Conditionally Active Biologics Eliminate Senescence Cells in Cancer and Aging

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INTRODUCTION

- Cellular senescence is characterized by stable cell cycle arrest and a secretory program that modulates the tissue microenvironment. The aberrant accumulation of senescent cells in aged and cancerous tissue triggers inflammatory signaling through a senescence-associated secretory phenotype (SASP), promoting aging and tumor progression (1).
- Senescent cells exhibit high metabolic activity and create a high glycolytic microenvironment with low pH that can promote inflammation, angiogenesis, and cell proliferation (2).
- Senescent cell accumulation causes local and systemic effects that damage tissue and promote age-related pathologies such as kidney failure, atherosclerosis, Type 2 diabetes, arthritis, and chronic pain (3).
- Most of senescent cell elimination strategies are focused on intracellular senescence targets that often have important functions in normal cell populations. Consequently, senolytics in the clinic is limited by their cytotoxicity to normal cells. To date, there are no universal senescence cell-surface specific markers (4). A more effective senescence cell targeted approach is needed to increase the efficiency of senescent cell removal and to reduce harmful side effects.
- Conditionally Active Biologics (CAB) technology is a proprietary platform that is unique in its ability to selectively activate in the context of diseased tissues, but not normal tissues, taking advantage of the acidic pH conditions in the inflammatory tumor/aging tissue microenvironment (5). Senescent cells developing in aging and cancer tissues, are dependent on glycolysis for synthesis and over-production of inflammatory molecules, and thus generate a glycolytic/acidic microenvironment (GME) (2). Since our CAB technology is currently being deployed in cancer therapy by targeting cell surface markers such as AXL, ROR2, CTLA4 and EpCAM in clinical studies, we explored the use of CAB technology to enable selective removal of senescent cells in SASP microenvironments.

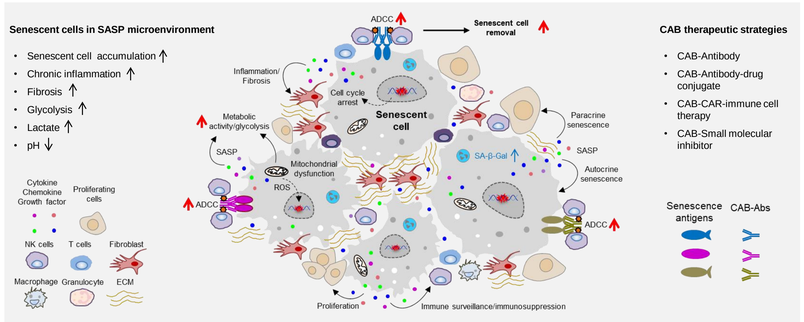


Figure 1. CAB antibodies eliminate senescence cells preferentially in glycolytic/acidic SASP microenvironments. Senescent cell accumulation in SASP microenvironment results in increased tissue inflammation and fibrosis. CAB therapeutics aim to preferentially target senescent cells in SASP, glycolytic/acidic microenvironment and trigger their clearance, while allowing non-senescence cells and non-SASP senescence cells to survive.

RESULTS

1. Elevated expression of a novel senescence target (ST), in Palbociclib-induced senescent human breast cancer MCF-7 cells

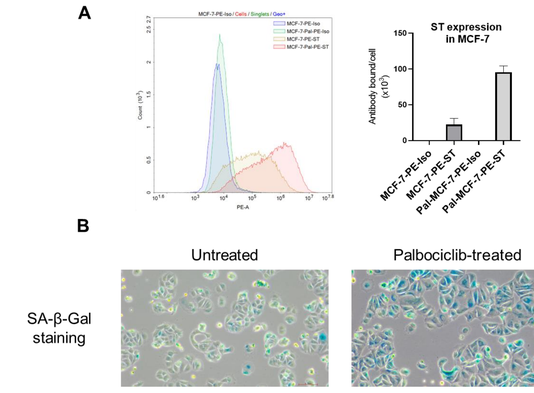
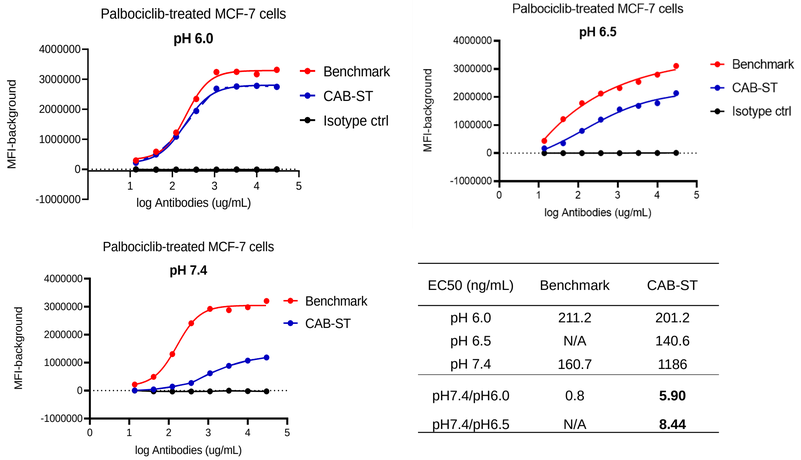


Figure 2. Validation of a novel senescence biomarker on Palbociclib-induced senescent cells. MCF-7 cells were treated with 3μM Palbociclib for 6 days. (A) The levels of ST expression were detected by FACS analysis using phycoerythrin (PE)-conjugated antibodies. (B) The newly formed senescent cells were detected by using the Senescence β-Galactosidase Staining Kit (CST, #9860).

2. CAB-ST antibody shows pH selective binding to senescent human breast cancer cells

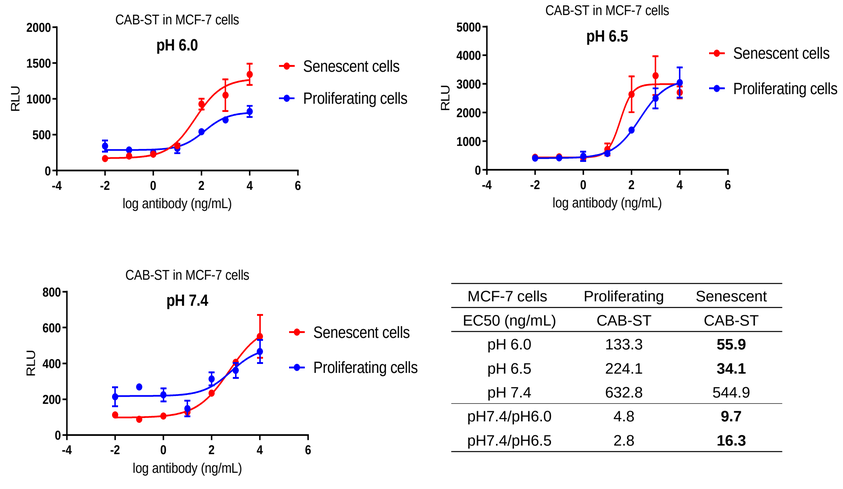


EC50 (ng/mL)	Benchmark	CAB-ST
pH 6.0	211.2	201.2
pH 6.5	N/A	140.6
pH 7.4	160.7	1186
pH7.4/pH6.0	0.8	**5.90**
pH7.4/pH6.5	N/A	**8.44**

Figure 3. pH FACS binding assays in Palbociclib-treated MCF-7 cells in different pH culture conditions. CAB-ST antibody, the benchmark, non-CAB antibody and isotype control were tested. N/A=EC50 values not determined.

RESULTS

3. High selectivity and potency of CAB-ST antibody against senescent cells in the glycolytic/acidic (pH 6.0-6.5) microenvironment condition



MCF-7 cells	Proliferating	Senescent
EC50 (ng/mL)	CAB-ST	CAB-ST
pH 6.0	133.3	**55.9**
pH 6.5	224.1	**34.1**
pH 7.4	632.8	544.9
pH7.4/pH6.0	4.8	**9.7**
pH7.4/pH6.5	2.8	**16.3**

Figure 4. CAB-ST antibody mediated ADCC assays. Palbociclib-induced senescent cells or proliferating cells were treated with CAB-ST antibody for 6 hours in pH 6.0, pH 6.5 or pH 7.4 culture conditions. ADCC assay was performed using ADCC Reporter Bioassay, Core Kit (Promega Cat. G7018).

CONCLUSIONS

- CAB antibodies preferentially eliminate senescent cells by targeting novel senescence markers in glycolytic/acidic SASP microenvironment (low pH 6.0-6.5) but display low activities in the presence of senescent and proliferating cells in alkaline physiological conditions (pH 7.4).
- In addition to on-going human clinical trials in cancer, CABs are currently being evaluated as senolytic therapies utilizing disease models associated with aging.
- CAB technology provides a new generation of biologics with an increased safety margin and therapeutic index for targeting SASP senescence cells in cancer and age-related diseases.

References:
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