Human Reproduction Update, Vol.24, No.5 pp. 577–598, 2018
Advanced Access publication on June 11, 2018 doi:10.1093/humupd/dmy020

human reproduction update

Is it time for a paradigm shift in drug research and development in endometriosis/adenomyosis?

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Submitted on February 20, 2018; resubmitted on May 9, 2018; editorial decision on May 15, 2018; accepted on May 21, 2018

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BACKGROUND: The drug research and development (R&D) for endometriosis/adenomyosis has been painfully slow. Most completed clinical trials on endometriosis did not publish their results, and presumably failed. While few published trials did report how they foundered, the reasons why they failed are often completely unclear. Surprisingly, there has been no open discussion on why these trials failed. If the causes for these failed trials remain unelucidated, mistakes made in these failed trials may be repeated in the future. Since failure can be infinitely more instructive and educational than success, elucidating the causes for failed clinical trials may yield a treasure trove for future drug R&D. Given our growing understanding of the natural history of ectopic endometrium, it is also important to make an inventory of biologicals/compounds that are currently under development to see where we stand and whether they would stand a better chance of gaining regulatory approval than their predecessors.

OBJECTIVE AND RATIONALE: We provide an overview of all compounds under clinical investigation and in development in order to assess the evolution of R&D since the last inventory, reported in 2013. We also have attempted to analyse selected failed clinical trials in the context of published translational/preclinical research and our growing understanding of the natural history of endometriotic/adenomyotic lesions, in the hope that the lessons learned will steer investigators toward the right track in future drug R&D.

SEARCH METHODS: We searched ClinicalTrials.gov and a database containing information on drugs gathered daily by Thomson Reuters from a wide range of sources (e.g. patent offices, biomedical literature, congresses, symposia, meetings, company information, regulatory information) for all therapeutic compounds that have undergone or are under clinical trials, or in the developmental stage, and then searched PubMed and Google to determine their publication status using trial identifiers. For trials that were completed at least 2 years ago and have, or have not, published their results, a PubMed search was performed using the name of the therapeutic that has been tested and 'endometriosis' or 'adenomyosis' to identify published preclinical studies prior to the launch of the trial. For those published trials, the cited preclinical studies were also retrieved and scrutinized.

OUTCOMES: Despite repeated calls for more transparency, only a small fraction of completed trials on endometriosis has been published. A large number of 'novel' compounds under development are simply repurposed drugs, which seem to be ill-prepared to combat the fibroproliferative nature of endometriosis/adenomyosis. This sobering picture indicates an alarming innovation 'drought' in the drug R&D front, resulting in trickling drug pipelines.

Some trials foundered owing to unanticipated serious side-effects, or because attempts were made to suppress a target that can be compensated for by redundant pathways, but many failed in efficacy, indicating that the translational value of the current models is seriously questionable. All existing animal models of endometriosis do not recapitulate the key features of human conditions.

WIDER IMPLICATIONS: The glaring innovation drought in drug R&D for endometriosis/adenomyosis should sound alarms to all stake-holders. The failed clinical trials in endometriosis also indicate that some past research had serious deficiencies. In light of the recent understanding of the natural history of ectopic endometrium, it is perhaps time to shift the research paradigm and revamp our research focus and priorities.

Key words: adenomyosis / clinical trial / drug research and development / endometriosis / innovation drought / pathophysiology / preclinical studies / transparency

Introduction

Next to uterine fibroids, with an estimated prevalence ranging from 5 to 21% (Zimmermann *et al.*, 2012), endometriosis (prevalence ranging from 6 to 10%, see (Giudice and Kao, 2004)) and adenomyosis (estimated prevalence ~20%, see (Naftalin *et al.*, 2012)) are two of the most common gynecological disorders in women of reproductive age worldwide. Both diseases can cause dysmenorrhea, pelvic pain, dyspareunia, infertility and in adenomyosis in particular, heavy menstrual bleeding, impacting negatively on the wellbeing of the patients (Nnoaham *et al.*, 2011) and leading to a significant loss of work productivity and heavy burden on healthcare costs (Simoens *et al.*, 2011a, b, 2012). Adenomyosis is well recognized as one of the leading causes for abnormal uterine bleeding that significantly reduces the quality of life and work productivity (Cheong *et al.*, 2017). The cost associated with endometriosis/adenomyosis treatment in referral centers is similar to that of other chronic high-impact diseases such as diabetes, Crohn's disease and rheumatoid arthritis (Simoens *et al.*, 2012, 2011a, b; De Graaff *et al.*, 2013; Klein *et al.*, 2014). Yet, in contrast to these disorders, endometriosis/adenomyosis are hardly recognized as high-impact disorders by general practitioners, society, funding organizations and the pharmaceutical industry due, in no small part, to the lack of awareness of these two diseases.

Both endometriosis and adenomyosis are estrogen-dependent, chronic and inflammatory disorders (Giudice and Kao, 2004; Kitawaki, 2006; Vannuccini *et al.*, 2017). The list of therapeutics for endometriosis/adenomyosis used in the daily practice is seemingly quite extensive, however, the variety of mechanisms targeted is quite limited and mostly aimed at reducing pain and/or abnormal uterine bleeding (i.e. non-steroidal 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 (Brosens, 1997). Another concern is the fact that most therapies often provide merely partial or temporary symptom relief at the cost of a plethora of negative side effects of varying degrees. While surgery can be effective, the recurrence risk is high (Guo, 2009). For adenomyosis, hysterectomy offers a curative treatment, yet the removal of the uterus, which is viewed by many as the symbol for womanhood, can be quite emotionally traumatic, especially for younger women who still desire a family (Streuli *et al.*, 2014). Moreover, many women, especially those in their 30 and 40s, are very keen to preserve their fertility yet repeated surgery increases the risk of premature ovarian failure (Chen *et al.*, 2014). Thus, the development of novel therapeutics with better safety profiles is an unmet medical need yet to be fulfilled.

Drug research and development (R&D) in endometriosis/adenomyosis has been painfully slow (Guo, 2014), and the disappointment is unmistakable (Vercellini *et al.*, 2011), which becomes painfully clear when looking at the three products that have been launched for the treatment of endometriosis-related symptoms since the GnRH agonists were introduced 20 years ago, namely Depot Provera (medroxyprogesterone acetate), dienogest and Yasmin (drospirenone and ethinyl estradiol). Depot Provera contains a progestin discovered in the 1960s, dienogest was originally discovered by Jenapharm in then East Germany in 1979, and Yasmin, containing drosperinone and ethinyl estradiol, has only been approved in Japan. Dienogest is even now the top-of-the-line drug for treating endometriosis, despite the fact that it merely alleviates symptoms, but does not reduce the volume of the endometriotic nodules (Leonardo-Pinto *et al.*, 2017). In an overview of 80 interventional trials on endometriosis registered in ClinicalTrials.gov ~5 years ago, it was concluded that 'no blockbuster drug for endometriosis seems to be on the horizon yet' (Guo, 2014).

It has proven to be quite a challenge to develop therapeutics with improved efficacy and/or safety profiles, and because drug R&D is an arduous, risky and costly endeavor without any guarantee for return on the investment, pharmaceutical companies are hesitant to enter this arena. The only way to persuade drug developers to invest in endometriosis programs is to provide evidence that certain drug classes and/or targets are worthwhile pursuing (Groothuis and Guo, unpublished data).

While all preclinical work is closely monitored by discovery units in pharmaceutical companies, results from RCTs are not as closely monitored as preclinical studies, even though they are considered to be level I evidence and provide the first proof-of-concept that a drug is effective in women with endometriosis/adenomyosis. Since clinical trials consume a lion's share of the drug R&D budget (Paul *et al.*, 2010), and are time- and energy-consuming and logistically challenging to conduct, the decision to advance the R&D program to the clinical stage is not made lightly in industry. For academic investigators, the decision to conduct a trial certainly is not made easily either. Funding, time and efforts aside, a failed trial would also mean a steep opportunity cost. Nobody is interested in initiating a clinical trial that is doomed to fail.

Therefore, to expedite drug R&D innovation in endometriosis/adenomyosis it is imperative that the outcomes of the clinical trials become available to the entire scientific community, whether they yielded positive results or not. Unfortunately, and somewhat disturbingly, the majority of clinical trials in endometriosis, especially those that are industry-sponsored, has never been published (Guo *et al.*, 2009), despite repeated calls for more openess or transparency regarding clinical trial outcomes in endometriosis (Guo *et al.*, 2009; Guo and Evers, 2013). Of course, trial non-disclosure is not a problem restricted in endometriosis *per se*. Rather, it is an issue that was made public over 20 years ago (Simes, 1986) and is well documented (Easterbrook *et al.*, 1991; Zarin and Tse, 2008), and still remains a pervasive problem in medicine (Miller *et al.*, 2015, 2017).

Most unpublished trials evaluated drugs that did not lead to any approval for marketing and, as such, are presumably failed owing to either lack of efficacy, safety concerns or both, or were at least viewed as unworthy for further development. While the published trials did report how they failed, the reasons why they failed are often murky or completely unclear. Worse yet, there has been no open discussion on why trials failed. This manner of dealing with foundered clinical trials surely hinders progress in the field and raises the prospect that many missteps, miscalculations and mistakes made in these apparently failed trials may be repeated in the future. Understanding why the drug failed can be far more instructive and educational than cases of successful trials.

In this paper, we have compiled an exhaustive overview of all compounds under clinical investigation and in development (in academia and the pharmaceutical industry), by combining a thorough review of trials in ClinicalTrials.gov plus a search of the Thomson Reuters Integrity^{SM} database, in order to assess what evolution has taken place in drug R&D since 2013 when we assessed it the last time. Are the current drug R&D pipelines full of innovative compounds or have they dwindled and are on the verge of drying up? In addition, we have attempted to dissect and scrutinize a selection of potentially high-impact clinical trials that have failed unexpectedly in the context of published translational/preclinical research and our growing understanding of the natural history of ectopic endometriotic lesions (Zhang *et al.*, 2016a, b, 2017b; Guo, 2018), in the hope that the lessons learned will help to guide investigators on the right track and that more innovative drug development programs will be launched.

Methods

Data sources

ClinicalTrials.gov (ClinicalTrials.gov) and the Thomson Reuters Integrity^{SM} drug pipeline database were used in this study.

ClinicalTrials.gov

All trials registered as interventional were retrieved manually into an Excel file through the query of the ClinicalTrials.gov site on 8 November 2017. The Advanced Search mode was used employing the terms 'endometriosis', or 'adenomyosis', 'interventional', and '(early) Phase I, II or III'. The resulting Excel file was further double checked manually. Interventional trials on procedure, diagnostics, behavioral (including dietary supplementation) and devices (except drug-eluting intra-uterine systems) were excluded. In addition, trials that focused explicitely on diseases or conditions other than endometriosis or adenomyosis, such as fibroids or hot flashes, were also excluded. Trials in healthy women testing drugs or biologicals that were used in other endometriosis/adenomyosis trials, such as Proellex (Telapristone acetate), and CDB-2914 (ulipristal acetate, UPA), were included. For some trials that listed more than a single phase (e.g. Phases I and II), the correct phase was confirmed by examining the context and the intention of the trial (e.g. safety and/or efficacy).

By definitions provided at ClinicalTrials.gov, a trial can have one of the following recruitment statuses:

- 'Suspended', which means that the clinical study has stopped recruiting or enrolling participants, i.e. because of strategic reasons, safety concerns or shortage of funding; sometimes these studies may start again.
- 'Terminated' which means that the clinical study has stopped recruiting or enrolling participants and will not start again, participants are no longer being examined or treated.
- 'Withdrawn' meaning that the clinical study stopped before enrolling its first participant.
- ''Unknown', which in ClinicalTrials.gov means that the trial had a status of 'Recruiting', Not yet recruiting' or 'Active and not recruiting', but whose status has not been confirmed within the past 2 years.

Since the present study used only data extracted from a publicly accessible registry and had no access to any patient data, the study was exempted from obtaining ethical approval from the Institutional Ethics Review Board of Shanghai OB/GYN Hospital.

Publication status and information on relevant preclinical studies

We determined the publication status of each and every trial retrieved with the 'Completed' status by querying PubMed using the trial identifier. Unfortunately, it is not universally accepted or required to put the trial identifier as a footnote to a publication. If the PubMed search did not yield any publications, a PubMed or Google search was performed using details of the trial, plus the name of the principal investigator. This yielded additional matches. The publication status of three trials (NCT01218581, NCT00185341and NCT02271958) were determined in this manner.

In addition, we searched PubMed for any published preclinical studies related to the compounds in clinical trials, in order to inventarize the targets and mechanisms that were targeted, and what translational studies were used that led to the launch of the clinical studies.

Thomson Reuters Integrity^{SM}

The information in the Thomson Reuters Integrity^{SM} database is created by Thomson Reuters and gathered from patent offices, the biomedical literature, congresses, symposia, meetings, company information, regulatory information, scientific websites, clinical trial registries and press releases, and is updated daily. It integrates biological, chemical, pharmacological and clinical data on more than 450 000 compounds and 297 000 patent family records.

Thomson Reuters Integrity^{SM} was interrogated with the search terms 'endometriosis' and 'adenomyosis' on 13 November 2017. This search yielded a list of drugs that have already been launched for these indications, the drugs that are currently in development, including those in biological and preclinical phase, and also a list of drugs that are currently not in active development. The Integrity database was initiated in 2001 and contains information about drug programs that were ongoing at that time or have been initiated (and abondoned) since then. Only the therapeutics that are presumably in 'active' development were extracted, and the list was sanitized by removing the drugs that have not yet reached the 'preclinical development stage', meaning that they have not been included in any project portfolio, or for which there was no further substantiation that the drugs are actually in clinical development. This list was integrated with the list of drugs from the ClinicalTrials.gov search. Drugs that were listed in Integrity, but not ClinicalTrials.gov were re-investigated mostly by searching for press releases/announcements from the companies to confirm (pre)clinical activities. Ultimately, we obtained a comprehensive list of drugs (Table I) that are currently being, or recently have been, investigated for the treatment of endometriosis and/or adenomyosis.

Statistical analysis

The difference in frequency between two, or among more groups was evaluated using Fisher's exact test. The comparison of medians between the two or more groups was made using the Wilcoxon's rank-sum test and Kruskal–Wallis test, respectively. P values of <0.05 were considered statistically significant. All computations were made with R 3.4.2 (Inhaka and Gentleman, 1996) (www.r-project.org).

Results

Poor trial outcomes and the lack of transparency

The search of ClinicalTrials.gov, performed on 8 November 2017, yielded 287 trials on endometriosis and 44 trials on adenomyosis alone. Among them, 194 and 30 trials on endometriosis and adenomyosis, respectively, were of an interventional nature; the remaining trials (93 and 12, respectively) were of an observational nature. After removal of trials meeting the exclusion criteria described above and one trial (NCT02587000) that was found to be listed in both endometriosis and adenomyosis trials, a total of 91 trials (endometriosis $n = 85$, and adenomyosis $n = 6$) were identified and included. The 85 trials on endometriosis and 6 trials on adenomyosis are listed in the Supplementary Tables S1 and S2, respectively.

Among the 91 trials, 56 (61.5%) were completed, 17 (18.7%) were 'recruiting', 6 (6.6%) were 'terminated', 5 (5.5%) studies were 'withdrawn', one each (1.1%) was listed as 'not yet recruiting', 'suspended' and 'active', and 4 (4.4%) were 'unknown' (Table I). Overall, 61 of the 91 (67.0%) trials were sponsored by industry. Four trials had no completion date and 45 trials were completed 2 years or longer ago. The other 42 trials are either ongoing or were completed within the past 2 years. The four trials with 'unknown' status were all sponsored by non-industry, whereas industry-sponsored trials all had a known status ($P = 0.010$, by Fisher's exact test).

The drug classes investigated by industry and non-industry seem to be quite different (Fig. 1). While industry-sponsored trials focused largely on 'proprietary' drugs, such as GnRH antagonists and selective progesterone receptor modulators (SPRMs), academic institutions concentrated mostly on more 'generic' or off-the-shelf non-traditional drugs and progestins (Fig. 1).

Despite the large number of finished trials in the registry, the outcomes of the majority of the trials have never reached the public domain. A total of 45 trials finished more than 2 years ago, a period we presume to be sufficiently long to publish the trial results. Among them, eight trials (17.8%) were sponsored by non-pharma institutions and 37 (82.2%) registered by pharmaceutical companies. Of the eights trials sponsored by non-pharma institution, six (75%) were published, whereas of the 37 pharma-sponsored trials only five (13.5%) were published ($P = 0.0013$).

The troubling outlook of drug innovation for endometriosis and adenomyosis

Combining the ClinicalTrial.gov registered trials with the information gathered by Thomson Reuters from all publically accessible data sources yielded a comprehensive list of, presumably, all drugs that are, or recently have been, in one form or another, in clinical or active (as pharma program) development for endometriosis and/or adenomyosis (Table I). At first glimpse, it seems quite promising, as there appears be a reasonably diverse spectrum of drugs and targets, but upon close scrutiny, the findings become rapidly more sobering and disquieting. Overall, 46 of the 65 drugs (70.8%) evaluated are still aiming to suppress the hypothalamic–pituitary–gonadal (HPG) axis and estrogen activity. The other 19 drugs (29.2%) are directed at targets or pathways not related the HPG axis or steroid hormone activity, but only nine (13.8%) of these are being tested in trials under the supervision of a pharmaceutical company. Of these nine drugs, one is a generic (lignocaine, synthesized in 1947) and the other eight all have been under evaluation in other indications, in other words they are repurposed drugs: cognate chemokine receptor 1 antagonist, tanezumab (an anti-nerve growth factor, antibody), JNK inhibitor, microsomal prostaglandin E synthase-1 (mPGES-1) inhibitor, interleukin-1 receptor-associated kinase 4 (IRAK-4) inhibitor, aldo-ketoreductase

Table I The integrated short list of drugs registered in ClinicalTrials.gov and the Thomas Reuters Integrity database for endometriosis and/or adenomyosis.

Name	Stage	Sponsor	Country	Drug/Biological class	[a]Status
Endometriosis					
Norethisterone/ Ethinylestradiol	III	Nobelpharma	Japan	Combined oral contraceptive	C, NP
NBI-56 418 (Elagolix)	III	AbbVie	USA	GnRH antagonist	C, P
Dienogest (Visanne)	III	Bayer	Germany	Progestin	C, P
Pentoxifylline	III	Hospital Clinic of Barcelona	Spain	Nonselective phosphodiesterase inhibitor	C, P
Levonorgestrel IUD	III	Mahidol University	Egypt	Progestin	C, P
Triptorelin	III	Taipei Veterans General Hospital and others	Taiwan, China	GnRH agonist	U, NP
NPC-01	III	Nobelpharma	Japan	Norethisterone + ethinyl estradiol	C, NP
Norethindrone	III	NIH	USA	Progestin	U, NP
TAK-385	III	Takeda	Japan	GnRH antagonist	C, NP
Degarelix	III	Centre for Endocrinology and Reproductive Medicine	Italy	GnRH antagonist	C, NP
Mifepristone	III	MediterraneaMedica S. L	Cuba	PR antagonist	C, NP
Lipiodol	III	University of Auckland	New Zealand	Anti-inflammation	U, NP
BAY 86–5300	III	Bayer	Germany	Ethinylestradiol (β-CDC) and Drospirenone	C, P
Merional	III	Cairo University	Egypt	hMG	R, NP
Pleyris	III	University Magna Graecia		Progesterone s.c.	R, NP
DLBS1442	III	DexaMedica	Indonesia	Plant extract	R, NP
Nexplanon	III	Centre Hospitalier Universitaire de la Réunio	France	Progestin	N, NP
Relugolix	III	Myovant Sciences GmbH	Switzerland	GnRH antagonist	R, NP
OC versus Depot-Leuprolide/ Norethindrone	III	NICHD	USA	Progestin	C, NP
Asoprisnil	II	Abbott	USA	SPRM	C, NP
Infliximab	II	Katholieke Universiteit Leuven	Belgium	Anti-TNF antibody	C, P
Raloxifene	II	NICHD	USA	SERM	C, P
Rosiglitazone	II	NICHD	USA	PPARγ Agonist	T, P
Cetrorelix	II	Solvay Pharmaceuticals	Belgium	GnRH antagonist	C, NP
ERB-041	II	Wyeth (Pfizer)	USA	ERβ agonist	C, NP
BAY86-5047 (ZK811752)	II	Bayer	Germany	CCR1 antagonist	C, NP
DR-2001a/DR-2001b	II	Duramed Research/Teva	Israel	Danazol vaginal ring	C, NP
Letrozole	II	Novartis	Switzerland	Aromatase inhibitor	C, NP
Danazol	II	KV Pharmaceutical	USA	Vaginal danazol	C, NP
Proellex (CDB-4124)	II	Repros Therapeutics Inc	USA	SPRM	T
Lignocaine	II	Isifer AB	Sweden	Nerve numbing agent	C, P
Tanezumab	II	Pfizer	USA	Anti-NGF antibody	T, NP
BGS649	II	Novartis	Switzerland	Aromatase inhibitor	C, NP
Pioglitazone	II	University of Wisconsin	USA	PPARγ agonist	W, NP
PGL5001	II	PregLem SA	Switzerland	c-Jun-N-Terminal Kinase Inhibitor	C, NP
Norethindrone	II	Children's Hospital Boston	USA	Progestin	C, P
Ascorbate	II	Cairo University	Egypt	Antioxidant	C, NP
PGL2001	II	PregLem SA	Switzerland	Steroid sulfatase inhibitor	C, NP
ASP1707	II	AstellasPharma Europe BV	Netherlands	GnRH antagonist	C, NP
Botuninum toxin A	II	NICHD	USA	Muscle relaxant	R, NP

Continued

Table I *Continued*

Name	Stage	Sponsor	Country	Drug/Biological class	[a]Status
BAY98-7196	II	Bayer	Germany	Anastrozole + Levonorgestrel	RC, NP
Leuprolide oral	II	Enteris BioPharma Inc	USA	GnRH agonist	R, NP
Traditional Chinese medicine	II	Guang'anmen Hospital of China	China	Unknown	R, NP
Ulipristal	II	Assistance Publique—Hôpitaux de Paris	France	SPRM	R, NP
Cabergoline	II	Children's Hospital Boston	USA	Dopamine receptor agonist	R, NP
EGCG	II	Chinese University of Hong Kong	China	Anti-oxidant a.o.	R, NP
KLH-2109	II	Kissei Pharmaceutical	Japan	GnRH antagonist	C, NP
NS-580	II	Nippon Shinyaku	Japan	Microsomal Prostaglandin E2 Synthase-1 (mPGES-1) Inhibitors	O, NP
ASP-1707; Opigolix	II	AstellasPharma Inc	Japan	GnRH (LHRH) Receptor Antagonists	C, NP
MPI-676	II	Meditrina Pharmaceuticals	USA	Aromatase Inhibitors	U, NP
PF-02413873	I	Pfizer	USA	Non-steroidal PR antagonist	C, NP
Thalidomide	I	University of North Carolina	USA	Immunomodulatory	T, NP
TAK-385	I	Millennium Pharmaceuticals	USA	GnRH antagonist	C, NP
BAY1128688	I	Bayer	Germany	An aldo-ketoreductase AKR1C3 inhibitor	RC, NP
SKI2670	I	SK Chemicals Co.Ltd.	Republic of Korea	GnRH antagonist	RC, NP
Vilaprisan (BAY1002670)	I	Bayer	Germany	SPRM	RC, NP
BAY-1834845	I	Bayer	Germany	Interleukin-1 Receptor-Associated Kinase 4 (IRAK-4) Inhibitors	U, NP
BAY-1158061	I	Bayer	Germany	Prolactin Receptor Antagonists	U, NP
BAY-1817080	I	Bayer	Germany	P2X3 Receptor Antagonists	O, NP
E2MATE; J-995, Estradiol-3-O-sulfamate	I	Bayer	Germany	Estrogen Receptor (ER) Agonists/Steryl-Sulfatase (STS) Inhibitors	C, P
NBI-42902	Preclinical	Neurocrine Biosciences	USA	GnRH (LHRH) Receptor Antagonists	
FP-5677	Preclinical	ForendoPharma	Finland	Estradiol 17-beta-dehydrogenase 1 (HSD17B1; 17-beta-HSD1) Inhibitors	
EVE-104	Preclinical	Evestra	Germany	Progestagen	
NHP-07	Preclinical	Predictive Technology	USA	Progestagen/NSAID/cannabis derivative	
VAL-201	Preclinical	ValiRx	UK	Androgen Receptor Antagonists	
Adenomyosis					
Letrozole	III	Mansoura University	Egypt	Aromatase inhibitor	C, P
Epelsiban	II	GlaxoSmithKline	UK	OTR antagonist	W, NP
Ulipristal	II	Assistance Publique—Hôpitaux de Paris	France	SPRM	R, NP
Bromocriptine	I	Mayo Clinic	USA	Dopamine receptor agonist	O, NP
Metraplant-E v. Yasmin	I	Ain Shams Maternity Hospital	Egypt	Progestins	R, NP

The list is arranged by drug R&D stage.
[a]Trial and publication status: N = Not yet recruiting; R = recruiting; O = ongoing; C = completed (at least 2 years ago); RC = recently completed (less than 2 years ago); T = terminated; S = suspended; U = Unknown; W = withdrawn; P = published; NP = not published yet. SERM = selective estrogen receptor modulator; SPRM = selective progesterone receptor modulator; ER = estrogen receptor; PR = progesterone receptor; PPARγ = peroxisome proliferator-activated receptorγ; CCR1 = cognate chemokine receptor 1 (which has a high-affinity to normal T-Cell expressed and secreted or RANTES); NGF = nerve growth factor, AR = androgen receptor; DRD2 = dopamine receptor D2; OTR = oxytocin receptor; NICHD = Eunice Kennedy Shriver National Institute of Child Health and Human Development; NIH = National Institutes of Health.

(AKR) 1C3 (AKR1C3) inhibitor, purinergic receptor P2X ligand-gated ion channel 3 (P2X3) antagonist, and prolactin receptor (PRLR) antagonist. The situation in adenomyosis is even bleaker. Only five intervention studies were found, of which only one was registered by a pharmaceutical company, and this study was actually withdrawn even before any patients were recruited.

The repurposed compounds are clearly directed against more non-traditional targets, but the reasons why these compounds are under investigation is not always straightforward. In endometriosis, mPGES-1 expression is elevated, and inhibition of the enzymatic activity seems to be the appropriate approach (Chishima *et al.*, 2007; Lousse *et al.*, 2010; Numao *et al.*, 2011; Hayashi *et al.*, 2013).

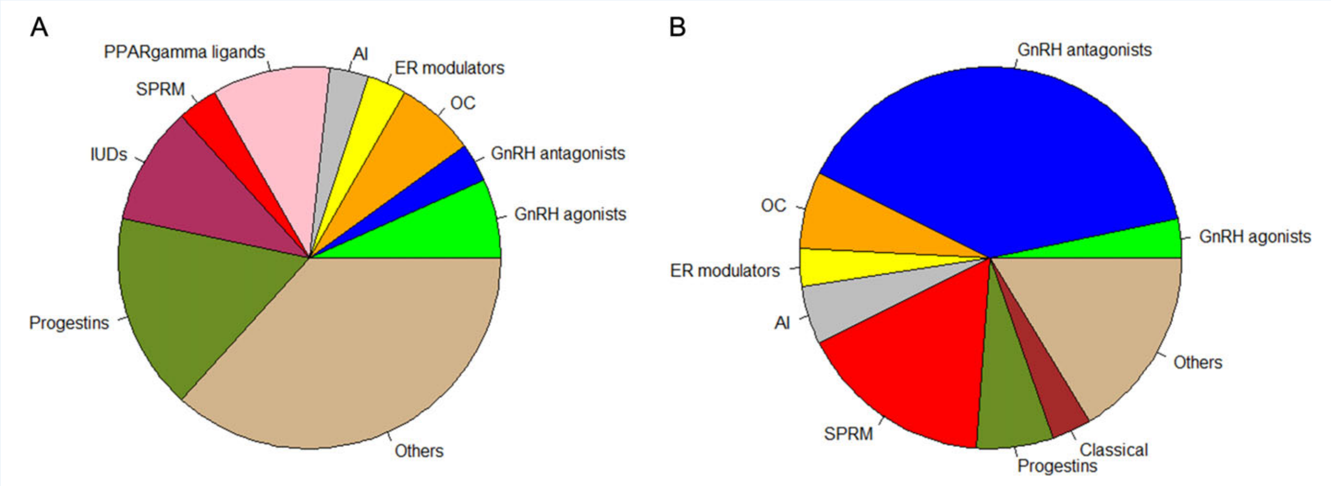

Figure 1 The composition of biological classes in trials sponsored by industry and non-industry academia. AI = aromatase inhibitors; OC = oral contraceptives; SERM = selective estrogen receptor modulator; SPRM = selective progesterone receptor modulator; ER = estrogen receptor; PR = progesterone receptor; PPARγ = peroxisome proliferator-activated receptorγ.

However, deficiency in mPEGS-1 for instance has been shown to exacerbate pulmonary fibrosis (Wei *et al.*, 2014), raising the question as to whether inhibition could actually exacerbate endometriosis—as it is now also recognized as a pro-fibrotic disorder (Zhang *et al.*, 2016a, b; Vigano *et al.*, 2017). In addition, the natural history of ectopic endometrium is recently emerging: endometriotic/adenomyotic lesions are fundamentally wounds undergoing repeated tissue injury and repair (ReTIAR) through microenvironment-mediated epithelial–mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), smooth muscle metaplasia (SMM), and fibrosis (Shen *et al.*, 2016; Liu *et al.*, 2016b, Zhang *et al.*, 2016a, b; Guo, 2018) (Fig. 2). This, coupled with the well documented diagnostic delay in endometriosis (Hadfield *et al.*, 1996; Dmowski *et al.*, 1997), suggests that endometriotic/adenomyotic lesions are mostly highly fibrotic, especially in deep endometriosis (Liu *et al.*, 2018c) and adenomyosis (Liu *et al.*, 2018a, c). Once fibrotic, the lesions would have reduced vascularity and progesterone receptor (PR) expression (Liu *et al.*, 2018a, c), and conceivably be resistent to drug treatment, especially hormonal drugs.

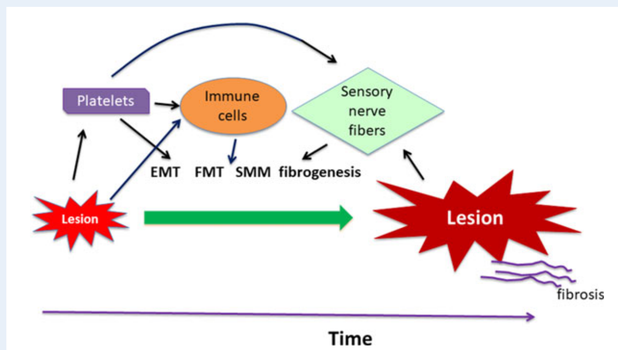

Figure 2 Schematic illustration of the natural history of ectopic endometrium. The arrows indicate the crosstalk between endometriotic/adenomyotic lesions and other cells in the lesional microenvironment. EMT = epithelial–mesenchymal transition; FMT =: fibroblast-to-myofibroblast transdifferentiation; SMM = smooth muscle metaplasia.

AKR1C3 has been documented to be involved in steroid and prostaglandin metabolism in endometriosis and endometrial carcinoma (Smuc *et al.*, 2007; Hevir *et al.*, 2011; Beranic and Rizner, 2012; Beranic and Lanisnik Rizner, 2013; Sinreih *et al.*, 2015). Because of the multi-substrate specificity, it is very difficult to predict how the intracrine and endocrine milieu are affected. There are no data to show that it plays a critical role in lesional development or pain and that its suppression can have desired therapeutic effect.

Another interesting target is PRLR. PRL and PRLR levels are elevated in patients with endometriosis and/or adenomyosis, but hyperprolactinemia and PRLR overexpression is not only seen in endometriosis/adenomyosis but also in a plethora of conditions, including iatrogenic ones (Muse *et al.*, 1982; Chew *et al.*, 1990; Lupicka *et al.*, 2017). Aside from being a lactogenic hormone, PRL is implicated in islet differentiation, adipocyte control and immune modulation (Gorvin, 2015). Thus this raises the questions of whether the activation of the PRL-PRLR signaling pathway is critical to endometriosis/adenomyosis and whether PRLR inhibition would be sufficiently effective, or innocuous to normal physiology. Again, there are no published preclinical data whatsoever to show that PRLR inhibition has any desirable effect in the context of endometriosis/adenomyosis.

Endometriosis is associated with elevated levels of the inflammatory cytokine IL-1 in the circulation, but also with an imbalance in IL-1 receptor subtypes due to increased expression of the activating type I and concomitant decreased expression of the inhibitory type II IL-1 receptors (Akoum *et al.*, 2007). A key component of IL-1R signaling is IRAK-4 (Wang *et al.*, 2009). Hence, it is logical to investigate the therapeutic potential of IRAK-4 inhibitors in endometriosis models. However, no data are available, at least in the public domain, to support this. Suppression of IL-1 through a soluble IL-1 type II receptor or IL-1β antagonist did inhibit lesion development and associated adhesion formation in a mouse xenograft model (Khoufache et al., 2012; Stocks et al., 2017), but it is unclear whether an IRAK-4 inhibitor is equally effective in human endometriosis as well.

A more interesting target is P2X3. P2X3 is expressed in sensory neurons that innervate the uterus and the colon, and its expression is elevated in ectopic and eutopic endometrium (Ding et al., 2017) and in peritoneum in women with endometriosis (Greaves et al., 2014), and lesional P2X3 expression correlated positively with the severity of pain (Ding et al., 2017). These findings make P2X3 a candidate protein that may be involved in endometriosis/adenomyosis-associated dysmenorrhea and other types of pelvic pain (Chaban, 2008), and is worthwile investigating. Indeed, treatment with A-317 491, a selective P2X3 receptor antagonist, delivered by glycolipid-like polymeric micelles to mice and rats with induced endometriosis, is reported to reverse mechanical and heat hyperalgesia (Yuan et al., 2017a). While these data strongly suggest the involvement of P2X3 in endometriosis-associated pain, it also should be noted that it is not the only purinoceptor that is involved in pain or inflammation. P2X7 and even P2Y receptors, for example, also have been known to play important roles in pain and inflammation (Hughes et al., 2007; Burnstock, 2013). Before a systematic assessment of the roles of each and every P2X and P2Y receptor in endometriosis-associated pain and inflammation, there is a question of whether or not P2X3 is the ideal target, and whether it will be effective against any other endometriosis-related symptoms such as abdominal adhesion formation, invasive behavior or subfertility.

The most exciting drugs in the pipeline at this point are the oral GnRH antagonists, of which Elagolix is the most advanced program and is poised to get Food and Drug Administration (FDA) approval. It is the first drug in its class, being an orally active GnRH antagonist, and a true revolution in the field of endocrine disorders. However, even though it is innovative from a chemical class point of view, it is far less so from a mechanism of action point of view, as it still aims to modulate the HPG axis through a validated target and may still share the same side-effects as its agonist counterpart. Granted, it can eliminate the ‘flare-up’ phenomenon, but its promise of more precise control of estrogen production could be seriously subverted by the vast inter-individual variations in response to the drug. While the trial used placebo as a comparator, which was required by regulatory agencies, for a drug that will be presumably expensive and interferes with ovulation and other normal physiology yet still not sufficiently investigated, one could argue that a more appropriate and relevant comparator would be progestins, which are well studied in the context of endometriosis/adenomyosis.

Interestingly though, now that one company has recognized the prospect of oral GnRH antagonists in the treatment of endometriosis/adenomyosis as well as in a wide range of other endocrine disorders, other companies—eight, to be precise—are also pursuing this drug class, which seems to epitomize the risk-averse attitude of companies.

Consequently, it seems that other than the oral GnRH antagonists, there are hardly any noteworthy innovative therapeutics in the pipelines that have the potential to revolutionize endometriosis/adenomyosis therapy for at least the coming 5–10 years. This glaring innovation drought is a really serious problem that should concern all patients, healthcare providers, policy-makers and all investigators working in this area.

Dissecting failed clinical trials in light of the natural history of ectopic endometrium

Obviously, we are doing a very poor job in predicting clinical benefits and risks, which 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 optimal drug for this particular target and indication. But why is it that endometriosis/adenomyosis drug R&D is now in such dire straits? What we do know is that apparently we do a very poor job in predicting the safety and efficacy of the drugs. This is not unusual as most drug development programs fail after reaching the clinical stage, and in this regard Women's Health programs have the worst performance (Kola and Landis, 2004).

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 (Cook et al., 2014). Focussing on the reasons 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 (Cook et al., 2014). However, in the phase II studies the primary cause for ceasing drug development projects turns out to be the lack of efficacy. This is counter-intuitive, 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.

For endometriosis and adenomyosis, a more likely explanation for why these trials failed is the lack of understanding of the natural history of the ectopic endometrium, which comes to light only recently. In the next section we attempt to dissect a few cases of unexpected failures of compounds that have been tested in clinical trials based on preclinical data that were available then and now, in the light of the ReTIAR theory.

The failed clinical trials in endometriosis on non-hormonal drugs highlight the fact that the harm-benefit (efficacy) ratio of these drugs is also mostly tilted because of lack in efficacy. The lack of efficacy that at least some drugs may have could very well be related to the fact that it is becoming increasingly clear that endometriosis and adenomyosis are fibroproliferative diseases rather than endometrium-derived disorders (Guo et al., 2015; Zhang et al., 2016a, b, 2017b). So much so that a recent paper even proposed to change the definition of endometriosis to include its pro-fibrotic nature (Vigano et al., 2017). All lesions are associated with α-smooth muscle actin positive fibromuscular tissue (Donnez et al., 1996; van Kaam et al., 2008; Odagiri et al., 2009). Fibrosis is renowned for the fact that it is really difficult to treat, in part because the fibrotic areas are poorly vascularized (Liu et al., 2018c), and also because the excessive production of extracellular matrix leads to increased interstitial tissue pressure that impairs blood flow (Lutz et al., 2012; Provenzano et al., 2012). In addition, myofibroblasts are known to gain resistance to apoptosis induction (Jelaska and Korn, 2000; Nishida et al., 2005). Conceivably, the low vascularization combined with reduced expression of PR in the fibrotic tissues (Liu et al., 2018c) are the major determinants for failure of the traditional hormonal and many non-hormonal drugs.

It should be noted that, due to the non-transparent decision-making process in the corporate world, people outside the company are typically not privy as to why a particular R&D program did not advance to the next development stage. Given the lack of transparency, the best we could do is try to identify the most probable culprit(s) that are responsible for the failure based on the best available evidence.

The raloxifene trial: surprising exacerbating effects

Raloxifene was one of the drugs for which development was ceased, not only because of a lack of activity, but also a worsening of the clinical endpoint—time to post-operative relapse of pain.

Raloxifene is a selective estrogen receptor modulator (SERM), approved in the USA in 1997 for the prevention of postmenopausal osteoporosis, and more recently for the treatment of postmenopausal osteoporosis. It binds to both estrogen receptor (ER) subtypes α and β, with an affinity similar to 17β-estradiol (Bryant *et al.*, 1999). Depending on the expression of ERα and ERβ, as well as co-activators and co-repressors, raloxifene has tissue-specific activities and can either act as an estrogen agonist, like, for instance, on bone, serum lipid metabolism, and a number of coagulation factors, or act as antagonist, as f.i. on breast and uterus (Delmas *et al.*, 1997). Since endometriosis is an estrogen-dependent disease, the thinking went that estrogen antagonism or the suppression of estrogen production should have therapeutic effect (Vignali *et al.*, 2002).

Indeed, in ovariectomized rats, it has been shown that raloxifene does not stimulate the endometrium and inhibits estrogen-induced endometrial proliferation (Black *et al.*, 1983, 1994; Fuchs-Young *et al.*, 1995; Sato *et al.*, 1995). Raloxifene has undergone some testing in animal models of endometriosis, and as expected it was able to suppress ectopically transplanted endometrium in intact and ovariectomized, estrogen-supplemented rats (Swisher *et al.*, 1995; Yao *et al.*, 2005). Head-to-head comparison also indicated that raloxifene is as effective as aromatase inhibitor in suppression of lesion volume in rats with induced endometriosis (Altintas *et al.*, 2010). The drug profile seemingly satisfied a lot of the requirements for an endometriosis therapeutic, but it came as a complete surprise when Stratton *et al.* (2008) reported the early termination of a randomized placebo-controlled clinical trial to evaluate whether raloxifene (180 mg daily) improves post-operative pain relief. Quite unexpectedly, patients treated with raloxifene experienced return of pain sooner.

The cause for the failed raloxifene trial has been attributed to the dose used in the trial, which is less than the weight-adjusted effective dose in animal studies (Naqvi *et al.*, 2014). Indeed, a rat study clearly demonstrated dose-dependent regression of ectopic endometrium (Yao *et al.*, 2005). In addition, SERMs block the feedback inhibition of sex steroids on the hypothalamus and pituitary, and the resultant ovarian stimulation and increased estrogen production may have contributed to the failure of the trial (Naqvi *et al.*, 2014). However, if dose were the culprit for failure, then the raloxifene group should have a comparable outcome to the placebo one, but not worse. Moreover, the trial actually reported significantly reduced bone mineral density in the raloxifene group, with a few cases of vaginal dryness (Stratton *et al.*, 2008), suggesting that, at least systemically, the estrogen production may have been decreased after taking raloxifene of the given dosage and that the dosage seemed to have worked as intended.

Similar to estrogen and other SERMs (Canonico *et al.*, 2008), the use of raloxifene is associated with an elevated risk of venous thromboembolism as compared with placebo (Grady *et al.*, 2000, 2004; Barrett-Connor *et al.*, 2006). Raloxifene has been reported to increase tissue factor protein expression in platelets (Jayachandran *et al.*, 2005), inhibit endothelial production of tissue factor pathway inhibitor 1 (TFPI) (Dahm *et al.*, 2006), and to accelerate platelet aggregation (Minamitani *et al.*, 2008). Since the roles of platelets and coagulation in the development of endometriosis are now well established (Ding *et al.*, 2015; Wu *et al.*, 2015; Zhang *et al.*, 2017a, b, 2016a, b), it is possible that raloxifene failed because it actually intensified the hypercoagulable state in women with endometriosis, resulting in the growth, instead of suppression, of endometriotic lesions. In addition, platelet activation also results in the release of platelet-activating factor (PAF) and thromboxane A2 (TXA_2), but PAF can induce uterine contractility (Montrucchio *et al.*, 1986; Tetta *et al.*, 1986; Medeiros and Calixto, 1989; Hellman *et al.*, 2018), so can TXA_2 (Shaala *et al.*, 1984; Dyal and Crankshaw, 1988). TXA_2 could also induce hyperinnervation (Yan *et al.*, 2017a). Hence, taking raloxifene could lead to increased uterine contractility and hyperinnevation, resulting in more intense pain. This is highly plausible since the time-to-return-of-pain appeared to diverge at around 1 year after taking raloxifene (Stratton *et al.*, 2008), which may be sufficient for regrowth of residual lesions or establishing lesions *de novo*.

Alternatively, the pain exacerbating effects of raloxifene may have been mediated through ERβ. The trial was initiated under the general assumption that the SERM activity of raloxifene would be beneficial for the patients. Meanwhile investigators demonstrated that ERβ expression is strongly elevated in endometriotic tissue as a result of demethylation of the gene promoter region (Bulun *et al.*, 2012), and that ERβ, binding to estradiol with the same affinity as ERα, could be a key player in the pathophysiology of endometriosis. Raloxifene is not only a SERM for ERα, but also a potent ERβ antagonist. Moreover, others showed that co-culture of sensory neurons with an ERβ agonist elevated expression of nociceptive genes (Greaves *et al.*, 2014). Recent evidence showed that when activated, ERβ was actually antinociceptive in models of neuropathic and visceral pain (Cao *et al.*, 2012; Piu *et al.*, 2008), indicating that suppression of ERβ function may actually worsen the symptoms. This knowledge, if known earlier, could very well have made the decision-makers think twice before launching the clinical studies at that time, as it would clearly point to a mechanism in which raloxifene may pose a risk for the patient. Regardless, the publication of the trial results helped get to the bottom of the failure.

This analysis may also shed light on a mystery as to why a fulvestrant trial apparently failed. Almost 20 years ago, a clinical trial on the use of fulvestrant, an antiestrogen, was launched with great fanfare (Johnston, 2002). Yet in contrast to its boilsterous launch, it ended unceremoniously without a trace, and presumably foundered. Since fulvestrant has been approved for the treatment of breast cancer, its safety is not a problem. Hence, it presumably must be the efficacy that ended the trial. Since fulvestrant also has been shown to inhibit endothelial production of TFPI (Dahm *et al.*, 2006) and thus may facilitate hypercoagulation in endometriosis, it may also have worsened the pain in women with endometriosis, just like raloxifene. Alternatively, it may have no suppressive effect on the growth of ectopic endometrium (Wu and Guo, 2006) and it suppresses ERβ, which could be antinociceptive as alluded to above.

The ERB-041 trial: unexpected lack of efficacy

Since raloxifene, an ERβ antagonist, caused earlier relapse of post-operative pain in women with endometriosis (Stratton *et al.*, 2008), and the fact that selective ERβ agonists were antinociceptive in animal models of neuropathic pain (Piu *et al.*, 2008; Cao *et al.*, 2012), one would expect that a selective ERβ agonist would be effective in women with endometriosis. In a human endometrium xenograft model in athymic nude mice, it was indeed shown that treatment with ERB-041, a selective ERβ agonist, initiated 11–14 days post induction in mice with endometriosis, significantly reduced the number of lesions by ~82% (Harris *et al.*, 2005). The authors also published a review paper summarizing the anti-inflammatory properties of selective ERβ agonists (Harris, 2006). Two Phase II trials (NCT00110487 and NCT00318500) were launched, both sponsored by Wyeth (now a subsidiary of Pfizer) and completed over a decade ago.

It is likely that the promising preclinical study (Harris *et al.*, 2005) could have influenced the company to launch the trial. However, with the benefit of hindsight and also of the recent discoveries showing the pro-fibrotic nature of endometriotic lesions, it is very likely that the period of 11–14 days is simply too short for lesions to contain any fibrotic tissues (Zhang *et al.*, 2017a, b) as most human lesions do, in part because of the diagnostic delay (Hadfield *et al.*, 1996). Assuming 2 and 70 years of lifespan for nude mice and humans, respectively, the period between the implantation and treatment is 11–14 days for mice or slightly over 1 year for humans. One year is simply too short for the accurate diagnosis followed by medical treatment of endometriosis in humans. On the other hand, if the lesions are 'young', inflammation, which occurs in the early stage of wound healing, is at its peak and ERB-041 could well be very effective. Of course, the valididty of such a linear correlation between lifespan and lesional age across humans and rodents is debatable since, in the absence of any data in support of, or against, such a correlation, the assessment of the lesional age in humans could go either way. However, it does raise the issue as to whether or not this animal model of endometriosis fully recapitulates its human counterpart. If the answer is negative, then it means that ERB-041 treated the wrong disease. Granted, ERB-041 may be effective if one can diagnose the presence of endometriotic lesions within, say, 1.5 years after their establishment. Unfortunately, currently there is no such method to accomplish this task.

The Infliximab (anti-TNF-α antibody) trial: an avoidable failure

It is well known that inflammatory cytokines, such as tumor necrosis factor (TNF)-α, are elevated in the blood and peritoneal fluid of women with endometriosis (Eisermann *et al.*, 1988; Bedaiwy *et al.*, 2002). However, another well known fact is that NSAIDs are actually not effective for the management of pain in women with endometriosis (Brown *et al.*, 2017), which indicates there is quite some redundancy among the inflammatory mediators.

TNF-α effects are transmitted via cross-linking of two different membrane bound receptors (TNFRs): a TNFR of 55 kD (p55 or TNFR type I) and a 75 kD (p75 or TNFR type II) receptor. The soluble forms of both receptors, deriving from the shed extracellular portion of the TNFRs (Nophar *et al.*, 1990), are able to inactivate TNF activity by formation of high-affinity complexes, thereby hampering the binding of TNF to target cell membrane receptors. The soluble TNFRs were first purified from human serum and urine and termed TNF binding proteins, TBP-1 (p55-sR) and TBP-2 (p75-sR) (Engelmann *et al.*, 1990).

A single-center, randomized, double-blind, placebo-controlled clinical trial (NCT00604864) on the use of Inflixmab to treatment deep endometriosis-associated pain, which recruited 21 women with deep endometriosis, was published in 2008 (Koninckx *et al.*, 2008). During the 12 week treatment period a similar exponential decrease in pain of some 25–30% was observed in both the control and the infliximab group, and no statistically significant difference was found between the two groups (Koninckx *et al.*, 2008). The authors attributed the failure of the Inflixmab trial to the pathophysiology of the severe pain associated with deep endometriosis, which is supposedly different from that caused by typical lesions, i.e. inflammation might be more important in superficial peritoneal endometriosis whereas nerve invasion or compression is more important in deep lesions (Koninckx *et al.*, 2008).

However, a more likely explanation for the failure is that in published preclinical studies, which all showed promising therapeutic potential for blocking the TNF-α pathway, the animal models used were not representative of the deep endometriosis that was evaluated in the trial, or other signals in the studies were not picked up or duly appreciated. One of the earliest studies reported that the administration of recombinant human TNF-α binding protein-1 (r-hTBP-1) in rats with ectopically transplanted endometrial tissue resulted in defective development of implants compared with controls (D'Antonio *et al.*, 2000). Three weeks after transplantation of the endometrial tissue, the animals underwent a second laparotomy to evaluate the size and viability of the ectopic lesions, and drug treatments started 1 week later. Hence, the induced endometriotic lesions only had a total of 4 weeks to develop, which is approximately the equivalent of ~2 years for humans. In other words, the induced endometriosis may not have had sufficient time to develop into a more advanced disease, which is usually associated with fibrosis. Again, caution should be exercised when inference is made based on such parallelism. However, the issue of whether or not the animal models used in preclinical studies recapitulate the key features of human endometriosis is not addressed.

Anti-TNF-α therapies were also extensively investigated in non-human primate models with spontaneous or induced endometriosis. The baboon antibody c5N, which is the equivalent of Inflixmab in humans, was tested in baboons (*Papio anubis*), in which endometriosis was induced by laparoscopic seeding of endometrial tissues, harvested through curettage, into the pelvic area (Falconer *et al.*, 2006). Twenty-five days later, a second laparoscopy was conducted to quantify and stage the extent of induced endometriosis, after which the treatment was commenced. Twenty-five days after the treatment, a third laparoscopy was conducted to quantify and stage the endometriosis. The total lesional surface area and volume was significantly reduced by 25.1 and 22.6%, respectively, in baboons treated with c5N, while they were increased by, respectively, 5.5 and 11.3% in the placebo group. The authors concluded that anti-TNF monoclonal antibody therapy may have therapeutic potential for active peritoneal endometriosis (Falconer *et al.*,, 2006). In retrospect, it should have been a first warning that anti-TNFα therapies should do well for newly formed or red lesions, but not for advanced, fibrotic lesions, since the number of non-red lesions was actually increased by 58.6% in the c5N treated group.

In baboons, endometriotic lesions typically do not show any signs of fibrosis until 6 months after induction (Zhang *et al.*, 2016a, b), and the period of 25 days, or <1 month, between induction and the start of treatment is very likely to be too short for fibrosis to develop. Of course, the second laparoscopy, as a surgical stress, may have precipitated the lesional development (Liu *et al.*, 2016a, Long *et al.*, 2016), but 25 days for baboons, equivalent to ~3 months for humans, may still be too short for lesions to develop a phenotype similar to deep-invasive endometriosis in humans.

This assessment can be supported by another published baboon study. Etanercept, a fusion protein consisting of human recombinant soluble TNFRII (p75) conjugated to a human Fc antibody subunit which can neutralize TNF-α activity, had been evaluated in a model of spontaneous endometriosis in baboons (Barrier *et al.*, 2004). In that study, the average age of the baboons was 10.8 years, and thus it was possibly a model that presumably mimicked its human counterpart quite closely. The study was carefully conducted, separating lesions with different colorations into red, black and white, which roughly correspond to younger, intermediate and older lesions, respectively. Interestingly, the study reported that the size of peritoneal red lesions was significantly decreased in comparison with a control group, whereas the sizes of black and white lesions were not. In fact, the total surface area for white lesions, that were much older, was even increased after treatment (Barrier *et al.*, 2004). Hence, the authors concluded that etanercept effectively reduces the amount of spontaneously occurring active endometriosis in the baboon (Barrier *et al.*, 2004). However, similar to the study of Falconer *et al.* (2006), no evidence was found that anti-TNF-α therapies would provide therapeutic benefit for older lesions or advanced disease (Fig. 3).

In view of the above, it seems that all preclinical studies on TNF-α neutralization relied on animal models of endometriosis that simply do not recapitulate their human counterpart, especially for deep endometriosis, or used the animal model that is closest to the human condition but interpreted their data incorrectly—sort of perceiving a half-full glass as a glass full of water. These studies may simply provide false hopes, resulting in unrealstic expectations for TNF-α neutralization treatment and, ultimately, the failure of the Inflixmab trial.

Trials on SPRMs: the jury is still out

SPRMs are a class of PR ligands that exert tissue-selective progesterone agonist, antagonist, partial or mixed agonist/antagonist effects on various progesterone target tissues such as endometrium (Chwalisz *et al.*,

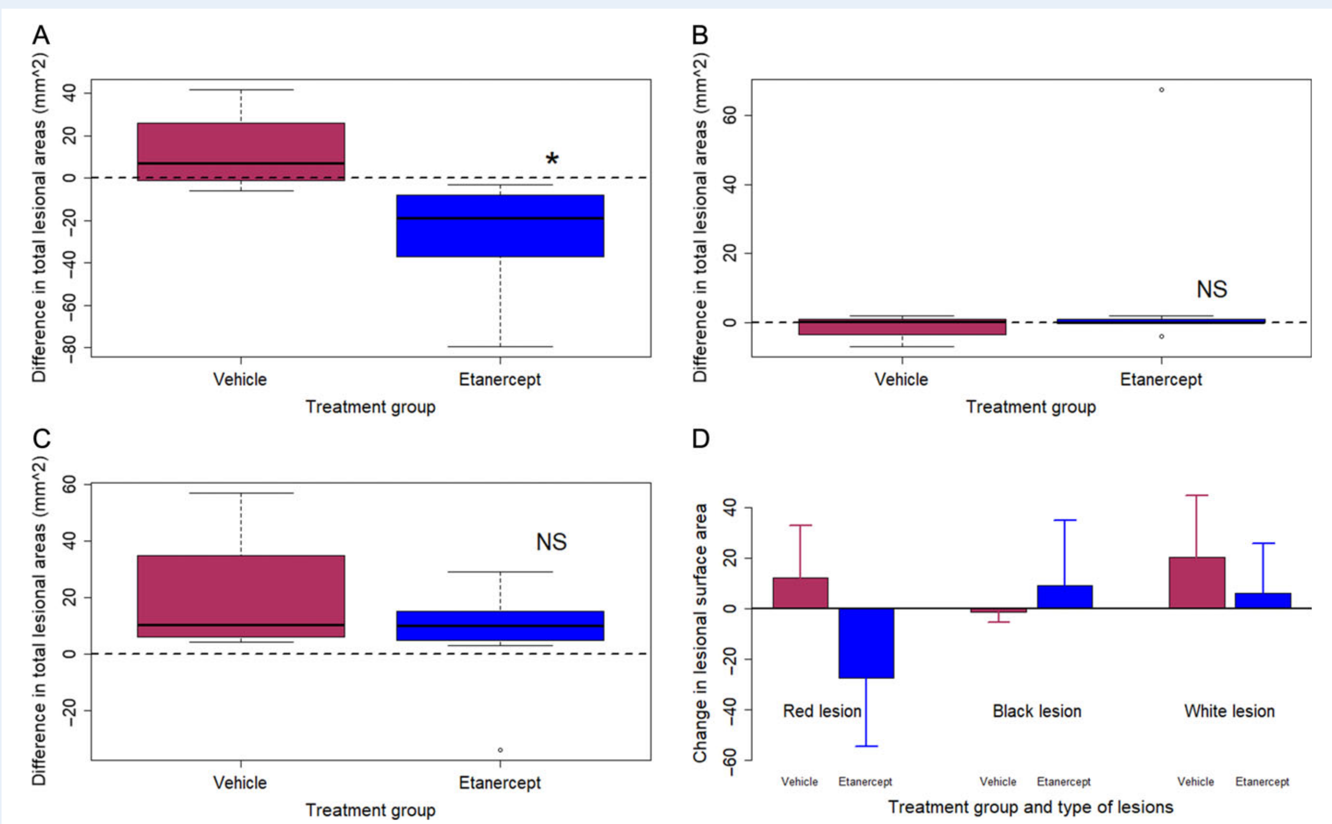

Figure 3 Boxplot of the change in lesion surface area before and after treatment in baboons (*Papio Anubis*). Treatment was with c5N or placebo for red lesions (A), black lesions (B), and white lesions (C) in baboons with spontaneous endometriosis. (D) Summary of the average changes in total lesion areas before and after treatment for the two treatment groups and different lesions. Data are represented by the mean and SD. The data are extracted from Table I in Barrier *et al.* (2004). *$P < 0.05$; NS: $P > 0.05$, by Wilcoxon's rank test.

2005a, b). Currently, the SPRMs include mifepristone/RU486, onapristone/ZK 98 299, lilopristone/ZK98734, lonaprisan/ZK230211, aglepristone, asoprisnil/J867, proellex/CDB-4124/telapristone, UPA/CDB-2914, JNJ-17 072 341 (an SPRM synthesized by Johnson and Johnson) and vilaprisan/BAY-1 002 670. These compounds differ in their progesterone agonistic/antagonistic activities, with onapristone, lonaprissan, vilaprisan and mifepristone at the extreme of the antagonistic end, asoprisnil at the other end of the agonistic end, and others somewhere in between, in the progestin agonistic/antagonistic spectrum (Chwalisz *et al.*, 2005a, b).

Although mifepristone was the first SRPM tested on human endometriosis in 1991 (Kettel *et al.*, 1991), its formal registered trial had to wait for over 20 years (Carbonell *et al.*, 2015). In the interim, well over 100 trial-like studies have been conducted and then published in China (Guo *et al.*, 2011). Unfortunately, due to poor design, execution, data analysis and reporting, no credible conclusion regarding the indications, dosage, efficacy, and adverse events can be drawn (Guo *et al.*, 2011).

The Phase III trial on mifepristone (NCT02271958), sponsored by Mediterranea Medica S. L., was completed in December, 2013, and later published in a journal not indexed by PubMed (Carbonell *et al.*, 2015). It reported a double-blinded, randomized trial on the use of three doses of mifepristone (2.5, 5 and 10 mg per day) versus placebo to treat laparoscopically confirmed endometriosis. The diagnostic laparoscopy was performed but apparently did not remove lesions. The mifepristone was administrated for 6 months but for the placebo group, only 3 months. No justification was given as to why there is such a discrepancy. At the end of the treatment (presumably 3 months for the placebo group but 6 months for all mifepristone groups), a second laparoscopy was performed. The primary outcome measures were the presence or absence of dysmenorrhea, and the revised The American Society for Reproductive Medicine scores.

The authors concluded that mifepristone is efficacious, especially the 5 mg group, in treating endometriosis. However, a close reading of the paper indicates that the mifepristone treatment dose-dependently resulted in amenorrhea in 78.6–98.9% of patients (as compared with 1.1% in placebo group) 3 months after treatment, and in 85.9–88.6% of patients 6 months after treatment (no data for the placebo group) (Carbonell *et al.*, 2015). Nonetheless, the authors report that mifepristone treatment resulted in a significantly lower prevalence of dysmenorrhea (1.1–10.2%, versus 39.3% in placebo group) and of dyspanreunia (from 1.1 to 10.4%, versus 19.1%) after 3 months of treatment. Mifepristone treatment also resulted in a significantly higher prevalence of hot flushes and of fatigue (Carbonell *et al.*, 2015). Apparently, mifepristone treatment also suppressed ovulation, inducing a hypoestrogenic state, and thus effectively eliminated dysmenorrhea. What is left unanswered is what happened when mifepristone treatment was discontinued.

Similar to SERMs, the tissue-selectivity of SPRM is determined by the expression of the different PR subtypes and their co-activators and co-repressors. One commonality shared by all existing SPRMs, including mifepristone, asoprisnil, proellex, UPA and JNJ-1 707 234, is that they induce a constellation of histopathologic features with the spectrum of PR modulator-associated endometrial changes (PAEC) (Ioffe *et al.*, 2009; Brenner *et al.*, 2010; Whitaker *et al.*, 2017). The cystic changes in the endometrium remain unexplained, but may very well be the result of the observed induction of apoptosis (Nogales *et al.*, 2017) and collapse of stromal vessels in the endometrium (Chwalisz *et al.*, 2000) leading to necrosis and obstruction of the luminal openings of the uterine glands.

The first three trials on the SPRM asoprisnil (NCT00160446, NCT00160433, NCT00160420), all Phase II and all sponsored by TAP Pharmaceuticals, were launched in 2001, 2003 and 2004, respectively. Asoprisnil was shown to induce amenorrhea by directly targeting the endometrium and has direct endometrial anti-proliferative effects (Chwalisz *et al.*, 2000). Early and later studies showed that the amenorrhea is caused by ovulation suppression and the endometrium specific vascular effects in women treated with asoprisnil (Chwalisz *et al.*, 2005a, b; Wilkens *et al.*, 2013).

Since mifepristone is often considered as an anti-progestin *in vivo*, with a potent PR antagonist activity, asoprisnil can be viewed as the first genuine SPRM to reach the Phase II stage of clinical development for the treatment of endometriosis (Chwalisz *et al.*, 2005a, b). The decision to advance was made apparently based on extensive in-house research frequently using expensive non-human primates within TAP Pharmaceuticals, a joint venture between Takeda and Abbott. Some results were summarized in a review paper on the use of non-human primates in drug R&D (Chwalisz *et al.*, 2006) or published only in abstract form (Chwalisz *et al.*, 2004).

A Phase II 4-arm trial on asoprinil did show its efficacy in treating endometriosis-related pain (Chwalisz *et al.*, 2004), but the results have not been published in peer-reviewed journals. Essentially, the trial showed that after treatment with asoprisnil for 3 months, all three dose groups (5, 10 and 25) showed a mean reduction in 4-point pain scores of ~0.5 compared to a decrease of less than 0.1 in the placebo group (Chwalisz *et al.*, 2004). The asoprinil treatment also induced amenorrhea during the entire treatment period in a dose-dependent manner (placebo: 0%; 5 mg: 50%; 10 mg: 71%; and 25 mg: 93%) (Chwalisz *et al.*, 2004), suggesting that the drug also suppressed ovulation in a dose-dependent manner.

Unfortunately, the asoprisnil program did not go further and the trial results have never been published, for several reasons. First, the company shifted its focus from endometriosis to uterine fibroids at that time (Dr Kristof Chwalisz, personal communication). Second, there were issues in study design and the learning curve. In contrast to UPA, which is associated with endometrial thickening early on (starting at 3 months after taking the drug), the cystic endometrial changes due to PAEC and endometrial thickening (as detected by ultrasound) occurred very late (> 8–12 months) during asoprisnil treatment. While the cystic changes were a begnign histology, they nonetheless resulted in an increase in diagnostic and therapeutic procedures and cost. Many believe this is one reason for the termination of the trial (Bedaiwy *et al.*, 2017; Tosti *et al.*, 2017). It was realized at the end of a Phase III trial on uterine fibroids that an intermittant treatment regimen should be used to prevent endometrial thickening, but this would require the launch of another Phase III trial on fibriods. Conceivably, asoprisnil-induced endometrial thickening, if it also occurred in ectopic endometrium, would mean increased lesion size and, as such, more developed endometriosis. Thus, there was concern that asoprisnil-induced cystic endometrial changes, which persisted during the drug-free interval, may also occur in ectopic endometrium. In addition, there was concern over the inconsistent effects on non-menstrual pelvic pain (Dr Kristof Chwalisz, personal communication)—an outcome measure required by the US FDA for approval of endometriosis drugs (Dr Kristof Chwalisz, personal communication). Moreover, there was a rapid return of pain after the treatment was stopped. These factors contributed to cessation of the development of asoprisnil for the management of endometriosis. The dissolution of TAP Pharmaceuticals in 2008 may add the last straw to terminate the project and, understandably, publication of the trial results became a low priority.

There are four trials on proellex (NCT00556075, NCT00958412, NCT01961908, NCT01728454, all Phase II and all sponsored by Repros Therapeutics), but the first two, started in July 2007 and February 2009, respectively, were terminated because of safety concerns (mainly liver toxicity), and the third, started in December 2013, was withdrawn for unknown reasons. The last trial, which substantially lowered the dosages and started in November 2012, was completed in July 2017. Again, the launch of four trials and the completion of one must have been a decision made based on findings from in-house research within the company, some of which were later published (Ioffe *et al.*, 2009). Several SPRMs with a dimethyloamino-phenyl group in the 11th position (onapristone, lilopristone, proellex and, to some extent, mifepristone) all have this problem. In fact, the development of both onapristone and lilopristone was haulted in Phase IIa because of cases of acute hepatitic failure (Dr Kristof Chwalisz, personal communication).

Similar to asoprisnil, proellex administration at all doses caused some degree of ovulation suppression and amenorrhea (Ioffe *et al.*, 2009), although whether it alleviated endometriosis-associated non-dysmenorrhea pain is nowhere to be found in the public domain. Given the documented SPRM-induced PAEC, whether such PAEC-like changes also occurred in endometriotic lesions is unclear. Also, while UPA may be efficacious to alleviate dysmenorrhea due to its amenorrheal effect, it is unclear whether it is efficacious to suppress non-menstrual pelvic pain.

SPRMs have been demonstrated to be very effective in the treatment of uterine fibroids (Donnez *et al.*, 2012a, b, 2014, 2015), which is understandable since these benign growths are mostly progesterone induced. While SPRMs can alleviate dysmenorrhea through induction of amenorrhea, they are a drug class that is not likely to be beneficial for the treatment of endometriosis-associated non-menstrual pain, because these compounds are mostly antagonistic in the presence of progesterone, which is the natural suppressor of estrogenic activity in endometrial tissues, and progesterone resistance mostly due to reduced PR expression levels is a common feature in endometriosis (Lessey *et al.*, 1989; Bergqvist and Ferno, 1993; Attia *et al.*, 2000). In adenomyosis, PR isoform B is reported to be silenced by promoter hypermethylation (Jichan *et al.*, 2010), which likely results in progesterone resistance.

Despite that SPRMs show anti-progestogenic activity, they might still lead to endometrial hyperplasia after prolonged, uninterrupted use (Vercellini *et al.*, 2018). Thus, 'intermittent courses [of UPA] allow menstrual shedding of the endometrium and allow a complete menstrual cycle to take place between each treatment course, with physiological progesterone influence on the endometrium' (Therapeutic Goods Administrations, 2016). In light of the histological changes, there is a concern for the long-term safety for SPRMs in the context of uterine fibroids (Stewart, 2015).

UPA was approved in 2012 by the European Medicine Agency (EMA) for treatment of moderate and severe uterine firbiods. While UPA is shown to have a good long-term safety profile (Fauser *et al.*, 2017), the EMA started a review of women experiencing liver toxicity during UPA use for fibroids based on serious cases of liver failure and liver transplant in late 2017 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/002 041/WC500131813.pdf). On 16 February 2018, the EMA issued recommendations indicating that, while waiting for the final results of the review, all women taking Esmya (UPA) should have a liver function test at least once a month during treatment. If the test is abnormal, treatment should be stopped and the patient closely monitored. Given that two proellex trials were terminated also due to liver toxicity, there is reason to believe that the SPRMs may have the same safety concerns, and this should be resolved in future studies.

While ectopic endometrium is fundamentally different from normal endometrium (Anglesio *et al.*, 2017), and in fact it is also quite different transcriptionally from eutopic endometrium (Wu *et al.*, 2006a), there is a possibility that SPRM-induced atypical changes of ectopically implanted endometrium may increase the incidence of 'ovarian' endometrioid carcinomas. In light of the currently accepted theory that most endometrioid and clear-cell ovarian adenocarcinomas originate from pelvic endometriosis (Kurman and Shih, 2016), naturally there is a concern that SPRM may potentially induce endometrial hyperplasia precisely in women who are already at increased risk of developing endometrioid ovarian cancer (Vercellini *et al.*, 2018).

In addition, given the fibroproliferative nature of endometriotic lesions (Vigano *et al.*, 2017; Guo, 2018) as well as adenomyotic lesions (Liu *et al.*, 2016b, 2018a, c, Shen *et al.*, 2016), there is a real question as to whether SPRMs can have any impact on advanced endometriosis/adenomyosis. More important, since one major motivation for the use of SPRMs in treating endometriosis is to mimic the progestin action selectively in target tissues (Chwalisz *et al.*, 2006), it seems unlikely to reduce the fibrotic content in endometriosis. It is also unclear how it will fare when PR-B is silenced by promoter hypermethylation (Wu *et al.*, 2006b; Jichan *et al.*, 2010), which can be further compounded by reduced vascularity and epigenetic changes (Liu *et al.*, 2018c).

In view of these points and the uncertainty in relieving non-menstrual pelvic pain, there is a doubt that SPRMs can be used as an efficacious therapeutic in endometriosis. Tellingly, in an open-label assessor-blind study on the use of UPA to treat uterine fibroids with co-occurrence of adenomyosis, one recent abstract reported that among 26 women enrolled in the study, six (23.1%) interrupted the treatment because of increased severity of pain. In addition, while the treatment resulted in significant improvement in abnormal uterine bleeding and decreased fibroid volume, it actually exacerbated pain symptoms in more than half of the patients concomitant with an increased junctional zone and number of myometrial cysts, along with worsening adenomyosis, as detected by ultrasound (Ferrero *et al.*, 2016).

At time of writing, one Phase IV trial on UPA (NCT02213081) sponsored by the Northwestern University and another Phase II trial on the use of UPA to treat adenomyosis (NCT02587000), sponsored by Assistance Publique—Hôpitaux de Paris, are underway. A Phase I trial on vilaprisan/BAY1002670 (NCT02975440) was completed in April 2017.

Trial on oxytocin receptor antagonist: dead on arrival?

The oxytocin receptor (OTR) antagonist Epelsiban (NCT02794467) was going to be tested in women with adenomyosis in a Phase II trial (scheduled to start in October 2016). It is currently listed as 'withdrawn', because it was stopped before recruiting any patients. The trial was halted presumably because the program was deprioritized. This was quite unfortunate since as of now there is no effective medical treatment for women with adenomyosis, and the circumstantial evidence that this drug may be effective to treat adenomyosis-associated dysmenorrhea is quite extensive. OTR antagonists have clearly been shown to suppress oxytocin-induced and spontaneous myometrial contractions (Wilson *et al.*, 2001; Pierzynski *et al.*, 2004), and have an acceptable safety profile (Tsatsaris *et al.*, 2004). Moreover, OTR expression is elevated in adenomyosis (Nie *et al.*, 2010), and its expression correlates with the contractile amplitude in myometrial tissues as well as with the severity of dysmenorrhea in women with adenomyosis (Guo *et al.*, 2013). Hence, OTR appears to be a good therapeutic target for treating adenomyosis-related dysmenorrhea. In endometriosis, OTR expression is elevated in uterine junctional zone (Huang *et al.*, 2017) and lesional smooth muscle cells (Mechsner *et al.*, 2005; Barcena de Arellano *et al.*, 2011), the latter probably resulting from platelet-induced smooth muscle metaplasia (Zhang *et al.*, 2016a, b, 2017b).

Preclinical data on the use of OTR antagonists in adenomyosis is scanty, however. Only one paper was published on the preclinical evaluation of an OTR inhibitor, atosiban, in a rat model of endometriosis (Simsek *et al.*, 2012). The authors reported that atosiban treatment, just 4 weeks after endometriosis induction, reduced the size of the lesions, but effects on OTR-mediated functions, such as uterine contractility and pain behavior were not reported. Hence, again, the clinical trial was launched without any preclinical evidence that OTR has any efficacy in treating adenomyosis. In addition, elevated OTR expression may not be the only mechanism underlying uterine hyperactivity in adenomyosis. Vasopressin and prostaglandin F2α may be responsible as well (Price and Bernal, 2001). Moreover, TXA_2 (Wilhelmsson *et al.*, 1981) and PAF (Hellman *et al.*, 2018), which are aplenty when platelets are activated and aggregated, can also be responsible for uterine hyperperistalsis/dysperistalsis in women with adenomyosis. Therefore, there are multiple and redundant pathways that result in uterine hyperactivity and thus dysmenorrhea. Consequently, it is not entirely surprising to see that this drug may have limited efficacy in treating adenomyosis, which might explain its untimely withdrawal.

Barking up the wrong tree?

As eluded to above, the clinical trials on non-hormonal drugs are a parade of intrigue, surprise, and disappointment. Yet the decision to launch these trials certainly was not made lightly. Rather, the decision was made based on the best available data and information then, including, but not limited to, promising *in vitro* data.

The dissection of those presumably failed trials on endometriosis/adenomyosis underscores the importance of knowledge on the natural history of endometriosis/adenomyosis. Indeed, if we knew that the baboon model of endometriosis used in preclinical studies does not recapitulate its human counterpart, we would have insisted on a much longer period between induction and treatment. This may have prompted more scrutiny of the animal models and perhaps would have not advanced the drug development into the phase of clinical trial, at least for ERB-041 and Inflixmab. Or we could have been more critical and discerning on the study showing the efficacy of etanercept in treating spontaneous endometriosis in baboons and not to take its conclusion at face value. We might even have concluded, correctly, that the biological is not likely to work for deep endometriosis, which features smooth muscle metaplasia and fibrosis. Also, had we known that women with endometriosis are in a hypercoagulable state (Wu *et al.*, 2015) and that raloxifene and fulvastrant are pro-coagulable, we might have thought twice before launching the trials on them.

Yet the inadequacy of animal models that likely led to the debacle of many trials should not be construed to mean that results from *in vitro* studies are more reliable. Far from it, in fact. One telling example is that, several years after the presumably failed ERB-041 trial, one *in vitro* study reported that ERB-041 inhibits inducible nitric oxide synthase production in lipopolysaccharide (LPS)-activated peritoneal macrophages of endometriosis through the suppression of nuclear factor (NF)-κB activation (Xiu-li *et al.*, 2009). As elaborated in the following, this study is unfortunately misguided.

Macrophages are known to be a key regulator of tissue repair as they scavenge invading pathogens, remove cellular debris, and express a multitude of cytokines, chemokines, and growth factors, which are necessary to mediate subsequent repair (Shaw and Martin, 2009; Brancato and Albina, 2011). They are known to display heterogeneity and plasticity per lineage and response to the tissue microenvironment (Gordon and Taylor, 2005; Biswas and Mantovani, 2010). They have at least two distinct states of polarized activation: the classically activated (M1) phenotype and the alternatively activated (M2) phenotype (Gordon and Taylor, 2005; Biswas and Mantovani, 2010). M1 macrophages mediate inflammation while M2 macrophages are involved in reparative anti-inflammation, tissue remodeling and pro-fibrotic activity (Wynn and Barron, 2010). Since endometriotic lesions are fundamentally wounds undergoing ReTIAR (Zhang *et al.*, 2016a, b), macrophages have long been reported to be involved in the development of endometriosis (Halme *et al.*, 1983; Zeller *et al.*, 1987; Olive *et al.*, 1991; Gazvani and Templeton, 2002), and recently the M2a macrophage subset, which is actively involved in tissue repair, has been shown to be actively involved in lesional fibrogenesis (Duan *et al.* Revised and resubmitted). Viewed from this vantage point, the results reported in (Xiu-li *et al.*, 2009) appear to be genuine and credible, but are nonetheless unwittingly misguided. This is because the research was performed out of context, making no distinction between different subsets of macrophages, and the finding may have nothing to do with what actually is happening in endometriosis patients, particularly so since given the accumulating evidence that there are multiple subsets of macrophages within endometriotic lesions (Bacci *et al.*, 2009; Itoh *et al.*, 2013; Yuan *et al.*, 2017b), with each subset having different functions. Indeed, unpolarized macrophages do express both ERα and ERβ, and M1 macrophages express ERβ as well (Toniolo *et al.*, 2015). Yet LPS stimulation also downregulates CD163 and CD206 (Toniolo *et al.*, 2015), which are markers of M2 macrophages. In fact, for M1 macrophages, not only ERB-041 can suppress NF-κB activation but also estrogen alone can (Toniolo *et al.*, 2015). Thus, given the increased local estrogen production in endometriosis (Bulun *et al.*, 2006) and that estrogen may enhance IL-4-induced M2 gene expression (Keselman *et al.*, 2017), the problem that study tried to solve appears to be quite contrived.

Examples abound for *in vitro* studies that have seemingly been conducted meticulously yet with complete disregard for the natural history and core drivers of lesional progression. The above study on macrophages is just one of them. Uncritically accepting the face value of the results reported by these studies can lead us astray.

The mishap of the inflixmab and ERB-041 trials seems to suggest that compounds aimed at inflammation exclusively, without any regard for lesional progression, may not fare well. Inflammation is just one of the four somewhat overlapping phases during wound healing, which begins immediately with the passive leakage of circulating leukocytes from damaged blood vessels into the wound (Shaw and Martin, 2009). Although any perturbation in this tightly controlled process can lead to delayed healing, fibrosis or the incomplete healing as in chronic wounds (Shaw and Martin, 2009), endometriotic/adenomyotic lesions may already be highly fibrotic at the time when the patient seeks medical attention due to diagnostic delay. Hence, strategies targeting inflammation exclusively might not be able to change anything, rendering the treatment ineffective.

Most, if not all, published molecular and/or cellular studies of endometriosis/adenomyosis focus on cellular proliferation, invasion, production of pro-inflammatory cytokines/chemokines, autophagy, EMT, angiogenesis, steroidogenesis, lymphangiogenesis and neurogenesis, often using primary endometriotic stromal cells and macrophages. While all these events may be involved in fibrogenesis, so far very little attention has been paid to role of EMT, FMT and SMM in fibrogenesis, especially in the context of ReTIAR. This may be one important reason for why the translational research of endometriosis/adenomyosis appears to progress stagnantly, and may well be responsible for the innovation drought in drug R&D, as eluded to above. This actually raises a serious question as to whether those published *in vitro* studies based on mostly primary endometriotic/adenomyotic stromal cells would help us to find the Achilles' heel in endometriosis/adenomyosis. Since fibrogenesis is the major theme in the development of endometriosis, and since myofibroblasts are the key cell type in the production and turnover of extracellular matrix products, a major focus should be placed on myofibroblasts, instead of fibroblasts/stromal cells or just epithelial cells.

Discussion

We have provided a comprehensive overview on all therapeutics that are in clinical development or have been subjected to clinical testing currently and in the recent past and have shown an unsettling lack of innovation in the current drug R&D pipelines for endometriosis, and in particular for adenomyosis. Despite the high prevalence of adenomyosis and the lack of medical treatment options, it receives far less attention than endometriosis, which is evidenced by just over 2300 PubMed-indexed papers on adenomyosis published in the last 60 years versus ~25 000 papers on endometriosis. Presumably this is related to the fact that hysterectomy effectively takes care of the condition, in contrast to endometriosis, and, perhaps to a lesser extent, to the practice that drugs used to treat endometriosis are often repurposed to treat adenomyosis as well.

The glaring innovation drought and the trickling drug pipelines for endometriosis/adenomyosis should sound alarms to all patients, researchers, gynecologists, pharmaceutical companies, funding agencies and healthcare decision-makers. Even though endometriosis and adenomyosis are the two most common gynecological diseases after uterine fibroids, neither of them have been accorded high-impact disease status, simply because they are benign and they are not fatal. While the awareness of the two diseases is improving, a diagnostic delay is still common. Despite the fact that the diagnosis and management of patients places a heavy burden on society, the endometriosis/adenomyosis research field is not very attractive for young investigators to build their careers owing to inadequate funding. Certainly this has to change.

In addition, despite extensive research, the genomics, transcriptomics, proteomics and metabolomics approaches that have been employed with much anticipation and excitement so far have not lived up to their promises. In this sense, taking stock of all biologicals that are currently in the pipeline and the dissection of apparently and presumably failed clinical trials on endometriosis, as attempted in this study, are very timely, since this, first of all, prompts all stake-holders to become acutely aware of just how unsettling the reality is. In addition, it also urges researchers to scrutinize the traditional ways and methods, and to think of new approaches. After all, failure is more educational and instructive than success. Perhaps it is time for a paradigm shift in research on endometriosis/adenomyosis.

More transparency on clinical trials

The well-documented lack of transparency in clinical trials on endometriosis has changed very little, despite repeated calls for change (Guo *et al.*, 2009; Guo and Evers, 2013). Of course, the issue of lack of transparency is not limited to endometriosis trials per se. In clinical trials in general, non-disclosure is a pervasive problem (Ross *et al.*, 2009; Song *et al.*, 2010; Schmucker *et al.*, 2014; Miller *et al.*, 2015, 2017). The human experimentation that is conducted in clinical trials creates ethical obligations to make research findings publicly available (Anderson *et al.*, 2015). In 2007, Section 801 of the FDA Amendments Act (FDAAA) expanded this mandate by requiring sponsors of applicable clinical trials to register and report basic summary results at ClinicalTrials.gov, and that trial results be reported by the sponsor within 1 year after the completion of data collection for the pre-specified primary outcome (primary completion date) or within 1 year after the date of early termination, unless legally acceptable reasons for the delay are evident (Anderson *et al.*, 2015) (ClinicalTrials.gov. FDAAA 801 requirements (http://clinicaltrials.gov/ct2/manage-recs/fdaaa)). Studies have shown that compliance with the FDAAA provisions is generally poor. An interrogation of over 13 000 registered studies between 2008 and 2013 reported that only 17% of industry-sponsored and 13.8% of non-industry-sponsored studies were published (Anderson *et al.*, 2015). Fortunately, the respective number of published studies increased to 41.5 and 66.6% after 5 years, but in the end roughly 30–50% of the studies still remain unpublished (Bourgeois *et al.*, 2010; Ross *et al.*, 2012; Miller, Korn and Ross, 2015). Encouragingly, pressure for more transparency has been mounting increasingly, as evidenced by the recent launch of the restoring invisible and abandoned trials (RIAT) initiative (http://www.alltrials.net/news/riat-initiative-for-publication-of-historical-clinical-trial-findings/) within the framework of the AllTrials (All trials registered, all trials reported) campaign (http://www.alltrials.net).

The dissection of the failed clinical trials and the excavation of possible causes for failure can be expedited by published trials, such as the raloxifene (Stratton *et al.*, 2008) and infliximab trials (Koninckx *et al.*, 2008). As discussed before, the lack of transparency in pharma-sponsored clinical trials is not going to help future drug R&D in any way. Failure to publish trial results, in particular because of negative results or safety concerns, may unnecessarily expose patients who will participate in trials on drugs with similar modes of action to risks. This practice betrays the very purpose for the mandatory registration, per FDAAA or Public Law 110–85 (Guo *et al.*, 2009). It also betrays the trust that many brave and altruistic trial participants place on trial sponsors, who have put themselves purposefully at risk by volunteering for clinical trials in the hope that a better treatment for endometriosis might be discovered. Without any disclosure of the end results of the trial, nobody will benefit from hard-earned lessons to be drawn from failed trials and everybody will be condemned to repeat others' mistakes and miscalculations.

In addition to many benefits of sharing data—positive or negative—with the scientific community, there are compelling moral and ethical reasons for transparency (Brassington, 2017). While some patients participated in clinical trials because they may benefit from receiving otherwise unavailable treatment, many may simply have done so mainly because of altruistic motivation. Regardless of their motives, they participated in trials knowing completely that there is a certain degree of risk of experiencing adverse events and/or of inferior efficacy that are intrinsic to all experimental studies. Nevertheless, many of them still chose to take part in the trial, hoping that their participation will generate generalizable medical knowledge that might benefit not only themselves but also other and future patients, so that the trial and other scientific research collectively will eventually improve patient care. However, this can only be accomplished when sufficient details of the clinical trial are made available to the public in a timely manner (Drazen and Wood, 2005).

Moreover, many trials are conducted in public hospitals. Therefore, a certain respect is due to these hospitals and, in the UK, the publicly funded National Health Service (NHS) at large. In fact, since most public hospital physicians in many countries are public employees and are thus morally responsible to their community, independent of the industry financial support for the studies, the trial data should be placed in the public domain within a reasonable timeframe after trial completion, especially when a trial is conducted within public hospitals (or within the NHS in the UK) by investigators paid by public universities. The data may not be owned by private enterprises that use them in light of their benefit, not in the interest of patients.

For these and other reasons, the International Committee of Medical Journal Editors have recently reiterated their commitment to improving trial transparency by sharing individual patient data from RCTs (Taichman *et al.*, 2016, 2017). Recently, the World Health Organization also issued a joint statement on clinical trials transparency, signed by 15 major non-industry research funders (Goldacre, 2017). The statement uniquely and very simply covers all trials, and commits to share results within 12 months of trial completion. More remarkably, it seems to leave no loopholes by specifically requiring that all trial results must be reported on the registry where the trial was registered, not self-published on an obscure industry website that might disappear; not an academic paper that is hard to locate; not the grey literature; not a conference presentation (Goldacre, 2017).

It should be noted that the public disclosure of trial outcomes is not an insurmountable problem when it comes to patient confidentiality issues. GlaxoSmithKline, for example, has publicly committed to share clinical study reports for all clinical trials dating back to 2000 when the company was formed (Kmietowicz, 2013). This demonstrates that 100% trial transparency is achievable.

The validity of animal models

The outcomes of most clinical trials in endometriosis/adenomyosis have been really disappointing, because none of them have yielded an effective treatment with the equivalent efficacy and/or safety profile of the current standard of care. Yet the decision to launch these trials certainly was not made lightly. The decision to launch a trial is most likely to be made based on the best available data about the drug and its mechanism of action, *in vitro* data, animal studies, and a large dose of faith. As alluded to previously, more scrutiny of the animal models and the responses might perhaps have blocked the advancement of drug R&D to clinical trials in endometriosis. The animal studies were sometimes limited to merely the evaluation of drug effects on reproductive functions, which basically confirms the mechanism of action, but is hardly ever an appropriate endometriosis model. The major conclusion here is that the animal models used to date simply do not adequately reflect the deep-invasive, fibrotic lesions found in women with advanced disease.

All the therapeutics that have been tested in clinical trials so far were aimed at suppressing individual mechanisms usually associated with wound repair and tissue remodeling (i.e. cellular proliferation, invasion, production of pro-inflammatory cytokines/chemokines, epithelial–mesenchymal transitions, angiogenesis, lymphangiogenesis and neurogenesis) but also aimed at suppressing ovarian function and blocking estrogen activity. However, the poor vascularization (Liu *et al.*, 2018c) and high interstitial tissue pressure in the fibrotic areas could prohibit the drugs from reaching the target cells, rendering the lesions refractory to medical treatment. In addition, the decreased expression of PR as lesions become more fibrotic (Liu *et al.*, 2018a, c) suggest that the lesions are unlikely to respond well to hormonal treatment. Therefore, the promising results from questionable animal models would likely fool unwitting investigators into believing that the drug is effective.

To avoid such mistakes in the future, the induction period (i.e. from the induction to the start of treatment) in animal models of endometriosis should be sufficiently long to allow fibrogenesis to develop fully. Recently, a mouse model of deep endometriosis mimicking the human condition that is characterized by a high fibromuscular content has been developed (Liu *et al.*, 2018b). The use of the appropriate animal model should improve the chance of a successful drug development program.

Time for a paradigm shift

The dissection of select failed trials has taught us a few useful lessons. First of all, in light of the newly emerged natural history of ectopic endometrium, it becomes evident that many animal models used in preclinical studies in the past simply do not recapitulate the real human conditions and are thus inadequate. This understanding only becomes clear when we have a better grip of the pathophysiology. Second, the natural history and the dynamic nature of several cell types involved in the process tell us that the cellular identity of lesions is simply not immutable. Rather, through active interaction with other cells and mediators in their microenvironment, endometriotic/adenomyotic cells may acquire a new morphology, new function, new phenotype, and even new identity, and collectively drive lesional fibrogenesis. This dynamic view and the importance of microenvironment have not been fully appreciated before. Third, linear thinking, while intuitive, can lead us astray. Just because endometriosis is an estrogen-dependent disease does not automatically mean that an antiestrogen should be effective. However, without carefully evaluating all the other, possibly unintended consequences, failure may be unavoidable. While it may be natural to pound everything with a hammer when the only tool available is just a hammer, extreme caution should be exercised since not everything is a nail.

Fibrogenesis has emerged as a major theme with variations in the development of endometriosis/adenomyosis, and since myofibroblasts are the key effector cell type in the production and turnover of extracellular matrix products, a major focus in endometriosis/adenomyosis should be placed on myofibroblasts, instead of fibroblasts/stromal cells or just epithelial cells alone. In addition, the lesional microenvironment also should be a major focus since increased tissue stiffness due to excessive extracellular matrix production, as well as the continuous presence of activated immune cells within, propagate and facilitate myofibroblast differentiation (Huang *et al.*, 2012; Matsuzaki *et al.*, 2016; Koyama and Brenner, 2017; Wynn and Barron, 2010; Yan *et al.*, 2017b; Duan *et al.*, revised and resubmitted).

Despite the somewhat bleak picture of the current drug R&Ds, there is still hope for the patients. The endometriosis/adenomyosis research community, the women suffering from the disease and their families, primary care physicians, gynecologists, governments, and even companies, all are extremely motivated to make a difference. The newly unearthed global picture of the natural history of ectopic endometrium is now more or less in full view. This view helps us to understand possible causes for failed clinical trials on endometriosis, and calls for a paradigm shift in drug R&D so that we can refocus and reorient future research efforts towards more effective therapies and develop more adequate animal models for endometriosis/adenomyosis. The understanding of the dynamic and progressive nature of ectopic endometrium should also help to identify biomarkers for a non-invasive diagnosis and the identification of key pathophysiological mechanisms and druggable targets, which, in turn, will undoubtedly arouse the interest of pharmaceutical companies.With the establishment of globally harmonized and standardized networks of translational preclinical models and centers of excellence in place, close collaboration between the pharmaceutical companies and academia could hopefully expedite the development of promising drugs.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Acknowledgements

The authors would like to thank Dr Kristof Chwalisz for sharing his expert knowledge and insight on SPRMs and his information on asoprisnil trials. The authors also would like to thank the two anonymous reviewers and the Associated Editor for their constructive comments and suggestions, especially on the use of SPRMs to treat endometriosis.

Authors' roles

S.W.G. carried out the ClinicalTrials.gov and PubMed searches, analyzed the data, and drafted the article, P.G. performed the search of Thomson Reuters Integrity[SM], and integrated the search results into Table I. Both revised and approved the article.

Funding

Grants (81471434, 81530040 and 81771553) from the National Natural Science Foundation of China, and a grant for Shanghai Medical Center for Female Reproductive Disease (2017ZZ01016) from the Science and Technology Commission of Shanghai Municipality.

Conflict of interest

S.W.G. has no conflict of interest to disclose. P.G.G. is currently an employee of Synthon Biopharmaceuticals bv.

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