

Industry Insights

 Next-Generation
Undruggable

October 3rd | Boston, MA



Klaus Hoeflich

**Chief Scientific Officer
& Co-founder**

Nested Therapeutics

What are the biggest challenges facing those working to target the 'undruggable'?

Firstly, despite the fact that oncology targets having a strong genomic rationale are ideal for drug discovery, we tend to ignore the 95% of tumor genetics that aren't blindingly obvious driver mutations. There is a lot of signal in that noise, if you know how to decode it.

Secondly, as drug hunters, we tend to rely on our most

established approaches, such as targeting the active sites of enzymes.

However, most driver mutations occur outside of active sites, and there are new chemical biology opportunities if you closely follow these mutational mechanisms. Thirdly, effective integration of computational and experimental methods is no longer an option. A robust platform that spans biology to biophysics, and includes dynamic simulations and machine learning, is a prerequisite for this type of drug discovery.

How are Nested Therapeutics working to overcome these challenges?

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. Our approach is to (1) map and validate mutational clusters onto the structural proteome, (2) identify novel druggable pockets and cancer-driving mutational mechanisms, and (3) design novel small molecule medicines optimized for the druggable pocket. With a platform that utilizes insights from genomics, computational chemistry, proteomics, and AI, we are working to reach untapped mutations and novel mutational mechanisms with the potential to improve

www.nextgenerationundruggable.com

Industry Insights



October 3rd | Boston, MA

outcomes for patients. To learn more, visit www.nestedtx.com.

What does the future look like for Nested Therapeutics?

Nested's lead compound, NEST-1, is a non-degrading dual molecular glue that targets multiple components of the MAPK pathway and has demonstrated potentially superior efficacy, tolerability and CNS activity relative to both single agents and combinations in RAS/MAPK-driven models. We plan 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. For the NEST-2 program, we anticipate nominating our second development candidate in 2024.

What are you most looking forward to at Next-Generation Undruggable 2023?

I am looking forward to connect with like-minded scientists from diverse areas to explore future directions in our field. It is my hope that the conference will stimulate

more discussions and possible collaborations for those working in academia and biopharma.

Hear More From Klaus Hoeflich During His Presentation At Next-Generation Undruggable 2023 in Boston, MA on October 3rd