AB020. Inhibition of cyclic-AMP-response element binding protein and its impact on corneal wound healing *in vitro* and *in vivo*

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Background: The cornea composes the outer surface of the eye and its transparency is required to allow light transmission to the retina. However, because of its position, the cornea is subjected to chemical and mechanical injuries that may lead to blindness. Our studies conducted using the human tissue-engineered cornea (hTEC) as a model provided evidence that the cyclic-AMP-response element binding protein (CREB) pathway is repressed during closure of corneal wounds. Based on these results, we hypothesized that closure of corneal wounds can be enhanced by preventing activation of CREB with the pharmacological inhibitor C646. Our goals were to proceed to the pharmacological inhibition of CREB (I) *in vitro* using the hTECs as a model, and then (II) *in vivo* using the rabbit as a model.

Methods: The self-assembly approach was used to create hTECs, that were then wounded with an 8-mm diameter biopsy punch to create an epithelial defect. The tissues were then incubated with 10 µM of C646 (n=8). DMSO was used alone as a negative control (n=4). Closure of the wounds was monitored over a period of 5 days. Besides, the cornea of New Zealand white rabbits was debrided with an ethanol 70% solution to create an epithelial defect of 8-mm diameter. Several concentrations of C646 (1, 10, 100 µM et 1 mM) were applied as eye drops 3 times a day for up to 7 days. The wounded corneas (n=4 per concentration) were stained with fluorescein and photographed every day.

Results: *In vitro* pharmacological inhibition of CREB with C646 considerably accelerated wound closure of all treated hTECs (4 days) compared to the control group (7 days). Moreover, the *in vivo* C646 treatment also accelerated wound healing of the corneas compared to the control group. The most effective concentration of C646 tested was the lowest (1 µM), as it considerably enhanced the wound healing process.

Conclusions: This study demonstrates that wound healing both *in vitro* and *in vivo* can be enhanced by preventing activation of CREB using a pharmacological inhibition approach. Most of all, this experiment suggests mediators from the CREB pathway as potential therapeutic targets on which we may influence to alter the wound healing dynamic of the cornea. We believe this study will lead to significant advancements in the clinical field of corneal defects.

Keywords: Cyclic-AMP-response element binding protein (CREB); protein kinase B (AKT); healing corneal wound; tissue-engineering

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