

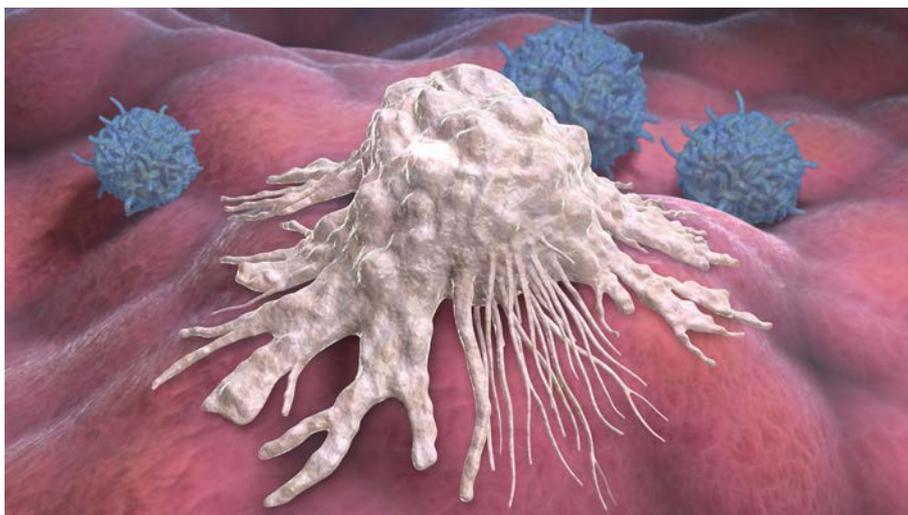
## Targeting tumor-associated myeloid cells: the new grail in immuno-oncology?

A commentary

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Treatment of cancer has historically first focused on targeting the main culprit, tumor cells. With immuno-oncology, the focus has drastically shifted to immune cells, providing novel therapeutical targets with very high potential. The revolution that immunotherapies represent is now a milestone in the history of oncology.

Interestingly, these therapies have first targeted effector immune cells, i.e., T cells. [Immune checkpoint \(ICP\) blockade](#) has been shown to be efficient in numerous cancers, but there is a broad variability in patient responses, with some tumors being or becoming resistant to such treatments.<sup>1</sup>



New therapies, many considered for combotherapies with ICP blockade, are now developed to target another category of cells in the tumor microenvironment (TME), in order to surmount or avoid resistance to immunotherapies. Among these TME cell types, tumor-associated myeloid cells such as tumor-associated macrophages (TAM) or myeloid derived suppressors cells (MDSCs) have attracted a

lot of attention. Indeed, they are now known to promote tumor progression and metastasis, favor angiogenesis, and suppress anticancer immune responses, thus representing a potent immunosuppressive population in the TME.<sup>2</sup> Many groups now focus on targeting these tumor-associated myeloid cells to prevent or overcome immune evasion.

### Strategies to target tumor-associated myeloid cells

Different strategies are explored in targeting tumor-associated myeloid cells.<sup>2</sup> One is to deplete these cells or inhibit their infiltration in the tumors. An explored approach for this strategy is to shut down the signals attracting MDSCs to the tumors—in other words, chemokine blockade. Different compounds have been tested to target CCR5 and CXCR2 receptors, showing promising results in preclinical settings, and are currently in clinical trials.<sup>3</sup> Another strategy is to induce differentiation and/or maturation of these cells, i.e., reprogram them toward an anti-tumor function. For example, TAMs are heterogeneous but considered M2-like macrophages, meaning with a pro-tumorigenic profile. Compounds are now designed to reprogram them toward an anti-tumor M1-like profile. One of the targets studied for this strategy is the T-like receptors family. These proteins, highly

expressed on innate immune cells, are known to detect microbes and trigger an inflammatory immune response through activation of these cells. An historically known activator of TLRs, bacillus Calmette-Guérin (BCG) was “repurposed” from a tuberculosis vaccine to a bladder cancer treatment in the 1970s, and is still used today in combination with anti-PD-1 therapy, although its precise mechanism of action remains unclear.<sup>4</sup> Different TLR-targeting compounds have been investigated as potential trigger to reprogram TAMs, but to date, Imiquimod is the only TLR agonist to be approved by the FDA for the treatment of squamous and basal cell carcinomas.<sup>2</sup>

As mentioned, tumor-associated myeloid cells are receiving a lot of attention these past few years, and rightly so as targets for not just novel therapies but as a tool for clinical prognosis. These cells are highly heterogeneous and complex, and they interact with virtually all other cellular components of the TME. Therefore, a better understanding of the myeloid landscape in tumors will help develop novel, or improve existing, treatments. As such, [relevant physiological preclinical models](#) for their study are of paramount importance.

#### References:

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