New-generation polymyxins that target multidrug-resistant Gram-negative bacteria. The lead candidate novel lipopeptide antibiotic is in advanced preclinical development and has demonstrated superior \textit{in vivo} efficacy and safety over currently used polymyxin antibiotics.

\begin{itemize}
  \item Novel lipopeptide antibiotics targeting multidrug-resistant Gram-negative bacteria
  \item Greater efficacy (particularly against lung infections) and significantly less nephrotoxicity in animal models than currently available antibiotics
  \item Identified lead candidate that is amenable to scale-up manufacturing and ready for IND-enabling studies
  \item Potential for administration via intravenous, inhaled or topical routes
\end{itemize}

\textbf{THE CHALLENGE}

The WHO has identified antimicrobial resistance as one of the three greatest threats to human health.\textsuperscript{1} There is an enormous and growing threat from the emergence of bacteria that are resistant to almost all available antibiotics. Whilst a few new antibiotics targeting multidrug-resistant Gram-positive bacteria have been approved in the past two decades, there has been a marked decline in the discovery of novel antibiotics for infections caused by Gram-negative pathogens.\textsuperscript{2}

In the 2017 WHO Priority Pathogen List, \textit{Pseudomonas aeruginosa}, \textit{Acinetobacter baumannii} and \textit{Klebsiella pneumoniae} are identified as the top concerns urgently requiring novel antibiotics.\textsuperscript{3} Hospitals worldwide have experienced outbreaks of infection from these bacteria that are resistant to all commercially available antibiotics except last-line therapy polymyxins.\textsuperscript{3}

Use of available polymyxins to treat certain Gram-negative bacterial infections is limited by their narrow therapeutic window and nephrotoxicity. Parenteral administration of colistin (as its inactive prodrug) and polymyxin B is associated with potential kidney injury in up to 60\% of patients, limiting routine use of these agents in treating multidrug-resistant Gram-negative bacteria.\textsuperscript{4} Both show negligible efficacy against lung infections in animals and patients. However, polymyxins are being used as the last-line option to treat infections where all other antibiotics are inactive.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Mic (\mu g/mL) & in vitro & in vivo & Pharmacodynamics & Medicinal Chemistry & Pharmacokinetics/
\hline
\textbf{P. aeruginosa} & FADDI-PA038 & FADDI-KP032 & FADDI-AB032 & FADDI-PA034 & FADDI-KP022 & FADDI-AB034
\hline
\textbf{A. baumannii} & FADDI-AB034 & FADDI-KP024 & FADDI-AB034 & FADDI-PA034 & FADDI-KP022 & FADDI-AB034
\hline
\textbf{K. pneumoniae} & FADDI-PA034 & FADDI-KP032 & FADDI-AB032 & FADDI-PA034 & FADDI-KP022 & FADDI-AB034
\hline
\end{tabular}
\caption{Minimum inhibitory concentrations (MICs) of polymyxin B and lead candidate against MDR clinical isolates.}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Peptide} & \textbf{n} & \textbf{Graduation of Kidney Damage} & \textbf{Control} & \textbf{3} & \textbf{No Grade} & \textbf{Polymyxin B} & \textbf{3} & \textbf{Grade 2 Damage} & \textbf{Lead candidate} & \textbf{3} & \textbf{No Grade} \\
\hline
\end{tabular}
\caption{Assessment of kidney histological damage after treatment (72 mg/kg) with polymyxin B or the lead candidate lipopeptide in a mouse nephrotoxicity model.}
\end{table}

\textbf{THE OPPORTUNITY}

Monash University has extensive academic and industrial experience in medicinal chemistry, pharmacokinetics/ pharmacodynamics, and \textit{in vitro} and \textit{in vivo} evaluations of antibiotics. Monash seeks a partner to complete advanced IND-enabling preclinical assessment of its lead candidate lipopeptide and to undertake clinical development.

\textbf{THE TECHNOLOGY}

Using their polymyxin drug discovery platform, researchers from the Monash University have identified a series of proprietary polymyxin analogues that are active against Gram-negative ‘superbugs’ (Table 1).

\textit{In vivo} efficacy and toxicity studies in rodents demonstrate that, compared with polymyxin B and colistin, the lead candidate lipopeptide can be safely dosed at higher levels to achieve significantly improved efficacy against infections, particularly pneumonia (Figure 1), with significantly less nephrotoxicity (Table 2).

\textbf{References}


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