordinated by non-governmental organisations recruiting local scientists and international experts.

2- Conservation leading to market-based bioprospecting could be a fundamental source for a lot of pharmaceuticals innovation, not only as a source for "raw materials", but also as "blueprints or as leads" in developing drug compounds (Frisvold & Day-Rubenstein, 2008)

3.1.b. Bridging the Cultural gap: Fungal Conservation as a case in point

With the Neil's Young's Album "Rust never Sleeps" on, there was placed - in a gigantic glass box (during the First Exhibition of Fungal Conservation in the Natural Museum, Whitby); a huge pile of "stuff"! Wool, papers, wood, meat, vegetables, bread, milk products, medicine

packets, etc. A small sign read: Which of these products do fungi contributes to? Any attempt from the visitors to pick any (or some) of the products was a wrong answer! The answer by the organiser of the exhibition, Dr David Minter; as I witnessed, was simply; All of them! (see Allen, 1988:98)

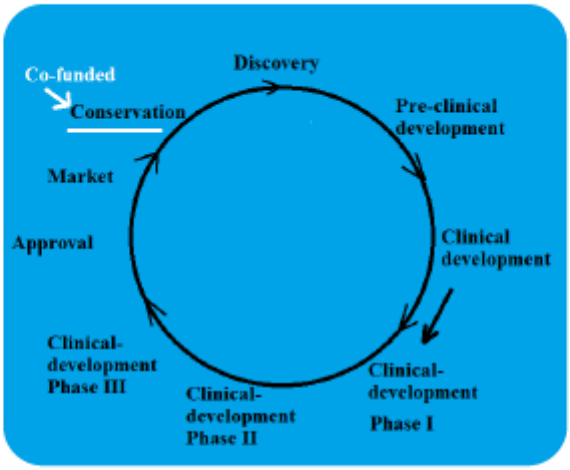
Although Fungi are significant to all life processes, the Kingdom Fungi receives the least attention - in terms of conservation, compared to the "charismatic megagfauna" (Buchanan, 2011), as it often erratically get listed under the plants (Minter, 2011:2013). In India as an example of a country that is considered as a diversity hotspot fungi are "grossly underexplored". Constraints to study fungal diversity in India are typical!: "Lack of training in fungal identification using classical and molecular methods, shortage of fungal repositories and reference books, non-availability of funds for taxonomic studies and difficulty in convincing politicians and policy makers of the importance of conserving fungi" (Minter, 2011:2013; Soliman and Abdel-Azeem, 2011:2013; Verma, 2013); in addition to species rapid loss as a result of habitat destruction/degradation, over-grazing, pollution, commercial collection etc. (Balbul et al., 2013) with not adequate data and not adequate mycologists in "key organization" (fungal conservation, 2011). The expertise of Indian mycologists, as a case in point, have been described as "limited and scattered" while conservation of species has been described as a case of "'now or never' challenge"!

I found it hard to determine whether the "forgotten kingdom" has missed the attention of pharmacologists, ministries (Soliman and bdel Azeem, 2011) and many prestigious organisations[1], is an underestimation of the role the Kingdom Fungi plays in life, or a sub-conscience fear from the power of mycology (Global security.org) ! In all cases, the result is that crucial information, "exploitable science" and expertise are being overlooked - to a great deal. The most "disruptive patent" has been known to be fungi related. There has been also about six recent patents on desert truffles (Gajos, 2014*); a rich* socioeconomical *and medicinal resource (Al-Laith and Ahmed, 2010;* Harsh, 2014).

3.1.c. Aligning objectives

[1] – Such as the Edinburgh Botanic Garden which list them under plants (Annex 1)

For conservationist, the target is to *conserve*, even if that meant less development or in case of threat to species: no development at all! But while they conserve, they necessarily produce databases that can be highly specific, classified and "exploitable", provided that the preservation of their "magnificent organisms" is guaranteed. A conservational grant from Mohamed Ibn Zayed Conservation of Species Fund to the recently-established Arab Society of Fungal Conservation has resulted in promising socio-economic and medicinal properties for 10 species. (Azeem and Salem, 2014). A more specific example of a pharmaceutical company investing in conservation (set as the primary mission while bioprospecting comes next, for a potentially win-win-situation) has been the partnership between the National Biodiversity Institute (INBio) in Costa Rica, and Merck's drug-screening program September 1991(Blum,1993). The contract stipulates that INBio provides naturally-occurring chemicals for Merck, rather than species, while Merck provides training programmes for local scientists to collect the specimens and undergo the extraction, in local laboratories. Both investing in each other's programme. However, each deal might have its specificity, and the idea here is not (yet) to set an ideal case-study for such a dynamic model, but examples on how different objectives may be made to lead to the same goal - but not without challenges of course.



Discovery ➔ Pre-clinical development ➔ Clinical development Phase I ➔ Clinical Development phase II ➔ Clinical Development Phase III ➔ Approval - Market ➔ conservation: bioprospecting/bioinformatics ➔ Discovery (Ongoing).

Fig. 1. The proposed dynamic loop –

Based on the traditional model (Kaitin and DiMasi, 2011).

Conclusion

To address the decline in the pharmaceutical industry, there has been proposal of developing the business model through adopting Open Innovation (Subramanian, 2014) approaches. I propose that engaging in co-funded conservation leading to market-based bio-prospecting (rather than the bio-prospecting-as-a-tool-of conservation pattern), might actually be the missing link to make the pharmaceutical cycle work more efficiently for the pharma entrepreneurs, and for the community. I propose that by adding conservation of biological and genetic resources to the holistic business model, it will become circular, dynamic and potentially more viable, as it allows the pharma entrepreneurs to have an input at the emerging point and thus have significant control over the sustainability of the process, while they also

contribute to the welfare of the community and get some public confident back without compromising profit.

This might seem like a naïve addition to a very complex business model, but it serves as I propose, in enhancing the input into the pharmaceutical industry, re-gaining the public trust, reserving life, and boosting the economy of many local communities by getting them engaging in conservation and bioprospecting activities and contribute to a potential global synergy**.**

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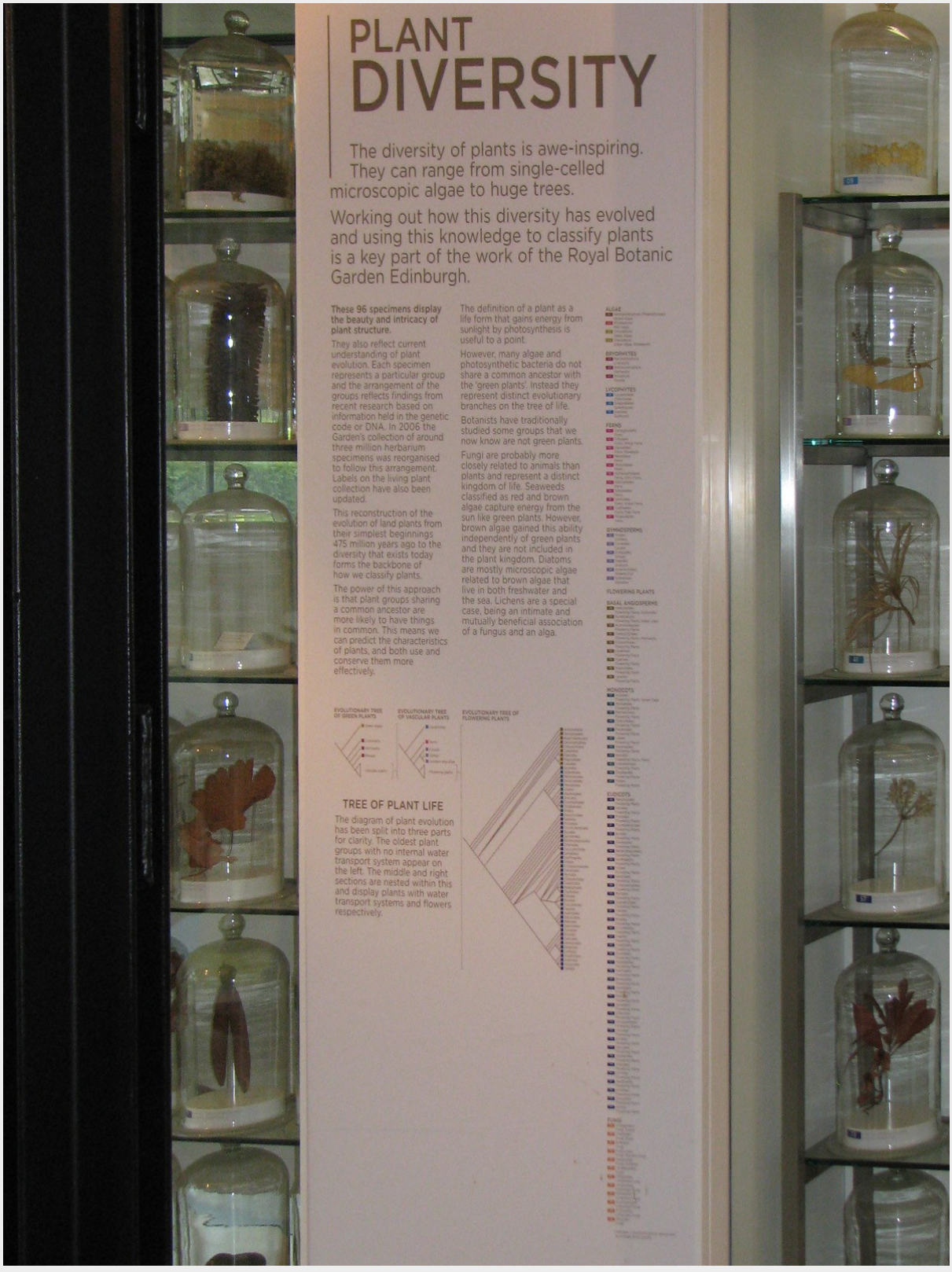

Fungi in red, under plants. Botanic Garden. Edinburgh. Last visited in March 2015.