SELECTED OPPORTUNITY IN ONCOLOGY

Sphingosine kinase 2 inhibitors in combination with immune checkpoint blockade therapy for the treatment of cancer

(BIO18120)

SK2 INHIBITORS IN COMBINATION WITH IMMUNE CHECKPOINT BLOCKADE THERAPY FOR THE TREATMENT OF CANCER

Product factsheet

Preclinical

- **Target:** Sphingosine kinase 2 (SK2)

- **Application:** Treatment of cancer in combinaison with Immune Check Point Inhibitors

- **Potential Product** : a SK2 inhibitor such as Opaganib (Yeliva® ,RedHill Biopharma Limited)

- **Rationale:**

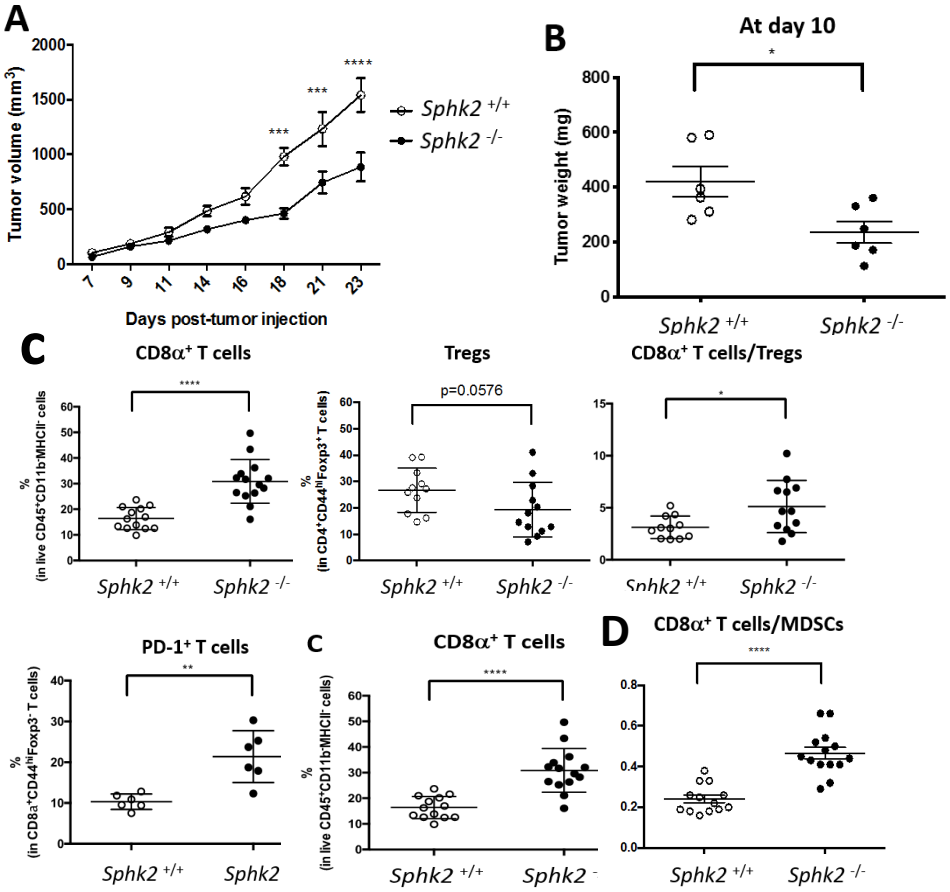
- Sphingolipid biosynthesis involves the hydrolysis of ceramides to generate sphingosine, which is subsequently phosphorylated by one of two sphingosine kinase isoforms (SK1 or SK2) to generate sphingosine-1-phosphate (S1P). S1P, acts as signaling molecule that regulates apoptosis and tumor cell survival in contrast to the generally pro-apoptotic function of ceramides, S1P promotes cell proliferation and survival.
- Genetic deletion of SK2 leads to a delay in the melanoma tumor growth and an increase in tumor-infiltrating effector lymphocytes in immunocompetent mice;
- Combination of SK2 deficiency with immune-checkpoint blockade leads to tumor rejection, increases survival rate and induces potent vaccination;
- SK2-deficient $CD8\alpha^+$ T cells are the key immune regulators in the control of tumor development

- **Patent Applications** :EP19305461.6: USE OF SK2 INHIBITORS IN COMBINATION WITH IMMUNE CHECKPOINT BLOCKADE THERAPY FOR THE TREATMENT OF CANCER

Proof of concept

Preclinical

Genetic deletion of SK2 leads to a delay in the melanoma tumor growth and an increase in tumor-infiltrating effector lymphocytes in immunocompetent mice

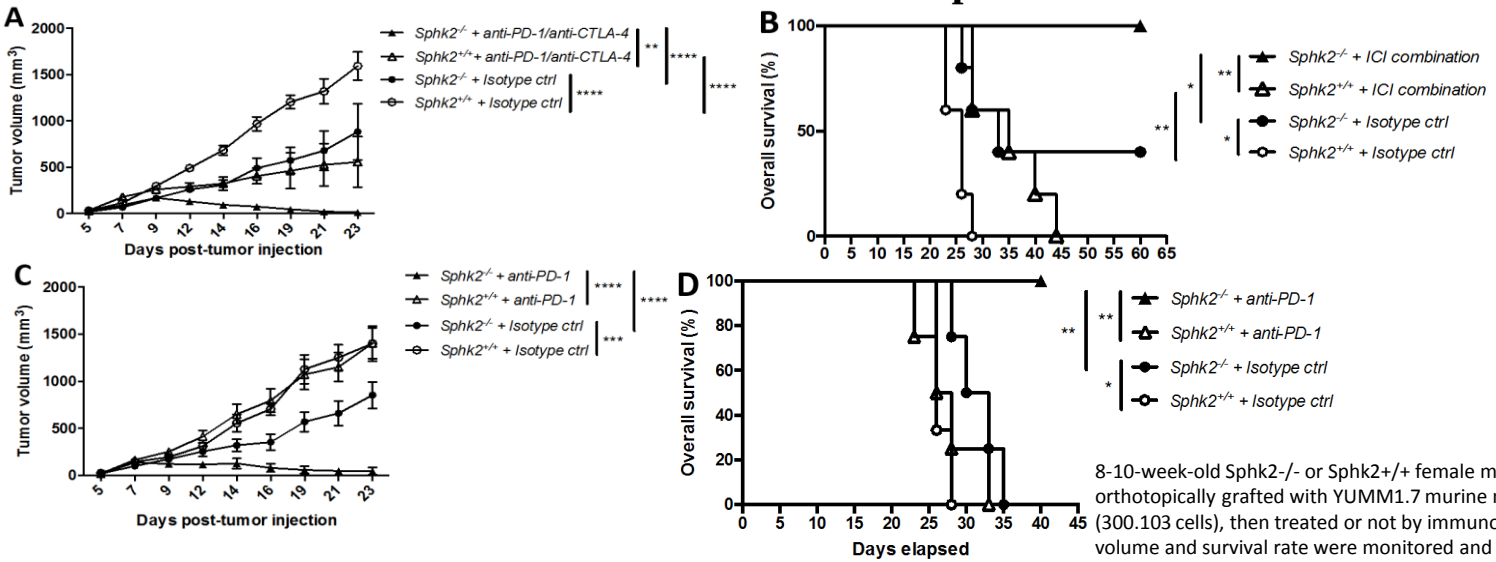


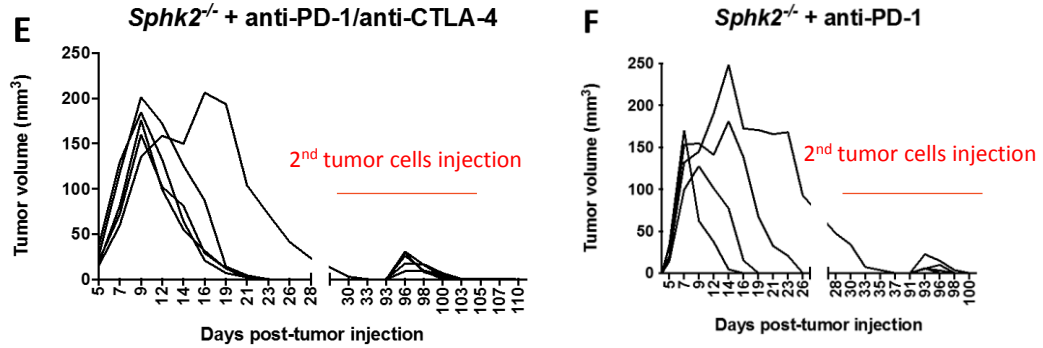
8-10-week-old *Sphk2-/-* or *Sphk2+/+* female mice were orthotopically grafted with YUMM1.7 murine melanoma cell line (300.103 cells), tumor volume was monitored over time and tumor weight was measured at day 10 post-tumor injection. **(A)** Growth curves are presented as mean of tumor volume ± SEM for each depicted day post-tumor injection and are representative of at least two independent experiments (n = 6-8 mice per group). **(B)** Tumor weight graph shows in milligrams (mg) the differences observed at day 10 after tumor inoculation. **(C-D)** Immune infiltrate within the tumor was analyzed at day 10 post-tumor injection for lymphoid lineage-derived populations (C) and myeloid lineage-derived populations (D) by flow cytometry. Frequencies of CD8α+ T cells, regulatory CD4+ T cells (Tregs), PD-1+-expressing CD8α+ T cells, and CD8α+/Tregs ratio; and PD-1 MFI are represented (C). Frequencies of neutrophils and polymorphonuclear-MDSCs; and CD8α+/MDSCs ratio are represented (D). Each symbol represents an independent tumor (n = 6-8 mice per group). Graphs are representative of two pooled independent experiments. (A) Growth curves were compared using repeated measures (RM) two-way ANOVA/Sidak's test. (B) Tumor weights were compared using Mann-Whitney test. Frequencies data were compared using Mann-Whitney test (C and D). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Proof of concept

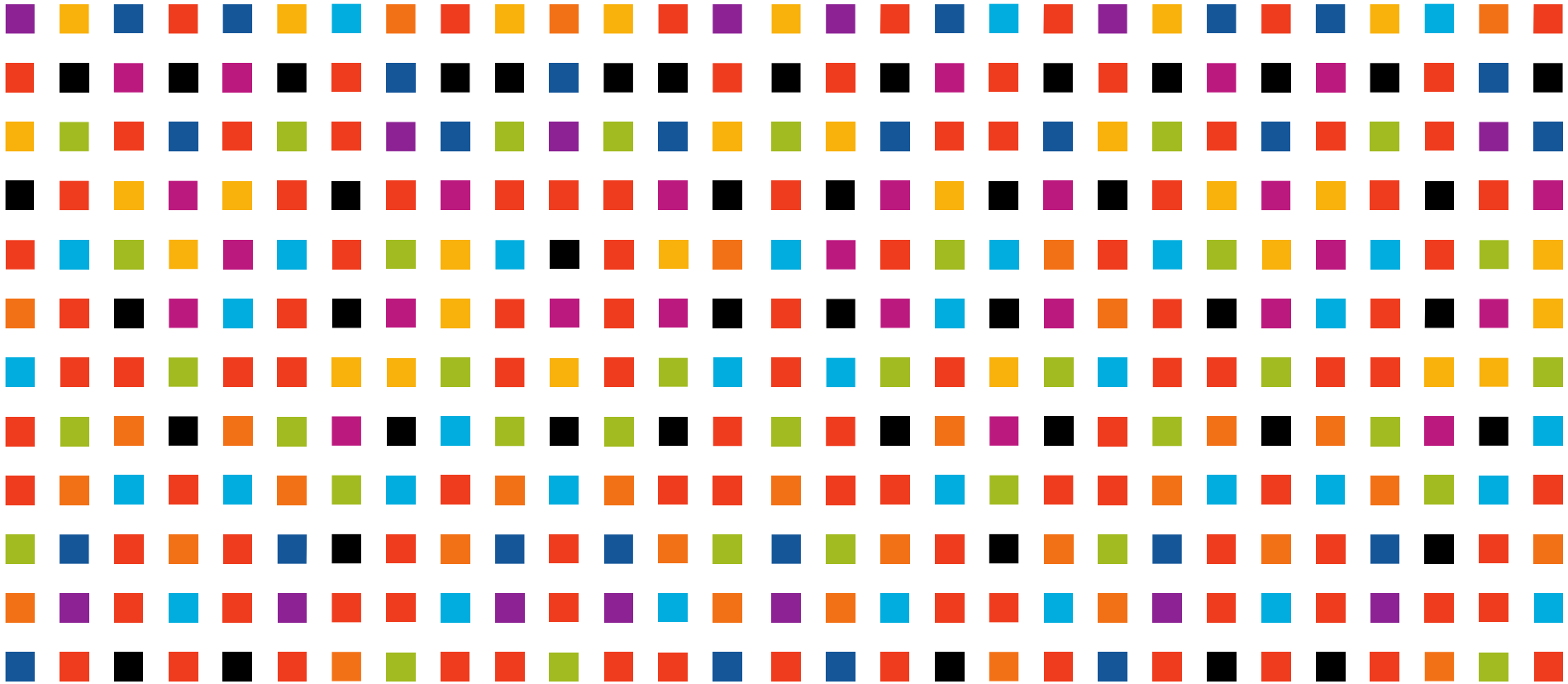
Preclinical

Combination of SK2 deficiency with immune-checkpoint blockade leads to tumor rejection, increases survival rate and induces potent vaccination





8-10-week-old Sphk2-/- or Sphk2+/+ female mice were orthotopically grafted with YUMM1.7 murine melanoma cell line (300.103 cells), then treated or not by immunotherapy and tumor volume and survival rate were monitored and estimated over time (n = 4-5 mice per group). Tumor volumes are presented as mean of tumor volume ± SEM for each depicted day post-tumor injection. (A) Mice received a combo treatment of anti-PD-1/anti-CTLA-4 or isotype control at days 5, 8 and 12 post-tumor injection. (C) Mice were treated with anti-PD-1 or isotype control at days 5, 8 and 12 post-tumor injection. (E, F) Sphk2-/- mice treated with combo or only anti-PD-1 were re-challenged around 90 days post-tumor injection at the same site of primary injection with YUMM1.7 cells (1.106 cells). (A, C) Growth curves were compared using repeated measure (RM) two-way ANOVA/Sidak's test. (B, D) Cumulative survival curves were analyzed using Log-rank (Mantel-Cox) test. *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001



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