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Drug Development in Endometriosis and Adenomyosis: It Takes More Than Just Good Science

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Abstract

The pipelines of pharmaceutical companies are filled with thousands of promising new compounds for a plethora of indications. Yet, a close review of the drugs that have recently been in clinical trials quickly reveals that only a handful of drugs under evaluation in women with endometriosis can be genuinely qualified as truly innovative and breakthrough drugs. Why is there such an industry-wide lukewarm interest in drug research and development for endometriosis/adenomyosis? Why are pharmaceutical companies so reluctant to initiate programs or invest in academic research in endometriosis/adenomyosis? It is evident that a substantial part of the novel druggable targets originate from research in academia. However, only the pharmaceutical industry has the resources and expertise to bring drugs to patients. In other words, we are fully dependent on the pharmaceutical industry to bring new therapeutics to the market. The aim of this editorial is to make scientists from academia aware of the enormous complexity of the drug development process, the drivers that propel pharmaceutical companies to initiate new programs and to prioritize their portfolios, the value of intellectual property rights, and also about the importance of scientific rigor, predictive translational models, and biomarkers. At the same time, the pharmaceutical industry must be made aware of the enormous opportunity at hand, as the current patient population with endometriosis/adenomyosis is just the tip of the iceberg. We hope that the insights presented here will enable the endometriosis/adenomyosis research community to find ways to valorize their knowledge and attract the interest of the industry.

Keywords

endometriosis, adenomyosis, drug development, pharmaceutical industry, program drivers, translational research

Introduction

Endometriosis is a gynecological disease affecting 6% to 10% of reproductive-age women.[1] Although not fatal, it is nonetheless a major contributor to pelvic pain and subfertility and a leading cause of gynecological hospitalization in the United States[2] and likely in many other countries in the world as well. The disease has a negative impact on women's quality of life, work productivity, sexual relationship, and self-esteem mainly because of chronic, incapacitating pain and infertility.[3-7] In addition, the economic burden associated with endometriosis, incurred either to the patients themselves or to the society as a whole, is enormous.[8-12]

Although surgery is often efficacious in treating endometriosis, there is a pressing need for more efficacious medical treatment, preferably with more tolerable side effects and lower cost. Yet despite extensive research and sometimes exciting preclinical results, so far the results of most clinical trials on endometriosis—some were launched with great fanfare—are not published and are presumably unsuccessful or at least viewed as unworthy for further development.[13,14] It is no wonder that there is an audible disappointment over the drug research and development (R&D) in endometriosis, a situation Vercellini and coworkers recently referred to as "waiting for Godot."[15]

Adenomyosis shares a similar definition and symptomology as endometriosis but resides in the uterine wall.[16] Similar to endometriosis, its pathogenesis and pathophysiology are poorly understood,[17,18] but adenomyosis, despite being hormone sensitive,[19] turned out to be even tougher to treat, with hysterectomy ultimately being the treatment of choice.[17] Adenomyosis is severely underresearched which is illustrated by the

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complete absence of industry-sponsored trials in Clinical Trials.gov as of now.

Next to uterine fibroids, endometriosis and adenomyosis are 2 of the most common gynecological disorders in reproductive-age women worldwide, and the cost associated with endometriosis/adenomyosis treatment in referral centers is similar to that of other chronic high-impact diseases such as diabetes, Crohn disease, and rheumatoid arthritis.[17] Yet, in contrast to these disorders, endometriosis/adenomyosis are hardly recognized as high-impact disorders by general practitioners, society, funding organizations, and pharmaceutical industry due, in no small part, to the lack of awareness of these 2 diseases.

Why is there a seemingly innovation drought in drug R&D in endometriosis/adenomyosis? Is there anything we can do to change this? It is our belief that the answer to the last question is a resounding yes, but in order to do so, the pharmaceutical industry and academia have to find ways to leverage the knowledge and expertise available on both sides of the fence, which is not an easy task. One of the first steps for academic institutions and investigators would be to have a much more thorough understanding of the drug R&D process and the *modus operandi* of the pharmaceutical industry. Here, we will take a closer look at who actually contributes to the development of innovative drugs and discuss the drivers that propel pharmaceutical companies to initiate new programs and to prioritize their portfolios. There are some important lessons to be learned, and we hope that the insights presented here will enable the endometriosis/adenomyosis research community to find ways to valorize their knowledge and attract the interest of the industry.

State of the Art and Future of Medical Therapy in Endometriosis/Adenomyosis

Both endometriosis and adenomyosis are estrogen-dependent, chronic, and inflammatory disorders, which are reflected by the medical therapies used in the daily practice. However, while the list of therapeutics for endometriosis/adenomyosis is quite extensive, the variety of mechanisms that are targeted is quite limited and pretty much have similar goals: to reduce pain (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs]) or to hormonally alter the menstrual cycle in order to produce a pseudo-pregnancy, pseudo-menopause, or chronic anovulation in an acyclic, hypoestrogenic environment.[20] Of concern, however, is the fact that most therapies often only provide partial or no symptom relief at the cost of a plethora of negative side effects of various degrees, and there are no drugs that can enhance fertility or reverse infertility for these 2 conditions.

Because of the progressive nature of endometriosis/adenomyosis[21-26] and of the fact that there is no noninvasive diagnostic test for endometriosis, most (young) women who visit a general practitioner or gynecologist for the first time with chronic or cyclic pelvic pain or dysmenorrhea are actually treated empirically. The generic nature of the pain symptoms obscures the fact that a woman may have endometriosis, and a laparoscopic examination is considered an invasive procedure. As it is easy to prescribe NSAIDs to manage the pain or hormonal contraceptives to control menstrual bleeding,[27] these are often offered to the patients as a first-line treatment. Ironically, by recommending empirical treatment in symptomatic (young) women, one unintentionally, but evidently, contributes to the delay in diagnosing the disease.[27] Once endometriosis is suspected, the diagnosis is corroborated by physical examination and imaging techniques and finally proven by histology of either a directly biopsied lesion or from tissue samples collected during laparoscopy.[27]

At first glimpse, the current pipelines of the pharmaceutical industry seem to display a reasonably diverse and promising landscape of drugs and targets, but the appearance can be deceiving.[28] The majority of drugs still aim to suppress the hypothalamic–pituitary–gonadal (HPG) axis and estrogen activity, and the majority of the drugs aiming less traditional targets are all repurposed. The situation in adenomyosis is even worse, since at this point in time, there is no drug indicated for the treatment of adenomyosis per se nor are there any drugs in development for adenomyosis. Overall, the innovation drought in drug R&D for endometriosis/adenomyosis is conspicuous and unmistakable.

Developing drugs for endometriosis/adenomyosis has proven difficult. Since the introduction of gonadotropin-releasing hormone (GnRH) agonists 20 years ago, only 3 drugs have been approved for the treatment of endometriosis-related symptoms: the progestin Depot Sub-Q Provera in 2005 (medroxyprogesterone acetate), dienogest in 2007 (Visanne), and Yasmin, a combination of ethinyl estradiol and drosperinone, a mineralocorticoid receptor antagonist (Japan only). On top of that, these are all "ancient" steroid hormones that have been repurposed for the treatment of endometriosis, and as such they are hardly innovative and certainly do not qualify as a new medical entity (NME). Even dienogest, now the top-of-the-line drug for treating endometriosis, only alleviates symptoms without reducing the volume of the endometriotic nodules.[29] The only drugs that have emerged in the past decade that come close to being revolutionary are the oral GnRH antagonists, of which Elagolix from Abbvie is the most advanced program. It can be called revolutionary because they are a new chemical class. Unfortunately, they still aim to modulate the HPG axis, and consequently Elagolix was shown to have a similar side-effect profile as its agonist counterpart. However, since it is an oral drug, the dose can be adjusted to alleviate symptoms on short notice.

Interestingly, the excitement around Neurocrine's Elagolix has resulted in the initiation of multiple clinical trials by various companies, which is a very typical example of the risk-aversion attitude of pharmaceutical companies toward drug development in female reproductive health. Next to the oral GnRH antagonists, however, there is no noteworthy innovative therapeutics in the pipelines that have the potential to revolutionize endometriosis/adenomyosis therapy for at least the coming 5 to 10 years. This is a really serious problem that should be of concern to all patients, health-care providers, policy makers as well as investigators working in this area.

Academia Discovers, Pharma Develops

An NME is a drug that contains an active moiety that has never been approved by the US Food and Drug Administration (FDA) or marketed in the United States; in other words, it must be a novel compound. To date, approximately 1600 NMEs have been approved by the FDA. It is of interest to see who actually contributes what to the development of these NMEs, the innovative drugs. The Center of Drug Evaluation and Research of the FDA traced the development route of 252 drugs approved in the period of 1998 to 2007.[30] Of these projects, 58% originated in large pharmaceutical companies, whereas 34% of the drug programs came from small biotech companies, which are often spin-offs from universities, and the remaining 8% of the programs found their origin at an academic institution after which they were directly transferred to large pharma. It is thus clear that to bring high-impact innovative drugs to patients, the contributions of the pharmaceutical industry is indispensible. This is illustrated by the fact that only 1 NME has ever been brought to market by a government-funded institution, the US Army (New Drug Application 021084, drugs@fda). This well-funded government agency developed a skin exposure reduction paste against chemical warfare: perfluoropolymethylisopropyl ether/polytetrafluoroethylene, or by its more common brand name, Teflon. Although academic institutions do not have the resources, means, and, frequently, the expertise to get drugs registered and make them available to patients, they are responsible for the discovery of more than half of the NMEs that have been approved to date,[31] thus underlining a predominant role of academia in lead and target discovery and validation.

Drug Development: An Arduous, Risky, and Costly Endeavor

In the past decades, drug discovery and development has become increasingly more challenging because of the fierce competition, increasing demands regarding safety and efficacy, and growing costs. Granted, the revenues and profits in the pharmaceutical industry are enormous, but so are the investments in R&D. It is estimated that in 2020, physicians will prescribe for US$1000 billion in drugs,[32] and the profit margins are one of the highest among all industries in the corporate world, averaging about 20% of the total revenues.

The vitality of a pharmaceutical company depends on successful market introductions or, in case of a business-to-business strategy, to sell or license high-value drug programs to interested parties looking to fill their pipelines. As eluded to earlier, investing in future NMEs is essential, and it is for this reason a frequently underrecognized and underappreciated fact, that among all manufacturing industries, the pharmaceutical companies invest almost 3 times as much on a per-employee basis in R&D than the runner-up, which is the chemical industry, and even 13 times more than the average of all other manufacturing industries, which includes the chemical, semiconductor, computer and electronic products, and aerospace industry. The overall cost of drug R&D can be calculated in many different ways, but in the end what truly matters is the amount a company has invested versus the amount of income which is generated by the drug sales, and this is referred to as the R&D efficiency. The general impression is that the development of a novel drug costs roughly about 500 million to 1 billion dollars, but in fact the cost can be a lot higher. Schuhmacher et al calculated the R&D efficiencies, the output generated in relation to the total R&D expenditure, for the top 14 largest pharmaceutical companies.[33] A simple calculation shows that the R&D efficiency varies wildly, ranging from 3 up to 30 billion per marketed NME. The reason for this is that the cost of the development of an innovative drug is composed not only of the cost for drug discovery and preclinical and clinical development but also includes the investments that were made in programs that ultimately failed (ie, sunk costs) as well as a profit margin. In addition, larger companies often have an extensive infrastructure to maintain, that is, pharmacovigilance departments for the postmarketing registration of side effects, a sales and marketing organization, in-house manufacturing facilities, and so on. The increasing regulatory strictures, rising bars for drug approval, and frequent astronomical compensation awarded to patients who succumb to untoward side effects of the medications and litigated against the manufacturer also help propel the rising cost of drug R&D.

The actual cost for the preclinical and clinical development of drugs is only a fraction of the total R&D budget, and the majority of this budget, about 60% to 65%, is spent on the clinical studies.[34] The cost of clinical development has increased steadily and dramatically in the past decades. There are several reasons for this. To start off, the size and duration of studies is increasing. The size of the clinical studies is largely determined by the sponsor's desire to minimize the chance of failure to detect a true difference between the new drug and the control group. The more the patients are included, the larger the chance one will find a statistically significant difference. Also, there is an increasing demand from primary care physicians, insurance companies, and patients for drugs with proven better efficacy or safety profiles than the current standard of care. Because of the expected small differences, again larger numbers of patients are required for the studies. In addition, many diseases of interest nowadays are complex, heterogeneous, and chronic in nature (ie, cancer, metabolic disorders, chronic inflammatory disease, etc), so clinical trials, by necessity, have to last longer and require large sample sizes. Consequently, the cost of clinical development escalates.

Evidently, bringing novel therapeutics to patients is only possible and sustainable in a commercial environment in order to be able to make the financial investments.[35] At the same time, this model seems to be difficult to sustain, and companies are exploring new ways to increase their R&D efficiencies. This includes activities to reduce portfolio and project risk, that is, through mergers and acquisitions and licensing, activities to reduce R&D costs, that is, through outsourcing and risk-sharing in late-stage development, as well as activities to increase the innovation potential. This paradigm shift generates ample

opportunities for academic institutions, as collaborations are more and more used to get access to the required enlarged set of skills and technologies, such as novel drug targets, validation of targets, signal transduction pathway know-how, animal models, disease expertise, translational medicine know-how, and biomarkers.

It Takes 2 to Tango

Although both academia and industry act in the best interest of the patient, namely, to develop better drugs and diagnostic tools, there are fundamental differences in the motives that drive industry and academia. In academia, the greatest good is to expand knowledge and disseminate that knowledge. The industry, in contrast, relies solely on the successful development and marketing of better products, and to this end the generation of patents and obtaining intellectual property (IP) rights are vital not only to protect and maximize later returns on investment but also to block the competition.

Successful partnerships will require cultural changes in both industry and academia, but it may be particularly important for academic investigators to understand and appreciate the *modus operandi* of the pharmaceutical industry, because it is this lack of understanding that often leads to a lot of frustration or even despair among academic investigators in research collaborations with pharmaceutical companies. Vallance and coworkers[36] investigated what scientists considered to be the most frustrating experiences in their collaborations with pharma. The top 5 were (1) early termination of the project or change in strategy (67%); (2) changing point of industry contact (57%); (3) restrictions on publications (50%); (4) IP negotiations (38%); and (5) lack of clarity of mutual objectives (29%). From an academic point of view, these responses are very understandable but, at the same time, illustrate the cultural gap between academia and industry, as the first 4 experiences are related to the daily practice in the industry, whereas the last experience is often related to poor communication. Collaborations can be terminated prematurely because of changes in strategy or project priorities, and points of contact can change because investigators in the pharmaceutical industry frequently move between departments, teams, projects, or move to another company. This complicates communication and is sometimes perceived, justifiably or otherwise, by academics as rude, impersonal, and apathetic or annoying when their alternative points of contacts are relatively junior and inexperienced staff member who are not always well informed about the science. With regard to publication, it is fair to say that in most cases, the industry will agree to publish, but sometimes it may request a reasonable delay in order to submit patent applications, or, in rare occasions, data are not allowed to be disclosed. The discussions around IP are often a reason for premature cessation of negotiation efforts. Generally speaking, a company has to initiate 50 or 60 of these projects, across indications, to end up with 1 successful launch in the market. It is important to acknowledge the significance of patents and IP rights for the industry as well as the enormous amount of chemical, biological, drug metabolism, safety assessment, and pharmaceutical data (and effort) that are needed to develop a lead into a molecule with properties that give it a reasonable chance of being a safe, effective, well-tolerated, and original medicine in humans. Also, academic investigators often tend to have unrealistic expectations with regard to the IP rights generated in the collaboration or overvalue their own IP and the impact of their findings. It is a general misconception that every novel finding automatically leads or could lead to a new therapeutic target, diagnostic, or marketed drug.

Collaborations are usually initiated because of the expertise, skill set, or drug candidates an academic research group or institution can provide. This means that (almost) everything is negotiable. The contingencies discussed above that can lead to premature ending of the collaboration should be anticipated and can be negotiated when drafting the collaborative agreement so that certain investments made by the academic collaborator are compensated or to agree to an appropriate period of continued support once such a situation occurs.

Critical Program Drivers in Pharma

Drug R&D is ultimately a number game. Of all potential drugs that have been discovered and synthesized in the early drug development phases, more than 99.99% fail to get regulatory approval for marketing. This high attrition rate, coupled with often fierce competitions from rival companies and pressure for higher return from shareholders, forces companies to regularly and critically scrutinize their programs and portfolios as well as to employ stringent selection criteria for new programs. Rang and Hill[37] distinguished 5 driver categories (Figure 1) to address 3 burning questions a company board wants answered when deciding the fate of a program: Should we do it? Could we do it? Can we do it? In the next section, we will discuss a selection of critical drivers, where academia could have a significant impact.

Should We Do It?

This question mostly deals with strategic drivers such as market size, the unmet or pressing medical need, does the program fit the franchise and current pipeline, what is the competition, and so on. With regard to endometriosis/adenomyosis, this usually already leads to some serious discussions in companies. Evidently, endometriosis/adenomyosis has a severe impact on the personal and professional life of afflicted women, but the annual sales of endometriosis/adenomyosis drugs, which add up to approximately 1.2 billion US dollars annually worldwide, are considered decent, but not overly appealing. However, the potential for market growth in endometriosis/adenomyosis is enormous. A widely used estimate is that about 10% of reproductive-age women have symptomatic endometriosis, which amounts to roughly 170 million women worldwide, not counting the women with adenomyosis or patients taking alternative medications, such as traditional Chinese medicine. The anticipated availability of a noninvasive diagnostic test in the

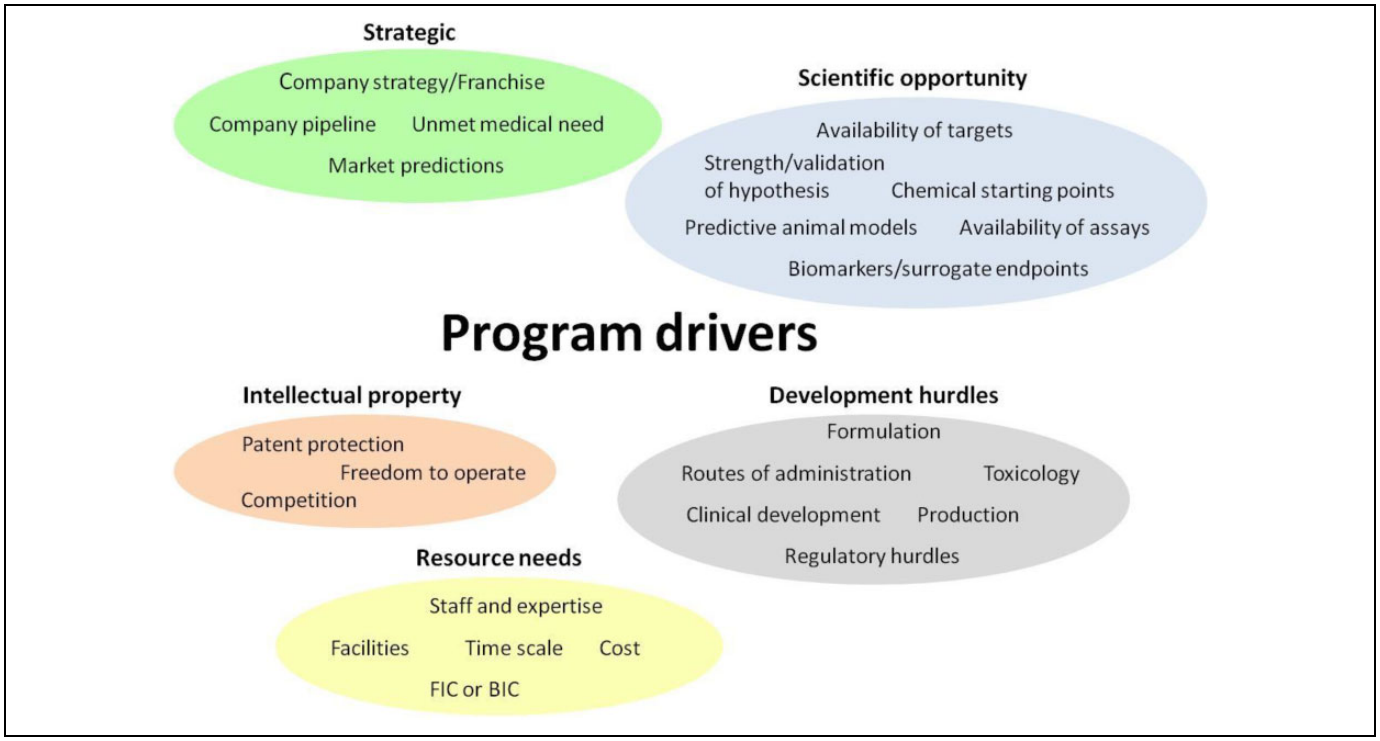

Figure 1. Critical program drivers in pharma

near future will allow the physicians to determine whether a woman has endometriosis/adenomyosis or not so that they can be treated adequately, with minimal delay, leading to rapid and vast expansion of the market. Companies, risk averse as they are by nature, often prefer to wait until such test has become available. In addition, current medical therapies are not curative, insufficiently effective in many women and associated with high relapse rates, and the drugs that are given to the women nowadays are associated with a plethora of side effects of varying degrees. Consequently there is a lot of room for improvement. However, endometriosis/adenomyosis is a complex, multifactorial disease, and because of our fragmentary knowledge of its pathophysiology, there have been limited target discovery efforts, leading to a continuous shortage in the supply of novel targets.

Another issue is that endometriosis/adenomyosis is often perceived as a "low-profile" disease because, first and foremost, it is found only in women, it is not deadly, and it ceases after menopause. More poignantly, only in the past 1 to 2 decades, it has become clear what the extent is of the negative impact of endometriosis/adenomyosis on the lives of the afflicted women, their families, and the society as a whole and how debilitating the disease is during the reproductive and most productive years of their lives, and it is imperative that companies are made more aware of this. Furthermore, because there are not many alternatives for the medical treatment of endometriosis, physicians often resort to off-label use of other, often generic, drugs that are usually cheap and sometimes partially effective. This makes companies wonder why they should invest heavily in the development of new medicines for endometriosis. It is therefore imperative to inform the industry that physicians do prefer to prescribe drugs that are indicated for endometriosis, proven effective, superior to the current standard of care, and have an acceptable safety profile. Hence, as in any indication, if a drug excels, there will be a good market for it. Even if the efficacy is not superior to the standard of care, a significantly improved safety and tolerability profile will also allow good penetration of the market—which will certainly grow to a substantial market once noninvasive diagnostics tests are introduced.

Another hurdle that seems to scare companies away from initiating new programs is the fact that demonstrating efficacy in endometriosis/adenomyosis clinical trials is perceived to be challenging because of the use of subjective clinical end points in endometriosis/adenomyosis trials, which leads to substantial placebo effects[37] that are sometimes hard to overcome. For this reason, the search for quantifiable clinical biomarkers for efficacy and safety should be intensified.

An argument often used against investing in an endometriosis/adenomyosis program is that these indications do not fit the strategy or franchise. Endometriosis/adenomyosis is a hormone-dependent disorder, with clear characteristics of autoimmune and chronic inflammatory disease, and in many ways resembles fibrotic disorders, with clear parallels with neuropathic conditions and cancer. Therefore, one can just as easily argue that endometriosis/adenomyosis would in fact fit any franchise.

Knowing what the key competitors are will help assess whether there is a potential market share for the product, so a competitive landscape will be depicted: what therapeutics are

used for the treatment of endometriosis, what is the golden standard, how efficacious are these drugs, what is their safety profile, and is there any room for improvement. Also, in the course of the program, which may take about 8 to 12 years before market entry is awarded, it is important to continue monitoring the competition, as different products may dominate the market by the time a company launches its product.

Clearly, to a large extent, it is sentiment rather than knowledge that directs many of the initial discussions about taking up endometriosis/adenomyosis as indication, and it is essential to have buy-in from all program/company stakeholders. This is where the lobbying of "project champions" and external scientific advisors can make a difference by creating awareness about the serious nature of endometriosis/adenomyosis as a disease, but also to convince the board and the stakeholders of the opportunities there are and safeguard project continuation once initiated.

Could We Do It?

An important aspect of the due diligence investigation into the endometriosis/adenomyosis opportunity is to assess whether it is realistic for a company to successfully bring a novel drug to the market. At this stage, a lot of important questions are raised (Figure 1): Do we have a promising target? Is the hypothesis plausible? Are there tools, such as animal models, biomarkers, and so on, available to evaluate and predict efficacy and safety? Are there chemical starting points to begin lead optimization? Or do we have to start from scratch and perform high-throughput screening to find new compound classes. Is there freedom to operate and are there opportunities to generate new IP? Are there foreseeable developmental hurdles? and so on.

Validation of hypotheses. From an industry perspective, the availability of targets and validation/confirmation of the hypothesis are vitally important and certainly decisive. The enthusiasm of pharmaceutical companies to work in endometriosis/adenomyosis and to collaborate with academic research groups has been tempered the past decades, since our understanding of the etiology and pathophysiology of endometriosis/adenomyosis is meager or fragmentary at best. Even traditional genomics, transcriptomics, proteomics, and metabolomics approaches that have been employed with much anticipation and hope have not lived up to their promises yet. As a result, the discovery of novel druggable targets has been disappointingly and painfully stagnant. Also, the endometriosis/adenomyosis research arena is not attractive for young, aspiring investigators who wish to advance their careers. Since endometriosis/adenomyosis is not high on the agenda of funding agencies, acquiring sufficient funding to establish successful research groups dedicated to endometriosis/adenomyosis research is extremely challenging, and chances to publish their work in high-impact journals are slim. They are much more likely to succeed in other disease areas with high mortality rates, such as cancer and cardiovascular disease.

Another important aspect is that pharmaceutical companies go to great lengths to independently validate targets and hypotheses in order to build confidence in the biology of the target and project. Dishearteningly and disturbingly, much of the work published in peer-reviewed journals cannot be repeated, thus invalidating hypotheses and hampering the target validation efforts. Depending on the source, in as little as 20% to 50% of cases, industry scientists have been able to reproduce findings from literature, and this includes some landmark studies from top-tier academic journals.[38,39] The reasons for this lack of reproducibility were all related to poor experimental design, a lack of robust supportive data and replication, or selective data presentation—unconsciously or otherwise. Ioannidis estimated that this would mean that about 85% of the resources, for a large part contributions from tax payers and donations, are actually wasted because of the reporting of false or exaggerated findings.[40] In cases when the data could be reproduced, the authors had paid close attention to for instance describing controls and reagents in detail, providing the complete data sets and eliminating any investigator bias. For basic laboratory and preclinical studies, replication should be feasible by default,[40] and it is therefore important that all scientists adhere to the highest standards of rigor, quality, and ethics so that hypotheses can be verified and targets validated by independent research groups.

Translational models. Most drug development programs fail after reaching the clinical stage, and in this regard Women's Health programs have the worst performance.[41] Drug developers at AstraZeneca took a closer look at what stage the projects fail, and why, and it was evident that the project failure rate is highest in the phase IIa proof-of-concept phase.[42] Zooming in on the reasons as why drugs failed, it is interesting to note that, as expected, in the early stages of development, the preclinical phase and clinical phase I studies, insufficient safety and tolerability are the major reasons for project termination. However, in the phase II studies, the primary cause for ceasing drug development projects turns out to be the lack of efficacy. This is counterintuitive as the whole purpose of phase II trials is to establish proof of concept for the best drugs selected up to that point and demonstrate efficacy in the patient population. Apparently, such an abject failure is disquieting and disconcerting, since a great deal of time and resources are spent in preclinical models, which are purported to be translational in order to select the most optimal drug for this particular target and indication. Obviously, we are doing a very poor job in predicting clinical benefits and risks.

Why is that? And can we improve the translational value of animal models of endometriosis? Investigators at Pfizer have carefully studied the shortcomings of animal models in endometriosis/adenomyosis and acute kidney disease and came to some interesting conclusions and recommendations.[43,44] The most important being that investigators employing animal models should reach consensus, not only about which disease model(s) to use but also about standardizing protocols and procedures across laboratories globally, which end points to

monitor (including their magnitude), increase statistical rigor (ie, by employing proper power calculations), avoid investigator bias (ie, through "blinding," randomization), and publish both negative and positive results.

The choice of animal model for preclinical testing of new therapeutics is crucial and is often motivated by cost, ease of access and use, the mechanism of action under investigation as well as the general consensus in the research community. However, the purpose of a translational model is not only to test whether a compound has a beneficial effect in the disease model but also to demonstrate that the drug gets to the site of action, that the target is engaged, that the desired pharmacological effect is produced, and possibly identify key (surrogate) biomarkers for use in clinical trials. Most importantly, however, the responses seen with a novel therapeutic in the animal model should ideally correspond to the clinical response in patients.

Any therapeutic used for the medical treatment of women with endometriosis has also been demonstrated to work quite well in nonhuman primate (NHP) and even all the rodent models. For obvious reasons, because they are mostly aimed at processes that can readily be mimicked, modulated, and monitored in animal models, that is, inflammation or the production and activity of estrogens. The problems start when compounds are explored against targets beyond the HGP axis, that is, the estrogen receptor (ER)-β (raloxifene; ERB-041), peroxisome proliferator-activater receptor (PPAR)-γ (pioglitazone and rosiglitazone), cholesterol synthase inhibitors (statins), and immunomodulators (thalidomide). All of these compounds have demonstrated efficacy in animal studies, but the ClinicalTrials.gov listing shows that pretty much all studies involving these therapeutic classes were either terminated or withdrawn. The point is, that until today, none of the therapeutics which have been registered for endometriosis have been selected on the basis on superior efficacy in a rodent and/or NHP model for endometriosis. Basically, there is no unequivocal evidence of translational or prognostic value of any of the models that are currently being used.

The selection and validation of an appropriate animal model is a significant undertaking and investment and will only be fruitful if global consensus can be reached on the choice of model, and protocols and procedures can be harmonized. An interesting example of an international initiative in this regard is the EurOPDX initiative. EurOPDX is a European network dedicated to the development of clinically relevant and annotated models of human cancer. The key objectives are "to elucidate **standard operating procedures and harmonize working practices** for implementation of PDX models, biobanking, biostatistics, protocol design and logistics for multicentre trials, data analyses and reporting, with the goal to improve the reproducibility and predictability of preclinical and co-clinical studies; in particular patient-derived xenografts (PDXs), but also to **avoid duplication of efforts.**"

To date, NHP models are considered to be the most adequate animal models for translational research in endometriosis.[45,46] The NHPs menstruate, have an intact immune system, and sometimes develop mild, moderate, and severe forms of endometriosis spontaneously. However, despite the close similarities of endometriotic lesions in NHPs with human endometriosis, even the predictive value of NHP models for the preclinical selection of therapeutics has never been convincingly established. On top of that, NHP models are not very suitable for larger scale screening and selection of compounds because NHP studies are extremely expensive, labor intensive, and increasingly ethically challenging and thus not easily accessible to most academic groups.

So, more attention should be focused on advancing rodent models to the point it can be shown that they have predictive value. An important step in the process is to accept that endometriosis is a complex multifactorial disease and that ectopic endometriotic tissue is fundamentally different from normal endometrium.[47-50] It may therefore never be possible to completely mimic human endometriosis. The next best thing would then be to focus on critical determinants such as treatment resistance and/or to make use of endometriotic tissue (patient-derived xenografts [PDXs]), analogous to the cancer PDX models. The disadvantage of PDX models is that the tissue has to be transplanted into an immunodeficient background and thereby underestimating the potential influence of the immune system, but the advantage is that for a short period of time you may be able to maintain the (epi)genetic and phenotypic makeup of the human endometriotic tissue. The potential of such an approach was nicely illustrated by Fritsch and coworkers who studied the effect of drugs in mice transplanted with human uterine fibroid tissue.[51]

Evidence is growing that treatment resistance in endometriosis may be related to the fact that endometriosis and adenomyosis (endometriosis in the uterine wall) can be qualified as fibrotic disease, disorders that are usually associated with, but exclusively, constitutively activated transforming growth factor-β signaling, myofibroblast differentiation, high collagen content, poor vascularization, impaired local immune cell function, and the occurrence of nerve compression pain. In addition to these mechanisms, there are many more parallels that exist between adenomyosis and endometriosis.[25,52] It may therefore be logical to invest in mouse models of adenomyosis. Adenomyosis is induced either through neonatal exposure to tamoxifen or toremifene or through the intrauterine or subrenal grafting of pituitary tissue in adult mice.[53-55] The advantages of these models are that the mice are immunocompetent, that the lesions are fibrotic and localized, and that, once induced, the lesions remain present and progress through the lifetime of the mice allowing long-term studies.

A third option could perhaps be the spiny mouse (*Acomys cahirinus*). It was recently discovered that this mouse actually has a menstrual cycle. It lasts longer ($\sim$9 days) than the estrous cycle in normal laboratory mice and consists of an estrogen-dominant follicular phase, a progesterone-dominant luteal phase, and a menstrual period of approximately 3 days during which blood loss is observed.[56] At this point, no endometriosis or adenomyosis has been described in this model, but this mouse species is certainly worth exploring.

In 2004, Fiebig and coworkers introduced the concept of a "co-clinical" trial in oncology. This basically means that tumor tissue from patients collected at surgery was grafted in mice, and the patient and the mice were treated with the same drugs (also referred to as "avatar" mice). The concordance among 80 comparisons (in 55 different tumor types) was 90% for the responders and 97% for the nonresponders.[57] The "avatars" are basically personalized mouse models used nowadays to identify therapeutics that tumors are sensitive to.[58] Upon the installment of an endometriosis/adenomyosis PDX consortium, "co-clinical" trials can be initiated to interrogate the translational value of this approach. In parallel, the same therapeutics can be evaluated in the other animal models to demonstrate their translational worth. Once the models are up to standard, procedures harmonized, and the translational value verified, this platform will surely be appealing to companies that have an interest in these indications. Granted, initiatives like this are costly, but funding by means of an industry-wide precompetitive collaboration is an attractive way to share the cost burden for the industry and for the establishment predictive, preclinical animal models. Another important aspect often overlooked or simply disregarded by researchers in academia is the incorporation of additional pharmacological end points to confirm the target is engaged (ie, surrogate biomarkers—although a consensus needs to be reached as what these proxy biomarkers are) and modulated in a desired and dose-dependent manner. To this end, the pharmacokinetics (PK) of the drug must also be determined in the animals if possible. By no means an easy task but essential to establish a PK–pharmacodynamics (PD) relationship to support the estimation of the anticipated human dose, once the mandatory nonclinical safety studies have been completed. In addition, adherence to the Animals in Research: Reporting In Vivo Experiments guidelines[59] when writing up reports should increase the chance of reproducibility and is strongly recommended.

Clinical development and biomarkers. Even after reaching the late clinical stage, about 50% of the drugs still fail. They fail mostly because studies do not meet their efficacy end points but sometimes because of safety concerns, strategic choices, unexpected toxicities due to long-term treatment, regulatory hurdles, and so on. These are often unforeseen and unpredictable, but when this happens, it is a tough "pill" for the company to swallow. Companies are frantically searching for novel ways to improve the odds. One obvious way to achieve this is by the implementation of noninvasive companion diagnostics to improve patient stratification and quantifiable (surrogate) biomarkers for endometriosis-related pain and efficacy. The value of including selection biomarkers to enroll patients was elegantly demonstrated by Thomsen et al.[60] The authors reviewed the clinical development success rates gathered by Informa's Biomedtracker service over the past decade, 2006-2015. A total of 9985 clinical and regulatory phase transitions, from 7455 development programs, across 1103 companies, were included in the analysis. Implementation of selection biomarkers to enroll patients increased the successful phase transitions from phase I to phase II by 63% to 76%, from phase II to phase III by 28% to 46%, but most significantly from phase III to market entry by 8.4% to 25.9%. The availability of noninvasive diagnostic tools for patient stratification and monitoring efficacy and safety will help minimize the risk of failure and as a consequence reduce the reluctance of pharmaceutical companies to enter the endometriosis/adenomyosis arena.

Analogous to the importance of reaching consensus regarding the choice and validation of translational animal models, it is also imperative that global consensus is reached among all stakeholders regarding the key end points in clinical trials of endometriosis. This will allow comparison of trial results, improving evidence-based practice. A significant step in the right direction was made by the publication of the recommendations of the Art and Science of Endometriosis Meeting convened by the National Institutes of Health in 2010,[61] made by a panel of invited scientists and clinicians on outcome measures for use in international clinical trials in endometriosis with regard to pain symptoms. A revised consensus document was approved by professional bodies such as the Special Interest Group on Endometriosis of the American Society for Reproductive Medicine (ASRM) and the European Society for Human Reproduction and Embryology. The recommended outcome measures are a combination of adapted recommendations from other chronic pain conditions and endometriosis-specific and patient-centered measures. Despite close adherence to these recommendations in, for instance, the recent Elagolix trials, Elaris EM I and II,[62] the placebo effects were still quite prominent, a common phenomenon in endometriosis trials. Clearly, this issue cannot be resolved through the harmonization of clinical trial protocols but can only be addressed through the implementation of objective clinical biomarkers for efficacy and safety.

Intellectual property. Freedom to operate and IP are crucial to the survival of companies. Patents and IP rights are needed not only to assure a return on investment when a drug reaches the market but also to block the competition. In order to assess whether a program may lead to a patentable drug or process, a very rigorous and extensive evaluation of the literature and patent landscape is performed. Preparing a patent application is not that straightforward. Not every interesting finding qualifies as a druggable target or developable compound. There are some strict criteria that have to be met. It must be a patentable subject matter, it must be novel and nonobvious, and it must involve an inventive step and be applicable to industry. Patentable subject matter means a process, machinery, manufacture or composition of matter, or any new and useful improvement thereof. Examples of subject matter that are not patentable are for instance naturally occurring biological material, genetic sequences, and stem cells, programs for computers, and mathematical and business models.

Every now and then, investigators do come up with very interesting ideas or a promising therapeutic, publish it, and wonder why no pharmaceutical company wants to adopt the concept and develop it. Most investigators do not realize that the moment something is in the public domain it has become a

"prior art." The consequence is that it will be almost impossible to create new IP around these concepts, which means that a company cannot protect the product from for instance the generic companies when they go to the market and are therefore not sufficiently profitable. Due to the lack of any financial incentive, no company will invest in these compounds anymore. Hence, investigators need to think hard about the potential impact of their finding before publishing it. The companies do. If you do a novel finding, file the patent first, as you have a year to collect data to support the claim before the patent is published. Immediately after submitting the patent application, you can already submit your manuscript for publication, because your finding is protected from the patent application date on. Patent protection will greatly enhance the commercial value of your discovery. If you do not wish to maintain the patent, you simply do not pay the annual fees, and the patent loses its protection automatically. Of note, patent life is finite, which is part of the reason why companies prefer to wait with disclosing their preclinical data for as long as possible. If data are not published, they can wait with filing the patent which will give them longer patent protection when they are on the market.

Can We Do It?

The target/hypothesis has been validated; the market, patent landscape, and competition inventarized; a target product profile has been made; and it is likely that a high-quality therapeutic can be produced for the clinical studies and market. So the question "Can we do it?" has become almost obsolete because all other critical drivers have received a "go." Still, portfolio management is responsible for the allocation of resources to the programs, and these priorities may change at any point in time, that is why companies prefer to use "rolling forecasts" because it enables organizations to adapt plans and resource allocations based on the successes or failures in clinical development, the occasional in-licensing of promising drugs, issues in chemistry, manufacturing and control (CMC), or changes in the economy. Sometimes, another company registers a drug with a superior profile, which does not come as a surprise as the clinical progress of the competition has been inventarized and monitored closely. It does open the discussion as what to do in such circumstance. Obviously, being the first in class with an efficacy/safety profile better than the current standard of care and the competitor drug is very attractive, because you can potentially dominate the market and be rewarded handsomely. However, even if a drug is not the first to reach the market, such as, for example, the oral GnRH antagonists in the slick stream of Elagolix, it is still quite possible to become a dominant player in the market.[63]

Where Do We Go From Here?

Identifying the common ground is quite simple: We all want better and safer drugs for the patients, but we cannot do it alone. Bringing drugs to the market is a shared responsibility. It is important to acknowledge the fact that pharmaceutical companies bring the drugs to the market and at the same time that discoveries in academia actually contribute to about half of all targets used in the drug development programs. To draw the attention of pharmaceutical companies to invest in endometriosis/adenomyosis drug development programs, scientists must continue to focus on the obvious: increase the supply of novel, robustly validated targets, identify and validate the quantifiable (noninvasive) diagnostic biomarkers for patient stratification, efficacy, and safety, and monitoring treatment response as well as improve the translational value of the therapeutic animal models. The way to go about this, however, should radically change if progress is to be made. For example, investigators should cross-collaborate much more with experts in other disease areas to pick up new ideas and hypotheses, which will enable them to look at and study endometriosis/adenomyosis from new angles and increase the likelihood of uncovering new insights in the etiology and pathophysiology of endometriosis and discover novel targets and biomarkers. There is another good reason to collaborate with investigators from other disease areas. Companies are not very keen on developing drugs that only serve one indication, which is why a lot of drugs are repurposed. It is more attractive if a drug targets a mechanism which is the key to more than 1 indication. Obviously, this will surely increase the R&D efficiency and enhance the bottom line.

The high attrition rate remains a major concern for the pharmaceutical industry. Clearly, in order to reduce attrition, the translational value of our preclinical models have to be improved, both in vitro and in vivo. To realize this, it is fundamentally important not only to standardize/harmonize the animal (rodent and NHP) models but also to make use of primary endometriotic tissues to create PDXs. There is a golden opportunity to turn this into a global initiative. The Endometriosis Phenome and Biobanking Harmonization Project organized by the World Endometriosis Research Foundation published a series of consensus papers on standardized sample collection protocols for banking of different biological samples from women with endometriosis and controls.[64-67] If, in addition, working practices regarding the establishment of the PDX models can be harmonized as well, the infrastructure to create a global endometriosis/adenomyosis PDX model network would be in place.

Continuously advocating the unmet medical need, the assured exponential market growth once noninvasive diagnostic tools become available, the mediocre efficacy and questionable side effect profiles of the drugs that are currently on the market, and the minimal competition are instrumental to raise awareness of all stakeholders in the companies and pique their interest to invest in endometriosis/adenomyosis drug development programs once an opportunity is presented. The most effective way to do this is through "project champions," they know who the decision makers are and have access to them.

Finally, value comes with IP. So, if you believe to have made a discovery, a novel and usable finding, take some time to prepare and submit a patent application before you publish

your data. It will be the first question asked when you present your opportunity to a pharmaceutical company.

There is hope for the patients. The endometriosis/adenomyosis research community, the women suffering from the disease, primary care physicians, gynecologists, governments, and even companies, all are extremely motivated to make a difference. Breakthroughs in the noninvasive diagnosis and identification of key pathophysiological mechanisms and druggable targets are about to be realized, which will undoubtedly arouse the interest of pharmaceutical companies. If at that point the IP is secured, and the globally harmonized and standardized networks of translational preclinical models and centers of excellence are in place, close collaboration between the pharmaceutical companies and academia could expedite the development of promising drugs. So all hands are required on deck.

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