Why do we need new drugs for hypertrophic scars?

- Often described as the greatest unmet need in the management of burn injuries
- Currently, there are no drugs on the market to prevent scar formation
- Hypertrophic scars affect 91% of burn patients, costing the NHS £20 million per year

AIM: Validate the anti-scarring properties of hydroxypropyridine anti-fungals by investigating their effect on aspects of the scarring process

1. Preventing myofibroblast transformation
   - During scar formation, resting fibroblasts continue to transform into activated myofibroblasts
   - Fibroblasts isolated from the scars of burn patients were exposed to TGF-β1 to induce myofibroblast transformation, and co-treated with the hydroxypropyridines at various concentrations
   - The cells were stained for α-SMA (the myofibroblast marker) after 72 hours

2. Reducing matrix protein production
   - Myofibroblasts are responsible for the excessive production of matrix proteins (e.g., collagens) which contribute to scar tissue formation
   - Fibroblasts isolated from the scars of burn patients were exposed to TGF-β1 to induce matrix production
   - The cells were incubated with TGF-β1 and the hydroxypropyridones for 7 days, before staining the matrix with Coomassie blue

3. Inhibiting keratinocyte epithelial-mesenchymal transition
   - To aid wound closure, keratinocytes will transition from stationary epithelial cells to migratory mesenchymal cells
   - Once in their new position, they return to their epithelial state
   - During scarring, keratinocytes maintain their migratory properties – preventing wound closure
   - Keratinocytes were exposed to TGF-β1 to induce epithelial-mesenchymal transition (EMT), and co-treated with the hydroxypropyridones at various concentrations
   - The cells were stained for vimentin (marker of EMT) after 72 hours

4. Inducing myofibroblast cell death
   - During scar formation, myofibroblasts evade cell death with cell clearance not beginning until 12 months post-injury – compared to a few weeks normally
   - Established myofibroblast cultures were produced by exposing burn scar fibroblasts to TGF-β1 for 72 hours
   - Myofibroblasts were treated with 10 μM of the hydroxypropyridones for 72 hours, before using TUNEL staining to label cells undergoing cell death

Next steps:
- Our data suggests that hydroxypropyridone anti-fungals could be repurposed for the prevention of hypertrophic scars, by targeting several aspects of the scarring process.
- Current safety data suggests that we will be able to reach the desired drug concentration needed to elicit the anti-scarring effects in patients, using the 1% CPX cream that is on the market in Europe.
- We are currently seeking funding and support for clinical trial studies, to succeed in taking this drug from bench to bedside in a shorter amount of time, compared to traditional drug discovery.