AMR

Can rapid diagnostics make the required difference?

Christoph Wälti

Drug-Resistant Infections

Can rapid diagnostics make the required difference?

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AMR – Antimicrobial Resistance

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In 1928, Alexander Fleming discovered that mould produced penicillin, and within 12 years, the first antibiotic was available.

Antimicrobials are drugs that are active against a range of infections

Including infections caused by organisms such as

- bacteria – antibiotics
- viruses – antivirals
- fungi – antifungals

by killing or stopping the growth of these organisms.

AMR – Antimicrobial Resistance

A range of further antibiotics were discovered over the following decades, and completely revolutionized healthcare provision.

Antibiotics are nowadays used to treat many previously likely fatal infections, but also to protect us after common surgery such as caesareans, joint replacements, chemotherapy and transplant surgery.

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Global consumption of antibiotics in human medicine rose by nearly 40% between 2000 and 2010 (declining usage in some countries and rapid growth in others).

The pace at which new antibiotics are discovered has slowed considerably.

Antibiotics use (non-therapeutic reasons) in agriculture is very high.

The organisms can develop a defense mechanism against the drug (and become resistant – AMR) rendering the drug ineffective.

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The most prominent of such resistances is for antibiotics (ABR).

Resistance to antimicrobials is nothing new, and some of the genes that confer drug resistance have been around for many millions of years.

However, AMR has become a very significant problem in recent years, mainly because of overuse/misuse and the rapid spread of resistances.

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In January 2008, a patient was transferred from a New Delhi hospital to a Swedish hospital. *Klebsiella pneumoniae* which was resistant to multiple antibiotics including carbapenems was found in his urine.

The resistance was due to the production of an unknown metallo-β-lactamase (MBL), now referred to as New Delhi MBL (NDM-1).

Johnson *et al.* J Med Microbiol (2013) **62**, 499

AMR – Antimicrobial Resistance

New Scientist

DAILY NEWS 24 June 2016

Tourists pick up antibiotic-resistance genes in just two days

A study in the Netherlands on 122 travellers showed that the percentage of those with bacteria carrying antibiotic-resistance genes in their gut increased from <10% before they left to >55% when they returned.

von Wintersdorff, et al (2014) Emerging Infectious Diseases, 20(4), 649-657.

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"The emergence of the MCR-1 gene in China heralds a disturbing breach of the last group of antibiotics – polymixins – and an end to our last line of defence against infection."

"The rapid spread of similar antibiotic-resistant genes such as NDM-1 suggests that all antibiotics will soon be futile in the face of previously treatable gram-negative bacterial infections such as *E.coli* and salmonella."

"We now have evidence to suggest that MCR-1-positive *E.coli* has spread beyond China, to Laos and Malaysia, which is deeply concerning."

Prof Tim Walsh, Cardiff University in 2015 after on his discovery of MCR-1

(Liu *et al.* (2016) The Lancet Infectious Diseases **16**(2), 161)

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Guardian sustainable business

Business and the sustainable development goals

Antibiotic waste is polluting India and China's rivers; big pharma must act

06.05.17 ANTIBIOTIC RESISTANCE

BIG PHARMA'S POLLUTION IS CREATING DEADLY SUPERBUGS WHILE THE WORLD LOOKS THE OTHER WAY

Environmental standards do not feature in international regulations governing drug production

AMR – Antimicrobial Resistance

Table 2 Detection of active pharmaceutical ingredients in environmental specimens using liquid chromatography-tandem mass spectrometry

Antimicrobial agent (μg/L)	Number of samples tested positive for (%)	Proposed environmental regulation limit (μg/L)	Sample ID (corresponding location with GPS coordinates: see Table 1)															
			S1*	S2*	S3*	S4*	S5*	S6*	S8*	S9*	S11*	S12*	S21*	S22*	S23*	S24*	S26*	S27*
Fluconazole	13 (81.3)	0.25	N/D	N/D	24,007	48,311	1753	**236,950**	261.5	37.1	199.8	13.1	37.1	18.5	N/D	1331	243.8	147.3
Voriconazole	12 (75.0)	N/A	N/D	N/D	306.4	324.9	4.3	5.0	1.5	**2500**	4.0	1.7	24.5	45.4	N/D	N/D	6.2	8.0
Moxifloxacin	9 (56.3)	0.125	BDL	N/D	31.7	7.1	8.3	29.5	N/D	N/D	279.4	BDL	N/D	N/D	N/D	N/D	**694.1**	BDL
Linezolid	8 (50.0)	8	BDL	N/D	**37.0**	13.6	BDL	N/D	N/D	N/D	N/D	6.7	8.5	5.4	N/D	N/D	N/D	N/D
Levofloxacin[a]	6 (37.5)	0.25	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	2.1	**12.8**	10.0	4.6	N/D	N/D	2.2	N/D
Clarithromycin	6 (37.5)	0.25	N/D	N/D	N/D	N/D	N/D	13.5	N/D	N/D	N/D	BDL	**27.7**	13.3	N/D	BDL	N/D	N/D
Ciprofloxacin	5 (31.3)	0.064	BDL	N/D	N/D	N/D	NN	19.4	N/D	N/D	N/D	40.1	**44.7**	BDL	N/D	N/D	N/D	N/D
Trimethoprim	5 (31.3)	0.5	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	BDL	BDL	BDL	N/D	N/D	N/D	N/D
Sulfamethoxazole	4 (25.0)	16	N/D	N/D	N/D	N/D	N/D	BDL	N/D	N/D	N/D	BDL	**10.6**	BDL	N/D	N/D	N/D	N/D
Ampicillin	3 (18.8)	0.25	N/D	N/D	N/D	N/D	N/D	BDL	N/D	N/D	BDL	N/D	N/D	N/D	N/D	N/D	**29.1**	N/D
Doxycycline	1 (6.3)	2	N/D	N/D	N/D	N/D	N/D	N/D	N/D	**14.9**	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D
No. of proven antimicrobials in the same sample			3	0	4	4	4	7	2	3	5	9	8	8	0	2	5	3

The highest value of individual antimicrobials is given in bold print. Environmental regulation limits (cut-off for resistance selection) suggested by Bengsson-Palme and Larsson in 2015 [3] are given in the third column. Amoxicillin, anidulafungin, caspofungin, cefazolin, ceftazidime, cefuroxime, clavulanic acid, flucloxacillin, meropenem, penicillin G, piperacillin, tazobactam, posaconazole, and isavuconazole were not detectable in any of the tested samples

Lübbert, C., Baars, C., Dayakar, A. *et al.* Infection (2017). doi:10.1007/s15010-017-1007-2

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"The lack of *instant* and *accurate* diagnostic tools for infectious diseases leads to inappropriate antimicrobial prescribing."

For example, Antibiotic prescriptions in USA (primary and outpatient) for respiratory problem (accounts for ca 40% of all antibiotic prescriptions):

- For a total of 106 million visits in one year, 86 million patients did not benefit from antibiotics (for example bronchitis or asthma)
- **Of this 86 million, 27 million patients still received antibiotics!**

Shapiro *et al*., Journal of Antimicrobial Chemotherapy, 2014, doi: 10.1093/jac/dkt301

O'Neill report (2015): "… there is a fundamental supply and demand problem that needs to be fixed."

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"The lack of *instant* and *accurate* diagnostic tools for infectious diseases leads to inappropriate antimicrobial prescribing."

- Increased antimicrobial prescribing is *directly* associated with increased antimicrobial resistance
- Antibiotics can select for potentially life-threatening infections (such as *Clostridium difficile* infection – CDI) and thus contribute *indirectly* to AMR

Rapid and high-sensitivity point-of-care diagnostics (e.g. biosensors) can contribute to address the problem of rising AMR.

AMR – Antimicrobial Resistance

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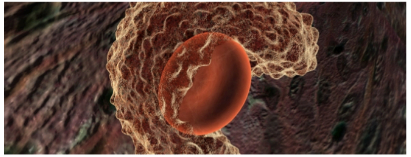
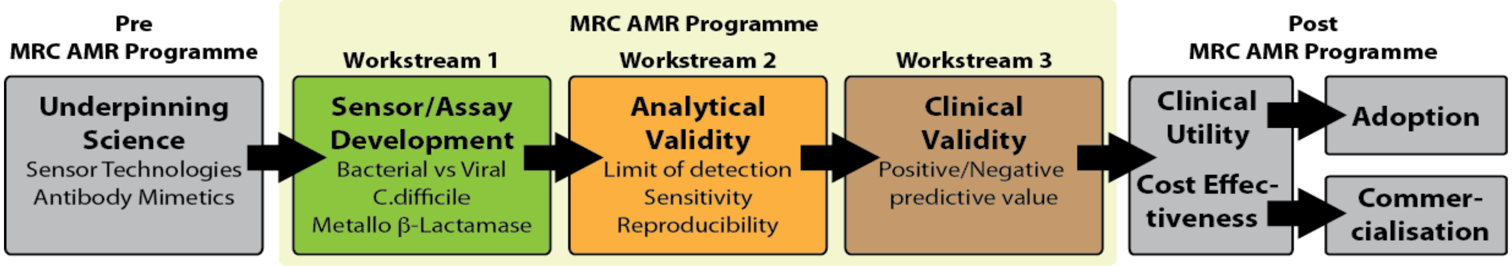


MRC announces cross-council awards worth nearly £10m to tackle antibiotic resistance

Infection Diagnostics for Patient Management and Reduction of Antibiotic Misuse



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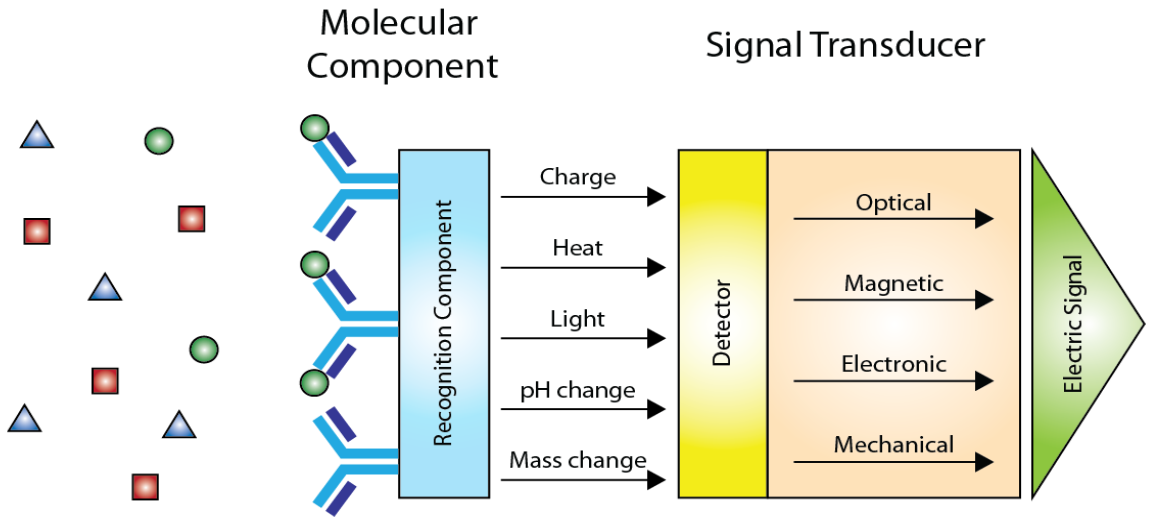
Biosensors for Clinical Diagnostics

A biosensor is an analytical device for the detection of a biomarker that combines a biological component with an electronic component.



AMR – Antimicrobial Resistance

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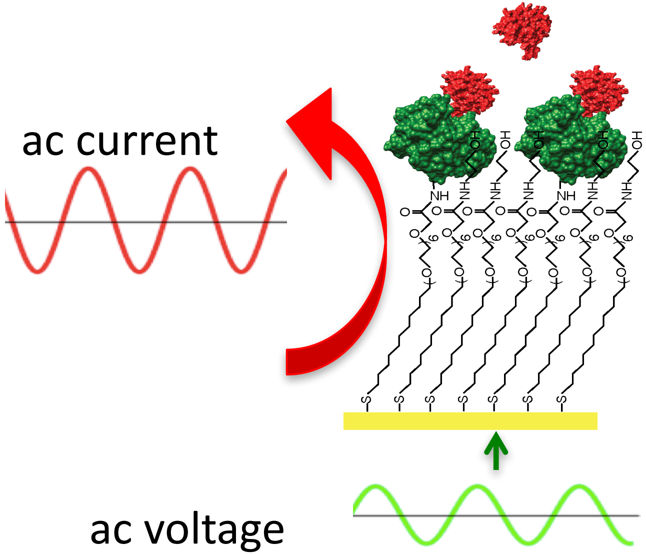
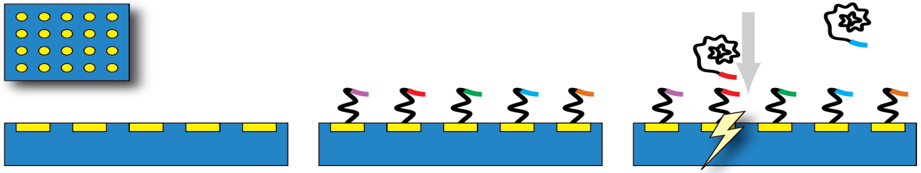
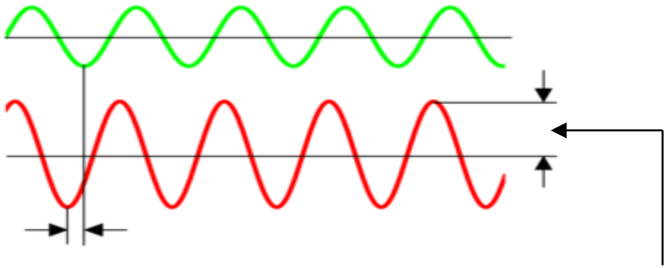
Electronic Biosensors – Electrochemical Impedance Spectroscopy



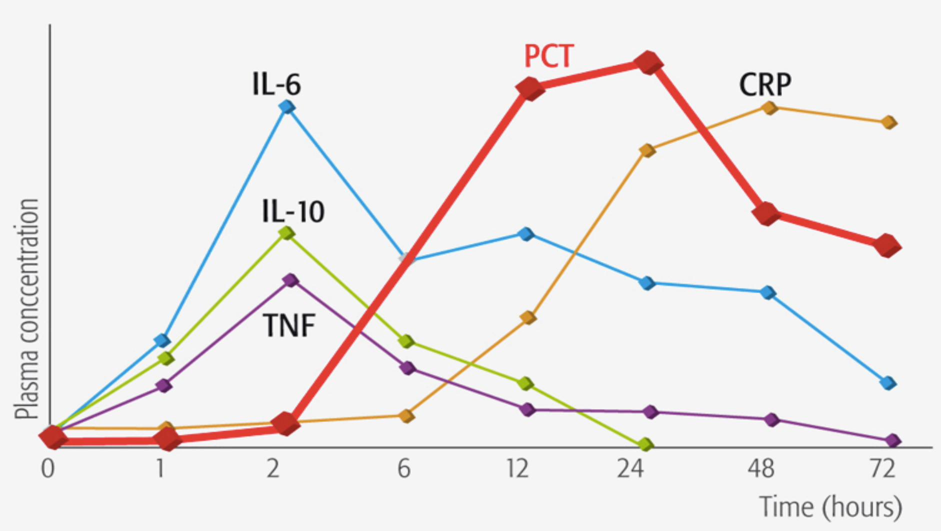




Phase of response/ impedance $\varphi(\omega)$

Absolute value of response/impedance $|Z(\omega)|$

Electronic Biosensors – Multiplexing



Kinetic profiles of different biomarkers of bacterial infection.

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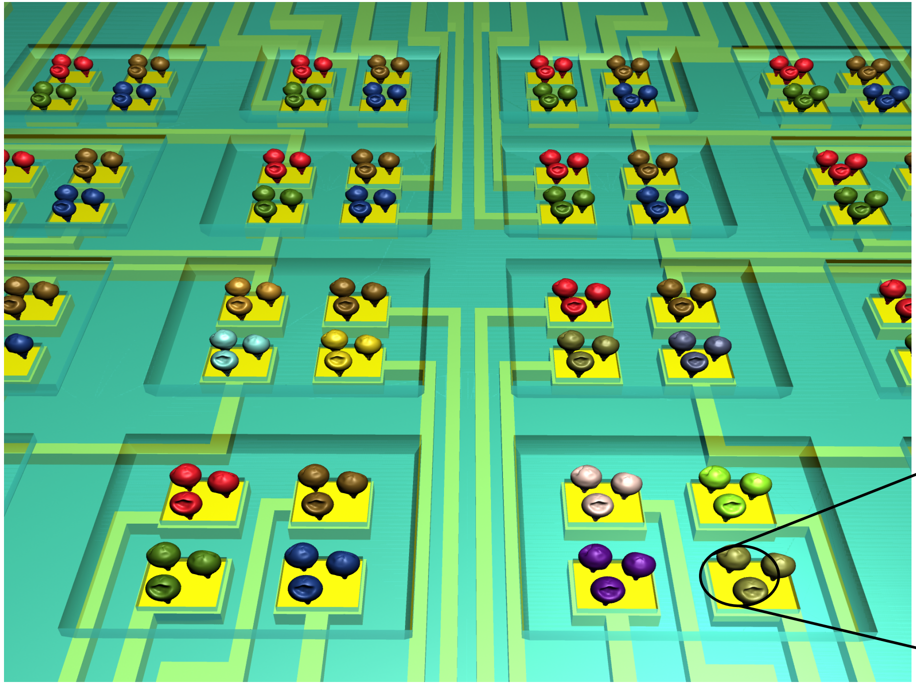
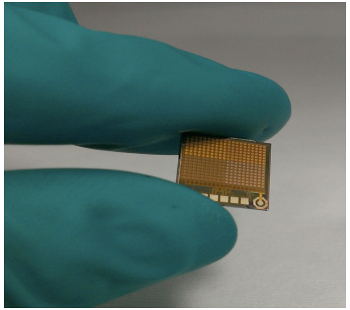
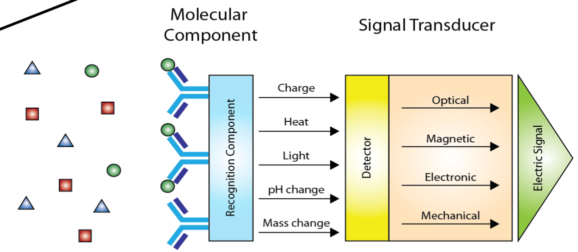
Electronic Biosensors – Multiplexing







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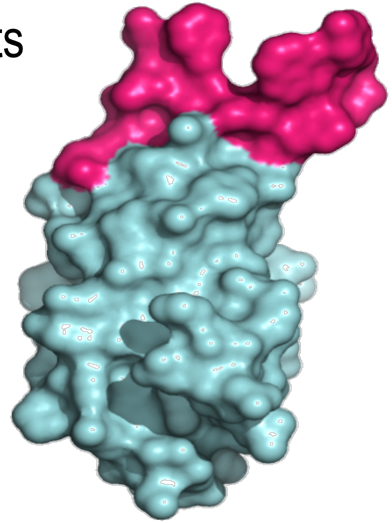
Capture Molecules – Affimers

- Highly effective binding reagents than antibodies
- Novel consensus protein
- Small only 81 amino acids
- Extremely stable and robust scaffold (T_m = 101˚C)
- No cysteines



Variable sequence Regions (pink)

- Library sizes > 10^{10}
- High Binding Affinities – nM to pM
- Simple high yields from *E. coli*
  - Cost effective
  - Reproducible
- Discriminate between similar proteins

M. McPherson Group, University of Leeds

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Tackling Antimicrobial Resistance

Thank You