



Editorial

Molecular Mechanisms of Tumor Progression and New Therapeutic Strategies for Urological Cancers, 2nd Edition

Vicenç Ruiz de Porras ^{1,2,3}

¹ GRET and Toxicology Unit, Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain; vruizdeporras@ub.edu; Tel.: +34-606587010

² Badalona Applied Research Group in Oncology (B-ARGO), Catalan Institute of Oncology, Camí de les Escoles, s/n, 08916 Badalona, Spain

³ CARE Program, Germans Trias i Pujol Research Institute (IGTP), Camí de les Escoles, s/n, 08916 Badalona, Spain

Urological cancers, including malignancies of the bladder, kidney, prostate, upper urinary tract, and penis, are among the most common cancers globally [1] and present significant heterogeneity in terms of clinical behavior, molecular biology, and therapeutic responsiveness [2]. Despite considerable advancements in local and systemic treatments, including immunotherapy and targeted therapies, the prognosis for many patients with advanced disease remains poor. Understanding the underlying molecular mechanisms of tumor progression and treatment resistance is essential to improve existing strategies and identify novel therapeutic targets.

In this second edition of the Special Issue “Molecular Mechanisms of Tumor Progression and New Therapeutic Strategies for Urological Cancers,” we feature seven contributions that shed light on critical aspects of tumor biology, biomarker discovery, and therapeutic innovation across various urological malignancies. These studies provide compelling evidence of the evolving landscape in precision oncology and liquid biopsy applications.

Non-invasive biomarkers based on liquid biopsy, capable of dynamically reflecting tumor behavior, are critical for real-time monitoring and therapeutic decision making [3]. In this context, two studies in the current Special Issue focus on circulating tumor-derived components as emerging tools in the management of urological tumors.

Carrasco et al. [4] explored a tumor-agnostic circulating tumor DNA (ctDNA) approach for monitoring patients with muscle-invasive bladder cancer (MIBC) after radical cystectomy (RC). By targeting common mutations (TERT and ATM) using droplet digital PCR, they demonstrated that ctDNA positivity was significantly associated with tumor progression at multiple timepoints. Importantly, ctDNA dynamics provided prognostic information superior to conventional imaging, aligning with prior reports that underscore the utility of ctDNA for early relapse detection [5,6] as well as for predicting immunotherapy efficacy in the adjuvant setting of MIBC [7]. This reinforces ctDNA as a minimally invasive and cost-effective strategy that can overcome the shortcomings of tissue-based biomarkers—including limited tissue availability, reliance on archival samples, and tumor heterogeneity—and is, as a result, increasingly used to guide treatment decisions [8].

In addition, Figols and colleagues [9] reviewed the role of tumor-educated platelets (TEPs) as a liquid biopsy source across urological tumors. TEPs, altered by interactions with tumors and their microenvironment, carry transcriptomic and proteomic signatures reflective of tumor burden and biology [10,11]. Their analysis highlighted TEPs’ diagnostic potential, especially in early cancer detection and non-invasive therapy monitoring, and



Received: 27 June 2025

Accepted: 2 July 2025

Published: 5 July 2025

Citation: Ruiz de Porras, V. Molecular Mechanisms of Tumor Progression and New Therapeutic Strategies for Urological Cancers, 2nd Edition. *Int. J. Mol. Sci.* **2025**, *26*, 6496. <https://doi.org/10.3390/ijms26136496>

Copyright: © 2025 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

support recent findings in other solid tumors, including non-small cell lung, glioblastoma, and pancreatic cancer [10,12,13].

On the other hand, treatment resistance remains a major challenge, particularly in bladder cancer, where cisplatin-based chemotherapy is still a cornerstone despite limited response rates [14]. Therefore, a better understanding of the mechanisms underlying therapy resistance is essential to developing novel treatment strategies and predicting drug response, ultimately advancing progress toward precision medicine. In this context, two articles in this Special Issue contribute to unraveling the molecular resistance mechanisms.

Elahi Najafi et al. [15] identified GABBR2 as a novel downstream effector of androgen receptor (AR) signaling, conferring cisplatin resistance in bladder cancer cells. The authors demonstrated that AR activation upregulates GABBR2, while its inhibition sensitizes cells to cisplatin. These findings suggest that targeting the AR-GABBR2 axis could reverse resistance, especially in AR-positive tumors. This is consistent with previous evidence that androgen signaling modulates bladder tumorigenesis, tumor progression, and therapy response, suggesting a potential role for androgen deprivation therapies in patients with bladder cancer [16,17].

In a related investigation, Vukovic et al. [18] explored the prognostic relevance of the IL-1 β /IL-1RA axis in invasive bladder cancer. Their immunohistochemical analysis revealed that IL-1 β expression correlated with aggressive pathological features but paradoxically conferred favorable survival. Moreover, IL-1 β levels were positively associated with AKT and Ki-67 expression, implicating a role in autophagy and proliferation. These results reflect the complex dual role of inflammation in cancer, where pro-inflammatory cytokines may drive both tumor progression and anti-tumor immune responses [19].

In clear-cell renal cell carcinoma (ccRCC), extracellular matrix remodeling enzymes contribute to angiogenesis, invasiveness, and metastasis [20]. Młynarczyk et al. [21] compared MMP-14 and MMP-15 expression and activity in tumor and normal kidney tissues. They found that MMP-14 was significantly more active and expressed, particularly in higher-grade tumors, supporting its role in angiogenesis and invasiveness. These results reinforce earlier reports that link MMP-14 to disease progression and poor short-term prognosis in RCC and bladder cancer [22,23].

Although rare, penile squamous cell carcinoma (SCC) presents therapeutic challenges in advanced stages. Fahey et al. [24] described a case of metastatic penile SCC with a durable response to the antibody–drug conjugate, enfortumab vedotin, a human anti-nectin-4 antibody linked to the cytotoxic microtubule-disrupting agent monomethyl auristatin E [25]. Based on the results of the EV-301 phase III trial [26], enfortumab vedotin was approved by the FDA in 2019 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum-based chemotherapy and checkpoint inhibitor therapy. Interestingly, this report highlights the potential application of novel targeted agents beyond their initial indications and supports further investigation into Nectin-4 as a therapeutic target in penile cancer, consistent with expression patterns reported in urothelial and squamous histologies [25,27].

Prostate cancer (PCa), especially in its metastatic castration-resistant form (mCRPC), remains a challenging clinical entity that, despite significant advances in the treatment in the last decade, still carries a poor prognosis, with a median overall survival of approximately three years [28]. In this context, Porcel-Pastrana and colleagues [19] explored a combinatorial approach using hydroxytyrosol (HT), a phenolic compound from olive oil, and metformin, a widely used antidiabetic agent. Their in vitro data showed a synergistic inhibition of cell proliferation, migration, and tumorsphere formation across multiple PCa cell lines. Mechanistically, the combination suppressed key oncogenic pathways including MAPK, AKT, and TGF- β . These findings build upon prior preclinical evidence

supporting the repurposing of metabolic regulators—primarily drugs used to treat diabetes, such as metformin, or to lower cholesterol, such as simvastatin—for cancer treatment and prevention [29–31].

Collectively, the contributions in this Special Issue reflect the diversity and depth of current research in urological oncology. From liquid biopsy technologies to resistance mechanisms and novel therapeutics, these studies point toward a future where disease management is increasingly personalized, biology-driven, and minimally invasive. We hope this compilation stimulates further research and translational efforts, ultimately improving outcomes for patients affected by these complex malignancies.

Acknowledgments: The authors thank Sara Bystrup for assistance in drafting the manuscript.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2024**, *74*, 229–263. [\[CrossRef\]](#)
2. Antar, R.M.; Fawaz, C.; Gonzalez, D.; Xu, V.E.; Drouaud, A.P.; Krastein, J.; Pio, F.; Murdock, A.; Youssef, K.; Sobol, S.; et al. The Evolving Molecular Landscape and Actionable Alterations in Urologic Cancers. *Curr. Oncol.* **2024**, *31*, 6909–6937. [\[CrossRef\]](#)
3. Ma, L.; Guo, H.; Zhao, Y.; Liu, Z.; Wang, C.; Bu, J.; Sun, T.; Wei, J. Liquid biopsy in cancer current: Status, challenges and future prospects. *Signal Transduct. Target. Ther.* **2024**, *9*, 336. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Carrasco, R.; Ingelmo-Torres, M.; Trullas, R.; Roldan, F.L.; Rodriguez-Carunchio, L.; Juez, L.; Sureda, J.; Alcaraz, A.; Mengual, L.; Izquierdo, L. Tumor-Agnostic Circulating Tumor DNA Testing for Monitoring Muscle-Invasive Bladder Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 16578. [\[CrossRef\]](#)
5. Christensen, E.; Birkenkamp-Demtroder, K.; Sethi, H.; Shchegrova, S.; Salari, R.; Nordentoft, I.; Wu, H.T.; Knudsen, M.; Lamy, P.; Lindskrog, S.V.; et al. Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients with Urothelial Bladder Carcinoma. *J. Clin. Oncol.* **2019**, *37*, 1547–1557. [\[CrossRef\]](#)
6. Christensen, E.; Nordentoft, I.; Birkenkamp-Demtroder, K.; Elbaek, S.K.; Lindskrog, S.V.; Taber, A.; Andreassen, T.G.; Strandgaard, T.; Knudsen, M.; Lamy, P.; et al. Cell-Free Urine and Plasma DNA Mutational Analysis Predicts Neoadjuvant Chemotherapy Response and Outcome in Patients with Muscle-Invasive Bladder Cancer. *Clin. Cancer Res.* **2023**, *29*, 1582–1591. [\[CrossRef\]](#)
7. Powles, T.; Assaf, Z.J.; Davarpanah, N.; Banchereau, R.; Szabados, B.E.; Yuen, K.C.; Grivas, P.; Hussain, M.; Oudard, S.; Gschwend, J.E.; et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature* **2021**, *595*, 432–437. [\[CrossRef\]](#)
8. Corcoran, R.B.; Chabner, B.A. Application of Cell-free DNA Analysis to Cancer Treatment. *N. Engl. J. Med.* **2018**, *379*, 1754–1765. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Figols, M.; Chekhun, S.; Fernandez-Saorin, M.; Perez-Criado, I.; Bautista, A.; Font, A.; Ruiz de Porras, V. Tumor-Educated Platelets in Urological Tumors: A Novel Biosource in Liquid Biopsy. *Int. J. Mol. Sci.* **2025**, *26*, 3595. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Best, M.G.; Sol, N.; Kooi, I.; Tannous, J.; Westerman, B.A.; Rustenburg, F.; Schellen, P.; Verschuere, H.; Post, E.; Koster, J.; et al. RNA-Seq of Tumor-Educated Platelets Enables Blood-Based Pan-Cancer, Multiclass, and Molecular Pathway Cancer Diagnostics. *Cancer Cell* **2015**, *28*, 666–676. [\[CrossRef\]](#)
11. Best, M.G.; Wesseling, P.; Wurdinger, T. Tumor-Educated Platelets as a Noninvasive Biomarker Source for Cancer Detection and Progression Monitoring. *Cancer Res.* **2018**, *78*, 3407–3412. [\[CrossRef\]](#)
12. Nilsson, R.J.; Balaj, L.; Hulleman, E.; van Rijn, S.; Pegtel, D.M.; Walraven, M.; Widmark, A.; Gerritsen, W.R.; Verheul, H.M.; Vandertop, W.P.; et al. Blood platelets contain tumor-derived RNA biomarkers. *Blood* **2011**, *118*, 3680–3683. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Zaki-Dizaji, M.; Taheri, Z.; Heiat, M.; Hushmandi, K. Tumor-educated platelet, a potential liquid biopsy biosource in pancreatic cancer: A review. *Pathol. Res. Pract.* **2025**, *270*, 155986. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Ruiz de Porras, V.; Pardo, J.C.; Etxaniz, O.; Font, A. Neoadjuvant therapy for muscle-invasive bladder cancer: Current clinical scenario, future perspectives, and unsolved questions. *Crit. Rev. Oncol. Hematol.* **2022**, *178*, 103795. [\[CrossRef\]](#)
15. Elahi Najafi, M.A.; Yasui, M.; Teramoto, Y.; Tatenuma, T.; Jiang, G.; Miyamoto, H. GABBR2 as a Downstream Effector of the Androgen Receptor Induces Cisplatin Resistance in Bladder Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 13733. [\[CrossRef\]](#)
16. Sundi, D.; Collier, K.A.; Yang, Y.; Diaz, D.A.; Pohar, K.S.; Singer, E.A.; Gupta, S.; Carson, W.E., 3rd; Clinton, S.K.; Li, Z.; et al. Roles of Androgen Receptor Signaling in Urothelial Carcinoma. *Cancers* **2024**, *16*, 746. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Li, P.; Chen, J.; Miyamoto, H. Androgen Receptor Signaling in Bladder Cancer. *Cancers* **2017**, *9*, 20. [\[CrossRef\]](#)

18. Vukovic, M.; Chamlati, J.M.; Hennenlotter, J.; Todenhofer, T.; Lutfrenk, T.; Jersinovic, S.; Tsaur, I.; Stenzl, A.; Rausch, S. Interleukin-1beta/Interleukin (IL)-1-Receptor-Antagonist (IL1-RA) Axis in Invasive Bladder Cancer-An Exploratory Analysis of Clinical and Tumor Biological Significance. *Int. J. Mol. Sci.* **2024**, *25*, 2447. [\[CrossRef\]](#)
19. Greten, F.R.; Grivennikov, S.I. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity* **2019**, *51*, 27–41. [\[CrossRef\]](#)
20. Oxburgh, L. The Extracellular Matrix Environment of Clear Cell Renal Cell Carcinoma. *Cancers* **2022**, *14*, 4072. [\[CrossRef\]](#)
21. Mlynarczyk, G.; Tokarzewicz, A.; Gudowska-Sawczuk, M.; Mroczko, B.; Novak, V.; Novak, A.; Mitura, P.; Romanowicz, L. MMP-14 Exhibits Greater Expression, Content and Activity Compared to MMP-15 in Human Renal Carcinoma. *Int. J. Mol. Sci.* **2024**, *25*, 8107. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Zhao, Y.W.; Ma, W.; Jiang, F.; Xie, Y.; Tang, L. Upregulation of matrix metalloproteinase 14 (MMP14) is associated with poor prognosis in renal clear cell carcinoma-a bioinformatics analysis. *Transl. Androl. Urol.* **2022**, *11*, 1523–1534. [\[CrossRef\]](#)
23. Wang, J.F.; Gong, Y.Q.; He, Y.H.; Ying, W.W.; Li, X.S.; Zhou, X.F.; Zhou, L.Q. High expression of MMP14 is associated with progression and poor short-term prognosis in muscle-invasive bladder cancer. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 6605–6615.
24. Fahey, C.C.; Nebhan, C.A.; York, S.; Davis, N.B.; Hurley, P.J.; Gordetsky, J.B.; Schaffer, K.R. Metastatic Penile Squamous Cell Carcinoma Responsive to Enfortumab Vedotin. *Int. J. Mol. Sci.* **2023**, *24*, 16109. [\[CrossRef\]](#)
25. Heath, E.I.; Rosenberg, J.E. The biology and rationale of targeting nectin-4 in urothelial carcinoma. *Nat. Rev. Urol.* **2021**, *18*, 93–103. [\[CrossRef\]](#)
26. Powles, T.; Rosenberg, J.E.; Sonpavde, G.P.; Loriot, Y.; Duran, I.; Lee, J.L.; Matsubara, N.; Vulsteke, C.; Castellano, D.; Wu, C.; et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N. Engl. J. Med.* **2021**, *384*, 1125–1135. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Klumper, N.; Tran, N.K.; Zschabitz, S.; Hahn, O.; Buttner, T.; Roghmann, F.; Bolenz, C.; Zengerling, F.; Schwab, C.; Nagy, D.; et al. NECTIN4 Amplification Is Frequent in Solid Tumors and Predicts Enfortumab Vedotin Response in Metastatic Urothelial Cancer. *J. Clin. Oncol.* **2024**, *42*, 2446–2455. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Yamada, Y.; Beltran, H. The treatment landscape of metastatic prostate cancer. *Cancer Lett.* **2021**, *519*, 20–29. [\[CrossRef\]](#)
29. Dhas, Y.; Biswas, N.; M, R.D.; Jones, L.D.; Ashili, S. Repurposing metabolic regulators: Antidiabetic drugs as anticancer agents. *Mol. Biomed.* **2024**, *5*, 40. [\[CrossRef\]](#)
30. Luconi, M.; Cantini, G.; Crescioli, C. Repurposing glucose-lowering drugs for cancer therapy. *Trends Cancer* **2025**. [\[CrossRef\]](#)
31. Maurya, S.K.; Chaudhri, S.; Kumar, S.; Gupta, S. Repurposing of Metabolic Drugs Metformin and Simvastatin as an Emerging Class of Cancer Therapeutics. *Pharm. Res.* **2025**, *42*, 49–67. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.