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Review Article

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The Role of Membrane Progesterone Receptor Associated Proteins in Gynecological and Reproductive Disorders, and Cancers: An Editor's Historical Perspective

Part 3: The Role of mPRs and Immunomodulatory Proteins in Development of Benign and Malignant Tumors and Endometriosis

The Probable Role of PIBF in Allowing Cancer Progression and the Potential for a Novel Highly Effective Treatment

Jerome H Check[1,2*] and Naomi Ganpo-Nkwenkwa[1]

[1]*Cooper Medical School of Rowan University, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ*

[2]*Cooper Institute for Reproductive Hormonal Disorders, P.C. Mt. Laurel, NJ*

[*]**Corresponding author**

Jerome H Check, MD, Ph D, Cooper Medical School of Rowan University, Camden, NJ, USA.

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ABSTRACT

This is the third and final perspective discussing the critical role of membrane progesterone receptors (MPRs) in allowing the achievement of a live delivery, but also its role in allowing malignant tumors to develop and metastasize by negating immune surveillance, and the possible role they play in the development of endometriosis and even uterine leiomyomata. Part 1 discussed the molecular biology of MPRs and their function in allowing both the fetus and malignant tumor to proliferate, invade normal tissue, and evade immune surveillance. Part 2 discussed the role of mPRs in establishing a pregnancy and preventing both miscarriage and preterm labor. This final perspective provides the historical studies involving evidence that drugs that negate the function of mPRs cannot only inhibit cancer cell lines from proliferating, but also demonstrate marked clinical benefit, not only for several types of spontaneous murine cancers, but also very terminal human patients with a large variety of cancers by treating these moribund patients with a selective progesterone receptor modulator (SPRM) especially mifepristone. The hypothetical mechanism of action of SPRMs is by inhibiting the production of immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF) or the progesterone receptor membrane component-1 (PGRMC-1) proteins that occur when the mPR is activated by progesterone (as in pregnancy) or other ligands made by cancer cells. Whereas splice variance of the 90kDa parent protein of PIBF seem to function to inactivate the killing aspects of natural killer (NK) cells, macrophages, and cytotoxic T cells, the parent 90kDa protein may be involved in rapid proliferation of cells and invasion into normal tissue for both the fetus and the malignant tumor. This perspective hypothesizes how this 90kDa parent PIBF protein may also allow endometriosis or even uterine leiomyomata to grow and invade normal tissue and even how it may help eradicate implants to spread to ectopic places. This could possibly explain the paradox of the use of progestins to ameliorate the symptoms of endometriosis or estrogen suppressing drugs, yet also respond to SPRMs which theoretically should increase estrogen simulation of endometrial implants. However, by blocking mPRs and thus inhibiting production of immunomodulatory proteins, e.g., PIBF, SPRMs could improve endometriosis by inhibiting the effect of PIBF on proliferation and invasion of normal tissue.

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Historical Perspective

The original interest of the lead author was cancer immunology. Though we developed a better immunoassay for serum PIBF, our concept was that probably the most important role for PIBF in promoting successful conception with a live delivery is the production of the splice variant immunosuppressive form of PIBF protein in the fetal and placental microenvironment by rapidly proliferating embryonic cells, mesenchymal cells, and trophoblast cells. The contribution of these fetal-placental cells would not add much to serum assays (where the main contribution was from the circulating gamma/delta T cells in the bloodstream which correlate mostly with the serum P level). Thus, we did not think that it would be of much value to measure serum PIBF in infertile women or women prone to miscarriage since we are very aggressive with P supplementation in the luteal phase and during the 1st trimester. Thus, we thought P supplemented women would not yield meaningful results if we measured serum PIBF in the 1st trimester or luteal phase when they are taking extra P. We did think that evaluating serum levels in the last trimester or even second trimester could be of value in creating an effective therapy for preterm labor and possible preeclampsia by emphasizing the importance of restarting P which usually is stopped after 12 weeks. Unfortunately, the maternal fetal medicine department was not interested in that study. Thus, we redirected our efforts in trying to substantiate that cancer cells will utilize the same mechanism as pregnancy, to not only invade normal tissue, but avoid immune surveillance, even though the oncofetal antigens were a lot less immunogenic than the fetal paternal antigens [1].

Even before this concept of mPRs and P induced immunomodulatory proteins was hypothesized, nuclear hormone receptor studies found certain cancers had the nuclear estrogen (E2) receptor (ER)and nuclear progesterone receptor (nPR) present. A beneficial effect was found with blocking the ER in certain cancers by treating with selective estrogen receptor modulators (SERMS) e.g., tamoxifen. Data suggested that one could extend tumor free intervals and extend life [2]. Thus, these findings suggested that the ER was important in the aggressiveness of these cancers and that blocking the ER could inhibit products of the ER that were important for breast cancer proliferation [2]. Thus, it was thought perhaps that the nPR may also be needed for tumor aggression. Therefore, studies were conducted using PR modulators e.g., mifepristone, to see if this type of treatment would provide clinical benefit for cancers positive for the nPR similar to SERMS. However, the results were disappointing [3-5]. There is evidence that the presence of the nPR is protective with less likelihood of recurrence or metastasis in those cancers that are positive for the nPR [6-8]. In fact, for cancers positive for the nPR, it is typical for these malignancies to become more aggressive and metastasize when the cancer loses the nPR [9].

Cell line studies found that the parent kDa parent PIBF protein and the immunosuppressive splice variants were not only secreted by rapidly growing fetal placental cells (e.g., embryotic, mesenchymal, and trophoblast cells) but also by cancer cells [9,10]. Thus, we considered that since PIBF is made by rapidly proliferating cancer cells, to prove the potential benefit of PR antagonists, we should choose a cancer cell line that is not known to be associated with a positive nPR, to not only determine that these human cancer cell lines produce PIBF, but also hopefully show that a PR antagonist/modulator e.g., mifepristone, could suppress PIBF production. Thus, the lead author met with Dr. Srivastava at Roswell Park Cancer Institute in Buffalo, New York to see if he would collaborate using many of his leukemia cell lines for the aforementioned research study. Dr. Srivastava's research over 30 years involved studying protein synthesis by leukemia cell lines. We found that not only do these leukemia cell lines produce PIBF, but we found that there was more mRNA dedicated to making PIBF by far than any of the other proteins that Dr. Srivastava evaluated over 30 years of research [11]. Even more importantly, adding mifepristone to the media markedly down regulated mRNA for PIBF and the PIBF protein itself [11].

Subsequently another research study was performed using different cancer cell lines than those studied by Lachman et al and our study of leukemia cell lines which included 6 different human glioblastoma multiforme cell lines, and these researchers found them all to produce PIBF [10-12]. Even more important, mifepristone was found to inhibit the growth of various cancer cell lines including those that have and do not have nPRs e.g., endometrial cancer; human gastric adenocarcinoma, non-small cell lung cancer and ovarian cancer [13-16]. Others found that supplementing the media with either mifepristone by itself or in combination with some chemotherapy drugs (e.g., cisplatin with or without paclitaxel) can inhibit cancer cell proliferation in ovarian cancer cell lines better than chemotherapy alone [17-20]. There have been other cancer cell lines where the nPR is either present or absent whose proliferation is inhibited by mifepristone e.g., cancers of the central nervous system, prostate, breast and bone [21]. The assumption is that they all are positive for the mPRs.

Since some of these human cancer cell lines are positive for the nPR, and yet PIBF secretion was still present, and was inhibited by mifepristone, it suggested to us that the better prognosis with the nPR present in certain cancers is not through silencing the production of PIBF by rapidly proliferating cancer cells. One other thing to rule out was whether cancers, similar to pregnancy, may also utilize the PIBF found in the serum made by gamma/delta T cells even in the absence of P. Thus, we used our improved PIBF immunoassay to evaluate serum PIBF in patients with cancer. As we suspected, in the absence of P exposure, serum PIBF levels are not increased in patients with cancer [22,23]. Thus, the stimulation of the mPRs making PIBF in rapidly proliferating cells is from some other activating mechanism than P [24,25]. Nevertheless, P can upregulate mRNA for PIBF and the PIBF protein itself when added to the media of leukemia cell lines [11]. Thus, we decided that we would forego any more studies with the improved immunoassay for PIBF and concentrate on determining if PR antagonists/ modulators have any clinical benefit for inhibiting cancer progression. We first studied spontaneous murine cancers and found that mice gavaged with the weight equivalent of 200 mg/day of mifepristone in humans did have significant clinical benefit compared to controls gavaged with olive oil for leukemia, lung, testicular, and prostate cancers [26-28].

Related to the sensitivity of certain parts of the world about drugs approved for therapeutic abortion, mifepristone had an unusual

restriction in that despite the fact that it had a good safety profile, and was non-addicting, and thus no additional risks as seen with narcotics, one could not write the prescription for off-label use unless the physician applied for, and acquired, a compassionate use investigational new drug application (IND) approval from governing bodies (in the United States from the Food and Drug Association). We have demonstrated in anecdotal cases marked extension of life and marked palliative benefits in patients with widely advanced metastatic cancers who had no more treatment options with conventional anti-cancer drugs or a clinical trial. These cancers included colon cancer, thymic epithelial cell cancer, glioblastoma multiforme stage IV, leukemia, leiomyosarcoma, transitional cell cancer of the renal pelvis, renal cell carcinoma, pancreatic cancer, fibroblastic osteosarcoma, urothelial cancer, and non-small cell and small cell lung cancer [29-41]. Almost every patient treated showed some significant benefit [42]. How long the patient lived depended on how close to death they were when mifepristone was started. Some patients who were considered to be within 6 months of death lived more than 5 years with a high quality of life, and the death was frequently from a non-cancerous etiology [36,37,39,41-43]. However, no one failed to show at least some demonstratable palliative benefit compared to their previous anti-cancer therapy.

Generally, the mifepristone was not started until all these conventional and clinical trial drugs failed, and frequently left the patients in a weakened state before starting mifepristone [44,45]. There are more than one P induced immunomodulatory proteins important in the growth and avoidance of immune surveillance in both normal pregnancies and cancer. One of these very important proteins is called the progesterone receptor membrane component-1 protein (PGRMC- 1). There is some evidence that with cancer, PIBF plays a more important role than PGRMCI-1 in preventing metastases, but PGRMC-1 may be more involved in local tumor growth of the primary tumor [46]. There is preliminary evidence that although in high concentration the PR "modulator" mifepristone does suppress the production of PGRMC-1, in the lower serum levels achieved by using 200 to 300mg per day of mifepristone that we have used to treat advanced cancer, the drug actually increases PGRMC-1 [47]. Thus, we believe that the main beneficial effect of mifepristone in ameliorating cancer in the dosages that we use is by suppressing PIBF [48]. Unfortunately, one cannot use higher dosages of mifepristone to suppress PGRMC-1 because in higher dosages, it will block the glucocorticoid receptor and cause adrenal insufficiency.

Larger clinical studies have been thwarted by the lack of interest by oncologists in trying PR modulators for advanced cancer patients, probably, at least partially related, to not being able to reimburse the oncologists for conducting a clinical trial. Thus, we have suggested that this type of immunoendocrine therapy may be more suited for reproductive or medical endocrinologists to treat these advanced cancers rather than the clinical oncologists who usually refer these patients to palliative care or hospice [49]. Considering PGRMC-1, there are some alternative therapies which could appeal to endocrinology research [50].

Hypothetical Relationships Between mPR Immunomodulatory Proteins, Endometriosis, and Infertility

Endometriosis and malignant tumors share the characteristics of ability to invade normal tissues and to spread even outside the uterus or organ of origin. We are not aware of studies evaluating the effect of endometriosis on PIBF and PGRMC-1 levels or vice versa.

Theoretically, at least one could envision the possibility that endometriosis increases local PIBF production. The increase in the 90kDa parent form of PIBF may promote increased invasion into normal tissue, and the increase in the immunosuppressive splice variants may allow growth of endometriotic lesions without immune destruction. Though suppression of estrogen could help shrink endometriotic lesions by inhibiting the development of nPRs, which may be needed for the slower growth of ectopic endometriosis, it may also help to thwart induction of mPRs, thus inhibiting the 90-kDa form of PIBF which may allow invasion into normal tissue of ectopic endometrium, and also suppressing the 35-kDa immunosuppressive splice variants thus negating its possible role of immune rejection of ectopic endometriosis. Thus, one could consider the possibility that at least part of the mechanism allowing proliferation of ectopic endometrium is the increased production of PIBF by endometrial implants. Therefore, suppressing estradiol (E2) production by the ovaries by the use of gonadotropin releasing hormone agonists or antagonists or aromatase inhibitors could, at least in part, cause regression of endometriotic implants by suppressing the induction of both nPRs and mPR receptors by E2, (as mentioned mPRs are needed to make the immunosuppressive proteins e.g., PIBF and PGRMC-1). Since PIBF and PGRMC-1 production are enhanced by the interaction of P with the mPR, the use of a PR antagonist e.g., mifepristone, could also suppress growth or even cause regression of endometriotic lesions by allowing immune destruction of endometriotic lesions by suppressing these immunomodulatory proteins which otherwise would block cellular immune destruction [51-53].

Synthetic progestins or impeded androgens may act as a competitive inhibitor of the interaction of P and its receptor thus inhibiting PIBF and PGRMC-1 production. None of the synthetic progestins were found to stimulate PIBF [25]. Thus, the beneficial effects in reducing pelvic pain with E2 suppression, other than simply causing palliation of dysmenorrhea by the absence of menses, may be at least partially related to immune destruction of endometriotic implants by suppressing excessive PIBF or PGRMC-1 proteins. If the etiology of pelvic pain syndrome with or without documented evidence of endometriosis or adenomyosis is related to a onetime event that allowed the development of ectopic endometrium to gain a foothold, then one may expect to see long term relief after a course of estrogen treatment, similar suppression to antibiotics for infection. However, though sometimes long periods of relief ensue following standard medical or even surgical therapy, frequently symptoms return after a short interlude. Thus, the evidence suggests that this "condition" of pelvic pain and endometriosis is a dynamic process, and without correcting the main etiologic factor (possibly increased cellular permeability), the condition will likely resume after a period of time. We have evidence to support the concept that pelvic pain and many other clinical conditions are related to defects in certain tissues, whether genetic or acquired, that causes increased cellular permeability allowing unwanted excessive irritants to infuse into the tissue causing inflammation and pain [54-57].

When taking GNRH agonists or antagonists, or impeded antigens, or progestins or PR antagonists, achieving a pregnancy is precluded. However, there are many anecdotal reports of the marked benefit of treating pelvic pain and other clinical disorders with dopaminergic drugs [57-57]. Dopamine acts to decrease cellular permeability. If while being treated with the above-mentioned non-dopamine agonists drugs the immunological inflammatory endometrial issues are being obviated., the problem is that either these drugs prevent pregnancy while they are being taken either suppressing ovulation or causing adverse uterine receptivity, e.g., the use of low dosages of norethindrone. The advantage of taking dopaminergic drugs, e.g., dextroamphetamine sulfate, is that not only are they more effective in relieving pelvic pain, but they allow attempts to become pregnant while being taken. Furthermore, there is evidence that they can enhance fecundity especially when the woman is being treated with luteal phase P [54-57].

Many women with pelvic pain and endometriosis have other associated chronic conditions related to increased cellular permeability [55-57]. Sometimes these conditions exist without the presence of pelvic pain, but still suggest an endometrial permeability defect leading to an adverse immunologic milieu as evidenced by correcting very refractory infertility by adding dopaminergic drugs even in those failing to conceive with supplemental P with or without follicle maturing drugs [56-59]. This concept is supported by the marked amelioration of the other medical morbidities at the same time [56,57,59].

It is well known that surgical removal of endometriosis can sometimes provide long lasting relief of pelvic pain However, more often the relief is short lived supporting the dynamic concept that the cellular permeability defect will quickly allow return of the inflammatory state. Because of the potential damage to the ovaries following surgery that can further compromise ovarian egg reserve (which may already be compromised because of chronic inflammation of the ovaries), we favor dopaminergic therapy over surgery except in some rare cases where pain is not relieved by dopaminergic drugs or surgery is needed to correct pelvic adhesions compromising tube-egg pick-up. Nevertheless, the large majority of patients will find pain relief with dopaminergic therapy [60-65].

One question arises, and that is why does the removal of even mild endometriosis implants provide any pain relief even if only for a short period of time [64]? Our hypothesis is that somehow the ectopic presence of these implants further exacerbates the cellular permeability disorder. In fact, we did a study where women supplemented with P in whom all other infertility factors were seemingly corrected for 8 cycles, were laparoscoped. One group without pelvic adhesions agreed to electrocoagulation of mild endometriosis, and in the other group the endometriosis was not removed. They resumed their fertility treatment plus luteal phase P after 8 months; we found that 61% of 69 women whose endometriosis was ablated conceived vs only 18% of 54 women where the endometriotic implants were not removed [63]. Thus, our own studies favor the concept that removal of mild endometriosis can improve fecundity (not all studies agree) but we favor dopaminergic drugs to not only avoid the risks of surgery but to not potentially compromise egg reserve. If, in fact, dopaminergic drugs will reduce the inflammatory state causing egg depletion, possibly dopaminergic therapy could retard somewhat the further depletion of eggs [66].

There is a strong possibility that either surgery or dopaminergic drugs or even the other aforementioned medical treatment options for pelvic pain could improve the endometrial inflammation, but there still is the need to increase mPR immunomodulatory proteins to sufficiently suppress the adverse endometrial immunological environment. Whether P supplementation was provided after surgery or not could explain some of the discrepancies in studies concerning the beneficial effect of surgery for endometriosis in subsequent correction of infertility [64]. If medical treatment other than the dopaminergic drugs has some transient benefit in suppressing excessive endometrial inflammation, it seems logical to also treat this group with supplemental P after stopping these drugs for the purpose of procreation [54].

Treating Endometriosis with Selective Progesterone Receptor Modulators (SPRMs)

Synthetic progestins are well known to improve the symptoms of endometriosis. These progestins include norethindrone and medroxyprogesterone acetate. Since P itself stimulates mPRs leading to the production of PIBF and PGRMC-1, and thus suppresses inflammation, theoretically the use of SPRMs may be counterproductive by suppressing these immunomodulatory proteins, and thus promoting, rather than suppressing premenstrual pelvic inflammation. That is why one 200mg pill of mifepristone can cause autoimmune destruction of the fetus, thus causing a therapeutic abortion. There have been studies evaluating the efficacy of mifepristone or other SPRMs for pelvic pain related to the presence of endometriosis [67-75]. These were all randomized controlled trials (RCTs). Some studies used gastronome which has anti-P effects but it probably should not be considered as an SPRM. These studies were the ones used in a Cochrane Database of systemic reviews entitled "Progesterone receptor modulators for endometriosis" [53]. The conclusion by the authors were stated as follow; "Among women with endometriosis, moderate- quality evidence shows that mifepristone relieves dysmenorrhea, and low-quality evidence suggests that this agent also relieves dyspareunia" [53].

Author's View of the Potential use of SPRMS for Treating Endometriosis

There is considerable evidence that E2 signaling is a major driver for the development of endometriosis [76,77]. Most theories hold that P resistance may be related to increased levels of the enzyme 3 beta hydroxysteroid dehydrogenase (HSD3B) which converts dehydroepiandrosterone into androstenedione which is converted to estradiol (E2), the most potent estrogen, estradiol, is converted to less potent estrogens e.g., estrone. Increased mRNA expression for HSDB3 enzyme and higher HSDB3 activity was found in endometriotic endometrium vs eutopic endometrium [78]. There is evidence that P increases the expression of retinoic acid in endometrial stromal cells which in turn may induce the formation of another enzyme, 17 beta hydroxysteroid dehydrogenase type 2 (17BHSD2). This enzyme converts the potent estrogen E2 to the less potent estrogen, estrone [79]. Thus, theoretically by blocking P actions by an SPRM, this may block the beneficial action of converting potent

E2 to estrone which may increase the estrogen effect for eutopic endometrial growth [80, 81]. Thus, one potential reason for abnormal growth of ectopic endometrium vs eutopic is that the stromal cells of the eutopic endometrium may be less sensitive to the production of retinoic acid and thus retain higher sensitivity to estrogen from lack of converting E2 to estrone. Theoretically blocking the action of P even more by treatment with an SPRM should enhance rather than inhibit growth of endometriotic tissue [82,83].

As mentioned, synthetic progestins have clearly demonstrated amelioration of dysmenorrhea and other types of pelvic pain in women with endometriosis [65]. Related to their high safety profile, lack of expense, and efficacy of synthetic progestins by themselves or combined with ethinyl estradiol, low dosage oral contraceptives could be considered first line therapy for women with exclusive pelvic pain not interested in conception [65]. Dopaminergic drugs may be the better choice for women with pelvic pain trying to conceive. So, the question arises with the potential adverse consequences of using SPRMs for treating pelvic pain associated with the presence of endometriosis why did the meta-analysis by Fu et al find a clear-cut benefit for dysmenorrhea and probably benefit for dyspareunia by using SPRMs? One possible explanation is that by suppressing the production of immunomodulatory proteins e.g., the 90kDa form of PIBF, which allows rapid proliferation of embryonic cells and cancer cells and promotes invasion into normal tissue, that this benefit outweighs the negative benefit of negating the role of P in inhibiting the mitogenic effort for E2 in causing endometrial growth [53]. Since mifepristone is well tolerated and has a good safety record one could consider using synthetic progestins to inhibit the mitogenic action of estrogen and thus reduce pain while concomitantly treating with an SPRM to suppress the 90kDA form of PIBF to inhibit endometrial tissue from invading normal pelvic tissue and inhibit the proliferation of endometriotic cells [81]. One caveat however is that mifepristone seems to work better with malignant versus benign tumors. The clinical benefit of using mifepristone for benign slow growing meningiomas was not that impressive [84]. However, one factor for less impressive results was that meningiomas usually are positive for the nPR [84].

One caveat is that the dosage of mifepristone used that provided relief of pain was 5- 10mg/day whereas all the cancer studies e.g., cell lines, animals, or humans used the weight equivalent of 200mg/day. Thus, the question arises as to whether the lower dosage of mifepristone adequately blocks mPRs sufficiently to inhibit PIBF? As mentioned, since lower dosages of mifepristone even 200-300mg may act as an agonist for PGRMC-1 [50], the assumption is that if SPRMs do, in fact, inhibit proliferation of endometriotic cells and their invasion into normal tissues, it is probably operating by blocking PIBF secretion rather than PGRMC-1[46,47,50].

Obviously since the original use of mifepristone was to be an abortifacient, and indeed one of its two approvals for use is to terminate unwanted pregnancies, if an effective SPRM becomes available in the pharmaceutical market the drug would prevent conception while it is given. Thus, in the opinion of the authors, if a woman has pelvic pain (even if endometriosis is not documented first) but is no longer interested in having more children the authors would start with norethindrone 0.35mg per day continuously or use a lower dosage oral contraceptive (or transdermal or intranasal) If the pain is insufficiently relieved, or if there are vasomotor symptoms, if gonadotropin releasing hormone antagonists are used for treatment, a dopaminergic drug should be used [54-57,85]. The presence s of an extra pelvic pathological condition e.g., Crohn's disease or headaches should dictate the use of sympathomimetic amines that release more dopamine from sympathetic nerve fibers (but also other biogenic amines e.g., norepinephrine) e.g., dextroamphetamine or more pure dopaminergic drugs e.g., cabergoline or even levodopa/carbidopa [54-57,85]. In case of symptoms in multiple organ systems, it would probably make sense to start with a dopaminergic drug but add progestin therapy if the relief of pelvic pain is better but still present.

If an SPRM came onto the pharmaceutical market, the authors' opinion would be to add this type of therapy to progestins and/or dopaminergic drugs if they did not provide satisfactory relief of pelvic pain rather than drugs that markedly suppress estrogen e.g., gonadotropin releasing hormones agonists or antagonists in view of significant side effects from estrogen deficiency both short term and long term, One may question that if a synthetic progestin improves pelvic pain, could the progesterone negate the benefit of the SPRM in inhibiting ectopic endometrial cell proliferation and invasion of normal tissue by stimulating, rather than inhibiting the production of the PIBF protein? This will probably not happen because it has been shown that only P and not synthetic progestins activates the mPR with the production of the PIBF protein [25]. A synthetic progestin may also negate the effect of unopposed estrogen in the endometrium when using an SPRM, causing theoretical (but not observed) an increased risk of endometrial hyperplasia and/or endometrial carcinoma. Progestin and P may activate different receptors.

Possible Role of mPRs in Development of Uterine Fibroids

Uterine fibroids are the most common benign tumors of the female genital tract. They are commonly located in the myometrial smooth muscle cells of the uterus. The prevalence of fibroids is over 3-fold higher in black women compared to white women. They experience earlier onset and more complex disease [86]. Uterine fibroids are associated with abnormal and heavy uterine bleeding, pelvic pain, and reduced fertility [86]. While estrogen (E2) is considered the major mitogenic factor for fibroids in the uterus, clinical studies support the conclusion that progesterone, specifically P4, also plays an important role in hormone-dependent fibroid growth and development [86]. P4 is theorized to stimulate fibroid growth by regulating growth factor function, extracellular matrix (ECM) activity, microRNA expression, and angiogenic growth factors [87-89]. P4 interacts with progesterone receptors (PR-A and PR-B) and nongenomic membrane receptors (including mPRs) to activate signaling pathways [89]. One of the recent proposed treatments for fibroids includes SPRMs which acts through different P4-dependent mediators [90].

Mifepristone works to reduce fibroid size by suppressing genes (e.g. KLF11) associated with cell proliferation and suppressing Transforming Growth Factor-beta (TGF-beta) activity [91,92].

According to the literature, mifepristone is well tolerated by phase I-III studies [93,94]. Asoprisnil, another SPRM, inhibits uterine fibroid growth by downregulating mRNA and protein expression of various hormones including Epidermal Growth Factor (EGF), Insulin-like Growth Factor-1 (IGF-1), and TGF-3, while also inducing apoptosis in fibroid cells [95, 96]. Ulipristal is a SPRM which works through an antiproliferative, proapoptotic, antiangiogenic, and antifibrotic manner in uterine fibroid cells [90]. It does so by decreasing the expression of Bcl-2, and Proliferating Cell Nuclear Antigen (PCNA), and increasing cleaved caspase-3 and cleaved Poly ADP-Ribose Polymerase (PARP); overall increasing apoptosis and inhibiting cell proliferation [90].

Ulipristal is the only SPRM which has been approved in Europe for uterine fibroids with some success [97, 98]. Rozenberg et al elaborates on the types of growth promoting factors that can increase expression of metalloproteinases [98]. The dosage used for fibroids is 5mg/day. For cancer, we have used 30mg/day [99]. All of the aforementioned mechanisms of how P may contribute to the production of uterine fibroids in susceptible women can be all attributed to the production of mPR associated proteins e.g., PIBF. Thus, the mechanism of action of SPRMs in inhibiting these critical pathways for fibroid growth may be by inhibiting these critical pathways for fibroid growth of, may be by inhibiting production of these mPR proteins e.g., PIBF and PGRMC-1, or both.

Conclusion and Summary- Parts 1-3.

The large majority of studies involving the interaction of P with its receptor have involved nPRs. The objective of this opinion/perspective study was to present a somewhat different view as to the role of mPRs in reproductive disorders and general pathological conditions even outside the pelvis. The studies were originally performed to try to determine if malignant tumors may utilize some of the same mechanics as the fetal-semi allograft to proliferate, invade normal tissue, and evade immune surveillance. Based on the authors' scientific studies and the scientific studies of other researchers a model for potential tumor immunotherapy was developed based on the increased knowledge that was obtained related to immune mechanism responsible for spontaneous abortion and was published in 2001 [1]. With more scientific studies, this model has been updated significantly and was published in 2021 [46].

There will probably be many more modifications to this model as more scientific studies are performed, However, there is no question that based on this model it seemed likely that all cancers need the PIBF protein as a result of activating mPRs as long as the cancer is negative for the nPR. Recently, at the 2025 American Association for Cancer Research, our group showed a 66.7% 5-year survival with good quality of life in terminal treatment refractory patients male or female with either non-small cell lung cancer (NSCLC) or SCLC [100].

Based on the cancer model and the role of mPRs in procreation, and the scientific knowledge of the potential role of both nPRs and mPRs in allowing the birth of a healthy baby despite its status as a semi-allograft, and some similarities between endometriosis, cancer, leiomyoma, and fetal development, we created a model to show the potential role of very important mPRs rather than nPRs in the development of the endometriotic implants to proliferate, invade normal tissue, and evade immune surveillance. This may also apply to uterine fibroids.

The hope of any model is to hopefully lead to therapies that can alleviate suffering from pathological entities. Most of the data in treating cancer and endometriosis has been with the SPRM mifepristone. However, there are other SPRMs that are already available on the pharmacological market or are being studied for certain pathological entities. These include onapristone, azoprismil, ulipristal, telapristone acetate, vilapristone and others [90].

On the other hand, studies of the mechanisms related to successful embryo implantation and the delivery of a live baby determined the importance of the need to quickly develop thin- walled blood vessels (spiral arteries) to allow nutrient exchange between mother and fetus. These changes occur quickly beginning in the luteal phase. The uterine arteries during the proliferation phase mostly have thick walls. Neovascularization is a slow genomic process. Thus, to quickly develop new vessels, it was thought that the mechanism must act through membrane receptors whose reactions are much quicker. Since this occurs shortly after P is secreted, the concept was to remodel already existing thick-walled uterine arteries by autoimmune stripping of the cell wall seemed more logical [100]. This led to the concept of P blocking dopamine allowing irritants to infuse into pelvic tissues causing an inflammatory reaction. However, then to prevent subsequent destruction of the fetal allograft by the increased number of natural killer cells, macrophages, and cytotoxic T cells a need exists for the production of immunosuppressive proteins e.g., PIBF and PGRMC-1. The hypothetical model proposes that these immuno-modulatory proteins are secreted from the rapidly proliferating fetal placental cells [101]. These immunomodulatory proteins and their splice variants then act to negate the killing effects of the increased local cellular immune cells.

Based on this model consideration was given to treating pelvic pain with dopaminergic drugs in case of an existing cellular permeability defect exacerbated by the action of P blocking dopamine effect. This defect could be found in other tissues, and indeed endometriosis frequently co-exists with other co-morbidities. This led to the use of dopaminergic drugs that have markedly improved many pathological entities, including but not limited to pain. Thus, studies of mechanisms involved in successful embryo implantation have led to novel highly effective treatments of a plethora of chronic illnesses and advanced cancers [102].

Informed Consent Statement: Almost all patients when they provide their demographics sign a consent that their results without their names or initials may be used for research studies. Rarely does someone not sign the consent, and their chart is flagged and not used. All patients with cancer signed an informed consent not only to use their data but to acknowledge that they are using an approved drug but off-label. All potential side effects were made clear.

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Conflicts of Interest: None

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