
"Resistance is futile!"
Developing highly adaptive approaches to tackling multi-drug resistant infection
David Cook PhD FSB
Chief Scientific Officer. Blueberry Therapeutics
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BLUEBERRY THERAPEUTICS…

- …is a modern drug discovery and development company which puts people first whether patients, employees, investors or partners
- …has an open, imaginative and fun team environment with a very serious objective: to create new, safe and effective medicines to treat human disease and make patients feel better
- …has a team with extensive experience across all phases of pharmaceutical R&D- idea to clinic and market
- …operates through collaboration and partnership, bringing the best minds and technologies to the problems at hand
- …is committed to the development of innovative therapies to treat diseases where infection and/or inflammation are major factors
- …employs cutting-edge nanopolymer drug delivery technology to exploit both small molecule and biologic approaches in developing treatments

Blueberry Therapeutics site located within the BioHub at Alderley Park

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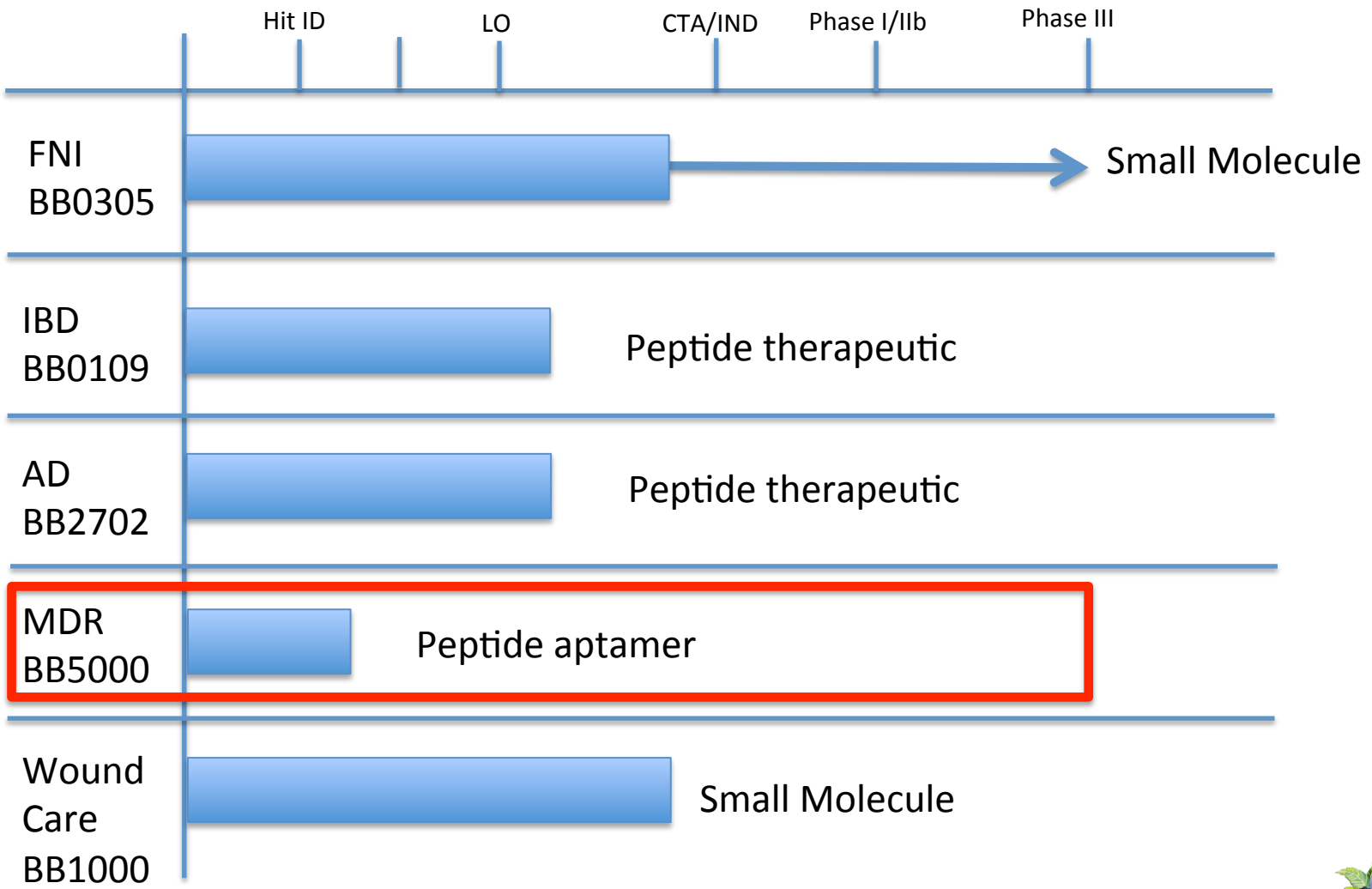

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DEFINING THE PROBLEM

"Antimicrobial resistance poses a catastrophic threat. If we don't act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can't be treated by antibiotics"

– *Professor Dame Sally Davies. Chief Medical Officer, England. March 2013*

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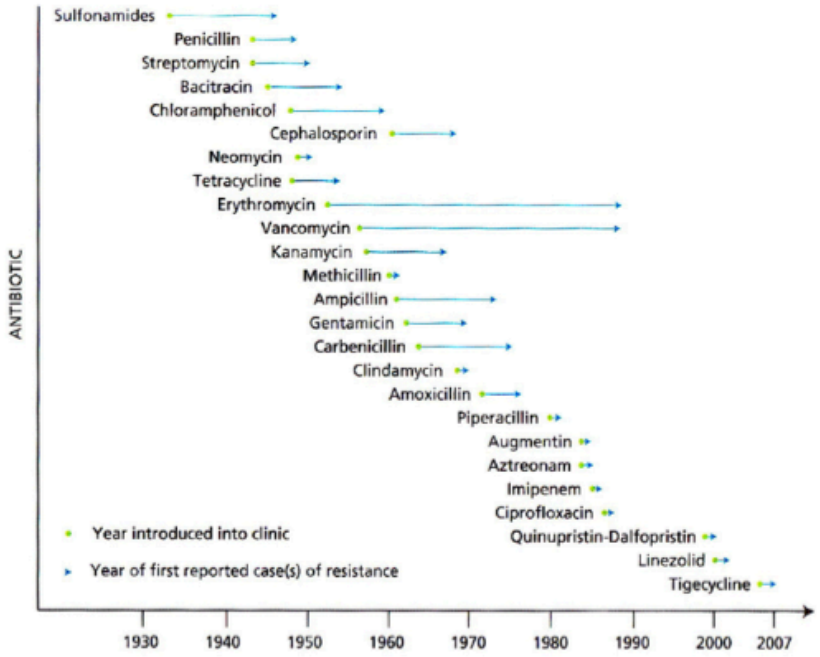
DEFINING THE PROBLEM

Many small molecules are evolutions of existing antibiotics and as such bacteria are “primed” for the emergence of resistance. Resistance may even emerge during clinical trials



Need a fundamentally different approach to tackling bacterial drug resistance

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LOOKING FOR NEW SOLUTIONS
LEARNING FROM ONCOLOGY?

- Move away from general "broad spectrum" approaches (e.g. chemotherapy, radiotherapy)
- Better disease understanding and diagnostics have enabled development of targeted therapies

Cancer
→ *Lung cancer*
→ *Non-small cell lung cancer*
→ *EGFR +ve NSCLC* ← *Treatment*

- R&D concentrates on "narrow spectrum" treatments
- **Is our focus on developing new broad spectrum antibiotics part of the problem?**

Bacterial Infection
→ *Gram+ve bacterial infection* } ← *Current treatment paradigm*
→ *S. aureus infection*
→ *MecA +ve MRSA infection* ← *Treatment?*

WHAT IF…we focus on treating individual infections as such and develop narrow spectrum, species specific antibiotics?

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LOOKING FOR NEW SOLUTIONS

RESISTANCE IS THE PROBLEM…LET'S TREAT RESISTANCE

- We have a number of clinically well understood antibiotics
  - Is the problem therefore one of needing new anti-bacterial targets?
- They just don't work in bacterial species that have either acquired resistance or have intrinsic resistance mechanisms

WHAT IF we block resistance mechanisms…could we restore (or confer) sensitivity to treatment with standard antibiotics?

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BUILDING A DIFFERENT THERAPEUTIC APPROACH

- Narrow spectrum, species specific antibiotic approaches
  - May be less challenging that broad-spectrum approaches
    - Don't need to "treat" organisms that are not part of the disease
  - Will need many therapies
  - Will need rapid diagnostic approaches
  - Will need better understanding of different infectious diseases?
- Treat mechanisms of resistance
  - Would restore sensitivity to well understood antibiotic treatments
  - Will need approaches that can tackle challenging targets (e.g. channels)
  - Respond in a rapid way to new resistance mechanisms as they emerge
- Need an approach that has a rapid development cycle, has a broad range of pharmaceutical modalities and can be coupled to diagnostics in an effective way

LOOKING FOR NEW SOLUTIONS

WHY PROTEIN THERAPEUTICS MIGHT BE THE ANSWER

	Small Molecule Therapeutics	Protein Therapeutics
Typical development cycle to generate a high quality lead	1-3 years	6-12 months
Range of pharmaceutical modalities	Limited	Extensive
Safety considerations	Xenobiotic: every molecule has unique safety profile Target, off-target and compound safety to consider	Based on naturally occurring amino acids. Safety concerns mainly focus on target based liabilities
Use in diagnostics	Limited	Extensive
Target accessability	Intracellular Extracellular	~~Intracellular~~ Extracellular

- Protein based therapeutics have a lot of potential IF we can overcome the problem of intracellular delivery

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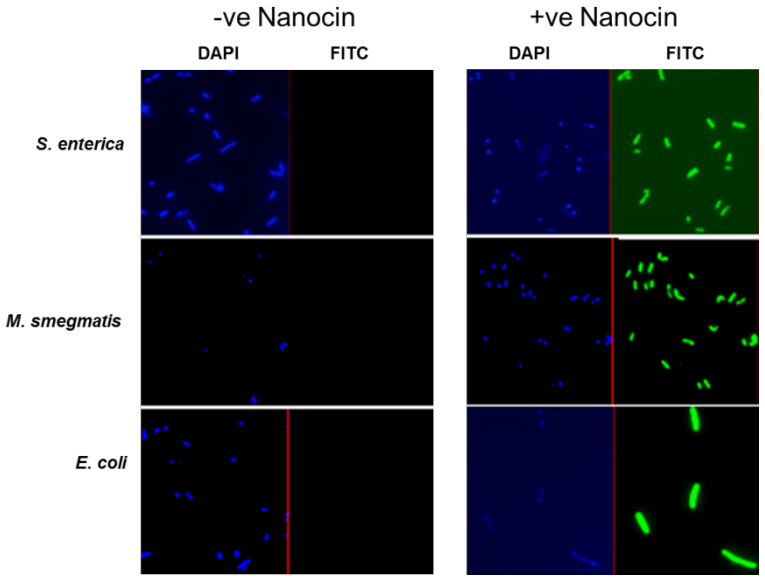
LOOKING FOR NEW SOLUTIONS

USING NANOTECHNOLOGY TO OVERCOME THE DELIVERY PROBLEM

- **Nanocin™**: A non-lipid based cationic nanopolymer with high hydrogen binding capacity. Over 30 years safe use in human health.
- Rapidly self assembles into nanoparticles with cargo molecule to form nanoparticles in the 40nm -200nm range.
- **Can package a range of molecules including peptides and proteins**
- Massively enhances delivery into cells, tissues and microbes



Utilising Nanocin™ we can overcome the problem of cell delivery of protein therapeutics, opening up a new class of compounds for development as antibacterial agents and antibiotics: **intracellular biologics**

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PROOF-OF-PRINCIPLE

TARGETING PBP2A IN MRSA

- MRSA is a hospital and community acquired infection that can cause major complications
- Resistance is conferred when SA acquires the MecA gene
  - Codes for the PBP2A protein
  - A PBP with greatly reduced sensitivity to beta-lactam antibiotics
- Develop peptide-aptamers specifically targeting PBP2A
- Deliver these into a range of clinical isolates of MRSA using Nanocin™
- Aim to restore MRSA sensitivity to beta-lactam antibiotics e.g. oxacillin

PROOF-OF-PRINCIPLE
THERAPEUTIC: PEPTIDE APTAMERS

Characteristics of peptide aptamers:

- Small (~80aa)
- Stable and robust scaffolds
- No disulphides
- Easily produced in *E. coli*
- Can rapidly screen large libraries: >$3x10^{10}$
- Rapidly generate high affinity binders
- Use as pharmaceuticals and in diagnostics

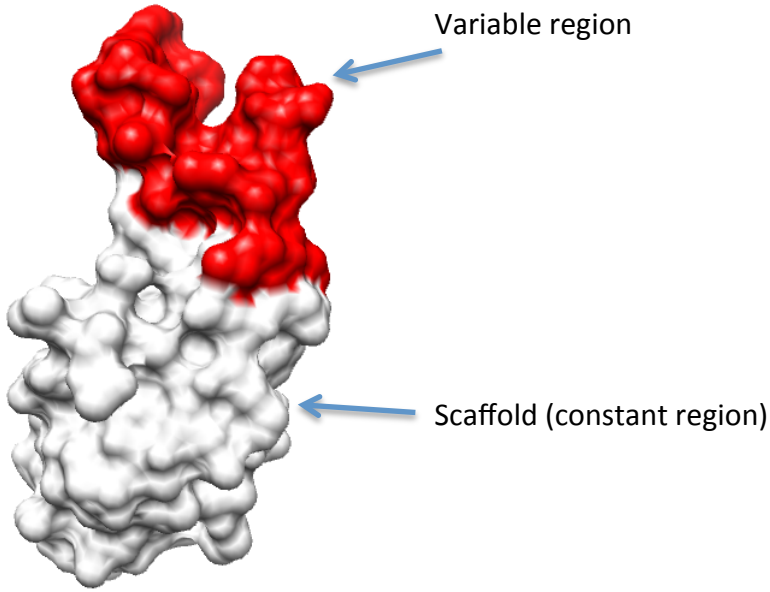

Image courtesy of Darren Tomlinson University of Leeds

- Developed several high affinity peptide aptamers that bind PBP2A
- Based on two different scaffolds
  - Avacta Ltd
  - Leeds University

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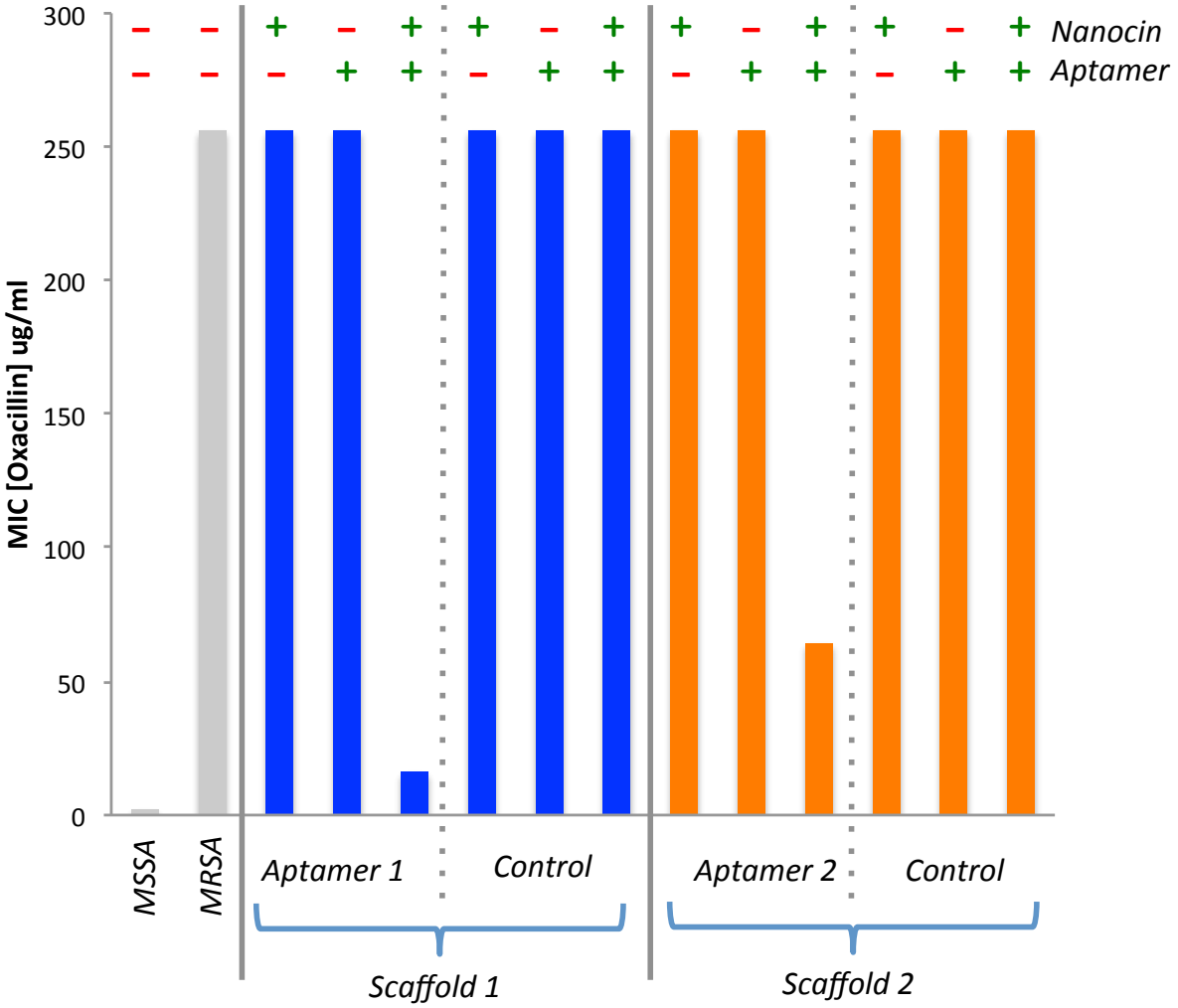
PROOF-OF-PRINCIPLE

Demonstrating feasibility of restoration of oxacillin sensitivity in MRSA by peptide aptamers



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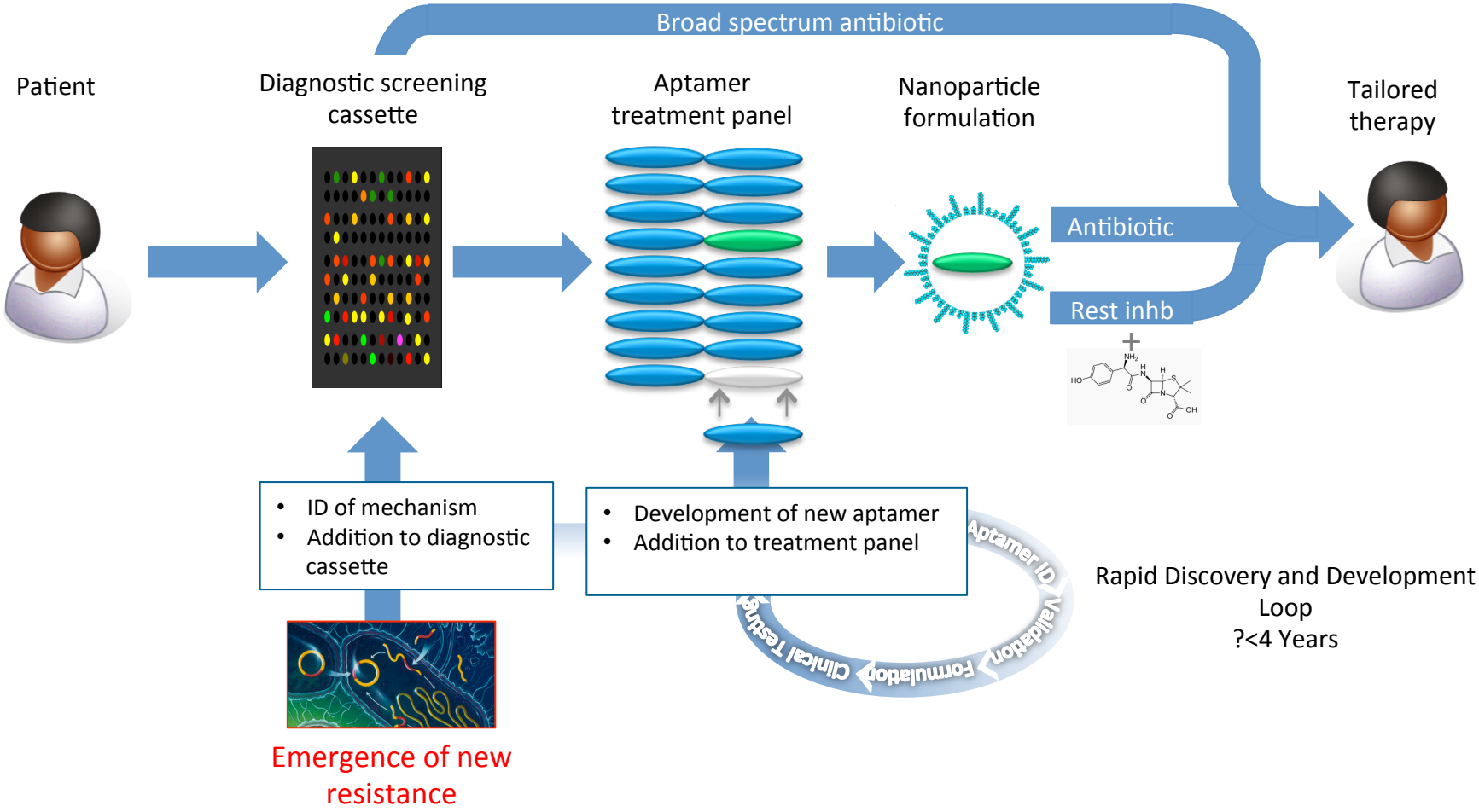
Multi-Drug Resistance: Long-term strategic vision

Achieving sustainable response to antibiotic resistance



Rapid development loop and aptamer treatment panel coupled to standard formulations allow us to respond to emerging resistance

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Looking to the future

Developing a siege mentality

- Intracellular biologics open up a new front in the treatment of infectious diseases
- Early days and many challenges ahead but the potential is huge
  - Will be part of the solution
- Need to lay siege to the problem and persevere
  - Small and large molecule approaches: narrow and broad spectrum
  - Develop more effective treatment regimes
  - **Parallel investments in better, more rapid diagnostic tests**
  - "Hunt in packs"

Underpinned by investment in basic disease research

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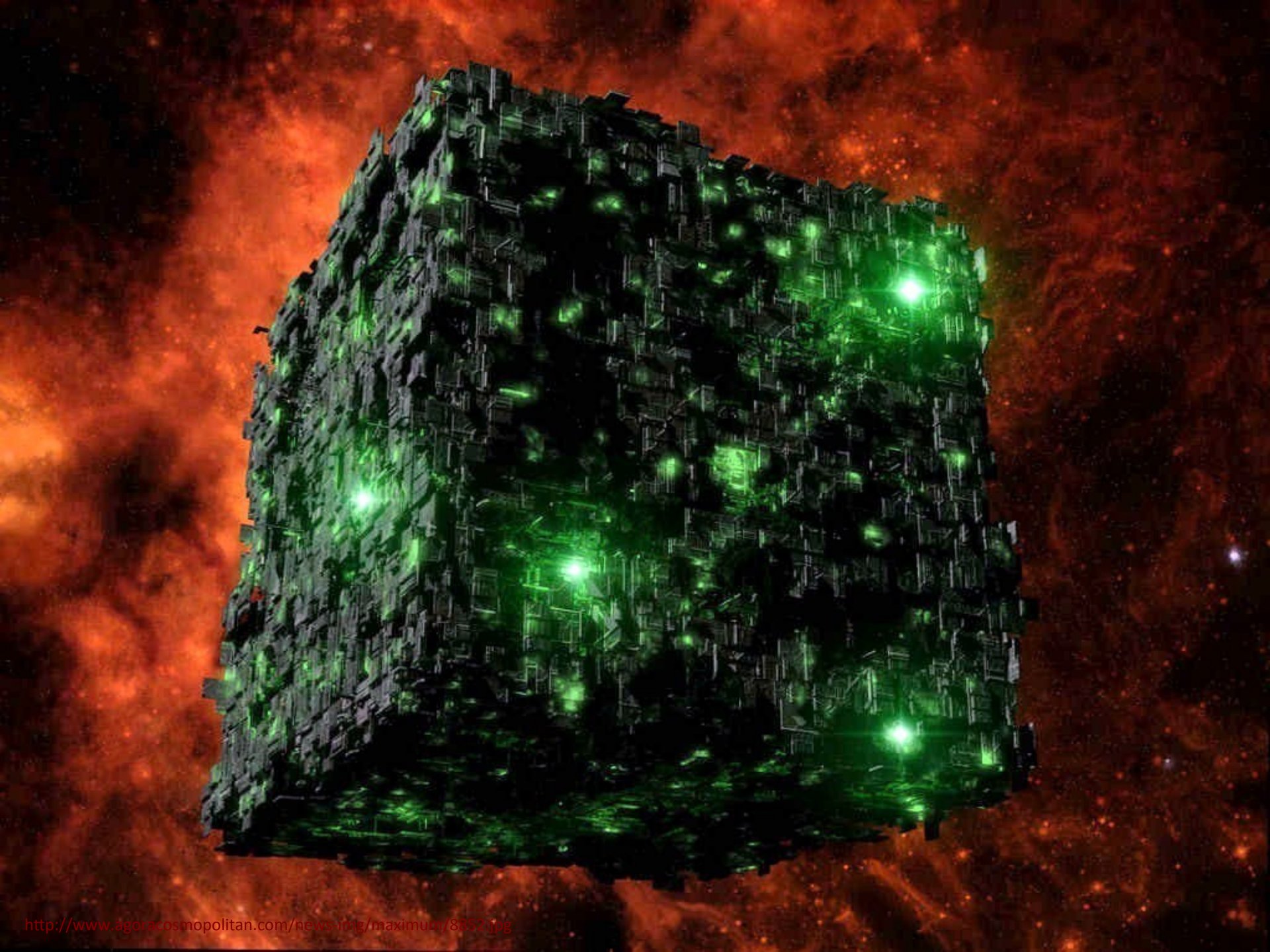

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ACKNOWLEDGMENTS

- The Blueberry Team
- Tecrea Ltd
- Leeds University
  - Darren Tomlinson
- Avacta Life Science
- Public Health England
  - Mark Sutton
- Technology Strategy Board
- Liverpool University
- Euprotec Ltd
- Manchester University
- BBT SCAB
  - Alex O'Neill
  - Maria Marlowe
  - Liam Good

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