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EDITORIAL

Anticancer drugs: where are we now?

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Cancer remains one of the most common diseases nowadays [1–3], and although being characterized by a huge heterogeneity and multiple manifestations, the relevant progress achieved in the last decades in genomics, molecular biology, crystallography, drug design and computational techniques led to the development of a large number of effective therapeutic agents, small molecules, antibodies and cell-based therapies, which took advantage mainly of the metabolic and physiological differences between normal and tumor cells [4–8], although at a rather high cost [6]. However, many tumors remain difficult or impossible to be treated or they develop drug resistance to clinically used agents [4–7], and thus, the search for innovative, more effective and less toxic anticancer drugs than those currently available is still continuing. Two issues of *Expert Opinion on Therapeutic Patents*, one published in 2023 [9–13] and the second one in 2024 [14–17], present the state of the art and the relevant discoveries of last years in the field.

The first review article [9] in the first issue deals with tumor associated carbonic anhydrases (CAs) as drug targets for the management of hypoxic metastatic tumors. This field is in a very rapid progress [18–21], since these enzymes are involved in pH regulation, CO_2/bicarbonate sensing, metabolism [21,22] and ferroptosis [23], and their targeting with small molecules or antibodies leads to significant antitumor effects, alone or in combination with other drugs [9]. One of the most advanced small molecule inhibitors, which is presently in Phase Ib/II clinical trials, is the sulfonamide SLC-0111, for which several clinical trials are ongoing [24], but many other compounds have been developed and are in various stages of preclinical assessment [9,18–21].

Natural products represent a highly important source of innovative chemotypes possessing a variety of pharmacological activities [25] including antitumor ones [10]. Thus, the review from Carradori's group [10] in the first collection of articles presents the updated information in the field of natural products possessing anticancer activity, particularly reviewing the flavonoids, chalcones, stilbenes, xanthines, various alkaloids, lignans, cannabinoids, terpenes, terpenoids, and their anticancer mechanisms of action. This exhaustive review may allow medicinal chemists for new ideas in the design of this type of pharmacological agents based on a variety of structures which are presented in the article [10].

The article from Randazzo's group [11] presents in detail the guanine-rich DNA sequences which fold into noncanonical, four-stranded secondary structures, known as G-quadruplexes (G4s), which are targetable for obtaining anticancer drugs [26,27]. The role of G4s as human oncogene promoters is presented in detail for various targets such as KRAS, NRAS, c-MYC, c-KIT, HIF, VEGF, etc., together with the classes of ligands which bind to them, leading to antitumor effects [11].

The proteasome inhibitors, a class of anticancer agents successfully introduced in oncological therapies two decades ago, are dealt with in the review from Ronca's group [12]. From the first-generation, clinically used agents such as bortezomib, to the second-generation inhibitors such as carfilzomib and ixazomib and to the many new developments in the area, with a vast number of structural variants available, the article represents an updated review of the field. Furthermore, the detailed mechanism of inhibition based on biochemical and X-ray crystallographic studies are also presented in detail [12].

Tubulin inhibitors such as the taxanes, vinca alkaloid derivatives (vincristine and vinblastine), combretastatin, and many others, have been in clinical use for decades and although rather toxic, have a firm position in the anticancer therapies [7,13]. The review by Peerzada et al. [13] in the first collection of anticancer articles of the journal presents an exhaustive update on this target, presenting the various binding sites of the classical and new inhibitors to tubulin, as well as many novel principles for developing less toxic such compounds. In fact, many tubulin inhibitors (auristatin, maytansine, tubulysine, etc.) possess significant antitumor activity but are too toxic to be used clinically, and recent developments for their derivatization using cargo moieties (for the precise targeting only at the tumor site, avoiding thus severe side effects) have been proposed and worked better than the original, toxic compounds [28].

In the second collection, Gioiello and colleagues [14] present an interesting review article on the farnesoid X receptor (FXR), which is a key transcription factor involved in bile acid signaling, and ultimately shown to have connections also to tumorigenesis. Although at the moment only obeticholic acid (Ocaliva) has been approved for primary biliary cholangitis therapy as FXR agonist [29], the field

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is in constant evolution, with a high number of interesting compounds in Phase II/III clinical trials for various pathologies, including cancer. The review presents in detail all the latest developments with many natural and synthetic compounds presented from the scientific and patent literature [14].

The second paper in the second collection, by Rotili's group [15] examines bromodomain and extra-terminal (BET) domain proteins, which are transcription cofactors recognizing acetylated lysines of histone (and also non-histone) proteins and can thus modulate gene expression. These proteins have been recognized as anticancer drug targets. The review examines the various strategies for obtaining BET inhibitors and their applications as antitumor agents.

Protein kinases (PKs) play many relevant roles in cell signaling and regulatory processes in physiologic and pathologic conditions [7] and are among the most investigated enzymes for the development of drugs modulating their activity. Tyrosine PK inhibitors have been in clinical use as antitumor agents for more than 20 years, with a rather large number of clinically approved agents available, which however easily lead to drug resistance problems [7,16]. The review by Carta et al. [16] thus presents the state-of-the-art in the field, with an update on the many new structural classes, their various applications and approaches for avoiding the rapid drug resistance emergence.

The review by Gasparrini et al. [17] deals with nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting enzyme in the biosynthesis of nicotinamide adenine dinucleotide (NAD), a fundamental molecule for all living processes. In addition to its role as redox cofactor, NAD also functions as a substrate for NAD-consuming enzymes, regulating multiple cellular processes such as DNA repair and gene expression, being thus involved in tumor growth. The review presents an update in the field of NAMPT inhibitors belonging to a large variety of chemotypes, which might soon lead to antitumor agents with innovative mechanisms of actions.

In conclusion, the two article collections on antitumor agents published in the last years in the journal provide a very positive reply to the question from the title of this Editorial: we are at a crucial point for the development of next generation anticancer agents. The valuable articles from the two collections [9–17] presented a multitude of drug targets and approaches for obtaining drugs, which are already validated or in course of being validated, demonstrating thus that this disease might become less terrible in the future for the millions of patients affected worldwide.

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References

1. Jassim A, Rahrmann EP, Simons BD, et al. Cancers make their own luck: theories of cancer origins. Nat Rev Cancer. 2023;23(10):710–724. doi: 10.1038/s41568-023-00602-5
2. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. Cell Metab. 2016;23(1):27–47. doi: 10.1016/j.cmet.2015.12.006
3. Chiarugi A, Dölle C, Felici R, et al. The NAD metabolome–a key determinant of cancer cell biology. Nat Rev Cancer. 2012;12(11):741–752. doi: 10.1038/nrc3340
4. Neri D, Supuran CT. Interfering with pH regulation in tumours as a therapeutic strategy. Nat Rev Drug Discov. 2011;10(10):767–777. doi: 10.1038/nrd3554
5. Schwartz L, Supuran CT, Alfarouk KO. The Warburg effect and the hallmarks of cancer. Anticancer Agents Med Chem. 2017;17(2):164–170. doi: 10.2174/1871520616666161031143301
6. Mullard A. The high, and redundant, cost of failure in cancer drug development. Nat Rev Drug Discov. 2023;22(9):688. doi: 10.1038/d41573-023-00132-7
7. Peerzada MN, Hamel E, Bai R, et al. Deciphering the key heterocyclic scaffolds in targeting microtubules, kinases and carbonic anhydrases for cancer drug development. Pharmacol Ther. 2021;225:107860. doi: 10.1016/j.pharmthera.2021.107860
8. Tao R, Han X, Bai X, et al. Revolutionizing cancer treatment: enhancing CAR-T cell therapy with CRISPR/Cas9 gene editing technology. Front Immunol. 2024;15:1354825. doi: 10.3389/fimmu.2024.1354825
9. Supuran CT. Targeting carbonic anhydrases for the management of hypoxic metastatic tumors. Expert Opin Ther Pat. 2023;33(11):701–720. doi: 10.1080/13543776.2023.2245971
10. Melfi F, Carradori S, Mencarelli N, et al. Natural products as a source of new anticancer chemotypes. Expert Opin Ther Pat. 2023;33(11):721–744. doi: 10.1080/13543776.2023.2265561
11. Romano F, Di Porzio A, Iaccarino N, et al. G-quadruplexes in cancer-related gene promoters: from identification to therapeutic targeting. Expert Opin Ther Pat. 2023;33(11):745–773. doi: 10.1080/13543776.2023.2271168
12. Gazzaroli G, Angeli A, Giacomini A, et al. Proteasome inhibitors as anticancer agents. Expert Opin Ther Pat. 2023;33(11):775–796. doi: 10.1080/13543776.2023.2272648
13. Peerzada MN, Dar MS, Verma S. Development of tubulin polymerization inhibitors as anticancer agents. Expert Opin Ther Pat. 2023;33(11):797–820. doi: 10.1080/13543776.2023.2291390
14. Gioiello A, Rosatelli E, Cerra B. Patented farnesoid X receptor modulators: a review (2019 – present). Expert Opin Ther Pat. 2024 Feb;26:1–18. doi: 10.1080/13543776.2024.2314296
15. Viviano M, Cipriano A, Fabbrizi E, et al. Successes and challenges in the development of BD1-selective BET inhibitors: a patent review. Expert Opin Ther Pat. 2024 Mar;11:1–17. doi: 10.1080/13543776.2024.2327300
16. Carta F, et al. Kinase inhibitors: 20 years of success and many new challenges. Expert Opin Ther Pat. 2024; in press.
17. Gasparrini M, Giovannuzzi S, Nocentini A, Raffaelli N, Supuran CT. Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) in cancer: a patent review. Expert Opin Ther Pat. 2024; in press.
18. Nerella SG, Singh P, Arifuddin M, et al. Anticancer carbonic anhydrase inhibitors: a patent and literature update 2018–2022. Expert Opin Ther Pat. 2022;32(8):833–847. doi: 10.1080/13543776.2022.2083502

19. Supuran CT. Carbonic anhydrase inhibitors: an update on experimental agents for the treatment and imaging of hypoxic tumors. Expert Opin Investig Drugs. 2021;30(12):1197–1208. doi: 10.1080/13543784.2021.2014813
20. McDonald PC, Chafe SC, Supuran CT, et al. Cancer therapeutic targeting of hypoxia induced carbonic anhydrase IX: from bench to bedside. Cancers (Basel). 2022;14(14):3297. doi: 10.3390/cancers14143297
21. Angeli A, Carta F, Nocentini A, et al. Carbonic anhydrase inhibitors targeting metabolism and tumor microenvironment. Metabolites. 2020;10(10):412. doi: 10.3390/metabo10100412
22. Supuran CT. Carbonic anhydrase versatility: from pH regulation to CO2 sensing and metabolism. Front Mol Biosci. 2023;10:1326633. doi: 10.3389/fmolb.2023.1326633
23. Chafe SC, Vizeacoumar FS, Venkateswaran G, et al. Genome-wide synthetic lethal screen unveils novel CAIX-NFS1/xCT axis as a targetable vulnerability in hypoxic solid tumors. Sci Adv. 2021;7(35):eabj0364. doi: 10.1126/sciadv.abj0364
24. McDonald PC, Chia S, Bedard PL, et al. A phase 1 study of SLC-0111, a novel inhibitor of carbonic anhydrase IX, in patients with advanced solid tumors. Am J Clin Oncol. 2020;43(7):484–490. doi: 10.1097/COC.0000000000000691
25. Atanasov AG, Zotchev SB, Dirsch VM. International natural product sciences taskforce; supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200–216. doi: 10.1038/s41573-020-00114-z
26. Clark GR, Pytel PD, Squire CJ, et al. Structure of the first parallel DNA quadruplex-drug complex. J Am Chem Soc. 2003;125(14):4066–4067. doi: 10.1021/ja0297988
27. Ahmed AA, Chen S, Roman-Escorza M, et al. Structure-activity relationships for the G-quadruplex-targeting experimental drug QN-302 and two analogues probed with comparative transcriptome profiling and molecular modeling. Sci Rep. 2024;14(1):3447. doi: 10.1038/s41598-024-54080-2
28. Krall N, Pretto F, Decurtins W, et al. A small-molecule drug conjugate for the treatment of carbonic anhydrase IX expressing tumors. Angew Chem Int Ed Engl. 2014;53(16):4231–4235. doi: 10.1002/anie.201310709
29. Pellicciari R, Pruzanski M, Gioiello A. The discovery of obeticholic acid (Ocaliva™): first-in-class FXR agonist. In: Fischer J, Klein C Childers W, editors. Successful drug discovery. Vol. 3. Wiley-VCH Verlag GmbH & Co. KGaA; 2018. p. 197–244. doi: 10.1002/9783527808694.ch8