Nicotiana Produced Broadly Neutralizing Monoclonal Antibodies as a Microbicide Strategy
Zhao C1, Connor-Stroud F3, Sharma P2, Oviedo-Moreno P2, Whaley K2, Bohorov G3, Moen T1, Anderson DJ4 and Villinger F3.
1Div Pathology, Yerkes National Primate Research Center & Dept. of Pathology and Laboratory Medicine, Emory University, Atlanta, GA.
2Mapp Biopharmaceutical, Inc. San Diego, CA.
3Regent Inc. Baltimore, MD.
4Dept of Obstetrics, Gynecology and Microbiology, Boston University, Boston MA.

Background
In the absence of an effective vaccine to prevent the transmission of HIV, alternative prevention methods need to be explored to slow the progression of the epidemics. While condoms have provided good protection from transmission, their use is not necessarily acceptable in select communities and therefore the development of a female controlled efficacious microbicide remains a top priority. Such goal has however been a challenge for HIV as most common approaches have failed or promoted transmission. Our team has taken a different strategy proposing the use of recombinant human monoclonal antibodies (Mabs) broadly neutralizing HIV produced in nicotiana as a cost effective approach.

Methods of Study:
We have studied the HIV neutralizing efficacy of nicotiana produced Mabs VRC01-N and 4E10-N in vitro against panels of HIV and SHIVs. We then tested the pharmacokinetic and distribution of VRC01-N and 4E10-N in the vaginal environment of cynomolgus macaques following administration in 1.5% hydroxyethyl cellulose gel (HEC). Sequential collections of vaginal fluid were performed using TearFlo strips from 5 vaginal sites at 0.5, 4, 24 and 72 hour and cervicovaginal lavages (CVL) at 4, 24 and 72 hour time points. Cynomolgus were chosen due to their relative abundance and the fact that similar to humans and unlike rhesus macaques, they reproduce cycle is continuous as opposed to seasonal.

Results:
- Nicotiana produced Mabs neutralization potency are comparable to hybridoma produced Mabs
- 4E10-N and VRC01-N are broadly neutralizing antibodies which can neutralize different strains of SHIV. While 4E10-N has a broader spectrum, its efficacy is markedly lower than the neutralization potency of VRC01-N
- At 4 hours after administration, the Mab concentration is still high enough to neutralize virus
- Innate immune molecule may exist in cynomolgus vaginae inhibit virus
- Vaginal biopsies show limited penetration of Mab into the vaginal tissue, which was not enhanced by repeated administration

VRC01-N alone is fully protective at high dose from vaginal SHIV162p3 challenge, while the efficacy of 4E10-N appears limited

Conclusions:
We submit that cynomolgus macaques constitute a good model to study not only the pharmacokinetic but also the efficacy of HIV broadly neutralizing Mab base microbicides.

This work was supported by NIHU19AI096398-02