

Obituary: Prof. Yun Zhang (1963–2023) – A scientist focused on toxins and their underlying mechanisms to decipher human diseases

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Prof. Yun Zhang was born on 9 July 1963 in Kunming, Yunnan, China, during a tumultuous period which he often referenced. Throughout his life, he harbored a steadfast belief in using knowledge to unravel the mysteries of human diseases. His educational journey was marked by frequent changes in schools due to his parents' occupational relocations. However, despite these challenges, he consistently displayed diligence and was admitted to the East China University of Science and Technology, Shanghai, after completing high school in 1980. He remained an active and loyal member of the School of Biotechnology at the university. Upon completing his bachelor's degree in 1984, Yun Zhang began his master's studies in biochemistry, focusing on snake toxin research, at the Kunming Institute of Zoology, Chinese Academy of Sciences (CAS) under the supervision of Prof. Yu-Liang Xiong in 1987. He later progressed to a dual doctoral program in science at the Kunming Institute of Zoology and Pasteur Institute at Paris, mentored by both Prof. Li-Ming Shi and Dr. Cassian Bon. Yun Zhang obtained his PhD in September 1992, followed by a tenure at the Pasteur Institute from December 1993 to September 1995. Subsequently, he conducted postdoctoral research at the Pasteur Institute at unite de venom, under the direction of Dr. Cassian Bon. In February 1998, Dr. Yun Zhang joined the Kunming Institute of Zoology, CAS, as a researcher, a role that proved pivotal in his career. He dedicated himself to the study of venoms, with a particular focus on snake venom and active proteins from the amphibian species *Bombina maxima*. His PhD thesis, which primarily involved the isolation, characterization, and expression of a plasminogen activator termed TSV-PA — the first plasminogen activator isolated from snake venom (Zhang et al., 1995) — earned the Special Award of the Chinese Academy of Sciences Dean's Reward. Later, the crystal structure of the first snake venom serine protease, represented by TSV-PA, was successfully elucidated (Parry et al., 1998) and Dr. Yun Zhang identified that the unique Phe 193 feature in TSV-PA is crucial for its high substrate specificity, rendering it incapable of forming stable complexes

with bovine pancreatic trypsin inhibitors and other extended substrates and inhibitors (Zhang et al., 1997). The study of TSV-PA significantly advanced our understanding of the structure-function relationships of human plasminogen activators, specifically tissue-type (tPA) and urokinase-type (uPA), and provided an excellent template for modeling other homologous family members. Dr. Yun Zhang and his research team also discovered a host-derived, pore-forming toxin-like protein and trefoil factor complex, termed $\beta\gamma$ -CAT (Gao et al., 2011; Liu et al., 2008), which plays a crucial role in protecting hosts against microbial infection (Xiang et al., 2014) and tissue injury (Gao et al., 2019), mediated via activation of inflammasomes. Subsequent research indicated that $\beta\gamma$ -CAT also neutralizes the acidification of endocytic organelles to counter intracellular pathogen invasion (Li et al., 2017), acts directly on the herpes simplex virus type 1 (HSV-1) envelope to form a channel in the viral membrane to block infection (Liu et al., 2021), and augments antigen presentation by modulating cellular endolysosomes (Deng et al., 2020). Their original discovery helped clarify the potential involvement and mechanisms of aerolysin-like proteins and/or trefoil factors, widely present in vertebrates, in defending hosts against pathogens. Additionally, Dr. Yun Zhang and his research team elucidated the role of $\beta\gamma$ -CAT in stress response and nutrient acquisition (Shi et al., 2022), with the complex shown to drive the host to scavenge extracellular proteins for nutrient supply and survival (Liu et al., 2023) and to acquire and maintain water via macropinocytosis induction and exocytosis modulation (Zhao et al., 2022). He also led the team in systematically exploring the mechanistic actions of $\beta\gamma$ -CAT, including identification of its receptors and regulatory mechanisms (Bian et al., 2023; Guo et al., 2019; Wang et al., 2020). As a consequence of his important contributions to the field, Prof. Yun Zhang served as the director of the Academic Committee of the Kunming Institute of Zoology; deputy

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director of the Academic Committee of the Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences; council member of the Asia-Pacific region of the International Society on Toxinology; executive director of the Chinese Society of Toxicology; director of the Bio-toxins Professional Committee; editorial board member of the international journal *Toxicon*, associate editor of the international journal *Zoological Research (ZR)*; and a drug evaluation expert for the National Medical Products Administration.

Throughout his life, Prof. Yun Zhang exemplified dedication, meticulousness, innovation, and a quest for truth in his scholarly endeavors. He consistently engaged in cutting-edge scientific research, focusing on the molecular biodiversity, structure, and function of animal toxin proteins and peptides, and significantly advanced our understanding of biological adaptation mechanisms, functional genomic evolutionary characteristics, and their molecular mechanisms. His contributions were pivotal in enhancing the scientific research capabilities of the institute. Prof. Yun Zhang dedicated his life to cultivating virtue and nurturing talent. He was a mentor and guide, fostering the younger generation and selflessly dedicating himself to the training of over 70 outstanding graduate students. His loyalty to the party and unwavering commitment to his profession were evident throughout his career. Even during his illness and treatment, he remained concerned about the development of the institute, continued to mentor his students, and stayed true to his original aspirations, striving forward until his final moments.

Scientific journals play a crucial role in disseminating knowledge, facilitating scientific exploration, and nurturing talent (Yao & Zhang, 2022). Owing to his exceptional academic expertise and great enthusiasm, Prof. Yun Zhang made enduring and generous contributions to the evolution of *ZR*. He served as an editorial board member from 1998–2014 and as an associate editor-in-chief from 2014 until his final days. Despite facing serious health challenges, he continued to fulfill his duties with utmost dedication. His significant contributions to enhancing the influence of *ZR* encompassed developing journal policies, offering insightful feedback for manuscript revisions, and authoring influential articles for *ZR*, among other pivotal roles. His notable publications in *ZR* include, but are not limited to, the following: (1) Comprehensive review papers summarizing current knowledge on venoms and their biological implications (Zhang, 2015) and on animal secretory endolysosome channel discovery (Zhang et al., 2021), with both featuring as highly cited papers in *ZR*. (2) Together with his colleagues, he found that amphibian pore-forming protein β -CAT drives metabolite release from small extracellular vesicles through channel formation (Wang et al., 2023), characterized protein composition of extracellular vesicles from skin secretions of the amphibian *Bombina maxima* (Wei et al., 2022), and performed a comparative analysis of diverse toxins from a new pharmaceutical centipede, *Scolopendra mojiangica* (Liu et al., 2020); (3) He also identified king cobra peptide OH-CATH30 as a potential candidate drug through clinical drug-resistant isolates (Zhao et al., 2018). Prof. Yun Zhang's positive and far-reaching impact on *ZR* will always be remembered and valued.

Despite his passing, the legacy of his spirit and demeanor persists. His relentless pursuit of truth, rigorous academic approach, dedication to selfless research, and commitment to



nurturing and supporting future generations remain enduringly worthy of our emulation and remembrance. Prof. Yun Zhang will forever reside in our hearts.

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