Myeloid cells composed of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) are a distinctive feature of many human cancers. For example, in non-Hodgkin lymphoma, variation between patients in the density of TAMs in their tumors is usually negatively correlated with survival. In follicular lymphoma, a landmark gene expression profiling study found that in patients treated with chemotherapy, prognostic gene signatures came not from neoplastic B cells but from T cells and MΦ, with respectively good and bad effects on outcome.  

In our recent publication, we demonstrated that MDSC are also present in the tumor microenvironment of mouse lymphomas and exert immunosuppressive and protumoral effects. Taken together, these reports suggest that tumor-associated myeloid cells in B-cell lymphomas exist in different functional states and may collectively promote tumor growth and confer poor prognosis. Studies using syngeneic, transplantable mouse tumor models showed that MDSC are a major component of tumor-induced immune suppression, that allows malignant cells to escape from immune attack. 

In mouse MDSC are a heterogeneous cell population that co-expresses Gr-1 and CD11b myeloid-cell lineage differentiation markers. Due to lack of human homology of the Gr-1 gene, identification of MDSC in cancer patients relies on combination of a range of lineage markers; however, none of these markers is unique for MDSC. Studies confirmed that HLA-DR+/CD33+CD11b+/CD14+ and/or CD15+ myeloid cells found in various cancer patients were immune suppressive and correlated with poor prognosis. It is speculated that novel agents targeting MDSC may ameliorate tumor-induced immune suppression and be combined with existing therapies, including chemotherapy, immunotherapies, and targeted therapies, potentially improving their efficacy without increasing toxicity. However, what hampers the current development of MDSC depletion therapy is the lack of a human MDSC-specific marker. Accordingly, discovery of such a therapeutic target has become a top priority in the field. 

Using competitive biopanning with a peptide phage library on splenocytes freshly prepared from tumor-bearing mice, we overcame current limitations and identified two novel, mouse MDSC-specific peptides. The peptides were further developed into therapeutic agents (peptibodies) that efficiently depleted splenic and intratumoral MDSC in tumor-bearing mice, but did not affect other proinflammatory cell types including dendritic cells, T, B, and NK lymphocytes, and immature myeloid cells in bone marrow, suggesting limited off-target activity. The peptibody treatment was associated with retardation of tumor growth in vivo highlighting the role of MDSC in tumorogenesis. Proteomic analysis of cell surface membrane proteins precipitated by the peptibodies suggests that the lead candidate target on the surface of MDSC is S100 family proteins (S100A9/A8). Through this proof-of-principle study, we established a technical platform of cell-specific marker discovery and a promising method to develop therapeutic reagents. 

Specific immunotherapy against cancer has been a long-sought, yet-to-be-achieved goal. Optimization of the therapeutic efficacy of specific cancer immunotherapy, to a large extent, may depend on correction of immune suppressive mechanisms in the tumor microenvironment, which renders tumor-specific cytotoxic T cells dysfunctional. Recently, a controlled vaccine clinical trial in patients with follicular lymphoma validated the concept of specific immunotherapy. The variable regions of the clonal Ig receptor on the surface of malignant B-cells contain determinants...
Figure 1. Targeting tumor associated myeloid cells for release of immunosuppression. In the tumor microenvironment, tumor associated myeloid cells can impair antitumor immunity though inhibitory effects on immune effector cells, including CD8\(^+\) T cells. Therapeutic peptibodies or monoclonal antibodies that specifically target tumor-associated myeloid cells can suppress the function of these cells and/or deplete these cells from the tumor microenvironment. This strategy has the potential to correct tumor-induced immunosuppression, and may be combined with other cancer treatments including immunotherapy or chemotherapy.
that can themselves be recognized as antigens, termed idiotypes (Id). Early pilot studies had demonstrated the immunogenicity of human lymphoma Id proteins, including CD8+ T-cell responses against processed Id peptides and molecular remissions. In the randomized controlled multi-center clinical trial, patients with previously untreated advanced stage follicular lymphoma were treated with a standard chemotherapy. Those achieving complete remission were randomized at a ratio of 2:1 to receive Id-KLH plus GM-CSF or KLH plus GM-CSF (control). Of 234 enrolled patients, 177 achieved complete response and were subsequently randomized to receive either active or control vaccine. Of these, 117 maintained a complete remission for the 6 m rest period and received vaccine. 76 patients received Id-KLH plus GM-CSF and 41 patients received KLH plus GM-CSF. Study arms were balanced for International Prognostic Index and other relevant clinical factors. After a median follow-up of 56.6 mo (range 12.6–89.3 mo), median time to relapse after randomization for the Id-KLH/GM-CSF arm was 44.2 mo, vs. 30.6 mo for the control arm, suggesting the benefit for this vaccine (30.6 mo for the control arm, suggesting the benefit for this vaccine (30.6 mo for the control arm, suggesting the benefit for this vaccine (30.6 mo for the control arm, suggesting the benefit for this vaccine (30.6 mo for the control arm, suggesting the benefit for this vaccine) 

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No potential conflicts of interest were disclosed.

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