TARGETING GPCRS IN *SCHISTOSOMA MANSONI*: ENHANCING RNAi KNOCKDOWN FOR EFFECTIVE CONTROL OF SCHISTOSOMIASIS

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Abstract

Schistosoma mansoni is a parasitic flatworm responsible for schistosomiasis, a neglected tropical disease affecting millions worldwide. Control of schistosomiasis is limited by the reliance on Praziquantel (PZQ) as the sole treatment, highlighting the urgent need for alternative drug targets. The reproductive biology of schistosomes is unique, as the female requires continuous pairing with a male to achieve sexual maturation. This study investigates G protein-coupled receptors (GPCRs) as potential drug targets, given their crucial roles in biological processes and druggability. However, despite extensive research on GPCRs in vertebrates, their roles in invertebrates like schistosomes remain poorly understood.We focused on the functional characterization of *S. mansoni* GPCRs differentially expressed in pairing-experienced males, pairing-inexperienced males, and females, hypothesizing their involvement in male-female interactions and reproduction. To overcome low RNA interference (RNAi) efficiencies, we developed a novel two-dsRNAs-one-target RNAi approach, achieving knockdown (KD) efficiencies of 92–99% for candidate GPCRs. Physiological effects were monitored over 21 days *in vitro*, evaluating pairing stability, attachment capacity, stem-cell activity, and egg production. Our findings revealed significant phenotypes following RNAi-mediated GPCR KD, including curling, tegumental damage, reduced motility, decreased stem-cell proliferation, and a decline in mature oocytes. These results strongly suggest that the selected GPCRs play critical roles in the vitality and reproductive biology of *S. mansoni*. In conclusion, this study optimized RNAi techniques for GPCR characterization and identified key candidates essential for schistosome survival and reproduction. Targeting these GPCRs could disrupt crucial processes in the schistosome lifecycle, providing promising alternatives to PZQ for combating schistosomiasis.

Supported by: Deutsche Forschungsgemeinschaft (DFG)

Keywords: *Schistosoma mansoni*, GPCRs, RNAi