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The Microbicide Pipeline: Clinical Development Success and Failure

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Oral Session 7: Microbicides, Drug Design and Late Breaker Presentations

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Design of Intravaginal Ring for Simultaneous Delivery of Antiretroviral Drugs

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Microbicides have recently become an attractive prophylactic method to prevent the male-to-female sexual transmission of HIV. Vaginal rings have shown high patient compliance and efficacy as a contraceptive and are thus being developed to deliver anti-HIV compounds. We developed a monolithic vaginal drug delivery system capable of delivering two drugs, with different mechanisms of action against HIV. The ring consists of two polyurethane segments that are optimized to release two different drugs with differing hydrophobicity—the first segment is composed of a hydrophobic polyurethane and incorporates the non-nucleoside reverse transcriptase inhibitor Dapivirine. The second segment is composed of a hydrophilic polyurethane and incorporates the nucleoside reverse transcriptase inhibitor Tenofovir. We observed an in vitro near-linear release profile of both drugs for a duration of 14 days. The release rates of Dapivirine and Tenofovir were loading-dependent, indicating that loading can be adjusted to reach therapeutic levels to inhibit viral infection. In solution, Dapivirine and Tenofovir were both stable up to 30 days at elevated temperature. In the ring dosage form, both Dapivirine and Tenofovir were stable for 90 days at 40 °C/75% humidity. Lastly, the two-component ring had similar mechanical properties to the contraceptive vaginal ring Nuvaring®, indicating that our ring would likely be well tolerated in vivo.

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Biophysical Mechanisms in Microbicide Pharmacokinetics

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Rational design of vaginal microbicide products should include delivery systems with properties giving rise to target pharmacokinetics. These depend upon the site of antiviral action, viz. the vaginal lumen (e.g. for entry inhibitors) or outer vaginal epithelium (e.g. for RTIs or NNRTIs). Delivery systems for the active pharmaceutical ingredients (APIs) can be semi-solid (e.g. gels) or solid (e.g. intravaginal rings, IVRs). We have created computational compartmental drug delivery models for all these scenarios. The models are being used to compute performance measures for current vaginal microbicide products and in the design of new, improved ones. Model inputs include: (1) diffusion coefficients of APIs and HIV virions in gels and vaginal fluids and tissue; (2) release fluxes from IVRs and gels; (3) vaginal coating thickness distributions by gels; (4) gel rheological properties (whole and during interaction with vaginal fluids); (5) vaginal mechanical properties, e.g. wall elasticity; (6) geometry of IVRs and of the vaginal canal. In vitro assays are measuring (1), (2) and (4), including development of new techniques for (1). We measure (3) in women using an optical vaginal scanning probe. Results to date suggest that vaginal coating layers ~100 μm can be sufficient to deliver doses of luminal APIs that limit infectious concentrations of HIV from contacting epithelial surfaces. Layer effectiveness is enhanced to the extent that HIV mobility within the layer is diminished. However, total protection for luminal APIs depends upon maintenance of such coating over a large fraction (>90%) of the surfaces. API transport via ambient vaginal fluids – which may be menstrual cycle phase dependent – can also play a significant role in increasing API delivery. This is particularly true for the delivery kinetics of intra-epithelial APIs by IVRs: here, model computations have shown that cyclic variations in vaginal fluid production give a range of time intervals after which prophylactic API concentrations are achieved in tissue, from hours after IVR insertion to days.

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Virtual Reality Applications in Antiviral Drug Design

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Structure-based drug design is a creative process that displays several features that make it closer to human reasoning than to machine automation. However, very often the user intervention is limited to the preparation of the input and analysis of the output of a computer simulation. In some cases, allowing human interactive intervention directly in the process could improve the quality of the results by applying the researcher's intuition directly into the simulation. Virtual reality applications can provide an effective way to convey information about a molecular environment in real time, engaging more than one sense at the same time.

We developed an immersive molecular mechanics simulator, where the user can probe a biological target and its interactions with a ligand, feeling the forces and molecular interactions on his/her hand while having a complete three-dimensional visual feedback. The movement of the user's hand are tracked in real time and used to stir the simulation.

We applied this methodology in the design of novel potential inhibitors of HCV helicase and the results obtained will be reported in this presentation.

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Identification of a Small-molecule Antiviral with Broad-spectrum Application to Multiple, Lethal Virus Types

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We report herein the identification of a small molecule therapeutic, FGI-103, which displays potent and broad spectrum in vitro inhibition of lethal viral hemorrhagic fevers to include Ebola, Rift Valley Fever and Dengue. Using lethal in vivo mouse model of Ebola