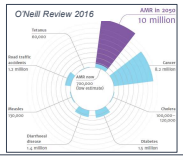
The discovery of novel gold(I) complexes for the treatment of Gram-positive and Gram-negative bacterial infections

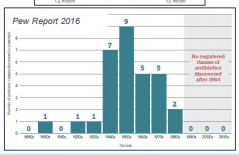
Jonathan Powell[1], Meriel Major[1], Gabriel Negoita-Giras[1], Lucie Guetzoyan[1], Danny Allen[1], Nicholas Chapman[1], Nikki D'Arcy[2], Nazila Jafari[2], Katja Brunner[2], Dagmar Alber[2], Ian Holmes[2], Alan Naylor[3], Richard Rutter[2], N. Paul King[2]

[1]Domainex Ltd, Chesterford Research Park, Little Chesterford, Saffron Walden, CB10 1XL;
[2]Auspherix Limited, Stevenage Bioscience Catalyst, Stevenage, Herts, SG1 2FX
[3]Alan Naylor Consultancy Ltd, Royston, UK

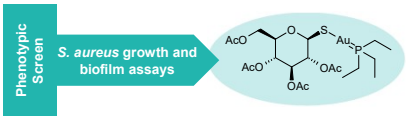
1. The Need for New Classes of Gram-negative Antibiotics

- Bacteria have become increasingly resistant to existing antibiotics and the spread of drug-resistant bacteria has become a significant issue.
- It is estimated that 50-60% of hospital-acquired infections (HAIs) in the U.S. are caused by antibiotic-resistant bacteria including the so-called ESKAPE pathogens (*E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa & Enterobacter* spp.).
- The discovery and development of new antibiotics has slowed in recent decades and no novel class of antibiotic has been brought to the market in >30 years.
- The World Health organisation (WHO) has stated that humanity is facing the prospect of returning to a pre-antibiotic era in which common infections and minor injuries could be lethal.
- Thus, there is a significant need for new antibacterial agents especially against Gram-negative bacteria.





2. Hit ID: Auranofin Exhibits Gram-positive Activity



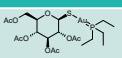
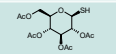
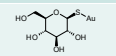
- Phenotypic screening a library of FDA-approved drugs led to the identification of Auranofin (Ridaura) as a potent agent against Gram-positive bacteria:
  - Inhibition of planktonic growth & prevention and dispersal of biofilms.
- Auranofin is a gold complex used in the treatment of rheumatoid arthritis.
- It is the 3rd member of this class and the only one with oral bioavailability.
- Auranofin exists as a discrete linear, monomeric complex containing a gold(I) ion coordinated to a triethylphosphine ligand & tetraacetylthioglucose ligand.

3. Strategy Overview: LO

Three key areas have been investigated:

- ***Linker (X):*** *S, N* and *C* linkers have been comprehensively explored.
- ***Ligand (R):*** Electronics & sterics within each series have been evaluated with respect to *in vitro* antibacterial activity.
- ***Phosphine:*** Simple, commercial analogues initially targeted. SAR suggested this was a key area of the molecule worthy of extensive investigation. A plethora of bespoke phosphines have since been synthesised.

4. Initial SAR

Compound	Structure	*S. aureus* MIC (μg/mL)*
Auranofin		0.9
Chloro(triethylphosphine) gold(I)		0.8
1-Thio-β-D-glucose tetraacetate		>2000
Aurothioglucose		>2000

Gold and phosphine are required for antibacterial activity

**Vancomycin: 0.25-4 ug/mL*

5. Phosphine Optimisation: Gram-negative activity

Phosphine	Ligand	*S. aureus* MIC (μg/mL)	*E. coli* MIC (μg/mL)	*K. pneumoniae* MIC (μg/mL)	*A. baumannii* MIC (μg/mL)	*P. aeruginosa* MIC (μg/mL)
		<0.8	3.1 - 6.3	3.1	0.8 - 1.6	6.3 - 12.5
		1.0	6.3	6.3	nd	12.5
		<0.8 - 1.6	25 - 75	25 - 50	nd	25
		1.6 - 3.1	>100	>100	nd	>100

- **Size** and **lipophilicity** of phosphine have a large influence on Gram-negative activity.
- Phosphines that provide Gram-neg activity sit within a defined physicochemical space.
- Me_3P-containing compounds often have good activity against Gram-negative bacteria.

6. Ligand SAR

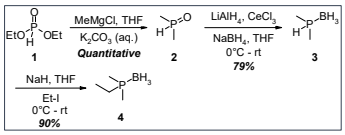
Ligand	Linker	Phosphine	*S. aureus* MIC (μg/mL)	*E. coli* MIC (μg/mL)	*K. pneumoniae* MIC (μg/mL)	*A. baumannii* MIC (μg/mL)	*P. aeruginosa* MIC (μg/mL)*
	*S*		0.8	1.6 - 3.1	1.6 - 3.1	0.8 - 1.6	3.1
			<0.8	3.1 - 6.3	3.1	1.6 - 3.1	3.1-6.3
	*N*		<0.8	3.1 - 6.3	3.1	0.8 - 1.6	6.3 - 12.5
			<0.8	<0.8	3.1	nd	12.5
	*C*		0.8	6.3	6.3	1.3	6.3
			<0.8	3.1	6.3	nd	12.5 - 50

- Broad-spectrum activity obtained for a variety of linkers and ligands.

**Levofloxacin: 7.5 ug/mL*

7. Synthetic Method Development

- The synthesis of lower alkyl phosphines is not trivial.
- Robust synthetic routes have been developed to provide access to phosphine ligands that probe the physicochemical space:

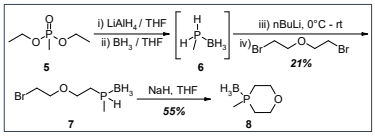


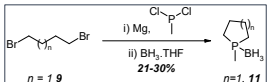
Ethyldimethyl phosphine:

- Efficient synthesis of key intermediate, dimethylphosphine borane **3** achieved.
- Synthetic route applicable to other PMe_2R analogues.

Oxaphosphinane:

- Synthesis *via* secondary phosphine borane developed.
- Route has also been utilised for the synthesis of other cyclic phosphines.

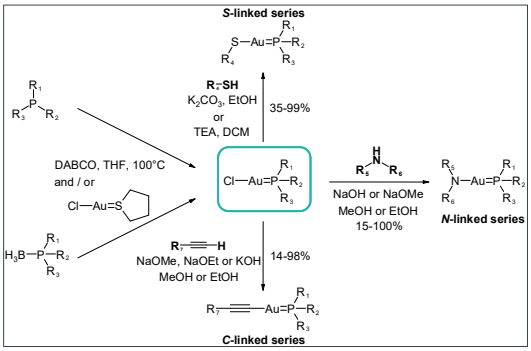




Phospholane & phosphinane:

- Efficient, one-pot double Grignard-cyclisation provides key phosphine borane intermediate in a single step.

8. Summary of Synthetic routes



- Synthesis of each series proceeds *via* a common gold(I) chloride intermediate.
- Robust chemistry – synthesis of final complexes on >1g scale have been performed.
- Synthetic methodology permit a wide variety of analogues to be prepared.

9. Conclusions & Future Work

- A novel class of gold(I) antibiotics have been developed, with broad spectrum antibacterial activity against the so-called ESKAPE pathogens.
- Three distinct chemical series have been identified and the specific structure of the phosphine ligand is a critical determinant of Gram-negative activity.
- Further exploration of the phosphine to probe the physicochemical space required for Gram-negative activity is currently underway.
- Following systemic dosing in rodents, compounds show activity in plasma and urine *ex-vivo* bioassays.
- Lead compounds are being evaluated in rodent infection models.
- Overall, these findings present a potential opportunity to tackle the growing threat of global antimicrobial resistance.

Domainex welcomes interest from any potential collaborators, industrial or academic. If you would like to learn more about applying our drug-discovery platform to other targets, please contact:
catherine.stace@domainex.co.uk or rachel.pearce@domainex.co.uk, www.Domainex.co.uk