

Peptide vaccines in immunocontraception

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Vaccines have been used successfully to treat and eradicate infectious diseases; this has encouraged a major drive towards development of contraceptive vaccines (immunocontraception) as an additional method against rising human and animal populations. Despite three decades worth of research in this field, there are no licensed human contraceptive vaccines and less than ten for use in animals. The development of peptide antifertility vaccines has had a substantial impact on improving safety and specificity of immunogens, but has resulted in efficacy problems. Innovative strategies have been developed to overcome these problems.

Keywords Antifertility, contraceptive, gametes, hormones, peptides, vaccines

Introduction

While global population rates continue to rise, contraceptives remain a crucial medical intervention [1]. Statistics indicate that, annually, nearly 38% of pregnancies around the world are unintended, while 22% end in abortion [2]. Contraceptive requirements are not limited to humans, there is also a growing need for population control in farming [3], in humane castration of companion animals and in pest management [4] (reviewed in reference [5]).

Vaccines have been used successfully to treat and eradicate infectious diseases; this has encouraged a major drive towards development of contraceptive vaccines (immunocontraception), as indicated by the number of recent reviews in this area [1,2,6••7,8,9••]. For decades, there has been a misconception that this could be safely and effectively achieved by simply causing the immune system to produce neutralizing antibodies against reproductive-associated components, in order to prevent fertilization or implantation. Chemically conjugating suitable components, which are often 'self' antigens to a 'foreign' carrier molecule, and co-administering them with an adjuvant have in part demonstrated the feasibility of this concept. However, in the last decade, problems with tolerance [10,11••] and the potential of long-term pathophysiology [9••,12] have led

scientists to examine reduction strategies, such as the identification of specific sequences within the antigen and carrier molecules (B- and T-cell epitopes), to construct peptide antifertility vaccines [8,13]. Unfortunately, in many cases this has resulted in lowered efficacy and inconsistency in responses between individuals. In order to compensate for this, the trend has been to try and improve efficacy by using multiple epitopes [13,14••] or non-protein mimetics [15], integrating adjuvants or immunostimulants into the immunogen [16], or developing constructs to enable adjuvant-free immunization [17]. The most recent innovations include phage-displayed multiple peptides [18] and carrier-free immunogens in the form of retro-inverso peptidomimetics (D-amino acid sequences) [17]. Concurrently, the search for potential vaccine candidates has progressed rapidly, throwing up a multitude of antigens, all facing the same technical hurdles preventing them from advancing to clinical or effective field trials and commercialization.

The molecular targets for immunocontraception can be broadly divided into hormonal, gamete-associated and embryonic components, although there is some overlap between the categories.

Hormone and receptor molecular targets

The hormone targets include gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and the related human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH). For several decades, GnRH was considered the main fertility-controlling peptide, with the function of regulating the synthesis and release of the gonadotropins LH and FSH [8]. GnRH is a small, ten-amino acid peptide and its successful ablation prevents gonadotropin and sex hormone production in both males and females. Therefore, as a contraceptive vaccine for clinical use, it has limitations and requires exogenous hormone replacement to maintain accessory gland function or libido [5]. Subsequently, GnRH vaccines are being developed for cancer therapy [8,19,20], humane castration of farm and companion animals [3] and for population control in pest species [4]. In the last five years, with the development of sensitive molecular biology technologies, over ten isoforms of GnRH have been identified in a number of mammalian species, as well as in tissues outside the brain, which has led to the questioning of the role of these peptides, if any, in reproduction [21,22]. This has resulted in two directions of thought. Firstly, the close sequence homology between the isoforms means that cross-reacting antibodies can neutralize more than one isoform, with unknown consequences and possible long-term health risks. Secondly, some of the GnRH isoforms may be better candidates than the original sequence (GnRH-I) for use in contraceptive vaccines, by virtue of a more specific role in reproduction or due to structural and conformational properties [21] that improve immunogenicity. For example, it has been speculated that the isoform designated GnRH-III is a putative FSH-releasing factor [23] and may have a similar 3-D hairpin loop structure to GnRH-I. Therefore, as

FSH is thought to have a role in spermatogenesis, specific ablation of GnRH-III would target gamete production without affecting testosterone. This has yet to be demonstrated and relies on the ability of specific isoform ablation [24].

In terms of other hormonal targets, the glycoprotein gonadotropin family (LH, FSH and hCG) and their related receptors (LHR, FSHR and hCGR, respectively), provide a range of candidates consisting of large proteins (as opposed to peptides). However, the major restriction is that their α subunits are identical in sequence and, therefore, neutralizing antibodies could potentially eliminate the function of the whole family. Due to this, the strategy has been to use the heterologous β subunit in its entirety in the case of hCG [2], or the β subunit from a different species for FSH and LH [25], or smaller peptide derivatives [26]. LH is not considered appropriate for contraception as it directly affects sex hormone levels and, as with GnRH-I, requires exogenous hormone supplementation [8]. On the other hand, FSH has been considered an attractive option, as it is believed to play a central role in the control of gametogenesis in both sexes [27]. FSH vaccines have mainly been targeted at the male, in the belief that the time is right for both genders to be responsible for family planning [6]. However, it is controversial whether spermatogenesis is wholly FSH dependent in all species and evidence for and against this steadily appears in the literature [28]. The most recent reference to clinical trials using the β subunit of ovine FSH, reported that there was a lack of significant azoospermia in males and some patients experienced hyperprolactinemia [M Rajalakshmi, unpublished data; 29]. A number of suitable peptide sequences have been identified for effective neutralization [26], however, these have not been pursued actively, as funding has not been forthcoming for the β subunit clinical trials. Nevertheless, some degree of success strongly suggests the potential of a combination treatment with other vaccine candidates. Furthermore, studies on non-vaccine contraceptives have demonstrated differences in azoospermia depending on the ethnicity of the volunteers [6]; therefore, it is important not to dismiss this hormone, through the failure of a limited number of pilot studies carried out in one country. FSH also plays different roles during the male lifespan; it functions as a growth factor during development, has a role in puberty and sustains spermatogenesis in adults [30]; these factors have yet to be exploited.

The receptors of FSH have also been considered a suitable target, as they are only expressed on testicular Sertoli cells and ovarian granulosa cells [18,27,30]. Despite being related to the other gonadotropin receptors, the N-terminal sequences of FSH receptors are heterologous and to this effect, several epitopes have been identified with the capacity to prevent binding of the hormone, including residues 18 to 38 [18,30] and 300 to 315 [31]. Recombinant filamentous phage-displayed sequences of residues between 18 and 38 that were used to immunize female mice and sheep caused impaired fertility and reversible inhibition of ovulation, respectively. In prepubertal male mice and goats, there was a transient reduction in fecundity and maintenance of sexual immaturity [18,30]. Again, there may

be potential for combining these peptides with other suitable immunogens.

By far the greatest success has been demonstrated with female-targeted hCG vaccines, which may be a reflection of the resources and considerable effort devoted to this particular target over close to three decades, despite their post-fertilization or abortifacient mode of action. The advantage of using hCG is that it is only present in the female body at pregnancy and is produced by some tumors [25]. Therefore, it is purported that there is no disturbance of menstrual regularity and women continue to ovulate normally [25]. Although several hCG vaccines are in development, in terms of peptide vaccines, only one design falls into this category, which has been constructed against the carboxyl terminal sequence (37 amino acids) to avoid sequence homology with LH [1,2,32]. However, low efficacy levels compared with the whole β subunit vaccines has meant modifications of the formulation before further progression.

One relatively new gender-specific contender worth mentioning is seminal plasma inhibin (SPI) [33]. A peptide (27-amino acids long) from the C-terminal region of human SPI has been used to immunize male rats and rabbits. The antibodies caused agglutination of spermatozoa and reduced fecundity in the rabbits only. Thus, it offers promise with further improvement as a contraceptive in some species, and falls into the next category of molecular target.

Gamete-associated molecular targets

By virtue of their unique role and specific physiological function, gamete-associated targets provide a more promising approach to contraception than hormones. In the male there are a plethora of identified sperm antigens from different species, epididymal secretory proteins and membrane-associated MDC (metalloprotease-like, disintegrin-like, cysteine rich) proteins [9••]. In contrast, there are only a limited number of female oocyte antigens, the zona pellucida (ZP) proteins [12,34] and oocyte membrane antigen (OM) [35].

The goal of vaccination against many of the sperm antigens is to cause spermatozoa agglutination in the female reproductive tract, by IgA and IgG antibodies in cervical mucus [9••]. Potentially, these vaccines could also be applied to males if it were possible to produce effective neutralizing antibodies in the relevant areas of the male reproductive tract [36]. The predicted success is supported by vast clinical data suggesting that human infertility is associated with the presence of anti-sperm antibodies [2]. As proteomic technologies have advanced, the number of putative sperm antigen targets identified has increased, and methods are required to rapidly screen the best candidates [37]. Most of these antigens are used singly as whole proteins, but with an appropriate screening procedure it should be possible to choose the best combinations and epitopes in order to develop multi-peptide vaccines.

Success with multi-peptide constructs has been best demonstrated with the ZP vaccines. As sperm-ZP recognition and binding constitutes the most important event in the fertilization process, molecules involved at this

site remain favored candidates for immunocontraception [7]. The ZP comprises of three biochemically and immunologically distinct glycoproteins termed ZP1, ZP2 and ZP3 [38]. Immunization of females with individual ZP glycoproteins leads to a block of fertility in several animal models. However, it is invariably associated with either a transient or an irreversible alteration in cyclicity, hormonal profile and follicular development in the ovary [2]. To elucidate these problems, attempts have been made to elucidate the appropriate B-cell epitopes, devoid of oocyte T-cell epitopes in multipptide constructs [39]. However, the lack of success in primate trials and the fear of causing permanent premature ovarian failure has meant that, as with GnRH vaccines, ZP vaccines are mainly developed for animal use and in particular for pest management, in species as diverse as seals [40], brushtail possums [34], wild mares [41], deer [42] and elephants [5]. Initial studies have used ZP derived from ovaries, however, the ultimate challenge from an economic manufacturing necessity has been to use recombinant ZP, and to attempt to overcome the inevitable lack of immunogenicity [2] that this has resulted in.

Embryonic targets

One promising vaccine, which is still at the laboratory stage, has been developed against riboflavin carrier protein (RCP), which is involved in yolk deposition of the vitamin riboflavin in the developing oocyte and is the prime mediator of vitamin supply to the developing fetus in mammals [43••]. Active immunization of female rats and bonnet monkeys with small N- and C-terminal haptens of avian RCP prevents pregnancy without causing any adverse physiological effects to vitamin status, reproductive cycles or reproductive-endocrine profile. Denatured, linear RCP N-terminal (residues 3 to 24) and C-terminal (residues 200 to 207) sequences containing B- and T-epitopes, to avoid the use of a carrier protein, are more effective in eliciting neutralizing antibodies capable of interfering with embryonic viability in early stages of development such as before or during peri-implantation [43••]. Helix stabilization, by introducing spaced salt bridges into a C-terminal analog of residues 200 to 219, increased immunogenicity and prolonged contraceptive potential [44].

The mode of action of RCP in pregnancy is poorly understood, but neutralization studies suggest that termination of pregnancy is largely due to failure of embryo implantation [45]. Studies over the decades, including in primates, have demonstrated that low IgG titers against RCP result in normal full-term pregnancies, without the development of a deformed fetus and that there is a critical antibody threshold that terminates pregnancy. It should also be noted that RCP is located on the acrosomal surface of mammalian spermatozoa and active immunization of male animals with denatured RCP also markedly reduces fertility by impairing the fertilizing potential of spermatozoa [46], thus providing an alternative target.

An immunological perspective

In the last two decades, numerous peptide targets for immunocontraception have been identified, yet the availability and prospect of licensed products remains scarce. The main reason for this is the need for contraceptive

products to provide protection in at least 98% of vaccinees. However, due to genetic heterogeneity, immunological responsiveness exhibits a high degree of inter-individual variation, which impacts heavily on the efficacy, reversibility and feasibility of this approach. Our ability to design effective vaccines is also hampered in part by deficiencies in our knowledge of the molecular mechanisms that regulate reproduction, as well as the complexities of the immune system [47••], including the causes of non-responsiveness [2] and, in particular, species differences [5].

Historically, problems experienced with immunocontraception have been caused by the strategies employed to overcome neutralization of 'self-antigens' and to obtain the highest antibody titers. Much of the early work concentrated on finding the most appropriate carrier proteins to enhance the immune response. The best responses were obtained with large carrier proteins [48], including tetanus and diphtheria toxoids [32,49], which resulted in an initial heightened response to both the carrier and the self-antigen, followed by a subsequent suppression in the antibody response to the latter, particularly of antibody subclasses associated with T-helper (Th)1. This phenomenon is known as epitope- or hapten-specific suppression and is believed to be a result of deficient hapten presentation by carrier-specific B-cells [11••]. The realization from this work is that antibody titers may not be as important as the subclass produced [47••], and this may be reflected in the future by the type of epitopes chosen [10,11••,14••], together with the immunostimulants necessary to drive the bias of appropriate Th [50] and memory responses [2,47••,51]. There is also a trend towards development of non-invasive immunogen delivery systems, and a move away from injections, to enable self-administration. However, compatibility with contraceptive immunogens requires a greater understanding of immune responses and a genetic basis, in order to utilize the appropriate vehicles and antigens targeted to a particular reproductive surface. Many studies to date have concentrated on the production of systemic circulating IgG levels, whereas local immune responses, particularly IgA, in the reproductive tract maybe of greater importance. Studies are beginning to show a preferential link between nasal-associated lymphoid tissue (NALT) and the female reproductive tract, which share common homing determinants for primed B-cells [9••].

From a formulation perspective, there is a need for a greater choice of adjuvants with compatibility with the chosen antigens and delivery systems. One problem with much of the research described in the literature is that it has been target driven. This means that in many cases, inappropriate adjuvants, routes of administration or immunization protocols have been used to demonstrate contraceptive feasibility, which bear little relevance to the final intended product. For example, in many cases Freund's complete adjuvant (FCA) and/or intraperitoneal administration have been employed; neither of which are acceptable in clinical- or veterinary-licensed applications, however, they have been used as they result in optimum antibody titers. To date, there are only a limited number of approved adjuvants, and only one for human use, which limits the choice. However, the routes of administration provide better scope, and innovative delivery systems are continuously emerging.

Current status of antifertility vaccines

Comparative data on the most advanced experimental antifertility vaccines have been reviewed in reference [32], describing the formulation composition, target animal species and efficacy. This is based on published literature; however, an examination of websites describing company and organization information provides additional information. To date, there are no human contraceptive vaccines available. The Canadian biotech company IMMUCON Inc has projected that it will have reversible male and female contraceptive vaccines commercialized between 2005 and 2007. These are based on fragments from the sperm acrosomal protein P34. It is envisaged that the male vaccine will provide protection for 12 months, with a 4- to 6-week recovery period following the end of the contraceptive target, while the female vaccine will have a target efficiency period of 18 months. Similar vaccines are envisaged for castration of companion animals (http://www.immucon.com/en/rsrch_vaccine.html).

In terms of animal health, by virtue of the need for less stringent requirements compared with clinical studies, products can be developed at a faster rate and with a greater chance of success. For example, ImmunoVaccine Technologies Inc has developed a ZP-based immunocontraceptive, SpayVac, used in conjunction with a proprietary adjuvant VacciMax, which is a single-shot, multi-lamellar liposome platform consisting of bilayers of phospholipids and cholesterol, designed for rapid uptake by antigen-presenting cells. The immunogen in SpayVac, consists of three porcine ZP components, integrated between the bilayers, and together this construct is administered with an adjuvant. Early studies in seals used 100 µg of antigen emulsified with FCA, administered intramuscularly [52]. A single administration is reported to have demonstrated maximal antibody titers after 3 to 5 months, and ten years later, an overall success rate of 90%. More recently, studies have been described in deer (using a modified FCA, AdjuVac, containing *Mycobacterium butyricum* instead of *M tuberculosis*) and in domestic cats (using an aluminum-based adjuvant). The deer studies have demonstrated less consistent antibody titers (although with 100% efficacy over three years) compared with FCA (<http://www.spayvac.org>); however, the cat studies, despite demonstrating the production of antibodies, demonstrated little effect on pregnancy. This has been attributed to a lack of cross-reactivity of the anti-porcine ZP antibodies with the *in situ* feline ZP targets [53]. Regulatory approval for a pest management vaccine is expected within four to five years.

Development of VacciMax and SpayVac began in the 1990s, around the same time that Zonagen Inc was founded to produce innovative reproductive products for human use, including immunocontraceptive vaccines based on hCG and ZP. The most recent immunogens examined were recombinant proteins, and a lack of efficacy in primate studies resulted in the development of chitosan-based adjuvants (Chito-ZN and Chito-SR) to enhance and confer long-term immunity (greater than 6 months) [54]. However, despite collaboration with large pharmaceutical companies such as Schering AG and Wyeth-Ayerst Laboratories, failure to achieve 100% efficacy and the possibility of ovarian

pathology has meant that further development of these human vaccines has been suspended indefinitely.

Another approach in the development of a clinical vaccine, used by the MRC Human Reproductive Sciences Unit in collaboration with NV Organon, was the use of peptide epitopes from ZP3, in order to reduce ovarian pathology [39]. However, success in reducing pathology led to a lack of efficacy in primate studies, and funding for this research was discontinued in 2000 [M Pateron, personal communication]; thus illustrating the use of three molecular design strategies applied to ZP-based vaccines to fulfill requirements of the final application and their ultimate fate.

Over the past three decades, a number of variations on two main developmental hCG vaccines have been examined; one based on whole β -hCG carried out in India and the other on the C-terminal peptide (CTP) funded by the World Health Organization (WHO) [32]. The most advanced formulation based on whole β -hCG consists of a conjugate linked to an ovine α -subunit (heterospecies dimer), coupled to diphtheria and tetanus toxoid (DT and TT, respectively) and administered alternately with alum and a sodium phythaly derivative of lipopolysaccharide. There was a 20% failure rate following three injections in phase II trials. Subsequently, further clinical trials were suspended, until an enhanced immune response could be demonstrated (http://www.cag.nic.in/reports/union/rep2003/2003_report_5/chapter3.pdf). On the other hand, the CTP vaccine formulation consisting of conjugation to DT, mixed with muramyl dipeptide and Arlcel A to form a slow release depot, caused local reactions at injection sites and phase II trials in the mid-1990s were abandoned. A number of re-formulations and optimizations have since been investigated [55], and in 2003, a partnership with Apton Corp was due to commence phase I trials. Interestingly, AVI BioPharma Inc in collaboration with SuperGen Inc is currently testing a CTP-hCG-DT formulation, CTP-37 (Avicine; AVI BioPharma Inc) in phase III trials to increase the survival rate of patients with pancreatic cancer, again illustrating that depending on the intention of the therapeutic, an accelerated rate of progression can be achieved.

Other commercially available non-contraceptive animal and human vaccines, based on GnRH, have been reviewed in reference [8]. Since then, the vaccines have been assigned the following product names: Prolog (ML Laboratories plc), Norelin (YM Biosciences Inc), GnRH Pharmaccine (Gonadimmune, Apton Corp/GlaxoSmithKline) and UBITH LHRH peptide (United Biomedical Inc). Successful commercialization of these vaccines will likely be achieved in the near future by overcoming efficacy problems, and it is a common trend that companies working on these types of vaccines eventually include immunopotentiators in their portfolios.

Ethical considerations

Often contraceptive research has been blocked for non-scientific reasons, therefore, it is worth drawing attention to some of the arguments. From an ethical perspective, perplexity comes from the idea of immunizing against pregnancy as it evokes an analogy between pregnancy and

infectious diseases [56]. Feminist scholars have severely criticized the idea of reducing pregnancy to a pathological process in which women are seen as 'wombs infected by pregnancy germs' [57]. The use of the term 'vaccine' exacerbates this image and from many religious perspectives, it is ethically untenable to treat pregnancy as if it were a disease [58•]. This is perceived to carry the message that giving birth is wrong and getting pregnant is actually a disease that should be prevented. Controversy is greatest with the vaccines that prevent implantation, which are not considered contraceptive but 'interceptive'; they do not prevent pregnancy but interrupt it, even if at a very early stage and for many people, these vaccines are totally unacceptable [59].

On another level, ethical issues regarding safety question whether even low health risks are ethically acceptable in order to prevent a condition that is not a disease and that can be readily anticipated. This is pertinent to negative effects on future pregnancies and, at present, the possibility of fetal damage cannot be excluded, even if low titers of antibodies below the contraceptive threshold have no apparent side effects on the progression of pregnancy, such as with the RCP and hCG vaccines. In addition, the risk that contraceptive vaccines may provoke sterility or long-term diseases such as autoimmune disorders and testicular or ovarian cancers, is at this stage very difficult to evaluate. This concern becomes even more serious if one believes that contraceptive vaccines are probably destined to be used in vulnerable populations such as deprived adolescent populations in urban areas and disadvantaged people in developing countries, where illiteracy, poor socio-economical conditions and lack of public awareness constitute the worst environment to protect patients.

Finally, many representatives of women's organizations and people in developing countries also object to the lack of user control and the enormous potential for misuse and coercion that this new biotechnology possesses. Theories such as contamination of drinking water or of vaccines used in mass immunization programs have raised fears, particularly with widespread communication over the world-wide web [8]. It is considered that strategies already adopted in veterinary applications and the possibility of using transgenic plants [25] or vectored vaccine in humans [60] without their consent is a real threat. Mainly for these reasons, in 1994, 230 groups and organizations from 18 countries sent an open letter to the main contraceptive research and funding institutions, calling for 'an immediate halt to the development of immunological contraceptives' and a 'radical reorientation of contraceptive research' [8]. On the other hand, a more positive outlook would be to consider the potential that this technology can provide in terms of treatment of disease and provision of contraception at the same time in countries that have this requirement. For example, in the future, it may be possible to produce a contraceptive vaccine that can protect against HIV or other sexually transmitted diseases. As the debate continues, there is also a counter argument that seeks the right to widen access to contraceptives, particularly those that are orientated towards men (<http://www.malecontraceptives.org>).

These views have had some impact on funding, and in particular investment from large pharmaceutical companies.

However, population control ideology should not guide the development of contraceptives, but it seems wise to recommend ethical scrutiny before introducing antifertility vaccines into current medical practice.

Conclusions and future outlook

The future of contraceptive vaccine development will clearly involve a continuation of the intense search for suitable targets and the development of improved immunization procedures that exploit the latest innovations in vaccine technology. Technological advancements from other vaccine fields play an important part in the progression of developments in immunocontraception. For example, use of genomics and proteomics [37], rational design and identification of suitable epitopes [51], and the development of consensus 'string-of-beads' vaccines [14••] with the ability to overcome major histocompatibility complex restrictions and provide broad protection have relevant application to both clinical and animal antifertility vaccines. It is unlikely to be considered cost-effective to carry out this type of research purely for immunocontraception; however, tailored therapy based on genetics is a growing market and could eventually impact on contraception. It is more likely that contraceptive vaccines that have an additional role in anticancer therapy [8] will be developed first in this way.

There is a need for a greater choice of effective, safer, non-barrier and non-surgical methods. Immunocontraception can in part fulfill the demand for niche markets, and specific consumer surveys are required to determine what these are. Depending on the final application (human or animal) and requirements of the contraceptive (long or short term), a range of immunocontraceptives will be available in the near future. The criteria and design of the vaccines may well vary depending on whether the need is for the developed or developing world and, although this remains a complex issue, it is commonly driven by politics and costs [61••]. Research and development into immunocontraception can only be sustained if funding issues can be addressed, and this will necessitate engaging the interest of appropriate organizations amidst competition with other therapeutics, not necessarily contraceptives. Clinical funding today appears to be mainly achieved through small biotech companies and University spin-outs, demonstrating a technology-driven market; although this may be indicative of a general trend in the biological sciences, rather than be specific to immunocontraception. In general [61••], funding trends in contraceptives have moved from large pharmaceutical company involvement in the period between 1951 and 1972, to public and non-profit private sector investment with a world-wide altruistic overview between 1973 and 1987. Subsequently, in the 1990s there was an influx of small biotechnology companies, which aim to license their technologies to larger companies. Similarly, veterinary research and development in the field has been possible through University and charitable funding, rather than investment from large animal health pharmaceutical companies. Overall, the dynamics of the funding situation have caused many established researchers to diversify into new areas, while the development of improved technologies has encouraged an influx of new researchers and transdisciplinarity, which may help to encourage funding in the future. One worrying aspect is that when the

developmental products move into larger companies or into the volatile biotech industry, technologies and expertise are easily lost when changing directions of priorities or fortunes are experienced. However, one way of retaining the knowledge base and to sustain the research seems to be the formation of new types of partnerships. Examples include the private-public partnership between Apton Corp and the WHO in the progression of the hCG vaccine, and the formation of the not-for-profit corporation SpayVac-for-Wildlife Inc (SFW) to fund commercialization of the ZP vaccine SpayVac and to obtain US FDA regulatory approval (<http://www.spayvac.org>).

The take home message from this review is that it is important to remember that technical hurdles overcome in the stringent immunocontraceptive field can provide many beneficial insights into disease preventative vaccine research, as well as increasing our understanding of the molecular mechanisms involved in the control of reproduction, infertility, cancer and autoimmunity.

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