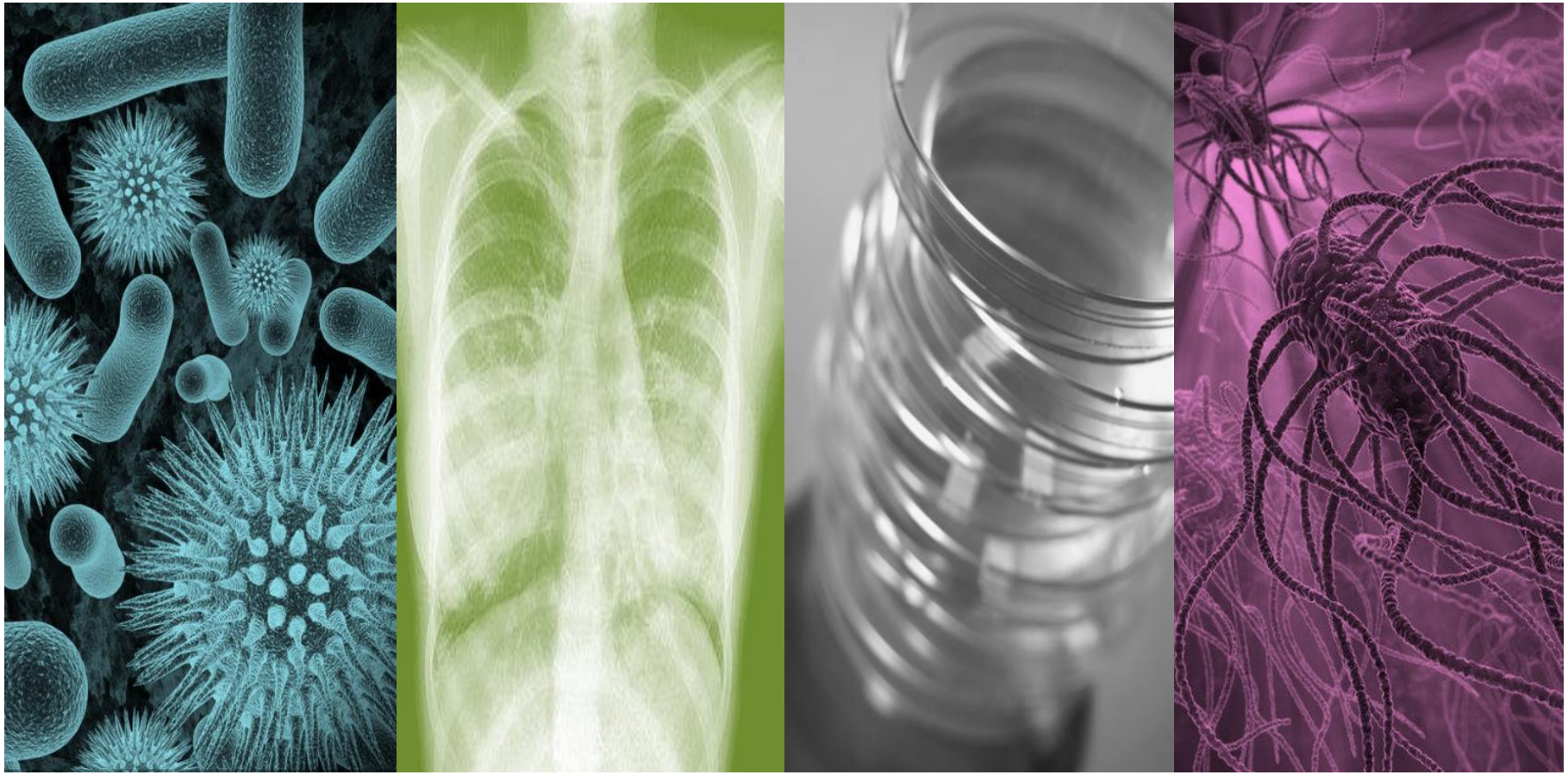
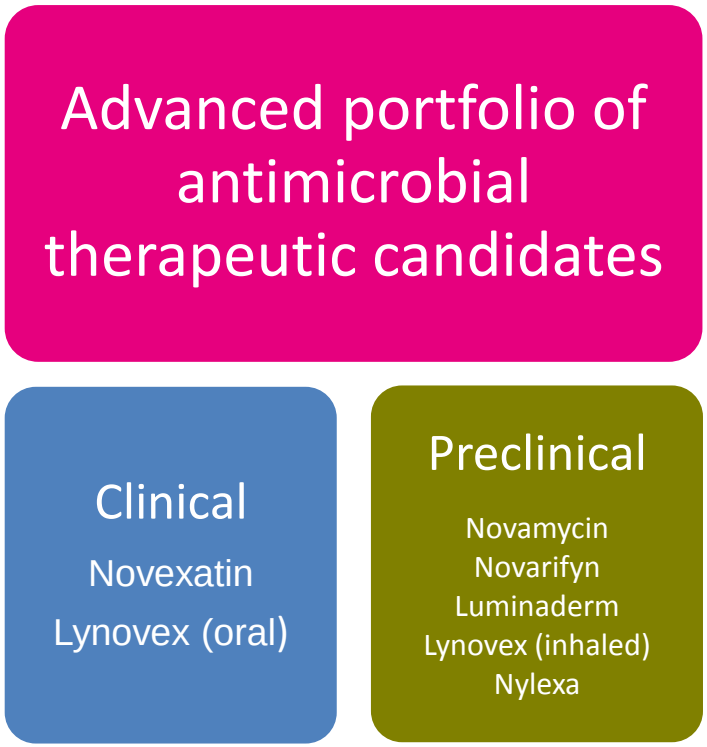
NovaBiotics

SULSA AMR event
April 26-27th, 2018



Overview

- Clinical-stage biotechnology business
- Developing novel approaches to tackling antimicrobial resistance (AMR)
- First-in-class therapies for difficult to treat, medically unmet diseases
  - Antifungal
  - Antibacterial
- Developed from clinically & commercially validated proprietary technology platforms

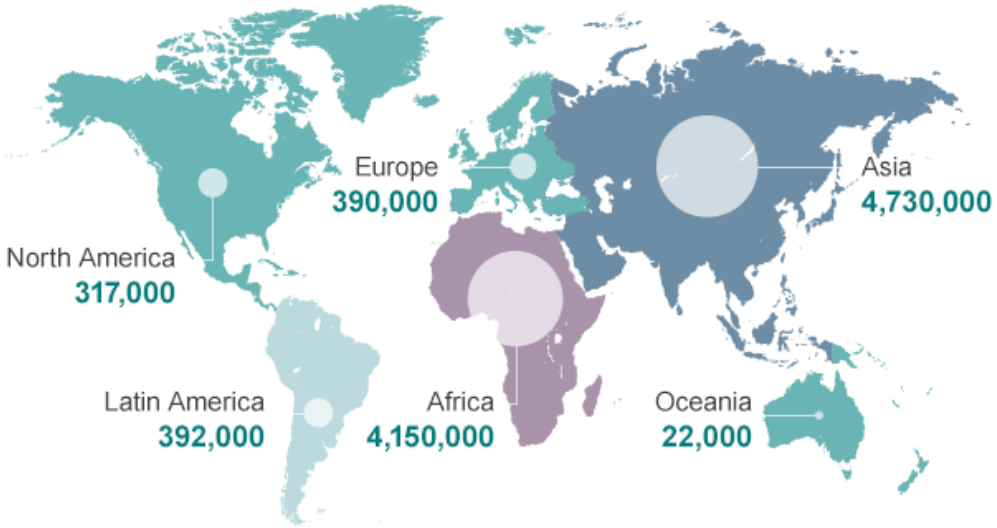


- Aberdeen, UK based (HQ)
- US office in Raleigh, NC
- Incorporated in 2004 (Spun out of the Rowett Research Institute(University of Aberdeen)

A Global Health Crisis

Antimicrobial resistance (AMR)

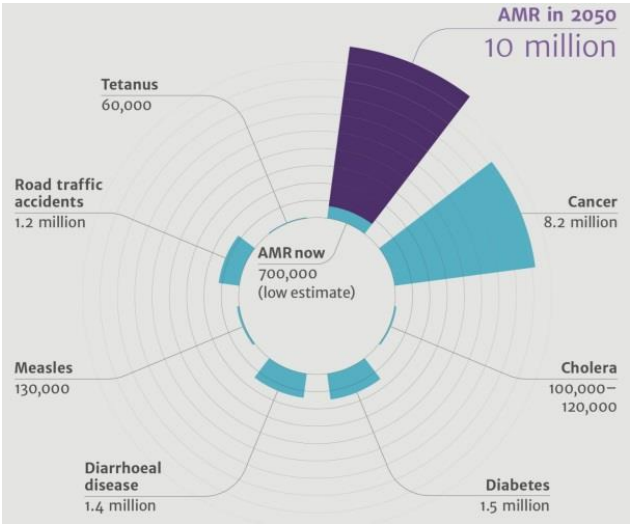
Over/inappropriate use (healthcare/agri) of antibiotics (1940s ++)



Source: Review on Antimicrobial Resistance 2014

10m deaths by 2050

Costing £66 trillion



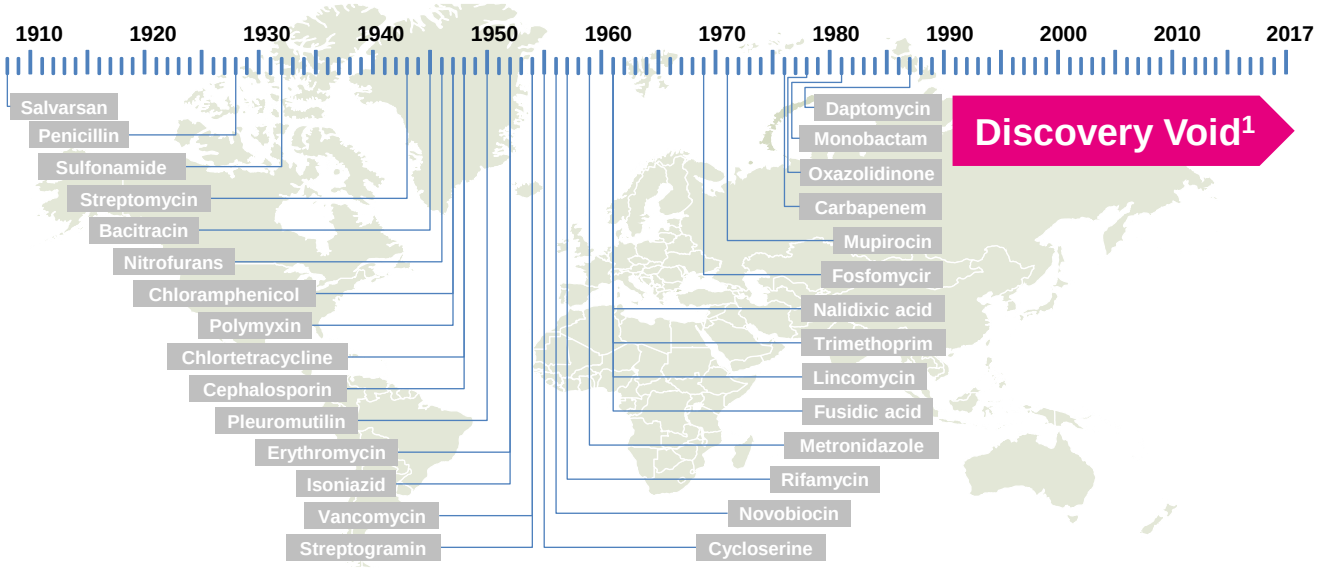
Massive Societal & Economic impact

- 700,000 deaths annually
- **>5 billion days** of lost productivity
- **>1,000,000** ++plus carers affected

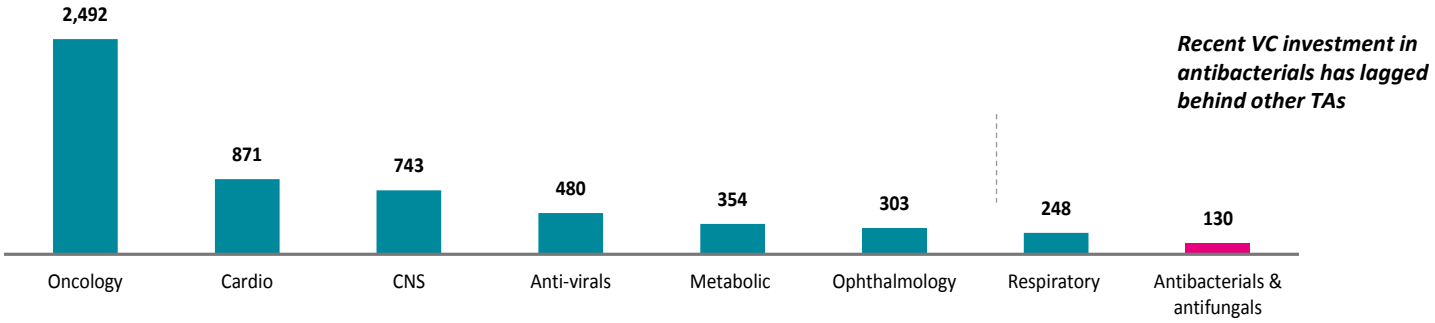
The Antimicrobial Paradox

Despite AMR crisis and a global anti-infectives market worth €80 bn: NO PIPELINE

- **Pharma "Discovery void" from the late 1980s**



- **"Underinvestment" – as seen by VC investment by therapeutic area ($m)[2]**

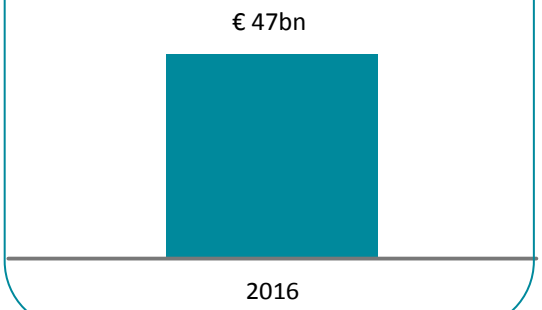


The Antimicrobial Paradox

Despite AMR crisis and a global anti-infectives market worth €80 bn: NO PIPELINE

- Increasing burden & HIGHLY significant POTENTIAL market

Global annual spend on antibacterials:

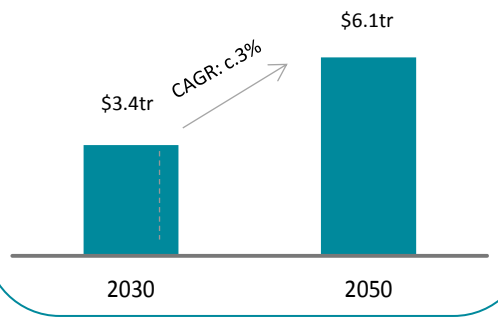


NovaBiotics now one of VERY FEW companies with Phase IIb + clinical stage anti-infective assets

'opportunities'/need for game-changing new therapies in fungal as well as bacterial disease

- 'Broken' economic model
- Pull incentives
- New-old drugs (restricted)
- Drug pricing not recognising life saving potential of antimicrobials
- Need next-generation antimicrobials with novel MOAs that mitigate/avoid shortcomings of existing classes

Estimated loss in global economic output p.a. if AMR is not addressed[3]:



The Concept

Targeting infection from the host's side

- With antimicrobial peptides (AMP) & aminothiols; cornerstones of first-line host defence
- AMP/host defence peptides long since mooted as a next generation of antimicrobial; "non-antibiotic anti-infectives"
- Therapeutic potential not yet realised however
  - Despite current desperate need for new antimicrobials
- Running before we could walk WRT previous forays into the therapeutic application of HDP versus AMP??
  - Naïve approach of applying endogenous AMP analogues or peptide fragments – has given AMP drugs a "bad rep"
- Endogenous AMP are not candidate drugs in their own right but are a blue print for novel druggable peptide antifungals and antibacterials
- Aminothiols and cysteamine…….

The Concept

Existing approaches

Microbial derived antibiotics

Facilitating ‘microbe-wars’, driving selection

Resistance inevitable

The Concept

Existing approaches → **New approaches**

Microbial derived antibiotics

↓

Facilitating ‘microbe-wars’, driving selection

↓

Resistance inevitable

Immune, host derived non-antibiotic antimicrobials

↓

Capitalising on host defence systems that have co-evolved with microbes, developed to mitigate resistance

↓

New drug classes - resistance mitigated

NovaBiotics

The Concept

Existing approaches

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New approaches

Immune, host derived non-antibiotic antimicrobials

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New drug classes - resistance mitigated

New approaches

Combine non-antibiotic antimicrobials with existing antibiotics

Potentiate the activity of existing classes

Extend lifespan/re-invigorate expiring antibiotic armoury

The Concept

NovaBiotics

arsanis

Nosopharm
First-in-class Anti-Infectives

PBD BIOTECH

AMPLIPHI BIOSCIENCES CORPORATION

MADAM THERAPEUTICS

mB

Adenium Biotech

POLYPHOR

MERCK

SPERO THERAPEUTICS

ENBIOTIX

ARIDIS Pharmaceuticals

New approaches

Immune, host-derived non-antibiotic antimicrobials

Capitalising on host defence systems that have co-evolved with microbes, developed to mitigate resistance

New drug classes - resistance mitigated

New approaches

Combine non-antibiotic antimicrobials with existing antibiotics

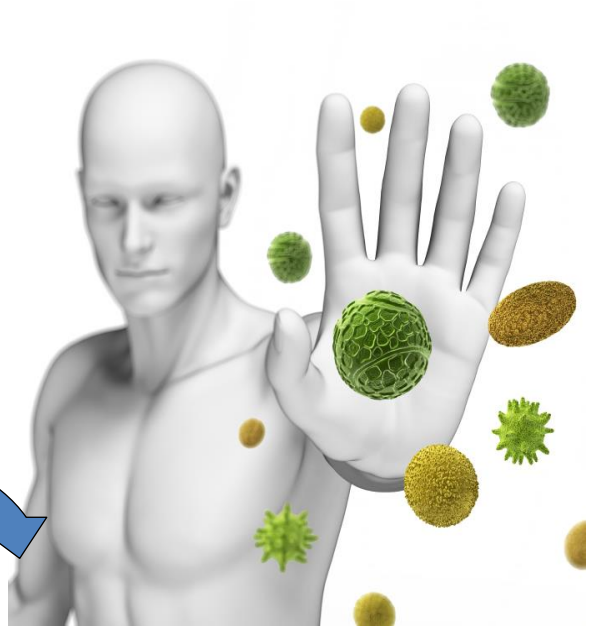
Potentiate the activity of existing classes

Extend lifespan/re-invigorate expiring antibiotic armoury

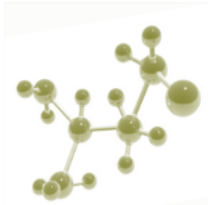
Leading Innovation

- Alternative approach - non antibiotic antimicrobials
- Developed through rational/intelligent drug design – smart immunology
- Created by nature – NOVEL therapeutic mechanism of action:
  - **Kills targets and does so more rapidly than conventional drug classes**
  - **Works against metabolically active and inactive microbes/biofilms**
  - **Agnostic to drug resistance status of the target**
  - **Acquired resistance mitigating mechanism of action**
  - **Distinguishes host from pathogen cells; placebo-like safety**

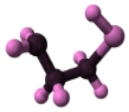
Immunology transforming infection in same way as it has oncology & inflammation



2 new classes of AMR mitigating antibacterial & antifungal treatments



Antimicrobial Peptides



Cysteamine

Innate effector molecules with MOAs agnostic to resistance status & minimise opportunities for acquired resistance developing

Re-engineer immune defence molecules produced by the body's white blood cells & epithelial tissues

Platform

- Two proprietary platforms
- Novel approaches to combatting AMR leveraging the innate immune system's defence mechanism

Novel peptide approach

Novel modified antimicrobial peptides (AMPs)

- Platform of novel synthetic peptide antimicrobials
- 'Druggable' molecules with enhanced functionality over endogenous forms
- Microbicidal, membrane-targeted MoA mitigates opportunities for acquired resistance
- Rapid time to kill with activity against non-metabolically active pathogens
- Active against multiple drug resistant (MDR) pathogens – agnostic with regard to existing AMR mechanisms in target pathogens
- Excellent safety profile: no off-target pharmacology
- Broad application: Gram negative and positive bacterial infections and fungal infections

Adjunct approach

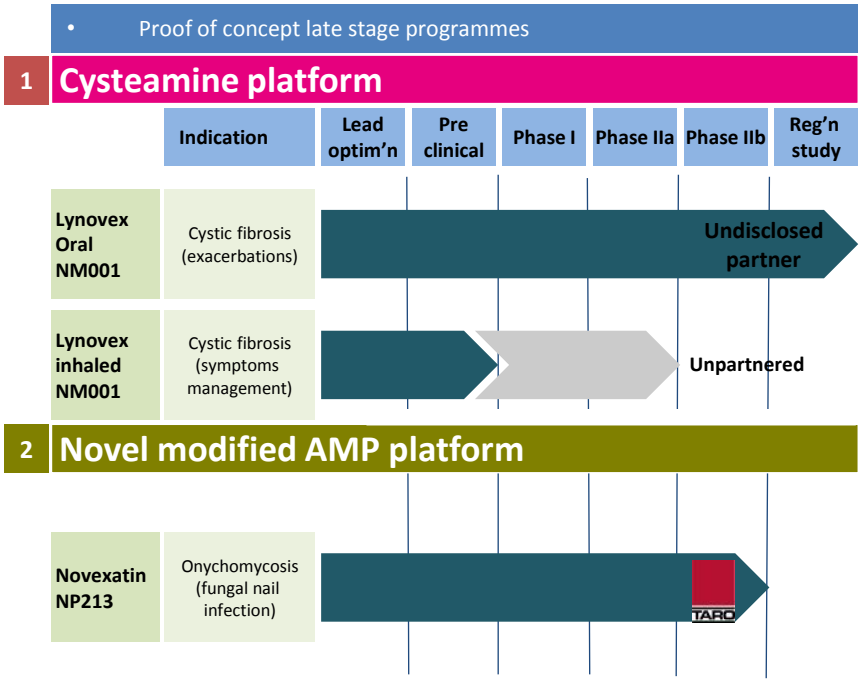
Re-activate ineffective existing antibiotics

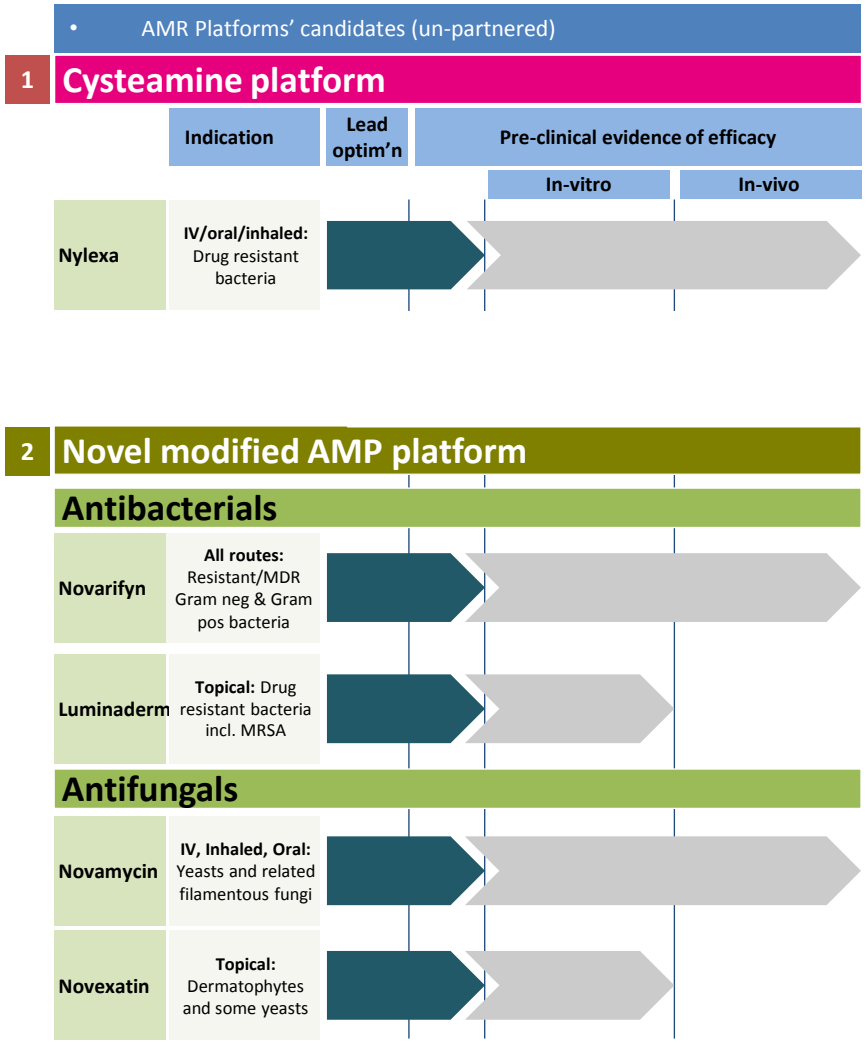
Cysteamine + Antibiotics

- Cysteamine is a well known API used in the clinic for >25 years
  - Low-risk, repurposed molecule
- Innate immune factor – breakdown product of Co enzyme A
- Adjunct mechanism of action potentiates existing antibiotic classes
- Stand-alone characteristics include antibiotic, anti-biofilm and anti-virulence properties
- Broad application: Gram negative and positive bacterial infections; respiratory, UTI and SSSI
- Pre-registration trial stage – cystic fibrosis exacerbations

Pipeline

•NovaBiotics' technological platform has been validated through late stage programmes and preclinical work





Advancing first-in class, non-antibiotic antimicrobials

5 molecules, 8 programmes

NovaBiotics

Market focus

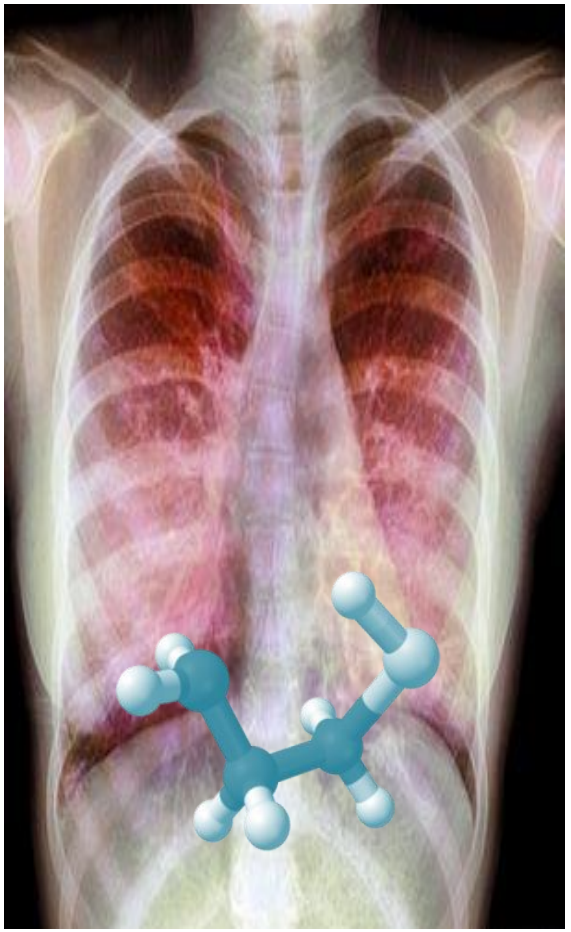
Lynovex	Novexatin
Market for this life limiting disease, affecting 70,000 globally (30,000 in US, 30,000 in Europe, 10,500 in UK) is $6 billion. Vertex(kalydeco and orkambi) therapies/pricing have massively impacted market value	Potential step change therapy for fungal nail infection (onychomycosis) which affects 12% of the worlds population. By 2022, the global market for this disease is forecast as being greater than $6 billion. Anacor (kerydin) and Valeant (jublia) therapies 'de-genericised' a terbinafine dominated market and switched to topical for oral treatments

Proof of concept
De-risk portfolio
Generate income

Luminaderm	Novarifyn	Novamycin	Nylexa
The Methicillin-Resistant *Staphylococcus aureus* (MRSA) treatment market will rise to $1.45 billion by 2024, according to research and consulting firm GlobalData. GSKs mupirocin as benchmark for nasal decolonisation market	The worldwide market for antibacterials is considerable at $ 45 billion; more than 50% of the overall anti-infectives market at $65 billion. Developed from the same technology platform as Novexatin so the route to clinic has already been significantly de-risked.	Global market for invasive fungal disease (IFD) of $5.7 billion and burden increasing with aging population and survival rates as low as 20% Novamycin is derived from the same peptide technology platform as Novexatin/NP213 and so the route to clinic and market for Novamycin has already been significantly de-risked. Isavuconazole/cresemba as relevant product valuation benchmark	One potential solution to the worsening antibiotic resistance crisis and a strategy that could be introduced into clinical practice within a much shorter timescale than any new antibiotic(s) developed from first principle. The estimated cost of global action to fight AMR is estimated to be $40 billion over a 10 year period.

First-in-class antibacterial and antifungal solutions
Differentiated classic and novel approach to combatting AMR
Leveraging the immune system's defence mechanisms

- First in class, **highly differentiated** approach to tackling cystic fibrosis
  - $6 Bn global market
- Orphan drug designation – EU & US
- Addresses CF lung disease symptoms
  - Antimicrobial
  - Antibiotic potentiating
  - Antibiofilm
  - Mucolytic
- CFTR mutation agnostic – use alongside standard of care therapy including disease modifiers (Vertex etc)
- **Multi-functionality**, two routes of **delivery**
- Oral form for acute (Gram negative bacterial) exacerbations: Global PhIIb study (CARE CF 1) underway; data read-out Q3 2018

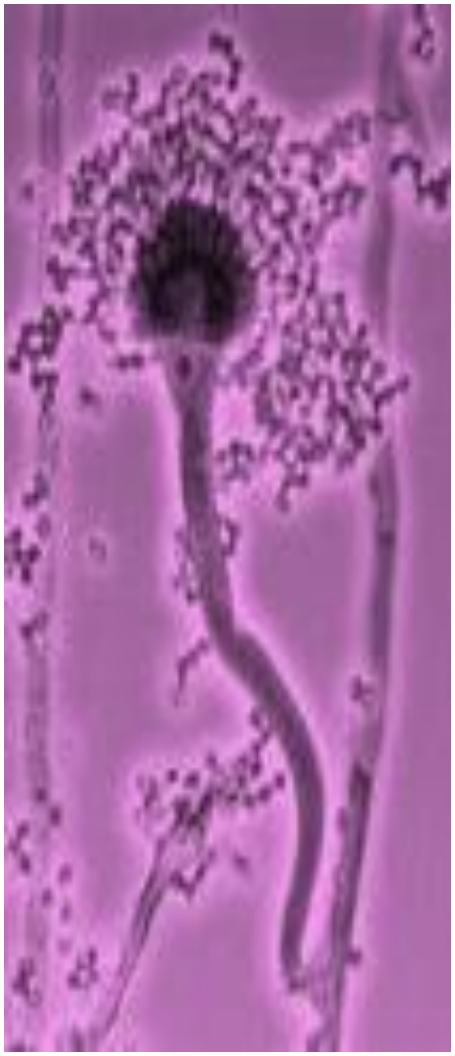


Repurposing an API with >25 y of clinical use history

	Exacerbation specific	Mucolytic	Antibacterial	Antibiofilm	Potentiatior	Modifier
Lynovex®	Yes (oral)	*****	**	****	****	No
Tobramycin	No	No	*****	No	No	No
Pulmozyme	No	***	No	No	No	No
Alginate Lyase	No	*	No	No	No	No
MucoMyst/NAC	No	**	*	No	No	No
Lumacoftor/ Ivacaftor	No	No	No	No	No	*****

A superior, multi-active therapeutic option for CF with unique application in exacerbations

- Global market for invasive fungal disease (IFD) ~$6bn
- Novamycin in development for IFD caused by *Aspergillus spp,* rare Mucorales moulds in the first instance, also *Candida spp*
  - Emergence of MDR fungi (*C. auris*)
- Novel, membrane lysing fungicidal mechanism of action
- Major therapeutic USPs over (limited) existing antifungal therapeutic classes include rapid cidal action & lack of any off-target pharmacology/tox
- Conclusion of IND-enabling preclincal work and entry to clinical phase 2019



Innovation - peptides

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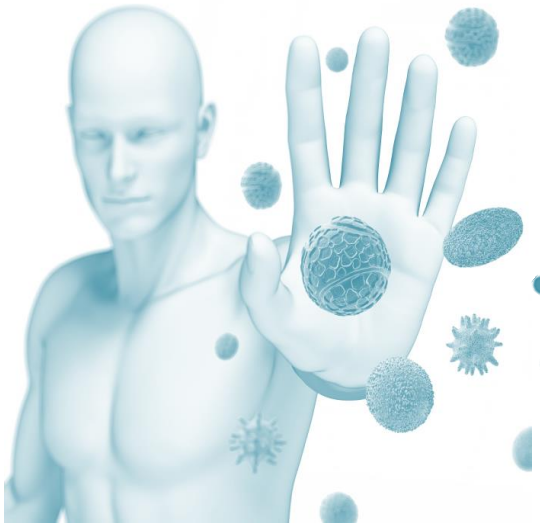
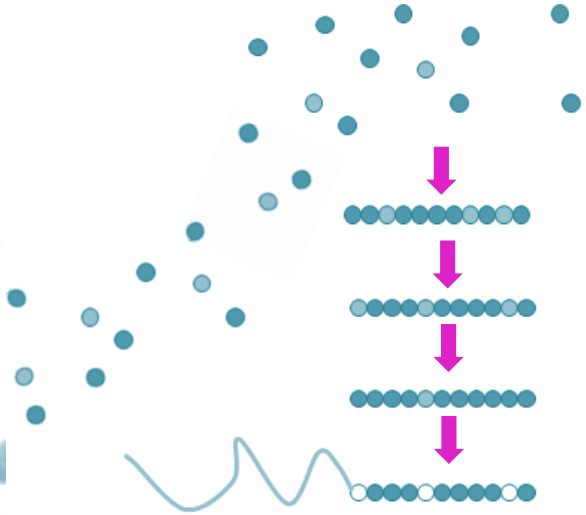
Immunology transforming infection as it has oncology & inflammation



Biology-led, rational/intelligent drug design process

Re-engineering immune defence molecules produced by the body's white blood cells & epithelial tissues; host defence peptides (HDP); cornerstone of innate immune defence



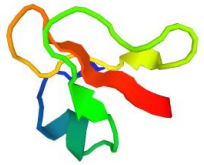
HDP are not druggable!

1.Identifiy essential cationic antifungal components within endogenous AMP

2. Determine optimal peptide length

3. Secondary structure

4. Modifications & formulation



Human β-defensin 2

HDP

AMP

$[Arginine]_{13}$

	Azoles	Echinocandins	AmB	**Novamycin**
Mechanism of action	Fungistatic	static/cidal	Fungicidal	Fungicidal
Time to kill	48 h >>MIC_{100}	12 h >>MIC_{100}	8 h >MIC_{100}	30 min at MIC_{100}
Drug target	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell membrane - lysis
Resistance	Yes	Yes	Yes	No
Broad spectrum coverage	No	No	??	Yes
Mode of delivery	oral, p/iv, mc	iv, mc	p/iv	Inhaled, parenteral, mc
Side effects	various, cardiotox	rare	various, renal	No
Empirical therapy/prophylaxis	??	No	No	Yes

In vitro broad spectrum activity data for Novamycin against yeasts & moulds

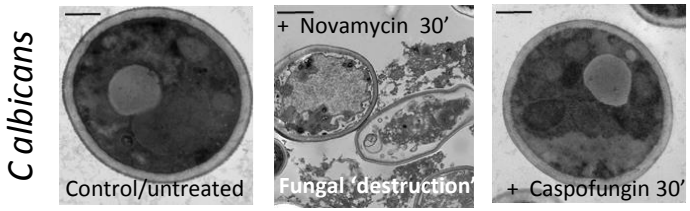
Fungal species MIC range 0.5-2 μg/ml
Candida albicans (n=50)
Candida glabrata (n=20)
Candida parapsilosis (n=20)
Candida krusei (n=16)
Candida tropicalis (n=17)
Candida auris (*)
Candida dubliniensis (n=7)
Cryptococcus neoformans (n=11)
Cryptococcus gattii (n=3)
Aspergillus fumigatus (n=13)
Aspergillus niger (n=2)
Aspergillus terreus (n=5)
Aspergillus flavus (n=3)
Exophiala dermatitidis (n=6)
Scedosporium apiospermum (n=3)
Mucorales strains

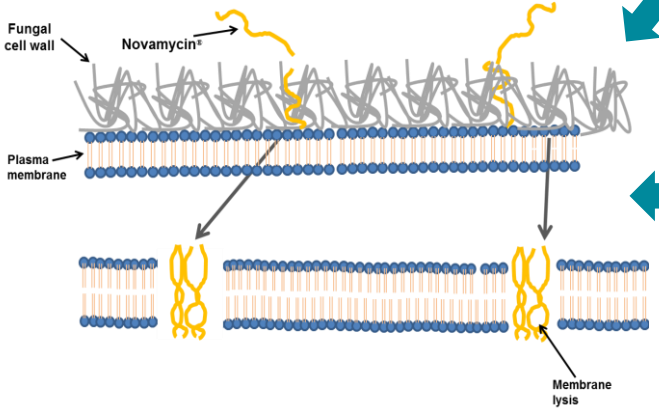
Peptides active against spores & hyphae (Novexatin & Novamycin)

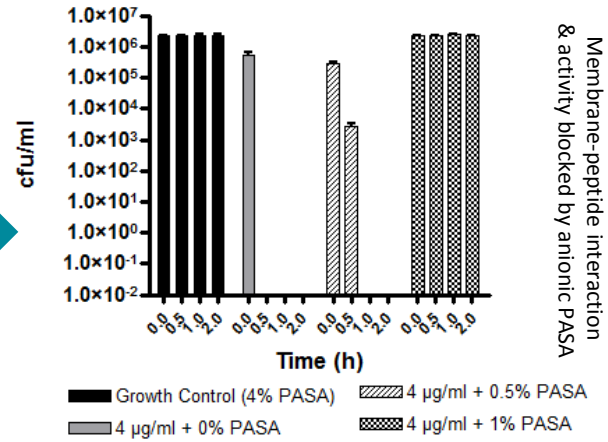
In vitro rapid time of kill data

Pathogen	Antifungal	Time taken
C. albicans	**Novamycin®**	**0.5 h**
	Fluconazole	6 h
	Caspofungin	4 h
C. auris	**Novamycin®**	**4 h**
	Amphotericin B	4 h
	Fluconazole	>48 h
	Caspofungin	6-24 h
A. fumigatus germlings	**Novamycin®**	**2-4 h**
A. fumigatus spores	**Novamycin®**	**2-4 h**
	Amphotericin B	48 h
	Voriconazole	48 h
	Posaconazole	24 h
	Caspofungin	48 h

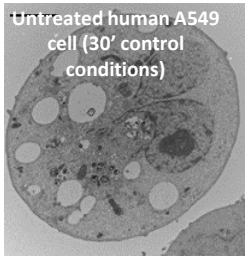
Data confirming Novamycin's membrane-acting, fungicidal mechanism

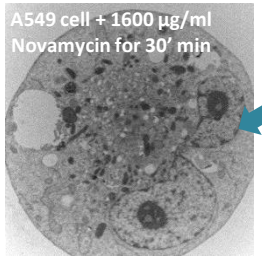




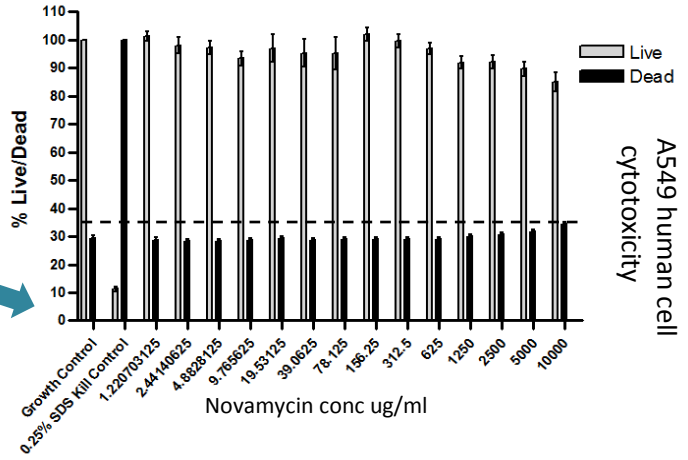


In vitro placebo-like safety profile confirmed for Novamycin – IND tox underway

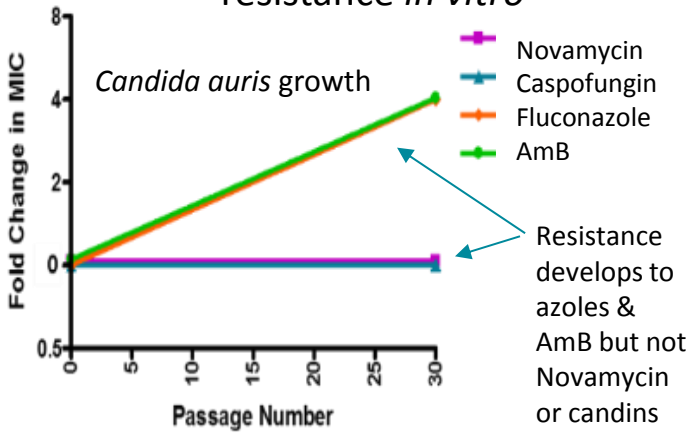




- No cytotoxicity or haemolysis *in vitro* at >1,000 x MIC_{100}
- Maximum Tolerated Dose in rodents & dogs >100 x MIC_{100}

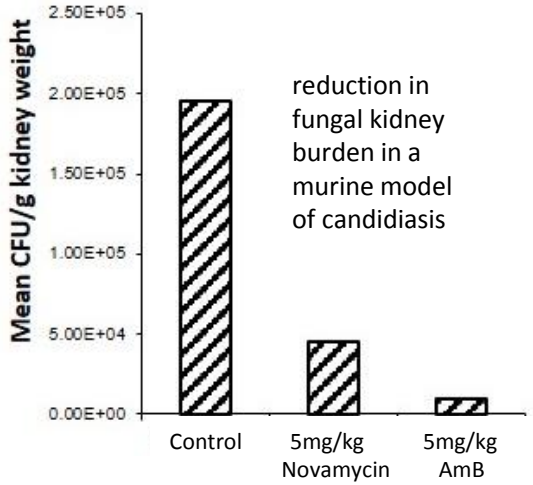


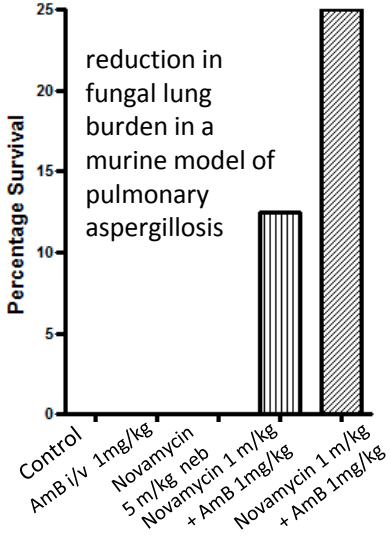
Activity against drug resistant fungi & no acquired drug resistance *in vitro*



Preliminary evidence of *in vivo* efficacy obtained

- models not optimised for AMP – API formulation > efficacy?
- Definitive pk/pd profile for Novamycin yet to be established



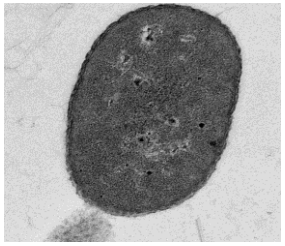


- 2kDa antibacterial peptide
  - Novarifyn 'family – NP432 lead peptide
- R-rich peptide backbone with polar residues at specific loci
- Bactericidal & rapid time of kill (TOK)
- Potent against Gram negative & certain Gram positive organisms (> activity Gram neg)
- Agnostic WRT antibiotic sensitivity
  - Active against MDR/inherently antibiotic insensitive isolates incl. *Acenitobacter baumannii*
- Anti-biofilm activity with MBECs≥MBC/MIC_{100}
- IND programme 2018-19 (use of proceeds)

Active against 'the toughest' resistant/MDR gran-negative bacteria versus existing antibiotic classes

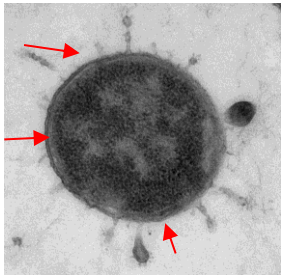
Species	Strain #	NP432 MIC (ug/ml)	Amikacin MIC (ug/ml)	Ceftazidime MIC (ug/ml)	Meropenem (MIC ug/ml)	Colistin MIC (ug/ml)	Levofloxacin MIC (ug/ml)	Aztreonam (MIC ug/ml)	Zosyn MIC (ug/ml)
K. pneumoniae	NDM-1	32	> 256	> 256	256	2	128	256	> 256
	KPC	8	1	64	64	0.5	0.5	> 256	> 256
E. coli	NDM-1 + CTX-M	16	16	> 256	64	2	16	> 256	> 256
	KPC-2 + SHV-12	16	2	> 256	64	1	16	> 256	> 256
	NDM-1	16	4	> 256	8	1	128	128	> 256
	KPC-3	4	2	> 256	32	1	8	> 256	> 256
P. aeruginosa	VIM-2	16	16	> 256	16	1	64	8	128
A. baumannii	OXA-32; TEM-1; OXA-132	16	64	> 256	64	2	8	64	256
	IMP-4	64	128	> 256	128	16	32	128	128
	OXA-66; TEM-1	32	4	256	4	16	32	256	256

Membrane acting mechanism within 15 min of exposure (by TEM)



A. Baumannii

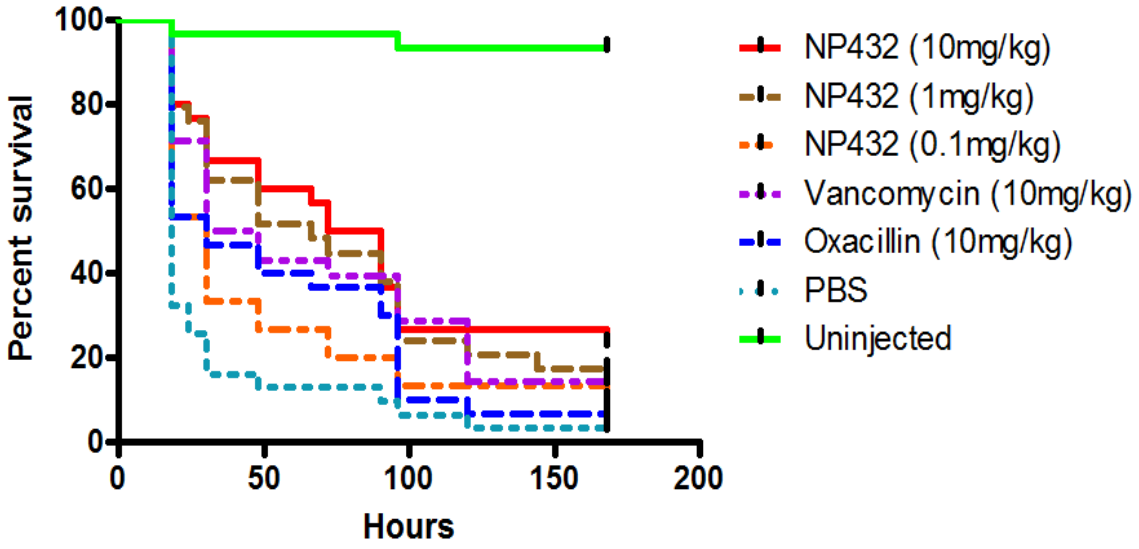
untreated



A. Baumannii

+ 0.25 MIC Novarifyn

Superior to oxacillin and vancomycin *in vivo* (*G mellonella* MSSA survival model)



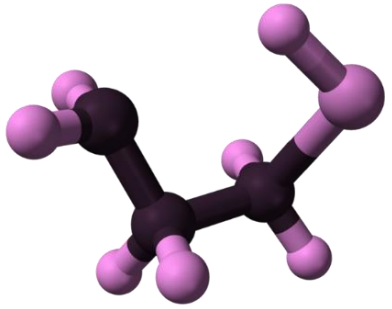
	Carbapenems	Polypeptides	Glycopeptides	Lipopeptide(s)	AM-Peptides Novarifyn
Mechanism	Bactericidal	Bactericidal	Static/cidal	Bactericidal	Bactericidal
Time to kill	> 6 h at MIC_{100}	> 6 h at MIC_{100}	> 6 h at MIC_{100}	> 6 h at MIC_{100}	<30 min at MIC_{100}
Drug target	Cell wall	Cell wall Cell membrane	Cell wall	Cell membrane	Cell membrane
Resistance	Yes	Yes	Yes	Yes	No *(in vitro)*
Coverage	Gram neg & Gram pos	Gram pos	Gram pos	Gram pos	Gram neg & Gram pos
Mode of delivery	iv	Topical, mc inhaled,(iv)	iv, oral, inhaled	iv	iv, inhaled, mc, topical
Active against…..	Metabolically active cells	Metabolically active and inert non-dividing cells	Metabolically active cells	Metabolically active and inert non-dividing cells	Metabolically active, static, SCV etc. cells
Origin	Bacterial	Bacterial Fungal	Bacterial	Bacterial	Human

NovaBiotics

Nylexa™

Patient with altered clinical microbiology	Pre trial microbiology	Post trial microbiology
Patient 1	MRSA	MSSA
Patient 2	PR *P. aeruginosa*	S *P. aeruginosa*
Patient 3	Cip^R *P. aeruginosa*	Cip^S *P. aeruginosa*

Observations from the Aberdeen phase IIa Lynovex clinical clinical trial



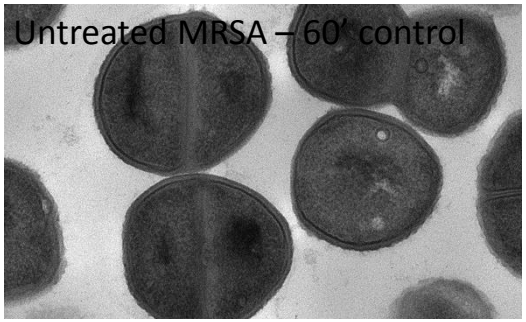
https://www.ncbi.nlm.nih.gov/pubmed/29581193

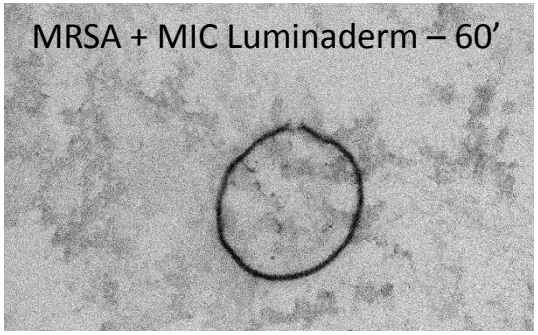
- Parenteral (IV) delivery of a resistance breaking adjunct to existing antibiotics
- 'reactivates' drugs to which bacteria have become resistant
  - Demonstrated *in vitro, in vivo* and clinically
- *In vitro* and *in vivo* data supported by Lynovex clinical data
  - Same active component
- AMR reversed/broken in pathogens of "urgent threat"
  - Public Health agency collaborations

Impact on clinical practice to extend lifespan & utility of existing antibiotic armoury could be highly significant

Luminaderm®

- Lysine based bactericidal polymers
  - Highly potent against MRSA and MDR SA
  - Lysine polymers already established in practice as preservatives
- Topical application
  - **Nasal decolonisation** https://www.ncbi.nlm.nih.gov/pubmed/?term=novabiotics+polymer , skin decolonisation, wound care
  - Outperforms mupirocin - MMRSA eradication
  - Active against biofilms and small colony variants
- **A non-antibiotic antimicrobial**
- Human & animal health applications





The Concept

NovaBiotics

arsanis

Nosopharm
First-in-class Anti-Infectives

PBD BIOTECH

AMPLIPHI BIOSCIENCES CORPORATION

MADAM THERAPEUTICS

mB

Adenium Biotech

POLYPHOR

MERCK

SPERO THERAPEUTICS

ENBIOTIX

ARIDIS Pharmaceuticals

New approaches

↓

Immune, host derived non-antibiotic antimicrobials

↓

Capitalising on host defence systems that have co-evolved with microbes, developed to mitigate resistance

↓

New drug classes - resistance mitigated

New approaches

↓

Combine non-antibiotic antimicrobials with existing antibiotics

↓

Potentiate the activity of existing classes

↓

Extend lifespan/re-invigorate expiring antibiotic armoury

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→ AMP

Novamycin, Novarifyn, Luminaderm

NovaBiotics

arsanis

Nosopharm
First-in-class Anti-Infectives

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→ Cysteamine (Lynovex & Nylexa)

NovaBiotics

SULSA AMR event
April 26th-27th, 2018

@novabiotics @debsoneil