Antitumor immunity boosted by GSDMD-induced necrosis

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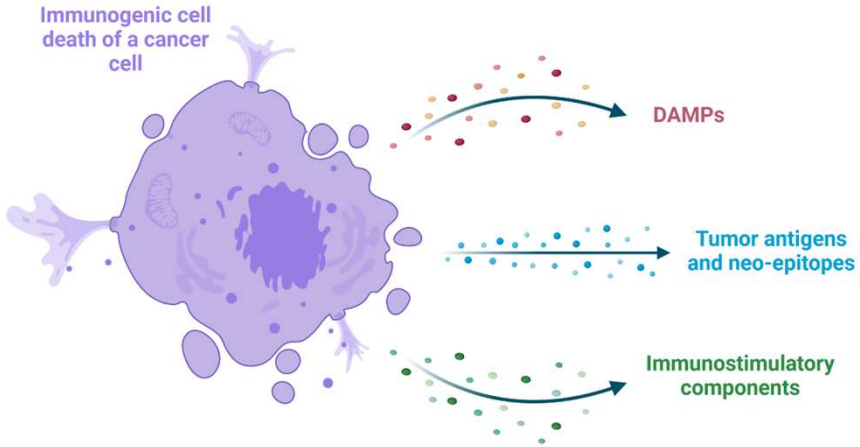
Cancer immunotherapy

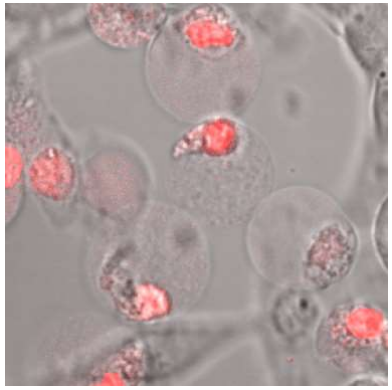
- Cancer immunotherapy → to trigger immune responses directed against the tumor
- Antigenicity of the malignant cells and their ability to generate adjuvant signals in the TME

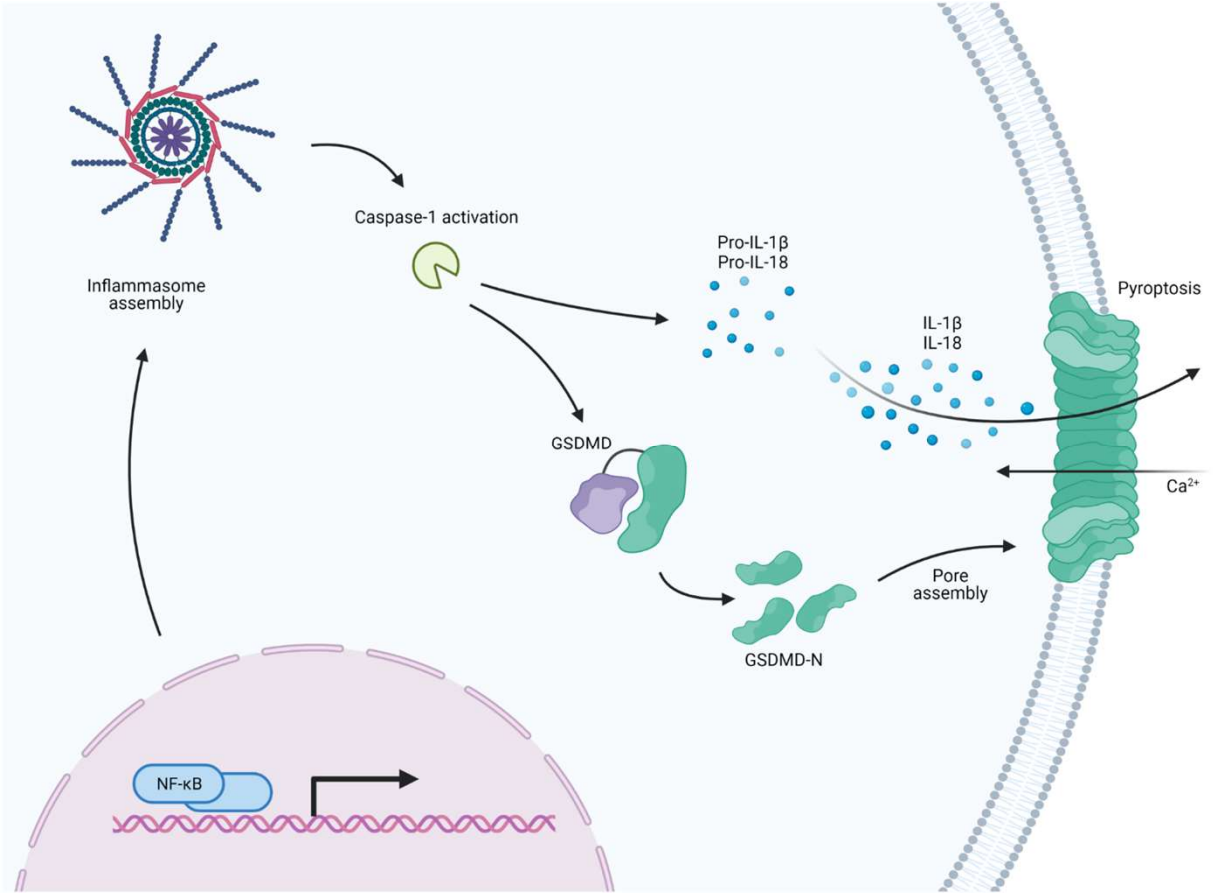


- Immunogenic cell death (ICD) → a functionally unique response pattern
- Infiltration of a different immune cells into the TME, their activation and maturation
- Pyroptosis → antitumor remedy, not only destroying cancer cells but also modulating TME

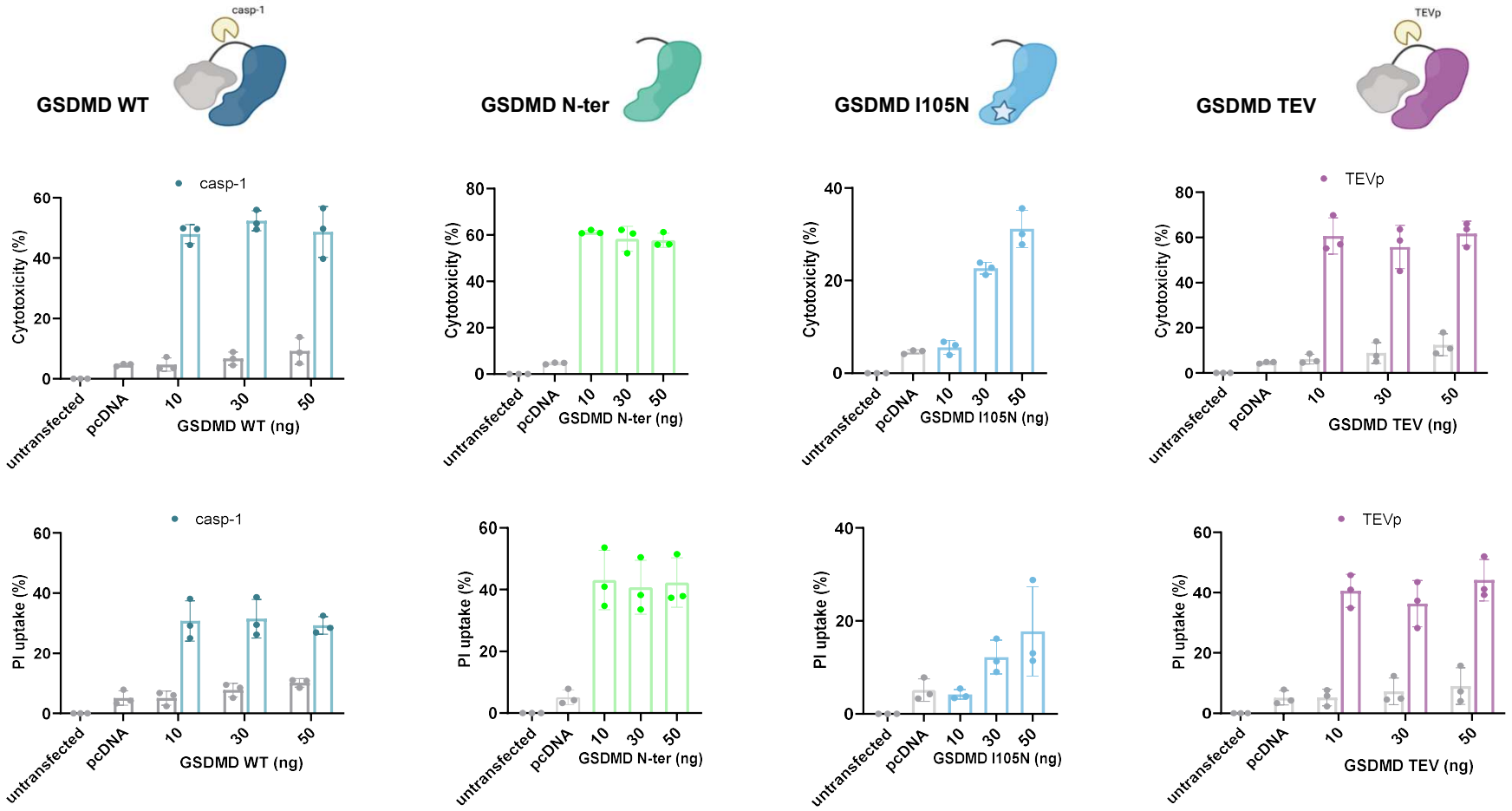
Pyroptosis - Immunogenic cell death

- Pyroptosis → programmed necrotic cell death
- NLRP3 inflammasome
- Gasdermin D (GSDMD) pore formation, oncosis, membrane ballooning, and release of cytokines IL-1β and IL-18
- GSDMD → C-terminal autoinhibitory domain and N-terminal pore-forming domain
- Expression level of gasdermin family proteins in tumor cells is low or absent
- GSDMA3 and GSDME → tumor supresson genes
- GSDMD-induced pyroptosis → antitumor agent
- Properly controlled formation of GSDMD pores → cancer cell destruction and moderation of immune response against the tumor

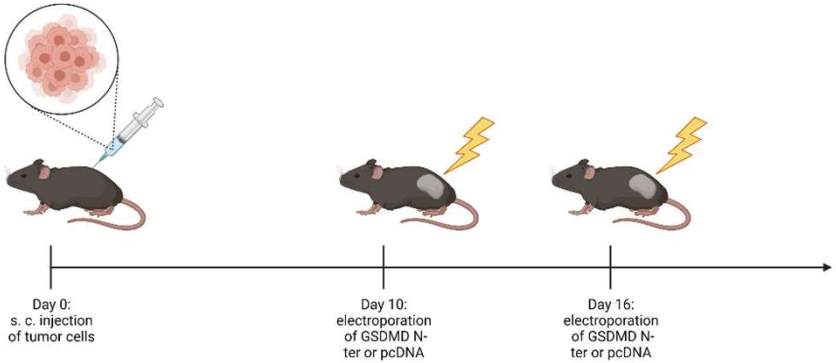


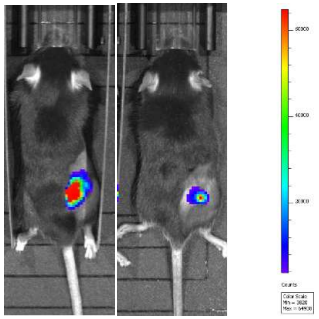


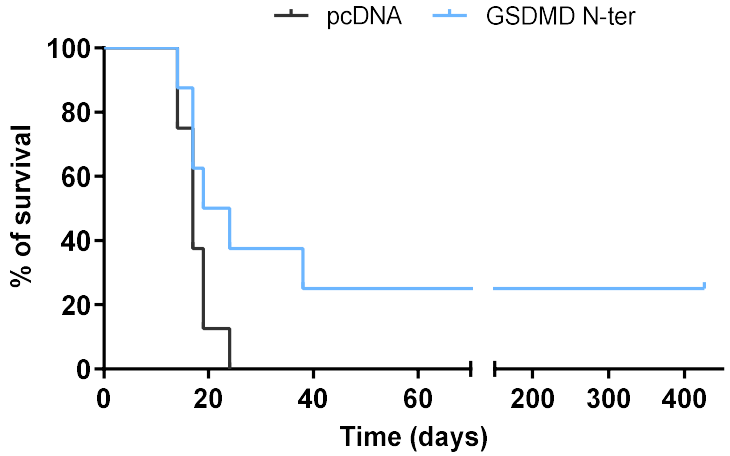
GSDMD variants induce pyroptosis

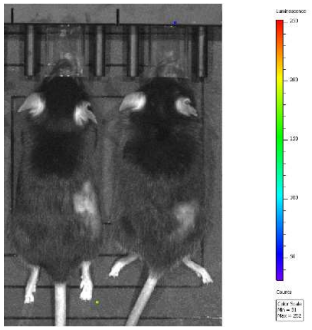


Intratumor delivery of GSDMD facilitates tumor regression

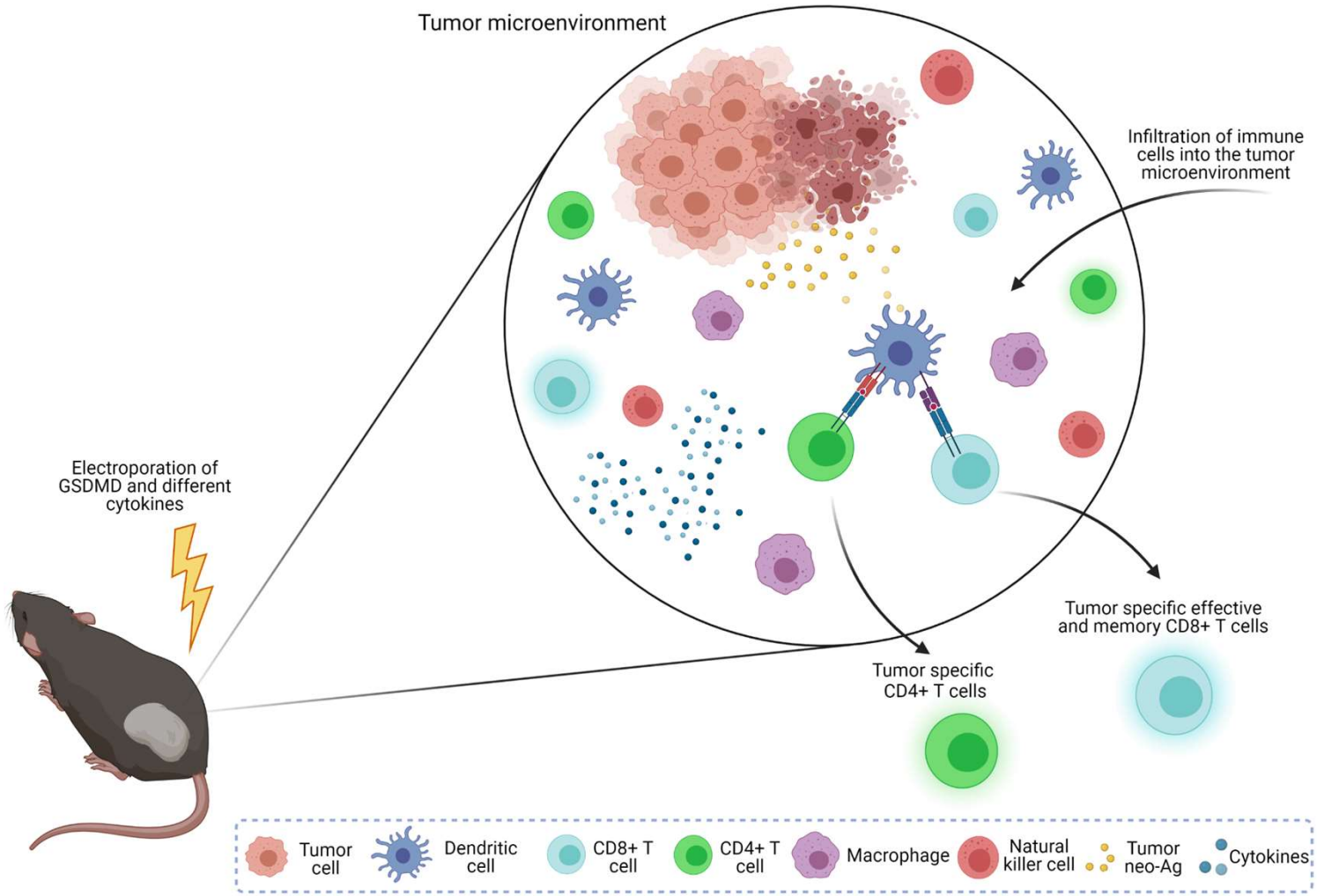


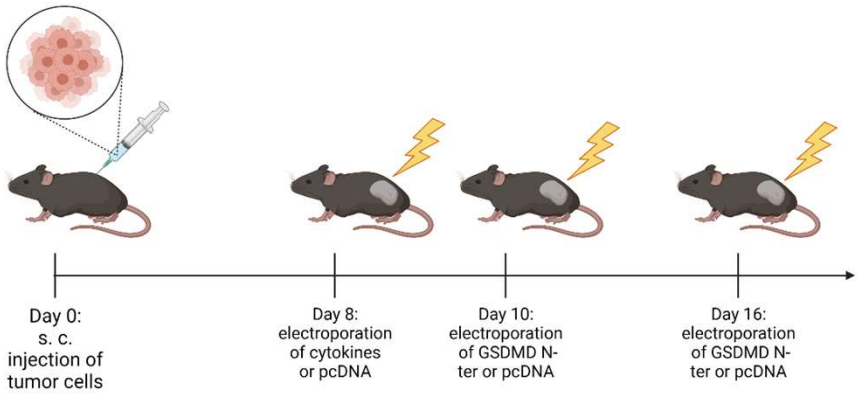


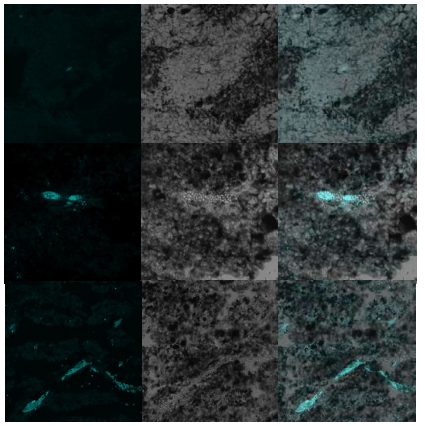


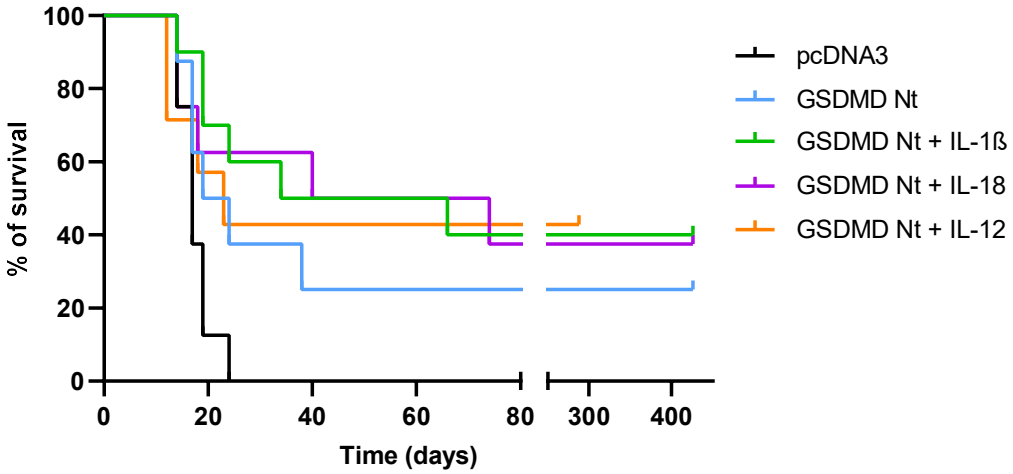


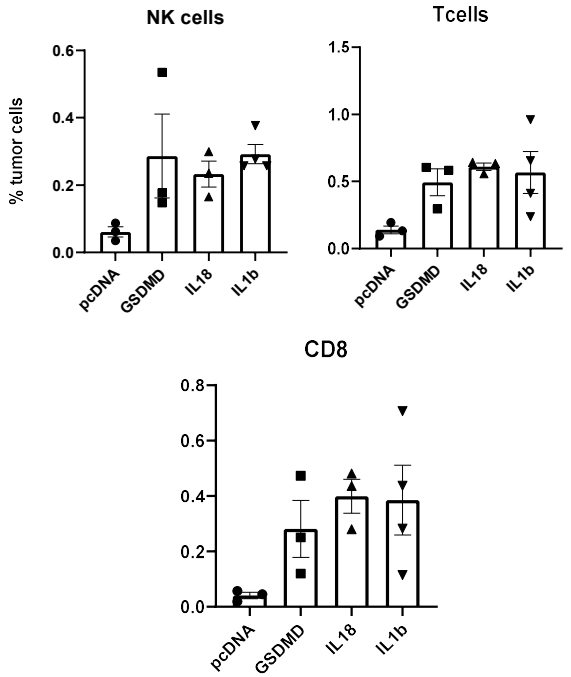
Modulation of antitumor immunity by GSDMD and cytokine treatment



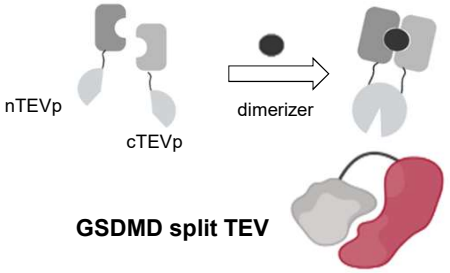

Day 0:
s. c.
injection of
tumor cells
Day 8:
electroporation
of cytokines
or pcDNA
Day 10:
electroporation
of GSDMD N-
ter or pcDNA
Day 16:
electroporation
of GSDMD N-
ter or pcDNA

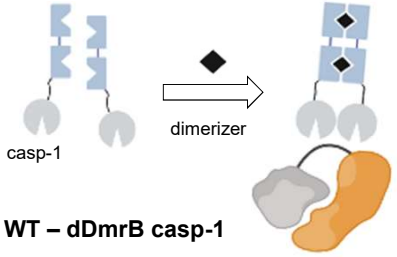

pcDNA
GSDMD N-ter
GSDMD N-ter
+ mIL-1β

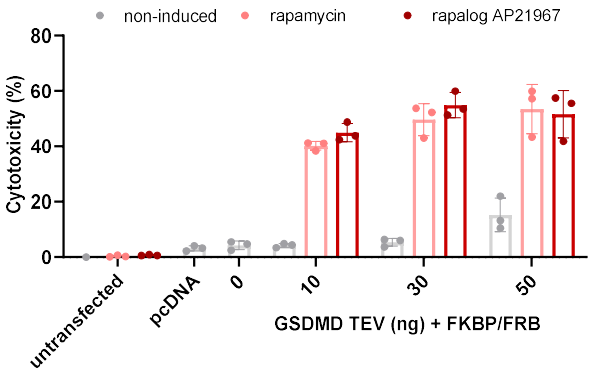

% of survival
Time (days)
pcDNA3
GSDMD Nt
GSDMD Nt + IL-1ß
GSDMD Nt + IL-18
GSDMD Nt + IL-12

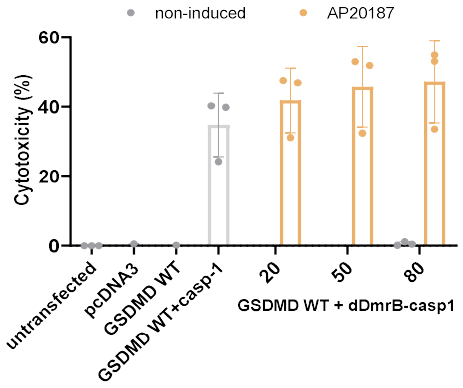

NK cells
Tcells
% tumor cells
pcDNA
GSDMD
IL18
IL1b
CD8

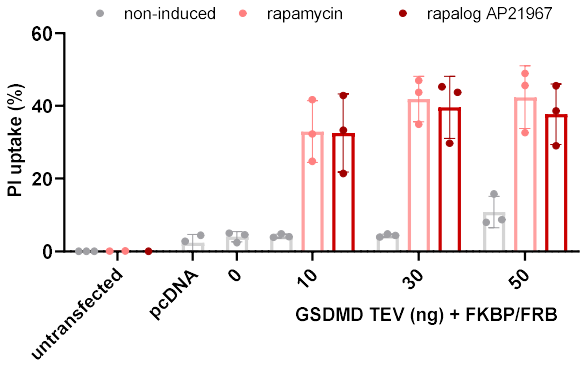
Engineered GSDMD variants facilitate regulated pyroptosis

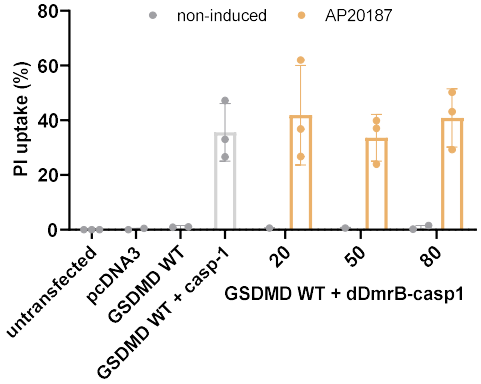


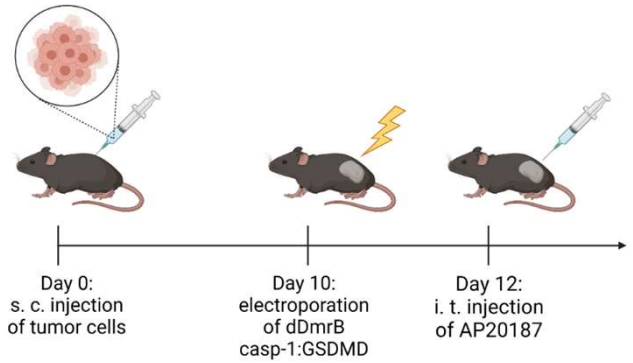


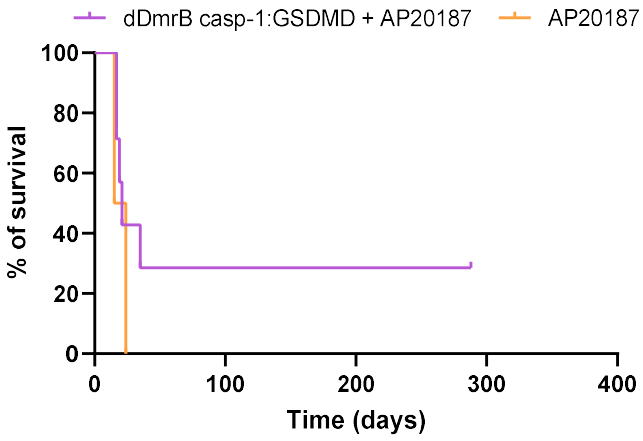












Overview

- Potential of regulated pyroptosis in promoting antitumor immunity
- GSDMD pore formation in the TME induces tumor regression and infiltration of CD8+ T-cells and antitumor immunity
- GSDMD acts as tumor suppressor gene when overexpressed in the B16F10 melanoma tumor cells
- GSDMD + IL-1β, IL-18 and IL-12 treatment stimulates the response against the tumor and formation of an immunogenic TME

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- Department of Synthetic Biology and Immunology