Dear colleagues

Thank you for gathering for this Translational Meeting, to share your laboratory’s progress with the support of a Bosch Institute Translational Grant-in-Aid.

The hope behind the TGIAs was to facilitate progress in the translation of your discoveries to application in a clinical or applied context.

I look forward very much to learning of that progress

Jonathan Stone DSc FAA  
Executive Director
9.00 am  Introduction  
  *Jonathan Stone*

9.05 am  A mechanism to inform antipsychotic drug selection for schizophrenia patients who use cannabis  
  *Jonathon Arnold and Natalia Brzozowska*

9.25 am  Making "platinum class" less exclusive (Copper transporters as predictors of response to platinum based cancer chemotherapies)  
  *Steve Assinder*

9.45 am  Identification and characterisation of regulatory immune cells in UV-exposed hosts  
  *Scott Byrne, Gary Halliday and Diona Damian*

10.05 am  The STRICT (Simvastatin Therapy for Reducing Inflammation in Colorectal cancer Trial) Study: A Pilot clinical trial in metastatic colorectal cancer patients with elevated markers of inflammation  
  *Kellie Charles, Stephen Clarke, Michael Michael, Lisa Horvath, David Goldstein, Connie Diakos, Prunella Blinman, Andrew McLachlan, Mark Molloy, and Donald McMillan*

10.25 am  Human Cardiac Tissue Spheroid (HCTS): A Novel Cardiotoxicity Assay  
  *Cris dos Remedios*

**Morning tea:** 10.45 am

11.00 am  Calming the beast: Assessing a novel therapeutic strategy to treat macrophage hyperactivation syndrome  
  *Stuart Fraser*

11.20 am  Additional sun-protective effects of a vitamin D like compound in sunscreen  
  *McCarthy BY, Han J, de Silva W, Song Ej, Coles L, Heber G, Stern H, Rybchyn MS, Dixon KM, Mason RS*

11.40 am  The development of albumin nanoparticles to selectively deliver novel chemotherapeutics  
  *Danuta S. Kalinowski, Phatsapong Yingchoncharoen, Binh Pham, Vien Huynh, Brian Hawkett, Sharon Leung, Kim Chan, Des R. Richardson*

12.00 pm  Potent anti-mycobacterial activity of the pyridoxal isonicotinoyl hydrazone analogue, 2-pyridylcarboxaldehyde isonicotinoyl hydrazone: A lipophilic transport vehicle for isonicotinic acid hydrazide  
Title:
A mechanism to inform antipsychotic drug selection for schizophrenia patients who use cannabis

Authors:
Jonathon Arnold and Natalia Brzozowska
Discipline of Pharmacology

Abstract:
We have identified a mechanism that accounts for the capacity of cannabis to decrease the efficacy of antipsychotic drugs. The magnitude of this problem is highlighted by the fact that >40% of schizophrenia patients also use cannabis. Our pilot data shows that mice exposed to Δ⁹-tetrahydrocannabinol (THC), the most abundant phytocannabinoid, displayed profoundly reduced behavioural responses to risperidone. Risperidone is a major first-line antipsychotic medication and many schizophrenics exhibit treatment-resistance to this agent. We found that the decreased efficacy of risperidone is due to altered brain disposition; THC exposure lowered the concentrations of risperidone and its active 9-hydroxy metabolite in the brain. We hypothesized THC might increase the abundance of ABC transporters at the blood brain barrier (BBB), which would lower brain risperidone levels via enhanced efflux. We have shown risperidone and its metabolite are excellent substrates of the ABC transporter P-glycoprotein (P-gp). Further, we discovered that THC activated P-gp expression at the BBB. Taken together, our results suggest that THC exposure, by increasing P-gp expression at the BBB, reduced the brain uptake of risperidone. Unfortunately, this mechanism may extend to other commonly used antipsychotic drugs, many of which are substrates of P-gp. We tested the non-P-gp substrate clozapine and found that its antipsychotic actions were not affected by THC exposure. Interestingly, clozapine is usually only administered as a last resort to drug-resistant schizophrenics and the mechanism underlying its efficacy in this population has been unclear for over 30 years.

Bio:
Jonathon Arnold is an Associate Professor at the University of Sydney and has over 19 years experience in behavioural neuroscience and psychopharmacology. In 2005 he conducted research at the Cajal Institute in Madrid, one of the world's premier neuroscience institutes. In 2009 A/Prof Arnold established the Neurobehavioural Laboratory at the Brain and Mind Research Institute (BMRI). He has published 47 manuscripts and has received over 1200 career citations (h-index = 22). His research has attracted national and international funding. In 2010, he was awarded an internationally competitive Young Investigator Grant from the Brain and Behavior Research Foundation (US). His laboratory aims to understand how stress and drugs affect the brain and behavior. He utilizes various mouse models of neuropsychiatric conditions including addiction, anxiety, depression, post-traumatic stress disorder (PTSD) and schizophrenia. A typical day in his lab will see students measuring animal behaviour, performing western blots or immunohistochemistry or analysing CNS-cell morphology (microglia, astrocytes, oligodendrocytes and neurons). He is currently developing new techniques such as in vivo imaging of synapses and optogenetics to establish brain cell-behaviour relationships.
Title:
Making “platinum class” less exclusive - Copper transporters as predictors of response to platinum based cancer chemotherapies

Authors:
Steve Assinder  
Discipline of Physiology

Abstract:
Copper transporters CTR1 and CTR2 are thought to be responsible for the influx of platinum-based cytotoxic drugs (eg. cisplatin) used in the treatment of cancers. These drugs are very effective in the treatment of some cancers, including testicular and bladder cancers. In stark contrast, some tumour types (eg. breast and ovarian cancers) have a varied response whilst others (eg. prostate cancer) are recalcitrant. Evidence suggests that insensitivity might relate to greater amounts of CTR2 being present. Immunohistochemical analyses of CTR1 and CTR2 in representative types of cisplatin sensitive, variable, and insensitive cancers tested the hypothesis that a higher ratio of CTR2:CTR1 is associated with decreased sensitivity to platinum based drugs. Contrary to this hypothesis, bladder cancers (cisplatin sensitive) had the greatest ratio of CTR2:CTR1, whilst seminoma’s (cisplatin sensitive) and prostate cancers (cisplatin insensitive) had the lowest ratios. Of all cancer types assessed, prostate cancers have the greatest levels of both copper transporters. Although the original hypothesis is not supported, it is suggested that the intracellular localisation of CTR2 is important. Seminomas displayed a predominantly nuclear localisation of CTR2. In a study of breast cancer cell lines, CTR2 was located in the cell nucleus of cell lines most sensitive to cisplatin. In the least sensitive cell line CTR2 was located predominantly to the cytoplasm. In conclusion, sensitivity of cancers to platinum-based drugs is not related to the ratio of CTR2:CTR1. However, findings suggest that sensitivity might be related to the localisation of copper transporter 2 to the nucleus of cancer cells.

Bio:
Associate Professor Steve Assinder is head of the Andrology Research Group, Bosch Institute, and Lecturer in Physiology, School of Medical Sciences.

His research expertise is in prostate disease and reproductive physiology of the male. Steve has headed his own research group since 2001, employing three full-time research fellows and supervising 8 postgraduate students.
Title:
Identification and characterisation of regulatory immune cells in UV-exposed hosts

Authors:
Scott N. Byrne¹,², Gary M. Halliday² and Diona Damian²

¹Cellular Photoimmunology Group, Infectious Diseases and Immunology
²Dermatology, Royal Prince Alfred Hospital

Abstract:
The ultraviolet (UV) wavelengths in sunlight are the prime cause of skin cancer. Despite widespread community awareness of the need to protect ourselves from UV exposure, the incidence of both melanoma and non-melanoma skin cancer continues to rise. For some patients, such as those with severe sun damage and immune-suppressed solid organ transplant recipients, this may lead to the occurrence of many highly aggressive metastatic skin cancers. UV-induced genetic damage and suppression of anti-tumour immunity are both causative for skin cancer. Protection from either of these could reduce skin cancer incidence particularly in high-risk individuals. While the mechanisms of UV-induced DNA damage have been topics of concerted research efforts, the cellular and molecular mechanisms underlying UV-immunosuppression are less well understood. We have uncovered that a major cellular target of immune suppressive UV are B cells. We call these cells “UV-BRegs”. Mice exposed to UV radiation have high numbers of activated B cells that are CD1dlowCD5 CD86hiCD274hi. These B cell produce high amounts of immunoregulatory IL-10 and IL-13. This is important because BRegs that express CD86 and CD274 and produce anti-inflammatory cytokines are known to mediate escape from anti-tumour immunity. With TGIA support we have now commenced our studies in human skin cancer patients. This is important because identifying the major immune regulatory subsets activated by UV radiation will allow us to design novel intervention strategies to target them therapeutically.

Bio:
Associate Professor Scott Byrne is interested in the cellular mechanisms underlying sunlight-induced immune suppression and tolerance. Specifically, he is exploring how ultraviolet radiation from the sun causes skin cancer by activating regulatory cells and suppressing the anti-tumour immune response. The cell to cell interaction and migration of mast cell and B lymphocytes are what he is currently focused on. Current and future research endeavours include investigating the role of regulatory cells and mast cells in autoimmune diseases such as multiple sclerosis, as well as dermatology related disorders such as polymorphic light eruption (PLE).
Title:
The STRICT (Simvastatin Therapy for Reducing Inflammation in Colorectal cancer Trial) Study: A Pilot clinical trial in metastatic colorectal cancer patients with elevated markers of inflammation

Authors:
Kellie Charles, Stephen Clarke, Michael Michael, Lisa Horvath, David Goldstein, Connie Diakos, Prunella Blinman, Andrew McLachlan, Mark Molloy, and Donald McMillan

Discipline of Pharmacology

Abstract:
Introduction: Advanced colorectal cancer (CRC) is a leading cause of death in Australia and internationally with more than 60% of patients dying within 5 years of diagnosis1. Pivotal studies from our research team have found that advanced CRC patients with elevated systemic inflammatory biomarkers, such as the Neutrophil-Lymphocyte Ratio (NLR) or C-reactive protein have a poor response to chemotherapy and markedly reduced overall survival (median overall survival 9 months v 18 months with no evidence of inflammation) with standard first line chemotherapy2. There are currently no clinical guidelines to assist clinicians in the management of these high-risk CRC patients. Hence, there is an urgent need to identify effective treatments for reducing inflammation in advanced CRC patients and improving patient outcomes.

Aim: The aim of this study is to determine whether simvastatin in addition to standard care reduces inflammation and improves anti-tumour response, while not increasing the toxicity profile of standard chemotherapy.

Method: This pilot study is a Phase II clinical of simvastatin (40mg/d) plus standard care (FOLFOX, FOLFIRI or XELOX plus bevacizumab) in 10 patients with metastatic colorectal cancer systemic inflammation (assessed by Neutrophil/Lymphocyte Ratio, NLR≥5). Changes in inflammatory status (CPR) and tumour response (CT scan) will be measured clinically.

Results: 4 patients were recruited to the study. The median change in inflammatory status was 72% in 2 weeks. 2 patients showed clinical benefit from treatment, while one patient experienced severe toxicity (to chemotherapy not simvastatin) and one withdrew due to a protocol deviation. New methods for phenotyping the inflammatory response were also optimized during this study.

Conclusion: Simvastatin shows promise as an anti-inflammatory agent in mCRC, however further randomized clinical trials are needed to confirm anti-tumour response.

Bio:
Dr Charles' research aims to investigate the interactions between malignant cells and immune cells that regulate tumour progression. Malignant cells secrete cytokines and chemokines that alter the phenotype and behaviour of tumour-associated leucocytes to promote tumour growth and orchestrate the immunosuppressant behaviour of the adaptive immune responses. Inhibiting the communication between cancer cells and immune cells is becoming an exciting potential target for cancer intervention strategies. Dr Charles conducts translational and clinical studies aimed to identify new molecular targets in cancer and in collaboration with biological chemists at the University of Sydney design and evaluate new cancer therapeutic agents.
Title: Human Cardiac Tissue Spheroid (HCTS): A Novel Cardiotoxicity Assay

Author: Cris dos Remedios
Discipline of Anatomy

Abstract: The heart, like all organs, contains many types of cells, of which cardiomyocytes are predominant. But it also contains a large number of capillaries lined by endothelial cells. In addition there are small numbers of resident cells such as stem cells, transient leukocytes, fibroblasts and “stem” cells. The interactions between these cell types will affect the overall function of the heart. The drug industry is continually testing compounds that assist the failing heart that we developed in compounds tested on mice. We now know that most compounds that help heart failure (HF) in mice fail in human trials, so this TGIA aims to develop an in vitro assay using isolated human cardiomyocytes combined with human endothelial cells, i.e. cardiospheres. This TGIA project has developed an in vitro model that combines cultured human cardiomyocytes isolated from healthy hearts that were snap frozen in liquid nitrogen (-196°C). These cells only survived for about a week. However, when they are co-cultured with endothelial cells (immortalized Human Umbilical Vascular Endothelial Cells - HUVECs) to form human cardiac tissue spheroids (HCTSs), they more robust. Data will be presented using two test compounds that have quite different cardiotoxic effects. We also cultured small (~50 mg) pieces of LV tissue that released large numbers of non-cardiomyocytes and plan to test whether cardiomyocytes survive for months in culture. If so, they will enable us to develop a high-throughput system for screening new drugs to treat heart failure.

Bio: Academic and Scientific Positions:

- Professor of Anatomy and Biophysics, Bosch Institute, Discipline of Anatomy & Histology, University of Sydney 2000-present.
- Associate Professor, Department of Anatomy, University of Sydney 1980-2000
- US Biophysical Society: Member of the Council (1997-2003), Member of the Executive (2004-2005). I serve on several of its Committees.
- Former President of the Australian Society for Biophysics.
- Director, Institute for Biomedical Research, University of Sydney (1998-2000).
- Associate Dean, Faculty of Medicine, University of Sydney (1999-2002).
- Member of the Scientific Advisor Board, Medsica Pty Ltd. (2005-2011).


Inventor: I hold several Australian, US and European patents on three patents (e.g. CG dos Remedios, AR Cooke, 2004, Biomolecular toxicity assay, European Patent 1292703).
Title:
Calming the beast: Assessing a novel therapeutic strategy to treat macrophage hyperactivation syndrome

Author:
Stuart Fraser
Discipline of Physiology

Abstract:
Macrophages are critical regulators of physiological health. These cells engulf and kill pathogens, ingest dead cells and destroy the billions of nuclei expelled by developing red blood cells. Under some conditions however, macrophages change from being supportive and immunoregulatory cells to become hostile phagocytes targeting cells of their host. In particular, these pathological macrophages engulf and destroy developing red blood (erythroid cells) leading to severe anaemia. Here, we have examined the function of macrophages in normal and pathological settings. We have discovered that macrophages interact with developing erythroid cells via a previously unreported cell-cell interaction we term the “erythroid synapse”. This synaptic pairing between erythroid cells and macrophages is dependent upon the presence of the transcription factor IRF-8 and the detoxifying enzyme heme oxygenase-1. Loss of either of these leads to profound red blood cell production disorders, anaemia and eventually death. We found also found that the copper is essential regulator of macrophage-erythroid cell interactions. The copper transporters CTR1 and CTR2 are mutually expressed in macrophages, particularly those controlling red blood cell production. Chelation of copper leads to collapse of this interaction and profound changes in macrophage phenotype, with eventual apoptosis. Due to technical difficulties, we have not yet been able to apply copper chelation to reduce the severity of macrophage hyperactivation syndrome though we still aim to do so. Finally, with support from the Bosch Institute and the National Breast Cancer Foundation, we have found that macrophages in normal tissue, adjacent to breast cancer, show greatly reduced levels of the copper transporters CTR1 and CTR2. These findings show that copper levels in macrophages can be manipulated in numerous pathological conditions. Collectively, our findings have formed the backbone of further funding applications to the NIH, Histocytosis Association and NBCF.

Bio: Stuart Fraser is a senior lecturer in the Disciplines of Physiology and Anatomy & Histology. He is the head of the Laboratory of Blood Cell Development in the Medical Foundation Building. Dr Fraser received his BSc from Monash University with Honours in Immunology & Pathology. He then received his PhD in Biochemistry from the University of Hong Kong. He was a JSPS postdoctoral fellow in the laboratory of Prof Shin-Ichi Nishikawa at Kyoto University for 4 years. He then completed his postdoctoral training at the Institute for Toxicology, Johannes-Gutenberg University of Mainz, Germany. Dr Fraser was Assistant Professor in Medicine at the Mount Sinai School of Medicine, New York for 6 years before becoming the Sesquicentennial Lecturer in Molecular Embryology at the University of Sydney in 2010. He teaches in over 12 different units of study and was part of the team that won the Faculty of Medicine Excellence in Teaching Award in 2014. He has obtained over $3 million in research funding either as an individual investigator, co-investigator or as part of a consortium and published over 50 research papers. He is the current Academic Director of the Bosch Institute Live Cell Facility.
Title: Additional sun-protective effects of a vitamin D like compound in sunscreen

Authors: McCarthy BY, Han J, de Silva W, Song EJ, Coles L, Heber G, Stern H, Rybchyn MS, Dixon KM, Mason RS.

Discipline of Physiology

Abstract: We have already shown that the active vitamin D hormone, 1,25-dihydroxyvitamin D and compounds which are predicted to act like vitamin D - vitamin D-like compounds - reduced UV-induced DNA damage in human skin cells in culture, in mouse skin and in human skin explants and human subjects. The studies also showed that both 1,25-dihydroxyvitamin D and a vitamin D-like compound reduced skin cancers which developed in mice as a result of chronic exposure to UV. The vitamin D hormone is expensive to produce and is unstable, so unsuitable for inclusion in a topical preparation like a sunscreen. In order to substantiate a claim that the inclusion of a vitamin D-like compound in a sunscreen would “help reduce DNA damage from sunlight”, we tested whether UV-induced DNA damage would be further reduced using a sunscreen formulated with a vitamin D-like compound, compared to sunscreen alone. Since SPF 50+ sunscreen markedly reduces UV transmission through the skin, we first had to design and optimize a UV exposure protocol, which used solar-simulated radiation, but which was energetic enough to produce DNA damage, even when sunscreen was applied to skin. A protocol involving 3 levels of solar-simulated UV exposure and 3 concentrations of sunscreen was tested in explants of human skin freshly derived from elective plastic surgery. DNA damage, measured as thymine dimers, the most frequent type of cyclobutane pyrimidine dimers, was quantified by our standard immunohistochemical stain and image analysis (Sequiera et al, 2013). DNA damage at 3h after exposure increased with increased dose of UVB from 200 mJ/cm² (about the amount of radiation that just produces faint redness on unprotected skin) to 800 mJ/cm² and decreased with increasing concentrations of 50+ sunscreen from 0.5 mg/cm² to the standard dose of 2 mg/cm². Using the highest UVB dose tested, DNA damage was measured (as percent area of epidermis above threshold) at 15 ± 3.5 (mean ± SD) without sunscreen; 5.2 ± 1.4 with sunscreen (p<0.0001); 1.1 ± 0.8 with 2 mg/cm² sunscreen formulated with a low concentration of vitamin D-like compound (p=0.05 compared with sunscreen alone) and 4.5 ± 1.2 with sunscreen with an alternative, unrelated, test agent (ns vs sunscreen alone). Parallel studies in human keratinocytes indicated that the protective effect of the vitamin D-like compound on UV-induced DNA damage depended on the presence of the vitamin D receptor and on a second receptor, ERp57, that we have shown to be essential for the protective effect of 1,25-dihydroxyvitamin D (Sequiera et al, 2012). The data support the proposal that vitamin D-like compounds indeed protect from UV-induced DNA damage by a vitamin D-like mechanism and could usefully be incorporated into sunscreens with the claim “additional protection from UV damage”.

References:

Bio:

Rebecca Mason, a medical graduate from Sydney University, has research interests in vitamin D, bone and skin. She is on the Editorial Board of the Journal of Bone and Mineral Research and the journal Endocrinology. She has been a member of the Cancer Councils of Australia Working Party on Sun and Health and consults on vitamin D with these groups, was a member of the International Commission on Illumination’s technical committee on Sunlight, Health and Vitamin D (reported in 2011) and will serve on a new technical committee for the Commission in 2013. In 2009, she received an award from the 14th International Workshop on Vitamin D for “career contributions to vitamin D research” and now is on the Executive Committee for a new series of International Vitamin D workshops. She is Head of Physiology and Deputy Director of the Bosch Institute, University of Sydney, a Board member of Osteoporosis Australia and Immediate Past President of the ANZ Bone and Mineral Society.

Dr Katie Dixon
Title:
The development of albumin nanoparticles to selectively deliver novel chemotherapeutics

Authors:
Danuta S. Kalinowski1, Phatsapong Yingchoncharoen1, Binh Pham2, Vien Huynh2, Brian Hawkett2, Sharon Leung3, Kim Chan3, Des R. Richardson1
1 Department of Pathology and Bosch Institute, University of Sydney, NSW, Australia
2 School of Chemistry, University of Sydney, NSW, Australia
3 Faculty of Pharmacy, University of Sydney, NSW, Australia

Abstract:
Defective metal homeostasis has emerged as a feature of cancer cells (Cancer Res 2011;71:1511-4). Hence, chelators offer a novel pharmacological intervention to target tumour cells that have disturbed metal metabolism. The chelators, di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT) and di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC), demonstrate potent in vitro and in vivo anti-cancer activity (PNAS 2006;103:14901-6; J Med Chem 2012;55:7230-44). Interestingly, recently human serum albumin (HSA) was shown to potentiate the cellular uptake and anti-cancer activity of Dp44mT (Oncotarget 2015;6:10375-98).

These results led to the current studies to develop HSA nanoparticles as a carrier to selectively target our agent to tumours. Notably, other cytotoxic agents (e.g., paclitaxel) are now being “packaged” into HSA-nanoparticles to improve their activity and tolerability, leading to new agents in clinical use (e.g., Abraxane®, Biotechnol Annu Rev 2007;13:345-57). In this investigation, we focused on the design and development of novel HSA-based nanoparticles containing our most promising anti-cancer agents, Dp44mT and DpC, to act as a carrier to selectively target our agents to tumours.

A number of nanoparticle preparation methods, including the desolvation, membrane emulsification and nanoprecipitation techniques, were utilised. Importantly, the nanoprecipitation of lipid-polymer hybrid nanoparticles resulted in higher encapsulation of Dp44mT. Our data demonstrate that the Dp44mT-loaded lipid-polymer hybrid nanoparticles had similar anti-proliferative activity to that of the free ligand. Our current studies aim to optimise the preparation conditions to promote greater levels of drug encapsulation efficiency and nanoparticle stability.

Bio:
Dr Danuta S. Kalinowski completed her undergraduate degree in Chemistry at Macquarie University, Sydney. She received her doctorate in Medicine in 2007 at The University of Sydney examining the design, development and medicinal chemistry of novel iron chelators as anti-cancer agents. Dr Kalinowski has held funding from the NHMRC (2009-2011) and the Cancer Institute NSW (CINSW; 2009, 2011). Additionally, she received a Cancer Institute NSW Early Career Development Fellowship (2009-2012) and is currently a Research Fellow at The University of Sydney. Dr Kalinowski currently holds funding from the NHMRC (2013-2015) and her research involves implementing albumin as a pharmacological carrier of novel anti-cancer agents.
Title:
Potent anti-mycobacterial activity of the pyridoxal isonicotinoyl hydrazone analogue, 2-pyridylcarboxaldehyde isonicotinoyl hydrazone: A lipophilic transport vehicle for isonicotinic acid hydrazide

Authors:
Molecular Pharmacology and Pathology Program, Department of Pathology, University of Sydney

Abstract:
The rise in drug-resistant strains of Mycobacterium tuberculosis is a major threat to human health and highlights the need for new therapeutic strategies. In this study, we have assessed whether high-affinity iron chelators of the pyridoxal isonicotinoyl hydrazone (PIH) class can restrict the growth of clinically significant mycobacteria.

Screening a library of PIH derivatives revealed that one compound, namely, 2-pyridylcarboxaldehyde isonicotinoyl hydrazone (PCIH), exhibited nanomolar in vitro activity against Mycobacterium bovis bacille Calmette-Guérin and virulent M. tuberculosis. Interestingly, PCIH is derived from the condensation of 2-pyridylcarboxaldehyde with the first-line antituberculosis drug isoniazid [i.e., isonicotinic acid hydrazide (INH)]. PCIH displayed minimal host cell toxicity and was effective at inhibiting growth of M. tuberculosis within cultured macrophages and also in vivo in mice.

Further, PCIH restricted mycobacterial growth at high bacterial loads in culture, a property not observed with INH, which shares the isonicotinoyl hydrazide moiety with PCIH. When tested against Mycobacterium avium, PCIH was more effective than INH at inhibiting bacterial growth in broth culture and in macrophages, and also reduced bacterial loads in vivo.

Complexation of PCIH with iron decreased its effectiveness, suggesting that iron chelation may play some role in its antimycobacterial efficacy. However, this could not totally account for its potent efficacy, and structure-activity relationship studies suggest that PCIH acts as a lipophilic vehicle for the transport of its intact INH moiety into the mammalian cell and the mycobacterium.

These results demonstrate that iron-chelating agents such as PCIH may be of benefit in the treatment and control of mycobacterial infection.

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Bio:
Dr. Des Richardson B.Sc., M.Sc., Ph.D., D.Sc., FFSc, FRCPath (UK) is Professor of Cancer Cell Biology and an NHMRC Senior Principal Research Fellow at the Department of Pathology, University of Sydney. He has published over 300 articles, chapters, patents and books and is commercially developing a new anti-tumour agent known as DpC in cooperation with Cthulhu Ventures, California, USA.