

The Stimulation of Natural Killer T (NKT) Cells to Fight Disease

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INTRODUCTION

Immunotherapy is a type of therapy in which the immune system is manipulated, suppressed or stimulated, to fight disease. One area of this vast topic involves the stimulation of Natural Killer T (NKT) cells. NKT cells are a type of white blood cell that have the ability to destroy damaged cells (i.e. cancer cells, infected cells). They are naturally present in our body and are a main contributor in Cell-Mediated immunity. Research presents a multitude of ways to stimulate NKT cells to produce and release cytokines.

OBJECTIVES

The aim of the project is to preform expository research in order to identify the most effective ways to stimulate NKT cells to produce and release cytokines. However, it is important to note that controlling the type of cytokines released is crucial to the success in fighting disease. While some cytokines trigger an immune response, others inhibit it. The stimulation of NKT cells is critical, but achieving the desired cytokine activity is a vital step as well.

METHODS

KRN7000

- Seven to Ten week old female mice were injected with Friend virus (FV) intravenously.
- During day 0 of the FV infection, mouse NKT cells were stimulated by alpha-galactosylceramide (KRN7000) or α GalCer.
- The number and effectiveness of NKT cells as well as their impact on restricting virus replication was observed and recorded .

AH10-7

- A α GalCer modified by the addition of a hydrocinnamoyl ester on to the sugar and the trimming of part of the molecule's sphingoid base was injected into wild and "humanized" mice with melanoma cells.
- The effects on the mice's NKT cells, as well as the stimulated cells ability to suppress the growth and replication of the melanoma cells was observed.

RESULTS

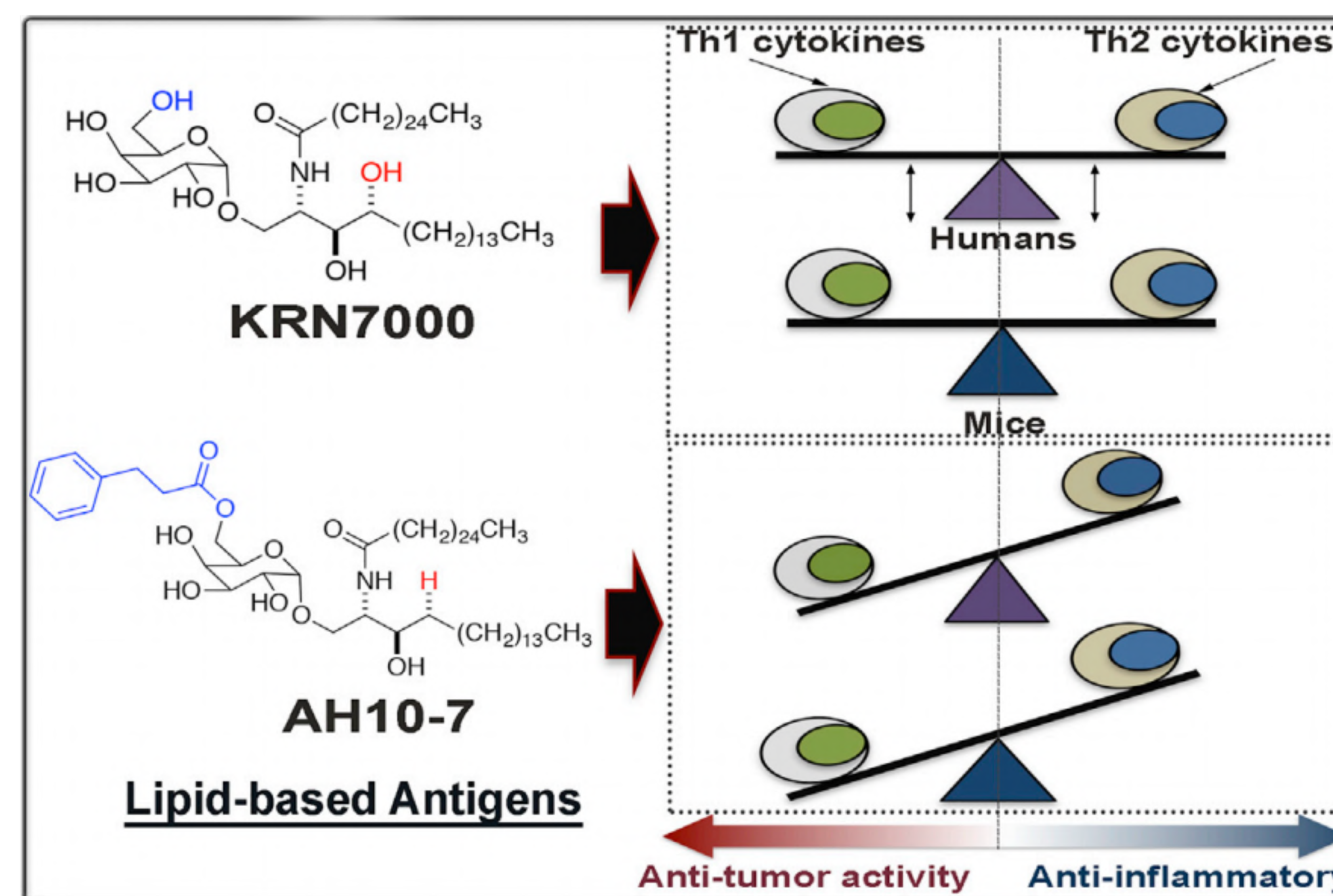


Figure 1. The differences in structural configuration and cytokine response in KRN7000 and AH10-7.

KRN7000

- After the injection of Friend virus, there was no change in the number of NKT cells, however an increase in activation of the cells was observed.
- Stimulation with α -Galactosylceramide (KRN7000) resulted in the significant increase in both the number and activation of NKT cells, as well as their anti-retroviral capacity (how effectively they can inhibit the replication process).

AH10-7

- The compound maintained strong activity in human NKT cells, while effectively triggering Th1-biased stimulation.
- AH10-7 was observed to be at least as effective predecessor in suppressing the growth of melanoma cells

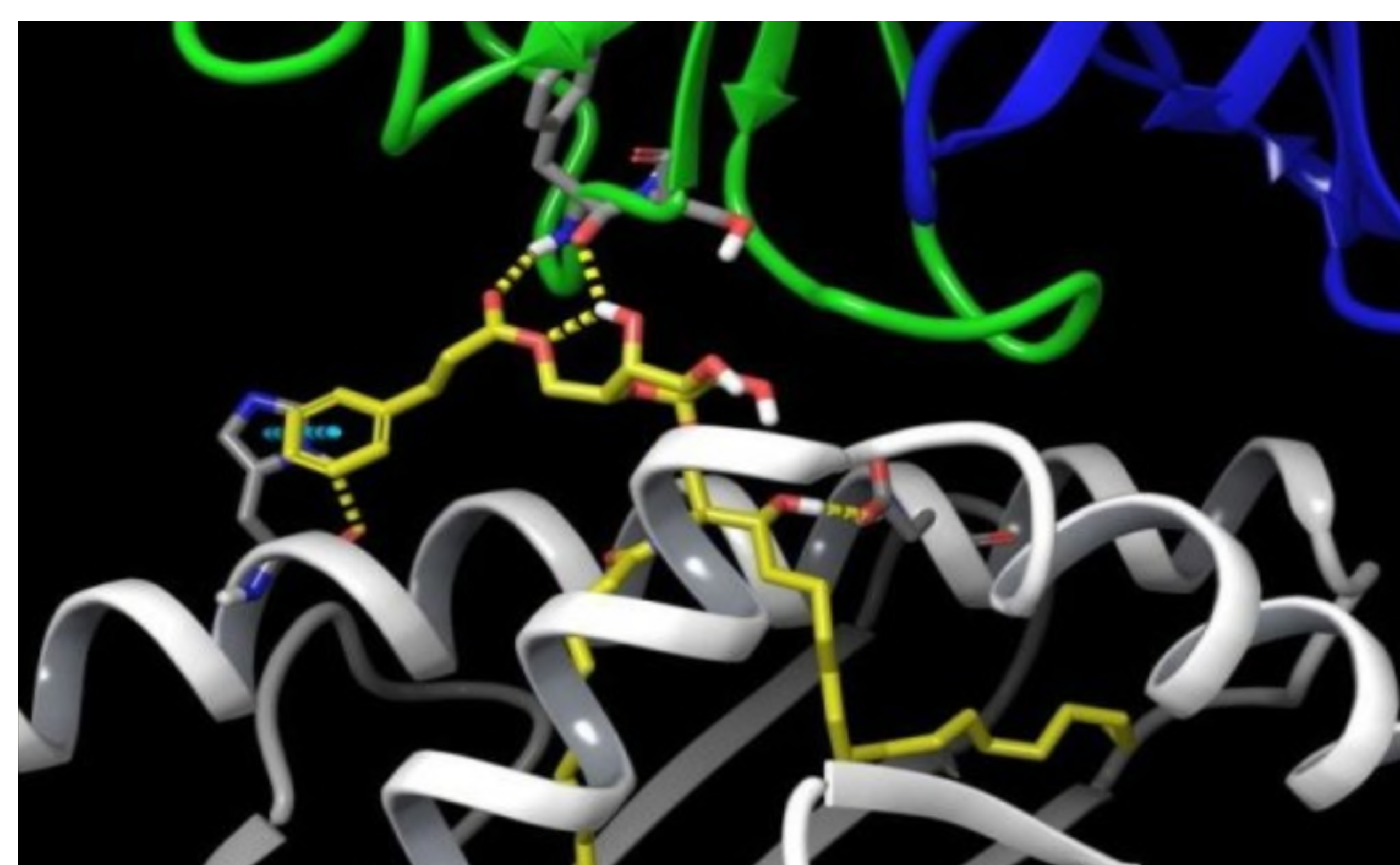


Figure 2. Illustration showing interactions between the AH10-7 compound (yellow), an immune system antigen-presenting cell (gray), and a NKT cell (green and blue) that trigger activation of the NKT cell in humanized mice.

CONCLUSIONS

In conclusion, there is credible research which shows the potential and effectiveness of the use of alpha-galactosylceramide (KRN7000) as a NKT cell stimulant in mice. However, the ability to achieve these same results in humans is unfortunately inconclusive. This is likely due to the KRN7000 compound triggering the release of both proinflammatory (Th1) and anti-inflammatory (Th2) cytokines. As mentioned earlier, the inability to control the release of cytokines hinders the effectiveness of the stimulant in fighting disease due to the conflicting activities of Th1 and Th2 cytokines.

The newer compound, AH10-7, was synthesized with a unique structure to trigger a more selective response from the NKT cells. This modified compound is observed to recover much of the activity in human NKT cells that was lost in KRN7000, as well as maintain the selective Th1 stimulation.

FUTURE WORK

The growth in the use and technology of the modification of alpha-galactosylceramides allows for endless opportunities in medical advancements. With the insight gained through the synthesis of AH10-7, similar molecules can be designed to elicit any desired NKT cell response. This could change the nature of treatments for cancers, infections, autoimmune diseases, and many other aspects of medicine.

References

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