New technologies to support dose optimisation

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New technologies to support dose optimisation: where will we be in 2024?

Declaration

- No conflicts to declare

Future technology for dose optimisation

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- Current challenges
- Biosensor technology
- Future wearable technologies
- Linked PK-PD monitoring
- Integrated individualised dosing systems

Antibiotic PK-PD

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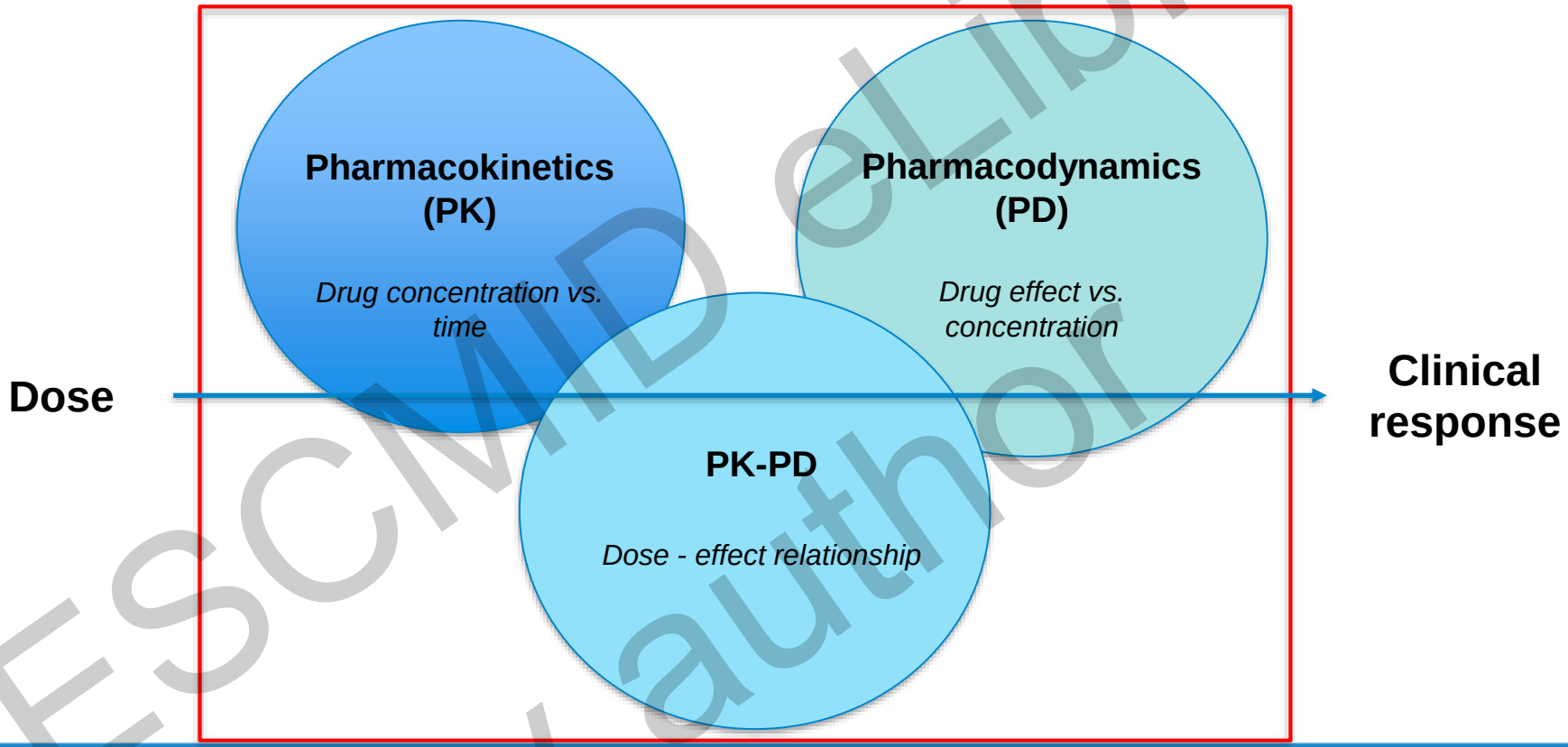

Dosing is a dynamic process

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Race

Weight

Age

Gender

Medications

Comorbidities

Inter-individual variability

Circulatory changes

Organ support

Renal failure

Hepatic dysfunction

Clearance

Fluid balance

Intra-individual variability

Why explore individualised antibiotic dosing?

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Improve treatment outcomes

Prevent toxicity

Minimize the impact on antimicrobial resistance

Utilisation of resources

Enhance our understanding of individual PK-PD

Current approaches to individualise therapy

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Current examples

Therapeutic drug monitoring

Dose optimization software

Prolonged infusions

New PD indicators


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A prospective study investigating the prediction of β-lactam pharmacodynamics using AUC:EC50

Methods

Results

NIHR | National Institute for Health Research

Conclusions

To deliver truly individualised therapy

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Ideally….

Real-time pharmacokinetics

In-vivo pharmacodynamic indices

- Organism
- Host

Individualised, automated methods for dose adjustment

Barriers to wider implementation of TDM

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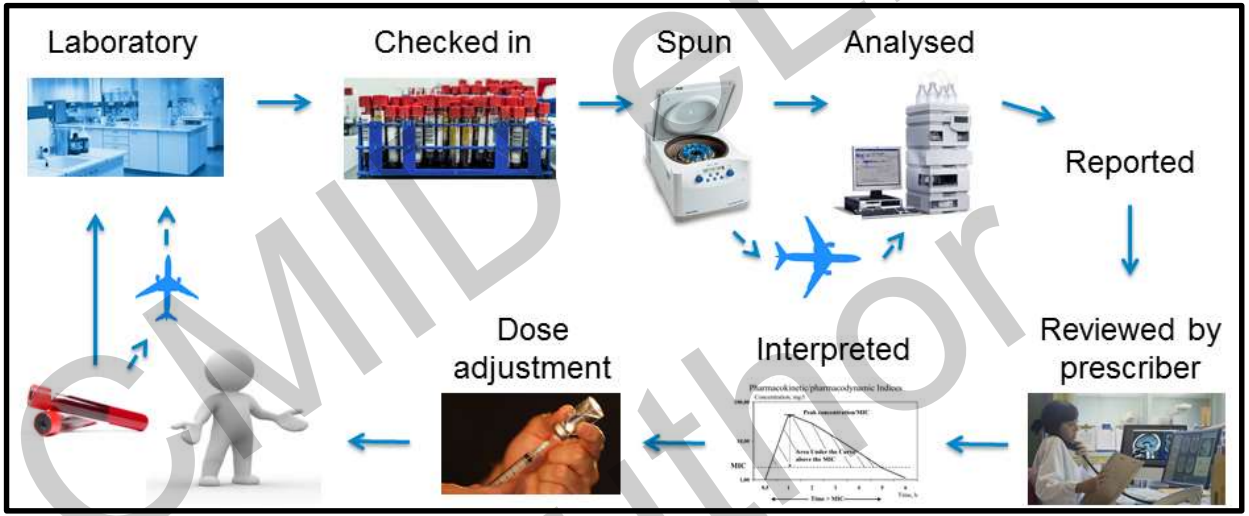
Risk of exposure to HCW's

Valid assay

Stability of drug



Equipment / staff costs

Timing samples

Delays in reporting

Population level estimates

Expertise to interpret

Rawson, O'Hare et al, JAC; 2018

Electrochemical Biosensors

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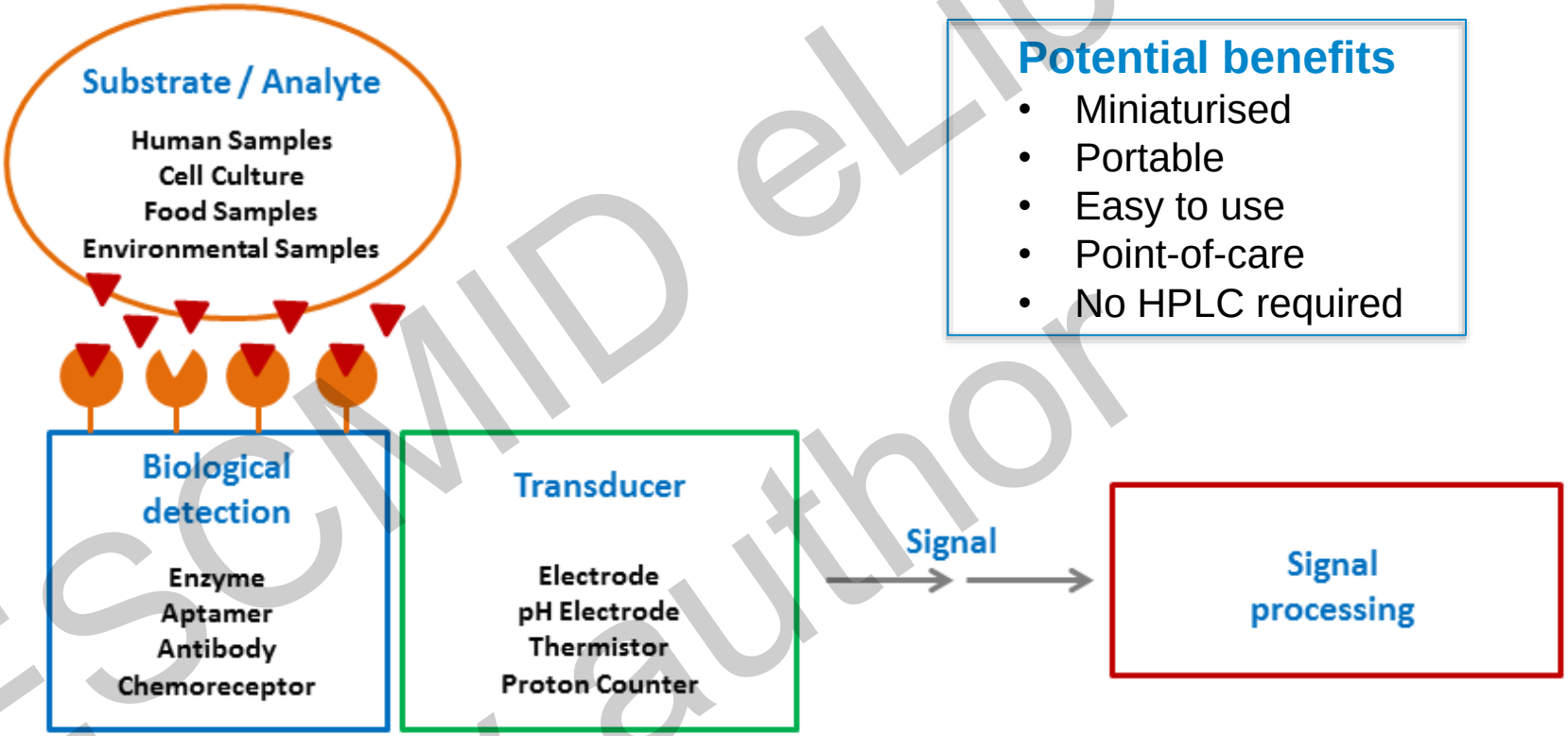

Potential benefits

- Miniaturised
- Portable
- Easy to use
- Point-of-care
- No HPLC required

Rawson, O'Hare et al, JAC; 2018

Biosensors in infection management

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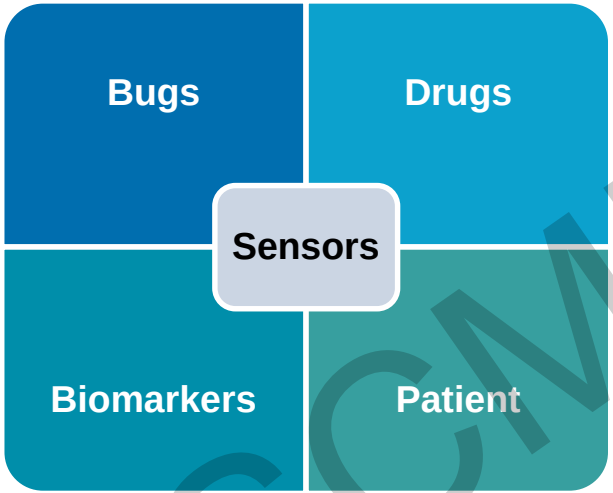

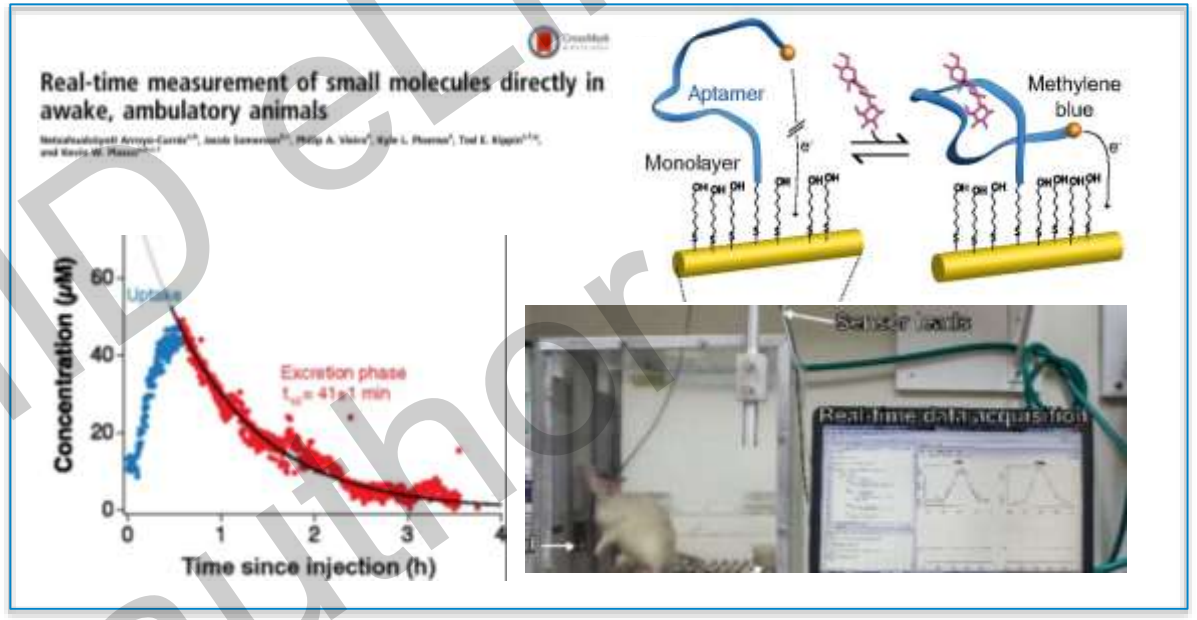

Rawson, O'Hare, et al, JAC; 2018, Arroyo-Currás et al, PNAS; 2017, Ferguson et al, Sci Trans Med; 2013

Wearable technology for dose optimisation

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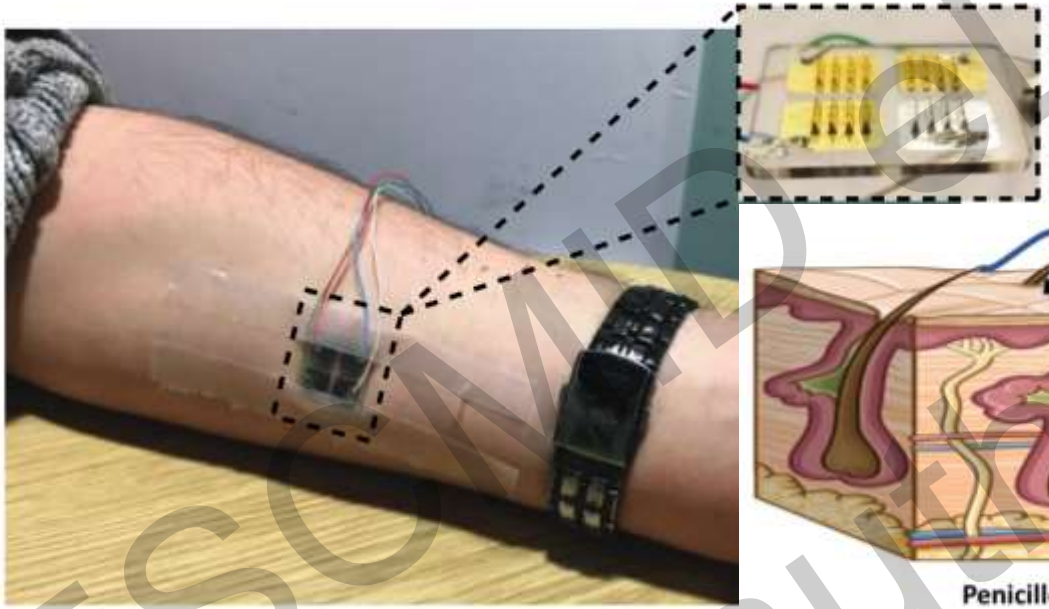

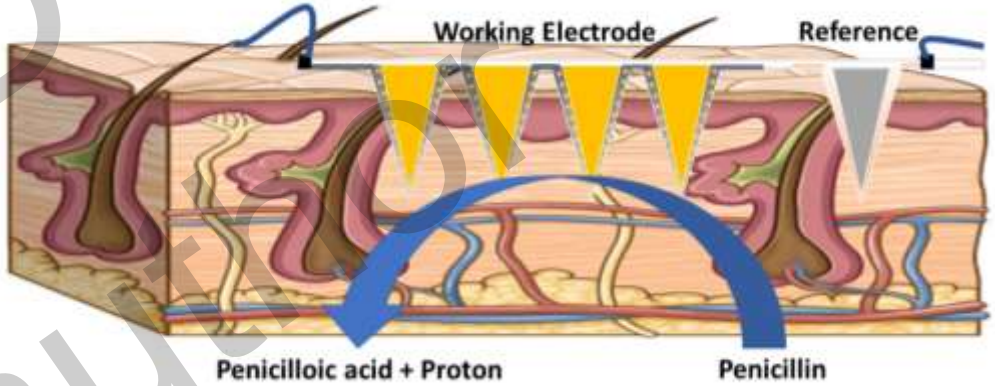

Rawson, et al. Electochem Comms 2017, Gowers, et al. ACS bio; 2019, Rawson, et al 2019

MISBLA study – Penicillin monitoring

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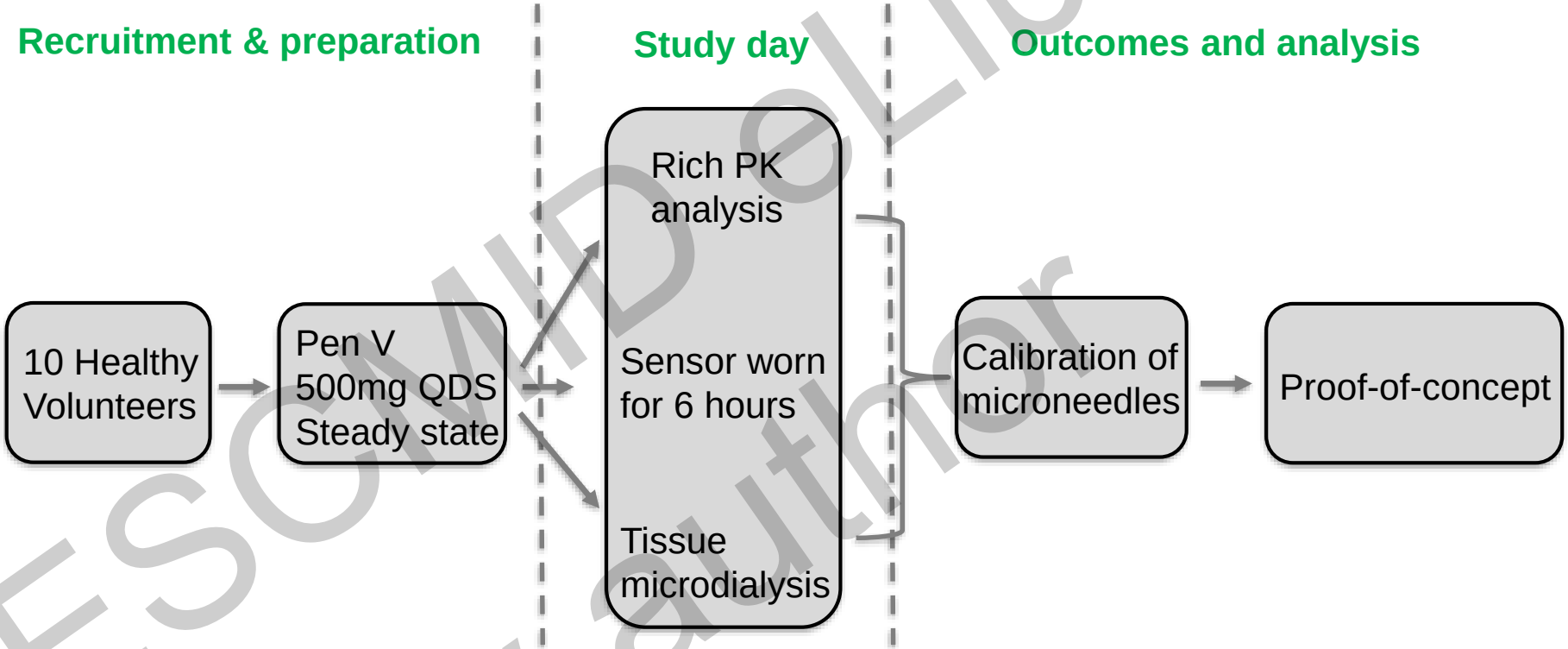

Rawson, et al 2019

In-vivo penicillin monitoring

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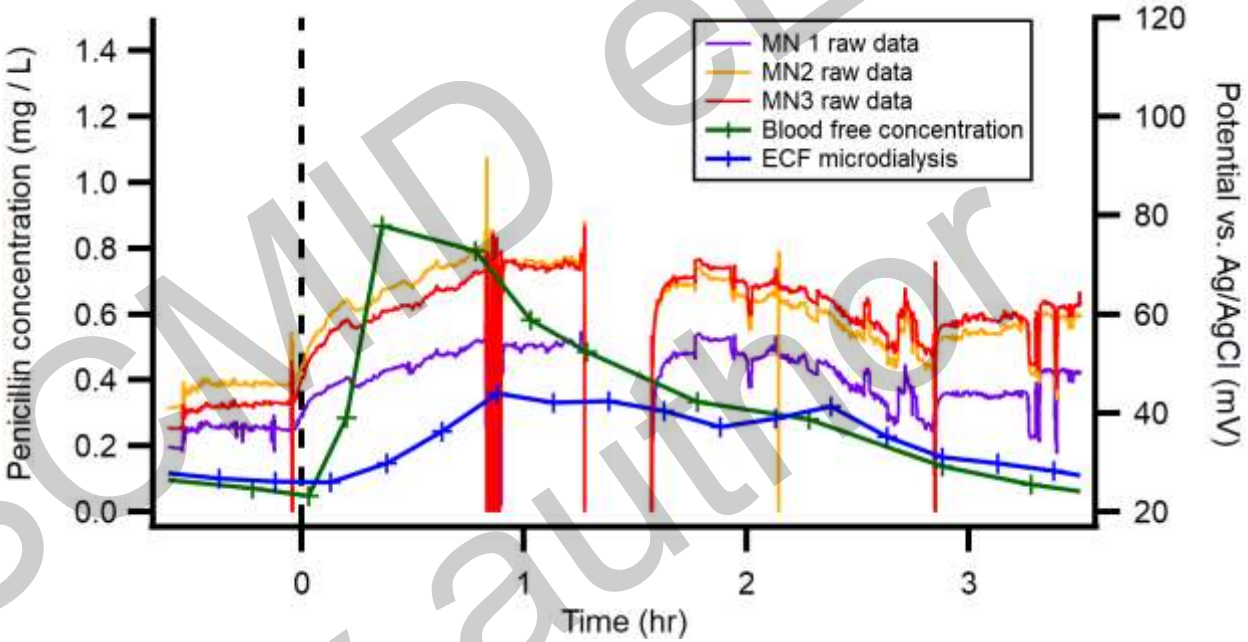
Microneedle raw data output



Gowers, et al. ACS bio; 2019, Rawson, et al 2019

In-vivo penicillin monitoring

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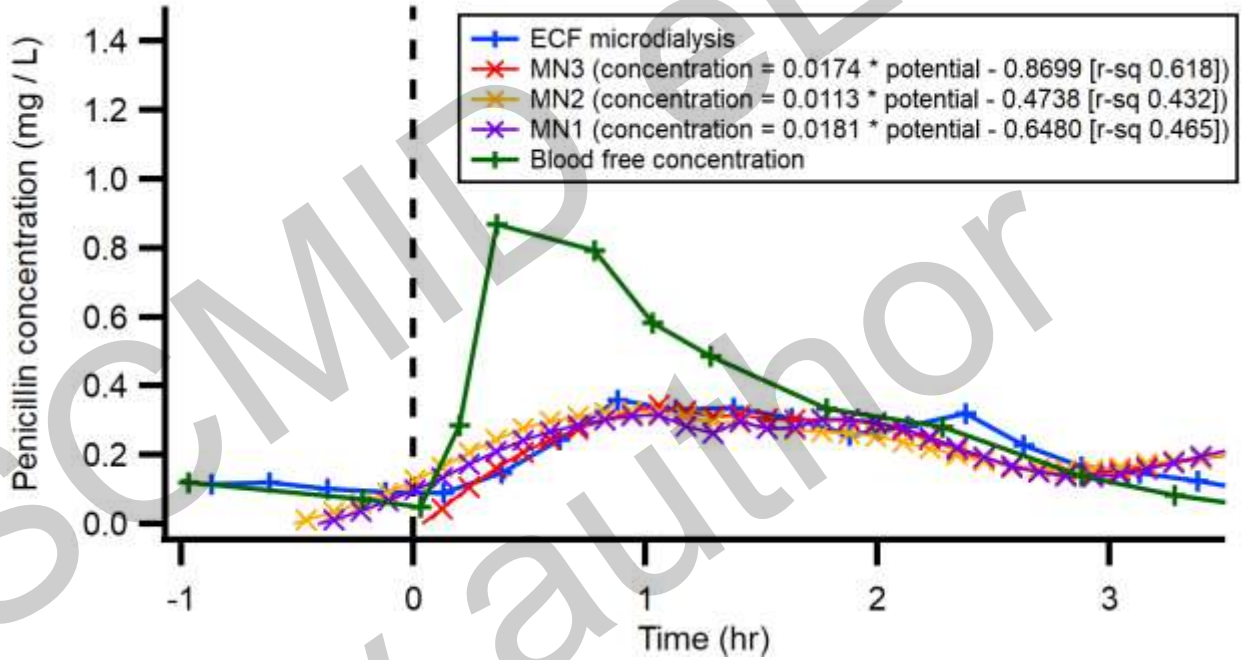
Microneedle calibrated to concentration



Gowers, et al. ACS bio; 2019, Rawson, et al 2019

In-vivo penicillin monitoring

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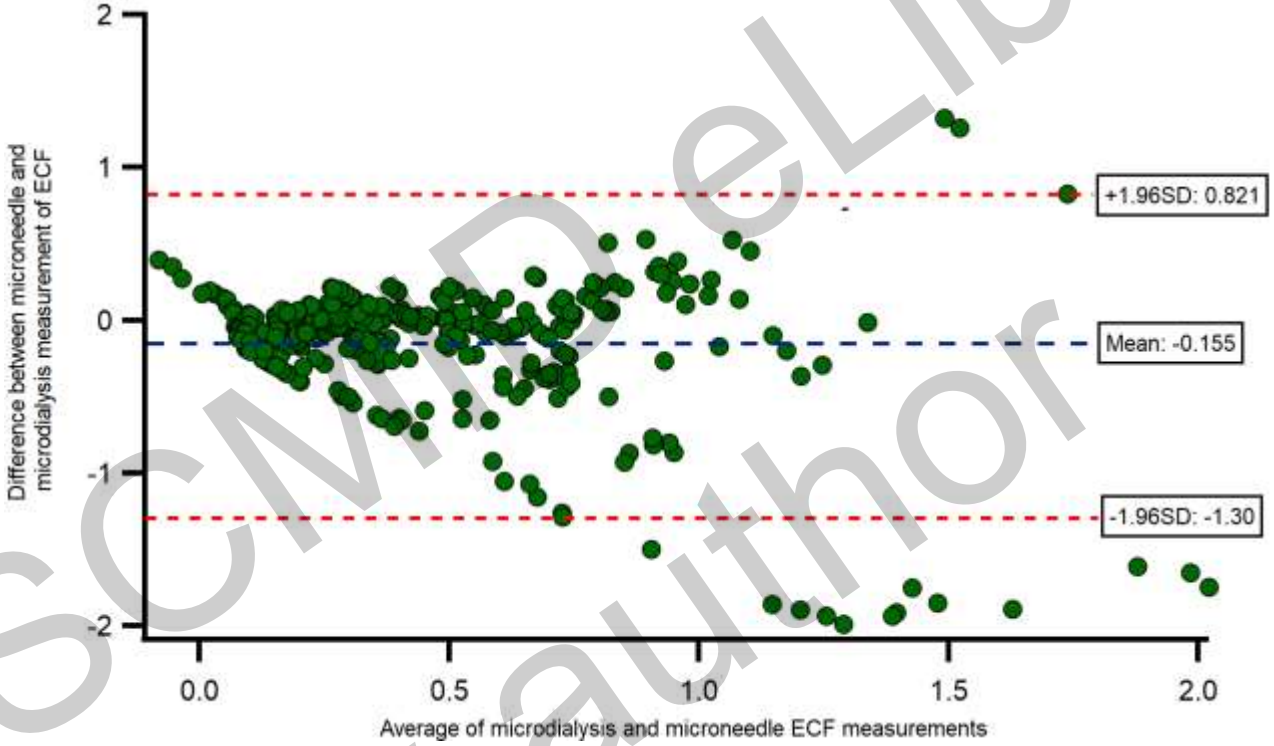

Rawson, et al 2019

A role for microneedle technology

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Benefits

- Direct in-vivo monitoring
- No need for HPLC / internal standard
- Application to wide range of settings
- Multiple agent sensing
- Potential to optimise multiple compartments

Ongoing challenges

- PK variation in critical illness
- Presence of inhibitors
- Paucity of data for agents
- Paucity of data for biomarker sensing

Is real-time measurement of in-vivo PD indices possible?

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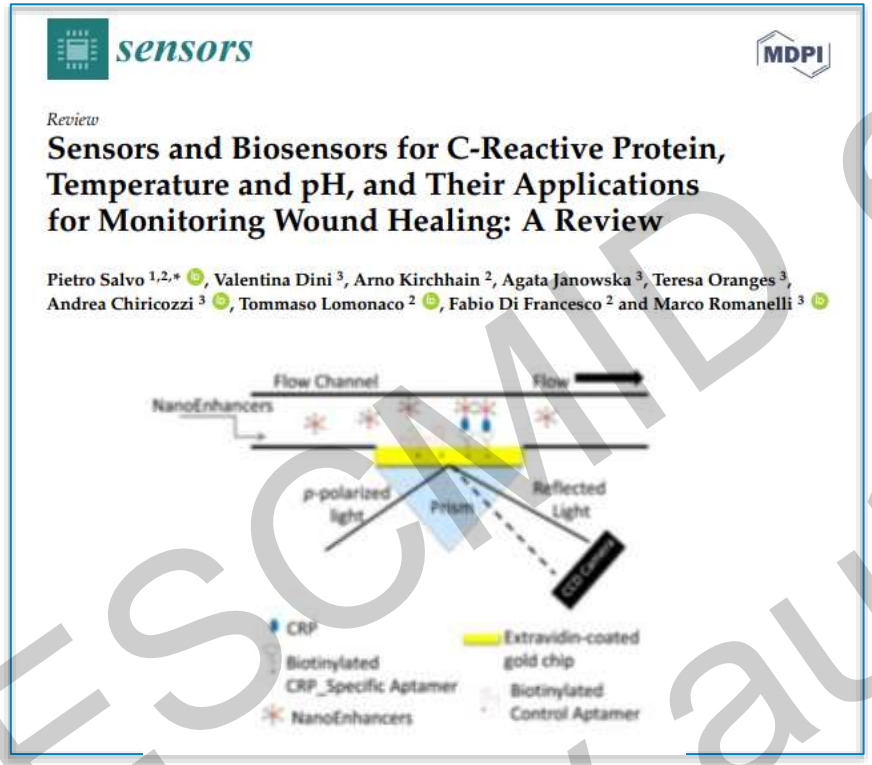

C-Reactive Protein

- Acute Phase Response protein
- Kinetics well understood
- Rationale for predicting response to infection
- ISF Indistinguishable in terms of protein diversity compared with plasma
- Over 60 types of CRP sensor reported

Salvo, et al. Sesnors; 2017, Pepys, et al, J Clin Inv; 2003, Tran et al. J of Proteom; 2018

Predicting antibiotic PD using CRP

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Antibiotic PK

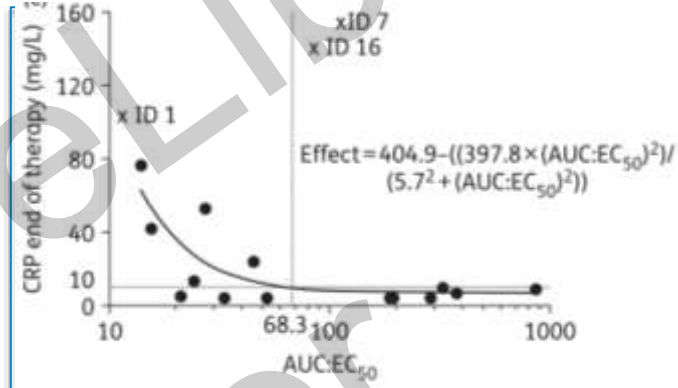
$$\frac{dX(1)}{dt} = R(1) + X(2) \cdot Kpc - X(1) \cdot \left(\frac{SCL}{V}\right) - X(1) \cdot Kcp$$

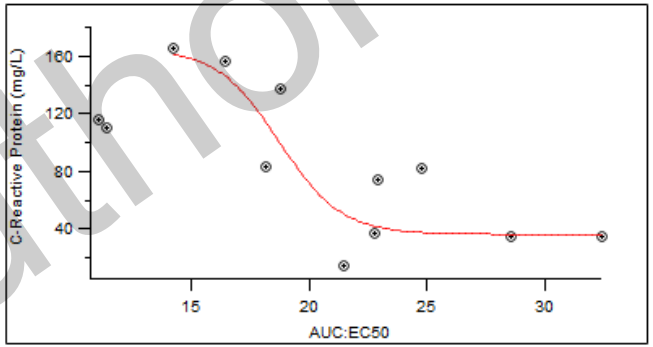
$$\frac{dX(2)}{dt} = X(1) \cdot Kcp - X(2) \cdot Kpc$$

C-reactive protein

$$\frac{dX(3)}{dt} = \left(KCRPp \cdot X(3) \cdot \left[1 - \frac{X(3)}{POPmax}\right]\right) - \left(\frac{KCRPi \cdot X(3) \cdot \left[\frac{X(1)}{V}\right]^H}{EC50^H \cdot \left[\frac{X(1)}{V}\right]^H}\right)$$

Individual AUC:EC$_{50}$





Antibiotic PD
Teicoplanin
Paediatrics

Antibiotic PD

Vancomycin
Adults

Ramos-Martin, et al. JAC; 2016, Rawson, Charani et al, TDM; 2018

Evidence for in-vivo biomarker monitoring

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Lactate important marker for sepsis

Ex-vivo validation on plasma

In-vivo monitoring with exercise bike challenge

Proof-of-concept

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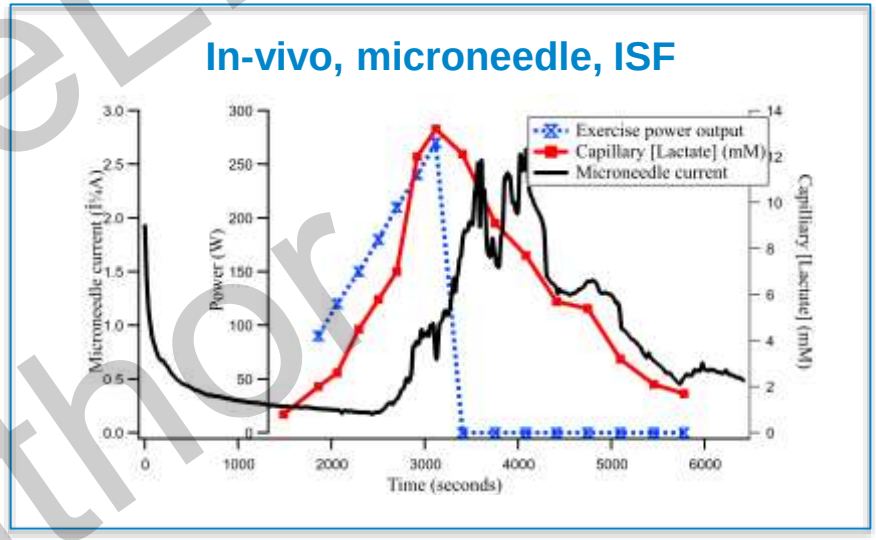

Damien Ming, et al. 2018

Next steps

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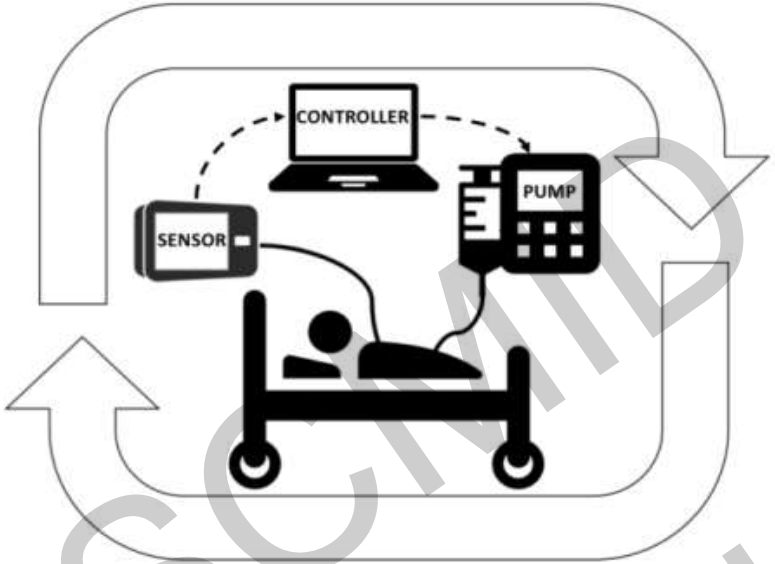

Closed-loop control of penicillin delivery in healthy volunteers

Antibiotic / biomarker sensing in patients

Validation of new PK-PD indices

Where will we be in 2024?

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- Microneedle based technology offers new frontier in individualised antimicrobial therapy
- New array of wearable technologies to support in-vivo PK-PD evaluation
- Greater understanding of antimicrobial PK-PD
- Automated dose optimisation

Acknowledgements

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