P.09-215-Tue
Targeting isocitrate lyase for the treatments of tuberculosis

R. Bhusal, K. Patel, B. Kwai, G. Bashiri, J. Reynisson, J. Sperry, **I. Leung**
The University of Auckland, Auckland, New Zealand

The enzymes isocitrate lyase (ICL) isoforms 1 and 2 are essential for the survival of *Mycobacterium tuberculosis* within macrophages during tuberculosis infection. ICLs are not present in humans and are therefore attractive therapeutic targets for the treatment of tuberculosis. In this talk, we describe our work in the development and design of new ICL inhibitors. A particular focus is the application our combined high-throughput virtual screening, nuclear magnetic resonance spectroscopy and thermal shift assay strategy, which has led to the discovery of several novel ICL inhibitor scaffolds that are the subject of ongoing medicinal chemistry studies in our laboratories. Finally, we will also describe our recent efforts in studying the structure and catalytic mechanism of ICLs. We hope our work will inspire the development of the next generation of ICL inhibitors that may be used to treat tuberculosis.

P.09-216-Wed
Toluidine blue O reduces APLP2 and APLP2 CTF levels in Hs766T cells

K. Biberoglu, M. Yüksel, S. Önder, Ö. Tacal
Department of Biochemistry, School of Pharmacy, University of Hacettepe, Ankara, Turkey

Cancer and neurodegeneration are two different pathological diseases but they share common mechanisms in many ways. Amyloid precursor-like protein 2 (APLP2) and its homologous family member, amyloid precursor protein (APP) are overexpressed in many cancers and they are linked to abnormal growth, migration, and invasion. A recent study has revealed that APLP2 has a role in the growth of pancreatic cancer cells. Besides, inhibitors that prevent APLP2 cleavage, leading to low APLP2 C-terminal fragments (CTFs), decrease the viability of pancreatic cancer cells. According to our recent studies, a phenothiazine-derived compound, toluidine blue O (TBO) was found to mitigate amyloid pathology by reducing APP and Aβ peptide levels in Chinese hamster ovary cells stably expressing wild type human APP and PS1. In present study, we aimed to investigate whether TBO may reduce the APLP2 and APLP2 CTFs, which have effective roles in pancreatic cancer growth and viability. Pancreatic cancer cells (Hs766T) were treated with a dose range of TBO (0–15 μM) or vehicle control for 24 h. After treatment of Hs766T cells with TBO without any side effect on cell viability, the levels of APLP2 and APLP2 CTFs in cell lysates were analyzed using Western blot and normalized to total protein levels. We observed a significant decrease in both intracellular APLP2 and APLP2 CTF levels in a dose-dependent manner compared to vehicle-treated cells. APLP2 levels were reduced by 26% ($*P < 0.05$) at 5 μM and 42% ($***P < 0.01$) at 10 μM TBO. Also, APLP2 CTF levels were decreased by 43% ($*P < 0.05$), 48% ($**P < 0.01$) and 66% ($***P < 0.001$) at 5 μM, 10 μM and 15 μM TBO. In conclusion, these results support the idea that TBO may be used as a therapeutic drug in pancreas cancer. Supported by a grant from the Scientific Research Unit of Hacettepe University (HUBAB, TSA-2017-13929).

P.09-217-Mon
Biological activity of South African macrofungi against respiratory and lung disease

J. Didloff[1], G. J. Boukes[1,2], T. C. Koekemoer[1], M. van. de Venter[1], S. Govender[1]
[1]*Department of Biochemistry and Microbiology, Nelson Mandela University, Port Elizabeth, South Africa,* [2]*Afrigen Biologics Pty Ltd, Cape Town, South Africa*

Macrofungi represent an untapped source of natural bioactive compounds for various diseases, which have been targeted as potential therapeutic agents. Respiratory disease and lung cancer places a global burden on health due to antimicrobial resistance, non-specific drug targeting and damaging side effects. This study investigated the antimicrobial activity and cytotoxicity of 21 South African macrofungi against respiratory pathogens (e.g. *Pseudomonas aeruginosa*, *Klebsiella pneumoniae, Streptococcus pneumoniae*, *S. pyogenes*, *Staphylococcus aureus*) and human lung adenocarcinoma A549 cells. Ethanol and aqueous extracts were screened for antimicrobial activity using the ρ-iodonitrotetrazolium chloride assay and the effect on bacterial morphology determined using transmission electron microscopy (TEM). Cytotoxicity was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay, and the mechanism elucidated by cell cycle analysis and fluorescent staining. Ethanol extracts showed higher antimicrobial activity against the Gram-positive bacteria than aqueous extracts. The macrofungal extracts of *Fomitopsis lilacinogilva* and *Pisolithus tinctorius* showed to cause cell membrane damage. Ethanol extracts of *Pycnoporus sanguineus, F. lilacinogilva* and *Gymnopilus junonius* and the aqueous extract of *Pseudophaeolus baudonii* showed cytotoxic activity against A549 cells, with IC_{50} ranging between 7.4–69.2 μg/mL. Fluorescent staining confirmed cell cycle arrest and apoptosis induced by extracts. Morphological and biochemical changes included chromatin condensation, membrane blebbing, loss of cytoskeletal structure, caspase activation and phosphatidylserine translocation. This study demonstrated the antimicrobial activity of South African macrofungi and their inhibition of A549 cancer cell proliferation by means of cell cycle arrest and induction of apoptosis.

P.09-218-Tue
Association between serum homocysteine levels and swimming stress in male and female rats

L. Alic, A. Kulo, E. Kiseljakovic, S. Hasic, R. Jadric
Faculty of Medicine University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Stress exposure has been associated with impaired homocysteine metabolism and consequently increased levels of homocysteine. Hyperhomocysteinemia is associated with increased risk of developing atherosclerosis, cardiovascular diseases, Alzheimer disease and other neurodegenerative diseases. Additionally, it was shown that prolonged stress exposure is a risk factor and female gender shows protective role for development of stress-related diseases. Aim of this study was to examine gender differences in serum homocysteine level (SHL) in rats exposed to swimming stress. Adult Wistar rats were distributed into three groups: control group (n = 12; CG), repeated swimming stress (n = 12; RSS) and single swimming stress (n = 12; SSS). Each of the rat groups were further equally divided by gender (n = 6; female and male control group – FCG and MCG, female and male repeated swimming stress – FRSS and MRSS, female and male single swimming stress – FSSS and MSSS). Rats exposed to repeated swimming stress