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## Evaluation of novel, non-hormonal male contraceptive drug prototypes acting in vas deferens

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The study is based on our discovery of the mode of action underlying the side-effect of two therapeutic drugs (thioridazine and phenoxybenzamine); inhibition of semen emission, which occurs without affecting penile erection, the sensation of orgasm, libido or blood pressure [1-4]. The side-effect has been exploited in treating nocturnal emission and premature ejaculation [5-6] and is a feasible approach towards developing a male contraceptive; phenoxybenzamine was tested as a possible male pill [2]. SAR studies led to our design and synthesis of novel prototypes. The aims of the pilot study were to evaluate the potential of the prototypes to reduce ejaculate sperm content and volume in animals (rams) and whether the prototypes possess suitable drug-like properties for oral delivery.

The exploratory prototypes were first evaluated in-vitro, on contractility of human vas deferens (using vasectomy specimens with patients' consent and ethical approval) and animal (ram) vas deferens. Prototypes producing the distinctive action that disrupts the tissues' propulsive function - a differential inhibition of longitudinal compared to circular muscle contractility [1] - were identified for evaluation of effects on animal ejaculate. Prototypes that reduced ejaculate sperm content and volume by  $\geq 50\%$  within 4-16 hr of administration were examined in physicochemical assays to establish drug-like properties. Blood samples were obtained for analysis of drug levels.

In the study, three out of five prototypes (dosed at 0.6-1.3 mg/kg, IV), reliably reduced sperm emission by 64-83%. Although optimal dose-effects are yet to be established, the values are well within the range expected of unoptimized prototypes. Bioanalysis revealed a decline in plasma drug levels as a factor contributing to the less than 100% efficacy. In physicochemical assays, all three compounds were soluble to  $>100 \mu\text{M}$  but whilst one prototype was deemed too lipophilic, two prototypes were in the ideal range to be orally bioavailable (log D7.4 2.56 and 2.11). CaCo-2 assays also established that both prototypes had adequate permeability with no significant asymmetry (Papp A-B  $2.6 \times 10^{-6} \text{ cm/s}$  and  $19.1 \times 10^{-6} \text{ cm/s}$ ).

The short-term efficacy, the absence of untoward physiological or behavioural effects in animals over 12 weeks of the study and favourable drug-like properties clearly demonstrate the potential of the prototypes. Notably, a male contraceptive pill with the potential to suppress semen emission has additional benefit as a transitory first-line preventive option for reducing male to female transmission of pathogens such as HIV. Some chemical modification of the key prototypes has been carried out in order to increase plasma levels of active microspecies and enhance contraceptive efficacy. Collaborative milestone-based funding is now required for work to evaluate and identify prototypes with the best efficacy profile, adequate oral bioavailability, metabolic stability and safety attributes.