Discovery of a novel Wnt inhibitor with potential to eradicate colorectal cancer stem cells

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National Cancer Center
RIKEN
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TOKYO, Japan (August 26, 2016) – A team including the National Cancer Center (NCC) (Tokyo, Japan), the RIKEN Center for Life Science Technologies (CLST) (Yokohama, Japan), and Carna Biosciences Inc. (Kobe, Japan) has jointly announced the development of a novel small-molecule Wnt inhibitor named NCB-0846. Wnt signaling is a key pathway of cancer stem cell (CSC) development. The inhibitor may provide a new therapy option for patients with drug-refractory colorectal cancer.

Colorectal cancer is a major cause of cancer death, accounting for 700,000 deaths annually worldwide. Over 90% of colorectal cancers carry somatic mutations in Wnt signaling component genes such as the adenomatous polyposis coli (*APC*) tumor suppressor gene, resulting in constitutive activation of Wnt signaling. This in turn leads to the generation of CSCs, which are intrinsically resistant to conventional chemotherapy. Therefore, therapeutics that can block Wnt signaling are likely to eradicate cancer stem cells and cure the disease (**Figure 1**). However, despite a wealth of data and investment in research and development, no Wnt-inhibiting drug has yet been incorporated into clinical practice.

NCC researchers have previously examined the components of the T-cell factor-4 (TCF4) and β-catenin transcription complex and identified Traf2- and Nck-interacting kinase (TNIK) as an essential regulatory component of the TCF4/β-catenin complex (Shitashige *et al.*, Gastroenterology. 134:1961-71, 2008). TNIK regulates Wnt signaling in the most downstream part of the pathway, and its pharmacological inhibition has been

anticipated to block the signal even in colorectal cancer cells with mutation of the *APC* gene (Shitashige *et al.*, Cancer Res. 70:5024-33, 2010).

NCC and Carna researchers screened a kinase-focused compound library followed by lead optimizations, leading to the discovery of NCB-0846, which can inhibit the kinase activity of TNIK with an IC50 value of 21 nM. X-ray co-crystal structure analysis performed by RIKEN CLST researchers revealed that NCB-0846 binds to TNIK in an inactive conformation, which is likely to be essential for Wnt inhibition.

NCB-0846 was orally administrable and suppressed the growth of patient-derived colorectal cancer xenografts. NCB-0846 suppressed various CSC activities of colorectal cancer cells and their expression of CSC markers (**Figure 2**).

"We're very encouraged by our promising preclinical data for NCB-0846, especially considering the difficulty in targeting this pathway to date, and shortly we hope to conduct a clinical trial at the NCC hospitals" said Dr. Tesshi Yamada, the chief of the Division of Chemotherapy and Clinical Research at the NCC research Institute. NCB-0846 is currently under preclinical development with the aim of Investigational New Drug (IND) filing.

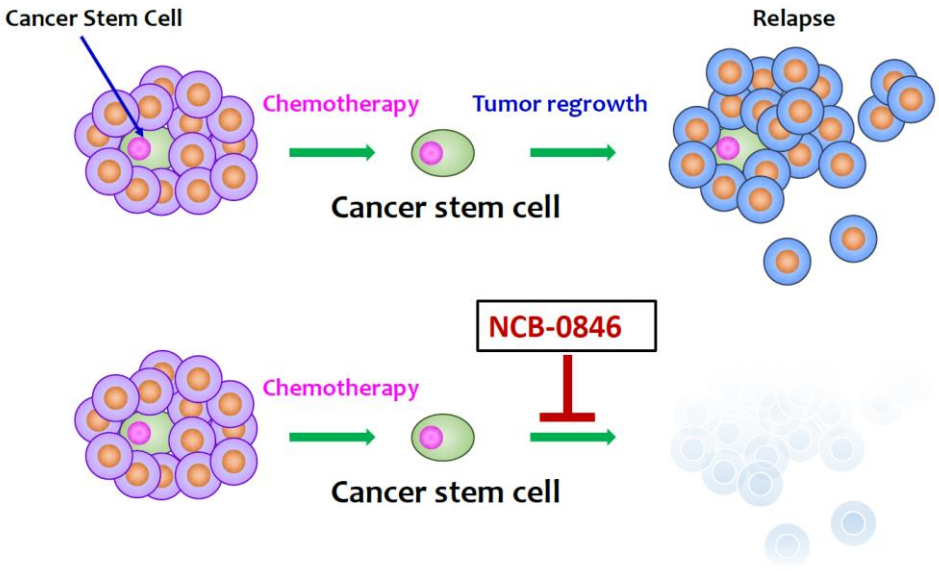

Figure 1. Therapeutics targeting cancer stemness

CSCs are intrinsically resistant to conventional chemotherapy and radiotherapy. CSCs surviving these treatments often grow back and eventually cause cancer relapse (Top panel). Therapeutics

blocking the aberrant Wnt signaling are likely to eradicate CSCs and cure the disease (Bottom panel).

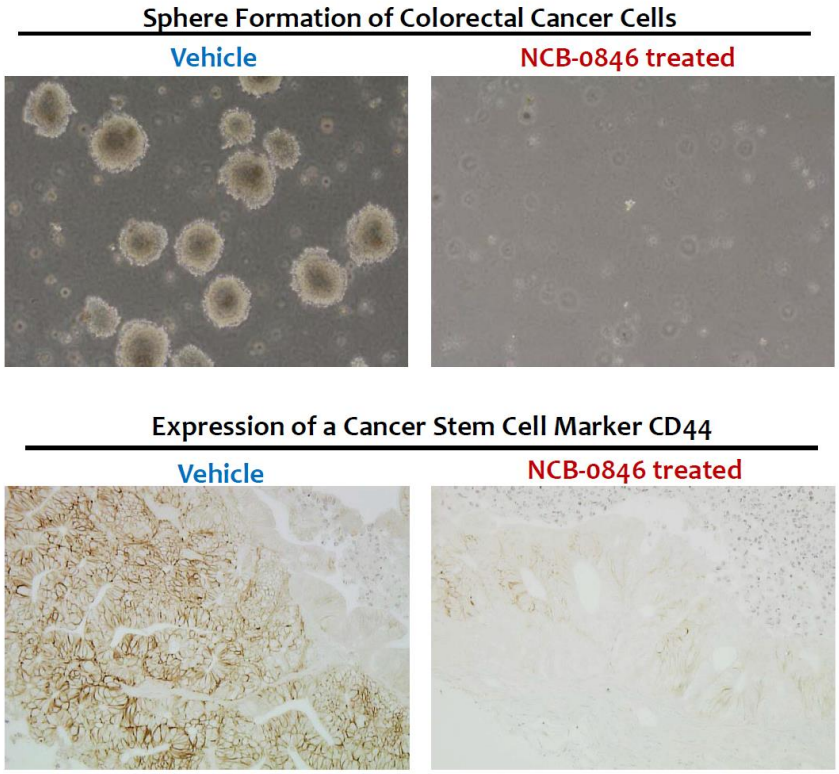

Figure 2. NCB-0846 abrogates cancer stemness

NCB-0846 suppressed sphere-forming activity (Top panel) and expression of a cancer stem cell marker CD44 by colorectal cancer cells (Bottom panel).

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