4224, a tumor exosome-transforming antibody targeting CD40 and EpCAM, induces superior anti-tumor effects compared to monospecific CD40 antibody

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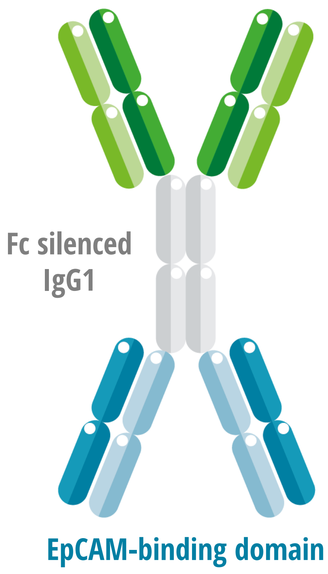
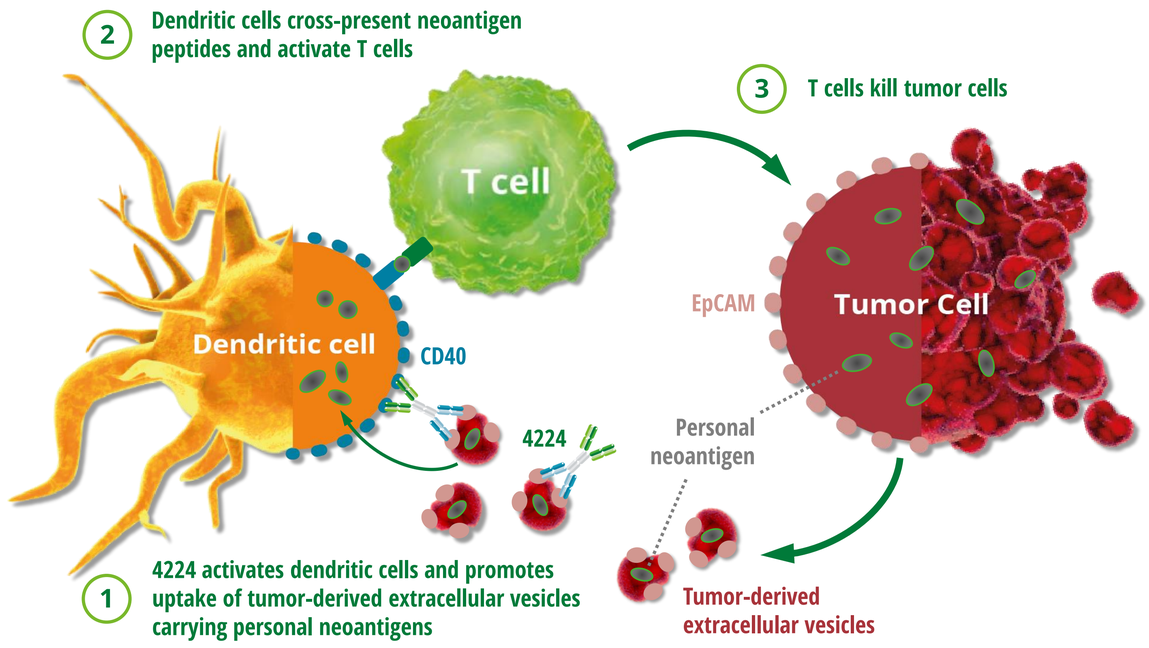
About 4224



- Bispecific antibody targeting CD40 and EpCAM
- TExTA – Tumor Exosome-Transforming Antibody
- Aims to transform tumor exosomes carrying neoantigen into immune-activating vaccination vehicles

Proposed mode of action of 4224



4224 induces an anti-tumor effect superior to monospecific CD40 antibody

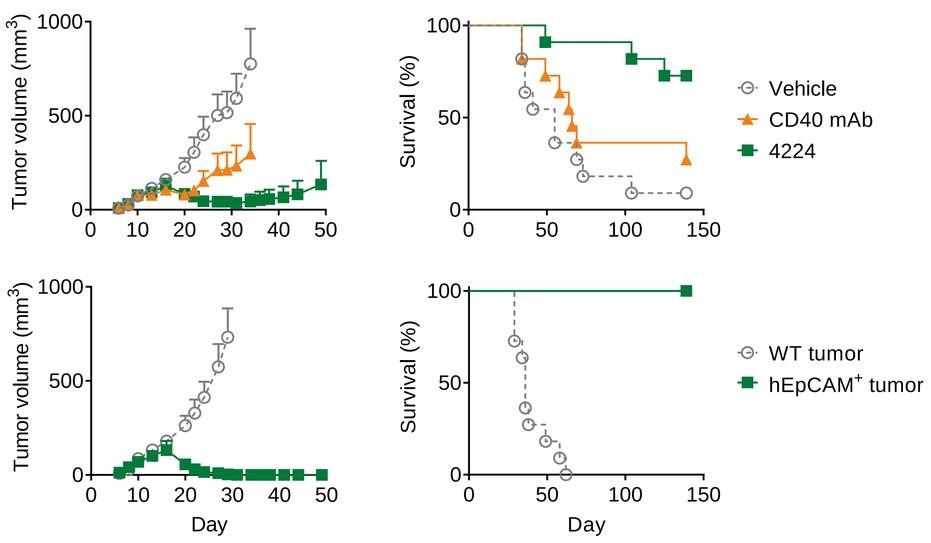


Figure 1. Human CD40 transgenic (hCD40tg) mice were inoculated with MB49-hEpCAM$^+$ cells s.c. and administered 100 µg anti-CD40 antibody (CD40 mAb) or an equivalent dose (167 µg) 4224 i.p. on days 10, 13 and 16 (top graphs). Alternatively, mice were inoculated with either MB49-WT or MB49-hEpCAM$^+$ cells s.c. and administered 417 µg 4224 as previously (bottom graphs).

4224 induces a broad anti-tumor immunity

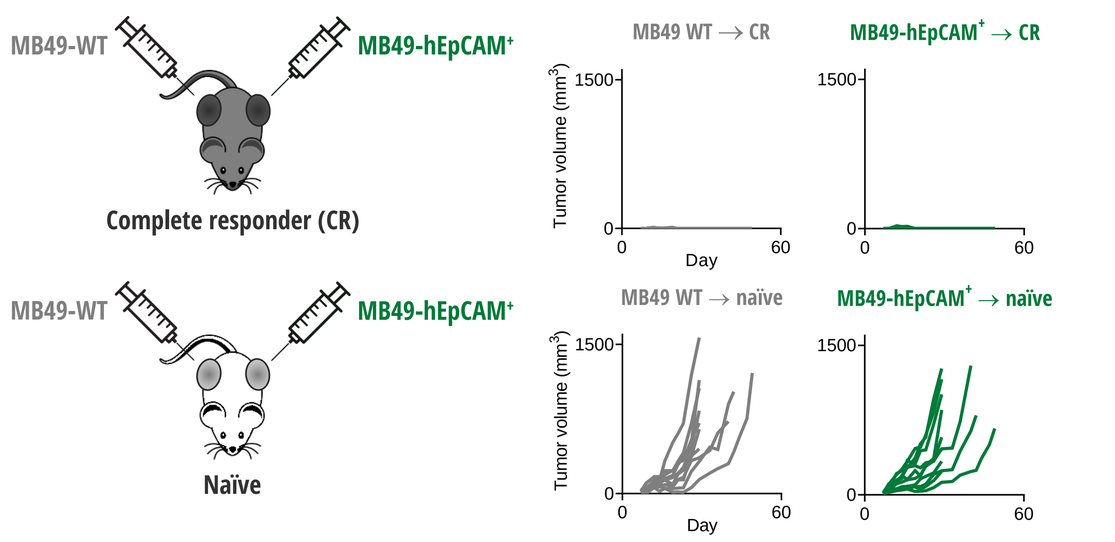


Figure 2. Complete responders (CR) cured from MB49-hEpCAM$^+$ tumors by 4224, were rechallenged with the same tumor on one flank and an MB49-WT tumor on the other flank. The same procedure was performed in a cohort of naïve hCD40tg mice. Graphs show individual tumor volume for WT tumors (left; grey) and hEpCAM$^+$ tumors (right; green) in CR (top) and naïve (bottom) mice.

4224 displays low systemic immune activation

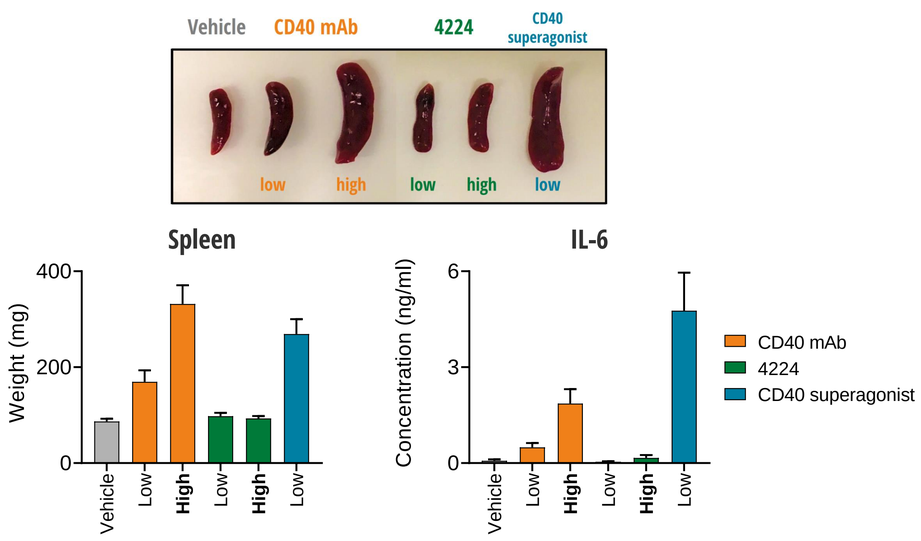


Figure 3. hCD40tg mice were inoculated with MB49-hEpCAM$^+$ cells s.c. and administered 100 (low) or 250 µg (high) CD40 mAb, or equivalent doses (167 or 417 µg) 4224, or 100 µg of a CD40 superagonist i.p. on days 10, 13 and 16. Systemic immune activation was evaluated by weighing spleens on day 19 (left) or by measuring plasma IL-6 levels 4 hrs after the second therapy dose (right).

4224 mediates EpCAM-dependent activation of dendritic cells

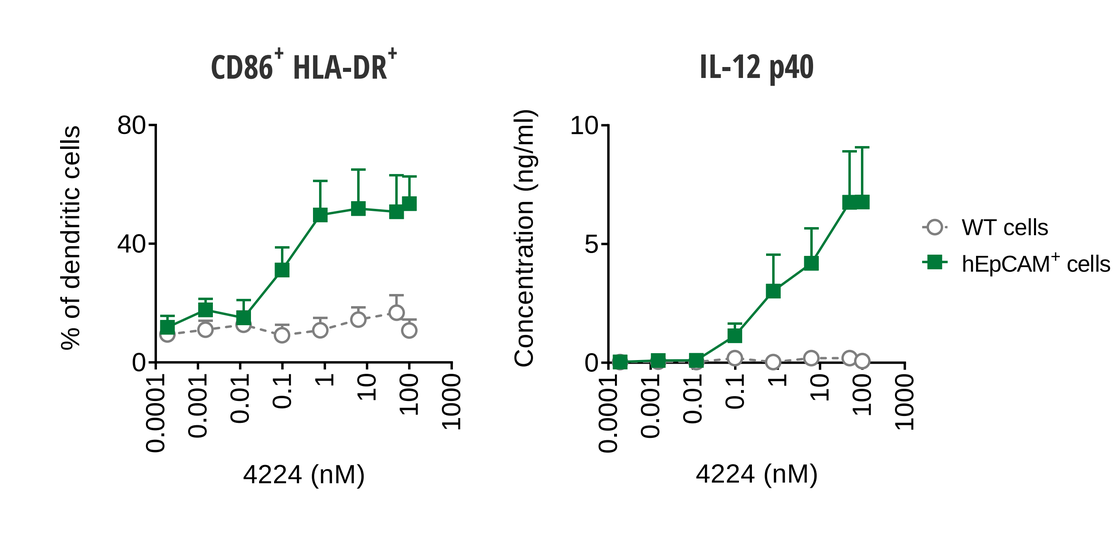


Figure 4. Human monocyte-derived dendritic cells were cultured with titrated 4224 in the presence or absence of hEpCAM expressed on CHO cells. After 2 days, expression of CD86 and HLA-DR on CD14$^-$ CD1a$^+$ dendritic cells was analyzed by FACS (left). Alternatively, supernatants were collected and IL-12 p40 content was analyzed by ELISA (right).

4224 mediates co-localization between tumor debris and CD40$^+$ cells

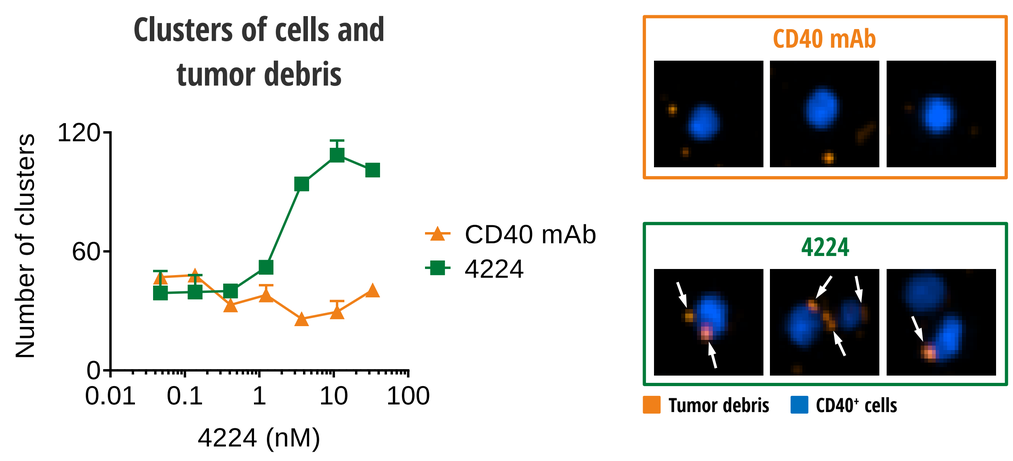


Figure 5. Fluorescently labeled CD40$^+$ Raji cells were cultured with fluorescently labeled hEpCAM$^+$ tumor debris in the presence of titrated CD40 mAb or 4224. Images were captured using a live cell imaging system and clusters of CD40$^+$ cells co-localized with tumor debris were quantified after 8 hrs of culture.

Summary

4224 – a Tumor Exosome-Transforming Antibody (TExTA):

- Aims to turn tumor exosomes into autologous immune-activating neoantigen vaccination vehicles
- Mediates activation of dendritic cells and co-localization between tumor debris and CD40$^+$ cells
- Induces a superior EpCAM-dependent anti-tumor effect compared to monospecific anti-CD40 antibody
- Induces a broad immunological memory against tumor antigen

CICON 2019
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