**FUNDING PROGRAM FOR NEXT GENERATION WORLD-LEADING RESEARCHERS**

| **Project Title**: Novel Therapeutic Strategies for Targeting Tyrosine Kinase Inhibitors (TKI)-resistant Cancer Stem Cells | |
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| **Name**: Kazuhito NAKA | **Institution**: Kanazawa University |

**1. Background of research**

Although the discovery of the tyrosine kinase inhibitors (TKI) have significantly improved the prognosis of chronic myeloid leukemia (CML) patients, a complete cure is not possible due to the existence of a rare population of CML stem cells known to be resistant to TKI therapy.

**2. Research objectives**

The purpose of our current research is to clarify the molecular mechanisms governing TKI-resistance of CML stem cells via TGF-β-FOXO signaling pathway.

**3. Research characteristics (incl. originality and creativity)**

We have recently reported that Forkhead transcription factor (FOXO) is essential for the TKI-resistance of CML stem cells (Naka *et al.,* Nature 2010). Furthermore, TGF-β originate from the microenvironment regulates FOXO activity in CML stem cells. Notably, a combined administration of TGF-β inhibitor and TKI leads to reduction of CML stem cells *in vivo*. Our results demonstrate a critical role for the TGF-β-FOXO pathway in the maintenance of TKI-resistant CML stem cells.

**4. Anticipated effects and future applications of research**

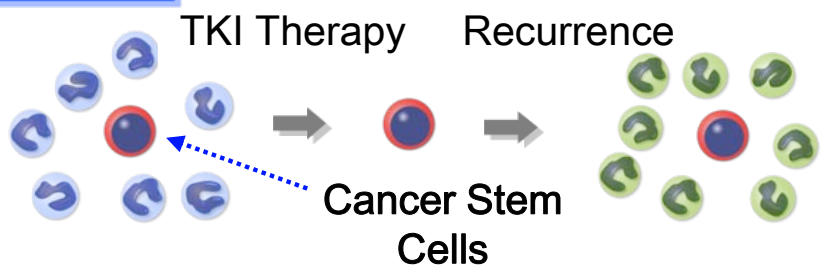
The long-term outcome of our investigation will hopefully be the development of novel agents that can specifically suppress the effects of these TGF-β-FOXO signaling pathway, and thereby provide a novel avenue for curative TKI-resistant cancer stem cell therapy for CML patients as well as breast cancer and non-small cell lung cancer patients.

Funding Program for Next Generation World-Leading Researchers, Cabinet Office, Government of Japan

# Novel Therapeutic Strategies for Targeting Tyrosine Kinase Inhibitors (TKI)-resistant Cancer Stem Cells

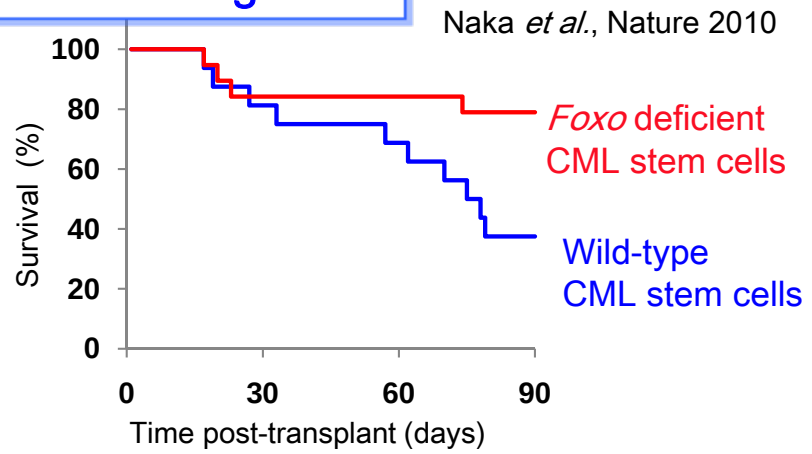
Kazuhito Naka, Kanazawa University

## Purpose



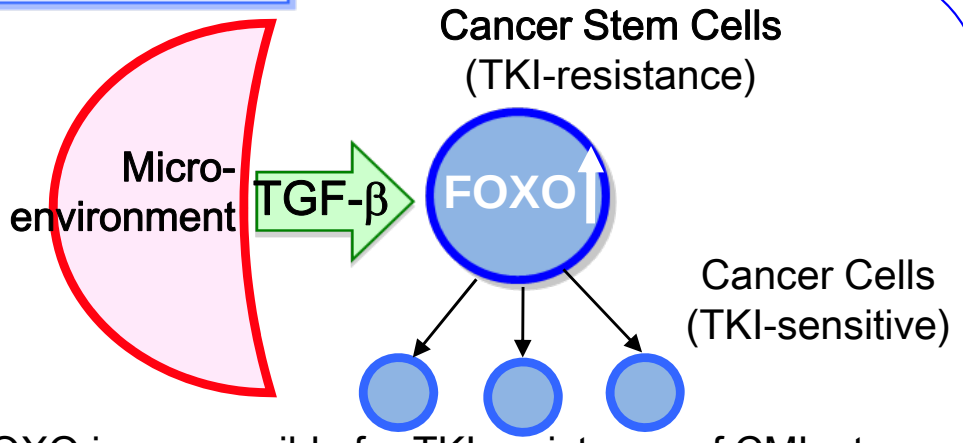

The purpose of our research is the development of novel agents that specifically suppress TGF-β-FOXO signaling pathway, and thereby provide a novel avenue for curative TKI-resistant cancer stem cell therapy.

## Previous Findings




Foxo deficiency promoted the survival of CML-affected mice after administration of TKI.

## Significance




FOXO is responsible for TKI-resistance of CML stem cells. TGF-β from the microenvironment activates FOXO in CML stem cells. Thus, TGF-β-FOXO signaling pathway maintains TKI-resistant CML stem cells.

## Strategy

Identification of Molecular Mechanisms Governing TGF-β-FOXO Signaling Pathway in TKI-resistant CML Stem Cells

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Development of Therapeutic Agents Targeting the TGF-β-FOXO Signaling Pathway

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Application of the Agents to Breast and Lung Cancer Stem Cell Therapy