100

Repurposing the repurposed: the evolving journey of methotrexate

Prof Arduino Mangoni, Strategic Professor of Clinical Pharmacology, Flinders University

Biography:

Arduino Mangoni is a Strategic Professor of Clinical Pharmacology at Flinders University, Senior Consultant in Clinical Pharmacology and General Medicine, and Head of the Department of Clinical Pharmacology at Flinders Medical Centre. Professor Mangoni has contributed to the development and updates of the 'Australian Hypertension Guidelines,' the 'Australian Guidelines on the Use of Ambulatory Blood Pressure Monitoring for the Management of Hypertension,' and the SIGN guidelines on the 'Management of Chronic Pain.' He has received approximately $15 million in research funding and published 454 articles and 24 book chapters in the fields of cardiovascular pathophysiology and pharmacology, geriatric pharmacology, biomarker discovery, and drug discovery/repurposing. He co-edited the books "Prescribing for Elderly Patients" and "Optimizing Pharmacotherapy in Older Adults – An Interdisciplinary Approach." He is the Editor-in-Chief of "Therapeutic Advances in Drug Safety" and Senior/Executive Editor of "Age & Ageing" and "British Journal of Clinical Pharmacology." Professor Mangoni was named a Fellow of the British Pharmacological Society in 2012 and a Fellow of the International Society of Hypertension in 2020 for his exceptional work in hypertension research and patient care. In 2019, he received an Honorary Professorship in Clinical Pharmacology from Technische Universität Dresden.

Repurposing the repurposed: the evolving journey of methotrexate

Experimental and clinical evidence continues to grow, supporting the critical role of dysregulated inflammation, immunity, and redox signalling in the pathophysiology of cardiometabolic diseases such as atherosclerosis, diabetes, and hypertension. While much research is ongoing to discover new anti-inflammatory and immunomodulatory treatments for these conditions, existing anti-rheumatic drugs may serve a similar purpose. One such drug, methotrexate, has been successfully used at high doses since the 1940s as an anticancer agent and, more recently, repurposed at lower doses as an anti-inflammatory and immunomodulating agent in patients with autoimmune diseases. Epidemiological studies over the past 20 years have also shown that low-dose methotrexate treatment is associated with a decreased risk of atherosclerotic cardiovascular disease, hypertension, and diabetes in patients with autoimmune conditions. This knowledge has prompted intervention studies investigating the effects of low-dose methotrexate on blood pressure and cardiovascular risk in patients both with and without autoimmune disorders. While methotrexate's therapeutic effects have traditionally been associated with its antiproliferative activity through modulation of folate metabolism, several additional targets have been identified more recently. These include AMP-activated protein kinase, Janus kinase/signal transducer and activator of transcription, high mobility group box 1 protein, gut microbiota, and other pharmacological effects of adenosine, a key mediator of methotrexate's anti-inflammatory actions. The available evidence suggests the potential for further repurposing of methotrexate to prevent and manage cardiometabolic diseases in specific patient groups and emphasizes the importance of pharmacogenetic factors in identifying these groups.

200

Role of Endothelial Receptors in the Hypertension Induced by VEGFR-2 Inhibitors

Prof Jeanette Woolard Isaac, University of Nottingham

Biography:

Prof Woolard Isaac leads one of the few laboratories in the world capable of monitoring complex cardiovascular responses in conscious animals. Her in vivo laboratory is internationally recognised for its unique capability to measure regional blood flow across three distinct vascular beds in conscious subjects. This expertise has enabled her to secure major external research grants and foster impactful collaborations with industry partners including AstraZeneca, Promega, Heptares, and Medicines Discovery Catapult. She has also established major international research collaborations with teams across Europe, the USA, and Australia. She is a co-applicant on a £2 million MRC programme grant and serves as Principal Investigator on a recently awarded £4.5 million Wellcome Trust four-year PhD programme in Drug Discovery and Team Science. Additionally, she is the Nottingham lead on a €3.8 million European Commission-funded Marie Skłodowska-Curie Actions ITN INSPIRE project (INnovation in Safety Pharmacology for Integrated cardiovascular safety assessment to REduce adverse events and late-stage drug attrition). Since January 2021, she has served as the Nottingham Director of the £10 million Centre of Membrane Proteins and Receptors (COMPARE), following her role as Deputy Director since the Centre's inception. In 2020, she was awarded a Fellowship by the British Pharmacological Society and received the Vice-Chancellor's Medal from the University of Nottingham in recognition of her contributions to Team Science. More recently, she was honoured with the BPS/AstraZeneca EDI Prize for her continued leadership in research culture development. Her research has led to highly cited publications in the areas of cancer and angiogenesis, with recent high-impact papers published in Cell Chemical Biology, Communications Biology, FASEB Journal, British Journal of Pharmacology, and Biochemical Pharmacology. Her work focuses on elucidating the molecular pharmacology of vascular endothelial growth factor (VEGF-A) isoforms and VEGFR2 receptors. She has contributed to the development of fluorescent ligands to study VEGFR2 (in collaboration with Promega), and has applied NanoBRET approaches to monitor GPCR target engagement in tumours in vivo (in partnership with Monash University). Her laboratory continues to explore the mechanisms underlying the hypertensive effects of receptor tyrosine kinase inhibitors, particularly those targeting VEGF pathways. In September 2024, she assumed the role of Associate Pro-Vice-Chancellor for the Research Academy and Research Culture Development. As a member of the University of Nottingham's senior strategic leadership team, she is focused on enhancing student engagement, experience, and learning. Her aim is to ensure the University remains at the forefront of research and teaching excellence, particularly at the postgraduate level. Central to this is her commitment to supporting supervisory teams, fostering an exceptional research environment, and ensuring the student voice is valued and aligned with the University's strategic priorities.

Role of Endothelial Receptors in the Hypertension Induced by VEGFR-2 Inhibitors

Vascular Endothelial Growth Factor (VEGF) is a key signalling molecule in angiogenesis. One of its three receptors, VEGFR-2, has been shown to be the dominant mediator of VEGF-A-induced cellular responses involved in the formation of new vasculature to support cancer growth [1]. Most human tumours overexpress VEGF messenger ribonucleic acid (mRNA), and many tumour cell lines have an increased expression of these receptors, emphasizing the crucial role of VEGF as a mediator in tumour angiogenesis. To inhibit angiogenesis in cancer, a number of therapeutic agents that interfere with VEGF signalling have been developed. These include small molecule receptor tyrosine kinase inhibitors (RTKIs) that target the intracellular adenosine triphosphate (ATP)-binding site of the VEGFR-2 kinase [2].

Hypertension is one of the most common complications reported in cancer patients treated with RTKIs such as axitinib, lenvatinib and sorafenib [3]. However, the mechanisms underlying these effects remain to be established. One proposed mechanism involves the endothelin-1 (ET-1) axis. ET-1 is a potent vasoconstrictor peptide, whose biological activity is mediated by its binding to two G protein-coupled receptors, ETA (endothelin receptor type A) and ETB (endothelin receptor type B), which are both expressed on vascular smooth muscle cells. We have therefore used the selective ETA antagonist, sitaxentan, and the non-selective ETA/ETB antagonist, bosentan, to investigate their effect on VEGFR-2 signalling and cardiovascular haemodynamics induced by two of the most potent VEGFR-2 inhibitors, axitinib and lenvantinib, in conscious, freely-moving rats [4]. These studies confirmed that two potent inhibitors of VEGFR-2-signalling (axitinib and lenvatinib) can induce a significant increase in mean arterial pressure that is accompanied by significant vasoconstriction within the mesenteric and hindquarters vascular beds. Data obtained with ET-1 receptor antagonists, however, show that the hypertensive response to both axitinib and lenvatinib can be prevented by selective ETA antagonism [4].

Taken together, these results indicate that treatment of patients with selective ETA antagonists might prevent the development of the drug-induced hypertension that is a common side effect of both axitinib and lenvatinib.

[1] C.J. Peach et al (2018) Molecular Pharmacology of VEGF-A Isoforms: Binding and Signalling at VEGFR2. Int J Mol Sci. 19, 1264.
[2] M. Van Daele et al (2023). Characterisation of tyrosine kinase inhibitor-receptor interactions at VEGFR2 using sunitinib-red and nanoBRET. Biochem Pharmacol. 214, 115672.
[3] J.J. Carter et al (2017). Effects of 4 multitargeted receptor tyrosine kinase inhibitors on regional hemodynamics in conscious, freely moving rats. FASEB J. 31, 1193-1203.
[4] P. Pannucci (2024) Role of endothelin ETA receptors in the hypertension induced by the VEGFR-2 kinase inhibitors axitinib and lenvatinib in conscious freely-moving rats. Biochem Pharmacol. 228:116007.

274

Body fluids and blood pressure: lost in translation

A/Prof Jens Titze, DukeNUS Medical School

Biography:

I began working on salt and water homeostasis as a medical student in 1991. At that time, the generally accepted belief was that body Na+ content is constant, and that any increase would elevate blood pressure. Measuring Na+ balance in humans preparing for long-term space missions, however, we found that rhythmically Na+ dis- and re-appeared from an at that time invisible storage site. Developing novel tools, we saw that rodents and humans store large amounts of Na+ under their skin and in skeletal muscle, and that the storage process is physiologically regulated. This new way of thinking about the body fluids quickly delivered new research avenues in immunology (immunological host defence and auto-immunity), endocrinology (insulin resistance, diabetes mellitus, and metabolic muscle function), and cardiovascular disease (hypertension research, heart failure). Today, our clinical research revolves around the fact that Na+ storage is secondary to intracellular K+ depletion, and that increasing K+ intake effectively reverses this process; with beneficial effects on blood pressure. In the basic research arena, we dream of solving a general methodological-physiological root problem in the field: our inability to visualize and quantify Na+ and K+ distribution disorders inside diseased cells at the µm scale in intact, hydrated organs.

Body fluids and blood pressure: lost in translation

The “salt equation” taught to medical doctors for more than 150 years is not difficult to understand. The body relies on this essential mineral for various functions, including blood pressure regulation and the transmission of nerve impulses. Consequently, sodium levels in the body must be carefully maintained within narrow physiological ranges. When we consume a lot of salt (sodium chloride) we become thirsty and drink water, diluting our blood to maintain the proper concentration of sodium. Ultimately, we will excrete much of the excess salt and water in the urine and reach a “steady state” of body Na+. This theory is intuitive and simple, but most likely incorrect.

We will first discuss how sodium and potassium hydrate the total body water space (first 5 min). We will then interpret experimental data showing that salt-sensitive hypertension initiates with potassium-driven dehydration of the intracellular volume space (second 5 min). We will then interpret data showing that sodium retention in (salt-sensitive) hypertension serves to re-hydrate the body water space back to normal and compare salt-sensitive with renal hypertension (third 5 min).

After half-time, we will discuss the physiological implications of interpreting salt-sensitive hypertension as a disease of potassium-driven intracellular volume shrinkage, and not as a disease of sodium-driven extracellular volume overload (fourth 5 min). We will then discuss non-invasive magnetic resonance imaging for transfer of these insights into the clinical arena (fifth 5 min).

We will finally discuss the promising success of potassium-enriched table salt supplements for disease prevention from a more mechanistic point of view (last 5 min).

275

Hormones and Hypertension; Medicine and Music

Prof Michael Stowasser, Frazer Institute, The University of Queensland, Princess Alexandra Hospital

Biography:

Michael is currently Director of the Hypertension Units and of the Endocrine Hypertension Research Centre within the University of Queensland Frazer Institute at Greenslopes and Princess Alexandra Hospitals in Brisbane. He has over 30 years clinical research experience in pathogenesis and management of hypertension and especially of endocrine varieties including primary aldosteronism, renovascular hypertension, pheochromocytoma and familial hyperkalemic hypertension. Working with mentor Richard Gordon, he helped to demonstrate that primary aldosteronism is at least 10 times more common than previously thought, and is the commonest specifically treatable and potentially curable form of hypertension. Subsequent studies have involved determining genetic bases for primary aldosteronism, examining non-blood pressure dependent effects of aldosterone excess, improving methods of detection, diagnostic workup and management of primary aldosteronism, exploring the pathogenesis and genetics of other salt sensitive forms of hypertension (including familial hyperkalemic hypertension) and investigating how dietary potassium lowers blood pressure.

Hormones and Hypertension; Medicine and Music

Michael Stowasser (MS) has 35 years clinical research experience in human hypertension (HT), and especially endocrine varieties such as primary aldosteronism (PA). Working within the Greenslopes Hospital Hypertension Unit (GHHU), he helped demonstrate that PA is 10 times more common than previously thought and to account for approximately 10% of HT, making it the commonest specifically treatable, potentially curable variety, and in the description of a new familial form (FH-II) which led to the elucidation of its genetic basis (published in Nature Genetics). The combined GHHU/Princess Alexandra Hospital HT Unit (set up by MS in 2000) has possibly the largest series (>2500) worldwide of patients with PA who have been thoroughly documented and meticulously studied, helping MS to become internationally recognized as an authority on pathogenesis/genetics, diagnostic workup and management of PA. MS served on an Endocrine Society international working group to develop the first guideline for diagnosis and management of PA in 2006 (cited >1200 times) the second in 2016 (cited >1900 times) and the third as Co-Chair from 2023-5. MS conceived, developed and validated the seated saline suppression test which has since become the favoured method for definitively confirming the diagnosis of PA. He has also made major contributions to the understanding of how various physiological and pharmacological factors affect the aldosterone/renin ratio as a screening test for PA and in optimizing approaches to adrenal venous sampling, the most reliable method of differentiating unilateral (surgically curable) from bilateral varieties. MS's other great loves are his wife of almost 30 years, Danielle, his extended family, his dogs and his passion for playing music which helped fund his undergraduate years.

300

Functional testing in autoinflammatory diseases

Prof Seth Masters, Centre for Innate Immunity and Infectious Disease, Hudson Institute of Medical Research

Biography:
Prof Seth Masters is Centre Head of the Centre for Innate Immunity and Infectious Disease at the Hudson Institute of Medical Research (Australia). He has uncovered the genetic basis for several autoinflammatory diseases and continues to manage the associated Australian Registry, AADRY. Mechanistically this work has defined the innate immune pathways driving inflammation as a result of aberrant proteasome function, retrograde transport and mitochondrial homeostasis. This has led to improved understanding of innate immune pathways in complex disorders such as inflammatory bowel disease and motor neuron disease. Prof Masters is a Scientific Advisor for NRG Therapeutics (UK) and Odyssey Therapeutics (USA) and was appointed as a Fellow of the Viertel Foundation, HHMI-Wellcome Trust and the NHMRC.

Functional testing in autoinflammatory diseases
Here I will discuss genes that we have found to be mutated in different autoinflammatory diseases, and how to determine if individual variants are pathogenic in certain cases using different functional tests.
Previously, our work focussed on the NLRP3 inflammasome, for which gene variants can cause Cryopyrin Associated Periodic Syndromes. Characterising these variants and understanding the underlying pathway provides answers for the affected families and facilitates successful anti-inflammatory therapeutic intervention. Now, we have data on the NLRP1 inflammasome variants that cause Familial Self-healing Palmoplantar Carcinoma and related inflammatory diseases.
There are several innate immune pathways which can drive the production of type I IFN production where gene variants can cause interferonopathies. I will present several recently identified gene variants that trigger elevated type I IFN. Some of these genes regulate linear ubiquitination (eg. OTULIN), mitochondrial RNA (eg. REXO2) or downstream innate immune signalling, for example with variants in UNC93B1 that regulate TLR signalling and drive childhood-onset lupus.

301

Rewriting blood pressure control through the gut microbiome: A translational odyssey

Prof Francine Marques, Monash University

Biography:

Professor Francine Marques is a Fellow of the NHMRC (Emerging Leader 2), the Viertel Charitable Foundation, and the National Heart Foundation (Future Leader 2). She earned her PhD in genomics from the University of Sydney in 2012, followed by postdoctoral training supported by prestigious fellowships from the NHMRC and the Heart Foundation. Since 2018, she has led the Hypertension Research Laboratory at Monash University, Australia, now based at the Victorian Heart Institute, where she also serves as Deputy Director (Discovery). Her research focuses on improving cardiovascular health by building exceptional researchers and exploring innovative, translational strategies to lower blood pressure through the gut microbiome. Professor Marques has secured $12 million in competitive funding and published more than 150 peer-reviewed papers. Her work has been recognised with 37 awards, including the 2019 AHA Hypertension Council Goldblatt Award, the 2021 Australian Academy of Science Gottschalk Medal, the 2024 Australian Society for Medical Research Peter Doherty Leading Light Award, the 2025 Australian Academy of Health and Medical Sciences Jian Zhou Medal, and the 2026 International Society for Heart Research Outstanding Investigator Award.

Rewriting blood pressure control through the gut microbiome: A translational odyssey

Cardiovascular disease and stroke account for 32% of all deaths globally. A key risk factor for these diseases is high blood pressure. Diet is an essential player in preventing these diseases – for example, diets high in salt are associated with higher blood pressure, while diets high in fibre are associated with lower blood pressure. Besides decades of clinical and epidemiological evidence, the mechanisms driving the association between dietary fibre and lower rates of cardiovascular disease and stroke remained unclear. Our research has pioneered the concept that dietary fibre protects against these diseases by manipulating the gut microbiota. Here, we will present key evidence from a combination of experimental and human studies of how gut microbiota-derived metabolites called short-chain fatty acids (SCFAs) facilitate gut-to-host communication that affects the immune system and results in an increase in blood pressure. These new mechanisms, primarily regulated by two classes of G-protein-coupled receptors, represent novel treatment targets for hypertension and associated diseases.

351

Hypertensive pregnancy: a truly multi-organ disorder…can the postpartum period offers a window to modulate lifetime risks of end organ damage?

Dr Jamie Kitt, Cardiology & General Internal Medicine (GIM) Consultant, Oxford & Thames Valley

Biography:

Dr Jamie Kitt is a dual accredited Cardiology & General Internal Medicine (GIM) Consultant trained in Oxford & Thames Valley, United Kingdom. He has sub-specialty training in Echo, Cardiac magnetic resonance (CMR), Cardiac CT, and Hypertension, the latter of which complements his research expertise within hypertensive pregnancy. He now works as an imaging cardiologist in London for the NHS and continues his post-doctoral research in Oxford in Hypertensive Pregnancy. He completed a PhD studying the cardiac complications of hypertensive pregnancy between 2018-2022. Under the supervision of Prof Paul Leeson, he was awarded a British Heart Foundation fellowship during which they performed a randomized trial on post-partum self-management of hypertensive pregnancy (POP-HT). This resulted in several high-impact publications in the field of hypertensive pregnancy, with the key POP-HT trial papers published in JAMA, Hypertension and Circulation to coincide with the trial's presentation at American Heart Association's late breaking Science in November 2023. He was awarded the early career research award of the British and Irish Hypertension Society in Autumn 2024 and the University of Oxford Graduate Prize Award in March 2025 for this body of work. The vascular paper is pending publication in Hypertension and the brain and renal outcomes from are under peer review. Prof Leeson and Dr Kitt are now collaborating in a multi-center PCORI funded trial of postpartum BP self-management in the USA, the multi-center validation of POP-HT in the UK (SNAP2), and help run dedicated postpartum hypertension clinics in Oxford and London. Dr Kitt looks forward to sharing this body of work at the Australian Hypertension society in late 2025 and working with Prof Larry Chamley to adapt the principles developed in POP-HT to the New Zealand model of postpartum care during a visiting lectureship in December 2025.

Hypertensive pregnancy: a truly multi-organ disorder…can the postpartum period offers a window to modulate lifetime risks of end organ damage?

Introduction. The Post-Partum Hypertension Trial (POP-HT1) demonstrated that improved blood pressure control in the pueperium, following hypertensive pregnancy, results in persistently lower blood pressure2, beneficial cardiovascular and cerebrovascular remodelling2-5 volumes ~9 months later.

Methods. POP-HT was a prospective, randomized, blinded outcome trial run in a single UK centre between March 2020 and December 2022.1 Participants were randomized to either remote telemonitored blood pressure self-management to keep BP <140/90 vs standard NHS care post-partum. Detailed multi-organ phenotyping was performed including; echocardiography at baseline and ~9-months; cardiovascular magnetic resonance at ~9 months, aortic stiffness at baseline and ~9-months (Vicorder® oscillometric device6-8 & aortic distensibility at ~9-months using MRI. Brain and renal volumes were also assessed at 9 months using MRI (3T Siemens PRISMA®).

Results. There were no significant baseline differences in demographic, medical or anthropometric measures or in the baseline organ phenotyping measures described above . By ~9-months postpartum systolic and diastolic blood pressure were ~ 6mmHg lower (diastolic between-group difference was -5.80 mm Hg (95% CI, -7.40 to -4.20; P < .001) and systolic was -6.51 mm Hg (95% CI, -8.80 to -4.22; P < .001). There was also beneficial cardiac, vascular, and brain remodelling3-5. Renal structure wasn't influenced by blood pressure

Conclusions. Short-term postnatal optimisation of blood pressure control after hypertensive pregnancy, through self-monitoring and physician-guided antihypertensive titration, associates with long-term changes in blood pressure, and beneficial changes in cardiovascular & cerebrovascular structure and function, in patterns associated with more favourable long-term outcomes9-10.

Disclosures:
Dr Jamie Kitt was funded by a BHF CRT-F during the POP-HT trial.

352

From Organ Baths to Omics: Unravelling Endothelial, Oxidative and Immune Mechanisms in Cardiovascular Disease

Prof Grant Drummond, La Trobe University

Biography:

Professor Grant Drummond is a pharmacologist and vascular biologist with over 30 years of experience in research and tertiary education. He holds senior leadership positions at La Trobe University including Co-Director of the Centre for Cardiovascular Biology and Disease Research and Associate Dean (Research Partnerships) for the School of Agriculture Biomedicine and Environment. Grant Drummond's research is focussed on understanding the roles of oxidative stress and the immune system in hypertension and its downstream complications including kidney disease, heart failure and atherosclerosis. His work has shown that hypertension is associated with activation of T cells, B cells and macrophages. These immune cells then accumulate in key blood pressure-regulating organs such as the blood vessels, kidneys, heart and brain, where they promote inflammation and tissue damage via the release of pro-inflammatory cytokines (e.g. interleukin 18, interferon-g) and autoantibodies. The long term goals of Grant Drummond's research are to develop novel therapies that alleviate hypertension and end organ damage by dampening inflammation. Grant Drummond has over 180 publications and his work has received more than 17,500 citations. His work has been continuously supported by the NHMRC and Heart Foundation of Australia for >20 years. He is a Fellow of the American Heart Association, and Associate Editor for the British Journal of Pharmacology, Cardiovascular Research and Pharmacology and Therapeutics.

From Organ Baths to Omics: Unravelling Endothelial, Oxidative and Immune Mechanisms in Cardiovascular Disease

It is a privilege to deliver the Rand Medal Lecture and to reflect on a career shaped by curiosity, collaboration, and the generosity of mentors.

My journey in pharmacology began over 30 years ago when Prof Tom Cocks, University of Melbourne, took a chance on a zoology graduate, first as a research assistant and later as a PhD student investigating endothelium-dependent vasodilator mechanisms in mammalian coronary arteries. This work helped define the roles of bradykinin receptors and the elusive endothelium-derived hyperpolarising factor (EDHF), revealing its interplay with nitric oxide and prostacyclin in vascular relaxation.

Postdoctoral training with Prof David Harrison at Emory University opened the door to molecular biology and the redox-sensitive pathways regulating endothelial nitric oxide synthase (eNOS). These studies highlighted how reactive oxygen species influence eNOS activity and vascular tone. Exposure to the pioneering work of Prof Kathy Griendling (Emory University) on NADPH oxidases (Noxes) inspired a new research direction. A conversation with Prof Greg Dusting at an American Heart Association meeting led to a program at the Howard Florey Institute exploring Noxes in atherogenesis. Using animal models, we demonstrated that Nox2 drives endothelial dysfunction and plaque formation, and that genetic or pharmacological targeting of Nox enzymes limits disease progression – work that seeded a start-up company, Radical Biotechnology.

With support from mentors including Profs Roger Summers and Michael Berndt, I established an independent team at Monash University, later moving to La Trobe University. Collaborating with Prof Chris Sobey, we integrated immunology

into vascular research, uncovering roles for B cells in hypertension, M2-like macrophages in vascular remodelling, and NLRP3 inflammasome activation in renal injury. These discoveries were made possible by a remarkable team of students and postdocs – over 100 in total – whose creativity and dedication have been the cornerstone of our success.

In this lecture, I will revisit these milestones and share recent work using omics and single-cell technologies to explore interactions between the gut microbiome, immune system, and cardiovascular health. Looking ahead, the challenge is to translate these insights into precision therapies that prevent and treat vascular disease – a goal that will demand the same spirit of collaboration and innovation that has defined my career so far.

429

It's what they do that counts: activity-based assays as a new approach in clinical and forensic toxicology

A/Prof Christoph Stove, Ghent University

Biography:
Christophe Stove is associate-professor at Ghent University, Belgium, where he heads the Laboratory of Toxicology at the Faculty of Pharmaceutical Sciences. Besides teaching several courses and being in charge of forensic toxicology service activities, he is an active researcher. Tow research lines can be distinguished: microsampling applications and associated challenges in the context of therapeutic drug monitoring and toxicology, and the pharmacological characterization and screening of new psychoactive substances. He was the promotor of over 20 PhDs and has published almost 300 peer-reviewed publications, which collectively have been cited over 10000 times (Google Scholar). He is currently Board/Council Member of 2 national (BLT, KBGGG) and 2 international (TIAFT and IATDMCT) associations.

It's what they do that counts: activity-based assays as a new approach in clinical and forensic toxicology
New psychoactive substances (NPS) are compounds designed to mimic the effects of traditional drugs while circumventing legal restrictions. These substances pose significant challenges for public health and forensic toxicology. Their structural diversity and high potency often result in unpredictable pharmacological profiles. Receptor-based and transporter-based in vitro assays can help elucidate the mechanisms underlying their effects. This presentation will highlight the application of activity-based detection and characterization strategies to identify and assess these compounds beyond conventional chemical analysis. Using split-nanoluciferase-based functional complementation assays developed at the Laboratory of Toxicology at Ghent University, a wide range of NPS has been pharmacologically characterized, including synthetic opioids, synthetic and semisynthetic cannabinoids, psychedelics, and cathinones. These assays provide insight into structure–activity relationships and allow identification of substances of particular concern—such as highly active compounds or those with profiles suggestive of high abuse potential. This information supports prioritization of legislative measures and harm reduction efforts. Moreover, the assays established for synthetic opioids and cannabinoids can also serve as universal tools to screen seized materials and biological samples for opioid or cannabinoid activity, enabling detection of all past, current, and future opioids and cannabinoids. When applied to drug preparations, these assays improve the interpretation of the intrinsic activity contained within that drug preparation (also in case of mixtures) and the associated risk. When applied to biological samples, they enhance understanding of concentrations and effects elicited by entirely new substances. Overall, the work presented underscores the importance of mechanistic insights for risk assessment and harm reduction strategies in an ever-changing drug landscape.