

## METHOD OF ACTION SUMMARY

The microRNA 302 (miR-302) is a human embryonic stem cell-specific microRNA. Over-expression of miR-302 has been shown to reprogram human body cells to stem cells (iPSCs) and promote numerous stem cell-mediated processes such as wound healing and tissue repairing.

RxGenesys has global rights to a proprietary technology able to cost-effectively produce a large scale of stem cell extracts containing the precursor molecules of miR-302 (miR-302 precursors or P-miR-302). Current data shows that, when dissolved with Mello Biotech's patented polysaccharide-based formulation, P-miR-302s remain stable for at least 2 years under room temperature (approx 5% degradation in this period of time; non- formulated P-miR-302s degrade completely within 2 hrs under room temperature). Another important factor affecting the stability of P-miR-302s is the pH value of the formulation, which cannot exceed 7.

Research (internal and collaborative) have confirmed the ability of miR-302 to enhance scarless wound healing. When a wound is treated with a gel or ointment containing the formulated P-miR-302 (at 1mg/mL concentration), the P-miR-302s are delivered into skin's adult stem cells located at the epidermis/dermis junction through their Glut1/Glut2 transporter proteins. Once in these cells' cytoplasm, the P-miR-302s are processed to yield mature and functional miR-302 microRNAs that inhibit the production of certain target proteins via a mechanism called RNA interference (RNAi; biologists Andrew Z. Fire and Craig C. Mello won the 2006 Nobel Prize in Physiology or Medicine for discovering RNAi and deciphering its underlying mechanisms). This in turn triggers the expression of transcription factors Oct4, Sox2 and Nanog and the subsequent expansion of skin's adult stem cell population. It is estimated that miR-302 induces approximately 40- to 100-fold increase in adult stem cell population in the treated wound area. These adult stem cells then differentiate into the necessary tissue cells to fill the wound area to complete the scarless wound healing process. Wounds treated this way healed 50- 60% faster as compared to those treated with control.

It is estimated, that the presence of approximately one million ( $10^6$ ) copies of miR-302 microRNA in a target cell's cytoplasm is needed to reprogram the cell into an iPSC. Application with gel or ointment containing 1mg/mL P- miR-302 results in approximately  $2.5-5 \times 10^5$  copies of miR-302 microRNA, in the cytoplasm of treated cells. Presence of miR-302 microRNAs in the amount of approx 25-50% of that required for somatic cell reprogramming, therefore, promotes adult stem cell expansion instead of reprogramming.

In summary, our miR-302 technology can potentially can be used to help heal all chronic and traumatic wounds, including new surgical wounds in an accelerated fashion, thus allowing scarless surgery.