Podoplanin, Cancer, and Inflammation:
Report from the 2018 International PDPN Meeting

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Abstract:
Podoplanin (PDPN) is a mucin transmembrane receptor with notable expression on kidney podocytes, type-I alveolar cells, and lymphatic endothelial cells. Importantly, PDPN is upregulated in cancer and inflammatory conditions including arthritis and sepsis where its expression affects disease progression and outcome. This letter highlights emerging themes that are central to PDPN function and role in disease detection and treatments. These include the use antibodies, chimeric antigen receptor (CAR)-T cells, and other biologics to treat cancer, as well as novel approaches to treat sepsis and arthritis.

Background:
Podoplanin is a unique mucin transmembrane receptor expressed during embryonic development, with adult expression restricted to tissues including kidney podocytes, type-I alveolar cells and lymphatic endothelial cells. Podoplanin is upregulated in cancer and aberrant inflammation such as arthritis and sepsis; its expression is associated with disease progression and outcome (1, 2). Podoplanin interacts with a number of soluble and transmembrane proteins including CD44, C-type lectin like receptor-2 (CLEC-2) and the ERM proteins to direct cell polarity and motility and the inflammatory phenotype (3).

Results and Discussion:
Podoplanin expression drives complex signaling events in the tumor microenvironment. For example, podoplanin empowers cancer associated-fibroblasts to forge avenues into surrounding tissue that enables the malignant progression of cancers including squamous and pulmonary carcinoma (4). This process appears to rely on the Src tyrosine kinase to disrupt cadherin junctions that normally impose order to tissue architecture (1).

In addition to cancer progression, podoplanin is also an important regulator of the inflammatory response under sterile and infectious conditions. During inflammation, podoplanin is upregulated on inflammatory macrophages and fibroblasts to regulate their migration and activation. The expression of podoplanin is driven by infectious agents, inflammatory cytokines, and is further regulated by association with endogenous ligands (3, 5) (6). Furthermore, podoplanin has also been identified as a co-inhibitory cell surface receptor that is expressed together with PD-1 and TIM3 and is induced by IL27 on CD4 T helper (Th17) cells, regulatory T (Treg) cells, and tumor infiltrating lymphocytes (7, 8). Podoplanin-overexpressing T cells show impaired peripheral survival, while deletion of either podoplanin or CLEC-2 results in spontaneous peripheral autoimmunity akin to multiple sclerosis and increased antitumor responses in mouse models (9).

Monoclonal antibodies that target podoplanin can also be used to inhibit cancer progression. Podoplanin binds to CLEC-2 on platelets increasing tumor embolization and metastasis. Platelet activation results in the release of growth factors that further enhance tumor expansion. Therefore, antibodies that block podoplanin-CLEC-2 interactions are able to suppress tumor progression and reduce metastasis. For example, the PG4D2 monoclonal antibody targets the CLEC-2 binding site on podoplanin, blocks podoplanin-dependent platelet aggregation, and suppresses human podoplanin-positive tumor progression and metastasis in a xenograft model (10). Podoplanin can also be targeted with third generation chimeric antigen receptor (CAR)-T cells that have been engineered with recombinant LpMab-2 cancer-specific mAb (CasMab) antibody which is specific for podoplanin produced by malignant cells. These CAR-T cells have been shown to target glioma cells without targeting podoplanin expressing normal cells, raising the possibility of cancer-specific targeting of podoplanin. Other agents such as *Maackia*

amurensis seed lectin (MASL) have also been found to target podoplanin in order to inhibit melanoma and oral squamous cell carcinoma cell growth and motility (11). Moreover, podoplanin expression on tumor cells represents a powerful biomarker that can be used to detect single tumor cells in liquid biopsies from patients. This is evidenced by fluidic arrays with anti-podoplanin antibodies that capture circulating mesothelioma cells in human blood (12).

Conclusions:

Podoplanin is emerging as a functionally relevant biomarker and therapeutic target for diseases related to cancer and inflammation. Therapies that target podoplanin offer new avenues to selectively treat cancer and inflammatory diseases in a cell-specific manner.

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Conflicts of Interest:

NF is the recipient of a research grant from Api, CO., Ltd, to develop anti-podoplanin antibodies as a therapeutic agent, and GSG has intellectual property and ownership in Sentrimed, Inc. which is developing agents that target PDPN to treat diseases including cancer and arthritis.

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