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The Queen Elizabeth Hospital Research Expo

2020

Thursday 15 and Friday 16 October
Program & Abstracts

TQEH
Main Building, Lecture Theatre 2
28 Woodville Road, Woodville South

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TQEH Research Expo

Thursday 15 & Friday 16 October 2020

Thursday: Student Mini-Oral Presentations

[Basil Hetzel Institute, Ground Floor Seminar Rooms, 37a Woodville Rd]

1:30pm	Mini-Oral Presentations
2:50pm	Afternoon tea

Friday: Student Oral Presentations & Plenary Lecture

[TQEH, Level 2, Main Lecture Theatre, 28 Woodville Rd]

8:15am	Honours Students
9:15 am	Junior PhD Students (Laboratory)
10:15am	Morning Tea & Trade Displays
10:45am	Senior PhD Students (Laboratory)
12:00pm	**Plenary Lecture: Professor Toby Coates**
	"Recycling Islets to Treat Diabetes"
1:00pm	Lunch & Trade Displays
2:00pm	Clinical Research Group 1
3:00pm	Clinical Research Group 2
4:00pm	3MT® & Award Presentations

Zoom links & more information: bit.ly/2FN2XDf

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TQEH Research Expo 2020

CONTENTS

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TQEH Research Expo 2020

Welcome to The Queen Elizabeth Hospital Research Expo 2020, the 29th consecutive TQEH Research Expo which now forms part of CALHN Research Week. The organising committee is delighted to be able to present a program that again showcases the valuable research being conducted at the Basil Hetzel Institute of Translational Health Research (BHI), The Queen Elizabeth Hospital (TQEH). TQEH Research Expo is a major event in our research calendar and plays an important role in the professional development of our research trainees. It is a relief for us all to be able to carry on in this year of COVID-19 with very few changes to the program. Please come along in person or attend via Zoom to support our research trainees and hear about the world-class research being done at the BHI, TQEH.

This year, the Committee was delighted to receive 34 Abstracts. 14 students will take part in the mini-oral presentation session being held on the afternoon of 15 October, 2020, and 20 students will give their oral presentations on Friday 16 October.

On Friday will be joined by Professor Toby Coates, our 2020 TQEH Research Expo Plenary Lecturer. The title of his presentation is 'Recycling Islets to Treat Diabetes.' We consider Toby to be one of our own, having been based at the BHI, TQEH in years gone by, and it is a pleasure to be able to invite him back to share his research with us.

While the judges scores are tallied and the prize winners determined, this year's BHI, TQEH 3MT® participants will present their 3 minute thesis presentations – a chance for these students to give their talks to a live audience given that the 3MT® competition went virtual this year. These talks will be followed by the Award Presentations, with generous prizes on offer courtesy of our sponsors. The support of the health and medical research community and our corporate sponsors is greatly appreciated.

Please make the time to support the presenters at all of the sessions – your time and your questions are so important for the success of this event.

Many people have contributed to the success of TQEH Research Expo 2020 and we would like to thank all those involved. In particular, we thank:

- Our Major Sponsor, The Hospital Research Foundation
- Other University, Hospital and Corporate Sponsors who have sponsored prizes and the catering
- Communications Teams from The Hospital Research Foundation & CALHN
- Our Plenary Speaker, Professor Toby Coates

- Chairs of the sessions

Andreas Evdokiou
Ben Kile
Cher-Rin Chong
Guy Maddern
John Beltrame
Laura Parry
Prue Cowled
Tania Crotti

- Abstract judges and judges for Mini-Oral and Oral presentations

Adrian Abdo
Amanda Townsend
Betty Sallustio
Branka Grubor-Bauk
Bron Lett
Catherine Hill
Cher-Rin Chong
Clare Cooksley
Clementine Labrosciano
Eric Gowans
Eric Smith
Jenny Hardingham
Jessica Reid
John Horowitz
Katharina Richter
Kevin Fenix
Mark Thompson
Markus Troschler
Nicky Thomas
Paul Drew
Peter Zalewski
Prue Cowled
Renuka Visvanathan
Rob Fitridge
Rosanna Tavella
Sarah Bernhardt
Sarah Vruedge
Sue Lester
Tamara Varcoe
Wendy Ingman
Yuliy Cherkov
Zoe Kopsaftis

- Members of the Research Expo Organising Committee for the work they have put in throughout the year in planning TQEH Research Expo.

Abbey Bell
Adrian Abdo
Anne Hamilton-Bruce
Eric Smith
Gwenda Graves
Jenny Hardingham
Joanne Young
Kathryn Hudson
Prue Cowled
Rebecca Anderson
Rosanna Tavella
Sue Lester
Yuliy Chirkov

We hope that you enjoy TQEH Research Expo 2020 and find it a valuable and worthwhile activity. If you have any comments on this year's program or any ideas for the future, do not hesitate to speak to one of the members of the Organising Committee. The Committee will be happy to incorporate any feedback received when planning for our 30th iteration, TQEH Research Expo 2021.

Joy Rathjen D. Phil.
Chair, Organising Committee
TQEH Research Expo, 2020

2020 TQEH Research Expo
Plenary Lecture
12pm Friday 16 October

"Recycling Islets to Treat Diabetes"

Professor Toby Coates

Director of Kidney and Islet Transplantation,
Royal Adelaide Hospital
Professor of Medicine, University of Adelaide

Session chair: Professor Guy Maddern

Professor Toby Coates is a Renal Transplant Nephrologist at the Royal Adelaide Hospital (RAH), whose work in the area of kidney and pancreatic islet cell transplantation has saved the lives of countless diabetes and kidney disease patients across South Australia. One of the highlights of his career is successfully performing the first islet cell transplant surgery in SA in 2010 as a cure for type 1 diabetes. Prof Coates also leads the Adelaide Medical School , University of Adelaide, in the Central Northern Adelaide Renal and Transplantation Service (CNARTS) at the RAH, focusing on the isolation and transplantation of healthy pancreatic islets as an innovative treatment and potential cure for type 1 diabetes. Prof Coates is committed to improving the lives of those living with kidney disease and diabetes.

TQEH Research Expo 2020

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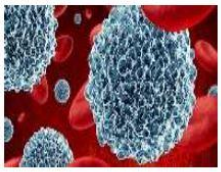

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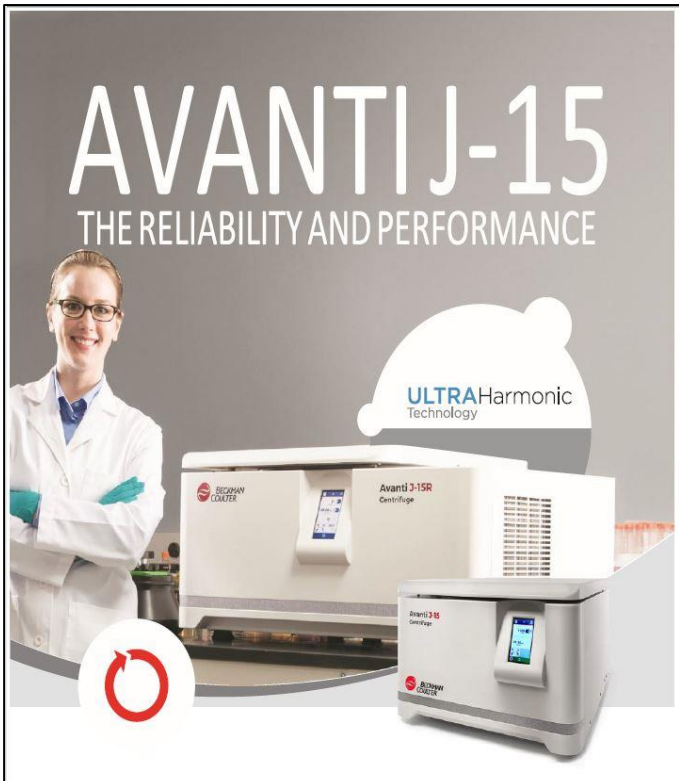

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2019 TQEH Research Expo Award Winners

L-R: Professor John Beltrame (CALHN Director of Research), Paul Flynn (THRF CEO), Ahad Sabab, Mark Thompson, Laurine Kaul, Dr Maryam Nakhjavani, Dr Oscar Russell, Dr Tom Eldredge, Minister for Health and Wellbeing The Honourable Stephen Wade MLC and Professor Guy Maddern (TQEH Director of Research). Absent from photo: Amita Ghadge, Unyime Jasper.

TQEH Research Expo 2020

Thursday 15 October
BHI Ground Floor Seminar Rooms, 37a Woodville Road

1.30-2.50pm: Mini-Oral Presentations

Chairs: Dr Prue Cowled & Dr Cher-Rin Chong

Abstract 1
1.30: Lucinda Adams, Susan Lester, Elizabeth Hoon, Heather van der Haak, Charlotte Proudman, Cindy Hall, Samuel Whittle, Susanna Proudman , Catherine Hill
Telehealth in COVID-19: what did we think and what can we learn?

Abstract 5
1.35: Kelly Dang, Anna Megow, Catherine Bennett, Shari Javadiyan, Sarah Vreugde, Peter-John Wormald, Alkis Psaltis
Participant satisfaction, motivations, and participation experiences of chronic rhinosinusitis clinical trial participants

Abstract 20
1.40: Andrea Lyon, Alannah Quinlivan, Susan Lester, Claire Barrett, Samuel Whittle, Franca Marine, Debra Rowett, Rachel Black, Premarani Sinnathurai, Lyn March, Rachelle Buchbinder, Catherine Hill
Vaccination rates, perceptions and information sources utilised by Australian patients with inflammatory arthritis

Abstract 32
1.45: Joanna Tieu, Susan Lester, Warren Raymond, Helen Keen, Catherine Hill, Johannes Nossent
Mortality in ANCA-associated vasculitis and polyarteritis nodosa: a Western Australian population based study

Abstract 2
1.50: Mirabel Alonge, Benedetta Sallustio
A clinical assay to measure plasma concentrations of tacrolimus and improve therapeutic drug monitoring

Abstract 3
1.55: Muhammed Awad, Clive Prestidge, Timothy Barnes, Nicky Thomas
Shine a light! Gallium protoporphyrin as a selective photosensitiser for antimicrobial photodynamic therapy

Abstract 8
2.00: Bimala Dhakal, Kevin Fenix, Man Ying Li, Paul Drew, Guy Maddern
Development of an *in vitro* system to identify novel drug candidates capable of manipulating tumour associated macrophages

2.05: 5 minute break!

Abstract 10

2.10: Jannatul Ferdoush Tuli, Mahnaz Ramezanpour, Clare Cooksley, Sha Liu, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde

Effect of *Pseudomonas aeruginosa* exoproteins on the nasal mucosal barrier in chronic rhinosinusitis in hypoxic condition

Abstract 12

2.15: Olivia Girolamo, John Horowitz, Yuliy Chirkov, Gao Jing Ong

Autacoid signalling in Takotsubo Syndrome: The Sibyl revisited

Abstract 16

2.20: Emily Kovacev, Irene Stafford, Adrian Abdo, John Horowitz, Cher-Rin Chong

The impact of PARP-1 inhibitor on endothelial cell viability and vascular reactivity in T2D model

Abstract 22

2.25: Martha Menberu, Sha Liu, Clare Cooksley, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde

***Corynebacterium accolens* isolated from Healthy Sinus Cavities have Antimicrobial Activity toward *Staphylococcus aureus* and Methicillin-resistant *S. aureus* (MRSA) clinical isolates**

Abstract 26

2.30: Namfon Pantarat, Irene Zinonos, Romana Panagopoulos, Ehud Hauben, Vasilios Panagopoulos, Andreas Evdokiou

Localized adoptive cellular therapy of gamma delta T cells for solid tumours

Abstract 29

2.35: Ryan Santos, Makutiro Masavuli, Zelalem Mekonnen, Arthur Yeow, Eric Gowans, Branka Grubor-Bauk

Novel DNA-Based Vaccine for Zika Virus

Abstract 34

2.40: Dawn Whelan, Makutiro Masavuli, Zelalem Mekonnen, Arthur Yeow, Eric Gowans, Branka Grubor-Bauk

Maternal immunisation with a novel Zika vaccine to protect offspring from congenital Zika syndrome

2.50-3.30pm: Afternoon Tea

TQEH Research Expo 2020

Friday 16 October
Student Oral Presentations & Plenary Lecture
TQEH, Level 2, Main Lecture Theatre, 28 Woodville Road

8.15 - 9.15am: Honours Students
Chair: Professor Andreas Evdokiou

Abstract 4
8.15: Sophie Camens, Sha Liu, Karen Hon, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde
Preclinical development of a *Pseudomonas aeruginosa* bacteriophage cocktail for treating multidrug resistant bacterial infections

Abstract 18
8.30: Sarena La, John Beltrame, Rosanna Tavella, Sivabaskari Pasupathy
Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA) Patients Undergoing Cardiac Magnetic Resonance Imaging (CMR)

Abstract 31
8.45: Michelle Sims, John Licari, Romana Panagopoulos, Vasilios Panagopoulos, Irene Zinonos, Benedetta Sallustio, Andreas Evdokiou
Exploring the TRAIL of doxorubicin-induced cardiotoxicity

Abstract 35
9.00: Kenny Yeo, Eric Smith, Amanda Townsend, Tim Price, Jennifer Hardingham
Overcoming chemo-resistance in triple-negative breast cancer and the mechanism of cell death by bacopaside II

9.15 - 10.15am: Junior PhD Students (Laboratory)
Chair: Associate Professor Tania Crotti

Abstract 9
9.15: Sholeh Feizi, Clare Cooksley, Shari Javadian, Clive Prestidge, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde
Treatment of bacterial infections in chronic rhinosinusitis with bio synthesized colloidal silver

Abstract 14
9.30: Ghais Houtak, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde.
Biofilm antibiotic resistance in chronic rhinosinusitis

Abstract 24
9.45 Roshan Nepal, Peter-John Wormald, Alkis Psaltis, Sarah Vreugde
Prophage integration in *S. aureus* increases its virulence as well as aids in its evolutionary diversification

Abstract 39
10.00: Gohar Shaghayegh, Clare Cooksley, Kevin Fenix, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde
The relationship between Staphylococcus aureus biofilm properties and the disease severity and inflammation in chronic rhinosinusitis

10.15 - 10.45am: Morning Tea and Trade Displays

10.45 - 11.45am: Senior PhD Students (Laboratory)
Chair: Professor Laura Parry

Abstract 11
10.45: Amita Ghadge, Pallave Dasari, Rebecca Robker, Wendy Ingman
Impact of pubertal adiposity on breast development, breast density and breast cancer risk

Abstract 13
11.00: Michael Gouzos, Clare Cooksley, Sholeh Feizi, Tom Coenye, Alkis Psaltis, Peter-John Wormald, Sarah Vreugde
A Pro-Healing Anti-Oxidant: Safety and Efficacy of Mitochondrially-Targeted Antioxidant Mitoquinone for Reducing Infections and Preventing Adhesions after Sinus Surgery

Abstract 21
11.15: Sean Mangion, Amy Holmes, Azadeh Alinaghi, Lorraine Mackenzie, Michael Roberts
Removing the blindfold: visualising the topical delivery of retinoids

Abstract 23
11.30: Maryam Nakhjavani, Eric Smith, Tim Price, Amanda Townsend, Jennifer Hardingham
Ginsenoside Rg3 enantiomers in a defined ratio as a novel treatment for triple negative breast cancer

12.00 - 1.00pm: TQEH Research Expo Plenary Lecture

Professor Toby Coates

Director of Kidney and Islet Transplantation, RAH

Professor of Medicine, University of Adelaide

'RECYCLING ISLETS TO TREAT DIABETES'

Chair: Professor Guy Maddern

1.00 - 2.00pm: Lunch and Trade Displays

2.00 - 3.00pm: Clinical Research Group 1

Chair: Professor Ben Kile

Abstract 15
2.00: Unyime Jasper, Renuka Visvanathan, Agathe Jadczak, Solomon Yu, Joanne Dollard
Clinical staff perspectives on sedentary behaviour and physical activity in hospitalised older adults

Abstract 19
2.15: Suellen Lyne, Sarah Downie-Doyle, Susan Lester, Alannah Quinlivan, Toby Coates, Tom Gordon, Maureen Rischmueller
Primary Sjogren's Syndrome in South Australia

Abstract 28
2.30: Alannah Quinlivan, Susan Lester, Claire Barrett, Samuel Whittle, Debra Rowett, Rachel Black, Vibhasha Chand, Franca Marine, Lyn March, Premarani SInnathurai, Rachelle Buchbinder, Catherine Hill
Attitudes of Australians with inflammatory arthritis to biologic therapy and biosimilars)

Abstract 33
2.45: Kai Tit Tan, Ellie Lawrence Wood, Andy Lawrence, Lynton Graetz, Catherine Toben, Oliver Schubert, Nigel Rogasch, Mitchell Goldsworthy, Scott Clark
The Association between Electroencephalography Aperiodic Slope, Symptoms, Cognition, Function and Neuroinflammation in Australian Defence Force Combat Veterans

3.00 - 4.00pm: Clinical Research Group 2

Chair: Professor John Beltrame

Abstract 7

3.00: Alice Day, Chu Kion Yao, Samuel Costello, Jane Andrews, Andrew Ruszkiewicz, Peter Gibson, Robert Bryant

Evaluation of the tolerance and effect on disease activity of a new dietary strategy (4-SURE diet) for mild-moderately active ulcerative colitis

Abstract 17

3.15: Giri Krishnan, Aidan Cousins, Benjamin Thierry, Peter-John Wormald, Andrew Dwyer, Sophia Otto, Shridhar Krishnan, James Badlani, Suren Krishnan, Andrew Foreman

An innovative magnetic approach for sentinel lymph node biopsy in head and neck cancer

Abstract 25

3.30: Gao Jing Ong, John Horowitz

Can we predict the development of hypotension after onset of Takotsubo Syndrome (TTS)?

Abstract 27

3.45: Huai Leng Pisaniello, Mark Lunt, Susan Lester, Samuel Whittle, Catherine Hill, John McBeth, William Dixon

Examining the Day-to-Day Pain Variability in Inflammatory and Non-Inflammatory Rheumatic Diseases Using Multilevel and Markov Transition Models: Cloudy with a Chance of Pain, a Nationwide U.K. Smartphone Study

4.00pm: 3MT® Presentations (Three Minute Thesis, University of Adelaide)

Chair: Associate Professor Joy Rathjen

Dr Anna Megow, Unyime Jasper, Dr Maryam Nakhjavani, Gohar Shaghayegh, Dr Huai Leng (Jessica) Pisaniello.

4.20pm: Award Presentations

ABSTRACT 1

Telehealth in COVID-19: what did we think and what can we learn?

Lucinda Adams (*), Susan Lester (*,#), Elizabeth Hoon (^,**), Heather van der Haak (#), Charlotte Proudman (*,%), Cindy Hall (^), Samuel Whittle (*,#), Susanna Proudman (*,%), Catherine L. Hill (*,#,%)

* Discipline of Medicine, University of Adelaide; # Rheumatology Unit, The Queen Elizabeth Hospital; ^ Discipline of General Practice, University of Adelaide; ** School of Public Health, University of Adelaide; % Rheumatology Unit, Royal Adelaide Hospital

Aims: To investigate patient and clinician satisfaction and acceptability of telehealth consultations at two public hospital outpatient departments (OPD) in South Australia during the COVID-19 pandemic.

Methods: A modified version of a validated survey for telehealth evaluation was posted to all patients attending the telehealth OPD rheumatology clinics at the Queen Elizabeth and Royal Adelaide hospitals, including balanced 5-point Likert scales and free-text responses. Concurrently, clinicians across 12 medical specialities at both sites were emailed a modified version of a previously used clinician satisfaction survey. Cluster analysis was applied to the Likert-scale questions, alongside thematic analysis of free-text responses.

Results: 128 patients responded (29% response rate); 69.5% females and majority were aged 50 years or older (87.5%). Nearly 1/5 patients indicated consistent dissatisfaction with telehealth across the range of questions. These patients were older, reported lower educational qualifications and lower health literacy scores and lacked access to the internet. 64 clinicians completed the satisfaction survey. Overall, only 4.7% of clinicians surveyed reported telehealth consults were of superior quality to face-to-face consults. Only 1.6% of clinicians surveyed reported telehealth was better at allowing them to manage patient need and problems when compared with face-to-face consults, with the highest portion believing face-to-face to be significantly better (43.8%). While both patients and clinicians acknowledged this mode of consultation to be convenient, both groups expressed concerns regarding the lack of physical examination. A recurrent theme was a desire for a mixed-model clinic in the future, with the flexibility of having both telehealth and face-to-face consultation options.

Conclusions: This study offers unique insights into patients and clinicians' experiences with telehealth, which until the current global pandemic, has been an uncommon mode of consultation delivery in urban areas. This study suggests that in defining the place of telehealth in future healthcare delivery, careful patient selection will be key. Disease progression, language and cognitive ability, health literacy, technology access, and patient and clinician preference are important consideration when deciding how to effectively embed and integrate telehealth into future consultations.

ABSTRACT 1 (continued)

LAY DESCRIPTION

COVID-19 forced nearly all doctor's visits were telehealth, via phone or video. Our aim was to capture both patient & clinician experiences of telehealth to inform how we deliver healthcare in the future. We surveyed patients & clinicians, asking multichoice and free-text questions.

128 patients and 64 clinicians completed our survey. We found that for many patients telehealth is convenient. But nearly 1/5 of patients were dissatisfied. Only 4.7% of clinicians thought telehealth was better than in person clinic. Both groups were concerned there is no physical examination and expressed a desire for both in person and telehealth clinics.

ABSTRACT 2

A clinical assay to measure plasma concentrations of tacrolimus and improve therapeutic drug monitoring

Mirabel Alonge, Benedetta Sallustio
Clinical Pharmacology

Tacrolimus (Tac) is an immunosuppressant used in solid organ transplantation to prevent rejection. Its low therapeutic index and highly variably pharmacokinetics warrants therapeutic drug monitoring to individualise dosing by keeping blood concentrations within a narrow therapeutic range. It is the unbound plasma concentration however, that is pharmacologically active and therefore basing dosage adjustments on whole blood concentrations may lead to misguided dosage adjustments.

Aims:
1. Develop and validate an assay to measure plasma concentrations of tacrolimus.
2. Investigate the relationship between whole-blood and plasma concentrations of tac and potential covariates in *de novo* renal transplant recipients.

Methods: Plasma tac concentrations were measured by liquid chromatography tandem mass spectrometry following solid phase extraction. The assay was then validated for linearity, accuracy, reproducibility and specificity and applied to plasma samples collected from 7 *de novo* renal transplant patients.

Results and Discussion: The assay was linear for tac concentrations between 100 - 5000ng/L with intra and inter-assay imprecision of less than 10% for both the lowest and the highest limit of quantitation. The matrix effect was -9.81% with a negligible loss during extraction of 0.61% and no overall loss. The relationship between whole blood trough concentrations and plasma concentrations was linear with an R-squared value of 0.75. Plasma trough concentrations ranged between 300 - 2500ng/l remaining well within the limits of the assay. Correcting for haematocrit did not significantly improve prediction of plasma concentrations.

Conclusion: Further investigation is needed to determine whether plasma concentrations will be a better surrogate for the active drug concentration and hence clinical outcomes.

LAY DESCRIPTION

Tacrolimus is a medication prescribed to individuals who have had an organ transplant to prevent their body from rejecting the transplanted organ. Whole blood concentrations are monitored to ensure concentrations are within therapeutic ranges however, the results can be misinterpreted early after a transplant because these concentrations are not representative of the active drug component. Our research aims to produce a clinical assay to measure the active drug component and so improve dosage individualisation and clinical outcomes.

ABSTRACT 3

Shine a light! Gallium protoporphyrin as a selective photosensitiser for antimicrobial photodynamic therapy.

Muhammed Awad1,2,3, Prof. Clive Prestidge 1,3, Dr. Timothy Barnes 1,3, Dr. Nicky Thomas 1,2,3
1. University of South Australia, Clinical and Health Sciences, SA, 5000, Australia; 2. Basil Hetzel institute for Translational Health Research, Woodville South, 5011, SA; 3. ARC Centre of Excellence in Convergent Bio-Nanoscience and Technology, Australia

Antimicrobial resistance is a major global threat claiming millions of lives every year due to the lack of effective antimicrobials against infectious diseases. The shortage of efficient antimicrobials calls for novel, unconventional treatment options. Antimicrobial photodynamic therapy (APDT) has evolved as a promising approach to overcome drug-tolerant and resistant pathogens. APDT relies on the generation of controlled amounts of reactive oxygen species (ROS) following light activation of photoactive dyes termed photosensitisers (PS). Current PS suffer from poor selectivity towards microbial cells, which lowers their activity and raises concerns of toxicity towards host cells, limiting the clinical application of APDT. Hence, novel PS with high selectivity are required.

Gallium protoporphyrin (GaPP) was hypothesized to act as a selective PS due to its structural similarity with heme, a favoured iron source for microbes, hence facilitates targeting to microbial cells. The photodynamic activity of GaPP was evaluated in the planktonic and biofilm mode of growth of *C. albicans* and *S. aureus*, two common microbial species in nosocomial infections. The minimum inhibitory concentrations of GaPP in the dark was determined as 16 µg/mL and 0.5 µg/mL for *C. albicans* and *S. aureus*, respectively. To assess its photodynamic activity, GaPP was incubated with microbial suspensions in the dark for one hour followed by light illumination for one minute, using a 100 mW blue LED lamp. The minimum biocidal concentrations of photoactivated GaPP were 5 µg/mL and 1 µg/mL against *C. albicans* and *S. aureus*, respectively. Moreover, photoactivated GaPP reduced the viability of microbial biofilms up to 97%.

These findings confirm that GaPP can act as an efficient, highly selective photosensitiser against bacteria and fungi.

LAY DESCRIPTION

The increasing number of microorganisms that do not respond to existing antibiotics poses a major threat to global societies. In this project we develop an unconventional and non-invasive treatment against resistant infectious diseases using light. A lower power light source (LED) in combination with a light-sensitive dye generates highly reactive oxygen species that destroy resistant microorganisms while reducing side effects in patients.

ABSTRACT 4

Preclinical development of a *Pseudomonas aeruginosa* bacteriophage cocktail for treating multidrug resistant bacterial infections

Sophie Camens# *, Sha Liu# *, Karen Hon# *, Alkis J. Psaltis# *, Peter-John Wormald# *, Sarah Vreugde# *

Department of Health and Medical Sciences-Surgery, The University of Adelaide; * Department of Surgery-Otolaryngology Head and Neck Surgery, Basil Hetzel Institute for Translational Health Research, Central Adelaide Local Health Network, Woodville South, Australia.

Pseudomonas aeruginosa airway infection is one of the predominant causes contributing to the high morbidity and mortality rates in cystic fibrosis (CF) patients. The emergence of multidrug resistant (MDR) *P. aeruginosa* strains has led to the urgent need for new therapeutic approaches. Bacteriophages (phages) are viruses that can infect and lyse specific bacteria, providing a potential alternative approach in targeting MDR strains. It is postulated that the combination of phages in a cocktail will increase their lytic activity by expanding the target hose range. The aim of this project is to develop a novel cocktail of *P. aeruginosa* phages to kill MDR *P. aeruginosa*.

P. aeruginosa phages were isolated from hospital wastewater using double agar overlay assays. Phages underwent testing for temperature and pH stability and characterisation for infectivity properties. Phages were tested against CF and non-CF *P. aeruginosa* clinical isolates (CIs) in planktonic and biofilm form to determine their host range. Transmission electron microscopy was used to investigate phage morphology. Fully characterised lytic phages were selected and applied to a *C. elegans* infection model to determine the effectiveness at reducing MDR *P. aeruginosa* infection. 15 *P. aeruginosa* phages were isolated and were stable at temperatures ranging between 4-50˚C and pH 3-11. 19/21 CF and non-CF *P. aeruginosa* CIs were susceptible to at least one of the phages with 2 phages (PA-4 and PA-6) lysing 15/21 and 16/21 CIs respectively. Those phages could lyse MDR *P. aeruginosa* within 1.5 hours when infected at multiplicity of infection (MOI) 1 ($P<0.0001$ and $P<0.03$ respectively, one-way ANOVA).

P. aeruginosa phages isolated from wastewater were stable and could kill MDR CF and non-CF *P. aeruginosa* CIs in both planktonic and biofilm form. Phage therapy represents a promising alternative treatment option to antibiotics when treating *P. aeruginosa* airway infection.

LAY DESCRIPTION

People with cystic fibrosis develop an abnormally thick and dehydrated mucus layer within the nose, sinuses and lungs. This is problematic as it favours infections with the aggressive bacteria, *P. aeruginosa*. Treatment historically involves the use of antibiotics, which often leads to the development of multidrug resistant bacteria. An alternative treatment option to antibiotics is bacteriophage therapy. Phages are viruses found in the environment that are able to kill bacteria. The objective of this project is to characterise *P. aeruginosa* phages that will be further developed for use in patients infected with highly resistant *P. aeruginosa*.

ABSTRACT 5

Participant satisfaction, motivations, and participation experiences of chronic rhinosinusitis clinical trial participants

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Background: Challenges in recruitment and retention rates are problems commonly encountered in clinical trials. Understanding motivations and measuring trial participation experience could improve the delivery of trials and address such challenges. This survey evaluates the participant satisfaction, motivations and participation experiences of chronic rhinosinusitis patients enrolled in a double-blinded randomised controlled trial testing the safety and efficacy of a Kappa-carrageenan buffered salt nasal rinse solution (Flo Kappa).

Aim: To determine the motivations of chronic rhinosinusitis patients for joining the Flo Kappa trial, and to obtain data on participant satisfaction and perspectives of trial procedures.

Hypothesis: Participants report high overall satisfaction with their trial participation experience.

Method: 50 patients will be recruited. We will invite Flo Kappa trial participants at their 6-8 weeks and 3 months post-operative visitations to complete a 16-item participant experience survey of their experiences of being in the Flo Kappa trial. The items on this survey evaluated include; previous trial participation, reasons for participation, expectations, overall experiences, perspectives of trial procedures, and likelihood of participating or recommending for others to participate in a clinical trial. Survey items are measured by free-text, visual-analogue scale and 5-point scale responses.

Results: 17 patients have been recruited to date and 6 have completed the survey. Preliminary results indicate high overall satisfaction with trial participation experience. Analysis will be completed once all patients have completed the survey.

Conclusions: Participants are expected to report high overall satisfaction with their trial participation experience. Determination of motivations and experiences of trial participation could help to provide data to optimise the delivery of clinical trials and improve the participation experiences of trial participants.

LAY DESCRIPTION

Little is known about the reasons why chronic rhinosinusitis (CRS) patients participate in clinical trial studies and what could be done to improve their participation experience. We surveyed CRS patients enrolled in a clinical trial investigating a post-surgery sinus wash. We collected data about their reasons for doing the trial, thoughts about different aspects of the trial, and experiences of being in the trial. This information could help to improve the general understanding of what could be done to improve the way we run clinical trials in the department as well as improve the participation experiences of future participants.

ABSTRACT 7

Evaluation of the tolerance and effect on disease activity of a new dietary strategy (4-SURE diet) for mild-moderately active ulcerative colitis

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Background and Aim: Existing therapies for ulcerative colitis (UC) are inadequate. A new dietary paradigm, 4-strategies-to-SUlfide-REduction (4-SURE diet), designed to modulate harmful metabolites implicated in UC pathogenesis offers an opportunity to bridge this therapeutic gap. This pilot study aimed to explore tolerability, influence over food-related quality of life and efficacy of the 4-SURE diet as a therapeutic strategy in UC.

Methods: Twenty-eight participants with mild-moderate UC were enrolled in an 8-week open label dietary advice study. A research dietitian advised on increasing fermentable fibres, restriction of total and sulphur proteins, with avoidance of sulphates/sulphites (4-SURE diet) with accompanying meal plans and recipes. The primary outcome was dietary tolerability at 8 weeks. Dietary adherence, clinical and endoscopic response, change in faecal calprotectin and change in food-related quality of life (FRQoL) at 8 weeks were also assessed.

Results: All participants (28/28) completed the 8-week exploratory dietary intervention. Adherence to the 4-SURE diet was excellent (95%). In the intention to treat analysis (n=28), dietary tolerability was high (median visual analogue score 19 (7, 31)). Clinical response occurred in 13/28 (46%) (p=0.003) with 2/28 (7%) worsening. Endoscopic improvement was noted in 10/28 (35%) (p=0.0098) with 2/28 (7%) worsening. Faecal calprotectin reduced by 65ug/g (95% CI 11, 1202) (p=0.03). FRQoL increased, median score 10.4 (95% CI 4.4, 16.4; p<0.001) There were 4 protocol violations: 1 commenced a steroid enema at day 2, 2 increased medical therapy at week 5, and 1 stopped therapy due to bushfire disasters. These 4 participants were removed from a subsequent per protocol analysis.

Conclusion: 4-SURE diet was very well-tolerated in participants with mild-moderate UC, improved FRQoL and yielded clinical, biomarker and endoscopic response. These pilot results indicate a randomised controlled study is feasible.

ABSTRACT 7 (continued)

LAY DESCRIPTION

New therapies for ulcerative colitis (UC) are required. A multidimensional dietary strategy (4-SURE diet) designed to target harmful by-products of bacterial fermentation in the colon may be a therapeutic option. This preliminary study explored whether the 4-SURE diet was tolerable and influenced disease activity. 28 participants received 4-SURE dietary advice and followed the diet for 8-weeks. At week 8, the diet was highly tolerable and food-related quality of life improved. Disease improved in 13/28 (46%), of which 10/28 (35%) had healing of the colon. These findings suggest diet has therapeutic benefits in UC. A larger study is warranted.

ABSTRACT 8

Development of an in vitro system to identify novel drug candidates capable of manipulating tumour associated macrophages

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Background: Tumour associated macrophages (TAMs) are a unique subset of macrophages with tumour promoting and immune suppressive properties. Therapies which block the generation or function of TAMs have gained considerable interest as novel therapeutics in cancer treatment. Studies have shown that monocytes can differentiate into classical M1 and M2 macrophage subsets *in vitro*, suggesting that an *in vitro* macrophage differentiation model could be useful in screening for novel drug candidates. In support, treating the immortalized myeloid leukemia derived cell line, THP-1 cells with a combination of cytokines and cancer cell line conditioned media led to the differentiation of macrophages with a TAM phenotype distinct from M1 or M2 macrophages. The aim of this project is to generate M1, M2 and TAMs from THP-1 cells *in vitro*, evaluate the phenotype, morphology, and function of these macrophages, and determine if drug candidates in our laboratory modulates the generation and function of these subsets. Due to the lack of a standardization in the literature, our first step was to develop a protocol for M1, M2 and TAM differentiation.

Methods: THP-1 cells were incubated for 24 h with 5 pg of PMA (Phorbol 12-myristate 13-acetate), then rested for 72 h in complete media, followed by incubation for 48 h with either IFN-γ (20ng/mL) and LPS (250ng/mL) to obtain M1 polarized macrophages, or IL-4 and IL-13 (20ng/mL) to obtain M2 polarized macrophages. After the incubation, macrophage subset percentages were determined by flow cytometry using antibodies to CD80 (M1) and CD209 (M2).

Results: The CD80 positive (M1) cells increased from 0.65% to 83% over the period on treatment, and the CD209 positive (M2) cells increased from 5% to 27.3%.

Discussion and Conclusion: These results confirm the polarization of THP-1 cells into M1 and M2 phenotypes *in vitro*. This model will be used to investigate the induction of TAMs by cancer cell conditioned medium, followed by examining the effect of our drug candidates on the induction and function of this tumour promoting macrophage subset.

LAY DESCRIPTION

Tumour associated macrophages (TAMs) are immune cells that have been attributed to cancer overgrowth and spread (metastasis). We are investigating if certain drugs can inhibit the generation or function of these cells. To achieve this, we are developing a method that can reliably generate TAMs in the laboratory. Once we establish a reliable protocol for our drug screens, we hope to publish these findings so that other scientists around the world can also use this system to study how TAMs work or if they also have potential drugs that would be useful in targeting TAMs.

ABSTRACT 9

Treatment of bacterial infections in chronic rhinosinusitis with bio synthesized colloidal silver

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Background and aim: Airway infections in Chronic Rhinosinusitis (CRS) are caused by planktonic and biofilm forms of different microorganisms. They are difficult to treat because of their emerging resistance to antibiotics. Colloidal silver has been proposed as safe and effective antimicrobials, however, their use is hampered by the lack of efficient production processes. We aimed to evaluate the antibacterial activity of bio synthesized colloidal silver (CS) against clinically isolated bacteria in CRS patients alone and in combination with antibiotics.

Methodology: Aquatic eucalyptus extract was used for the synthesis of CS. Their size and shape were characterized over time by transmission electron microscopy and Nano Sight, respectively. Microdilution method, Resazurin assay and *C. elegans* were used to assess antibacterial effects of CS alone and in combination with various antibiotics. Cell toxicity was assessed using LDH and FITC-dextran permeability assays after application of CS to primary human nasal epithelial cells (HNECs) for 2 hours. Results were analysed using one-way analysis of variance (ANOVA) (GraphPad Prism version 8.00).

Results: CS was rapidly produced within 5 minutes, was spherical in shape, 40 nm in size and stable for > 6 months at room temperature. CS had significant anti-bacterial activity against clinical isolates from CRS patients including *Pseudomonas aeruginosa*, Methicillin Resistant *Staphylococcus aureus* (MRSA), *Haemophilus influenzae* and *Streptococcus pneumoniae* ($p<0.05$). CS reduced colony forming units of *P. aeruginosa* and MRSA in *C. elegans* by 96.9% and 99.6% respectively ($p<0.05$). They were non-toxic to HNECs. The effect of combination of CS and antibiotics varied for the different antibiotics with synergism observed against MRSA and *P. aeruginosa* planktonic and biofilm forms for gentamicin and mupirocin.

Conclusion: bio synthesized CS has potential to be used against planktonic and biofilm infections in the context of CRS.

LAY DESCRIPTION

Longstanding inflammation of sinuses leads to the infection and cause nasal congestion and facial pain in chronic rhinosinusitis (CRS) patients. Microbial infection, one of the contributing factors to CRS, makes it difficult to treat with antibiotics, so, patients go through surgery, however, in some cases surgery fails. Therefore, researchers focus on finding alternative therapies in CRS patients one of which is silver nanoparticles. In this project, silver nanoparticles were used for bacterial killing in CRS patients which may potentially lead to the development of a new treatment for CRS.

ABSTRACT 10

Effect of *Pseudomonas aeruginosa* exoproteins on the nasal mucosal barrier in chronic rhinosinusitis in hypoxic condition

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Introduction: Chronic rhinosinusitis (CRS) is defined as a persistent inflammation of the mucosa of the paranasal sinuses associated with relapsing infections. Nasal blockage can result in hypoxic conditions promoting the expression of virulence genes in invading pathogens. *P. aeruginosa* is an opportunistic pathogen that can grow in hypoxic conditions and is one of the most common bacteria in severe recalcitrant CRS.

Aim: To determine the effect hypoxia on the production of exoproteins by *P. aeruginosa* clinical isolates in planktonic and biofilm form and evaluate their effect on the mucosal barrier structure and function.

Methods: *P. aeruginosa* clinical isolates of CRS patients were grown in hypoxic condition and exoproteins collected from planktonic and biofilm form. Exoproteins were applied to air-liquid interface (ALI) cultures of primary human nasal epithelial cells (HNECs) and membrane integrity was evaluated by transepithelial electrical resistance (TEER), passage of fluorescently labelled dextrans (FITC-dextrans) and immunofluorescence targeting the tight junction proteins Claudin-1 and Zonula Occludens-1 (ZO-1). Cytotoxicity assays were performed to measure cell viability and IL-6 ELISA was performed to evaluate induction of inflammation. Data analysis was performed using analysis of variance (ANOVA).

Results: 20 *P. aeruginosa* clinical isolates of CRS patients were grown in hypoxic condition (1% oxygen) and exoproteins harvested in late stationary phase. There was a disruption of barrier structure and function evidenced by a decrease in TEER value, an increase in permeability of FITC-dextrans ($p < 0.0001$) and a discontinuous localization of Claudin and ZO-1 after application of planktonic and biofilm exoproteins to HNEC-ALI cultures. There was a significant increase in IL-6 production ($p=0.002$) compared to negative control.

Conclusion: Exoproteins isolated from planktonic and biofilm forms of *P. aeruginosa* grown in hypoxic condition disrupt the mucosal barrier.

LAY DESCRIPTION

Human race cannot live without oxygen but some microbes can live with and without oxygen. Chronic rhinosinusitis (CRS) is a disease of inflammation in paranasal sinuses and create blockage of nose. This cause less oxygen in sinuses and affect the appearance of virulence and antibiotic resistance genes in attacking pathogens. *P. aeruginosa* is one of the most common pathogen in CRS and can live in both conditions. So we wanted to see the effect of *P. aeruginosa* proteins that grown without oxygen on mucosal wall of nasal epithelial cell. Mucosal wall damage is one of the major contributors to respiratory infection and airway inflammation.

ABSTRACT 11

Impact of pubertal adiposity on breast development, breast density and breast cancer risk

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Introduction: Puberty is a critical life stage for breast development as well as for establishment of breast density, which is an important risk factor for breast cancer (1). High pubertal adiposity is associated with low adult breast density and reduced lifetime breast cancer risk. However, the biological basis of these associations have not been explored.

Aim: To investigate the impact of pubertal adiposity on mammary gland development, density and cancer risk in adulthood in a mouse model.

Methods: Mice homozygous for a mutation in Alms1 gene exhibit pubertal adiposity. To investigate the effect of pubertal adiposity on mammary gland development, mammary glands were collected from pubertal Alms-/- mice (n = 10/group). From 7 weeks of age, food intake of a group of Alms-/- and Alms-/-xMmtv-PyMT mice were matched with their respective wild-type controls, whereas another group of Alms-/- and Alms-/-xMmtv-PyMT mice ate *ad libitum*. Mammary glands and mammary tumours were collected from adult Alms-/- (n=10/group) and Alms-/-xMmtv-PyMT mice (n=10/group) respectively. Statistical significance was considered at $p < 0.05$ by using Student's t test.

Results: During puberty, Alms-/- mice exhibited increased mammary adiposity with larger adipocytes (2205.1±109.4 um2; mean±SEM) compared to wildtype controls (1807.1±143.9 um2; p=0.03). High adiposity led to significantly greater number of terminal end buds in Alms-/- mice (15.8±1.4) than controls (9.67±1.39; p=0.007), and increased BrdU+ proliferative epithelial cells in terminal end buds in Alms-/- mice (3329.8±289.4) than controls (1608.3±232.6; p=0.0002). Further, significantly decreased percent fibroglandular density was observed in matched adult Alms-/- (1.6±0.2) compared to controls (3.7±0.5; p=0.004). Finally, matched Alms-/-xMmtv-PyMT mice exhibited significantly lower number of tumours (2.6±0.4) than controls (5.0±0.6; p=0.004), significantly decreased tumour burden (0.3±0.08 g) compared to controls (0.8±0.1 g; p=0.04) and significantly longer tumour latency (92.2±4.8 days) than controls (72.4±2.1 days; p=0.0009).

Conclusion: Increased adiposity during pubertal mammary gland development resulted in lower fibroglandular density and reduced mammary cancer development during adulthood.

(1) Engmann NJ *et al*. Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer. *JAMA Oncol*. 2017;3(9):1228-1236.

ABSTRACT 11 (continued)

LAY DESCRIPTION

Puberty is a critical stage for breast development. Epidemiological studies have suggested that abundance of adipose tissue in pubertal girls affects their future breast cancer risk through altering abundance of different cells types in breasts. However it is unknown whether this is a causal relationship and whether we could reduce adult breast cancer risk through interventions that promote optimal pubertal breast development. We have used mouse model to explore this relationship and provide first evidence that increased pubertal adiposity alters mammary gland development leading to reduced risk of mammary cancer development during adulthood.

ABSTRACT 12

Autacoid signalling in Takotsubo Syndrome: The Sibyl revisited.

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Background: Takotsubo Syndrome (TTS) occurs mainly in ageing women and consists of acute damage to the coronary vascular endothelium followed by inflammatory infiltration of the heart. TTS patients exhibit increased generation of, and tissue responsiveness to, nitric oxide (NO); variability in prostacyclin (PGI2) effect has not previously been evaluated.

Hypothesis: We hypothesised that the normal age-related decline in tissue responsiveness to NO is attenuated in TTS, and also sought to determine whether similar changes occur in response to PGI2.

Method: We utilised platelet aggregation in whole blood to compare variability in age: anti-aggregatory response relationships for normal subjects (n=11) and TTS patients (n=19). NO and PGI2 donors were studied. Data was analysed by ANCOVA and backwards stepwise multiple logistic regression.

Results:

(1) Normal ageing was associated with definite (p=0.04) and borderline (p=0.07) reductions in NO and PGI2 responses respectively.

(2) In TTS patients, there was no significant change in either NO or PGI2 response with age; this contrasted with data from normal subjects (P=0.02; F=6.5, and P=0.008; F=7.972, respectively [ANCOVA]).

(3) Significant positive correlates of NO response were presence of TTS, youth and male gender.

Conclusions:

(1) Normal vascular ageing selectively compromises anti-aggregatory responses to NO and possibly PGI2, especially in women, and thus PGI2 responses become relatively more important with increasing age.

(2) In TTS patients, both NO and PGI2 responses are well-preserved despite advanced age.

Implications:

These data suggest

(1) “normal” ageing, especially in women, increases propensity to thrombotic events

(2) In TTS, especially with advanced age, there may be greater predisposition to increased effects of NO and PGI2, such as development of hypotension.

ABSTRACT 12 (continued)

LAY DESCRIPTION

Takotsubo ("broken heart") syndrome (TTS) occurs especially in ageing women and causes dangerous falls in blood pressure in many patients. We sought to determine whether supra-normal tissue responses to nitric oxide (NO) and prostacyclin (PGI2), which dilate blood vessels and prevent clotting, might contribute to this problem. While in normal subjects responses to NO and PGI2 tended to decrease with ageing, this tendency was absent in TTS patients. These results raise the possibility that release of NO/PGI2 in TTS patients may contribute to dangerous falls in blood pressure.

ABSTRACT 13

A Pro-Healing Anti-Oxidant: Safety and Efficacy of Mitochondrially-Targeted Antioxidant Mitoquinone for Reducing Infections and Preventing Adhesions after Sinus Surgery

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Background: Favourable postoperative outcomes after sinus surgery hinge on avoiding re-establishment of a fastidious biofilm of bacteria and optimizing the quality of mucosal healing. Mitochondrial oxidative damage has been shown to antagonise both of these outcomes. The present study aims to evaluate the safety and efficacy of antagonising oxidative damage using a mitochondrially-targeted antioxidant called mitoquinone. We hypothesised that it would improve wound healing and disrupt bacterial growth, either alone, or in synergy with an antibiotic.

Methods: A dose-response curve of cell migration in nasal fibroblasts and epithelial cells was established for 1-20µM of mitoquinone using time-lapse confocal laser scanning microscopy. An effective range of doses was then tested for activity against three strains of *Staphylococcus aureus* planktonic cells and biofilm using optical density, colony forming units and cell staining. Combination therapy with existing antibiotics was also assessed.

Results: Mitoquinone showed a significant ($p < 0.05$), favourable slowing of fibroblasts across 1 to 5µM without an associated increase in epithelial migration. This effect is preventative for mucosal adhesion formation. 5µM mitoquinone also produced a Log 4-5 reduction in *S. aureus* planktonic colony forming units and killed an average of 51% of established biofilm ($p < 0.05$), whilst not provoking toxicity in human cells ($p < 0.05$). It also synergistically improved the activity of augmentin, doxycycline, clarithromycin and mupirocin ($p < 0.05$) against all strains of planktonic and biofilm *S.aureus*.

Conclusions: These results confirm our hypothesis that mitoquinone contains not only an antioxidant base that targets mitochondrial ROS, leading to a more favourable wound healing profile, but an antimicrobial moiety that is effective against a significant sinonasal pathogen. It is also safe for human sinonasal cells, making it an exciting prospect for future clinical trials in sinus surgery.

LAY DESCRIPTION

We investigated whether a special antioxidant call mitoquinone, that can penetrate deep into the powerhouse of the cell -the mitochondrion- could improve healing after sinus surgery. We treated cells with mitoquinone and used a microscope to see how long they took to heal after we made a scratch in them. Then we used it to treat infections, to see if we could slow down the rate of bacterial growth. Our results show that mitoquinone can improve healing and stop bacteria from growing at the same time! This makes it an excellent treatment for our patients that have just surgery on their sinuses.

ABSTRACT 14

Biofilm antibiotic resistance in chronic rhinosinusitis

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Background: Chronic rhinosinusitis (CRS) is a common disease affecting the paranasal sinuses. Despite established medical and surgical interventions a considerable proportion of CRS patients do not show sufficient reduction of symptoms. The aetiology of CRS is not fully understood, however, it is commonly described as a multifactorial disease where intrinsic host factors and extrinsic factors give rise to the disease. Of all the extrinsic factors, specific bacterial species present in their biofilm form seem to be a prevalent driver of disease. Particularly, *Staphylococcus aureus* (biofilm) has often been associated with CRS. Another significant aspect of bacterial biofilms is their resistance to antibiotics.

Aim: This study explores the biofilm antibiotic susceptibility of *S. aureus* isolated from CRS patients at different time points to commonly used antibiotics.

Methods: *S. aureus* clinical isolates were harvested from the sinonasal cavities at different time points from the same patient. Isolates were grown in 48-hour biofilms followed by CrystalViolet assay to determine the biofilm biomass. The susceptibility of planktonic cells and biofilms to antibiotics was tested using Minimum Inhibitory Concentration assays and a resazurin viability assay respectively. Results were analysed using the ANOVA tests.

Results: 68 *S. aureus* strains were analysed, harvested from 34 patients. All clinical isolates biofilms were highly tolerant to antibiotics (erythromycin, doxycycline, clindamycin, augmentin, gentamicin, mupirocin). Among all antibiotics tested, only doxycycline in high concentrations was able to significantly suppress the *S. aureus* biofilms. The biofilm antibiotic susceptibility of clinical isolates increased over time when grown in biofilm form ($p<0.05$).

Conclusions: Biofilm antibiotic resistance of *S. aureus* clinical isolates increases over time, with potential implications in CRS disease modification in response to antibiotics consumption.

LAY DESCRIPTION

Chronic sinus disease is a common burden in our population, which, in some cases does not alleviate after standard treatments. The main cause of the disease is not known, however, it is suspected that an interplay between multiple features give rise to the disease. Many scientific studies classify the bacteria *Staphylococcus aureus* biofilm as a major influencing component in this condition. This project investigated the resistance of biofilm formation, which is a community of bacteria in a gel like enclosure, to several antibiotics.

ABSTRACT 15

Clinical staff perspectives on sedentary behaviour and physical activity in hospitalised older adults

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Abstract: Older adults are sedentary (sitting and lying for prolonged periods) for 99% of their time in hospital with very little physical activity (PA). The consequences are a longer length of hospital stay and poor outcomes such as worsening frailty. The perspectives of hospital staff regarding sedentary behaviour (SB) and PA in hospitalised older people is currently unknown. Exploring staff perspectives assists the development of strategies to reduce SB and improve PA in hospital.

Aims: This study aimed to explore clinical staff:
• Knowledge of and attitudes to SB and PA;
• Strategies to support older patients reduce SB and improve PA

Methods: Semi-structured interviews were conducted with 18 clinical staff on the orthopaedic and geriatric medicine ward at The Queen Elizabeth Hospital. The grounded theory methodology guided data collection and analysis.

Results: Clinicians understood SB and PA, but with misconceptions. Staff were aware of the adverse physical and mental effects of SB while PA alleviates these negative consequences. Many staff perceived that older people preferred to be sedentary. Staff reported that in addition to patient's physical condition and patient concerns about their safety, hospital processes such as lack of activities, poor communication and uncoordinated care also influenced SB and PA. Staff stated that one primary reason for SB among hospitalised older people was that PA was not a ward priority and staff struggled with competing priorities. For example, it was quicker to assist patients with activities of daily living rather than allowing patients time to complete these tasks themselves with supervision.

Discussion/Conclusion: Reducing SB and increasing PA in hospital requires attention to staff knowledge and processes of care as well as working with clinicians to increase buy-in that increasing PA is essential parts of clinical care.

LAY DESCRIPTION

Prolonged sitting or lying negatively affects the recovery of older people during hospital admission. This study wanted to understand what hospital staff thought about prolonged sitting and lying among older patients and what can be done to help them move more in hospital. Staff identified barriers to moving more in hospital include lack of time to support older patients, poor communication and coordination among staff. To get hospitalised older people to move more, staff suggested reducing time staff spent doing non-clinical work, encouraging patients to set daily activity goals, and asking carers to support patients move more.

ABSTRACT 16

The impact of PARP-1 inhibitor on endothelial cell viability and vascular reactivity in T2D model

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Background: Type 2 Diabetes (T2D) is associated with endothelial dysfunction due to oxidative stress. Poly(ADP-ribose) Polymerase (PARP-1) is a DNA-repair enzyme activated during oxidative stress. However, its overactivation in T2D may lead to apoptosis and compromise cell survival. Therefore, in the current study, we hypothesised that inhibition of PARP-1 using 3-aminobenzamide (3-AB) in T2D would normalize the dysfunctional biochemical cascade associated with endothelial dysfunction.

Methods: In human coronary artery endothelial cells (HCAEC), alamar blue assays were used to evaluate the impact of 3-AB on cellular viability in response to a range of stressors. Then, isolated thoracic aorta segments obtained from rat models of T2D pre-treated with 2-weeks of 3-AB at 5mg/kg, 15mg/kg and 30mg/kg were used to investigate vascular reactivity using organ bath preparations. Changes to dose-responses to vasocontrictor phenylephrine, as well as endothelium-dependent and independent vasorelaxants acetylcholine, glyceryl trinitrate and forskolin, were recorded. Half-maximal effective concentration (EC50) between groups were compared.

Results: In HCAEC, 3-AB increased cell viability in response to dual stressors of 25mM glucose and 40-hours of hypoxia (10% increase, $p<0.05$), as well as the chemical stressor 500uM hydrogen peroxide (19% increase, $p<0.0001$), but not hyperglycaemia or hypoxia alone. In preliminary studies using isolated aortic segments from rats, T2D reduced EC50 in response to phenylephrine from 84nM to 30nM ($p<0.05$). However, there were no significant changes in response to vasorelaxants between treatment groups.

Conclusion: These data suggest that 3-AB may limit endothelial cell death under combined hyperglycaemia and hypoxia. The lack of induction of endothelial dysfunction with T2D in aortic segments suggests potential inadequate redox stress in the model.

LAY DESCRIPTION

It is estimated that someone dies from diabetes or its associated complications every 7 seconds. Type 2 Diabetes (T2D) is characterised by insulin resistance which impairs glucose uptake from the blood and into the tissues. The excess glucose in the blood causes stress and damages tissues such as the heart and blood vessels. This can result in failure of the blood vessels to relax leading to problems such as poor blood flow and peripheral vascular disease. We aim to target a DNA repair enzyme, Poly(ADP-ribose) Polymerase-1, in order to improve blood vessel function in a T2D rat model.

ABSTRACT 17

An innovative magnetic approach for sentinel lymph node biopsy in head and neck cancer

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Background: Sentinel lymph node biopsy (SLNB) is a well-established minimally invasive staging procedure that maps cancer spread from its primary site to regional lymph nodes. In head and neck cancer it can avoid complete neck dissection in 75% of patients who are currently exposed to unnecessary surgical morbidity. Unfortunately, it has not been widely adopted however, because conventional radionuclear technology does not provide enough spatial and anatomic resolution to confidently map lymphatic drainage in the complex head and neck environment. To overcome this, an innovative magnetic approach has been developed here in South Australia.

Hypothesis and aims: The aim of this study was to evaluate the safety and feasibility of a novel magnetic SLNB approach for head and neck cancer staging.

Methods: A phase 1 clinical trial was opened at the Central Adelaide Local Health Network. Patients with head and neck squamous cell carcinoma were recruited. Patients received peri-tumoural injection of a first-in-human superparamagnetic iron oxide nanotracer (SPION) prior to serial MRI. The following day, a SLNB procedure was performed using a novel hand-held magnetometer probe to identify the first lymph node(s) to receive afferent drainage of SPION. After this, a complete neck dissection was performed.

Results: Three patients were recruited at time of abstract submission. No adverse outcomes were reported. Serum iron levels remained stable prior to and 2-weeks following SPION injection. Sentinel lymph nodes were detected between 10-30minutes following injection on MRI. These lymph nodes correlated with lymph nodes identified intraoperatively using the magnetometer probe. Final pathology revealed no false negative findings.

Conclusion: This phase 1 clinical trial demonstrates safety and feasibility of a new magnetic approach to SLNB for head and neck cancer. Larger clinical trials will allow more robust evaluation of the accuracy of this technique.

LAY DESCRIPTION

In this early clinical trial, we evaluated a new minimally-invasive approach to identifying lymph node spread in patients with tongue cancer. Patients were injected with a tracer made of specialised magnetic particles used in humans for the first time. They then underwent MRI scanning to view the flow of tracer to the first draining lymph node. This node was biopsied in an operation using a specialised magnetic detector probe. Of all patients included in this world-first study, no patients had any complications and the technology was shown to be safe and feasible.

ABSTRACT 18

Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA) Patients Undergoing Cardiac Magnetic Resonance Imaging (CMR)

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Myocardial infarction with non-obstructive coronary arteries (MINOCA) occurs in 10% of patients with myocardial infarction (MI). It is characterised by clinical evidence of MI in whom angiography does not show obstructive coronary artery disease (stenosis severity <50%), and thus there is no immediately apparent cause for the presentation. Cardiac magnetic resonance imaging (CMR) is a key diagnostic tool in the evaluation of MINOCA patients as it provides a definite diagnosis (confirming myocardial necrosis) while also excluding other aetiologies. These patients are often discharged with minimal explanation for their MI presentation and limited understanding of their outcomes. To improve this knowledge gap, this study describes the 12-month clinical outcomes (readmission and mortality) of MINOCA patients according to the CMR diagnosis, categorised as: (i) confirmed infarction/myocardial necrosis, (ii) non-ischaemic aetiology, and (iii) normal CMR findings. The null hypothesis to be tested is clinical outcomes will not vary according to the CMR findings of MINOCA patients. In this retrospective analysis, 941 MINOCA patients were identified through the Coronary Angiography Database of South Australia (CADOSA) registry between 2012-2017, and 177 underwent CMR. The CMR diagnoses were: 9% infarction/myocardial necrosis, 70% non-ischaemic aetiology and 21% normal CMR. The infarct patients had the highest all-cause, 12-month mortality (6%), followed by the non-ischaemic patients (2%) and 0% for the normal patients. Over 12 months, non-ischaemic patients had the highest cardiac readmission rate (18%), followed by normal patients (14%) and infarct patients (13%). Overall, CMR had a significant clinical impact in 43% of patients by providing a new diagnosis and a specific diagnosis in 79% of patients. These findings highlight the heterogeneity associated with MINOCA patients and clinical outcomes, underscoring the need to individualise their management and follow-up

LAY DESCRIPTION

MINOCA patients present with a heart attack but have no blockages in their coronary arteries. A cardiac MRI scan can help diagnose the cause of the heart attack. This study assessed the outcomes of MINOCA patients according to their cardiac MRI results: infarction (reduced blood flow damaging heart muscle), non-ischaemic (other causes eg viral infections) and normal findings. The infarct patients had a higher rate of death within 12 months, whereas the non-ischaemic patients were most likely to be re-admitted to hospital. This study highlights how the outcomes can differ according to the different causes for heart attacks in MINOCA patients.

ABSTRACT 19

Primary Sjogren's Syndrome in South Australia

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Objective: To describe clinical and serological characteristics of a South Australian primary Sjogren's Syndrome (pSS) cohort.

Methods: The South Australian Sjogren's Syndrome Research Clinic and Database is a clinical cohort of patients with pSS at a single site. Baseline clinical and laboratory data from 172 patients were retrospectively examined to determine their prevalence and clinical associations. Results were compared to findings from 10,500 patients from The Big Data Sjogren Project Consortium; an international, multicentre registry established in 2014, which included the South Australian data.

Results: Of 172 South Australian patients with pSS, 90.1% were female with a mean age at diagnosis of 57 years. Ocular and oral sicca symptoms were common, affecting 97.1% and 99.4% respectively. Anti-Ro +/- La positivity was detected in 82.6%, ANA positivity in 77%, and in 9% of patients both ANA and ENA were negative. Mean ESSDAI was 6.8 at baseline, slightly higher than the international cohort at 6.1; the most commonly positive domains being biological, articular and glandular. Pulmonary manifestations represented the most significant morbidity over time. Lymphoma was recorded in 5.2% of patients and congenital heart block in the offspring of 7.7%, although incomplete data likely resulted in underestimation of both.

Conclusion: Despite the relatively small sample size of the South Australian cohort, clinical and serological characteristics correspond closely with international descriptions.

LAY DESCRIPTION

Sjogren's Syndrome is a rare autoimmune condition which is most commonly known to cause dry eyes and dry mouth. Recently, there has been improved understanding of how Sjogren's syndrome can affect many of the body's internal organ systems, with varying degrees of severity. Little research has been done among Australian patients to characterise the pattern of internal organ involvement and associated consequences. Our study therefore aims to describe the characteristics of Sjogren's Syndrome in a South Australian cohort and compare these findings to an international cohort of patients with Sjogren's Syndrome.

ABSTRACT 20

Vaccination rates, perceptions and information sources utilised by Australian patients with inflammatory arthritis

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Background: Inflammatory arthritis and immunosuppression both increase the risk of mortality and morbidity from vaccine-preventable disease. Our aim was to determine vaccination rates, perceptions and information sources, for Australians with inflammatory arthritis.

Methods: Participants with RA, axial SpA and PsA who were enrolled in the Australian Rheumatology Association Database (ARAD) were invited to participate in an online survey. Questions assessed vaccination history, information sources consulted and attitudes towards vaccination.

Results: 994 ARAD participants responded to the survey. Self-reported adherence to immunisation guidelines was 83% for influenza, 42% for pneumococcal and 19% for zoster vaccines. Older age was a predictor of current influenza vaccination (OR 1.6; 95%CI 1.36-1.88). Education and health literacy weren't predictors.

Participants expressed positive vaccination views generally, particularly regarding safety, efficacy and access. Predictors of positive views were older age and female gender. Again, education and health literacy weren't predictors. 57% of participants were uncertain about which vaccinations were recommended for them.

Participants consulted multiple vaccination information sources (median 3, IQR 3-7). Poorer health literacy was a predictor of a greater number of utilised sources. GPs (89%) and rheumatologists (76%) were the most common and were the most likely to yield positive views. Negative views were most often from internet chat rooms, social media and media.

Conclusion: Self-reported adherence to vaccination recommendations was excellent for influenza but low for pneumococcal and zoster vaccines. Participants generally held positive views about vaccination, though over half remained unsure of which vaccinations were recommended for them. This study highlights the need for improved consumer information about vaccination recommendations for people with inflammatory arthritis.

ABSTRACT 20 (continued)

LAY DESCRIPTION

People with inflammatory arthritis (e.g. rheumatoid and psoriatic arthritis) are at increased risk of harm from vaccine-preventable infections due to immune system suppression from both their disease and medications. Adults with inflammatory arthritis should be vaccinated against the flu and pneumonia. We undertook a survey on inflammatory arthritis patients to determine vaccination rates and views. 83% of participants were up to date with the flu vaccine but only 42% were up to date with the pneumonia vaccination. Participants held positive views about vaccination, but over half were unsure of which vaccinations were recommended for them.

ABSTRACT 21

Removing the blindfold: visualising the topical delivery of retinoids

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Retinoids are a diverse class of intracellular acting drugs that have become staples in treating skin conditions such as acne, psoriasis and photo-damage. Understanding of the sub-cellular spatial delivery of retinoids after topical application is currently limited, but critical for optimising safe and effective formulations. The aim here was to determine if cellular retinoid delivery could be visualised using a time-resolved method, fluorescence lifetime imaging microscopy (FLIM). Fluorescence emission spectra and lifetimes were obtained for natural and synthetic retinoids under 2-photon excitation (720–920 nm). The HaCaT keratinocyte cell line was treated with retinoids (100 nM-20 uM) and live cell FLIM imaging performed up to 96 hrs (λex 740 nm, λem 420-460 nm). 6 commercial formulations were optically characterised as per pure compounds, before application to fresh excised rat and human skin (10 mg/cm2). FLIM images were acquired from the skin surface, granular, spinous and basal layers over 48 hrs. Pure retinoids had 2-photon excitation maxima at 740 nm and could be distinguished by lifetime, ranging from 150 (tretinoin) to 2000 ps (retinol). Cell treatment resulted in distinct changes in lifetime, intensity and cell morphology (elongation and intracellular granulation) compared to growth control, especially with retinol (36-fold increase in intensity, $P<0.0005$, and 2.6-fold increase in lifetime, $P<0.0001$). Commercial formulation components were visible using a FLIM-phasor approach and could also be distinguished from skin autofluorescence in excised tissues. Intracellular delivery was observed as high lifetime granules and was more extensive in rat than human skin. FLIM is therefore useful for visualising retinoids in various systems from simple solution to keratinocytes *in situ* after topical application. This represents an important advance that will assist development of improved retinoid therapies for skin disease.

LAY DESCRIPTION

Drug delivery is like a game of darts: the aim of the game is to hit the bullseye. For retinoids, a group of drugs used to treat acne and skin aging, the bullseye is inside the skin cells. Just as our sense of sight is critical in darts, being able to 'see' retinoid delivery is useful for developing effective therapies. Up until now however we have been playing blind darts with retinoids. In this work, this has been overcome using state-of-the-art imaging to visualise delivery after application on the skin. Now with the power of sight we can help steer the development of better retinoid therapies – a bullseye win in tackling skin disease.

ABSTRACT 22

***Corynebacterium accolens* isolated from Healthy Sinus Cavities have Antimicrobial Activity toward *Staphylococcus aureus* and Methicillin-resistant *S. aureus* (MRSA) clinical isolates**

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Background: *Corynebacterium accolens* is the predominant species of the healthy human nasal microbiota and its relative abundance is decreased in the context of chronic rhinosinusitis (CRS). However, it is not known whether *C. accolens* affects the growth of pathobionts including *S. aureus* and methicillin resistant *S. aureus* (MRSA).

Aim: To evaluate the antimicrobial activity of *C. accolens* against *S. aureus* and MRSA CIs *in vitro*.

Methods: Twenty nasal swabs from control patients were screened for the presence of *C. accolens* using microbiological, biochemical and molecular techniques. *C. accolens* clinical isolates (CIs) and their culture supernatants were tested for their antimicrobial activity against 8 *S. aureus* and 8 MRSA CIs using deferred growth inhibition assays and, micro-dilution assays before and after protein purification, heat inactivation and proteinase K treatment of supernatants. The supernatants' effect on established *S. aureus* biofilms was assessed using crystal violet assays. One-way ANOVA was used to evaluate differences between groups.

Results: Ten *C. accolens* CIs were identified. All isolates showed variable antimicrobial activity against 8/8 *S. aureus* and 7/8 MRSA CIs. Culture supernatants from all *C. accolens* CIs exhibited a significant dose-dependent antibacterial activity ($p<0.05$) against 5/5 representative *S. aureus* and MRSA CIs. This inhibition was abolished after heat-inactivation and proteinase K treatment. Purified culture supernatants from 3 *C. accolens* CIs exhibited a significant strong antimicrobial effect against 3/3 *S. aureus* and MRSA CIs with a maximum reduction of 95% compared to negative control ($p<0.0001$). *C. accolens* supernatants induced a significant reduction in biofilm biomass of *S. aureus* and MRSA CIs compared to positive control ($P<0.05$).

Conclusion: *C. accolens* exhibited antimicrobial activity against *S. aureus* and MRSA CIs, and holds promise for the development of innovative probiotic therapies to promote sinus health.

LAY DESCRIPTION

Corynebacterium accolens is the predominant species of the healthy human nasal microbiota and its relative abundance is decreased in the context of chronic rhinosinusitis (CRS). However, it is not known whether *C. accolens* affects the growth of pathobionts including *S. aureus* and methicillin resistant *S. aureus* (MRSA). In this study, we demonstrated the first time that *C. accolens* isolates from healthy sinus and its secreted proteins exhibited good antimicrobial activity against pathogenic *S. aureus* and MRSA clinical isolates *in-vitro* and holds promise for the development of innovative probiotic therapy to promote sinus health.

ABSTRACT 23

Ginsenoside Rg3 enantiomers in a defined ratio as a novel treatment for triple negative breast cancer

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Chemotherapy is the main treatment for triple negative breast cancer (TNBC) but many patients develop resistance and progress to metastatic disease, with a 5-year survival rate of 11%. More effective and less toxic treatments are required. The hypothesis is that enantiomers of Panax ginseng, 20S-ginsenoside Rg3 (S) and 20R-ginsenoside Rg3 (R), are stereoselective and combinations will synergistically inhibit tumour growth and metastasis. The aims were to show efficacy of S+R on breast cancer cells *in vitro* and on tumour growth and metastasis in a mouse model of TNBC.

MDA-MB-231 and HCC1143 TNBC cell lines were treated with S+R and effects measured in *in vitro* assays of migration, mammosphere formation efficiency (MFE), apoptosis (annexin V/PI), cell cycle and expression of CD44 stem cell marker. Perturbation of PI3K signalling was analysed using gene expression microarrays. A mouse model of metastatic TNBC was developed by inoculating luciferase-expressing MDA-MB-231-Luc cells into the mammary fat pad of Nod Scid gamma mice. The effect of S+R treatment on tumour growth and metastasis was monitored using calliper measurements and bioluminescence imaging. Statistical analysis was performed using ANOVA (Prism v8).

Combined doses of S+R significantly inhibited the migration of breast cancer cells ($p < .0001$) and decreased MFE ($p < .0001$) without decreasing cell viability. Expression of CD44 was also decreased suggesting reversion to a more differentiated phenotype. In expression arrays, the treatment decreased the expression of BTK, a tyrosine kinase promoting cell death escape, and increased the expression of CASP9, promoting apoptosis. *In vivo* experiments showed that S+R reduced tumour volume ($p < .0001$), decreased body burden of tumour ($p < .0001$) and decreased the number of metastasis ($p = .002$). These results support the anti-cancer effects of the combination of S+R for the treatment of TNBC.

LAY DESCRIPTION

To enable a breast tumour to grow bigger and spread, more blood vessels form within it. Tumour cells can leave the tumour, migrating through the blood vessels to other parts of the body to make further tumours. This is the last stage of breast cancer. The available treatments for these patients are very toxic and still most of them die, so better less toxic treatments are needed. In our studies, we found that two purified compounds from herbal ginseng are good candidates that act together in stopping the growth of the tumour, inhibiting the formation of new blood vessels and reducing the number of tumours spread to other organs.

ABSTRACT 24

Prophage integration in *S. aureus* increases its virulence as well as aids in its evolutionary diversification

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Background: Prophage is a short sequence of viral DNA that is stably integrated into a bacterial genome, significantly contributing to bacterial fitness. Under normal conditions, prophage benignly replicates along with the bacterial genome, but under stress, they can switch to a lytic lifecycle in which they kill the host cell. We hypothesized that *Staphylococcus aureus* clinical isolates from chronic rhinosinusitis (CRS) patients harbor prophages that contribute to their pathogenicity and virulence and that can be activated to enter the lytic cycle thereby killing the host cell.

Methods: Genomic sequences of 58 *S. aureus* from CRS patients were analyzed using PHASTER webtool and identified prophages were further compared with each other for their phylogenetic relatedness using advanced bioinformatics pipelines. Bacteria in the log phase (OD600=0.6) were treated with a sub-lethal dosage of antibiotics and after filter sterilization, the activity of induced prophages was screened by spot assay using RN4220 as an indicator strain.

Results: All of the *S. aureus* genomes contained at least one prophage. Polylysogeny (presence of multiple prophages) was seen on 91% (53/58) of isolates. Prophage contributed up to 8% of the total bacterial genome. The prophage content increased with an increase in the bacterial genome size (t-test, $p<0.0001$). Prophages could be induced into the lytic cycle by a sub-lethal dosage of antibiotics mitomycin C (52%), amoxicillin (26%), azithromycin (21%), clindamycin (21%), doxycycline (24%), and mupirocin (24%) thereby producing virulent phages that could further infect and kill other pathogenic strains.

Conclusion: *S. aureus* clinical isolates from CRS patients carry multiple prophages suggesting strong evolutionary fitness between bacteria-phage as well as their role in the diversification of bacteria. Antibiotic-dependent prophage activation could be exploited as a new approach to antimicrobial treatment.

LAY DESCRIPTION

Prophage is an inactive virus integrated into a bacterial chromosome. It is usually lifeless, but under stress, activates itself and kills the host bacteria. We studied if such prophage is present in *Staphylococcus aureus* from the nose and if it can be re-activated into an active killer. We observed that all *S. aureus* bacteria carried at least one and 91% carried multiple prophages. Those inactive prophages turned into an active bacteria-killing virus in about 25% of cases when a sub-lethal dosage of antibiotics was applied suggesting a new treatment approach where we force bacteria to kill themselves activating the killer inside them.

ABSTRACT 25

Can we predict the development of hypotension after onset of Takotsubo Syndrome (TTS)?

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Background: Takotsubo Syndrome (TTS) is a form of adrenaline-induced myocardial inflammation which accounts for 10% of "myocardial infarctions (MI)" in females above the age of 50. TTS is associated with a substantial risk of in-hospital mortality, mainly driven by the development of hypotension and shock. The exact incidence of this hypotension is uncertain, and its cause remains unclear:- previous studies have not found a significant link between hypotension and the degree of left ventricular (LV) systolic dysfunction, while cardiac output is usually not markedly reduced.

Purpose: We sought to identify the incidence and clinical/laboratory correlates of early hypotension in TTS.

Methods: We analysed the data of patients recruited during hospital admission to the South Australian (SA) Takotsubo Syndrome Registry. Associations between the early development of hypotension and patient demographics, severity of the acute TTS attack, and key biochemical markers were sought. Hypotension was defined as a systolic blood pressure (BP) of ≤90mmHg. Parameters chosen were age, sex, a history of hypertension, prior use of renin-angiotensin system blockers, left ventricular ejection fraction (LVEF) on echocardiography, and plasma normetanephrine, NT-proBNP and CRP concentrations. To compare patients who developed hypotension and those who did not on a categorical basis, we used unpaired t-tests/Wilcoxon tests or Chi-squared tests as appropriate, followed by a backwards stepwise multivariate linear regression analysis, forcing all the above parameters into the analysis. The limit of statistical significance was set at $p<0.05$. Data are presented as mean ± SD or median (inter quartile range) as appropriate.

Results: Out of the 421 patients, adequate blood pressure readings were available for 319, of whom 113 (35%) were hypotensive during their index hospitalisation. A total of 8 (2.5%) patients died in hospital, all with prior hypotension and shock.

On univariate analyses, patients who developed hypotension were more likely to be females (p-value 0.01), with a lower calculated LVEF and higher plasma NT-proBNP concentrations (p-value 0.01 and 0.05 respectively), both markers of severity of the TTS attack. On multivariate linear regression analysis, female sex and a lower acute LVEF were independent correlates of the development of hypotension (p-values 0.009 and 0.005 respectively).

Conclusion: These data confirm that the development of hypotension is very common in TTS, and its presence is associated with a substantial risk of in-hospital mortality. Female sex, and a lower left ventricular ejection fraction are independent predictors of the development of hypotension during acute TTS. While it remains likely that hypotension in TTS is largely engendered by failure of sympathetic vasoconstriction, this is the first evidence to suggest that extent of contractile impairment also contributes to this complication.

ABSTRACT 25 (continued)

LAY DESCRIPTION

Takotsubo Syndrome (TTS) is a condition that mimics heart attacks, and primarily affects aging females. It is now apparent that TTS is not just common, but can also lead to poor outcomes in hospital, mainly due to low blood pressure (BP). However, the exact cause for this is not known. In this study, we aim to determine how frequently this occurs, as well as the factors that predict the development of low BP. Our results not only show that low BP occurs commonly in TTS, we also found that for the first time, both the female sex and a reduced contractility of the heart predict low BP in patients with TTS.

ABSTRACT 26

Localized adoptive cellular therapy of gamma delta T cells for solid tumours

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Introduction: Adoptive cell transfer (ACT) is poised to revolutionize cancer treatment. It involves isolation, expansion and reinfusion of cancer-specific T cells into patients with the goal of targeting tumour cells.

Gamma delta (γδ) T cells are highly cytotoxic T cells that detect tumour cells through changes in metabolic phenotype, recognizing the overproduction of phosphoantigen IPP. The addition of osteoporosis drug zoledronate (ZOL), which increases the IPP accumulation, render tumour cells more vulnerable to γδT-cell attack. While ACT based on systemic infusion showed promise for blood cancers, results in solid tumours have been disappointing, due to poor T cell trafficking to localized tumours. Hence, alternative modes of T cell delivery are required.

We developed a simple and non-invasive approach for local injection of γδT cells + ZOL embedded in a bio-compatible matrix at tumour lesions. This approach does not require migration from the circulation but instead the T cells are immediately released locally in large numbers for rapid killing. In this proof-of-concept study, we evaluated the anticancer efficacy of γδT cells + ZOL embedded in commercially available matrigel in both cellular and mouse cancer models.

Results: *In vitro*, upon release from matrigel, γδT retained cytotoxic against both breast and brain cancer cells. The co-addition of ZOL into matrigel remarkably potentiated γδT cell-mediated killing to nearly 100%.

In vivo, although the effect was short-lived, matrigel containing γδT cells+ZOL caused a delay in tumour growth after which treated tumours grew rapidly resulting in no growth inhibition compared to untreated controls. Using fluorescently labelled ZOL, we showed cancer cells in solid tumours failed to take up ZOL, instead cells of macrophage lineage were more efficient at internalising ZOL.

In summary, our *in vitro* models provided evidence that biomaterials may be used to enhance γδT localized immunotherapy. Unfortunately, this effect has not recapitulated in the animal model. Despite the strong supports from the scientific community, our findings argue against the use of ZOL to potentiate γδT cell killing in cancer patients.

ABSTRACT 26 (continued)

LAY DESCRIPTION

T cell therapy is a form of immunotherapy that uses patient's own T cells to fight cancer. Although successful in treating blood cancers, results in solid cancers have been disappointing as most transferred T cells will be lost elsewhere before reaching the tumour. Aiming at boosting the effectiveness, this study explores a new way to deliver the cancer fighting T cells in a gel carrier directly at the tumour site. Studies performed in culture dish showed effective killing of the surrounding cancer cells, which, unfortunately was not seen in laboratory mice. Further refinement to this approach is required to overcome this complexity.

ABSTRACT 27

Examining the Day-to-Day Pain Variability in Inflammatory and Non-Inflammatory Rheumatic Diseases Using Multilevel and Markov Transition Models: Cloudy with a Chance of Pain, a Nationwide U.K. Smartphone Study

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Aims: Chronic pain is common in rheumatic diseases. We hypothesised that the patterns and the extent of pain variability over time are significantly different among individuals across different rheumatic diseases. We examined the day-to-day pain variability in inflammatory and non-inflammatory rheumatic diseases using Cloudy with a Chance of Pain study.

Methods: 10,584 participants (18 years or above; chronic pain for 3 months or more) entered their daily pain using a downloaded smartphone app (five-point ordinal scale of 1 – no pain and up to 5 – very severe pain). 2,525 participants diagnosed with rheumatoid arthritis (RA), spondyloarthritis (SpA), osteoarthritis (OA) and chronic widespread pain/fibromyalgia (CWP/FM) were included. Long-term and short-term day-to-day pain variability for the first one-month period were examined using multilevel and Markov transition models respectively.

Results: From 29,705 daily pain scores (83% female; mean age 48), the average pain scores for the first one-month period were higher in individuals with SpA and OA compared with participants with RA (2.74±0.98, 2.61±0.96, and 2.53±0.98 respectively), although those with CWP/FM had the highest average pain score of 3.06±1.04. There were steeper time-based improvements in pain for those reporting higher initial pain scores across all diseases. The day-to-day pain state transitions were unchanged in 50% of days across diseases, although the event of any increase in pain state was noted in 25% of days (e.g., ≥2-point increase was noted in 4% of days). 53% of individuals with CWP/FM remained in the 'very severe' pain state with minimal variation.

Conclusion: Individuals with CWP/FM had the highest overall pain level followed by SpA, OA, and RA. Patterns of improvement in those with higher initial pain scores were seen across diseases, perhaps representing regression to the mean. The volatility of changing pain states was comparable across diseases, suggesting no difference in flares.

ABSTRACT 27 (continued)

LAY DESCRIPTION

In this study, we examined the pain variability in individuals with musculoskeletal conditions by using daily pain symptoms captured through a smartphone app. We found that those with chronic widespread pain/fibromyalgia (CWP/FM) had the highest average pain compared to those with spondyloarthritis, osteoarthritis and rheumatoid arthritis. There were improving pain trajectories for those with higher than average pain reporting at study entry. Across all diseases, fluctuations in day-to-day pain level were unchanged in 50% of days, and 53% of individuals with CWP/FM stayed at the 'very severe' pain level with minimal day-to-day change.

ABSTRACT 28

Attitudes of Australians with inflammatory arthritis to biologic therapy and biosimilars

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Introduction: The primary aim of this study is to investigate the knowledge and beliefs of Australian patients with inflammatory arthritis regarding biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) and biosimilars, a biological product highly similar to an original b/tsDMARD, and their sources of information.

Methods: Data was collected using an online survey sent via email to participants with Rheumatoid arthritis, Psoriatic arthritis and axial spondyloarthritis enrolled in the Australian Rheumatology Association Database (ARAD). Participants currently prescribed a b/tsDMARD were asked about their sources of information for b/tsDMARDs and how positive or negative they found the information obtained. The Beliefs about Medicine Questionnaire (BMQ), consisting of general medication (overuse and harm) and b/tsDMARD specific (necessity and concerns) questions was used to measure patient specific beliefs about b/tsDMARDs. All participants were then asked about their knowledge of biosimilars.

Results: 994 ARAD participants completed the survey. Patients currently taking b/tsDMARDs (N= 794) had a high b/tsDMARD specific 'necessity' score with their specific 'concerns' score similar to those regarding medicines in general. Participants consulted multiple information sources (median 2, IQR 3) with the most positive being rheumatologists and educational websites and the most negative being chat rooms/ media and social media. 75% of participants had never heard of biosimilars and of those who had, only 37% knew they were available in Australia. While 67% of participants were unsure if biosimilars were as safe or effective as biologics, 57% would switch if recommended by their rheumatologist.

Conclusions: Australian patients have positive attitudes towards b/tsDMARDs overall although little knowledge of biosimilars specifically. They have a high degree of trust in their rheumatologist with regard to treatment decisions even if they are unfamiliar with the medication recommended.

ABSTRACT 28 (continued)

LAY DESCRIPTION

This study investigated the knowledge, beliefs and information sources of Australians with inflammatory arthritis regarding biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) and biosimilars via an online survey to which 994 patients responded. It was found that Australian patients have positive attitudes towards b/tsDMARDs overall although little knowledge of biosimilars specifically. They have a high degree of trust in their rheumatologist with regard to treatment decisions even if they are unfamiliar with the medication recommended.

ABSTRACT 29

Novel DNA-Based Vaccine for Zika Virus

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Zika Virus (ZIKV) is a flavivirus which infects humans through the bite of infected Aedes mosquitos. There is currently no treatment or vaccine for ZIKV infection. Hence, there is a need for an affordable and effective vaccine. DNA vaccines use plasmids expressing viral antigens that are presented to the immune system via the major histocompatibility complex class 1 pathway, stimulating T-cell based immune responses. During natural lytic viral infection, infected cells undergo necrosis releasing viral antigen and natural adjuvants, known as damage-associated molecular patterns that elicit robust immune responses. Previous work has shown that inclusion of mouse perforin (PRF) in DNA vaccines, results in necrosis of vaccine-transfected cells and increases antigen-specific T-cell responses. In this study, we have developed DNA vaccines that express ZIKV non-structural proteins 2 and 3 (NS2/3) and/or PRF and assessed their immunogenicity. DNA vaccines were generated using codon optimised ZIKV NS2/3 in pVAX plasmids +/- PRF. Vaccine constructs were created using DNA Assembly Kit followed by transformation into DH5a *E. coli* and positive clones were validated using colony PCR, DNA sequencing and restriction digests. Antigen expression was assessed by indirect immunofluorescence of HEK293T cells transiently transfected with DNA vaccines. Subsequently, female Balb/c mice (n=7, 6-8 weeks old) were vaccinated intradermally three times at two-week intervals, with ZIKV NS3+/-PRF vaccine constructs or pVAX control. Vaccine immunogenicity was assessed with an *in vivo* fluorescent target array and an *in vitro* IFN-γ ELISpot. Results showed no significant difference in immune responses between vaccinated mice and controls, but data indicated that control mice had unusually high immune background. We are investigating reasons as to why pVAX vaccinated mice had high non-specific immune responses.

LAY DESCRIPTION

Infection with Zika virus (ZIKV) during pregnancy causes devastating defects in unborn children. There are currently no vaccines to prevent infection. Most vaccines in development focus on the use of a structural viral protein (envelope) as its immunogen, and none focus on the non-structural proteins (NS) of the virus. During natural ZIKV infection, NS proteins induce strong T-cell immune responses. Previously, we have shown that a DNA vaccine encoding ZIKV NS1 protects against ZIKV infection. This project expands on these findings to develop a novel T-cell based vaccine, by evaluating ZIKV NS2 and 3 as potential vaccine antigens.

ABSTRACT 30

The relationship between *Staphylococcus aureus* biofilm properties and the disease severity and inflammation in chronic rhinosinusitis

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Background: Chronic rhinosinusitis (CRS) is a highly prevalent inflammatory disease of the upper airway. Pathogenic bacteria especially *S. aureus* contribute to the persistent inflammation in CRS. However, the relationship between inflammation and *S. aureus* biofilm properties as well as the disease severity is unknown. It is hypothesised that the severity and type of inflammation in CRS is determined by differences in the properties of bacterial biofilm.

Aim: To analyse T and B cell subsets in CRS patients in relation to the disease severity and properties of *S. aureus* biofilm *in vitro*.

Methods: Sinonasal polyps or mucosal samples were collected from CRS patients with (CRSwNP) and without nasal polyps (CRSsNP) and controls (n=59). The frequency of B and T cell subsets was investigated using FACS analysis. The metabolic activity of *in vitro* grown *S. aureus* biofilm was quantified using Alamar Blue assay, and the disease severity was assessed with validated scoring systems. One-way ANOVA was used to compare between groups and Spearman was used for correlation analysis.

Results: A significant increase was observed in the cell number of CD19+, plasma and memory B cells as well as CD3+, CD4+, and IL-4+ cells whilst regulatory B cells, IFN-γ+, IL-17a+ and FOXP3+ cells decreased significantly in CRSwNP patients compared to control and/or CRSsNP ($p<0.05$). There was a significant increase in the biofilm metabolic activity of *S. aureus* in CRSwNP compared to CRSsNP ($p=0.002$). Plasma, CD19+ and CD4+ cell numbers were positively correlated with disease severity scores ($r>0.40$, $p<0.01$) while regulatory B cell numbers showed a strong inverse correlation with both the disease severity scores and the biofilm metabolic activity ($r=-0.66$, $p<0.001$).

Conclusion: This data supports a potential role of *S. aureus* biofilm in CRS pathogenesis and the potential of B and T cell subsets especially regulatory B cells as biomarker and therapeutic target in CRSwNP patients.

ABSTRACT 30 (continued)

LAY DESCRIPTION

Chronic rhinosinusitis (CRS) occurs when the sinuses get infected and make extra mucus. Staphylococcus bacteria are major players in CRS, causing persistent inflammation in the sinuses and the symptoms of the disease. I want to define the properties of the bacterial community or 'biofilm' and identify the patient's immune responses. I isolated bacteria from nasal swabs of CRS patients and analysed the biofilm properties in culture. I also looked at the inflammation in tissue biopsies of the patients. Bacteria with higher metabolic activity were seen in patients with a certain type of inflammation. This gives a better insight into the disease.

ABSTRACT 31

Exploring the TRAIL of doxorubicin-induced cardiotoxicity

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Doxorubicin (DOX) is a widely prescribed chemotherapeutic used to treat both solid and haematologic malignancies. However, its use is limited by irreversible cardiotoxicity, which can lead to lifelong, sometimes fatal, heart complications. Recent evidence suggests the involvement of the TNF-related apoptosis-inducing ligand (TRAIL) which through binding to its death receptors 4 and 5, initiates a signalling cascade leading to cell death. We hypothesise DOX upregulates death receptors in cardiomyocytes resulting in their sensitisation to TRAIL-induced death. We aimed to investigate the role of TRAIL and its pathway in DOX cardiotoxicity.

Using cultured human cardiomyocytes, we assessed the ability of DOX to elicit cardiomyocyte death, and measured changes in death receptors using flow cytometry. Wildtype and TRAIL knockout mice (TRAIL-/-)(n=7 per group) were also used to evaluate the effect of TRAIL deficiency on cardiotoxicity following chronic DOX dosing. Cardiac function was assessed by measuring left ventricular ejection fraction and fractional shortening using echocardiography. T-tests and two-way ANOVAs were applied for statistical analysis where appropriate.

In cell culture, we showed that (i) DOX treatment of cardiomyocytes was cytotoxic only in the presence of TRAIL,(ii) death receptor 5 on cardiomyocytes increased significantly (98%) with DOX treatment.(iii) Blockade of TRAIL signalling protected human cardiomyocytes from DOX-induced death and (iv) in wildtype mice, DOX caused a 15.6%($p<0.0001$) and 24%($p<0.0001$) reduction in ejection fraction and fractional shortening respectively, whereas DOX treated TRAIL-/- mice had no significant reduction in cardiac function.

Our data supports the hypothesis of DOX sensitisation of cardiomyocytes to TRAIL-induced death. Collectively, these findings strongly support TRAIL blockade as a novel therapeutic strategy to limit or eliminate DOX-induced cardiotoxicity and identify several targets for therapeutic intervention.

LAY DESCRIPTION

Doxorubicin (DOX) is a common chemotherapy drug used mainly to treat breast, lung, and childhood cancers. However, DOX causes many side effects, including severe toxicity to the heart. This toxicity can leave cancer survivors with life-long heart complications, which can lead to heart failure and sometimes death. Our lab believes this toxicity is the consequence of DOX increasing the action of a protein, called TRAIL, in heart cells which triggers cell death. An investigation into this DOX/TRAIL relationship could identify life-saving therapeutic medicines to prevent DOX cardiotoxicity.

ABSTRACT 32

Mortality in ANCA-associated vasculitis and polyarteritis nodosa: a Western Australian population based study

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1. Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia; 2. Basil Hetzel Institute, Adelaide, Australia; 3. Queen Elizabeth Hospital, Adelaide, Australia; 4. Lyell McEwin Hospital, Adelaide, Australia; 5. Rheumatology section, University of Western Australia, Perth, Australia; 6. Department of Rheumatology, Fiona Stanley Hospital, Perth, Australia; 7. Department of Rheumatology, Sir Charles Gairdner Hospital, Perth, Australia.

Aim: To determine all-cause and cause-specific mortality in Western Australian (WA) ANCA-associated vasculitis (AAV)/polyarteritis nodosa (PAN) patients.

Methods: Patients and controls were ascertained through the WA Hospital Morbidity Data System and WA death registry (1980-2014). Incident AAV or PAN was defined using International Classification of Disease-9 and -10 codes. Controls, with no rheumatological diagnosis, were age, sex and temporally matched at patient diagnosis date. Follow-up was censored at 20 years, or at age 85. Hazard Ratios (HR) and time-varying excess mortality rates were analysed using Stata v16.1.

Results: 615 patients with incident AAV/PAN (229 deaths, 5280 years at risk) were compared with 6700 controls (1063 deaths, 74133 years at risk).

All-cause mortality was increased in AAV/PAN: HR 3.0, 95%CI 2.6,3.5. The largest excess mortality rates were observed in patients aged 60+ at diagnosis ($p<0.001$). Excess mortality was greatest in the first year after diagnosis, and remained consistently elevated for the duration of follow-up.

Vasculitis contributed to death in 101/229 (44%) patients, but was not observed in controls. Cause-specific mortality was also increased for renal disease (HR 18.4, 95%CI 10.7,31.9), infection (HR 5.2, 95%CI 5.2,7.1), cardiovascular disease (HR 2.6, 95%CI 1.9,3.6) and malignancy (HR 1.6, 95%CI 1.1,2.1). A similar pattern of greater excess mortality early after diagnosis was observed for vasculitis, infection and cardiovascular disease. The excess risk of malignancy related death accrued during follow-up.

Conclusion: Mortality was increased in AAV/PAN compared with controls, with patients older at diagnosis at greater risk. Vasculitis, infection and cardiovascular disease contributed to an initial spike in deaths early after diagnosis. These findings provide mortality risk for AAV/PAN in an Australian population, highlighting key contributors to mortality and potential areas of focus for reducing mortality.

ABSTRACT 32 (continued)

LAY DESCRIPTION

ANCA-associated vasculitis (AAV) and polyarteritis nodosa (PAN) are severe, life-threatening diseases, causing inflammation of blood vessels (vasculitis). By linking information collected in Western Australia for hospital stays and death, we compared survival of these patients with people who had been in hospital for other reasons. We found AAV/PAN patients were more likely to die, especially if they were over 60 when diagnosed with AAV/PAN. The highest risk was soon after diagnosis, often from vasculitis, infections and heart problems. This information helps us understand how we could reduce AAV/PAN deaths in the future.

ABSTRACT 33

The Association between Electroencephalography Aperiodic Slope, Symptoms, Cognition, Function and Neuroinflammation in Australian Defence Force Combat Veterans

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Posttraumatic stress disorder (PTSD) is a chronic mental disorder triggered by exposure to traumatic events. Individuals with PTSD suffer from distressing symptoms including re-experiencing events, avoidance, increased arousal and cognitive impairment. Studies using electroencephalography (EEG) to explore brain activity in PTSD have failed to find a consistent link with symptoms, cognition and function. EEG measures are comprised of separable periodic and aperiodic activity. Traditional analyses measure periodic activity (neural oscillation) in frequency bands. Aperiodic activity is without a characteristic frequency and filtered out as noise during analyses. Both these signals are dynamic and overlapping. Recent evidence suggests both need to be considered in the analysis of brain activity. To explore the relationships between aperiodic EEG, symptoms, cognition, function in people exposed to combat trauma we have implemented a new analysis method, fitting oscillations & one over f (FOOOF).

The study sample is a subset of the Middle East Area of Operations (MEAO) Prospective Health Study with EEG measures. Data available at baseline include historical trauma and combat exposure, clinical symptom scales, a battery of physiological tests of arousal and cognitive tests with associated EEG recordings and blood inflammatory markers. Baseline EEG data was available for 285 participants and 263 (mean age 28.5 ± 6.7) had associated PTSD-checklist (PCL) scores. At baseline average total PCL score was 19.5 ± 4.8 (range 17 – 48) with 4.6% participants PCL > 30 meeting criteria for PTSD. Average PCL symptom domain scores were: re-experiencing 5.6 ± 1.4, avoidance 8 ± 2.3 and arousal 6 ± 1.9. Analysis of the relationship between historical and clinical data and PCL subdomain scores continues in parallel with processing of EEG data. The relationships between aperiodic and periodic EEG indices, PCL domain scores, cognitive function and inflammatory measures will be explored.

LAY DESCRIPTION

Posttraumatic stress disorder (PTSD) is a chronic mental illness that occurs following life threatening trauma. Its symptoms include the re-experiencing of distressing events, avoidance, increased arousal and impaired thinking. Past studies have failed to find a consistent relationship between brain signals measured at the scalp with electroencephalography (EEG) and features of PTSD. Using a new analysis method that considers the underlying baseline variation in EEG signal, we will explore the relationships between EEG, symptoms, cognition, function and levels of blood inflammatory markers in a sample of combat veterans.

ABSTRACT 34

Maternal immunisation with a novel Zika vaccine to protect offspring from congenital Zika syndrome

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Zika virus (ZIKV) causes severe birth defects following maternal infection during pregnancy. A vaccine for ZIKV is urgently needed. Most vaccines in development use ZIKV viral envelope (E) as a vaccine antigen as E elicits neutralising antibodies. Due to structural homology, these antibodies can cross-react with E of dengue virus (DENV), facilitating virus uptake, resulting in antibody-dependant enhancement of infection (ADE). There is significant concern that vaccine-induced anti-E ZIKV antibodies may lead to ADE of subsequent DENV infection. Our novel DNA vaccine (pVAX-tpaNS1) encodes secreted ZIKV non-structural protein (NS1) and provides T-cell mediated protection from infection in immunocompetent mice. NS1 is not expressed on the surface of the virion, thus eliminating the risk of ADE of DENV.

Protection in pregnancy is key for any ZIKV vaccine. This project aims to establish an immunocompetent C57BL/6 pregnancy model of ZIKV infection and assess the protective efficacy of pVAX-tpaNS1 in an established interferon receptor knockout (IFNAR-/-) model. To assess if pVAX-tpaNS1 protects fetuses and placentas during ZIKV infection, adult female IFNAR-/- mice (n=9) were vaccinated with pVAX-tpaNS1 (3 doses at 2-week intervals). Vaccination with pVAX-tpaNS1 induced high endpoint anti-NS1 antibody titres. After timed mating, pregnant mice were then challenged with ZIKV on embryonic day 6 (E6). Viral loads will be assessed by qRT-PCR on sera collected 2,4 and 6 days post-challenge. Histology will be completed to assess if vaccination prevented ZIKV-induced fetal brain and placental damage on E17.

To set up C57BL/6 ZIKV pregnancy model, female mice (n=6) were time mated and challenged with ZIKV at embryonic day 7 (E7). Fetuses and placentas were collected at E18, histological staining of fetal brains and placentas revealed significant pathological damage due to maternal ZIKV infection.
The outcomes of this study will contribute to future development of pVAX-tpaNS1 DNA vaccine.

LAY DESCRIPTION

Zika virus (ZIKV), a virus spread by mosquitos, caused a major epidemic in the Americas in 2015/16. Maternal infection during pregnancy leads to devastating, irreversible birth defects which place considerable emotional and financial burdens on families. There is no treatment for ZIKV and preventative methods are limited. A vaccine for ZIKV is urgently needed to protect women of childbearing age from infection.

A novel vaccine for ZIKV has been developed by our group. This study assesses how maternal immunisation with our vaccine can protect from placental and fetal injury during pregnancy and will inform future development of the vaccine.

ABSTRACT 35

Overcoming chemo-resistance in triple-negative breast cancer and the mechanism of cell death by bacopaside II

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Background: Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer and lack of targeted therapies, poor response to immunotherapy and development of chemo-resistance remain key issues. Failure of chemotherapy has been linked to cancer stem cells (CSC). Bacopaside II (bac II) induces vacuole formation and cell death in breast cancer cells, but the mechanism is unknown. We hypothesize that bac II induces cell death via a non-apoptotic pathway, which can overcome drug resistance and induce immune responses. We aim to study non-apoptotic pathways (methuosis, necroptosis) and determine if bac II can overcome resistance in our 3D-model.

Methods: To verify the type of cell death TNBC cell line, MDA-MB-231, was treated with bac II: caspase-3/7 activation and cell viability was measured using Incucyte S3 to specify apoptosis; labelled-dextran was used to show macropinocytosis in methuosis; phosphorylated MLKL (pMLKL) was measured by western blot to indicate necroptosis. Resistance to paclitaxel and doxorubicin was established in 3D-culture of mammospheres. Expression of CSC markers (NANOG, OCT4) was assessed using qPCR.

Results: Treatment with 15, 20 and 30 µM bac II for 72 h resulted in a 2.2- ($p < 0.0001$), 3-, and 4-fold decrease (both $p < 0.001$) in cell viability respectively. Caspase-3/7 was not activated, denoting a non-apoptotic cell death, and necroptosis was shown by a 2.3-, 3- and 6.8-fold increase in pMLKL respectively. Compared to 2D culture, 3D-model showed a 34- fold increase in NANOG, $p < 0.001$ and 1.8-fold increase in OCT4 ($p=0.003$), while IC50 of paclitaxel and doxorubicin rose by 1.4- and 2.1-fold respectively ($p < 0.0001$). We will test the efficacy of bac II in this model to overcome resistance.

Conclusion: We showed that bac II induced necroptosis, important for release of 'danger' molecules that initiate the anti-tumour cytotoxic T cell response. Future studies on the role of bac II as an adjunct to immunotherapy will be useful.

LAY DESCRIPTION

Triple-negative breast cancer makes up about 15% of all breast cancers cases. Lack of targeted therapies and development of resistance to standard chemotherapy are the main reasons for a low five-year survival rate after diagnosis. Our group found that herbal drug bacopaside II has anti-cancer effects, causing non-conventional cell death in breast cancer cells. We aim to find out how this cell death occurs and whether it can overcome resistance developed in the breast cancer cells. Potentially, this non-conventional cell death caused by bacopaside II may stimulate the immune system which will be beneficial to these patients.

TQEH Research Expo Prize Winners: 1992 – 2019

2019		2018	
Honours/Summer Student	Ahad Sabab	Honours/Summer Student	Ashley Twigger
Junior Laboratory PhD Student	Laurine Kaul	Junior Laboratory PhD Student	Giri Krishnan
Senior Laboratory PhD Student	Amita Ghadge	Senior Laboratory PhD Student	Lisa Cherian
Clinical Trainee	Oscar Russell	Clinical Trainee	Rachel Goggin
Clinical Higher Degree Student	Mark Thompson	Clinical Higher Degree Student	Anupam Gupta
Mini-Oral/Poster Prize (Lab)	Maryam Nakhjavani	Poster Prize	Namfon Pantarat
Mini-Oral/Poster Prize (Clinical)	Tom Eldredge	Best Lay Description	Rachel Goggin
Best Lay Description	Unyime Jasper	Ivan De La Lande Award	Clementine Labrosciano

2017		2016	
Honours/Summer Student	Sean Mangion	**Honours/Summer Student**	Bahador Assadi-Khansari
Junior Laboratory PhD Student	Sathish Paramasivan	**Junior Laboratory PhD Student**	Vahid Atashgaran
Senior Laboratory PhD Student	Christopher DeFelice	**Senior Laboratory PhD Student**	Dijana Miljkovic
Clinical Trainee	Fiona Chan	**Clinical Research Group 1**	Ben Thurston
Clinical Higher Degree Student	Mian Ooi	**Clinical Research Group 2**	Scott Ellis
Poster Prize	Alexandra Shoubridge	**Poster Prize**	Vasilios (Bill) Liapis
Best Lay Description	Maddison Archer	**Best Lay Description**	Vasilios (Bill) Liapis

2015		2014	
Honours Student	Aashray Gupta	**Honours Student**	Tammy Willsmore
Junior Laboratory PhD Student	Vasilios (Bill) Liapis	**Junior Laboratory PhD Student**	Kati Richter
Senior Laboratory PhD Student	Aneta Zysk	**Senior Laboratory PhD Student**	Bill Panagopoulos
Junior Clinical Researcher	Zoe Kopsaftis	**Clinical Research Group 1**	Shailaja Nair
Senior Clinical Researcher	Kristin Carson	**Clinical Research Group 2**	Harshani Jayasinghe
Poster Prize	Ben Thurston	**Poster Prize: Junior**	Alice Du
Best Lay Description	Kati Richter	**Poster Prize: Senior**	Helen Palethorpe
		Best Lay Description	Aneta Zysk

2013		2012	
Honours Student	Zacki Malik	**Honours Student**	Sathish Paramasivan
Junior Laboratory PhD Student	Vikram Padhye	**Junior Laboratory PhD Student**	Erin Swinstead
Senior Laboratory PhD Student	Amanda Drilling	**Senior Laboratory PhD Student**	Irene Zinonos
Clinical Research Group 1	Tharshy Pasupathy	**Clinical Research Group 1**	Neil CW Tan
Clinical Research Group 2	Shailaja Nair	**Clinical Research Group 2**	Rachel Dreyer
Poster Prize	Shalini Sree Kumar	**Poster Prize**	Michael Collins
Best Lay Description	Tamsin Garrod	**Best Lay Description**	Tessa Gargett

2011		2010	
Honours Student	Sam Biermann	**Honours Student**	Joshua Woenig
Junior Laboratory PhD Student	Amenah Jaghoori	**1st year PhD Laboratory**	Camille Jardeleza
Senior Laboratory PhD Student	Irene Zinonos	**2nd year PhD Laboratory**	Joshua Jervis-Bardy
Clinical Higher Degrees	Elsa Dent	**3RD year PhD Laboratory**	Sam Boase
Clinical Research	Scott Graf	**Clinical Higher Degree**	Rachel Dreyer
Poster Prize	Yang Du	**Poster Prize**	Sumithra Krishnan
Best Lay Description	Michael Djukic	**Best Lay Description**	Chris Lauder

2009

Honours Student	Raymond Yu
Junior Laboratory PhD Student	Kanchani Rajopadhyaya
Senior Laboratory PhD Student	Darling Rojas
Clinical Higher Degree	Andrew Foreman
Allied Health-Pharmacy	Nicole Such
Poster Prize	Shaundeep Sen
Best Lay Description	Michael Collins

2008

Honours Group 1	Krishna Jeyaraman
Honours Group 2	Kanchani Radjopadhyaya
PhD Basic Science Jnr	Tyson Matthews
PhD Basic Science Snr 1	Christine Ball
PhD Basic Science Snr 2	Victoria Kopetz
Nursing & Allied Health	Hayley Vasileff
Higher Degrees Clinical	Rowan Valentine
Poster Prize	Andrew Foreman
Best Lay Description	Boris Fedoric

2007

Honours student	Tyson Matthews
PhD Basic Science Jnr	Darling Rojas & Boris Fedoric
PhD Basic Science Snr	Nicola Leung
PhD Snr Clinical	Shilpa Prasad
Higher Degrees Clinical	Tong Le
Nursing & Allied Health	Hayley Vasileff
Undergraduates Vacation	Julia Kirby
Poster Prize	Alicia Chan

2006

Honours student	Darling Rojas
PhD Basic Science	Deirdre Zander
PhD Basic Science	Christine Ball
PhD Clinical 1	Alkis Psaltis
PhD Clinical 2	Achim Beule
Nursing & Allied Health	Wendy McInnes
Undergraduates Vacation	Khanh Tran
Poster Prize	Rosanna Tavella

2005

Honours Group 1	Boris Fedoric
Honours Group 2	Nick Mabarrack
PhD Junior Laboratory	Rebecca Dragovic
PhD Senior Laboratory	Theresa Hickey
PhD Clinical	Alkis Psaltis
Nursing & Allied Health	Peter Cheung
Undergraduates Vacation	Amellia Laidlaw
Poster Prize	Cadence Minge

2004

Honours Group 1	Kara Cashman
Honours Group 2	Joanne Reed
PhD Junior Laboratory	Rebecca Dragovic
PhD Senior Laboratory	Harshita Pant
PhD Clinical	Wai Lim
PhD Population Health	Mark Kohler
Medical Student	Anthony Pisanello
Poster Prize	Theresa Hickey

2003

Honours Group 1	Maggie Centenera
Honours Group 2	Claire Seymour-Griffin
PhD Junior Laboratory	Ben Davies
PhD Senior Laboratory	Madelyn Zawitkowski
PhD Clinical	Jim Jannes
PhD Population Health	Katie Kandelaars
Poster Prize	Melanie Bagg

2002

Honours	Deborah Marrocco
PhD Junior Laboratory	Ashley Newland
PhD Senior Laboratory 1	Cassandra Woithe
PhD Senior Laboratory 2	Madelyn Zawitkowski
Higher Degree Clinical	Matt Worthley
Higher Degree Surgical	Charles Morrison
Medical Student	Sasa Todorovic
Poster Prize	Lien Ho

2001

Honours	Ashley Newland
Higher Degree Jnr	Cassandra Woithe
Higher Degree Snr	Al Truong Tran
Higher Degree Clinical	Matt Worthley
Higher Degree Surgical	Fiona Court
Advanced Fellowship Trainee	Anita Lee
Medical Student	Aiden Burrell
Poster Prize	Greg Roach

2000

Honours Group 1	Ilse Dahn
Honours Group 2	Melanie Sutton
Higher Degree Group 1	Samantha Yates
Higher Degree Group 2	Tina Bianco
Higher Degree Clinical	Merlin Thomas
Nursing & Allied Health	Libby Birchmore
Medical Student	Victoria Tay
Poster Prize	Nicole Lamond

1999

Honours	Tenielle Webb
Higher Degree Group 1	Ai Truong Tran
Higher Degree Group 2	Damien Hussey
Higher Degree Clinical	Denise Roach
Advanced Fellowship Trainee	Justin Evans
Nursing & Allied Health	Terry Jones & Dorothy Pannell
Medical Student	Edmund Tse & Ru-Siang Cheng

1998

Honours	Ai Truong Tran
Higher Degree Group 1	Sarah Swinburne
Higher Degree Group 2	Damien Hussey
Higher Degree Clinical	Sarah Downie
Advanced Fellowship Trainee	Alan Wigg
Nursing & Allied Health	Robyn Clark
Medical Student	Rae-Wen Chang
Poster Prize	Lucia Sabordo

1997

Honours	Samantha Yates
Higher Degree Group 1	Lisa Butler
Higher Degree Group 2	Michael Texler
Higher Degree Clinical	Dorothy Keefe
Advanced Fellowship Trainee	Andrew Luck
Nursing & Allied Health	Simon Stewart
Medical Student	Nan Williams

1996

Honours	Anthony Kiosoglous
Higher Degree Group 1	Jennifer Hardingham
Higher Degree Group 2	Guy Patrick
Higher Degree Clinical	Christopher Zeitz
Advanced Fellowship Trainee	Alan Wigg
Nursing & Allied Health	Julie Lucker
Medical Student	Michael Osborn
Poster Prize	Matthew Callaway

1995

Honours	Antiopi Varelias
Higher Degree Group 1	Guy Patrick
Higher Degree Group 2	Andreas Evdokiou
Higher Degree Clinical	Christopher Zeitz
Advanced Fellowship Trainee	Toby Coates
Medical Student	Rohini Sharma

1994

Honours	Lucia Sabordo & Linda Dadds
Higher Degree Group 1	Rebecca Ritchie & James Moore
Higher Degree Group 2	Guy Patrick
Advanced Fellowship Trainee	David Campbell
Medical Student	I-Wen Chu

1993

Basic Science	Dean Bacich
PhD/MD	Cui Lan Zhang
In Training	Jennifer Hardingham
Clinical	Dorothy Keefe
Medical Student	Kenneth Ooi

1992

Basic Science	Yi Zhang
PhD/MD	Warwick Grooby
Clinical	David Campbell

TQEH Research Day Plenary Lectures: 1992 - 2020

2020 **Professor Toby Coates – Royal Adelaide Hospital and The University of Adelaide**
"Recycling Islets to Treat Diabetes"

2019 **Professor John Rasko AO – Centenary Institute, Sydney**
"Cell and Gene Therapy: great power brings great responsibility"

2018 **Professor Peter Rathjen – The University of Adelaide**

2017 **Hon. Mark Butler MP – Australian Labor Party**
"The Politics of Ageing"

2016 **Professor Anne Kelso AO – NHMRC**
"Medical research: why we mustn't stop now"

2015 **Professor Steve Webb – Royal Perth Hospital, University of Western Australia & Monash University**
"Pushing or pulling over the evidence-practice gap"

2014 **Professor Brendan Crabb – Burnet Institute**
"Malaria in the 21st century"

2013 **Professor Tanya Monro – The University of Adelaide**
"From theoretical physics to solutions in health and defence: a transdisciplinary journey"

2012 **Professor Barry Brook – The University of Adelaide**
"Future climate extremes and how to avoid them!"

2011 **Professor Steve Wesselingh - SAHMRI**
"Health Reform and Medical Research: Building better links between medical research and health care delivery to improve health outcomes"

2010 **Professor David Allen - The University of Sydney**
"Duchenne muscular dystrophy; connecting the gene to the disease"

2009 **Professor David Vaux - La Trobe University**
"Ten rules for the presentation and interpretation of data in publications"

2008 **Dr Bob Irving - Nanotechnology Victoria**
"Nanotechnology - Opportunities and Challenges at the Smallest Frontier of Science"

2007 **Jenni Metcalfe - President Australian Science Communicators**
"A Schizophrenic Life: the Career of a Science Communicator"

2006 **Dr Rob Morrison - Science Communicator**
"Trust me, I'm a Science Communicator"

2005 **Professor Rob Norman - The University of Adelaide**
"The reproductive revolution: How The Queen Elizabeth Hospital led the field"

2004 **Robyn Williams - Australian Broadcasting Corporation**
"How modern medicine changed the world - some anniversaries"

2003 **Dr Sarah Robertson - The University of Adelaide**
"Facing Challenges and Finding Solutions in Reproductive Medicine"

2002 **Professor John Chalmers - The University of Sydney**
"Enhancing Health and Medical Research in the Teaching Hospital Environment"

2001 **Professor Peter Rathjen - The University of Adelaide**
"Regenerative medicine using stem cells: Medicine for the new millennium"

2000 **Professor Grant Sutherland - The University of Adelaide**
"The human genome project: Applications to medical research"

1999 **Dr Philip Reece - Biota Holdings**
"Biota and Relenza: New drug discovery in Australia"

1998 **Professor Colin Matthews (Moderator) - The University of Adelaide**
Speakers: Dr Tim Kuchel, Dr David Turner, Dr John Chandler
"And Man-made Dolly: The ethics of cloning"

1997 **Dr Julian Cribb - CSIRO**
"The origin of AIDS"

1996 **Dr Deane Hutton - Science Communicator**
"20:20 vision – Living in the 21st Century"

1995 **Professor Mike Tyler - The University of Adelaide**
"Frogs – the new frontier for natural products pharmacology"

1994 **Dr Gael Jennings - Australian Broadcasting Corporation**
"Communicating research via the medium of television"

1993 **Dr Mark Wahlqvist - Monash University**
"Salt intake and the non-pharmacological treatment of hypertension"

1992 **Professor David Jarrett - The Queen Elizabeth Hospital**
"The place of research in the face of a shrinking medical budget"