Nanoapatite Delivery Platform for Antiviral Therapies

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Iron-doped apatite nanoparticles (IDANPs, *Fig. 1*) are patented as an antiviral additive treatment[1] that has demonstrated high efficacy against herpes simplex virus-1 (HSV-1) and human papillomavirus (HPV). In this work, IDANP additives were used in assays against 15 different viral strains, revealing the additive exhibits broad spectrum capacity with antiviral activity observed against both RNA and DNA viruses.

Previously, researchers reported that Fe(III) prevents replication of DNA and RNA viruses, although Fe ions were highly toxic to mammalian cells.[2] In our work, we showed that the predominate hydroxyapatite (HA) structure of IDANPs allowed metal delivery at a concentration 4.3X higher than reported, with minimal to no cytotoxicity detected, and a maintained capability to disrupt viral DNA replication. HA is found in mammalian bones and teeth[3] and has been cleared by the Food and Drug Administration for many biomedical applications.[4,5] Our preliminary research demonstrates a mechanism of action whereby IDANP components are internalized before disrupting viral DNA replication. IDANPs were not synthesized or designed to specifically interact with a particular virus or viral structure, and we therefore hypothesize that such a morphology has lent to its observed broad-spectrum capacity.

The IDANP antiviral additive was examined in a preliminary mouse model to determine efficacy against HSV-1 caused cold sores. Results revealed that mice treated with three different concentrations of IDANPs in two different commercial lip products (*Fig. 2*) did not exhibit redness, swelling, or abrasions (cold sores) during the treatment period, and up to nine days post-treatment (*Fig. 3*). Under the non-clinical and pre-clinical services program offered by the National Institute of Allergy and Infectious Diseases,[6] toxicity and efficacy profiles were obtained for 15 viruses in *in vitro* studies. Results revealed that IDANPs exhibited high efficacy against three strains of HPV. Compared to controls, the IDANP antiviral exhibited up to a 61 % increase in therapeutic index.

A toxicity profile of IDANPs was also developed and revealed minimal toxicity. When tested against six strains of mammalian cells *in vitro*, no toxicity was indicated in five cell lines. In the one cell line where toxicity was indicated, no toxicity was observed when a second (different) toxicity assay was performed. In the HSV-1 mouse study where the efficacy of IDANPs against cold sores was examined, no toxic side effects were observed in treated mice.

At present, HSV-1 treatments are minimally efficacious or exhibit frightening neural side effects, and there is no treatment for HPV. IDANPs can be stored at room temperature, exhibit broad spectrum capacity, and provide a promising alternative to treat these two pernicious infections.

[1] J.M. Andriolo, J.L. Skinner, M.K. Hailer, and M.L. Pedulla, US Patent No. 10532070 (2019).
[2] S. Terpiłowska, and A.K. Siwicki, "Chromium(III) and iron(III) inhibits replication of DNA and RNA viruses," BioMetals **30**(4), 565–574 (2017).
[3] P. Moerbeck Filho, M.A. Barreto, A.R.A.P. Medrado, M.T.R. Amaral, L.G. Moerbeck, D.S. Vale, and M.D. Calasans-Maia, "Biological principles of nanostructured hydroxyapatite associated with metals: a literature review," Insights Biomed **4**(3:13), (2019).
[4] C. Lee Ventola, *Progress in Nanomedicine: Approved and Investigational Nanodrugs* (2017).
[5] M. Rajan, and M. Sumathra, "Biomedical Applications of Hydroxyapatite Nanocomposites," in *Lecture Notes in Bioengineering*, (Springer, 2019), pp. 167–204.
[6]Alpha Technology, LLC will be utilizing/has utilized the non-clinical and pre-clinical services program offered by the National Institute of Allergy and Infectious Diseases under contract 75N93019D00016/75N93019F00131 (B01) to The University of Alabama at Birmingham.

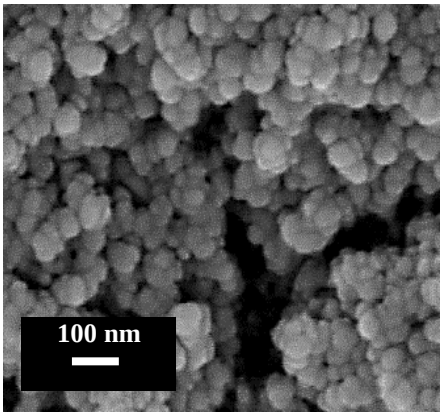

Fig. 1. Scanning electron micrograph showing the IDANP antiviral additive. IDANPs exhibit an amorphous, spherical morphology and consist of a hydroxyapatite delivery vehicle and active ingredient.

Fig 2. Image depicting pre-mixed and aliquoted doses of IDANP-embedded commercial lip product used for mouse cold sore studies. The antiviral was tested at three different concentrations per lip product and compared to control lip treatments consisting of commercial lip product with no IDANPs.

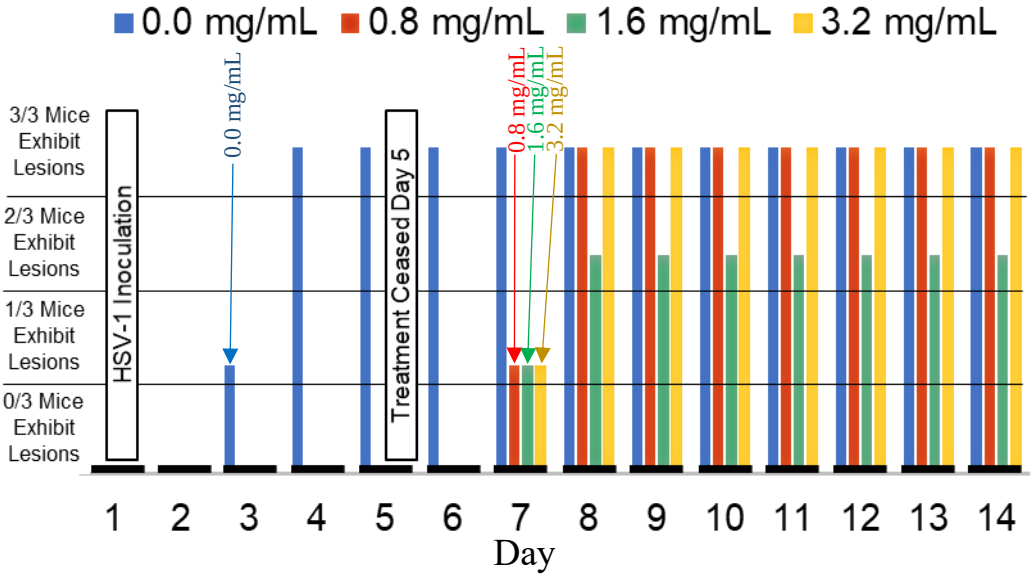

Fig 3. Graph showing results from one commercial lip product used to deliver IDANP antiviral treatment in mouse studies. Results show that all mice infected with HSV-1 and treated with lip product that *did not* contain IDANPs exhibited cold sores three days following inoculation. All mice that were infected with HSV-1 but treated with lip product containing one of three concentrations of IDANPs did not develop cold sores for at least one and up to nine days post-treatment.

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