of Gram-negative bacterial species and the infection sites. The PK/PD analysis for 3
hours of mice served as an endpoint.

Results. Four different mAb-producing hybridoma cells generated lg that
bound to AB and KPC. 40–80 µg/mL of mAb resulted in killing AB or KPC in vitro. Two of mAbs (25 µg/mL each) resulted in protecting A549 cells from AB- or KPC-induced damage by ~80% vs. cells incubated with isotype-matching Ab
bound to AB and KPC. 40–80 µg/mL of mAb resulted in killing AB and KPC.

Conclusion. The data indicate that these potent new nucleotide prodrugs are
metabolized to TPs that prevent RSV replication likely by inhibition of the viral RNA
polymerase. Additionally, the long t1/2 observed for many of the TPs suggest that it
might be possible to cure RSV infections with a single dose. IND enabling studies are
ongoing, targeting clinical evaluation in early 2018.

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Employee and Shareholder, Salary; R. Pietropaolo, Area Pharmaceuticals, Inc.: Board Member,
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1527. Novel Immunization Strategies Against Multi-drug-resistant Gram-negative
Bacteria
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Background. Healthcare-related infections due to multi-drug-resistant (MDR)
Gram-negative bacteria (GBN) such as Acinetobacter baumannii (AB) and carbapenemase
producing Klebsiella pneumoniae (KPC) are associated with high mortality rates. New
methods to prevent or treat these infections are needed. Candishantigenic Hyr1p is
predicted to share structural and sequence homology with the hemagglutinin/lipopolysaccharide
protein (Flb) and siderophore-binding protein of GNB including AB and KPC, respectively.
Indeed, active and passive immunization using Hyr1p as a target protect against AB infections in mice. Thus, we attempted to develop protective monoclonal antibodies (mAb) and test their efficacy against AB and KPC in vitro and in vivo.

Methods. Murine hybridomas were generated from Balb/c mice after vaccination
with recombinant Hyr1p. The concentration and identification of the collected mAbs was
determined using Bradford and SDS-PAGE. Binding ability of mAb was tested against AB and KPC using flow cytometry. In-vitro studies on the ability of these mAbs to kill KPC and AB were tested by quantitative culturing. The ability of these mAbs to protect from AB- or KPC-mediated alveolar epithelial cell (A549) damage was studied with
1Cr-release assay. The efficacy of mAb in protecting against AB- or KPC-induced
infection was studied in neutropenic or immunocompetent CD1 mice by administering
30 µg of mAb (i.p.) on Day +1 and +4, relative to infection, respectively. Survival of
mice served as an endpoint.

Results. Four different mAb-producing hybridoma cells generated lg that
bound to AB and KPC. 40–80 µg/mL of mAb resulted in killing AB or KPC in vitro. Two of mAbs (25 µg/mL each) resulted in protecting A549 cells from AB- or KPC-induced damage by ~80% vs. cells incubated with isotype-matching Ab
(P< 0.05). Finally, one of the mAb resulted in 70% or 100% long-term survival of mice
infected with lethal doses of KPC or AB, respectively (P< 0.05).

Conclusion. We used Candida Hyr1p to generate cross-protective mAbs against MDR
AB and KPC. Our results warrant the further development of these mAbs as novel
immunotherapeutics against MDR GNB.

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