In vivo efficacy of NP339 against Invasive Pulmonary Aspergillosis (IPA)

D. W. Smith, L. K. Katvars and D. A. O'Neil

NovaBiotics Ltd, Aberdeen, United Kingdom,

www.novabiotics.co.uk

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Introduction

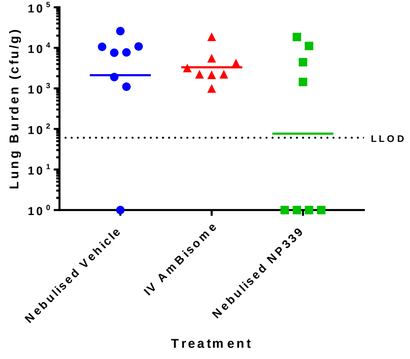
NP339 is a novel, cationic, synthetic antifungal peptide with anti-mould and anti-yeast activity demonstrated *in vitro*. NP339 is highly differentiated from existing antifungal drug classes with a membrane-targeting, rapidly fungicidal mechanism of action. NP339 is being developed for intravenous and also inhaled administration as an intervention for invasive pulmonary aspergillosis (IPA). Here we demonstrate the *in vivo* efficacy of nebulised NP339 in a murine model of IPA.

Methods

Immunosupressed, male CD1 mice were infected via intranasal administration of *A. fumigatus* conidia. NP339 was nebulised as a monotherapy (n=8 mice/treatemtent group). Lung burden of *A. fumigatus* was assessed by plating of homogenates at clinical end point. A second model investigated the combination of NP339 & AmB. Survival and serum Galactomannan index (GMI) was assessed for up to 96 h. *In vitro* intreactions of NP339 and AmB were determined in parallel by broth microdilution chequerboards *vs.* four *A. fumigatus* strains. Metabolic activity was assessed at 24 h by way of resazurin and FICIs were determined and annotated (Burkhart *et al* 2006).

Results

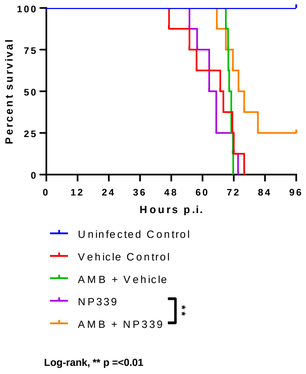
Nebulised NP339 monotherapy elicited a reduction in lung burden relative to vehicle control in a murine model of IPA.



Nebulised administration of NP339 resulted in a reduction in mean burden per group compared to vehicle of 1.43 log_{10} cfu/g. Sterilisation of lungs was observed in 4 animals suggesting that NP339 is fungicidal.

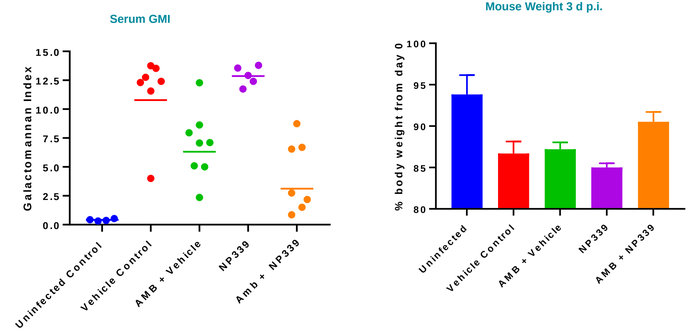
Results

Statistically significant improvement in survival with combination treatment in a highly virulent model



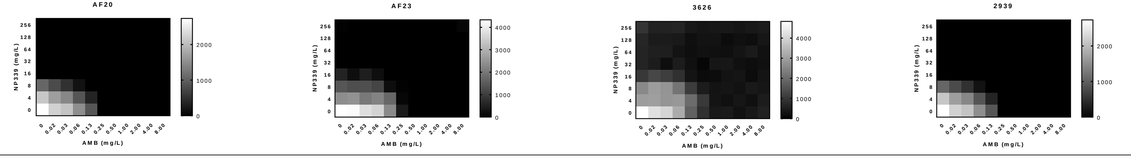
Log-rank, ** p =<0.01

Improvement in surrogate markers of disease following combination treatment even with models not optimised for AMP



Results

***In vitro* combinations of NP339 and AmB were additive against four *A. fumigatus* strains with no negative drug interactions observed**



Conclusions

This initial study demonstrates the *in vivo* efficacy of nebulised NP339. Combining NP339 with a parenterally administered antifungal led to survival of test subjects in a well-established murine model of IPA. This data supports the future development of NP339 as a component of a dual therapy for IPA. Although there is potential to apply nebulised NP339 (to directly address lung tissue burden) in combination with other antifungal agents (to target disseminated infection), NP339 will be developed for administration by both routes for optimal outcomes.

References

Disclosures

D. W. Smith, and L. K. Katvars are/were employees of NovaBiotics. D. A. O'Neil is a director, the CEO/CSO and a shareholder of NovaBiotics

dan@novabiotics.co.uk