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# Arming macrophages to stop cancer progression

Macrophages are a type of immune cells that fight infection and support tissue remodeling. They are best known as phagocytes which engulf bacteria and damaged cells stimulating other immune cells. In addition, macrophages assist wound healing processes by releasing substances called growth factors and cytokines that help a damaged tissue to replicate and repair itself. While macrophages positively contribute to wound repair, they become enriched within tumors and are known as tumor associated macrophages (TAMs). Similar to their role during wound healing, TAMs release factors that activate many cell types to promote tumor progression. Indeed, tumors are considered "wounds that do not heal". TAMs not only enhance tumor cell growth and suppress tumor immunity, but they promote tumor spreading to distant organs (metastasis) and help tumors ignore the effects of cancer therapy (drug resistance).

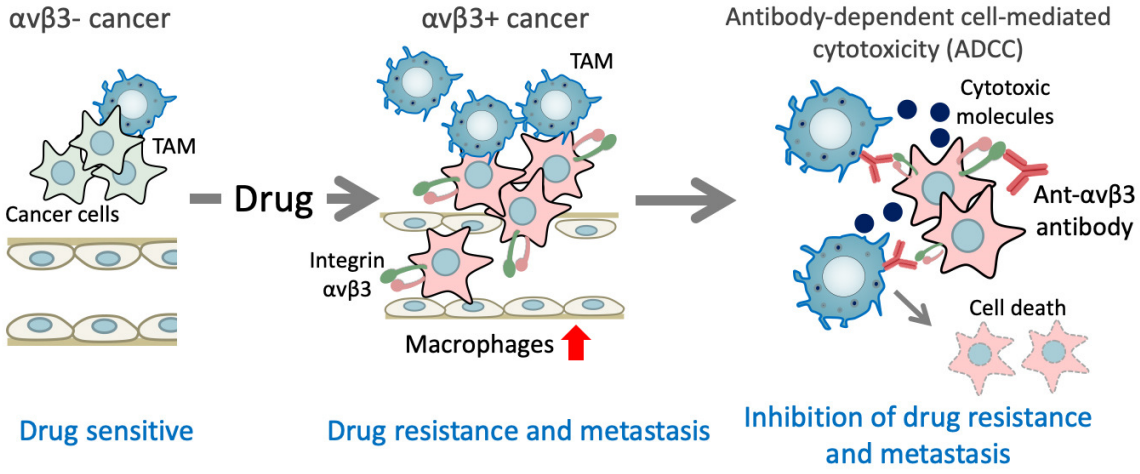


Fig. 1. Anti-αvβ3 antibody exploit the co-enrichment of TAMs and αvβ3-positive cancer cells by manipulating TAMs, to eradicate drug resistant and metastatic cells. TAM, tumor-associated macrophage.

We have observed that highly aggressive and drug resistant tumors are characterized by tumor cell expression of a cell surface protein, integrin αvβ3. Furthermore, we found that αvβ3-positive tumors have a higher accumulation of TAMs. Considering that αvβ3 integrin promotes tumor metastasis and drug resistance in various cancers, it is possible that this is linked to the accumulation of TAMs.

To take advantage of these new discoveries, we developed an antibody that is capable of directly targeting integrin αvβ3 on the surface of highly aggressive cancer cells. While this antibody is able to slow the growth of both the primary tumor mass and early stages of metastasis, this response depends on the presence of TAMs. We determined that the antibody can exploit TAMs to attack and kill αvβ3 expressing tumor cells. To our surprise, this antibody did not promote macrophage engulfment of the tumor cells but rather promoted a specific killing by a distinct process known as antibody-dependent cellular cytotoxicity (ADCC) which involves the secretion of tumor killing factors (Fig. 1). Treating tumors with this antibody led to the elimination of drug resistant tumor cells, resulting in prolonged sensitivity to standard cancer therapies.

While macrophages are mediators of wound healing responses that are critical for life, macrophages in tumors can play a highly detrimental role to promote a more dangerous and therapy-resistant tumor. Our antibody represents a novel approach to exploit the presence of TAMs to kill the most dangerous cells within a tumor (Fig. 1.). To bring this therapeutic approach to patients, we have engineered a humanized anti-αvβ3 antibody which selectively activates TAMs to target drug resistant and metastatic cancers.

***Hiromi I. Wettersten, Sara M. Weis, David A. Cheresh***
*Department of Pathology, University of California, San Diego, La Jolla, California, USA*
*Moores Cancer Center, University of California, San Diego, La Jolla, California, USA*
*Sanford Consortium for Regenerative Medicine, University of California, San Diego, La Jolla, California, USA*

## Publication

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