No.	K25-2184	
Project Title	Establishment of Humanized, Tumor Xenograft, and PDX Rat Model for Translational Research	
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(Form 2)

Principal Investigator
Byeong-Cheol Kang

IMSUT International Joint Usage/Research Center Project <International>

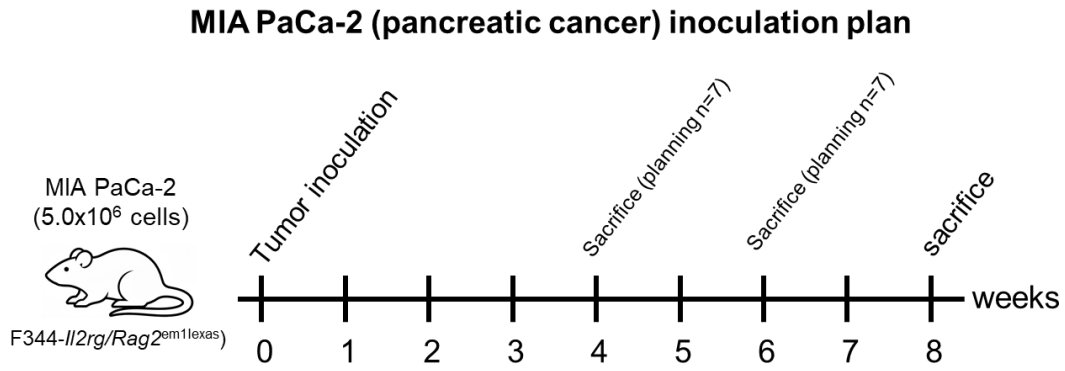
Joint Research Report (Annual/Project Completion)

Project Completion Report

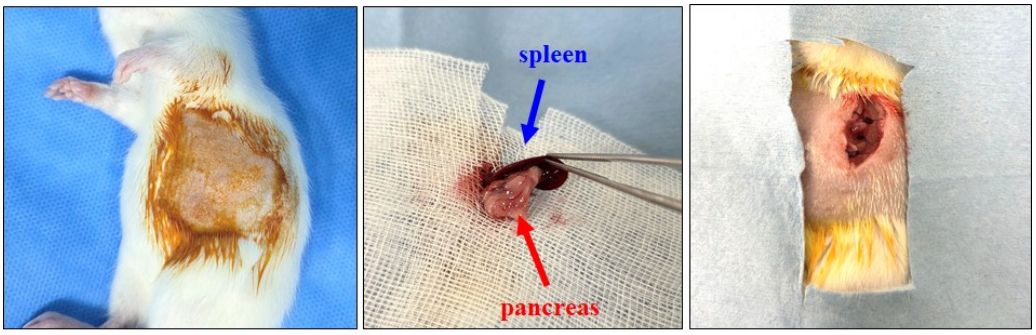
Report

1.*Successful establishment and phenotyping of an orthotopic pancreatic cancer rat Model*

- To overcome the limitations of conventional mouse models (e.g., difficulty in surgery and blood sampling), we established an orthotopic pancreatic cancer rat model
- We went beyond simple tumor formation checks and secured high reliability as a disease model through comparative studies with a sham control group

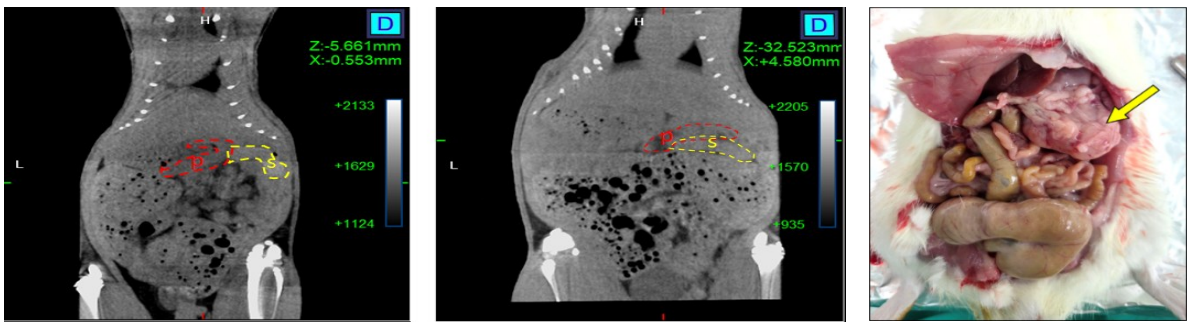


<**Figure 1.** Experimental schedule: MIA PaCa-2 administration and necropsy plan in SCID rats>



<**Figure 2.** Orthotopic implantation of the MIA PaCa-2 human pancreatic cancer cell line into the rat pancreas>

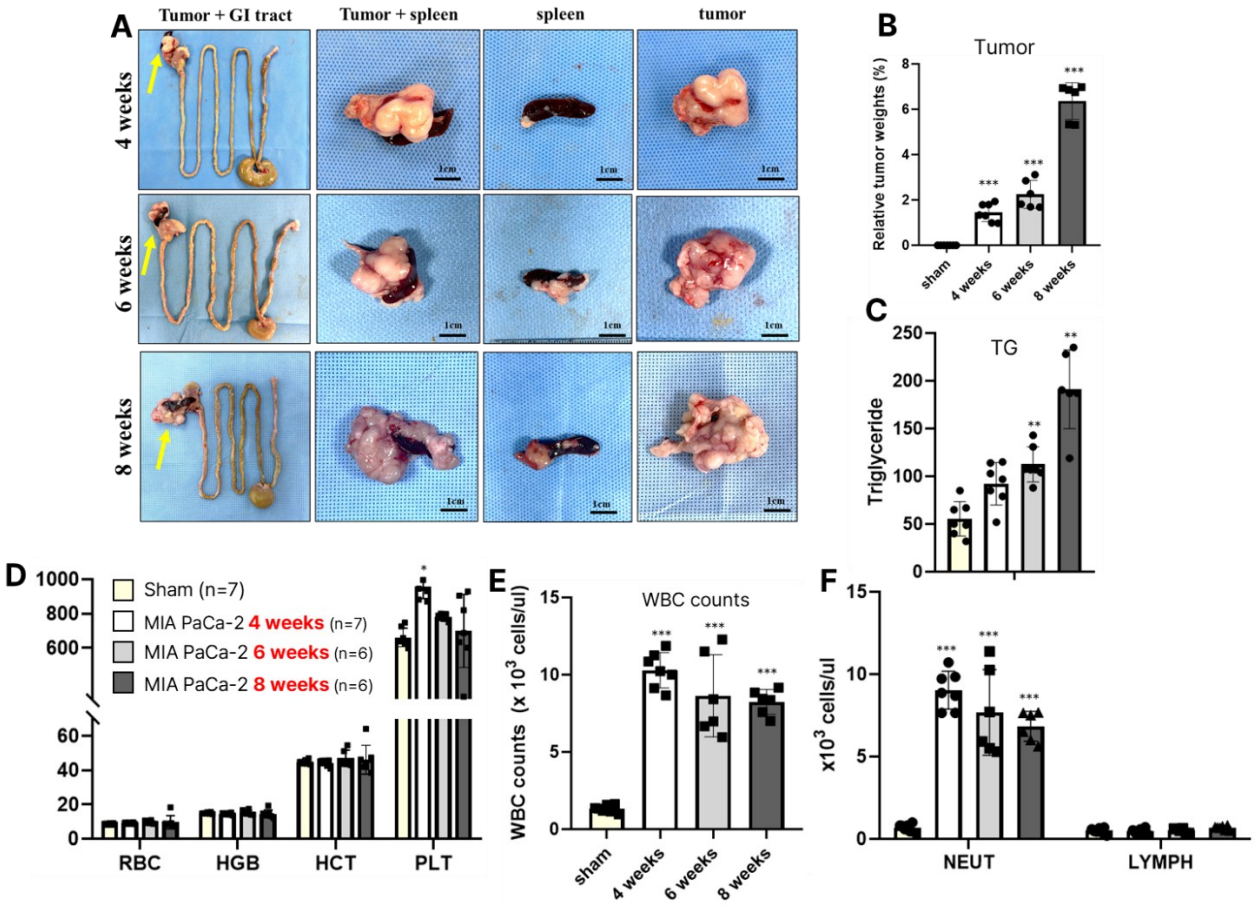
- We confirmed cancer cachexia-like symptoms through monitoring of clinical signs, body weight changes, food/water consumption, and micro-CT imaging for tumor visualization



<**Figure 3.** Verification of tumor engraftment using *in vivo* micro-CT imaging and gross pathology at necropsy>

- Utilizing the rat's physiological advantages, we performed CBC, serum biochemistry, and c oagulation tests. This allowed us to acquire systemic pathological data that is difficult to obtain in mice.
- we established foundational historical data for organ-specific toxicity and metastasis evalu ation through gross examination and organ weight measurement

2. *Changes in tumor size and hematological/biochemistry parameters following orthotopic xeno transplantation of MIA PaCa-2 in SCID rats*



<Figure 4. Progressive tumor growth and systemic hematological/biochemistry alterations following orthotopic xenotransplantation of MIA PaCa-2 cells in SCID rats. **(A)** Representative gross pathological images of the pancreas showing time-dependent tumor enlargement at 4, 6, and 8 weeks post-transplantation. **(B)** Quantitative analysis of relative tumor weights, demonstrating a highly significant, sequential increase over the study period (***$p < 0.001$). **(C)** Serum triglyceride (TG) levels exhibiting a progressive upward trend, culminating in severe dyslipidemia at 8 weeks (**p < 0.01). **(D)** Erythroid parameters (RBC, HGB, HCT) remained relatively stable, whereas platelet (PLT) counts significantly elevated at 4 weeks (*$p < 0.05$), suggesting an early acute-phase response. **(E)** Total white blood cell (WBC) counts and (F) differential neutrophil counts surged dramatically from 4 weeks onward (***$p < 0.001$), indicating a potent, tumor-driven systemic inflammatory response. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs sham group)>

3. Progressive tumor growth and morphological changes

- Following the orthotopic implantation of MIA PaCa-2 human pancreatic cancer cells into the pancreas of SCID rats, **robust tumor engraftment and time-dependent tumor progression** were successfully confirmed
- Because the **rat model offers a larger anatomical cavity** compared to mice, the progressive mass burden we observed allows for a more accurate assessment of local mechanical stress on surrounding organs. This structural progression validates the model as an **excellent platform for evaluating the local morbidities associated with advanced pancreatic cancer**

4. Validation of the therapeutic window

- While orthotopic pancreatic cancer models most closely mimic clinical pathology, there is currently a lack of established biomarkers or standardized criteria for determining the optimal timing of drug administration (unlike subcutaneous models, which typically use a threshold of $100mm^3$)
- Based on the definitive morphological establishment of the tumor by **week 4, we propose this time point as the optimal, standardized baseline** for initiating anticancer therapies. Intervening at this stage allows for the accurate evaluation of therapeutic efficacy before irreversible anatomical distortion occurs

5. Immunological baseline for advanced therapies

- By identifying this potent, tumor-driven myeloid expansion, this model proves highly valuable for testing advanced therapies targeting the tumor microenvironment or systemic inflammation. Understanding this dominant neutrophilic baseline is crucial when evaluating the **safety and efficacy of novel cell therapies (such as CAR-T or NK cell therapies) in a solid tumor** context, as this systemic inflammatory state directly impacts immune cell trafficking and exhaustion