Francois Villinger et al., J AIDS Clin Res 2014, 5:11
http://dx.doi.org/10.4172/2155-6113.S1.005

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
HIV/AIDS, STDs, & STIs
October 27-29, 2014 Embassy Suites Las Vegas, USA

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Monoclonal antibody based microbicides against HIV and other STDs: Technological advances to a cost effective prevention

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An effective vaccine to prevent the transmission of HIV remains an unmet goal, prompting the search for alternative prevention methods. Among such methods, microbicides have been the subject of intense investigations, though they often represent a compromise between the need to inactivate the incoming pathogen while leaving natural mucosal barriers and defenses intact. For HIV in particular, this challenge has been difficult to meet, and thus, the best approaches thus far seem based on antiretroviral drugs, administered systemically or topically. Prevention of infection of macaques with simian/human immunodeficiency virus administered vaginally or rectally has been relatively successful using passive protection with the administration of broadly neutralizing monoclonal antibodies (Mabs) to HIV. While Mabs are occupying an increasing share of various clinical treatments, their production cost and the need for careful quality control of biologicals renders them too costly for large prevention efforts. However, technical advances in the efficient production of Mabs in plants, such as *Nicotiana benthamiana* offer the potential for cost effective production of highly homogenous recombinant human Mabs, while minimizing the risk of transmitting unknown mammalian viruses. N-produced recombinant human monoclonal antibodies (N-Mabs) with broadly neutralizing activity against HIV were tested as a microbicides in cynomolgus macaques. Several N-Mabs such as VRC01-N, 4E10-N and HSV8-N were tested *in vitro* against panels of HIV, SHIVs and HSV-2 *in vitro*, showing equivalent of better IC_{50} than their mammalian cell produced equivalents. We then tested the pharmacokinetics and distribution of VRC01-N and 4E10-N IgGs in the vaginal environment following administration in 1.5% hydroxyethyl cellulose gel (HEC) and followed this by testing each Mab's ability to prevent repeat challenges with SHIV162p3 delivered vaginally at weekly intervals. VRC01-N concentrations at 0.5 and 4 hours post vaginal administration were well above the IC_{80} for SHIV162p3, even for a 1.25 mg administered dose. For 4E10-N, the concentrations detected at 0.5 and 4 hours were above the IC_{80} only for doses of 5 mg and above, while these values decreased below inhibitory concentrations by 24 hours. However the distribution of the Mabs was homogeneous across 5 vaginal sites sampled. Cervicovaginal lavages tested for pro-inflammatory cytokines showed no upregulation upon vaginal Mab administration. Repeated SHIV challenges led to infection of all 5 control monkeys treated with HEC vehicle within 3 vaginal challenges, whereas the 5 macaques administered VRC01-N 30 min prior to challenge resisted multiple challenges demonstrating an ED_{50} of <2 mg. In contrast, 4 out of 5 monkeys administered 19 mg 4E10-N gel became infected within 5 challenges. Next we have tested the delivery of N-Mabs formulated in biofilms and intra-vaginal rings. Both delivery methods efficiently released the N-Mabs in the vaginal environment against without causing undue inflammation, paving the way for future approaches combining multiple Mabs and more friendly formulation for the prevention of vaginally acquired infection.

Biography

Francois Villinger is a Professor in the Department of Pathology and Laboratory Medicine in the Emory School of Medicine and the Associate Director for the Yerkes Division of Pathology. He received his DVM and PhD in 1986 from the University of Zurich in Switzerland. He joined Emory University as a postdoctoral fellow in 1989 and joined the faculty in the Department of Pathology and Laboratory Medicine in 1995. In September 2007, he was appointed as the Associate Director for the Division of Pathology at the Yerkes National Primate Research Cent.

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