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Expert opinion on burning questions in cancer myeloid cell biology

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INTRODUCTION

As part of the special *Journal for Immuno-Therapy of Cancer* (*JITC*) series, "Myeloid Cells in Immuno-Oncology," leading experts were asked to provide their perspectives and answer provocative questions on controversial and evolving areas in the field of myeloid biology. Their responses below aim to further the discussion and help advance the biological understanding of myeloid cell biology within the tumor and strategies to modulate the function and activity of myeloid cells for anticancer therapy.

Controversial issues with new age multi-omics of myeloid cells

1. What is the biological relevance of diverse transcriptional subsets of myeloid cells?
2. What has myeloid multi-omics taught us about favorable and unfavorable immune responses?
3. What are the challenges of multi-omics?

Authors: Miriam Merad, Florent Ginhoux, Renato Ostuni

Granulocyte actions and functions in cancer immunotherapy

1. What are the protumor versus antitumor functions of neutrophils?
2. What is the role of eosinophils in tumors?
3. What determines the granulocyte response in tumors? (ie, cytokine secretion)
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Authors: Karin E de Visser, Mikael J Pittet, Dmitry I Gabrilovich, Sven Brandau

Promises and challenges of granulocyte targeting in cancer

1. Are neutrophils/neutrophil extracellular traps (NETs) good or bad?
2. When do we need to target granulocytes for cancer therapy?
3. What are the limitations of targeting granulocytes for cancer therapy?

Authors: Taha Merghoub, Mikala Egeblad, Viktor Umansky

What is the future of myeloid cells as clinical biomarkers (what definitive proof exists) in cancer immunotherapy?

1. Which kinds of myeloid cells are being identified in association with cancer?
2. What states of myeloid cells are associated with response to therapy?
3. What myeloid cell targets/biomarkers in preclinical and clinical testing are most promising?

Authors: Lillian van Vlerken-Ysla, Thomas U Marron, Lisa M Coussens

Promises and challenges of modeling the role of myeloid cells in cancer immunotherapy

1. What approaches exist to identify myeloid cells in human and mouse tumors?
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3. Challenges and solutions with the use of mouse models to study myeloid cells

Authors: Jelani C Zarif, Brian Ruffell, Simon T Barry

BURNING QUESTIONS

Controversial issues with new age multi-omics of myeloid cells

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What is the biological relevance of diverse transcriptional subsets of myeloid cells?

MM: The transcriptional diversity of myeloid cells reflects their functional specialization and adaptation to local context. These subsets arise from distinct developmental origins and are shaped by tissue-specific cues and inflammatory signals, enabling myeloid cells to mount highly tailored responses across a range of physiological and pathological conditions. Tissue-resident macrophages, derived from embryonic precursors, self-renew locally and occupy specialized microanatomical niches. They serve as sentinels and guardians of tissue integrity, supporting functions such as debris clearance, vascular remodeling, metabolic regulation, and early detection of tissue stress—while shaping the local immune landscape through cytokine and lipid mediator production.

Monocyte-derived macrophages, in contrast, are recruited from the circulation in response to tissue damage or infection. These are short-lived, inflammatory effectors tasked with pathogen clearance and wound debridement—but if dysregulated, they can drive chronic inflammation and tissue pathology.

Importantly, both tissue-resident and monocyte-derived macrophages encompass a spectrum of molecular states, which evolve dynamically in response to local environmental cues. This intralineage heterogeneity allows for graded and highly context-dependent responses—ranging from reparative to pro-inflammatory to immunosuppressive phenotypes.

Understanding the distinct roles, plasticity, and interactions of these myeloid subsets in settings such as infection, cancer, and aging is critical for identifying pathogenic versus protective programs, and for guiding the development of precision myeloid-targeted therapies.

FG: The biological relevance of diverse transcriptional subsets of myeloid cell is essentially to support context-dependent specialized functions, that can be immune related with specialized roles such as phagocytosis, antigen presentation and secretion of cytokines but also physiological processes supporting tissue functions. Such transcriptional states are both intrinsic, related to their ontogeny and developmental stage and extrinsic in response to tissue-specific signals reflecting the environments in which they reside in homeostasis and disease. These cellular states can act in a synergistic way to establish a global type of response or in an antagonizing way cross-regulating each other. Such transcriptional diversity among myeloid cells is not just descriptive but truly reflects functional heterogeneity essential for immune regulation, tissue specialization and adaptation to disease contexts. Understanding this diversity and their molecular underpinnings is crucial for the design of new immunotherapies and diagnostics.

RO: Perhaps unexpectedly, single-cell RNA sequencing (scRNA-seq) analyses of the tumor microenvironment (TME) led to the identification of a finite number of myeloid cell subsets that are recurrently found across tumor types and patients. Such reproducible patterns of diversity must imply biological relevance—we just need to prove this experimentally. In this context, deletion or targeting approaches of myeloid cell subsets are complicated by the fact that the underlying gene programs are often shared with cells of other lineages that are exposed to the same environmental cues. Going forward, elucidating the spatial distribution and local interactions of cells within tissue niches might help to uncover the biological relevance of myeloid cell diversity.

What has myeloid multi-omics taught us about favorable and unfavorable immune responses?

MM: Myeloid-focused multi-omics has revealed that immune outcomes are dictated not just by cell presence but by cell state. Favorable responses—such as effective antitumor or pathogen control—often correlate with myeloid cells that sustain antigen presentation, type I interferon responses, and inflammatory cytokine production. In contrast, unfavorable responses are characterized by suppressive or dysfunctional states, often marked by metabolic rewiring, chromatin remodeling, and expression of tolerance-inducing genes (eg, arginase-1 (ARG1), interleukin (IL)-10, Secreted Phosphoprotein 1/osteopontin (SPP1/OPN). These insights help explain why similar cell types can have opposing effects depending on context and highlight new targets for immune reprogramming.

FG: Myeloid multi-omics have not only revealed the diversity among myeloid cells in health and disease, but that such diversity is inscribed in multiple dimensions, from RNA, protein, epigenetic profile, metabolic states and spatial location. It also allowed us to associate specific myeloid states such as pro-inflammatory, anti-inflammatory, antigen-presenting, and/or phagocytic, for example, with disease progression, disease stages and/or response to treatment. For example, one of the most unfavorable programs in cancer is the SPP1/triggering receptor expressed on myeloid cells 2 (TREM2) macrophage program related to immunosuppression with a marked lipid metabolism, especially lipid droplet accumulation as well as suppressive metabolites, such as high lactic acid. Careful though, as in some certain types of cancer, the presence of such macrophage program can be protective! Recent spatial omics work revealed also macrophages near tertiary lymphoid structures. One last dimension that should not be forgotten is the time dimension, as the states described are dynamic and can be related to each other in a differentiation path, underlining the crucial need for ontogeny-resolved and spatiotemporal definition of tumor-associated macrophages (TAMs).

RO: Regardless of whether we can assign a specific function to the myeloid cell subsets identified by scRNA-seq, their association with clinical outcome is highly context-dependent and patient-specific. While some recurrent macrophage subsets are consistently linked to poor prognosis and unfavorable antitumor immunity, others appear to correlate with better outcomes. These observations

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highlight the need to carefully consider the heterogeneity of myeloid cells when designing therapeutic strategies.

What are the challenges of multi-omics?

MM: Temporal resolution: Most multi-omic data provide static snapshots, which can obscure dynamic transitions and causal relationships. Incorporating longitudinal sampling, perturbation experiments, and deep spatial mapping is essential to capture the full spectrum of immune cell behavior over time and space.

Data integration: Harmonizing information across molecular layers (eg, transcriptome, epigenome, proteome, metabolome) and across platforms or datasets remain both technically and analytically complex, requiring advanced computational tools and standardization strategies.

Scalability and cost: Despite progress, the high cost and technical demands of multi-omic platforms limit their widespread application in clinical settings, particularly for longitudinal studies or large, diverse patient cohorts.

FG: Beyond the challenges of sample preparation, quality, compatibility as well as data integration and analysis, the biggest challenge of multi-omics is to make sense of the complexity and validate the relevance of the states identified.

Multi-omics approach generates a lot of hypotheses but remains correlative in nature. It requires to be associated to validation experiments to confirm biological relevance and establish causality.

RO: Every technology has its own limitations. For instance, scRNA-seq analyses are not genome-wide, as they capture only a subset of genes per cell (between 1,000 and 3,000 for macrophages, even less for neutrophils). In my view, the biggest challenge of multi-omics is data integration. Artificial intelligence (AI) will undoubtedly become a mainstay of immune oncology research, but we must remain aware of its limitations. Although we are now able to measure many parameters at once, the inherent complexity of biological systems likely exceeds the depth and resolution of current datasets. We are only beginning to understand the importance of the physical distribution of cells within their microenvironments—yet this is clearly a fundamental variable. In conclusion, multi-omics approaches will fulfill their potential for discovery and therapeutic exploitation only if we can generate standardized datasets, analyze them through reproducible and open pipelines, and apply curated and rational interpretation coupled with validation experiments.

Granulocyte actions and functions in cancer immunotherapy

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2. What is the role of eosinophils in tumors?
3. What determines the granulocyte response in tumors? (ie, cytokine secretion)
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Authors: Mikael J Pittet, Dmitry I Gabrilovich, Karin E de Visser, Sven Brandau

What are the protumor versus antitumor functions of neutrophils?

MP: Neutrophils are functionally heterogeneous cells that can exert both protumor and antitumor activities. Tumor-promoting neutrophils can support cancer progression by stimulating tumor cell proliferation, enhancing angiogenesis, and facilitating invasion, dissemination, and metastasis. In contrast, antitumor neutrophils can be cytotoxic or activate other immune effectors, contributing to tumor control and possibly influencing responses to immunotherapy. However, the antitumor functions of neutrophils within tumors remain poorly understood. More broadly, a major challenge ahead is identifying actionable regulators of divergent neutrophil states and developing strategies to control neutrophil fate for therapeutic benefit.

DG: Neutrophils should not be characterized simply as protumor or antitumor cells. Their evolutionarily developed functions include phagocytosis, bacterial killing via respiratory burst, production of bactericidal peptides, nitric oxide, and other mechanisms aimed at eliminating pathogens. Additionally, neutrophils produce cytokines that support inflammation, tissue remodeling, and angiogenesis, with the overarching goal of restoring homeostasis. Under "normal" conditions, these functions are generally beneficial to the host and are activated primarily during periods of stress.

In cancer, however, neutrophil biology becomes altered, leading to dramatic increases in the production of many of these factors, which can become detrimental to the host. For example, reactive oxygen species have been directly implicated in immune suppression; while arginase, a minor regulator in steady-state neutrophils, becomes a major factor in immune suppression in the tumor context. Similarly, levels of PGE2 and pro-inflammatory mediators increase substantially, contributing to immune suppression. Pro-angiogenic factors and metalloproteases, which are usually present at low levels in neutrophils, are also significantly elevated, thereby promoting tumor progression. This shift in neutrophil activity underlies the concept of a pathological state of neutrophil activation, termed myeloid-derived suppressor cells (MDSCs).

KEdV: Neutrophils display diverse functions in tumors, which vary depending on tumor stage, tumor type, and cues from the TME. Moreover, tumor-associated neutrophils are not a uniform population, but encompass distinct functional states with context-dependent, sometimes opposing, roles. In advanced tumor settings, neutrophils can acquire protumor functions, such as becoming immunosuppressive—helping tumors escape immune control by suppressing CD8+T cells and promoting metastasis. Others have reported that neutrophils can also support tumor angiogenesis, protect circulating cancer cells, and remodel the extracellular matrix. Conversely, antitumor neutrophils have been observed in early-stage tumors or

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in tumors treated with immune checkpoint blockade, where they can directly kill tumor cells or enhance T cell responses through cytokine production.

SB: As a general rule, I would say that in chronically inflamed human tumors, which contain substantial amounts of tumor-associated neutrophils (TANs), TANs are protumorigenic across most cancer types and patients. In contrast, in most scenarios, the antitumor function requires a therapeutic intervention that may either directly or indirectly activate neutrophils, for example, by changing the TME. Mechanistically, direct (invasion, metastasis of cancer cells) or indirect (angiogenesis, immunosuppression) protumor activities are described. Similarly, direct (cancer cell cytotoxicity) or indirect (T cell activation) antitumor activities exist.

What is the role of eosinophils in tumors?

MP: There is emerging evidence that links eosinophils to improved responses to immunotherapy in several cancer types, including melanoma, lung cancer, renal cancer, and breast cancer. In these contexts, eosinophils may promote antitumor immunity by recruiting T cells and enhancing T cell-mediated tumor control. However, eosinophils are not a consistent or abundant component of the TME, raising the question of why they are present in some patients but absent in others. Additionally, although eosinophil infiltration has been associated with therapeutic benefit, the mechanism by which immunotherapy elicits this response remains unclear. Understanding these dynamics may help better engage eosinophil-mediated anti-tumor mechanisms.

DG: The role of eosinophiles is not clear to me. It appears their contribution to immune therapy is different from neutrophils and the concept of MDSC may not be applicable to these cells. There is evidence supporting the antitumor activity of these cells. More data are needed to clarify the role of these cells in cancer.

KdV: Eosinophils are among the most understudied immune cell types in cancer, partly due to their low abundance and fragility. Like other members of the granulocyte family, they can exert both antitumor and protumor effects, depending on the context. Recently, eosinophils have emerged as surprising contributors to antitumor immunity. In patients with breast cancer treated with immune checkpoint blockade, we observed that blood eosinophil levels increased during therapy in responders but not in non-responders. Supporting this clinical observation, our preclinical tumor models demonstrated that eosinophils contribute to immunotherapy response by promoting the intratumoral accumulation of activated CD8+T cells. However, many questions remain—such as whether eosinophils support antitumor immunity through direct interactions with CD8+T cells or indirectly by modulating other immune cells. Additionally, the functional heterogeneity of eosinophils within the TME remains poorly understood.

SB: Because both eosinophils and neutrophils express CD66b and CD15, some larger clinical studies that use broader, rather than in-depth, immune profiling may (unintentionally) combine the scores of both cell types into one granulocyte score. For more accurate identification of eosinophils, the use of eosinophil-specific proteins, such as major basic protein, is recommended. In terms of function and role in tumors, there seems to be some overlap between neutrophils and eosinophils. Eosinophils may also directly kill tumor cells but use granule proteins different from neutrophils. Protumorigenic activity may be executed via indoleamine 2,3-dioxygenase (IDO), transforming growth factor-beta (TGF-β) and other cytokines, which are again distinct from immunomodulators produced by neutrophils.

What determines the granulocyte response in tumors? (ie, cytokine secretion)

MP: The granulocyte response in tumors is shaped by a multilayered regulatory network. Tumor-derived chemokines and cytokines promote granulocyte recruitment, while systemic signals can enhance granulopoiesis in the bone marrow or extramedullary sites. Additionally, it is important to note that granulocyte dynamics are not solely tumor-intrinsic. Systemic inflammatory states linked to aging, obesity, and other comorbidities can induce a myeloid bias in hematopoiesis, thereby influencing granulocyte abundance and function. Once in the tumor, local factors such as hypoxia, cytokines, and cell-cell interactions further modulate granulocyte function. Successful therapeutic interventions may activate an antitumor granulocyte response; however, further study is required to better understand this process and determine whether it could be amplified to improve treatment outcomes.

DG: The response of neutrophils in cancer is shaped by multiple factors, beginning at the level of the bone marrow and involving apparent transcriptional rewiring. Triggers for these changes may include endoplasmic reticulum (ER) stress responses, pro-inflammatory cytokines, or other tumor-derived factors. However, despite extensive research, the precise mechanisms remain elusive—likely due to the multitude of factors involved. The neutrophil response appears to depend on the nature of the tumor and the specific factors it produces.

At the tumor site, neutrophils are influenced by hypoxia, nutrient depletion, changes in metabolites in TME, and an increased presence of tumor-derived signals, all of which can exacerbate their activity. While cytokine secretion may contribute to neutrophil function in cancer, it does not appear to play a major role. Instead, neutrophils possess a much more potent arsenal of factors that impact the immune system and the TME.

KEdV: Many variables influence the abundance and functional state of granulocytes in tumors. Host-related factors—such as age, gender, lifestyle, and prior therapies—can all shape granulocyte responses. However, a key determinant is the tumor itself. Cancer cells engage in complex communication with immune cells through secreted cytokines and chemokines, extracellular vesicles,

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metabolic byproducts, and cell surface molecules. These signals influence the recruitment, activation, and polarization of immune cells, including granulocytes. Notably, these communication mechanisms are often driven by the (epi)genetic makeup of the cancer cells. For example, in our preclinical breast cancer models, we found that loss of *Trp53* in tumor cells altered the cancer cell secretome, which in turn induced IL-1β production by tumor-associated macrophages. This IL-1β signaling contributed to a systemic neutrophilic response, promoting metastasis.

SB: The granulocyte response is regulated at the level of the bone-marrow, within the TME and at sites of extramedullary granulopoiesis and neutrophil immunoregulation, such as the spleen. Granulocytes (neutrophils) undergo alterations in differentiation, expansion and activation, driven by well-characterized inducers including growth factors, cytokines, as well as host-derived or exogenous danger signals. The signals that determine whether a given neutrophil executes angiogenic or cytokine-secreting or T cell suppressive activity are less well defined and are often elusive.

What makes granulocytes pathological? (ie, what causes changes in granulocytes in blood and tumor)

MP: Harold Dvorak famously described tumors as "wounds that do not heal". This concept suggests that cancer progression is not driven by entirely new biological mechanisms but involves the co-option of existing programs that normally serve to protect or restore tissue integrity. Granulocytes, which play essential roles in host defense by mediating processes such as inflammation, pathogen clearance, and tissue remodeling, can have their functions redirected in the TME to promote growth, angiogenesis, immune suppression, and metastasis. What makes granulocytes pathological in cancer is likely not a change in their core identity or function, but the pathological context in which their normal activities are deployed.

DG: There are multiple factors contributing to this process. They are different depending on the type of tumors. In general, persistent ER stress, growth factors driving myelopoiesis, persistent pro-inflammatory cytokines effects, accumulation of polyunsaturated fatty acids, and abnormal lipid metabolism associated with cancer, other metabolic changes, hypoxia in the tumor site, etc, all contribute to this phenomenon. It is important to recognize that the factors influencing cells in bone marrow and in tumors are different. For instance, growth factors like granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte-colony stimulating factor (G-CSF) that are critical for the development of pathological neutrophils (MDSC) in bone marrow are likely not to be important for the cells that already migrated to the tumor site. Severe hypoxia (<1% O_2) is not a factor for bone marrow but is in a solid tumor. This is the focus of extensive ongoing investigations, given its direct therapeutic implications.

KEdV: Emerging data suggest that the tumor-induced education of granulocytes is a multilayered process that begins early during their development in the bone marrow. Tumors can systemically alter hematopoiesis, leading to accelerated commitment to the neutrophil lineage and early tumor-directed immunosuppressive imprinting. This process shapes granulocytes, and in particular, neutrophils, toward pathological phenotypes even before they enter the circulation. Once in the bloodstream or TME additional cues—such as cytokines, metabolic factors, and cellular interactions—further skew neutrophil function toward tumor-promoting activities. This stepwise education results in neutrophils that support immune evasion, metastasis, and therapy resistance.

SB: This is a complex question, but I will try to use a simple answer (for cancer): chronic, long-term neutrophil expansion and stimulation predominantly generate pathological neutrophils, which may also exhibit an extended lifespan (in both cancer and non-cancer settings). Acute and short-term (mostly therapeutic) intervention often generates neutrophil activation that may contribute to tumor control. In non-malignant inflammatory or autoimmune disease, we face a different scenario. These diseases may need blockade of neutrophils and/or their functions to prevent tissue damage and immunopathology.

Promises and challenges of granulocyte targeting in cancer

1. Are neutrophils/NETs good or bad?
2. When do we need to target granulocytes for cancer therapy?
3. What are the limitations of targeting granulocytes for cancer therapy?

Authors: Viktor Umansky, Taha Merghoub, Mikala Egeblad

Are neutrophils/NETs good or bad?

VU: Tumor progression is associated with the stimulation of granulopoiesis, primarily mediated by increased concentrations of the G-CSF, which results in the accumulation of circulating, not terminally differentiated (immature) neutrophils and in their migration into the TME. Such predominantly low-density neutrophils (LDNs) possess a strong immunosuppressive effect on activated T and natural killer (NK) cells through various mechanisms, including the production of reactive oxygen species, upregulation of ARG1, CD73, and programmed death-ligand 1 (PD-L1) expression. Based on their immunosuppressive capacity, LDNs could be also described as polymorphonuclear MDSCs (PMN-MDSCs). The protumoral role of neutrophils is also supported by their ability to create NETs, containing decondensed DNA with several cytotoxic enzymes and proteases released in the extracellular space. NETs have been shown to play an important role in cancer initiation and progression, with NET accumulation observed in both premalignant and malignant lesions. In multiple contexts, NET formation has been associated with tumor growth, metastatic dissemination and immune suppression.

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TM: Neutrophil function depends on the context. In cancer, neutrophils infiltrate tumor tissues and are designated as TANs. TANs display significant heterogeneity and plasticity, capable of either promoting or suppressing tumor progression. They have different roles depending on the context and immune landscape and factors such as cancer type, disease stage, and therapeutic interventions.

Formation of NETs has been shown to support the formation of metastasis in human and mouse cancer models. In other settings, neutrophils have been shown to eliminate cancer cells. In patients receiving immune checkpoint blockade, elevated peripheral neutrophil-to-lymphocyte ratios have been associated with poor clinical outcomes. However, more recently, neutrophils in tumors have been shown to have an antitumorigenic role in the context of multiple immune modulatory-based therapies. Current published research indicates that nearly every recognized neutrophil marker/function has been linked to both tumor-promoting and tumor-suppressing activities, highlighting their complex plasticity and often paradoxical roles in cancer.

ME: Neutrophils are essential components of the innate immune system, protecting against infections through antimicrobial activity, protease activity, and the formation of NETs. However, in cancer, these same effector functions can be co-opted to promote metastasis and suppress antitumor immunity. Excessive neutrophil accumulation and persistent NET formation can remodel the extracellular matrix, facilitate metastatic dissemination, and suppress cytotoxic immune cells. Notably, under certain conditions, neutrophils can be cytotoxic to cancer cells or support antitumor immune responses. A major challenge is to identify the cues—whether local or systemic signals—that govern when, where, and how neutrophils exert protumor versus anti-tumor effects.

When do we need to target granulocytes for cancer therapy?

VU: Numerous recent studies have demonstrated that tumor-infiltrating immunosuppressive neutrophils (PMN-MDSC) could serve as a negative prognostic factor in patients with different tumors, including renal cell carcinoma, melanoma, colorectal cancer, hepatocellular carcinoma, head and neck cancer and non-small cell lung cancer. Therefore, successfully targeting this cell population should be combined with other cancer immunotherapies to increase overall responses. Current targeting strategies include: (1) the inhibition of neutrophil migration to the tumor site via blocking the interaction of CXC-chemokine receptor (CXCR)2 and CXCR4 with the respective ligands; (2) the depletion of immunosuppressive neutrophils with chemotherapeutics such as gemcitabine or 5-fluorouracil; (3) the induction of their differentiation into mature, non-immunosuppressive or even antitumor neutrophils; and (4) the blockade of their immunosuppressive function mediated by an increased expression of ARG1 and other immunosuppressive molecules.

TM: When thinking of therapeutic interventions, it is important to consider the TAN states and functions at the time of the intervention. Most approaches have focused on manipulating protumorigenic neutrophils, which are generally present in the context of chronic inflammation. In that case, approaches that have been used are TAN depletion, blocking their recruitment (eg, CXCR2 inhibitors), or attempting to reprogram. Importantly, neutrophils can display antitumorigenic activity in defined contexts, including acute inflammatory responses, early stages of tumor development, and in response to certain therapies; in these settings, indiscriminate neutrophil inhibition or depletion may be detrimental. It is therefore critical to therapeutically reprogram neutrophils rather than broadly deplete them. Multiple approaches are being explored, including targeting TGF-β signaling, modulating type I interferon pathways, reshaping the TME by altering the cytokine and chemokine cues, and targeting metabolic pathways in the TME. In sum, TANs with cytolytic capabilities need to be expanded to increase their therapeutic potential, but these approaches are not well defined and have not yet reached the clinic.

ME: Preclinical studies suggest that neutrophil and NET targeting is likely to be most effective during the pre-metastatic or micrometastatic phase, before clinical detection of metastasis. In this time window, NETs can prime the distant tissues to support metastasis, for example, by altering the extracellular matrix and suppressing antitumor immunity. Therapeutic inhibition of NETs—via peptidyl arginine deiminase 4 (PAD4) blockade or deoxyribonuclease (DNase) I treatment—has been shown to enhance the efficacy of chemotherapy and immunotherapy in mouse models with relatively low tumor burden. Combining neutrophil/NET targeting with chemotherapy or immunotherapy in high-risk patients, particularly in the neoadjuvant setting before overt metastatic disease, may therefore offer the best responses by preventing niche conditioning and enhancing antitumor responses. Future studies are needed to clarify when neutrophil or NET targeting would provide the greatest therapeutic benefit.

What are the limitations of targeting granulocytes for cancer therapy?

VU: For effective cancer immunotherapy, it is critical to selectively inhibit immunosuppressive granulocytes while preserving the normal immune functions mediated by other subsets of granulocytes. Moreover, immunotherapies targeting granulocytes can produce unintended toxicities, including collateral depletion of other immune populations such as monocytes and subsets of $CD8^+$ T cells. Thus, while selective targeting of immunosuppressive granulocytes represents a promising therapeutic strategy, current approaches risk eliminating immunostimulatory granulocytes and key monocyte and $CD8^+$ T-cell populations required for effective anti-tumor, antibacterial, and antiviral immunity.

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TM: The limited functional mechanistic understanding and characterization of TAN in different tumor context and existing therapeutic intervention limits the way in which we can modulate them in patients. An enhanced understanding of their dynamics and functions in patients will enable us to design better mechanistic-based adaptable strategies to manipulate TAN.

ME: Several limitations need to be considered for the clinical translation of granulocyte-targeting therapies. First, the mechanisms that dictate neutrophil heterogeneity and fate decisions remain incompletely defined, hindering efforts to selectively deplete tumor-promoting subsets while preserving antimicrobial and antitumor functions. Second, neutrophil-targeted therapies may increase infection risks, although antibiotic treatment can likely mitigate this. Third, the optimal target(s) remain unclear: should we inhibit recruitment (eg, via CXCR2 or G-CSF), suppress NET formation (eg, via PAD4 inhibition), or block downstream effectors (eg, proteases, histones, extracellular DNA)? Finally, the short lifespan of circulating neutrophils (hours to days) poses pharmacologic challenges, which may be overcome if neutrophil targeting treatments can be timed around surgery or delivered concurrently with cytotoxic therapy. Overcoming these limitations will require not only refined targeting strategies, but also a deeper understanding of neutrophil biology and of the dynamic interactions between neutrophils, their bone marrow progenitors, and the evolving TME.

What is the future of myeloid cells as clinical biomarkers (what definitive proof exists) in cancer immunotherapy?

1. Which kinds of myeloid cells are being identified in association with cancer?
2. What states of myeloid cells are associated with response to therapy?
3. What myeloid cell targets/biomarkers in pre-clinical and clinical testing are most promising?

Authors: Thomas U Marron, Lillian van Vlerken-Ysla, Lisa M Coussens

Which kinds of myeloid cells are being identified in association with cancer?

TUM: It is well established that TAMs with immunosuppressive functional states—which we now know are primarily monocyte-derived macrophages (moMacs), rather than derived from tissue-resident macrophages such as alveolar macrophages or Kupffer cells—are one of the key barriers to antitumor immunity, and responsiveness to checkpoint blockade. Many approaches have been tried to deplete macrophages from the tumor; however, when this is done in an agnostic or non-targeted fashion, with the aim of depleting all macrophages using approaches such as colony-stimulating factor 1 receptor (CSF1R) blocking antibodies or small molecules (highly effective in tenosynovial giant cell tumors), we may be "throwing the baby out with the bathwater". Rather, single-cell transcriptomic technologies have enabled resolution within the macrophage compartment, which has revealed a significant heterogeneity among the moMacs, with certain subsets classified by markers such as TREM2, SPP1 and folate receptor beta (FOLR2). It is notable that these subsets are consistently being identified across solid tumor histologies, both in immunogenic and non-immunotherapy-responsive tumors. This suggests not only that, while everyone's tumor is unique, there are a finite number of myeloid functional states that exist that are driving tumor progression and immune escape, and also that there are shared immune evasion programs across tumor histologies regardless of a tumor's classification as "hot" or "cold."

While selective depletion of immunosuppressive macrophages may improve response to cancer immunotherapies, and durability of response, conversely, it would be advantageous to enrich for immunogenic macrophages capable of supporting antitumor immunity. Macrophages may play key roles both by promoting a milieu that fosters antitumor immunity mediated by T cells, B cells and NK cells, and via direct phagocytosis of cancer cells in response to tumor intrinsic ligands or tagging of cancer cells with Fc-competent antibodies capable of binding to macrophages. Given this potential, it is key to pursue therapeutic approaches that either deplete discrete immunosuppressive subsets—for example, TREM2-depleting antibodies—and/or approaches that can reprogram (or augment) the beneficial antitumor functionality of macrophages.

LvV-Y: Irrefutable evidence exists to independently associate nearly all cell types from the major monocytic, granulocytic, and dendritic myeloid lineages with disease outcome or therapeutic responses across the solid tumor landscape. But a recent trend has emerged pointing to an unexpected role for neutrophils in cancer response. Historically, neutrophils have been attributed to poor outcomes, peripherally seen in neutrophil-to-lymphocyte ratio to outcome, and intratumorally from evidence demonstrating neutrophils undergo pathological activation in the TME to become more MDSC-like. However, newer evidence has attributed neutrophil subtypes as positive predictors of response and outcome across multiple solid tumor types, which are critically adding to our understanding of this complex myeloid cell. LY6E^{high} neutrophils associated with improved response to checkpoint therapy in patients with both lung cancer and melanoma, and interestingly, appeared to be more predictive of response than PD-L1 status. And in separate lines of evidence, neutrophils with apparent antigen-presenting capacity, marked as CD74^{+}, but also Human Leukocyte Antigen – DR isotype (HLA-DR^{+}) or CD63^{low}, associated directly with response to checkpoint therapy in lung cancer, and served as predictors of improved outcome across many solid tumor malignancies. Such evidence not only adds to the understanding of what myeloid cells are being identified in association with cancer but sheds new light on how we think about their functional roles in disease management.

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LMC: The better question is: Are there any myeloid cells that have not been identified as being associated with cancer? Answer: No. Akin to wound healing, resident and recruited myeloid subsets are rapidly "activated" or recruited (respectively) where many of their "wound healing" activities are co-opted by early neoplasms to aid tumorigenic processes, for example, extracellular matrix remodeling, angiogenesis, quelling T cell pathologies.

What states of myeloid cells are associated with response to therapy?

TUM: Historically in immunology we have attempted to dichotomize our understanding of cellular responses, with type 1 response (Th1 in the lymphoid compartment and M1 or N1 in the myeloid compartment) promoting antitumor immunity while type 2 response labels (Th2, M2, N2) correlating to cell states that promote tumor immune evasion and tumor growth and metastasis. Within macrophages, this M1/M2 differentiation is now clearly overly simplistic; rather, single-cell transcriptomic analysis has enabled ontogeny mapping and subclassifications that demonstrate significant heterogeneity, a spectrum of functionality in regard to antitumor immunity, and also evidence that these states are highly plastic and respond to tumor and metabolic cues that can be therapeutically targeted.

LvV-Y: Preclinical cancer immunotherapy studies using selective monocyte/macrophage or neutrophil depletion are a gold standard to validate the functional association of myeloid cells in therapy response. And while most models consistently demonstrate improved response to immunotherapy under myeloid depletion, confirming a suppressive functional state, the existence of studies in similar models demonstrating a reverse trend highlights the functional importance of antitumor myeloid states in the immunotherapy response as well. Which cellular states emerge as driving forces is context dependent and a factor of many intrinsic and external variables such as tumor type and location, treatment, genetic factors, and environmental cues, and likely a dynamic continuum. Newer approaches that measure the balance between tolerant and reactive states, for example, the measure of macrophage polarity defined by CXCL9:SPP1 ratio, and T-effector to macrophage ratio by CD8:C1QA may emerge as better predictors of immunotherapy response from capturing a balance between functional states, as opposed to a specific state in isolation.

LMC: Depends on the therapy. If referring to standard cytotoxic chemotherapies, several classes of which induce myelomonocytic recruitment into neoplastic tissues, as well as altering homeostatic immune composition in otherwise healthy tissues. RNA profiling reveals fostering of classical Th2-type transcriptional programs, many of which are regulated by phosphoinositide 3-kinase gamma (PI3Kγ) signaling, and largely drive "pro-tumorigenic" activities, for example, matrix remodeling, angiogenesis, hypoxia, fibrosis, T cell-suppression. Taxanes and anthracyclines also elicit release of tumor-derived prometastatic extracellular vesicle impacting endothelial and monocytic cells to aid seeding and expansion of tumors distally. Suppression of any of these myeloid-mediated activities makes sound biological sense—the key will be in understanding how to judiciously combine "myeloid" inhibitors with other therapies to achieve improved clinical responses.

What myeloid cell targets/biomarkers in pre-clinical and clinical testing are most promising?

TUM: Our group has demonstrated the systemic nature in which the tumor hijacks myeloid biology. Through production of chemokines and cytokines we have shown hyperactivation of type 2 granulocytes, importantly basophils, within the bone marrow which produce IL-4 promoting early imprinting and expansion of the granulocyte-monocyte progenitors. Similarly, in aged patients, we see progressive systemic hyperactivation of the inflammasome—so-called inflammaging—that is further exacerbated in the setting of cancer. This so-called "emergency myelopoiesis" that is induced by growing cancer promotes an efflux of immature monocyte progenitors that then traffic through chemokine gradients into the tumor where they differentiate into moMacs and further promote immune evasion, tumor growth, and metastatic potential. This phenomenon has been shown in numerous tumor types, and some patients may benefit from blockade of either the type 2 or inflammasome/IL-1 axes; however, clinical trials demonstrate that only a minority of patients will benefit from these approaches. These studies, though, support the development of blood biomarkers—easier to investigate with large cytokine/chemokine panel platforms now available—to identify specific mechanisms of immune evasion that may be targeted, whether this be through cytokine blockade in patients where this emergent myelopoiesis is a driving factor for tumor growth, through Janus kinase inhibitors in patients where systemic signatures of exhaustion are prominent, or through targeted administration of cytokines such as IL-12.

LvV-Y: A challenge in the field is that tumor-associated myeloid function has been largely restricted to interactions measured in the tumor tissue, leaving peripheral blood-based biomarkers to predict or track tumor myeloid function elusive. MDSCs being one notable exception, as these cells emerge from pathological influences unto myelopoiesis, and have demonstrated utility as blood-based biomarkers in prognostic and treatment response across many solid tumors. Related is the protein complex S100A8/A9, primarily secreted by myeloid cells, which is gaining traction as a plasma biomarker of prognosis in cancer. Several recent studies have shown utility as a liquid biomarker predicting response to checkpoint therapy across independent studies in lung cancer, melanoma, triple-negative breast cancer, and gastric cancer. And Wang *et al* found, in their model of neutrophil-mediated breast cancer metastasis, that S100A8/A9 differentially tracked with neutrophil accumulation into

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lung metastatic niches compared with neutrophil accumulation into healthy tissue, and that a ratio between CXCL1:S100A9 correlated not only with the aggressiveness of breast cancer in the model, but also with the survival outcomes when applied as a gene signature to data from patients with breast cancer. Thus, fueling interest in this target not just therapeutically, but as a putative liquid biomarker for myeloid function as well.

LMC: This depends largely on the subset of myeloid cells being evaluated. For myelomonocytic cells, several therapeutic targets have emerged in the preclinical arena. Our focus has been on colony stimulating factor 1 receptor signaling since it regulates a critical myelomonocytic survival pathway for recruited monocytes and macrophages. But we have also investigated Spleen Tyrosine Kinase (SYK) and Bruton's Tyrosine Kinase (BTK), both of which are activated downstream of Fcγ receptors, as well as PI3Kγ (for BTK) on myelomonocytic cells where they regulate Th2 transcriptional programs. As monotherapies, inhibitors of CSF1R, SYK, BTK or PI3Kγ minimize Th2 programming, but none have demonstrated antitumor efficacy when delivered as monotherapies at late stage. However, when combined with cytotoxic chemotherapy, preclinical tumor progression kinetics are significantly slowed, with tumor regressions observed only when an immune checkpoint inhibitor (ICI) is also added. Preclinical studies indicate that sequential addition of these combination approaches is critical—this makes sense biologically where the myeloid-reprogrammer first relieves T cell suppression and quells protumorigenic activities, followed by the cytotoxic to drive antigen priming (from cell death debris), followed by the ICI to drive T cell proliferation and cytotoxicity downstream of T cell receptor priming by antigens in a microenvironment where myelosuppression has been minimized. Other combination approaches are also demonstrating preclinical efficacy along these lines including epigenetic modifiers, and DNA repair Poly (ADP-ribose) polymerase (PARP) regulators. The key to success with all of these is the combination approach where multiple “hallmark” cancer programs are sequentially neutralized.

Promises and challenges of modeling the role of myeloid cells in cancer immunotherapy

1. What approaches exist to identify myeloid cells in human and mouse tumors?
2. How can human disease be modeled?
3. Challenges and solutions with the use of mouse models to study myeloid cells

Authors: Jelani C Zarif, Brian Ruffell, Simon T Barry

What approaches exist to identify myeloid cells in human and mouse tumors?

JCZ: Approaches to identify myeloid cells in tumors include surgical resection followed by digestion of the tumor into a single-cell suspension. For tumors with low numbers of immune cells, enrichment may be necessary, using magnetic beads or density gradient centrifugation for further downstream analysis such as flow cytometry and scRNA-seq. Other approaches for identifying myeloid cells in tissues include immunohistochemistry, spatial transcriptomics, and immunofluorescence on tissues from surgically resected tumors.

BR: Nothing special is required for the major populations once you have the correct markers, whether through-flow cytometry, immunohistochemistry, or scRNA-seq. Challenges mostly arise when trying to assign function to a phenotype or identify subpopulations. Although it has become easier to identify subpopulations with scRNA-seq, this does not necessarily mean a single marker can be translated to flow cytometry or spatial analysis, usually due to broad expression patterns. More importantly, markers associated with a particular function or phenotype are not sufficient to dictate that an identified population is performing that function within tissues.

STB: With successive waves of omics technologies, the field now has access to extensive datasets that characterize human and mouse myeloid cells at unprecedented resolution. Fluorescence-activated cell sorting (FACS), cytometry by time-of-flight (CyTOF), single-cell sequencing, and Cellular Indexing of Transcriptomes and Epitopes by sequencing (CiteSeq) offer powerful opportunities to generate complex maps of myeloid cell subsets. We are looking at myeloid cells with ever greater complexity. More often, studies are moving to using RNA signatures (often on tissue homogenate) to implicate different myeloid cell lineages or activity states or lineage switching (particularly with investment in CiteSeq). However, a critical gap exists in our ability or approaches to faithfully determine the specific activation state of the myeloid cells using biomarkers, and to use generic or standardized mechanistic biomarkers to guide therapeutic interventions.

Ultimately, what we need are accessible consistently used imaging (immunohistochemistry (IHC) or similar) based biomarkers that will enable us to navigate from mouse to human (improve predictivity and translatability of preclinical to clinical), and enable prospective patient selection for trials, and improve mechanistic or pharmacodynamic biomarker studies. With the caveat that the key markers may be different in different organs, it would still be a huge step forward to define the key markers for myeloid cell function/biology in specific disease settings. Studies are starting to emerge that address this.

Where we also struggle is managing, understanding and normalizing these diverse data sets. In particular, protein or RNA signature-based biomarkers can vary between preclinical studies depending on the code, isolation method, statistics, models/strains. Moreover, RNA signatures are not often interrogated at the individual transcript level to understand the dominant transcripts selecting the signature. In human disease, variability increases; therefore, better definition of tumor and organ (eg, primary tumor and liver or lung metastasis) specific myeloid cell content aligned to other tumor types is going to be important. It is possible that with the right data sets, AI approaches will help improve predictivity.

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How can human disease be modeled

JCZ: Human disease modeling remains challenging in both rodent and non-human primate models. Prostate cancer illustrates this clearly. In mice, the prostate gland differs substantially from that of humans in its anatomy, lobular organization, and physiology. Importantly, mice do not produce prostate-specific antigen. Approaches for other cancer types that have been widely used are genetically engineered mouse models (GEMMs) harboring mutations commonly observed in human cancers. More recently, Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9 (CRISPR-Cas9)-based strategies have enabled the targeted knock-in of human genes not natively expressed in mice, allowing investigation of gene regulation, tumor-immune interactions, and therapeutic targeting with the goal of improving translational relevance. Innovative organ-on-chip devices and the usage of humanized mice have also been developed to help translate findings.

BR: I am not convinced that current humanized murine models excel at reflecting the biology of human myeloid cells. It is also difficult to study myeloid biology in a dish when the cells are adapting to the cell culture conditions, although this approach works well for asking defined questions. What has been transformational for us has been the vast resource of publicly available human scRNA-seq data. This has allowed us to compare expression patterns and gene signatures across species as we continue to use murine models for mechanistic studies. As spatial scRNA-seq datasets begin to become available, our capacity to study myeloid cells in human disease will be further expanded.

STB: The best way to model human disease is in humans. The myeloid field has been hampered by a lack of interventional biomarker studies where proof of concept data in preclinical models has been directly translated into human clinical trials. I believe that as we deepen our understanding of human disease and more objectively align preclinical models with human biology, this will drive renewed investment in clinical trials. This should include repurposing of older agents—particularly when such molecules can potentiate emerging therapies such as bispecific antibodies, chimeric antigen receptor T cells and T-cell engagers to deliver improved therapeutic regimens.

Humanized engrafted models can provide insights into how tumors shape monocyte-derived cells from the bone marrow and influence their homing to the tumor. These systems may be useful as pharmacological models; however, when both human T cells and myeloid cells are co-engrafted, their translational relevance should be interpreted with caution. Modeling neutrophil-derived lineages remains particularly challenging in humanized models. Mouse models, in particular disease-relevant genetically engineered tumor models, will remain a backbone for elucidating the complexity of myeloid cell biology in the context of the tumor genetics, TME, the organ of residence and in some cases also the influence of other features such as diet and obesity or age.

I feel that efforts to align the features of disease-relevant models to human disease are most likely to give the best return on investment and build confidence in future investment in myeloid therapeutics. When validating a novel therapeutic target or developing a new therapeutic modality producing a data set that identifies a segment where the molecule is likely to be successful in combination with ICI or chemo/radiation is now essential. The field needs positive Phase I and IIa studies where meaningful changes in efficacy measures relative to standard of care are clear. Start small/focused and then build on findings based on positive data.

Challenges and solutions with the use of mouse models to study myeloid cells

JCZ: One challenge in certain tumor types is the availability of models of a particular tumor type. In addition to this, there are several tumor cell lines that grow in immune-competent mice that are either incapable of growing in vitro and thus, can only be passaged in vivo from one mouse to another. A few other major challenges with some of the models that grow in immune-competent mice have been whether the tumor is pathognomonic of human disease, whether it metastasizes from the primary site and, if it does, is it representative of human disease? In prostate cancer models, there are many tumors that express androgen receptor (AR), have a mutated AR, overexpress cellular myelocytomatosis oncogene (c-MYC), have a loss of Phosphatase and Tensin Homolog (PTEN), as well as express other key prostate adenocarcinoma markers, but the tumors do not exhibit treatment-resistant osteoblastic metastatic disease in vivo. Thus, these key prostate cancer features found clinically do not replicate the pathologic features of human prostate cancer, thus making it difficult to translate research findings to human disease. One method to overcome this is the utilization of better GEMMs and using patient-derived xenografts that are implanted into humanized mice.

BR: There is always a risk of having a vaccination effect when establishing a transplantable tumor. However, we have had great success in mirroring leukocyte infiltration in transplantable models by using tumor mixtures directly taken from spontaneous tumors or cell lines recently generated from such tumors. Provided that your transplantable system models the original tumor (and human disease), it is an excellent resource for genetic manipulation and conducting large preclinical studies. There is also the potential benefit of the cell line having a mutational signature more aligned with human cancers. There are two big issues when using transplantable models for myeloid research. The easiest one to address is the reliance on subcutaneous implantation, as there is now substantial literature establishing that the immunobiology of tumors is organ-specific and needs to be

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evaluated orthotopically. The second issue is that most of the commonly used cell lines express high levels of chemokines/cytokines that alter myeloid recruitment and function, thereby creating tumors dominated by monocytes or neutrophils. This can be addressed using newer cell line models or direct transplantation from mice with autochthonous tumors.

STB: The more disease-relevant models such as GEMMs, or organ-specific models are a step forward. With increased investment in omics approaches, it is possible to align these models to specific disease sets. While they are less likely to respond to an immunotherapy-based intervention, maybe this reflects the real situation in humans? Are myeloid therapies appropriate for only certain subsets of disease? These are expensive models to run, and maintaining a panel of these models for a specific disease type is likely prohibitive for many labs. That said, my experience is that myeloid cell therapies can generate positive immune effects in these models, and indeed different models can yield different outcomes, which is a starting point for refining patient selection. More work to refine the GEMMs and perhaps create "hotter" models that align to human data could be valuable as alignment to human segments needs to be an anchor point. This is not easy in the current funding environment. More inflammatory transplantable models, such as syngeneic models, have their place, but there is a danger of over-interpreting the data. While syngeneic models implanted subcutaneously are accessible and cheap, they will not mirror the specifics at the tumor/organ interface. They can allow relationships such as pharmacodynamics/pharmacokinetics, dose schedule to be defined with an agent but are not predictive of any human disease segment. Transplantable models derived from genetically engineered models are more likely to recapitulate human disease, particularly when established in primary or metastatic sites are more likely to give more confidence in where to focus a trial. But again, this should be interpreted with caution.

The time of treatment is also important to consider. Generally, most published studies with myeloid cell modulators are short term, lasting weeks. When thinking about how this translates to cycles in human disease, maybe we are only modeling the acute phase of treatment, but not the phase that results in sustained long-term therapeutic response. For a standard syngeneic model, are we commonly modeling the brake on the immune system and not the full immune cycle?

As a general comment on the preclinical models, we only see the positive data. Generally (and seen with most papers), it is hard to publish studies where pharmacologically active or functionally relevant myeloid modulators do not work. A vehicle to make available these types of data will help significantly in aligning both the models and the proposed mechanisms relevant to human disease, and also the probability of translating a myeloid cell targeting therapeutic to clinical proof of concept. This has driven transformational success for tumor-targeted drugs, and it is possible to do the same for myeloid cells.

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