Small molecules, big impact: Advancing immune checkpoint inhibitors for cancer

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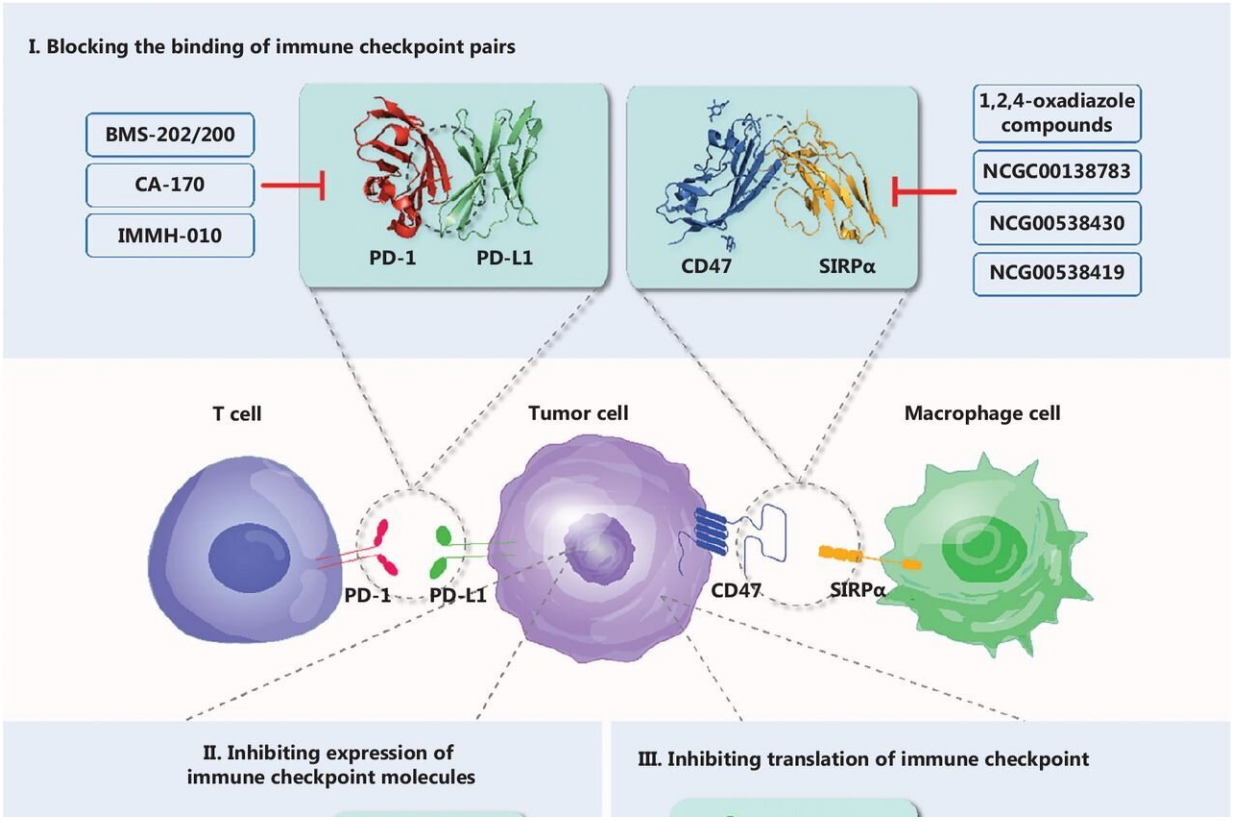

Summary of current small molecular drugs targeting PD-L1 and CD47. Small molecule chemical compounds block the function of major immune checkpoint molecules by (I) competitively binding with immune checkpoint molecules to block their combination with paired receptors (BMS202, CA-170, and IMMH-010 targeting PD-L1; NCGC00138783 and 1,2,4-oxadiazole compounds targeting CD47); (II) inhibiting the level of PD-L1 and CD47 expression (e.g., fraxinellone, RRx-001, and metformin); (III) inhibiting the translation of PD-L1 (e.g., eFT508); (IV) promoting degradation of PD-L1 (e.g., HIP1R). Credit:

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Immunotherapy has revolutionized cancer treatment, with immune checkpoint inhibitors (ICIs) playing a pivotal role. However, current ICIs, primarily monoclonal antibodies, face significant challenges like poor tissue penetration, high production costs, and off-target effects. These limitations hinder their efficacy and accessibility. Due to these issues, there is an urgent need to explore alternative approaches. Small molecule drugs targeting immune checkpoints offer a promising solution, potentially overcoming these barriers and providing more effective cancer therapies.

A recent review by researchers from the University of Electronic Science and Technology of China, affiliated with Sichuan Provincial People's Hospital, published in *Cancer Biology & Medicine*, explores the development of small molecule drugs targeting immune checkpoints. The study presents an innovative approach to cancer therapy by focusing on the efficacy and mechanisms of small molecule ICIs.

The study underscores the advantages of small molecule ICIs over traditional antibody-based therapies. These small molecule drugs exhibit superior tissue permeability, better oral bioavailability, and favorable pharmacokinetic properties. Key examples include BMS-202, which induces PD-L1 dimerization to block PD-1/PD-L1 interactions, and CA-170, the first oral ICI to enter clinical trials. Additionally, YPD-29B has shown promising results in promoting PD-L1 degradation and enhancing antitumor immunity.

The research also highlights the potential of combining small molecule ICIs with other therapeutic strategies, such as immune regulation and anti-angiogenesis, to amplify treatment efficacy. This comprehensive

analysis of various small molecule inhibitors demonstrates their potential to revolutionize cancer treatment by addressing the limitations of antibody-based ICIs and offering more effective and accessible options for patients.

Dr. Chuan Xu, the senior researcher, stated, "The development of small molecule ICIs represents a significant leap in cancer therapy. These drugs not only address the limitations of current antibody-based therapies but also offer new avenues for combination treatments, enhancing overall efficacy and patient outcomes."

The study's findings suggest that small molecule ICIs could revolutionize cancer treatment, providing more accessible and cost-effective options. By improving tissue penetration and reducing production costs, these drugs have the potential to make advanced cancer therapies more widely available. The research paves the way for further exploration and clinical trials, aiming to establish small molecule ICIs as a cornerstone of modern cancer treatment.

More information: Luoyi Chen et al, Development of small molecule drugs targeting immune checkpoints, *Cancer Biology & Medicine* (2024). DOI: 10.20892/j.issn.2095-3941.2024.0034

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