No.	K25-1185	
Project Title	The development of acral melanoma model and a novel early diagnostic method based on stem cell dynamics	
Principal Investigator	Iwei Yeh (University of California, San Francisco・Professor)	
Project Member(s)	**IMSUT Host Researcher**	Emi K Nishimura (The Institute of Medical Science, The University of Tokyo・Professor)
	Project Member (s)	Takeshi Namiki (Institute of Science Tokyo・Professor)

(Form 2)

Principal Investigator
Iwei Yeh

IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Project Completion)

Project Completion Report

Report

FY2025 (2025/4/1-2026/3/31) Progress Report:

In this fiscal year, we successfully explore an impact of the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING)-TANK-binding kinase 1 (TBK1) signaling on human melanomagenesis using both immunohistochemistry and rigorous statistical analyses. cGAS-STING signaling is a pivotal pathway to induce innate immuine responses by detecting cytosolic DNA, which is released during tumorigenesis due to aberrant genomic events such as chromothripsis. Although an activation of cGAS-STING signaling is crucial in melanomagenesis, a detailed examination to explore an activation of that signaling in melanomas using clinical specimens is limited to date. We collected 60 human specimens of melanomas with a variety of pathological stages and subsets, and performed immunohistochemistry using antibodies against cGAS, STING and phopho-TBK1 at serine 172 (*p*-TBK1) (Figure 1). We captured whole slide images using Hamamatsu Photonics NanoZoomer and acquired images were transferred to artificial intelligence (AI) assisted image analyzer HALO. With this method, we quantified expressions of cGAS, STING and *p*-TBK1 in melanoma cells by excluding expressions of those genes in surrounding inflammatory infiltrates and endothelial cells. We further analyzed those expressions and various clinical parameters statistically in order to explore an impact of cGAS-STING-TBK1 signaling on human melanomagenesis. This analysis revealed that cGAS expression decreased from pTis-pT1 to pT2-pT4, which suggested that cGAS suppressed the progression from early melanomas into invasive melanomas by exerting innnate immune responses. Furthermore, ROC analysis based on the predictive model for cGAS expression revealed the most discriminative value at the tumor thickness of 0.90 mm (Figure 2). Considering that melanomas with the tumor thickness of less than 0.80 mm will not metastasize, cGAS expression may suppress the progression of melanomas in terms of this statistical analysis emphasizing on tumor thickness. In this fiscal year, our international collaboration successfully steps forward to the initial elucidation of innate immunity and melanomagenesis in terms of an activation of cGAS-STING-TBK1 signaling and tumor thickness.

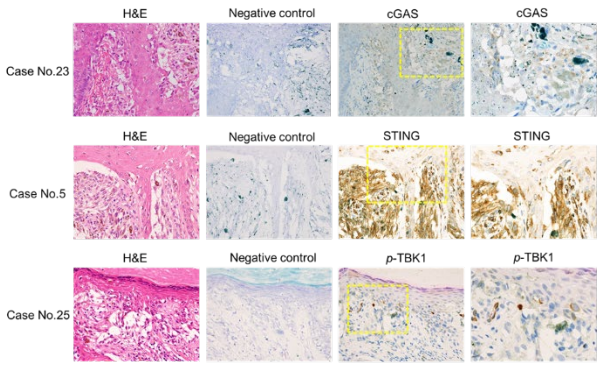

Figure 1 Expression of cGAS, STING and *p*-TBK1 in melanomas using immunohistochemistry.

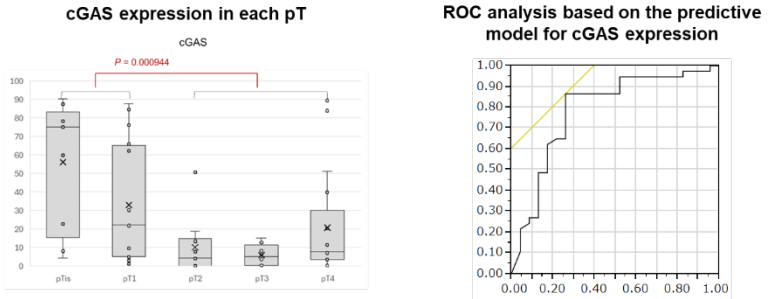

Figure 2 cGAS expression decrease from pTis-pT1 to pT2-pT4 (left). ROC analysis revealed the predictive model for cGAS expression can predict with the most discriminative value at the tumor thickness of 0.90 mm (right).