Project Title:	Screen for molecular targets in the senescence response of tumor cells to chemotherapy 化療導致腫瘤細胞衰老反應的分子靶標篩選
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With the funding support for this project, the team revealed a novel signaling mechanism that plays an important role in the malignant activity of lung cancer cells.

Misplaced IgG expression in cancer cells has been implicated in exacerbated malignancy and poor clinical prognosis. Accumulating evidence indicate that a nonconventional sialylation modification is critical for the function of cancer-derived IgG, rendering the name sialylated cancer IgG (SIA-cIgG). However, the knowledge regarding the regulatory mechanism that controls the expression and function of SIA-cIgG has remained rudimentary to the team.

Here, the team conducted genome-wide CRISPR activation screening and identified OCT4 and SOX2 as the key factors that promote SIA-cIgG expression. Interestingly, the team's functional investigation revealed that SIA-cIgG reciprocally stimulates SOX2 by activating the c-Met/Akt/Erk signaling axis, constituting a self-propagating loop of SIA-cIgG-c-Met-SOX2-SIA-cIgG signaling. This signaling loop is highly active in stem-like cells of many epithelial cancers and is crucial for cancer stemness in vitro and in vivo. Notably, this signaling loop can be effectively blocked by the monoclonal antibody RP215, which specifically recognises the Asn162 sialylation-related epitope on SIA-cIgG. Furthermore, RP215 significantly inhibited lung cancer cell stemness and tumor growth in a patient-derived xenograft model.

In conclusion, the research findings revealed a self-propagating c-Met-SOX2-SIA-cIgG signaling loop that promotes cancer stemness, conferring a novel therapeutic target for cancer treatment. The work has been published in the prestigious journal Cancer Research.

Moving forward, the team will develop immunotherapeutic tools that target this signaling axis to treat and cure cancer.