1 BACKGROUND

The development is based on our discovery of the mode of drug action for a side-effect shared by two therapeutic drugs, thioridazine and phenoxybenzamine (PBZ) inhibition of semen emission, which occurs without affecting penile erection, orgasm or libido.


- The potential of PBZ as a male contraceptive was tested by Homonnai et al. (1984) – reported total inhibition of semen emission within 3-4 days with little probability of female impregnation thereafter. Ejaculate recovery occurred within 5 days after cessation of dosing. However, for medical reasons PBZ and thioridazine are unsuitable for routine male contraceptive purposes.

2 PROPULSIVE MECHANISM AND MODE OF DRUG ACTION UNDERLYING THE SIDE EFFECT

Current study – novel prototypes [diphenyl-aryloxy-alkylamine derivatives] replicating this action in human and ram vasa were evaluated in vivo in order to identify prototypes producing ≥50% reduction in ram ejaculate within 4-16 hr.

3 RESULTS

Prototype XN73 – different doses reduced in vivo ejaculate sperm content & volume in two rams by 67-83%

Blood sample analysis - XN73 plasma levels were 16.7 ng/ml (IV - 0.67 mg/kg) and 66.2 ng/ml (IV - 1.4 mg/kg) after 4 hr of administration but declined rapidly to undetectable levels (animal 1) & 10 ng/ml (animal 2) within 16 hr.

In silico analysis of microspecies revealed a predominance of ionized microspecies with zero un-ionized microspecies at pH 1.5, 5.0, 6.5 & 7.4. The decline in plasma drug levels and inadequate microspecies distribution underlie the less than 100% efficacy in the ram experiments and corrected for in the latest chemically modified prototypes.

4 PROTOTYPE XN6 – REDUCED IN VIVO SPERM CONTENT & VOLUME BY 64 – 66%

Blood sample analysis - XN6 plasma levels were 94 ng/ml (IV - 0.7 mg/kg) and 44-138 ng/ml (1.4 mg/kg IV) after 4 hr and within 16 hr were 94 ng/ml (animal 3; IV 1.34 mg/kg) and 0-0.6 ng/ml (animal 4; IV 0.7 & 1.4 mg/kg).

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5 CONCLUSION

The prototypes, though unoptimized, have demonstrable potential in terms of

- Short-term inhibition of semen emission for male contraception &
- Drug-like properties

Collaborative milestone-based funding is required to start work on evaluating the modified prototypes and select drugs with the best contraceptive efficacy profile, oral bioavailability, metabolic stability and safety attributes.