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MINI-REVIEW

Passive immunization of the human vagina

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ABSTRACT

The vagina is an excellent site for topical passive immunization, as access is relatively easy, and it is an enclosed space that has been shown to retain bioactive antibodies for several hours. A number of sexually transmitted infections could potentially be prevented by delivery of specific monoclonal antibodies to the vagina. Furthermore, our group is developing antisperm antibodies for vaginally delivered on-demand topical contraception. In this article, we describe physical features of the vagina that could play a role in antibody deployment, and antibody modifications that could affect mAb retention and function in the female reproductive tract. We also review results of recent Phase 1 clinical trials of vaginal passive immunization with antibodies against sexually transmitted pathogens, and describe our current studies on the use of anti-sperm mAbs for contraception.

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Passive immunization, the transfer of antibodies to an unprotected individual for the prevention or treatment of diseases, has been used in humans for over a century, but has only recently become accepted as a highly reliable clinical procedure. This medical breakthrough is attributable to advances in monoclonal antibody (mAb) technology which can now produce reagent grade mAb reagents. Just in the past 10 years, over 100 mAbs have been approved for clinical use. The majority of clinical applications entail systemic administration of antibodies, but topical antibody applications are increasingly being explored, especially for mucosal surfaces that may not be adequately accessed by systemically administered antibodies or antibodies elicited by active systemic immunization. Topical passive immunization has the advantage of delivering mAbs in high concentrations to desired target surfaces. A number of groups are investigating passive immunization of the human vagina to prevent sexually transmitted infections (STIs), particularly the transmission of pathogenic viruses such as HIV-1 and HSV-2. In addition, vaginal application of antisperm antibodies, under development in our laboratory, could provide a mechanism for on-demand contraception. In this article we describe physical features of the vagina that could affect the efficacy of passive immunization, and antibody modifications that could affect mAb retention and function in the female reproductive tract. We also review results of recent Phase 1 clinical trials of vaginal passive immunization with antibodies against sexually transmitted pathogens, and describe our current studies on the use of anti-sperm mAbs for contraception.

Physical characteristics of the human vagina that may influence passive immunization

The human vagina is a tube-shaped structure extending from the introitus (vaginal opening) to the cervical os; it is usually a potential space with anterior and posterior walls in apposition. There are few published reports on the dimensions of the human vagina. In one study that used MRI to image the contours of vaginas of 28 reproductive aged women, the average length was determined to be 6.2 cm (range: 4.0–9.5 cm), and average width 3.25 cm (range: 1.5–3.6 at midvagina, and 2.6–8.3 at the fornix).[1] This group also demonstrated that the radiopaque gel used for imaging ascended from the vagina into the endocervical canal. In another study of 62 women that were administered vinyl polysiloxane casts, the surface area of the vagina was determined to range from 65 to 107 cm^2.[2] Factors affecting vaginal shape and size included age, height, weight, race, and parity.[1,3] In addition, the vaginal wall contains many rugae (folds) which allow it to distend during sexual intercourse and childbirth. As a consequence, the surface area and volume of the human vagina can be highly variable. Furthermore, the volume of secretions in the vagina varies between individuals and is affected by age, menstrual cycle stage, intercourse, and other factors. The volume of vaginal secretions ranged from 300 µl to 700 µl in reproductive-aged women from Africa and the US.[4,5] Sexual excitation can increase blood flow to the vagina, resulting in serum exudation, and stimulate the release of secretions from the Skene's and Bartholin's glands, located near the introitus;[6] semen can add up to 10 ml of volume to vaginal secretions after intercourse.[7] All of these factors could affect the distribution and final concentration of passively administered antibodies in the vagina.

The vaginal wall is comprised of a stratified squamous epithelium, approximately 30 cell layers thick, that transitions to a simple columnar epithelium (single-cell layer) at the endocervix. Basal epithelial cells in the vaginal mucosa express the immunoglobulin (Ig) transport molecule FcRn which transports IgG from the basal compartment into the lumen, but probably not in the other direction[8] (Figure 1a). The epithelial cells in the topmost layer of the vaginal mucosa, the

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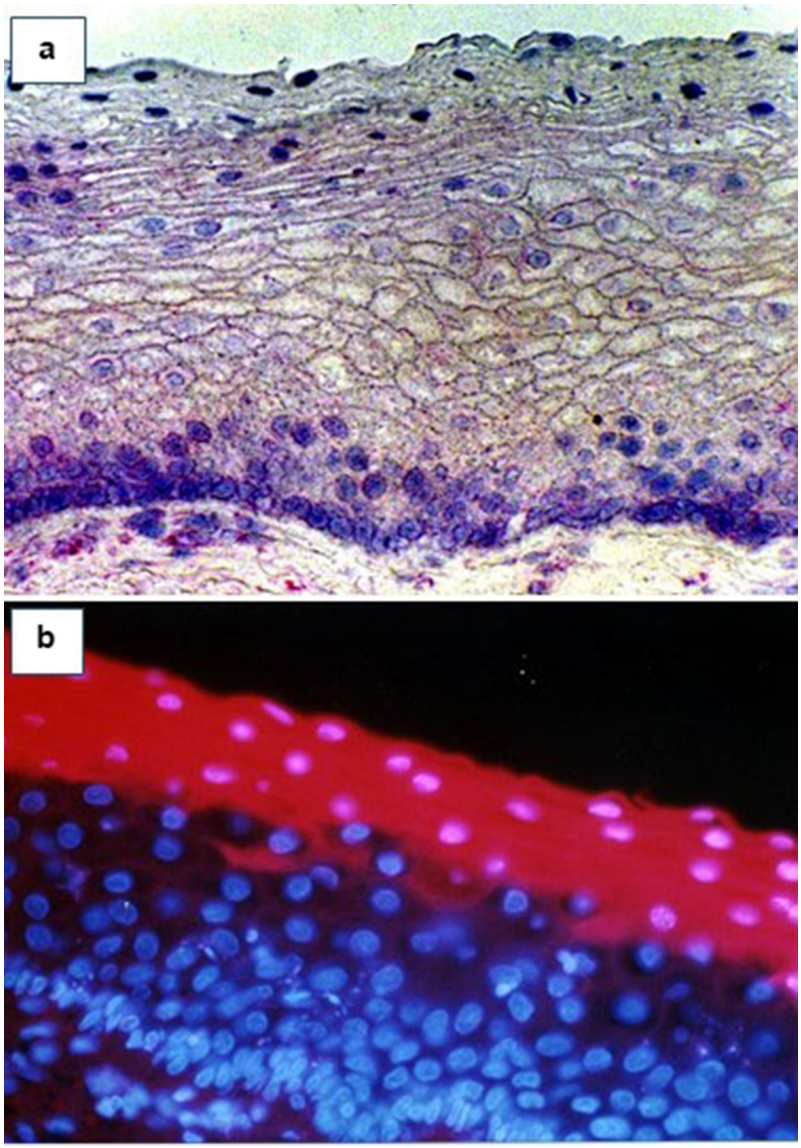

Figure 1. (a) FcRn (IgG transport molecule) expression by basal epithelial cells in the human vaginal epithelium, as visualized by immunohistology. FcRn-positive cells appear purple. (b) IgG uptake by apical epithelial cells in the stratum corneum of the human vaginal epithelium. Cy3-labeled (red) IgG, which had been added to the apical surface of vaginal tissue, was visualized by fluorescence microscopy in the apical cells.

stratum corneum, absorb and retain Igs until they are exfoliated, at which time the Igs are released[9] (Figure 1b).

Mucin glycoproteins constitute a large proportion of the apical glycocalyx that covers the vaginal surface. The vaginal mucosa expresses membrane-bound mucins (e.g., MUC 1, MUC 4), but does not contain glands that secrete high MW gel-forming mucins. On the other hand, the endocervix contains numerous glands that secrete high MW mucins (e.g., MUC2, MUC5AC, MUC5B, and MUC6) that flow into the vaginal cavity.[10] At least one of these, MUC5B, is under hormonal control and is secreted in abundance at midcycle.[11] Vaginal and endocervical mucins may play an important role in vaginal passive immunization. Various studies have shown that mucins can interact with Igs to impede the penetration of antibody-coated pathogens and sperm.[12–14]

The vaginal epithelium contains innate immune cells that express Fc receptors (FcR); these receptors bind to the Fc region of immunoglobulins and confer a variety of antibody-dependent protective functions on the immune cells.[15] In particular, macrophages and neutrophils in the FRT express FcRγ and FcRα, respectively, conferring the ability to phagocytose pathogens coated with IgG and IgA.[16] FcR functions of innate immune cells in the FRT have been implicated in the protective effects of antibodies following the administration of HIV vaccines,[17] and in animal studies of passive immunization to prevent HIV-1 transmission (described below).

The vagina is profoundly affected by its rich and varied microbiome. A majority of women in the US have a predominance of "healthy" lactobacillus species which create an acidic environment and support a healthy vaginal mucus. Antibodies function well and are relatively stable under these conditions.[18] However, many women worldwide have a more complex vaginal microflora, often referred to as dysbiosis or bacterial vaginosis (BV).[19,20] This condition is associated with an elevation in vaginal pH, and degradation of vaginal mucus which adversely affects antibody trapping defense

mechanisms.[21] Other sexually transmitted pathogens such as *trichomonas vaginalis* also produce glycosidases and other enzymes that degrade vaginal mucins.[22] The enzymes associated with abnormal vaginal flora (e.g. glycosidases, sialydases, sulphatases and proteases) could also directly affect the activity and stability of antibodies in the vagina.

Engineering antibodies to improve efficacy in the vagina

The overwhelming majority of FDA-approved mAbs for clinical use are dimeric IgG_1 antibodies. This is the most common antibody type found in blood and vaginal secretions, and has a number of immunological functions including viral neutralization, mucus trapping, complement fixation, and other FcR-mediated effects. However, there is increasing interest in using molecularly engineered antibodies for passive immunization to enhance retention and function. Common modifications entail engineering the Fab (antigen binding) region, engineering the Fc region (FcR-dependent mechanisms), and creating multivalent antibodies and antibody fragments.

Fab alterations are a common way to increase affinity for a target to improve binding and pathogen neutralization. An example of this is VRC07-523, a clonal relative of the anti-HIV mAb VRC01, engineered to have increased affinity; this antibody protected non-human primates from SHIV challenge at a 5-fold lower concentration compared to VRC01.[23] Increasing the valence of an antibody is another method to increase avidity and breadth. Techniques are currently being developed for the manufacture of s-IgA and IgM multivalent mAbs. In addition, bispecific antibodies potently and broadly neutralize HIV due to their ability to bind multiple epitopes.[24] The trispecific antibody VRC01/PGDM1400-10E8v4 also has broad specificity and neutralization potential.[25]

Another approach to antibody engineering entails alteration of the Fc region. The LALA-PG variant is comprised of a series of point mutations (L234A,/L235A/P329G) that inhibit mAb binding to FcγRs and complement to limit effector functions and possible inflammation.[26] An anti-HIV antibody engineered with these mutations, b12-LALA-PG, was shown to be less effective than wild type b12 in protecting rhesus macaques from low-dose repeated vaginal SHIV challenge.[27] On the other hand, the GASDALIE variant (G236A/S239D/A330L/I332E) confers enhanced Fc function, and anti-HIV antibodies engineered with these mutations were more protective in SHIV mucosal challenge studies.[28,29] In humanized mice, anti-HIV antibodies with the GASDALIE mutations also demonstrated enhanced protection against viral challenge.[30] These studies provide evidence that FcR-mediated immune functions play an important protective role in the vagina.

LS point mutations in the Fc region (M428L/N434S) increase antibody affinity for the FcRn receptor and increases serum half-life of systemically administered mAbs. In a recent clinical trial, VRC0-LS had an average half-life of 71 days in serum, about four times longer than wild-type VRC01 (15 days).[31] It is unknown whether the LS mutation would enhance mAb half-life in the vagina, as FcRn is only expressed on the basolateral side of the epithelium and appears to only transport IgG into the lumen.[32]

Alterations to glycosylation in the Fc region can also improve certain antibody functions. IgG molecules without the core fucose residue have an increased affinity for FcγRIIIa and enhanced antibody-dependent cellular cytotoxicity (ADCC);[33] nonfucosylated HIV antibodies have also demonstrated these effects.[29] Furthermore, a recent study demonstrated that nonfucosylated antibodies interact better with MUC16, a mucus glycoprotein found in the FRT, and therefore could enhance mucus trapping protective functions.[12]

Antibody fragments that still bind to antigens but do not have Fc regions may have enhanced pharmacokinetics and penetration into tissues due to their smaller size[47]. Common antibody fragments are Fab and $F(ab')_2$ regions, single-chain variable fragments (scFv), and single-domain antibodies. It is currently unknown whether the use of these antibody fragments would confer an advantage in the FRT.

Clinical trials demonstrating passive vaginal immunization for protection against STIs in women

A number of vaginal passive immunization studies have been conducted in nonhuman primates and mice using mAbs against HIV-1 and HSV-2. They have for the most part demonstrated efficacy of the passive immunization approach in preventing HIV/SHIV and HSV-2 infections (reviewed in Anderson et al.[34]). However to date only 3 Phase 1 clinical trials have been reported that describe the safety of mAbs delivered to the human vagina. They also provide data on pharmacokinetics and efficacy of the mAbs. We will review these reports in depth as they provide important information about the feasibility of vaginal passive immunization in women.

MABGEL is a vaginal microbicide developed by the European Microbicides Programme, containing three broadly neutralizing HIV antibodies: 4E10, 2F5, and 2G12.[35] The antibodies were formulated into 20 mg/mL high dose and 10 mg/mL low-dose gels which were applied vaginally for 12 consecutive days. No serious adverse effects were reported by the women in the study and effective concentrations of the antibodies were detected in cervicovaginal secretions up to 8 hours after application. Antibody activity was not assessed. There also appeared to be no systemic uptake of the antibodies. A trial by another European consortium conducted a first-in-human clinical trial of vaginal application of an anti-HIV antibody, 2G12, manufactured in *Nicotiana tobacum*.[36] In this trial, 11 participants were randomized into mAb vs. placebo groups and received either a single dose of 28 mg of 2G12 mAb in 1 ml of saline, or saline alone. None of the women reported serious adverse events, and no systemic absorption was observed. Pharmacokinetic data were not reported for this study.

Our group recently reported the results of a Phase 1 clinical trial that tested the safety, acceptability, pharmacokinetics, and ex vivo efficacy of MB66, a vaginal film containing 10 mg each of VRCO1 (anti-HIV mAb) and HSV8 (anti-HSV-1 and −2 mAb). The mAbs were produced by transfection into *Nicotiana benthamina* (a species of tobacco plant). Women received one dose of the film on one day only (n = 9), or daily for 7 days (n = 14 placebo film, n = 15 active film). The

product was generally safe and well-tolerated with no serious adverse events recorded. Acceptability and willingness to use the product were high in post-use interviews. Antibody levels peaked 1 hour post dosing with active film (median concentration 1,008 µg/ml in the midvagina), and remained significantly elevated at 24 hours after film use (median concentration 88ug/ml in the midvagina). Importantly, vaginal samples collected 24 hrs after MB66 insertion neutralized both HIV an HSV2 *ex vivo* providing evidence that antibodies remain stable and active in the vaginal environment for at least 24 hours. This study provides further data to confirm the safety and acceptability of vaginal passive immunization in women, and is the first study to demonstrate detailed pharmacokinetics and antibody activity of a mAb-based multipurpose prevention technology (MPT) product.[37]

Topical administration of antisperm mAbs for contraception

Our research team has produced an antisperm mAb in *Nicotiana* that shows excellent potential for topical contraception. The Human Contraception Antibody (HCA) was derived from an IgM antisperm mAb made by fusing lymphocytes from an infertile woman with mouse hybidoma cells.[38] We combined the variable sequence of this antibody with invariant IgG1 sequences to produce an IgG1 mAb for potential clinical use. Preclinical testing indicates that this mAb has potent sperm agglutination activity, and immobilizes sperm in the presence of complement.[39] Studies are underway to determine whether HCA traps sperm in cervical mucus and affects other sperm functions such as the acrosome reaction and oocyte fertilization. IND enabling studies including tissue cross reactivity, rabbit vaginal irritation and rat toxicology tests were successfully completed, and an IND for HCA film (ZB-06) was recently approved. A Phase I Clinical Trial testing ZB-06 for safety and efficacy in postcoital tests is underway.

General comments

Pharmacokinetic data from the MB66 clinical trial described above and presented in detail in Table 1 provide important information on mAb concentrations in vaginal secretions achieved through passive topical immunization. Antibody concentrations at the one-hour time point following administration of 10 mg of VRC01 IgG_1 were comparable to levels of natural IgG found in vaginal secretions of normally cycling women, which range from 70 to 200 ug/ml,[40] and levels of specific IgG antibodies found in female genital secretions following systemic immunization with tetanus toxoid (up to 59 ug/ml)[41] or HIV vaccines (range: 10 to 1,000ug/ml; median 100ug/ml).[42] A number of studies have compared HPV antibody levels in serum to those in cervicovaginal secretions following parenteral immunization with HPV vaccines.[43] Overall, levels of HPV-specific IgG and IgA antibodies in cervicovaginal secretions were much lower than those in serum (1–2%), but were correlated indicating that genital antibodies are transudated from the serum. Antibodies were detectable in genital secretions for at least 2 years after HPV immunization.[44] Clearly, in certain cases such as the HPV vaccine, a durable and effective antibody response can be elicited in the genital tract with parenteral vaccination that is superior to topical passive immunization. However, apart from HPV and hepatitis B vaccines, efforts to produce vaccines against other leading STI pathogens such as Chlamydia trachomatis, Neisseria gonnorhea, HIV-1, and Herpes simplex virus, have been unsuccessful. Until such vaccines are available, passive immunization with mAbs at the time of intercourse is a promising option to prevent STI transmission.

The data from the MB66 trial indicate that on average approximately one-tenth of the applied antibody remained in vaginal secretions after 1 hr, and 1/100 of the antibody remained after 24 hours. This information, while preliminary, begins to provide guidance for determining doses of antibodies required for passive vaginal immunization in future clinical trials. For example, since median antibody concentrations in midvaginal secretions were approximately 1/10 of the starting dose one hour after film insertion, one could multiply the target antibody concentration 10-fold to approximate the starting dose needed to achieve an effective concentration after one hour. However, there are two important caveats to applying this approach. First, antibody concentrations differed according to sample site, with highest concentrations detected in midvaginal secretions, and lowest concentrations detected at the cervical os and distal vagina (vaginal opening). Therefore, the proposed site of action of the mAbs must be taken into account when calculating the effective dose. Second, there was considerable interindividual variation in the amount of antibody present in vaginal secretions after film use. For example, midvaginal secretions contained the highest antibody concentrations of all the sites tested after 1 hour (median: 1,000ug/ml), but VRC01 antibody concentrations ranged from 15 to 3,174 ug/ml at this site amongst the 15 women in the active film

Table 1. MAb pharmacokinetic data from the MB66 trial.

	Cervical Os			Ectocervix			Mid vagina			Distal vagina		
Time point	Median*	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
Baseline	**<1.6**	<1.6	<1.6	**<1.6**	<1.6	<1.6	**<1.6**	<1.6	<1.6	**<1.6**	<1.6	<1.6
1 hr Post Film	**846.9**	73.4	4911.3	**748.8**	131.4	6768.3	**1008.0**	15.3	3174.2	**31.3**	1.6	1480.0
4 hrs Post Film	**630.8**	1.6	3788.9	**541.4**	112.1	3185.7	**387.4**	71.4	2622.0	**168.1**	1.6	8548.5
24 hr Post Film	**18.6**	1.6	128.2	**27.1**	1.6	162.3	**88.0**	5.0	746.9	**52.8**	1.6	509.2

*µg/mL; corrected for dilution factor (1:20)

Fifteen women received a vaginal film containing 10 mg of VRC01 and 10 mg of HSV8 monoclonal antibodies; four vaginal sites [cervical os, ectocervix, midvagina and distal vagina (vaginal opening)] were sampled by tear-flo wicks 1 hr, 4 hrs and 24 hrs post film insertion. VRC01 antibody concentrations in vaginal fluid over time are shown in this table. All 4 vaginal sites had significantly elevated antibody concentrations at 1 hr, 4 hrs and 24 hrs following insertion of film compared to baseline ($p < 0.0001$ for all except 24hr cervical os which was $p < 0.01$).

group at this time point. Variables such as film placement location, vaginal wetness and other factors could affect mAb concentrations in vaginal fluid after film insertion and should be further explored.

Future directions

- Multivalent variants of HCA are being developed that could reduce the amount of mAb needed for sperm immobilization.[45] More potent antibodies may make it feasible to deliver mAbs to the vagina via vaginal rings or other devices for long-term protection.
- It may be possible to deliver mAbs to the penis to deliver contraception and/or protection against STIs in men. The mAbs could potentially be applied to the penis as a lubricant or fast drying film. This is technically feasible because the lubricant/film can contain up to 20 mg/ml of mAb, and mAbs effectively inactivate viruses and sperm at concentrations below 10 ug/ml. The penile product could be billed as a male contraceptive or microbicide, and would protect both partners.
- We hope to eventually combine antisperm mAb(s) with HIV and HSV-2 mAbs in a single product to deliver mAb-based multipurpose technology for protection of women, and potentially men, against both STIs and unplanned pregnancies.

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Disclosure of potential conflicts of interest

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