**The potential of ROR1 as a novel therapeutic target for endometriosis**

K Gunther1,2, D Liu1, N Bowden3, G Stannard4, J Abbott1,2, C Ford1

1School of Clinical Medicine, UNSW Sydney, Kensington, Australia

2National Endometriosis Clinical and Scientific Trials (NECST) Network, Australia

3School of Medicine and Public Health, University of Newcastle, Newcastle, Australia, 4Cancer Voices Australia, Milsons Point, Australia

**Country: Australia**

**Introduction/Background**

Personalised medicine represents a promising therapeutic avenue in endometriosis, addressing the diversity of clinical manifestations, enhancing treatment efficacy and minimising side effects. Embryonic cell surface receptor ROR1 is a key target in oncology owing to its role in regulating cell growth, differentiation, and survival, but remains unexplored in endometriosis.

**Materials and Methods**

*ROR1* mRNA expression was analysed in a cohort of superficial (SUP n=76), deep infiltrating (DIE n=88), and endometrioma (OMA n=28) lesions, and control peritoneal (n=37) and endometrial (n=102) tissues. ROR1 protein expression was validated in an endometriosis tissue microarray (n=53). An *in silico* ligand-based virtual screening approach was undertaken to identify drugs with potential ROR1-binding activity, favourable pharmacokinetics and minimal side effects. A shortlist of 3 agents were tested in endometriosis cell lines and organoids.

**Results**

ROR1 is transcriptionally upregulated in peritoneal endometriosis tissues, but not endometrioma, irrespective of patient stage, age, or menstrual phase. Protein translation was confirmed in majority of patients within endometriosis microarrays (49/53, 92.5%), including SUP (9/12, 75/0%), DIE (33/33, 100.0%) OMA (6/9, 66.7%) and adenomyosis lesions (8/9, 88.9%). Ligand-based screening identified 263 agents with potential ROR1 inhibitory activity. Of these, cabergoline (a dopaminergic agonist), pirenzepine (an antimuscarinic and PARP inhibitor), and rimegepant (CGRP antagonist for migraine nociception) were prioritised and tested in a ROR1-expressing adherent cell line and patient-derived organoids. While no difference in cell proliferation or viability was observed after 72h of cabergoline or pirenzepine treatment, rimegepant demonstrated cytotoxic potential *in vitro*.

**Conclusion**

ROR1 is a promising target for precision endometriosis treatment due to its upregulation in endometriosis lesions and low expression in adult tissues. Investigating ROR1-targeting therapies is warranted, including the repurposing of migraine drug rimegepant, which may exert nociception effects while also preventing endometriosis lesion growth through ROR1 inhibition.

**Key words:** drug repurposing, personalised medicine, organoids