

NIFT- First in class NEDD4 Inhibitors For cancer Therapy

Introduction

NEDD4, an E3 ubiquitin ligase enzyme from the HECT family, selectively targets specific substrates for ubiquitination, and its upregulation has been observed in several cancers (e. g. gastric cancer, hepatocellular carcinoma, bladder cancer, glioma, lung and pancreatic cancer) making NEDD4 inhibitors a promising novel approach for solid tumors treatment.

Medical Need

Gastric cancer remains one of the most lethal malignancies worldwide due to its high aggressiveness and frequent late-stage diagnosis. Gastric cancer ranks as the **fifth leading cause of cancer-related mortality** worldwide, with approximately **1 million new cases** and over **650,000 deaths** annually. 60–80% of gastric cancers are **diagnosed at an advanced or late stage**, largely due to the subtle and non-specific symptoms at early stages. First-line treatments, including immunotherapy and targeted biological therapies in combination with chemotherapy, achieve response rates of approximately 35–45%, with overall survival of up to 14 months. Response rates decline dramatically in second- and third-line treatments, to approximately 15–25% and 4–16%, respectively, highlighting the urgent need for novel therapeutic approaches.

Solution

Our proposed solution relies on the discovery, through structure-based design, of **novel tricyclic compounds** that **inhibit NEDD4** with **high potency** (nM range) by binding the allosteric "Ub exosite" and blocking polyubiquitination. Our compounds show **high affinity** and **selectivity** for NEDD4 over other family members (including NEDD4-L, ITCH, and HECW2).

Competitive Advantages

- **First-in class high selective** drug like inhibitor preserving part of physiological function of NEDD4
- Potential for **reduced off-target effects**
- Translation-ready lead compound with potential for **oral administration**, supported by an *in vivo* proof-of-concept demonstrating good tolerability
- **Scalable chemistry** and **low manufacturing costs**

Opportunity

We are seeking **industrial partners** to advance our asset through preclinical and clinical development, with gastric cancer as the lead clinical indication and NSCLC and bladder cancer as additional indications, and **out-license** the asset.

Scientific leaderships



Ciro Mercurio, PhD

Operational manager of the [Therapeutic Discovery Platform](#) at IFOM, IT
Biologist with +25 years of drug discovery experience in oncology



Simona Polo, PhD

Director of the [Molecular Machines in Signaling Pathways](#) research program at IFOM, IT
Leader expert in ubiquitin biology

Contact us



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