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Speaker information

General Information

Name	Kunal Nepali	
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Education Background	PhD	
Professional Appointment	Associate Professor	
Research Interest	Drug discovery, drug design, medicinal chemistry, epigenetic targeting agents, DNA damage repair pathway inhibitors	
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Recent Publications

*** represents corresponding author**

1. Amandeep Thakur, Yi-Hsuan Chu, Vijayakameswara Rao, Jacob Mathew, Ajmer Singh Grewal, Prabhita Prabakaran, Santosh Guru, Jing Ping Liou, Chun-Hsu Pan, Kunal Nepali. Leveraging a rationally designed veliparib-based anilide eliciting anti-leukemic effects for the design of pH-responsive polymer nanoformulation. Eur. J Med. Chem. 2024, 273, 116507. (**Corresponding author, IF – 6.7).**
2. Amandeep Thakur, Mandeep Rana, Anshul Mishra, Charanjit Kaur, Chun-Hsu Pan, Kunal Nepali. Recent Advances and Future Directions on Small Molecule VEGFR Inhibitors in Oncological Conditions. Eur. J Med. Chem. 2024, 272, 116472. (**Corresponding author, IF – 6.7).**
3. Sachin Sharma, Kavya Chandra, Aliva Naik, Anamika Sharma, Ram Sharma, Amandeep Thakur, Ajmer Singh Grewal, Ashwani K Dhingra, Arnab Banerjee, Jing Ping Liou, Santosh Kumar Guru, **Kunal Nepali***. Flavone-based dual PARP-Tubulin inhibitor manifesting efficacy against endometrial cancer. J Enz. Inhib. Med. Chem. **2023**,38(1),2276665. (**Corresponding author, IF - 5.6).**

4. Mandeep Rana, Amandeep Thakur, Charanjit Kaur, Chun-Hsu Pan, Sung-Bau Lee, Jing Ping Liou, **Kunal Nepali***. Prudent tactics to sail the boat of PARP inhibitors as therapeutics for diverse malignancies. Expert Opin Drug Discov. **2023**, 18(10),1169-1193. (**Corresponding author, IF - 6.3).**
5. Sachin Sharma, Shao-An Wang, Wen-Bin Yang, Hong-Yi Lin, Mei-Jung Lai, Hsien-Chung Chen, Tzu-Yuan Kao, Feng-Lin Hsu, **Kunal Nepali***, Tsung-I Hsu*, Jing-Ping Liou*. First-in-Class Dual EZH2-HSP90 Inhibitor Eliciting Striking Antiglioblastoma Activity *In Vitro* and *In Vivo*. J. Med. Chem. 2024, 67, 4, 2963–2985. (**Corresponding author**, IF – 7.3)
6. Ram Sharma, Esha Chatterjee, Jacob Mathew, Sachin Sharma, N Vijayakameswara Rao, Chun-Hsu Pan, Sung-Bau Lee, Ashwani Dhingra, Ajmer S Grewal, Jing Ping Liou, Santosh K Guru, **Kunal Nepali***. Accommodation of ring C expanded deoxyvasicinone in the HDAC inhibitory pharmacophore culminates into a tractable anti-lung cancer agent and pH-responsive nanocarrier. Eur. J. Med. Chem. **2022**, 240, 114602 **(Corresponding author, IF - 6.7).**
7. **Kunal Nepali**, An-Chih Wu, Wei-Lun Lo, Bhawna Chopra, Mei-Jung Lai, Jian-Ying Chuang, Jing-Ping Liou. Rationally Designed Donepezil-based hydroxamates Modulate Sig-1R and HDAC isoforms to exert Anti-Glioblastoma effects. Eur. J. Med. Chem. **2023,** 248**,** 115054 **(First author, IF - 6.7).**
8. **Kunal Nepali**, Ram Sharma, Sachin Sharma, Amandeep Thakur, Jing-Ping Liou. Beyond the vaccines: A glance at the small molecule and peptide-based Anti-COVID19 arsenal. J. Biomed. Sci. **2022,** 29, 65 **(First author, IF: 11).**
9. Tung-Yun Wu, Michael Chen, I-Chung Chen, Yi-Jou Chen, Che-Yi Chen, Chang-Hung Wang, Jing-Jy Cheng, **Kunal Nepali***, Kuo-Hsiang Chuang, Jing-Ping Liou. Rational design of synthetically tractable HDAC6/HSP90 dual inhibitors to destroy immune-suppressive tumor microenvironment. J. Adv. Res. **2023**, 46, 159-171. **(Corresponding author, IF – 10.7).**
10. Amandeep Thakur, Chetna Faujdar, Ram Sharma, Sachin Sharma, Basant Malik, **Kunal Nepali***, Jing Ping Liou. Glioblastoma: Current Status, Emerging Targets, and Recent Advances. J. Med. Chem. **2022**, 65, 13, 8596–8685 (**Joint corresponding author**, **IF: 7.3).**

Speaker information

Speech Topic and Abstract

Title:

A drug discovery campaign to expand the application horizons of PARP inhibitors as cancer therapeutics

Abstract:

Poly (ADP-ribose) polymerases (PARPs) catalyze the transfer of ADP-ribose residues from nicotinamide adenine dinucleotide (NAD) onto target substrates (PARylation). Amongst the various members of the PARP family, PARP1 and PARP2 are major enzymes that regulate the DNA damage response in cancer [1]. PARP inhibitors block DNA repair, causing single-strand breaks to progress into double-strand breaks [2]. This effect is particularly lethal to cells with defective homologous recombination (HR), such as those with BRCA mutations, due to their inability to efficiently repair these breaks. Thus, the clinical use of PARP inhibitors is limited to cancers with BRCA1/2 mutations [3]. Literature precedents reveal that HDAC inhibition induces BRCAness in cancer cells and can broaden the therapeutic scope of PARP inhibitors [4]. Driven by such disclosures, dual inhibitors targeting both PARP and HDAC enzymes were designed by our research group to extend the efficacy of PARP inhibitors beyond BRCA-mutated cancers to cancers with induced BRCAness. The designed chemical architectures were synthesized and evaluated for antitumor efficacy. Delightfully, one of the compounds manifested impressive anti-leukemic effects mediated via dual inhibition of PARP and class I HDACs. Also, the dual modulator could arrest the cell cycle at the G0/G1 phase and induce autophagy.

Further, polymer nanoformulation of the dual inhibitor was furnished to afford targeted delivery at the cancer site. The polymer nanoformulation was monodispersed, spherical in form, and exhibited an appropriate particle size as demonstrated by Transmission Electron Microscopy (TEM). Delightfully, the polymer nanoformulation manifested pH-sensitive behavior, leading to selective cell growth inhibitory effects against the leukemia cell lines.

References

1. Liu C, Vyas A, Kassab MA, et al. The role of poly ADP-ribosylation in the first wave of DNA damage response. Nucleic Acids Res. 2017, 45(14), 8129-8141.
2. Rose M, Burgess JT, O'Byrne K, et al. PARP inhibitors: clinical relevance, mechanisms of action and tumor resistance. Front. Cell Dev. Biol. 2020, 8, 564601.
3. Eisemann T, Pascal JM. Poly (ADP-ribose) polymerase enzymes and the maintenance of genome integrity. Cell. Mol. Life Sci. 2020, 77, 19-33.
4. Rasmussen RD, Gajjar MK, Jensen KE et al. Enhanced efficacy of combined HDAC and PARP targeting in glioblastoma. Mol. Oncol. 2016. 10 (5), 751 - 763.