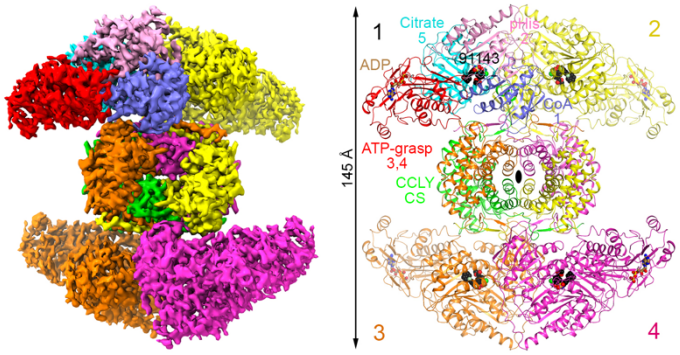
Nimbus Therapeutics Publishes First-Ever High-Resolution Structure of ATP-Citrate Lyase

Research published in Nature *utilizes cryo-EM to determine structure of critical metabolic protein*

CAMBRIDGE, Mass. – April 3, 2019 – Nimbus Therapeutics, a biotechnology company applying deep computational expertise throughout drug discovery and development, today published research in *Nature* describing the first high-resolution structure of full-length human ATP-citrate lyase (ACLY), a building block of human metabolism. Despite the ubiquitous role of ACLY in fatty acid and cholesterol synthesis throughout the body, conventional crystallography has not successfully elucidated its structure.



3D structure of the ACLY tetramer produced using cryo-EM (Credit: Liang Tong, Columbia University; Nimbus Therapeutics; *Nature*)

Nimbus scientists, in partnership with researchers at Columbia University and co-founder Schrödinger, used cryo-electron microscopy (cryo-EM) to produce the full tetrameric structure of ACLY. The cryo-EM research was funded by Nimbus and led by Professor Liang Tong at Columbia University. The cryo-EM data were collected at the New York Structural Biology Center.

In addition, the publication describes potent inhibition of ACLY by a series of computationally designed small molecules developed by Nimbus. Inhibition of ACLY has long been recognized as a potential pathway to treat cancer and metabolic disorders. This study describes a previously undiscovered allosteric site of ACLY as a promising target for inhibitory compounds, greatly enhancing the druggability of ACLY.

“This paper is a terrific example of how our work at Nimbus combines cutting-edge technology, computational approaches and deep drug discovery experience to generate new scientific insights,” said Jeb Keiper, Chief Executive Officer at Nimbus. “We’re excited to continue collaborating with experts as we interrogate new targets and deepen our pipeline of therapies.”

“This work is a major contribution to the scientific literature, and a remarkable demonstration of the potential of cryo-EM in drug discovery,” said Liang Tong, Ph.D., William R. Kenan, Jr. Professor and

Department Chair at Columbia University and lead author on the study. “Together, we’ve demonstrated how combining computational insights with cutting-edge tools like cryo-EM may spark significant progress in cancer and metabolic disease research.”

“Over the past decade, Nimbus has become known for major scientific advances in protein structure elucidation and development of small molecule therapeutic agents,” said Peter Tummino, Ph.D., Chief Scientific Officer of Nimbus. “We look forward to sharing many more firsts in our drug discovery programs in the months and years to come.”

The paper, entitled “An allosteric mechanism for potent inhibition of human ATP-citrate lyase,” published online in *Nature* today: https://doi.org/10.1038/s41586-019-1094-6.

About Cryo-EM
Cryo-electron microscopy (cryo-EM) is a cutting-edge microscopic imaging technique developed by Jacques Dubochet, Joachim Frank and Richard Henderson, who were awarded the 2017 Nobel Prize in Chemistry for this achievement. Cryo-EM allows researchers to freeze biomolecules mid-movement and visualize processes they have never previously seen, which is informative for both the basic understanding of life’s chemistry and for the development of pharmaceuticals.

About Nimbus Therapeutics
Nimbus Therapeutics is a biotechnology company headquartered in Cambridge, Massachusetts (USA). Nimbus is pioneering the application of highly advanced computational technologies to the design and development of novel treatments for substantial and underserved human diseases. The company’s focus on metabolic diseases, cancer and immune-inflammatory disorders reflects the mechanistic relationship between these disorders, and Nimbus’ ability to rapidly tackle well-validated targets as well as those that have proven intractable to others. The company’s LLC/subsidiary architecture enables diverse and synergistic partnerships to deliver breakthrough medicines. To learn more, please visit www.nimbustx.com.

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