Abstract

Psoriasis is a chronic inflammatory autoimmune skin disorder which affects a significant number of people worldwide. Although this disease is not life-threatening, it can lead to a significantly poor quality of life and negatively impact the mental health of the patients affected. For more severe psoriasis, both topical and systemic prescription medications exist. Unfortunately, all of these treatments carry significant risks that deterr patient adoption, such as general immunosuppression, the development of cancer, increased bacterial and fungal infections, damage to the kidney, lungs, or liver, and the development of blood abnormalities.

We are currently developing and testing DNA and modified DNA aptamers to target an extracellular, upstream mediator of psoriasis, the so called, “LL37” peptide. Promising candidate molecules are already in hand which show biological inhibitory activity. Using a patented multiplex approach to aptamer selection, we are developing a number of new candidate aptamers with a modified DNA chemistry. This novel aptamer chemistry has the potential to greatly enhance transport through the skin and will be incorporated during selection of the LL37 antagonists.

LL37 antimicrobial peptide as a target

✓ Extracellular – avoids issues with intracellular delivery
✓ Plasmacytoid dendritic cells (pDC’s) specifically involved. pDC’s only sense nucleic acids with TLR7 and TLR9
✓ PROVEN modulator of psoriatic inflammatory cascade [1-3]
✓ LL37 is only expressed in injured skin or in psoriasis

Advantages of Aptamers vs. Antibodies

✓ Synthetic – chemically defined; no lot-to-lot variation
✓ Easier to produce at GMP grade
✓ Enhanced transport properties incorporated during selection
✓ More stable, ready topical formulation

Future Work

➢ Selection of tighter LL37 binders (“Aptamer_222” is 60 nM)
➢ Incorporation of non-natural nucleotides
➢ Skin transport studies with modified DNA polymers
➢ Additional IFN-α measurements for aptamer candidates in pDC cell culture
➢ Test most promising in vitro candidates in xenoplant mouse model

Discussion / Conclusion

The data presented here demonstrate that it is possible to select a DNA aptamer with greater affinity for LL37 than its natural binding partner, genomic DNA. Furthermore “Aptamer_222” completely abrogates IFN-α production in pDC cell culture and thus shows great promise as a potential lead compound for psoriasis treatment. In future experiments discussed above, we plan to generate additional, aptamer-based lead compounds and characterize them in human xenograft mouse models.

References


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