



Targeting DGK α /PA axis inhibits tumor immune evasion and augments sensitivity to immunotherapy in gastrointestinal cancers

Jie Chen^{1,2,3}, Siqi Liu^{1,2}, Ting Peng^{1,2}, Fenglong Wang^{1,2}, Yuheng Zhu^{1,2}, Jingyuan Pang¹,
Qingnan Wu^{1,2}, Yan Wang^{1,2}, Qimin Zhan^{1,2,3,4}

¹Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing),

Laboratory of Molecular Oncology, Peking University Cancer Hospital & Institute

²Peking University International Cancer Institute

³Soochow University Cancer Institute

⁴Institute of Cancer Research, Shenzhen Bay Laboratory



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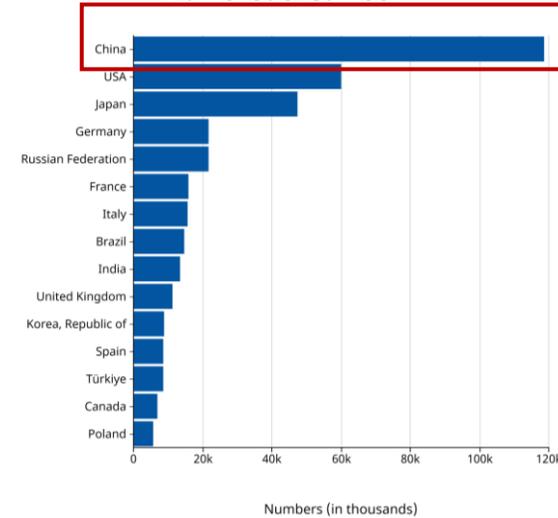
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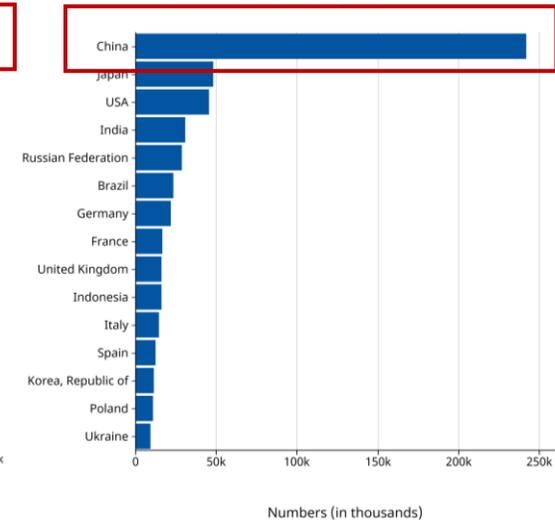
Background

- The newly diagnosed cases of the six major digestive system cancers account for approximately 24.6% of the total global cancer incidence;
- Gastrointestinal cancers are among the most prevalent cancers in China, with the incidence accounting for approximately 37% of the global total for similar cancers, and the mortality accounting for about 41% of the global total for this type of cancer;
- Clinically, immune checkpoint inhibitors (ICIs) for the treatment of gastrointestinal cancers are still in the exploratory stage;
- Clinical studies have shown that many gastrointestinal cancer patients who initially respond to immunotherapy develop varying degrees of resistance after the remission phase.

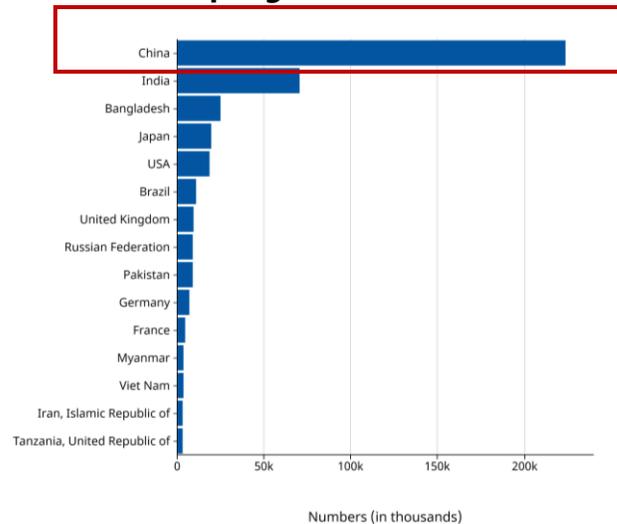
Pancreas Cancer



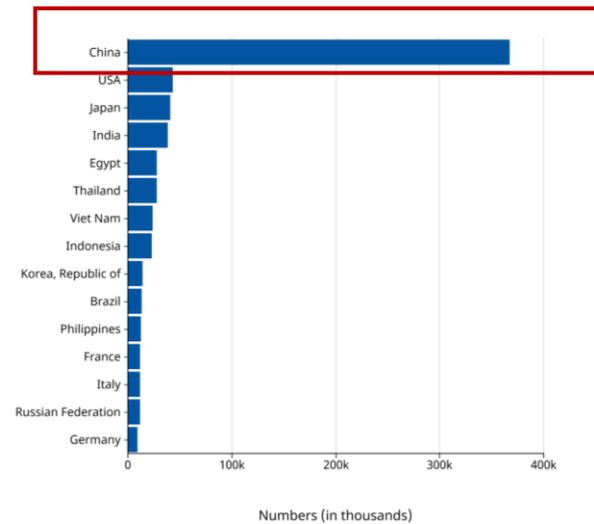
Rectum Cancer



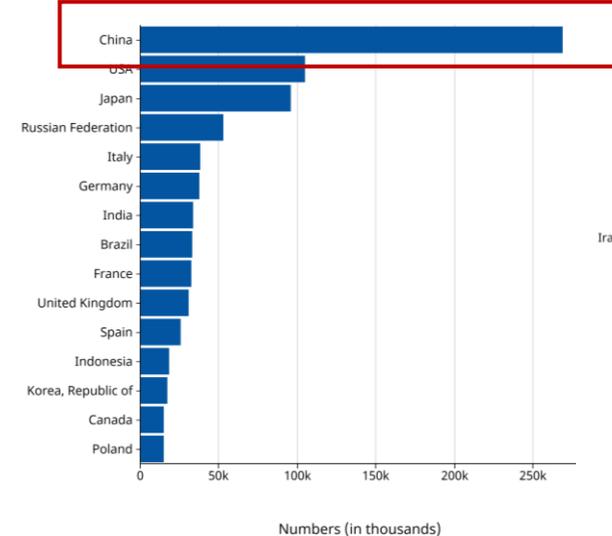
Esophageal Cancer



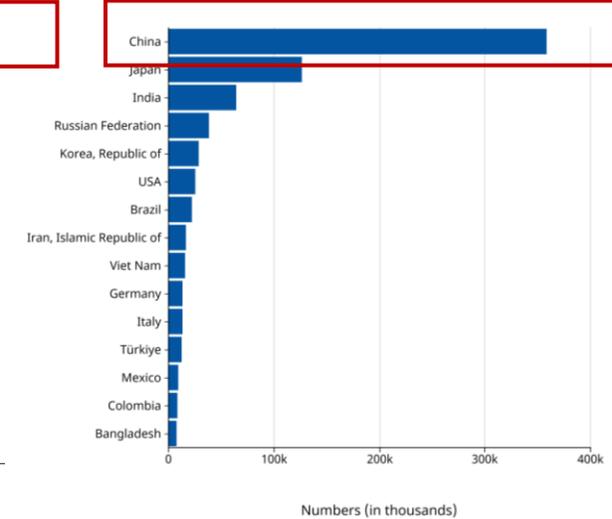
Liver and intrahepatic bile ducts Cancer



Colon Cancer



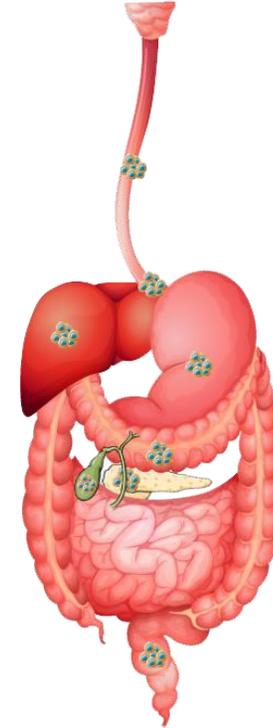
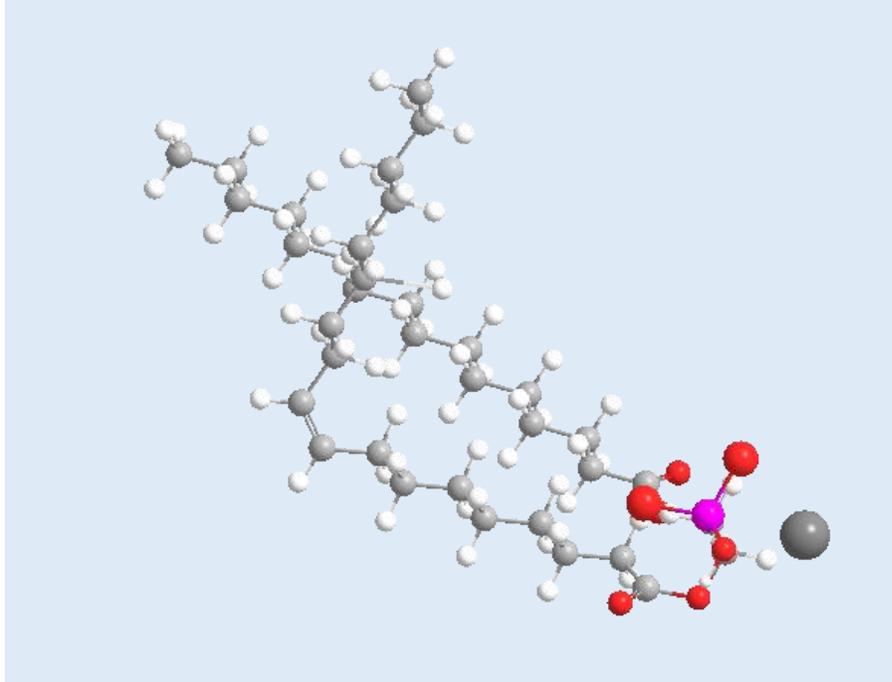
Stomach Cancer



The latest data on the incidence of gastrointestinal cancers. (Both sexes, data from Cancer Today-World health Organization)



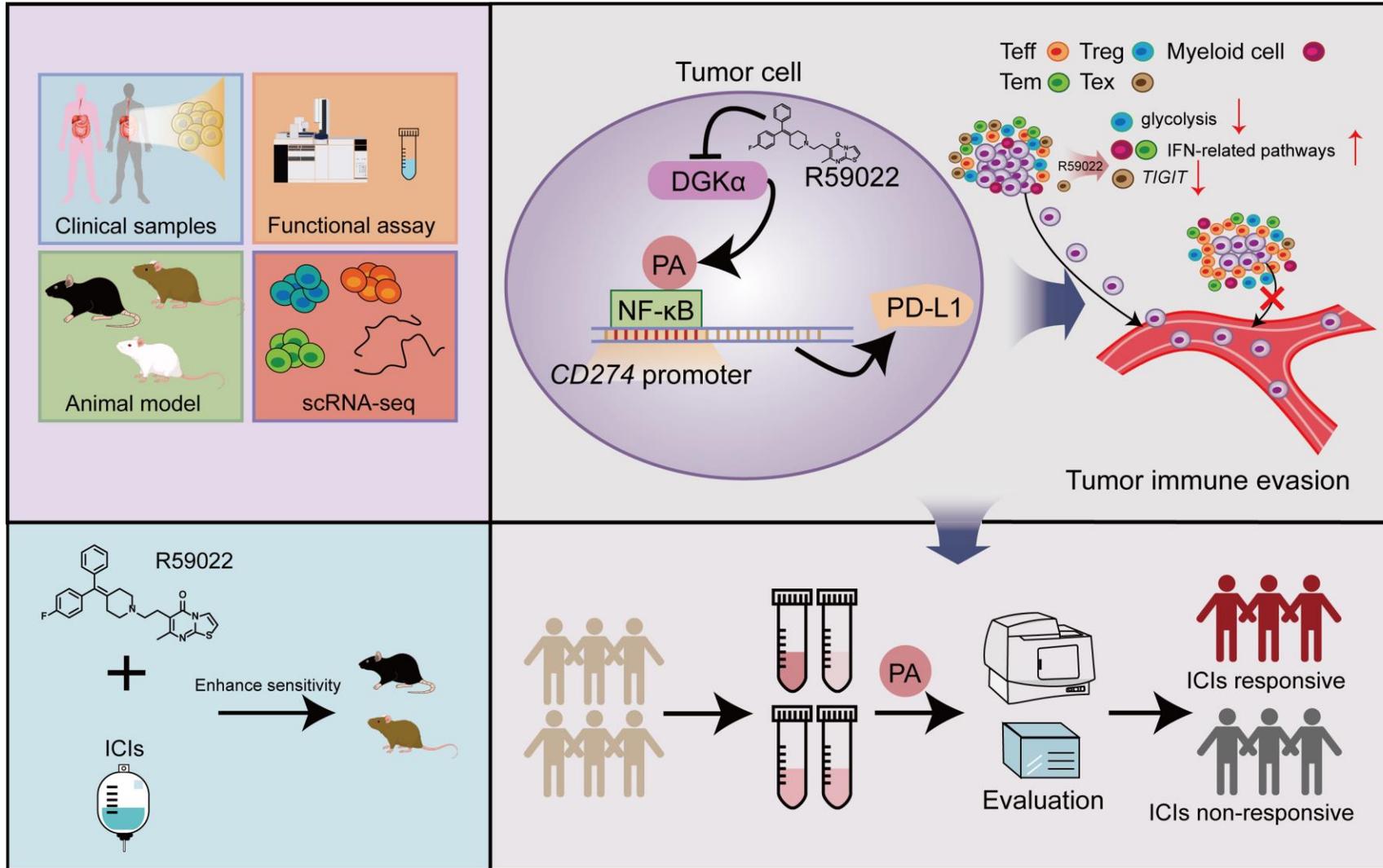
Background



- The tumor-promoting mechanisms induced by lipid metabolites are still underexplored;
- The lipid metabolism enzyme DGK α serves as a signaling hub that mediates the progression of various solid tumors. It is an important oncogene in tumor cells, catalyzing the conversion of diacylglycerol into phosphatidic acid (PA);
- The role of DGK α in the progression of gastrointestinal cancers remains unclear.



Highlights

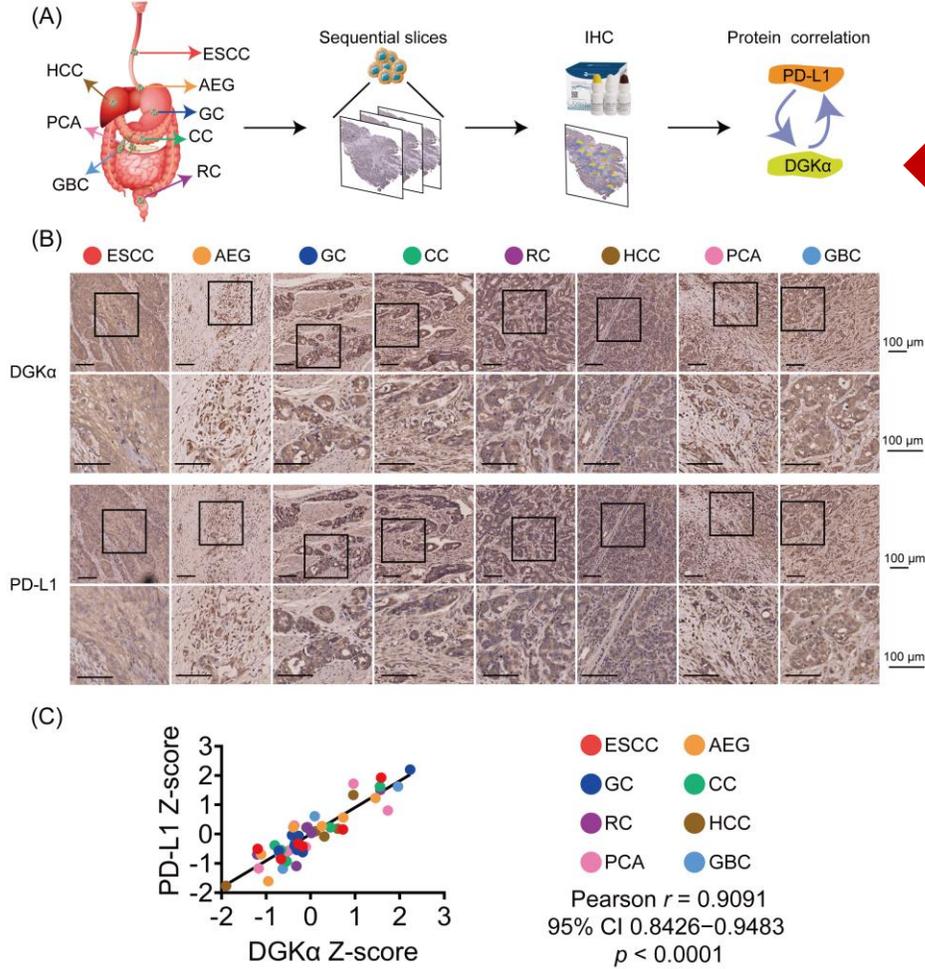


- ◆ PA directly binds to NF- κ B p65, facilitating its-mediated PD-L1 activation;
- ◆ Inhibition of DGK α /PA axis induces the infiltration of CTL in local tumor tissues;
- ◆ DGK α inhibitor R59022 enhances the antitumor effect of ICIs via blocking NF- κ B pathway;
- ◆ Plasma PA can be applied to judge the response of ICIs in gastrointestinal cancers treatment.



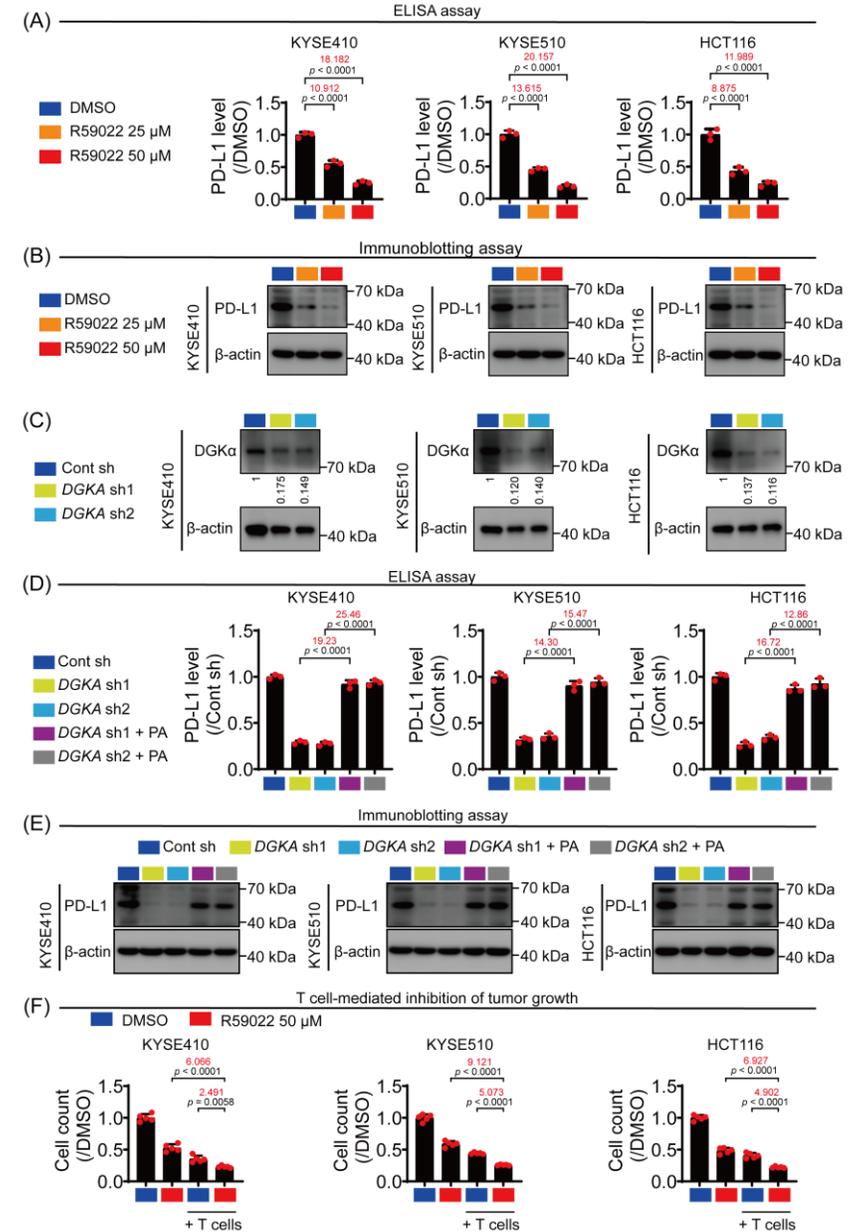
DGK α /PA axis regulates PD-L1 expression

Correlation between DGK α and PD-L1 in gastrointestinal cancers



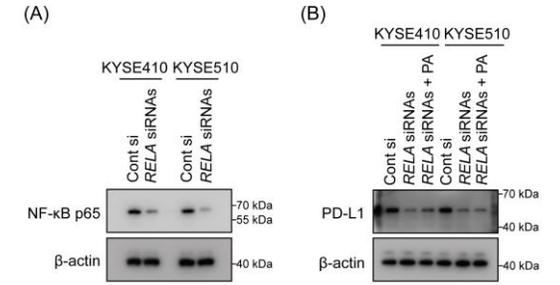
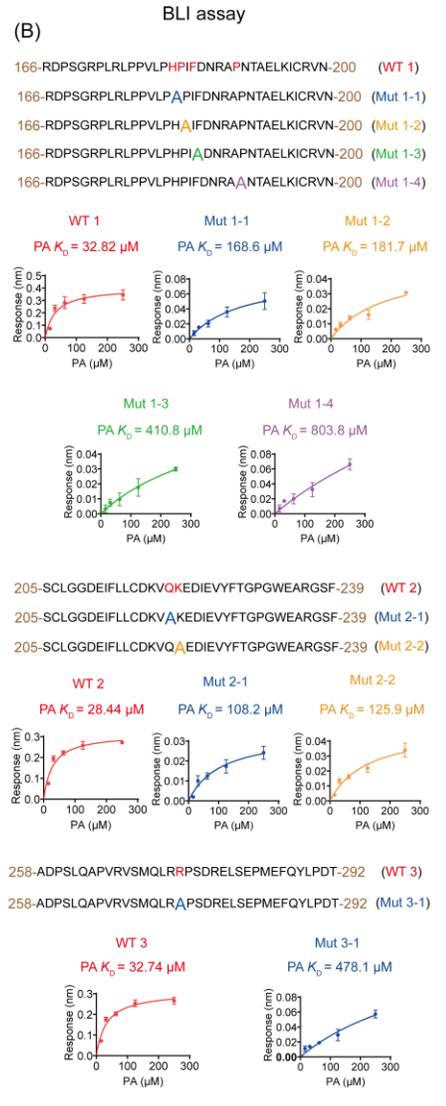
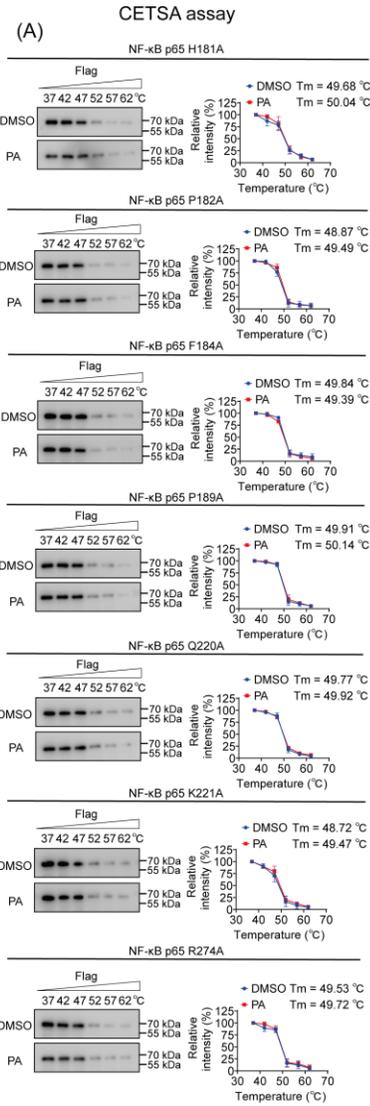
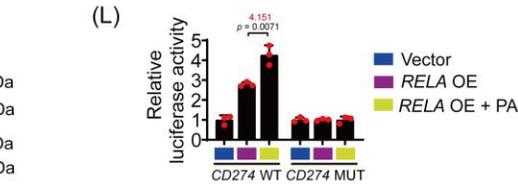
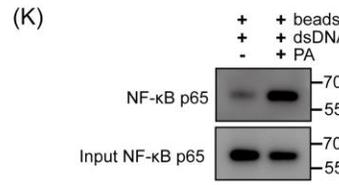
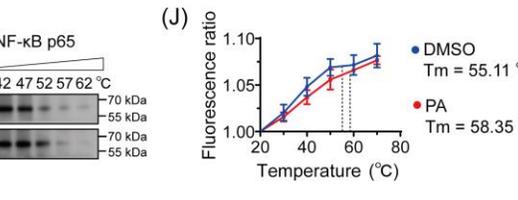
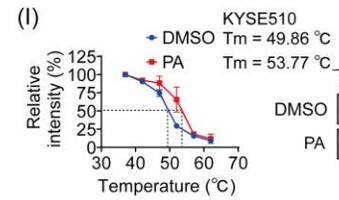
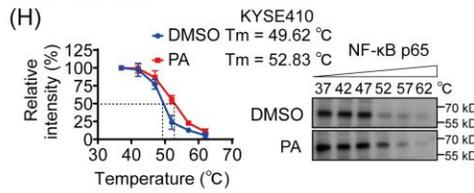
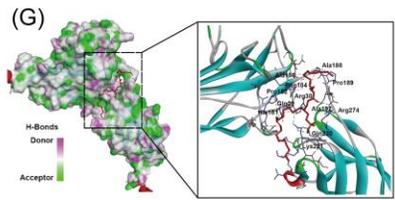
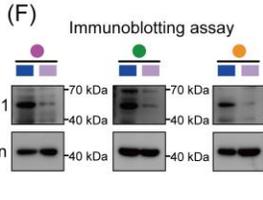
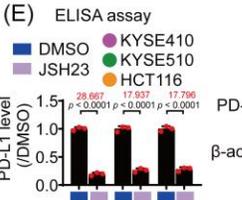
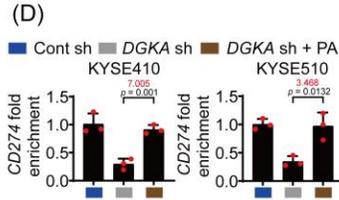
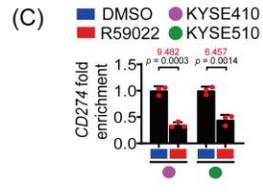
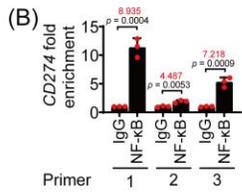
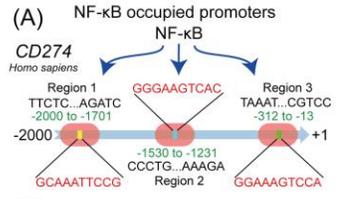
← The expression of DGK α positively correlates with that of PD-L1 in gastrointestinal cancers

→ Intratumoral DGK α /PA axis is critical for PD-L1 expression





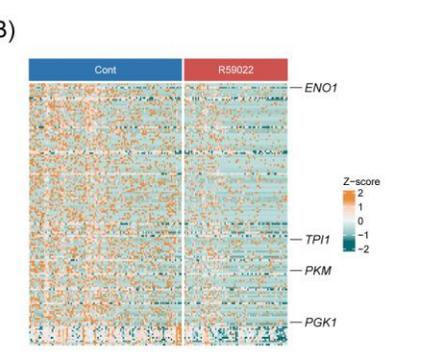
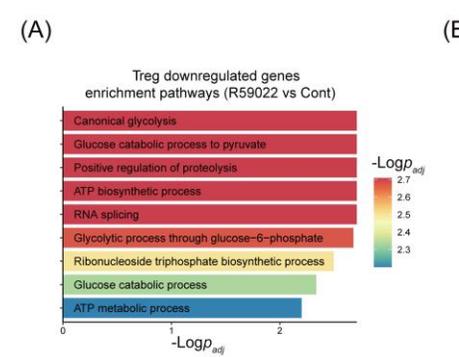
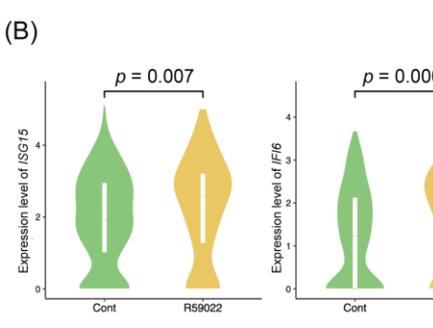
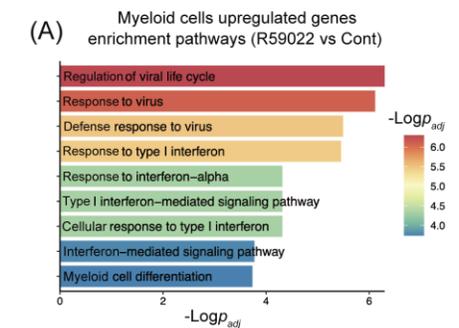
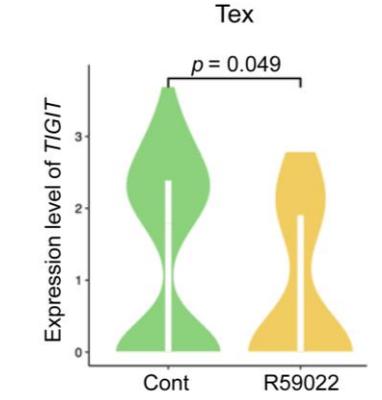
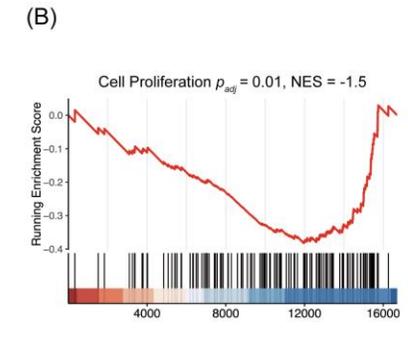
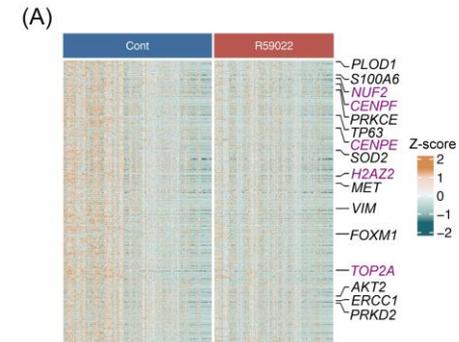
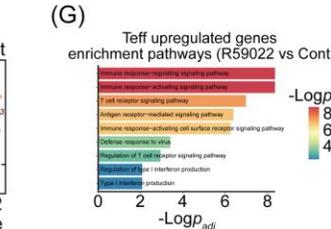
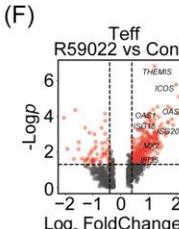
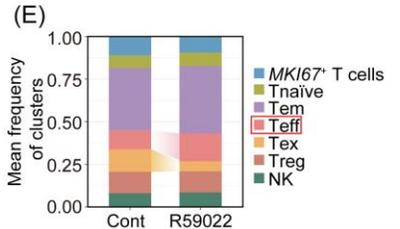
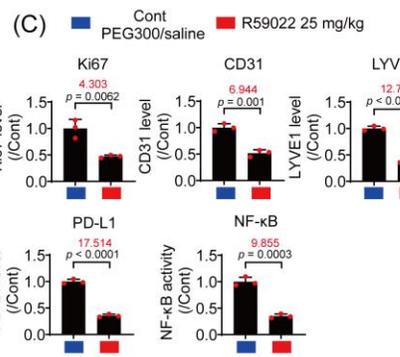
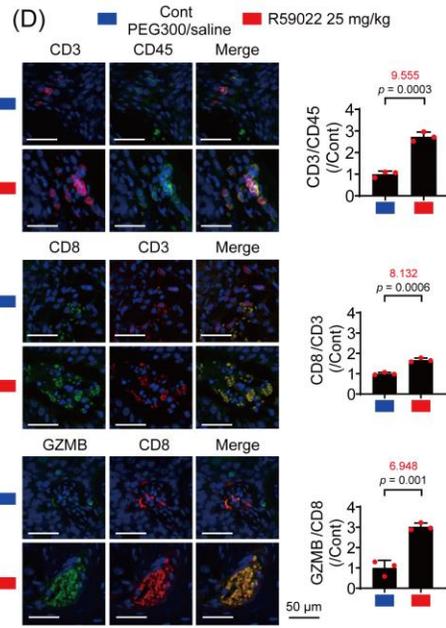
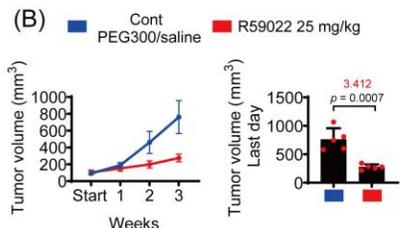
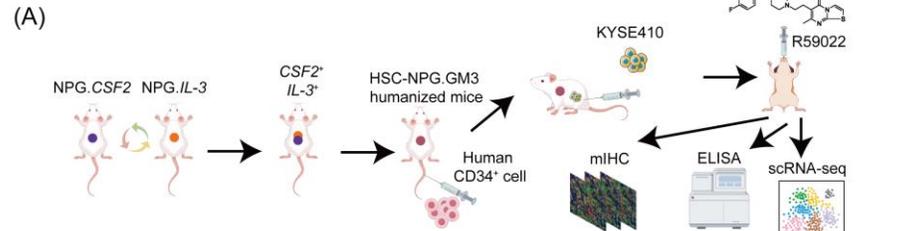
PA directly interacts with NF- κ B p65 to exert function



DGK α /PA axis stimulates the PD-L1 expression by directly interacting with NF- κ B p65 and activating its transcriptional activity



Inhibition of DGK α promotes CTL infiltration

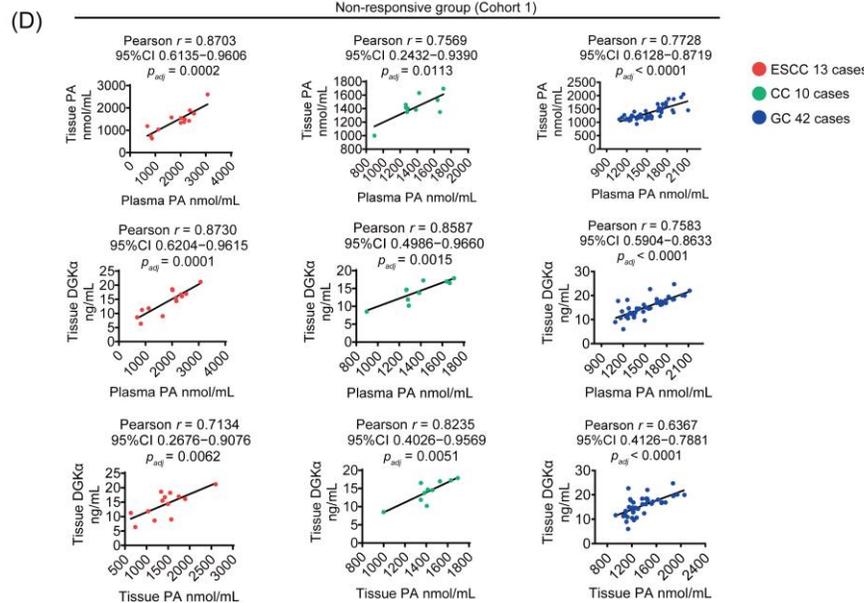
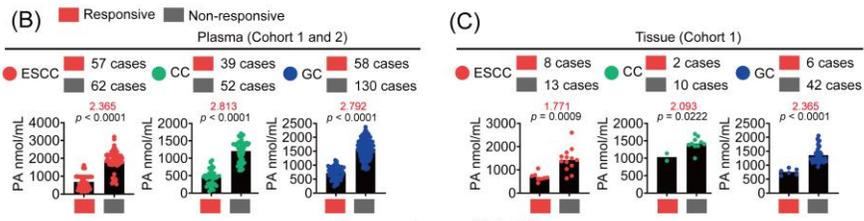
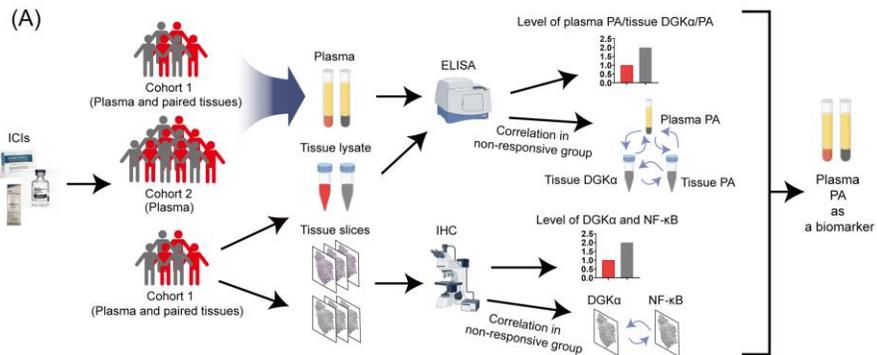


DGK α inhibition blocks ESCC malignancy and promotes cytotoxic T cells (CTL) infiltration in a humanized mouse model of ESCC.



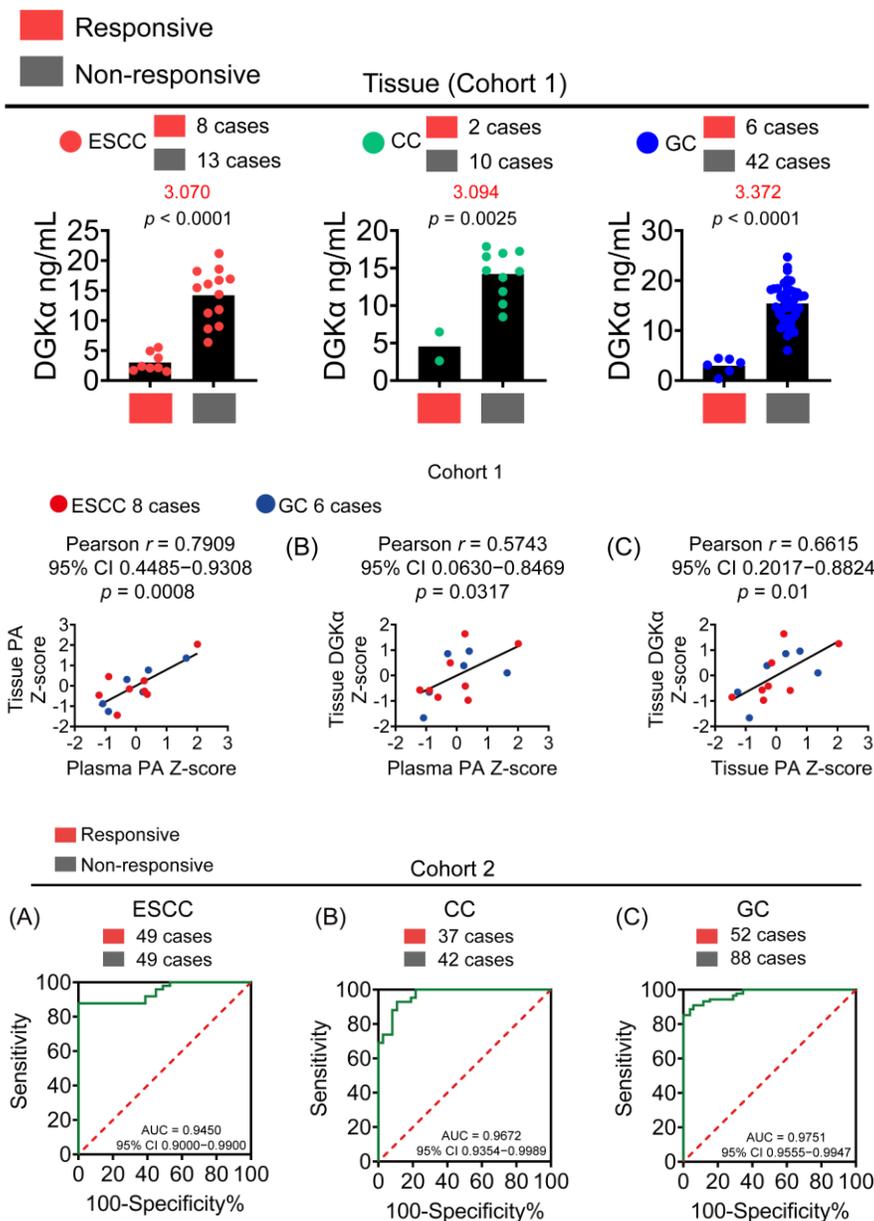
DGKα/PA axis and ICIs response/non-response in gastrointestinal cancers

Expression status of DGKα/PA/NF-κB axis in ICIs-treated gastrointestinal cancers



- plasma PA serves as a biomarker for evaluating ICIs response in gastrointestinal cancers.

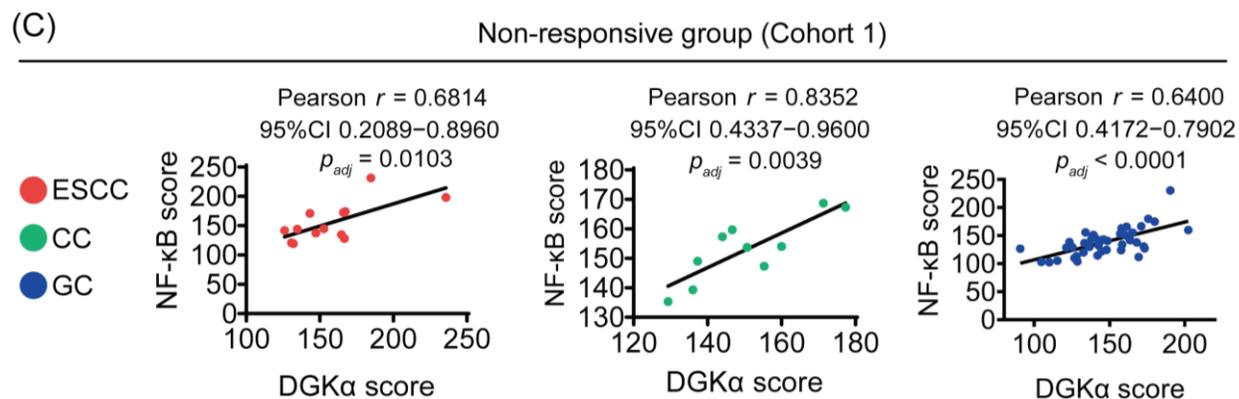
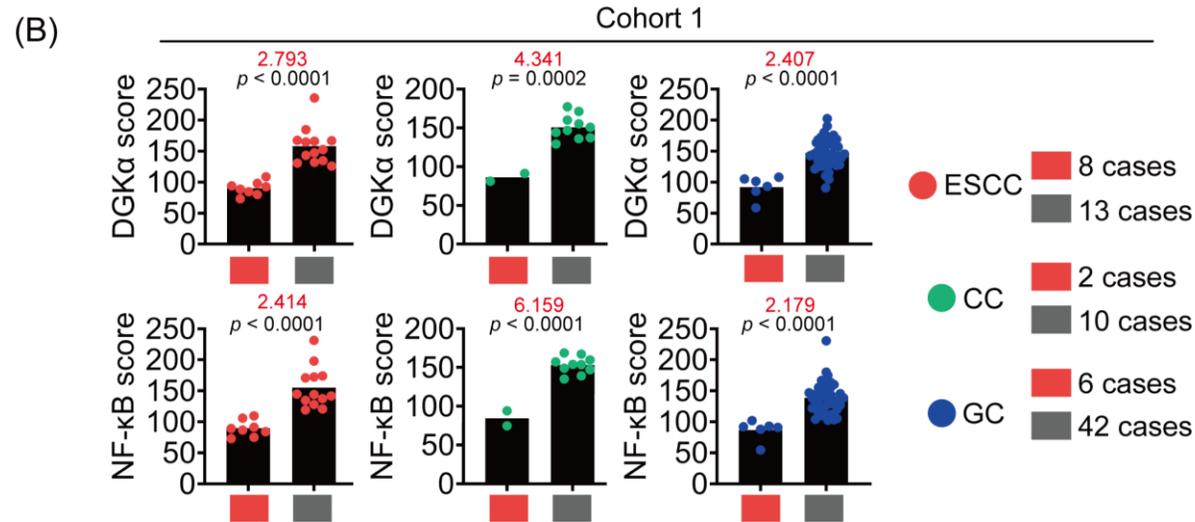
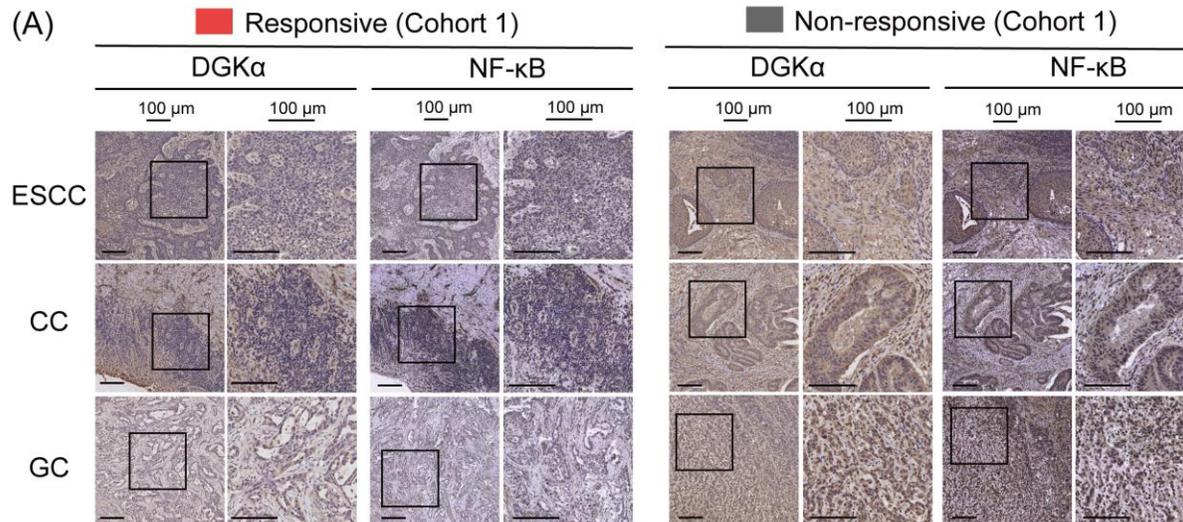
- PA could serve as a reliable biomarker for assessing tumor progression and therapeutic response.





DGK α /PA axis and ICIs response/non-response in gastrointestinal cancers

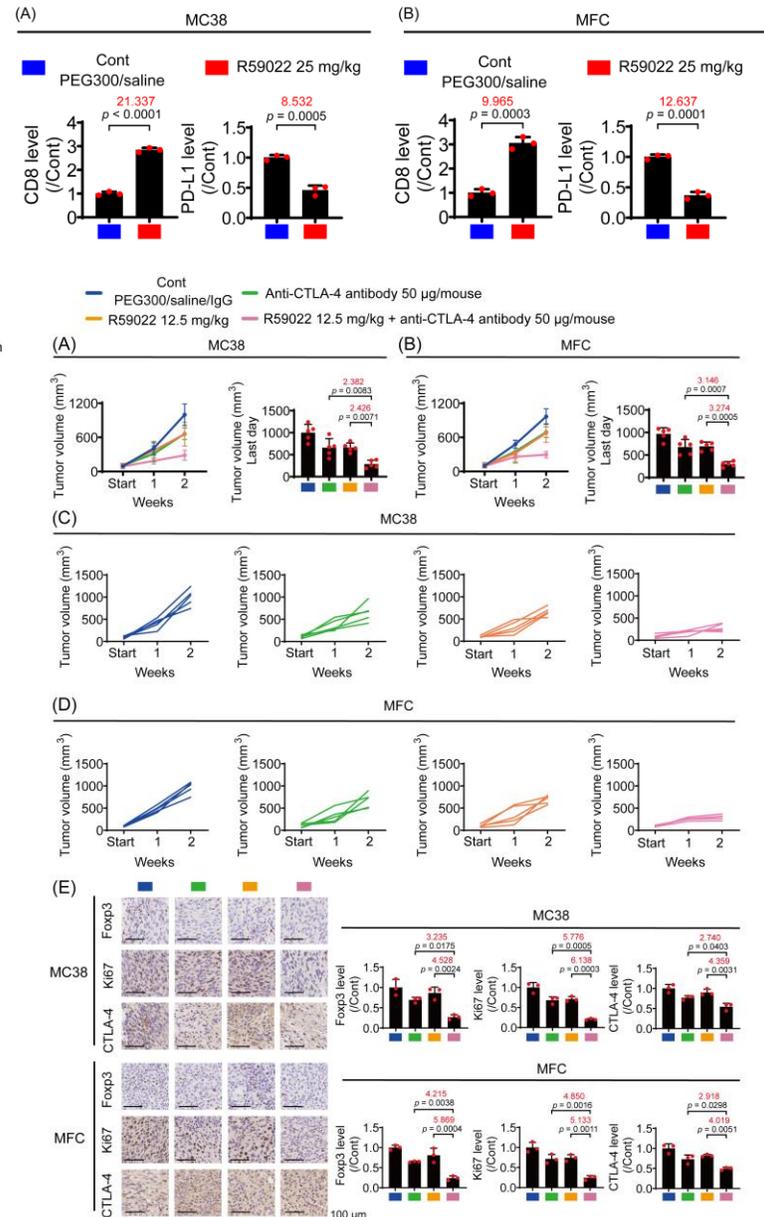
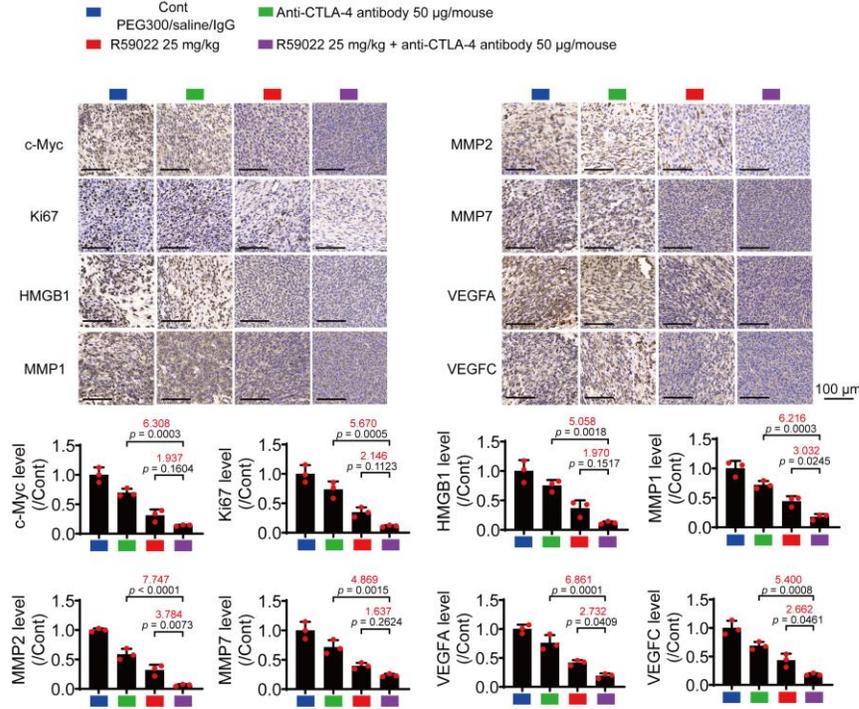
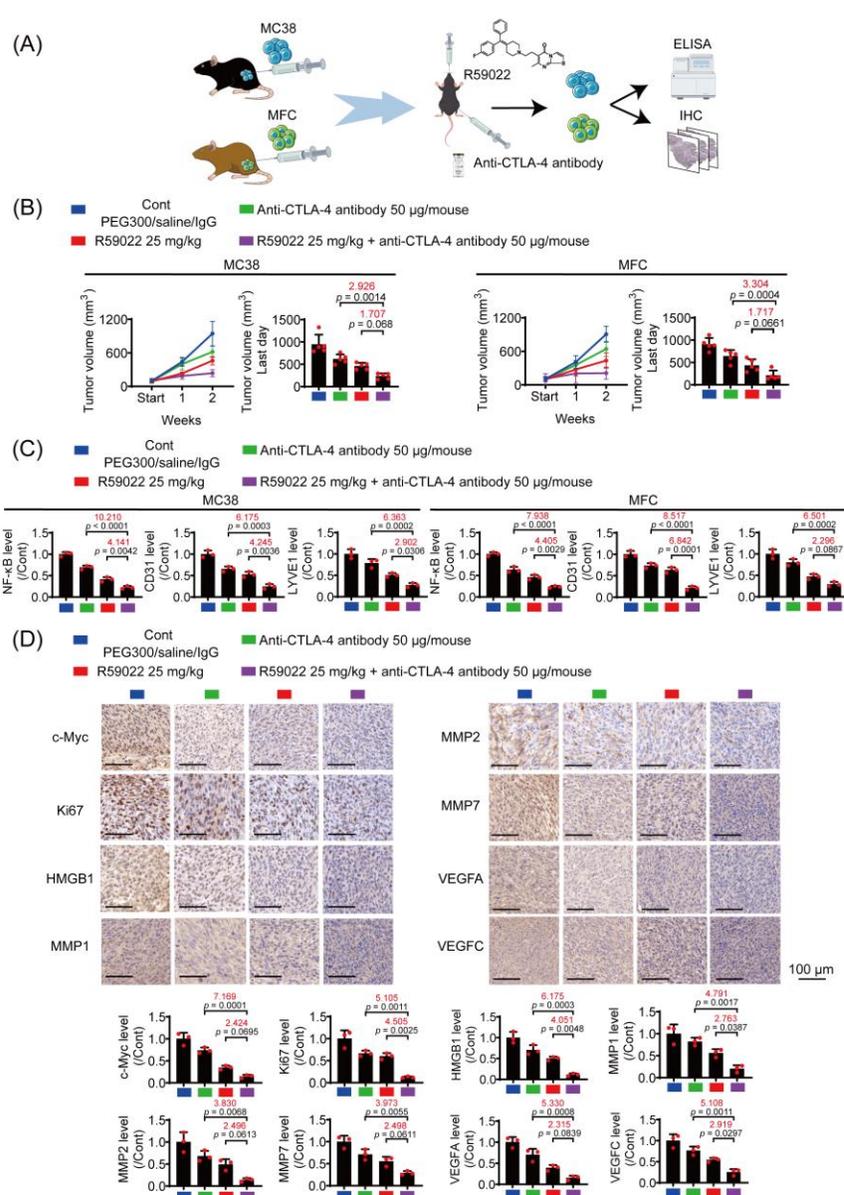
Correlation between DGK α and NF- κ B in the ICIs non-responsive group



Intratumoral DGK α /NF- κ B axis was positively correlated with non-response to ICIs in gastrointestinal cancers



Efficacy of combination of DGK α inhibitors and CTLA-4 inhibitors



Inhibition of DGK α synergistically enhances anti-CTLA-4 antibody efficacy by orchestrating immune microenvironment and promoting T cell-mediated antitumor response, providing novel strategy to develop the combination of antitumor agents.



Summary

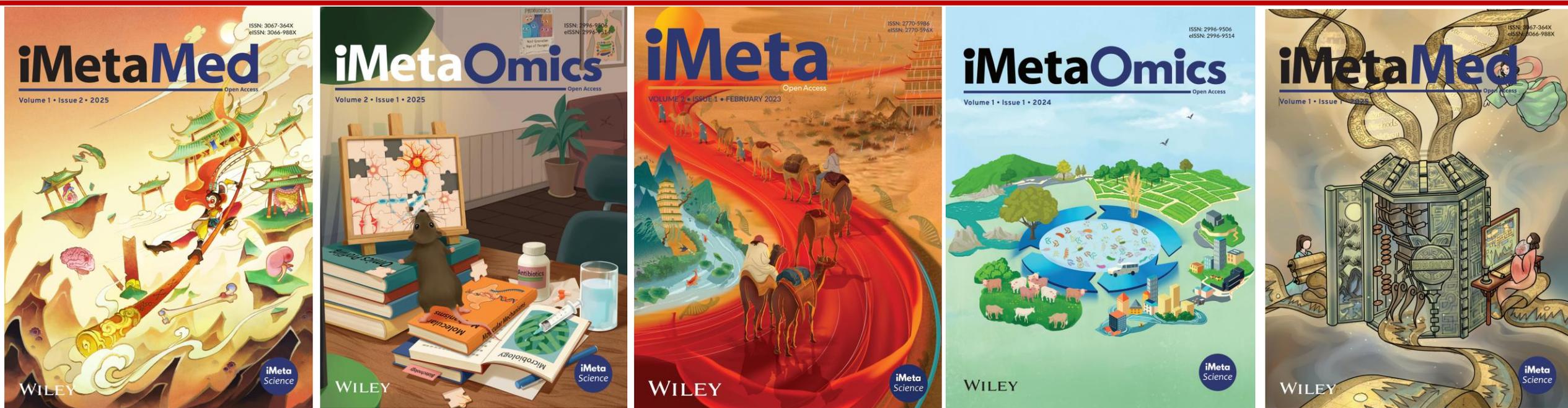
- ❑ DGK α drives immune evasion via through NF- κ B/PD-L1 signaling;
- ❑ Its inhibition orchestrates immune microenvironment to enhance ICIs efficacy;
- ❑ Plasma PA evaluates ICIs response in gastrointestinal cancers.

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