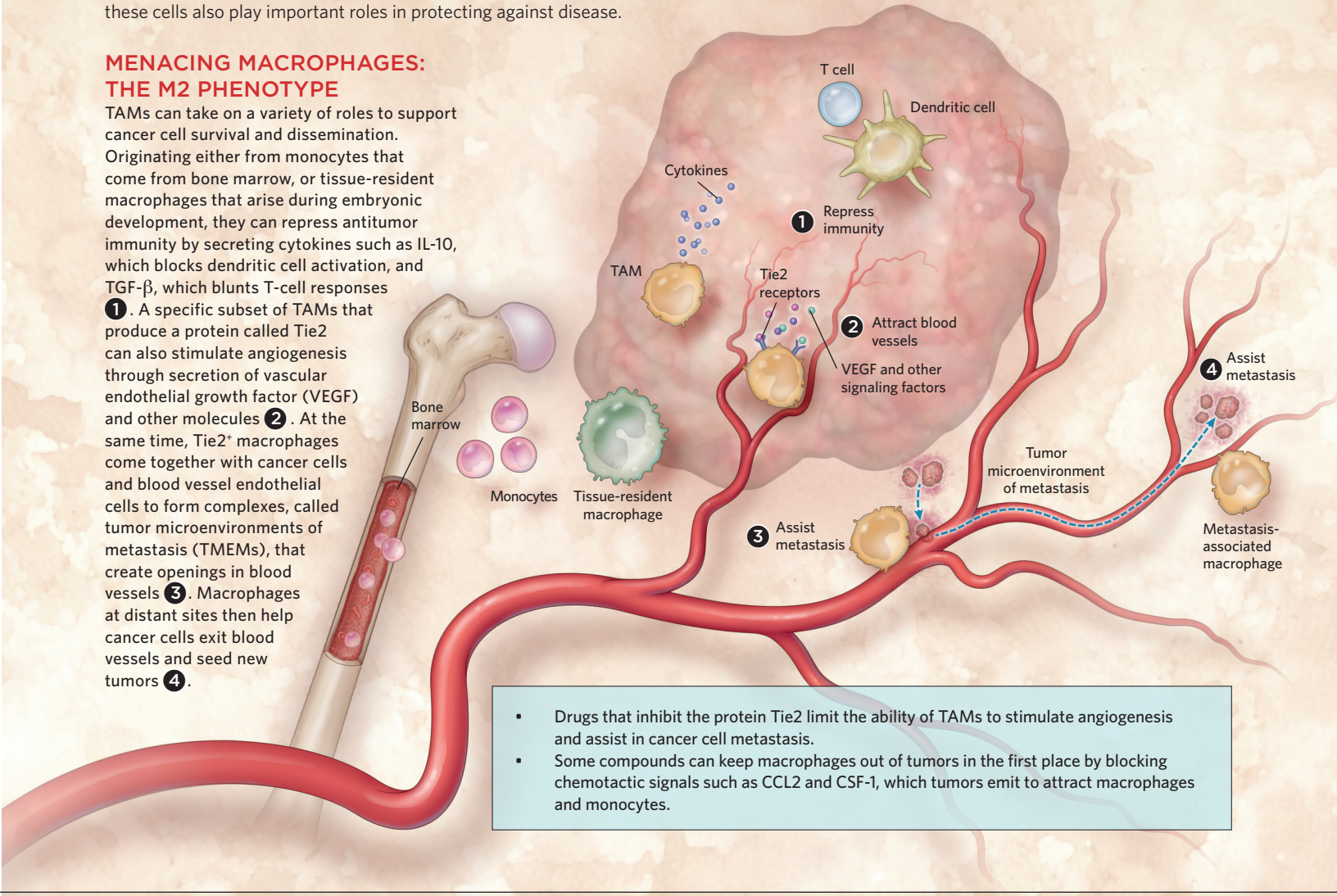
TWO-FACED MACROPHAGES

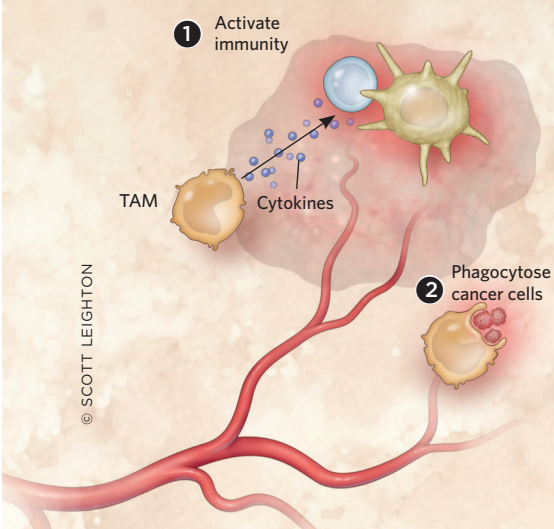
Tumors use chemokine signals to draw monocytes and tissue-resident macrophages into the tumor microenvironment, where the cells become tumor-associated macrophages (TAMs). Once believed to be wholly supportive of cancerous growth, these cells also play important roles in protecting against disease.

MENACING MACROPHAGES: THE M2 PHENOTYPE

TAMs can take on a variety of roles to support cancer cell survival and dissemination. Originating either from monocytes that come from bone marrow, or tissue-resident macrophages that arise during embryonic development, they can repress antitumor immunity by secreting cytokines such as IL-10, which blocks dendritic cell activation, and TGF-β, which blunts T-cell responses ❶. A specific subset of TAMs that produce a protein called Tie2 can also stimulate angiogenesis through secretion of vascular endothelial growth factor (VEGF) and other molecules ❷. At the same time, Tie2^{+} macrophages come together with cancer cells and blood vessel endothelial cells to form complexes, called tumor microenvironments of metastasis (TMEMs), that create openings in blood vessels ❸. Macrophages at distant sites then help cancer cells exit blood vessels and seed new tumors ❹.



- Drugs that inhibit the protein Tie2 limit the ability of TAMs to stimulate angiogenesis and assist in cancer cell metastasis.
- Some compounds can keep macrophages out of tumors in the first place by blocking chemotactic signals such as CCL2 and CSF-1, which tumors emit to attract macrophages and monocytes.



TUMOR-KILLING TAMS: THE M1 PHENOTYPE

TAMs have the potential to aid antitumor immune responses by presenting cancer cell antigens to T cells and producing cytokines that activate dendritic cells and T cells ❶. Macrophages are also experts at phagocytosing and degrading foreign cells, including cancer cells ❷.

- Stimulation with cytokines or immune agonists can reprogram TAMs and coax them toward the proinflammatory, phagocytosing M1 phenotype. Lately, epigenome-altering drugs have also been used to skew TAM phenotypes toward M1.
- Antibodies and peptides that block the cancer cell "don't eat me" signal CD47 give TAMs free reign to phagocytose cancer cells. Blocking the inhibitory protein PD-1 on TAMs also increases the cells' phagocytic activity.