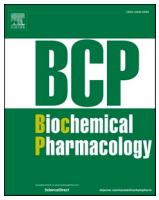
Biochemical Pharmacology 228 (2024) 116510

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm



Editorial

An introduction to the special issue "Sam Enna legacy of excellence"

When S.J. (Sam) Enna agreed to serve as Editor-in-Chief of *Biochemical Pharmacology* (BCP) in 2003, he already had a very clear vision of what must be done to help the journal increase its impact factor rating and world-wide recognition among pharmacologists. At that time, Sam identified the priority tasks were to rapidly implement (i) a substantially decreased turnaround time between manuscript submission and publication, (ii) recruitment of highly respected biochemists and pharmacologists to the Editorial Advisory Board (EAB) to serve as both peer-reviewers and contributors to the journal with high quality manuscripts and (iii) strict selection of only the top tier of submitted manuscripts to be evaluated by peer-reviewers. After a few years as Editor-in-Chief, these procedural modifications, and other new policies he introduced, made *BCP* one of the best rated journals in the field of pharmacology. In subsequent years, the journal continues to attract an ever-increasing number of submissions.

Sam's exceptional standard of quality influenced nearly every aspect of the journal's editorial operations. Therefore, we honor his memory by publishing a collection of articles reflecting his attention to detail, insatiable curiosity, and perpetual pursuit to understand the mechanisms of action of drugs with the aim to develop new and improved therapeutics.

Mike Williams beautifully summarized Sam's distinguished career [1], highlighting his extensive research activities in the field of γ-aminobutyric acid (GABA) pharmacology, his devotion to teaching, and leadership as Editor-in-Chief of three major pharmacology journals. Mike also detailed the important role Sam played in several pharmacological societies where, among many other initiatives, he protected and supported integrity in pharmacological research. The importance of this aspect is illustrated by Michael F. Jarvis [2], who explained the critical roles of pharmacology societies and pharmacology journals in implementing best practices to enhance experimental rigor in pharmacological research.

Among other initiatives as *BCP* Editor-in-Chief, Sam expanded the variety of sections in the journal, to better promote research in antivirals, antibiotics and chemotherapy. These additions quickly became some of the most popular areas of interest for the journal, garnering the highest proportion of submissions and EAB members. First headed by Jacques Piette, the accelerated rate of antiviral, antibiotic and chemotherapy submissions now require a team of editors, Giampietro Viola, Roberta Alfieri and Li-Juan Deng, to handle the volume.

An EAB member long associated with the growth of antivirals submissions in *BCP* is Erick DeClercq, who summarized more than 60 years of advancement in the field of antiviral drugs and emphasized the importance of his collaborators in the development of selective therapies for viral infections [3]. Erik also overviewed the success of several acyclic nucleoside phosphonates for the treatment or prophylaxis of DNA virus infection [4]. Irfan Rahman and his collaborators collated the emerging roles of senolytics/senomorphic drugs in HIV-related comorbidities [5] while Stefano Fiorucci and his group reviewed the promising potential of steroids, such as bile acids, in modulating SARS-CoV2 and host interactions [6].

The anti-cancer submissions have also been instrumental in the success of *BCP*. Giuliana Cassinelli and her colleagues described in this tribute that the discovery of non-oncogenic addiction uncovered novel opportunities for cancer therapy [7]. Non-oncogene addiction refers to genes/pathways not oncogenic, per se, but essential for the tumor cell growth or survival. Understanding the signaling pathways involved in cancer progression has been shown to be essential for the discovery of new drug targets. Valerie O'Brien and Val Watts summarized the involvement of the adenyl cyclase superfamily in cancer progression and how this family of glycoproteins contributes to cancer cell proliferation [8]. Cancer cells frequently adapt metabolic rewiring to support sufficient biomass production to sustain tumor cell survival. Parames Sil and his group explained how cancer cells reprogram the urea cycle to cut down unnecessary catabolic reactions and nitrogen elimination [9]. Venetoclax in combination with azacytidine is a promising treatment for relapsed/refractory patients with acute myeloid leukemia (AML). The group of Yubin Ge [10] showed that panobinostat, a histone deacetylase inhibitor, restores AML cells sensitivity to azacytidine and venetoclax by down-regulating c-Myc and Bcl-xl and up-regulating Bim.

Decades of research on phytochemicals demonstrated their importance not only in cancer therapy, but also in cancer chemoprevention, which Gian Luigi Russo and his group addressed [11]. The potential of the anti-tumor effects of Timosaponin AIII across diverse cancer progression has been detailed by Qi Qi and his associates [12]. The development of multidrug resistance to chemotherapy remains an important challenge in cancer treatment. Yixuan Li, et al. [13] revealed that Marein, a novel natural product, is capable of restoring chemosensitivity in cancer cells through a competitive inhibition of the ATP-binding cassette transporter 2. Berberine and emodin are two rather well studied natural compounds where Ajay Goel and his laboratory have investigated their synergic effects in pancreatic cancer treatment via the targeting of the EGFR signaling pathway [14].

Sam's expertise in neuropharmacology was recognized world-wide so this area of the journal increased in importance tremendously under his leadership. The Neuropharmacology section is now directed by Kenneth E. McCarson, who was a long-time colleague and collaborator with Sam. The incidence of neurodegenerative diseases has ballooned during the last 20 years. Ted M. Dawson and his group discussed the role of Parthanatos in neuroinflammation, a common denominator

https://doi.org/10.1016/j.bcp.2024.116510

Available online 30 August 2024

for many neurogenerative diseases [15]. Parthanatos is a cell death signaling pathway that emerged as a target for pharmacological intervention in these devastating pathologies. Among neurodegenerative diseases, priority has been given to Alzheimer's disease research, for which Stevin H. Zorn and his colleagues reviewed an important characteristic, the dysregulation of the innate immune system at the onset of its pathogenesis [16].

Schizophrenia is also on the rise. The dopamine hypothesis has dominated the understanding of the pathophysiology of schizophrenia. Joseph T. Coyle summarized the results of a mouse model in which one of the genes associated with a higher risk of schizophrenia has been inactivated [17]. Anthony A. Grace and his team explored the excitatory-inhibitory balance as a target for the development of novel pharmaceutical compounds to treat schizophrenia [18]. Post-traumatic stress disorder is an anxiety disorder triggered by traumatic stressors. Jun-Xu Li and his collaborators discussed the possible role of activating the trace amine-associated receptor 1 to ameliorate the symptoms of post-traumatic stress disorder [19].

Identifying new and effective agents to treat acute and chronic pain is an important goal for many pharmaceutical companies. James E. Barrett and Andrew R. Kohut showcased recent advances towards understanding the relationships between the underlying mechanisms of chronic pain, associated comorbidities and cardiovascular disease [20]. Pain is also the most burdensome symptom of osteoarthritis, which significantly lowers patients' quality of life due to induced comorbid anxiety and depression. Stefania Ceruti and her co-workers examined the role played by neuroinflammation in the development of pain in osteoarthritis [21].

Disruption of the blood–brain barrier during ischemic stroke is a leading cause of death. Thomas P. Davis and his co-authors evaluated the role of oxidative stress in this barrier disruption and the possible role played by antioxidants to treat and help patients who have suffered a stroke [22]. Spinal cord injury afflicts millions of individuals globally with few therapies available for patients. Jeffrey M. Witkin, et al. reviewed the critical role played by AMPA receptors in the biological consequences associated with spinal cord injury then discussed the importance of new studies on AMPA receptors as novel gateways for patients affected by spinal cord injury [23].

Dopamine plays a critical role in regulating movement but no naturally occurring dopamine receptor mutation causing movement disorder has been recently identified until the identification of changes of a residue located at the cytoplasmic face of the transmembrane helix 5. Kim A. Neve and his collaborators compared the function of two new variants and identified a possible mechanism for their pathogenicity [24].

Sam made seminal discoveries related to GABA neuropharmacology. In this special issue of *BCP*, several papers are dedicated to the biochemistry and pharmacology of G protein-coupled receptors (GPCRs), typically considered the largest family of druggable target in the human genome. Xenia Gonda and her associates reviewed the emergence of anti-depressant drugs targeting GABA-A receptors [25] and Bernhard Bettler and his group presented data demonstrating that the pre-assembly of specific Gβγ subunits of GABA-B receptors through auxiliary KCTD proteins accelerates K+channel activation [26]. Histamine H_3 receptor, another GPCR, is a neurotransmitter receptor primarily found in the brain where it controls the release and synthesis of histamine. Sabrina N. Rahman, et al. indicated that a ligand-directed biased agonism at H3R isoforms occurs across $G\alpha_{i/0}$- and β-arrestin 2 mediated pathways [27].

GPCRs transduce their signal via interactions with both heterotrimeric G proteins, arrestins, and other scaffolding proteins and kinases. Bryan L. Roth and Brian E. Krumm summarized molecular glues as useful small molecules modulators of GPCR function and their therapeutic potential [28]. Ya-Xiong Tao and his co-workers identified two peptide antagonists derived from the endogenous agonist α-melanocyte stimulating hormone as biased ligands for the melanocortin-4 receptor, another GPCR [29].

Recent evidence suggests a possible role of the tryptophan metabolite, kynurenic acid, in stress-related illness. Robert Schwarcz's group showed that adrenalectomy can exacerbate stress-induced impairment in fear discrimination and suggested a causal role for kynurenic acid [30].

Biochemical Pharmacology Editorial Board Meeting in Boston (USA) in 2018. From left to right: Raouf Khalil, Giampetro Viola, Jacques Piette, Jenn McNichols, Oberdan Leo, Lynn LeCount and Sam Enna

The second highest portion of submissions to BCP fall into the categories of inflammation, immunopharmacology, and gastrointestinal pharmacology, which are under the leadership of Oberdan Leo. Inflammation is a fundamental response of the host immune system, which plays a dual role in health and disease by acting as a protector but also as a potential initiator of pathologies. For example, a systemic low-grade inflammation characterized by increased concentration of pro-inflammatory cytokines is observed in the pathogenesis of metabolic disorders such as abdominal obesity. Chloé Wilkin, et al. described the

nature and function of metabolic factors influencing the biology of invariant Natural Killer T cells (iNKT) in obesity [31]. Young-Joon Surh and his cohort summarized the latest findings highlighting the dual functions of *cyclo*-oxygenase 2, a key enzyme in inflammatory signaling, in the development, maintenance and progression of cancer [32]. The group of Uday Bandyopadhyay reviewed the merits and demerits of non-steroidal anti-inflammatory drugs that, apart from inhibiting *cyclo*-oxygenases, they could improve mitochondrial health [33].

Osteoarthritis is a degenerative joint condition caused by chronic inflammation. Maria-José Alcaraz described the recent increase in interest about the immunomodulatory and regenerative properties of mesenchymal/stromal cells (MSCs). New therapeutic avenues, based on the use of extracellular vesicles derived from MSCs that may regulate chondrocyte functions and avoid cartilage destruction, appear to be possible [34].

Molecular characterization of pathways mediating NF-κB signaling and pro-inflammatory gene expression is central for the understanding of how inflammatory signals are sensed by cells and translated into protein expression. Caspase recruitment domain-containing protein 14 (CARD14) is an intracellular protein that mediates nuclear factor-kappa B (NF-κB) signaling and proinflammatory gene expression in skin keratinocytes. Several hyperactivating CARD14 mutations have been associated with psoriasis and other inflammatory skin diseases. Rudi Beyaert and his collaborators discovered that Polo-like kinase 1 (PLK1) is a novel CARD14 binding protein and indicated a possible negative regulatory role for PLK1 in CARD14 signaling [35].

Toxicology has historically been an important section of BCP and is currently under the leadership of Li-Juan Deng. Glutathione possesses two key structural features that allow it to act as an antioxidant and an anti-electrophile. Lawerence Lash reviewed the tripeptide glutathione (GSH) for its capacity to play dual roles in kidney: as an antioxidant protector and a bioactivation promoter [36]. Cytochrome P450 and flavin-containing monooxygenases are known to influence drug metabolism. Hiroshi Yamazaki and his co-authors outlined a variety of these important enzymes in animals used as preclinical models [37] and identified that cytochrome P450 2C18 effectively oxidizes 2C9/2C19 chiral substrates, such as warfarin and omeprazole with less stereoselectivity [38]. Nina Isoherranen and her collaborators reported that three cytochrome P450s (2C9, 3A and 2C19) metabolize Δ9-tetrahydrocannabinol to multiple metabolites and this reaction is affected by the human liver fatty acid binding protein [39]. Harmut Jaeschke's group detailed the clinically relevant therapeutic approaches against acetaminophen hepatotoxicity and acute liver failure [40] then Maxwell A. Gyamfi and his colleagues showed data indicating hepatotoxicity caused by ethanol in female mice targets the pregnane X receptor [41]. The central role played by the liver in drug disposition was reviewed by Jose J.G. Marin, et al. [42].

Linda Dwoskin's team demonstrated that JPC-141, an inhibitor of the vesicular monoamine transporter-2 prevents methamphetamine-induced dopamine toxicity and blocks methamphetamine self-administration in rats [43]. Jaime Arellanes-Robledo and his group showed a model of alcoholic liver disease based on the use of different hepatotoxics leading to liver cancer [44].

Venom has emerged as valuable source of potent modulators of acid-sensing ion channels. Lachlan D. Rash and his co-authors described a peptide derived from funnel-web spider venom that modulates the acid-sensing ion channel 1a desensitization [45]. Claudia Martini and her fellow researchers extensively reviewed the development of new in silico methods to study drug mechanisms of action and toxicities [46].

The section on endocrinology and metabolic disorders is headed by Aneta Balcerczyk and has always been quite successful. James P. Hardwick and his collaborators evaluated involvement of the fatty acid hydroxylase (CYP 4 family) in the progression of metabolic dysfunction associated with steatotic liver diseases [47] and Ann K. Daly's group explored pharmacogene expression during the progression of the same pathology [48]. The mechanisms behind the physiological effects of ketone accumulation in alcoholic liver disease is still poorly understood. Dianke Yu and his colleagues explained that lysine β-hydroxylation was induced by ketone accumulation in mice [49].

Polyphenols are known to have effects on glucose and body weight homeostasis. Marta Trius-Soler and Juan José Moreno reviewed the key role of bitter taste receptors to understand the effects of polyphenols [50]. W.S. Fred Wong and his associates explored the opportunities for reprogramming the metabolism as a therapeutic approach for respiratory diseases [51]. On a similar idea, the group of Roberta Alfieri demonstrated that targeting the metabolic adaptative responses induced by glucose starvation can inhibit the proliferation of osimertinib-resistant non-small cell lung cancer cell lines [52].

The cardiovascular, pulmonary, and kidney diseases sections are headed by Raouf Khalil and receive a rather high number of submissions. In this tribute, Bernardo J. Krause and co-authors summarized the pharmacological and molecular mechanisms of miRNA-based therapies for targeting cardiovascular dysfunction [53]. Darryl Zeldin and his colleagues introduced that the over-expression of the soluble epoxide hydroxylase can reduce the post-ischemic recovery of cardiac contractile function [54]. Raouf Khalil and his collaborators used a rat model of pre-eclampsia to generate data suggesting that uterine arterial remodeling by metalloprotease-1 and −7 would further reduce uterine blood flow and exacerbate uro-placental ischemia [55].

Stephen J. Hill and his team explored the role of endothelin ET-A receptors in hypertension induced in rats treated by VEGFR-2 kinase inhibitors [56]. Janette K. Burgess and Reinoud Gosens expounded the mechano-transduction and the role of the extracellular matrix in lung pathologies and in drug responsiveness [57].

Throughout his career, and especially during his two decades at the helm of BCP, Sam worked steadily towards publishing reproducible, mechanism based, thought fully designed pharmacology research to advance therapeutics to improve the quality of human health. It is our hope that this collection of articles, written by the colleagues Sam recruited to help build BCP to its current reputation, demonstrates his commitment to excellence and his legacy of success.

Acknowledgements

The authors wish to acknowledge the great and continuous support received from the Elsevier publishers during the past 20 years, thanking, in particular, Joke Jaarsma, Jaap Van Haarten, Anne-Marie Pordon and Katie Hammon. Jennifer McNichols also deserves recognition for a decade of hard work, common sense, and keeping Sam supplied with his favorite pens. We are thankful to the present and the past editors of the journal for their hard work and team spirit. We want also to thank Fer Mesman and Sajitha Sridhar for their help and daily attention to the submitted manuscripts.

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