ImmunoTools *special* Award 2026





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Defining cytokine programs regulating alveolar macrophage fusion and multinucleation

Background: Alveolar macrophages (AMs) are the predominant immune cells residing within lung alveoli, where they play essential roles in maintaining tissue homeostasis and coordinating immune responses to inhaled pathogens, allergens, and environmental particles. Traditionally, tissue-resident AMs have been considered highly specialized and relatively stable cells. However, recent work from our laboratory demonstrated that tissue-resident AMs are considerably more plastic than previously appreciated (Verwaerde et al., Immunity, 2026; PMID: 41386231). During IL-33-driven type 2 inflammation, ILC2-derived IL-13 reprograms AMs and promotes the formation of multinucleated giant cells within the alveolar compartment. These findings established that AM multinucleation is a regulated differentiation process rather than a mere consequence of chronic inflammation.

While multinucleated giant cells are frequently observed in inflammatory and granulomatous diseases, the signals that govern their formation and specialization remain incompletely understood. Importantly, multinucleation occurs across distinct cytokine environments. Instead, different cytokine milieus give rise to osteoclasts involved in bone remodeling, foreign body giant cells that develop around persistent materials, and Langhans giant cells that are characteristic of granulomatous inflammation such as Tuberculosis. Although these cells share a common myeloid origin, they arise in distinct immunological environments, present with a distinct morphology, and depend on different cytokine signals. Osteoclasts are classically generated in response to M-CSF and RANKL, foreign body giant cells are promoted by type 2

cytokines such as IL-4 and IL-13, whereas Langhans giant cell formation is associated with IFN-γ in combination with IL-3 or GM-CSF (Ahmadzadeh et al., Front Cell Dev Biol., 2022; PMID: 35478968). Together, these observations suggest that local cytokine milieus direct macrophage fusion toward specialized multinucleated states. Whether pulmonary multinucleated giant cells represent another such cytokine-instructed differentiation program remains unknown. Building on our recent finding that an IL-33-ILC2-IL-13 axis induces AM fusion, we will define cytokine networks controlling giant-cell formation and compare them with established multinucleated programs.

Hypothesis: We hypothesize that AM-derived multinucleated giant cells represent a distinct differentiation state that is instructed by specific cytokine milieus. Similar to osteoclasts, foreign body giant cells, and Langhans giant cells, different inflammatory environments may direct macrophage fusion and shape the resulting multinucleated cell phenotype. Finally, these cytokine networks might be transferable to human giant cell formation.

Role of ImmunoTools reagents for the experimental strategy:
This project critically depends on recombinant cytokines and growth factors. Primary murine AMs will be isolated and expanded using GM-CSF and TGF-β. Inflammatory environments will subsequently be recreated in vitro using cytokines implicated in multinucleated cell formation, including IL-13, IL-4, IFN-γ, IL-3, IL-33, IL-5, IL-6, TNF-α, IL-1β, GM-CSF, M-CSF and RANKL. These reagents will enable systematic assessment of how cytokine milieus regulate AM fusion and multinucleation. In parallel, M-CSF in combination with RANKL, IL-4 and/or IL-13, or IFN-γ will be used to generate osteoclast, foreign body, or Langhans giant cell cultures from murine total bone marrow as a reference model of macrophage fusion. Comparative analyses will identify shared and distinct features of pulmonary multinucleated giant cells and osteoclasts. Finally, these cytokine networks will be projected onto human giant cell formation from blood monocytes.

This work will provide insight into how distinct cytokine environments regulate macrophage multinucleation and determine the phenotype of resulting multinucleated giant cells across species.

ImmunoTools *special* AWARD for

Maxim Van Assel and **Lukas Amon** includes 2x 10 reagents

recombinant mouse cytokines: rm GM-CSF, rm M-CSF, rm IL-4 & rm IL-13, rm IFN-γ & rm IL-3, rm sRANKL, and inflammatory upstream mediators rm IL-33, rm TNF-α, and rm IL-1β.

recombinant human cytokines: rh GM-CSF, rh M-CSF, rh IL-4, rh IL-13, rh IFN-γ, rh IL-3, rh sRANKL, TNF-α, rh IL-1β, and rh IL-6.