

Nested Therapeutics Announces Nomination of First Development Candidate, a Potential First-in-Class Inhibitor of the RAS/MAPK Pathway

Pre-clinical studies of single agent NST-628 demonstrate superior efficacy, tolerability profile and brain penetration

IND-enabling studies to continue in anticipation of first in-human trials starting in 2024

Cambridge, Mass., February 28, 2023 – Nested Therapeutics, a biotechnology company pioneering a next-generation precision medicine platform to address hard-to-treat cancers, today announced the nomination of the company’s first drug development candidate from its NEST-1 program, NST-628, a mechanistically novel non-degrading molecular glue that targets multiple nodes in the RAS/MAPK pathway.

“This milestone was achieved in less than two years since inception of the company and represents an important step for Nested as it further validates our novel approach and the potential to unlock other cancer targets that are notoriously hard to drug,” said Darrin Miles, Chief Executive Officer of Nested Therapeutics. “By targeting the RAS pathway via the differentiated mechanism of a pan-RAF/MEK and KSR/MEK molecular glue compound, along with a balanced metabolic profile that includes complete brain penetration, we can potentially address the unmet needs of a large patient group, including those who do not have precision medicine options today.”

NST-628 is being developed with proprietary structural insights of how signaling complexes form and function in cancer and addresses common pitfalls of other MAPK-targeted compounds, which remain unable to circumvent the risk of intrinsic resistance via signaling pathway reactivation. In addition, NST-628 effectively crosses the blood-brain barrier, suggesting potential advantage for treatment of brain metastases and primary CNS malignancies with MAPK pathway alterations. Preclinical data evaluating several oncology biomarkers relevant to RAS/MAPK-driven models collectively demonstrate superior anti-tumor activity, including in central nervous system-implanted tumor models, and tolerability of NST-628 compared to other MAPK-targeted compounds administered as either single agents or combinations.

“By expanding to a 3-D view of mutations, we have the ability to look beyond active sites as targets, which allows us to locate unexplored driver mutations and druggable pockets across a protein’s surface,” said Klaus Hoeflich, Ph.D., Co-Founder and Chief Scientific Officer at Nested Therapeutics. “Leveraging



such structural insights allow us to gain a deeper understanding of the underlying molecular interactions that cause cancer progression and identify the right druggable pockets and novel targeting strategies.”

Nested Therapeutics plans to submit an IND for NST-628 following completion of ongoing preclinical and IND-enabling studies, to support first-in-human studies to start in 2024. The company’s pipeline also includes NEST-2, an allosteric molecule targeting a transcriptional regulator frequently mutated in cancer. Selective target binding to novel cryptic pockets has been demonstrated and lead chemical series are advancing to *in vivo* proof-of-concept. For its NEST-2 program, Nested Therapeutics anticipates nominating its second development candidate in 2024.

About DeCRYPTion Platform

Nested Therapeutics’ DeCRYPTion Platform is a purpose-built, insightful drug discovery platform that enables Nested to identify new, overlooked areas of opportunity in the form of high value targets and design therapeutics for a perfect fit. The platform includes three critical components: (1) mapping mutational clusters onto the structural proteome, (2) identifying druggable pockets and cancer-driving mechanisms, and (3) designing novel drugs optimized for the druggable pocket.

About Nested Therapeutics

Nested Therapeutics is a biotechnology company focused on discovering and developing novel, targeted, small molecule precision medicine therapies for patients with cancer by using mutation clusters to identify druggable pockets. With a platform that utilizes insights from genomics, computational chemistry, proteomics, and AI, Nested is working to reach untapped mutations with the potential to improve outcomes for millions of patients. To learn more, visit www.nestedtx.com and follow Nested Therapeutics on Twitter (@Nestedtx) and LinkedIn.

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Media Contact:

Peg Rusconi

prusconi@vergescientific.com