S11.4 ROLE OF THE GENITAL TRACT MICROBIOME IN SEXUAL AND REPRODUCTIVE HEALTH: REPORT FROM THE KEYSTONE SYMPOSIUM IN CAPE TOWN, 2018

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Background The Keystone Symposium on 'Role of the Genital Tract Microbiome in Sexual and Reproductive Health' was held in Cape Town in December 2018.

Methods The aims were to discuss the most current and cutting-edge research findings, consider future directions, stimulate collaborations, and provide a forum for trainees and new investigators to present, learn, and network.

Results/Conclusions All aims were met. The Symposium was particularly successful in bringing researchers in HIV/STI and maternal and child health together. Areas of scientific consensus included: 1) Optimal is a better term to use than normal in the context of vaginal microbiota. *L. crispatus*-domination is considered optimal. *L. iners* is sometimes a friend and sometimes a foe. 2) Vaginal microbiota diversity on its own misses important dysbiosis types (such as *G. vaginalis*-domination). 3) Taxonomic community state types are useful, but we may need to move towards community state types that incorporate pathogenicity (e.g. inflammatory potential), and are therefore more useful from the prevention, diagnosis, treatment and prognosis perspectives. For some key bacterial taxa (e.g. *G. vaginalis*), we should differentiate between clades. In the meantime, we should use precise definitions of predictors and outcomes. 4) Moving from correlation to causality, the field needs more mechanistic studies and sufficiently powered longitudinal human studies. The latter could include frequent sampling studies to determine community dynamics, observational studies with clinically relevant endpoints, and intervention studies. These studies should ideally include quantification of total bacterial load and bacterial species (not relative abundance only), and measurement of all relevant microorganisms, biofilms, and host responses in the genital tract. 5) The efficacy of existing interventions, and pipeline of new interventions, are limited. We should expand the pipeline, which requires industry involvement and more investment into the field in general. We now have the tools to assess the effects of those interventions.

Disclosure No significant relationships.

S12 – NEW APPROACHES FOR STI VACCINES

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S12.1 PROGRESS TOWARDS A GONORRHOEA VACCINE

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Introduction Gonorrhoea is becoming increasingly difficult to control due to antibiotic resistance and the absence of a vaccine. However, a vaccine to the closely related bacteria *Neisseria meningitidis*, the outer membrane vesicle (OMV) vaccine MeNZB, was reported to be associated with reduced rates of

gonorrhoea. To investigate this possible cross-protection we assessed serum raised to the meningococcal vaccine Bexsero, which contains the MeNZB OMV component plus three recombinant antigens (NadA, fHbp-GNA2091, NHBA-GNA1030), in terms of its cross reactivity and functional activity against *Neisseria gonorrhoeae*.

Methods The similarity of MeNZB and Bexsero antigens to gonococcal proteins was assessed bioinformatically. Sera from rabbits immunised with the OMV component or the three recombinant antigens of Bexsero, and sera from humans immunised with Bexsero were tested in Western blot, ELISA, serum bactericidal activity (SBA) and neutrophil opsonophagocytic (OPA) assays to assess the level and functional activity of antibodies recognising *N. gonorrhoeae*.

Results There is a high level of sequence identity between MeNZB/Bexsero OMV antigens and gonococcal proteins. NHBA is the only Bexsero recombinant antigen that is conserved and surfaced exposed in *N. gonorrhoeae*. Rabbit antibodies to the OMV component or to the three recombinant antigens of Bexsero recognise gonococcal proteins and mediate SBA and OPA killing of *N. gonorrhoeae*. Furthermore, Bexsero induces antibodies in humans that recognise gonococcal proteins. Analysis of the functional activity of Bexsero-induced human antibodies against *N. gonorrhoeae* is ongoing.

Conclusions The ability of antibodies induced by MeNZB OMV proteins to recognise and kill *N. gonorrhoeae* could explain the decrease in gonococcal cases associated with MeNZB vaccination. The presence of antibodies to OMV proteins plus NHBA following Bexsero vaccination may result in additional protection against gonorrhoea. Analysis of Bexsero-vaccinate human sera may also facilitate the identification of a correlate of protection to guide future development of a gonococcal vaccine.

Disclosure No significant relationships.

S12.2 A TRI-ANTIGEN PROTECTIVE SYPHILIS VACCINE DESIGN THAT ENHANCES TREPONEMAL CLEARANCE AND INHIBITS PATHOGEN DISSEMINATION

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Background A protective vaccine against *Treponema pallidum* subsp. *pallidum* (*T. pallidum*) would facilitate syphilis control at a global scale. We have identified three *T. pallidum* antigens that, when used separately as immunogens, either attenuate chancre development at the challenge site or pathogen dissemination. Here, we report protection induced by a vaccine design composed of these three antigens + two custom adjuvants containing Natural or Synthetic TLR4 agonists and a natural Mincle agonist.

Methods Recombinant TprK (aa 37–273), Tp0751 (aa 24–237), and Subfamily I Tpr (aa 23–351) peptides were emulsified in either adjuvant and used to immunize groups of eight rabbits. Immunized animals were challenged intradermally with $10^{5.5}$ *T. pallidum*/site at 10 sites, along with eight unimmunized control animals. Lesion development was recorded daily and treponemal burden measured by darkfield (DF) microscopy and qPCR of lesion aspirates and biopsies. Dissemination to distant tissues was evaluated by qPCR and rabbit infectivity test (RIT).

Results Compared to unimmunized, treponemal burden by DF in lesion aspirates at Day 19 was significantly lower in animals that received both Natural and Synthetic adjuvant groups. By qPCR, treponemal burden was significantly lower in the Natural group. At day 19 and 30, respectively, the proportion of lesions ulcerating was significantly lower in the Natural group, compared to Unimmunized. At day 30, the proportion of lesions ulcerating in the Natural group was significantly lower than in the Synthetic group. Mean lesion volume was smaller in immunized groups versus unimmunized on days 10–25 post-challenge. RIT indicated the lowest number of disseminated *T. pallidum* in rabbit tissues from the Natural group, followed by the Synthetic group, then the unimmunized group.

Conclusion Immunization with the three-antigen cocktail significantly attenuates syphilis infection: enhancing *T. pallidum* clearance, promoting lesion healing, and reducing dissemination. In rabbits, Natural adjuvant was more effective than Synthetic adjuvant in inducing protective immunity.

Disclosure No significant relationships.

S12.3 THERAPEUTIC VACCINATION TO TREAT HPV DISEASE: LESSONS LEARNED FROM HIGH GRADE INTRAEPITHELIAL LESIONS

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Malignancies caused by HPV represent a model clinical setting in which to test principles of immunotherapies, and to discover the consequences of interactions between tumors and their attendant immune milieu. A tumor-specific, non-‘self’ antigenic target is known, as HPV cancers are driven by constitutive and functionally obligate expression of the E6 and E7 viral oncoproteins, which bind and inactivate p53 and pRb, respectively. HPV disease can also be immunogenic; a growing body of evidence demonstrates that HPV-specific T-cell responses can mediate concomitant histologic regression and clearance of detectable virus in subsets of patients who have cervical HSILs. However, HPV researchers are faced with issues common to the development of effective immune-based therapies for every solid tumor, including determining the mechanisms that shape how a tissue microenvironment renders immune cells dysfunctional, deciphering the immunomodulatory effects of other treatment modalities such as targeted therapies, chemotherapy, and radiation, and identifying contributions to immune functional polarization mediated by tissue-specific microbiota. Insights gained from deconvolution of the cervical lesional microenvironment will be discussed.

S12.4 A MUCOSAL *CHLAMYDIA TRACHOMATIS* VACCINE STIMULATES PROTECTIVE MEMORY T CELLS

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Many non-mucosal vaccines are poorly protective against mucosal pathogens, presumably because they do not generate mucosa-tropic memory cells. Few mucosal vaccines are in clinical use because live vaccine vectors pose safety risks and

killed or molecular antigens (Ags) are weak immunogens when applied to intact mucosa. Adjuvants can potentially overcome this poor immunogenicity, however, conventional mucosal adjuvants possess unfavorable safety profiles. We have developed an adjuvanted vaccine against *Chlamydia trachomatis*. Genital *Ct* infection induced protective immunity that depended on interferon- γ (IFN- γ) producing CD4 T-cells, whereas mucosal exposure to UV-inactivated *Ct* (UV-*Ct*) generated tolerogenic *Ct*-specific regulatory T-cells, resulting in exacerbated bacterial burden upon *Ct* challenge. However, mucosal immunization with UV-*Ct* complexed with charge-switching synthetic adjuvant particles (cSAP) did not exert the tolerogenic effect of UV-*Ct* alone but elicited long-lived protection. This differential effect of UV-*Ct*-cSAP versus UV-*Ct* was because the former was presented by immunogenic CD11b⁺CD103⁻dendritic cells (DCs), while the latter was acquired by tolerogenic CD11b⁻CD103⁺ DCs. Genital protection was achieved after intrauterine or intranasal, but not subcutaneous vaccination and was inducible in conventional and humanized mice. Regardless of vaccination route, UV-*Ct*-cSAP induced robust systemic memory cells. However, only mucosal vaccination induced a wave of *Ct*-specific effector T-cells that seeded the mucosa during the first week and established resident memory T cells (T_{RM}). Without T_{RM}, mice were suboptimally protected, even when circulating memory cells were abundant. For optimal *Ct* clearance, both early seeding by T_{RM} and infection-induced recruitment of a second wave of circulating memory cells were required. Thus, using a novel mucosal vaccine platform, we demonstrate that protection against *Ct* depends on synergistic actions of two memory T cell subsets with distinct migratory properties.

S13 – CONTROVERSIES IN CLINICAL STI CARE

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S13.1 DOES AZITHROMYCIN HAVE A FUTURE IN THE TREATMENT OF GONORRHOEA AND CHLAMYDIAL INFECTION?

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Azithromycin, a second generation macrolide antimicrobial, has been widely used as a first line treatment for chlamydia and non-gonococcal urethritis and as part of dual treatment with ceftriaxone for gonorrhoea. Its unique pharmacokinetic properties including its extensive tissue distribution and long half-life, have enabled it to be administered as single dose treatment making it preferred for many STIs, particularly when there are any concerns about treatment adherence. A single dose regimen of azithromycin gives a larger maximum tissue concentration and has more rapid bacterial clearance than longer courses of the same overall dose suggesting that shorter durations of larger doses (>1g) will increase treatment efficacy and reduce the induction of resistance. However, the evidence suggests that the efficacy of azithromycin may vary by site of infection, particularly for chlamydia infection, with observational data finding that it might not be as effective for