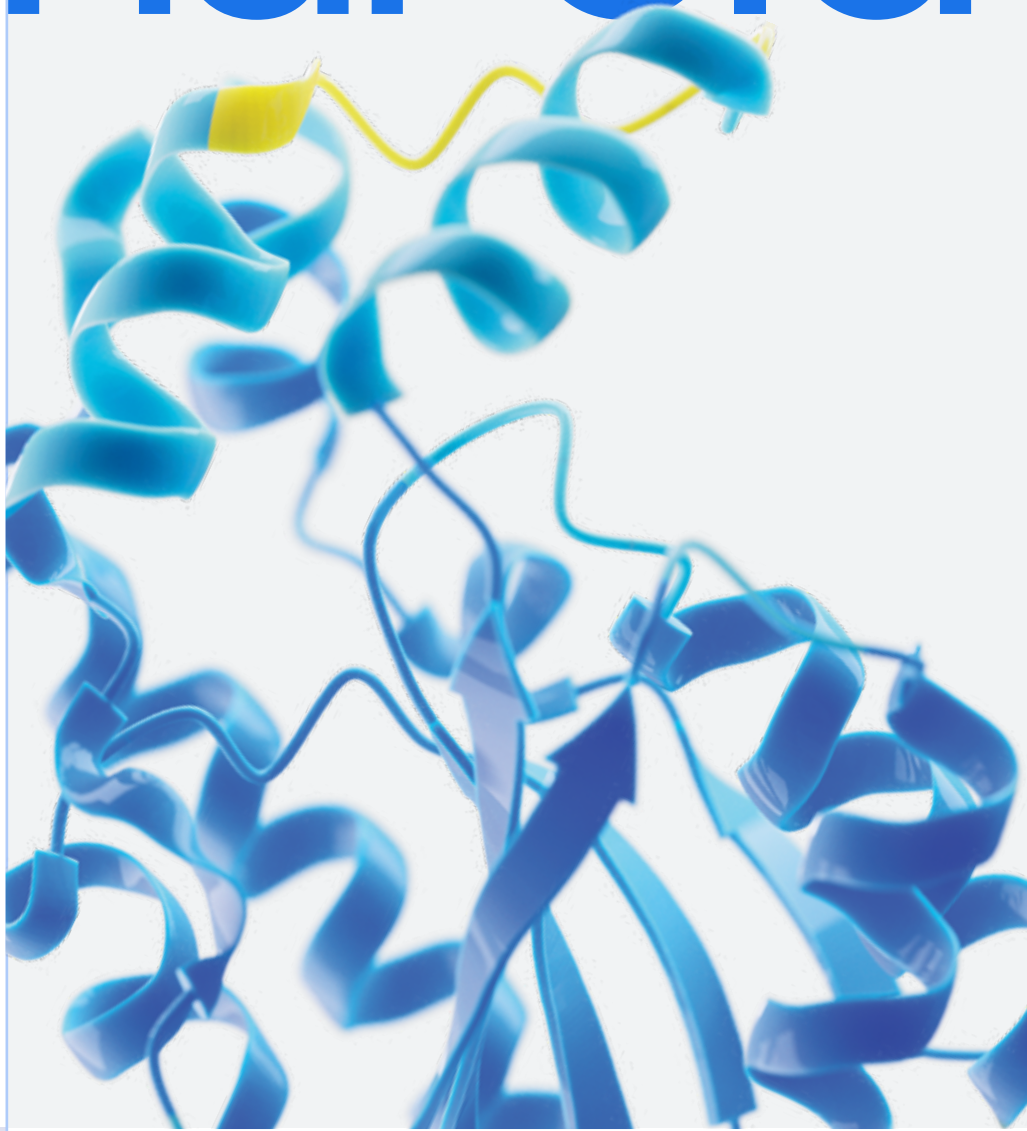


AlphaFold



Accelerating
breakthroughs
in biology with AI

Advancing epigenetics research to unlock new drugs against cancer

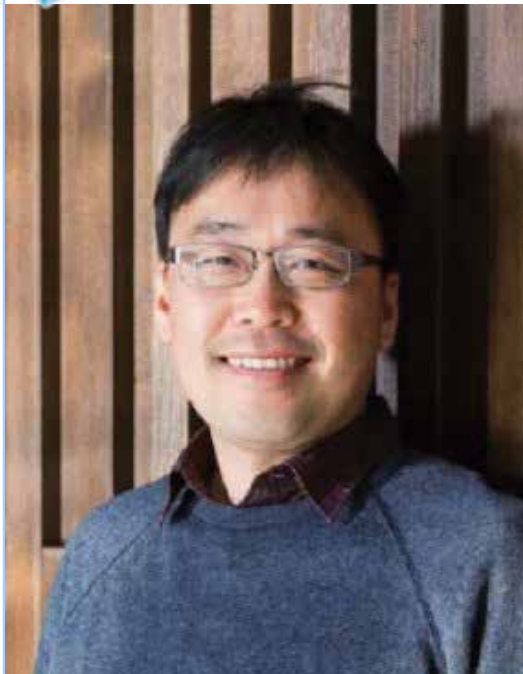


Unfurled and flattened, DNA measures about a meter long. Its home, a cell, is about a 10,000th the size. Now imagine trying to study the interactions between DNA, proteins and a myriad of other elements when they're all packed tightly in a single cell, and we start to see a key challenge in the field of epigenetics.



Epigenetic cellular memory and fueling drug research

Dr. Ji-Joon Song, Professor at the Department of Biological Sciences at KAIST (Korea Advanced Institute of Science and Technology) has been exploring epigenetic cellular memory for the past 20 years. This field investigates why different cell types, despite originating from the same genetic blueprint, express distinct sets of genes, dictating their unique functions and identities. A key focus for Dr. Song's team is understanding the CODANIN-1 protein, which negatively regulates the crucial high-order packing of DNA by sequestering another protein, ASF1. Unraveling these precise molecular interactions is fundamental to understanding processes closely related to diseases like cancer, where cells "forget who they are".



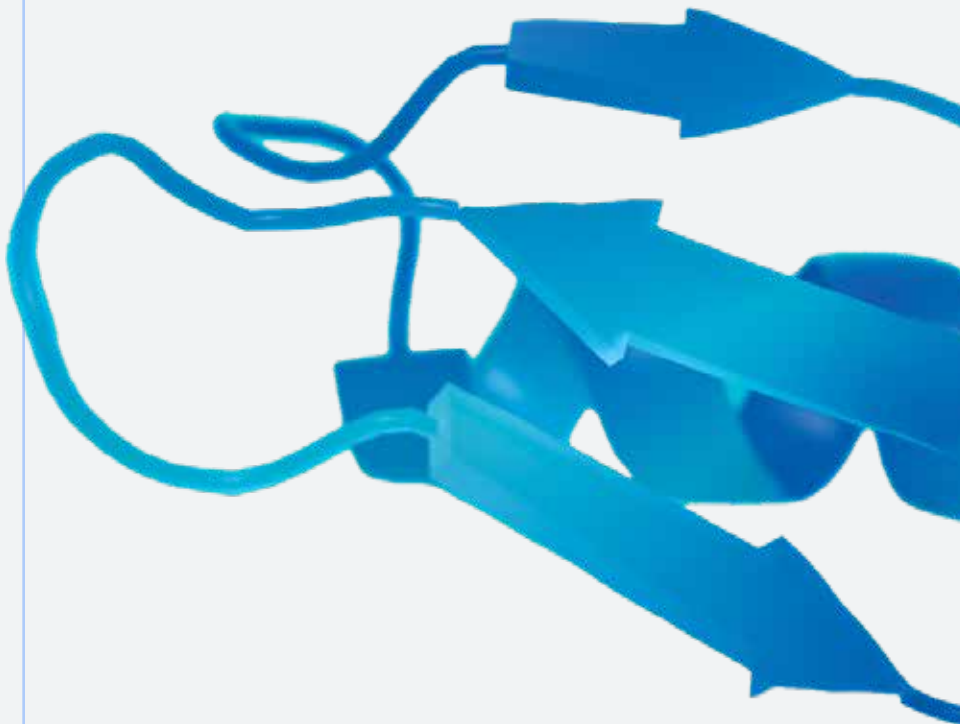
As Dr. Song emphasizes, "You have to first understand how the disease works before you can develop a drug against it. By providing as much information as possible, we can directly affect the possibility of developing a cure in the future."

Securing a clear visual of these tiny, dynamic cell structures at an atomic level, however, has long been a significant challenge. Dr. Song likens their approach to the anatomy of a car: "To understand how a car works, start the engine, then pop the hood for a bird's eye view of the parts that make up the car. Extract one piece at a time and examine its shape (structure). The shape of the piece will reveal its role." Similarly, a high-resolution 3D view of a cell would enable scientists to discern which elements constitute the cell's core structure and which are the functional protein complexes. This clarity would also help identify any mutations. More specifically, for Dr. Song's research, it would reveal precisely how CODANIN-1 binds to or sequesters ASF1, shedding light on how these interactions control cellular functions and maintain cellular identity.

AlphaFold, a catalyst for change

This is where Google DeepMind's AlphaFold offered new views of a cell's complex structure. Dr. Song's team had observed an unexpected phenomenon: when they mutated a known interaction surface of the CODANIN-1 protein, it surprisingly did not dissociate as expected. This suggested an undiscovered second interaction site! AlphaFold3 provided the crucial breakthrough by predicting the structure of the unvisualized and flexible regions of CODANIN-1, enabling the team to map this hidden second dimerization interface.

This atomic-level understanding of how CODANIN-1 forms a dimer and sequesters ASF1 provides a vital molecular blueprint, helping to explain how certain mutations in CODANIN-1 can lead to diseases like anemia. Beyond its predictive power, AlphaFold3's intuitive interface and reliable server proved easy to use, serving as an all-in-one hub for receiving the sequence, aligning it, predicting interactions between molecules and proteins, and ultimately producing a highly accurate 3D structure. As Dr. Song synthesized, "You send in your sequence, it pops out the structure."



Seemingly a basic input/output transaction on an everyday computer, inputting a sequence and outputting a structure can translate into incredible budget savings that can be funneled into other areas of research. AlphaFold's predictions also helped narrow down the scope of experiments, again saving time and resources - a trend Dr. Song hopes will continue.

Speaking to the monumental impact AlphaFold has had on epigenetics research, Dr. Song is optimistic: "Before the internet, researchers had to go to the library, look up physical journals, flip through thousands of pages to read a research. Multiply that by 20 researches. They'd repeat that next month to stay up-to-date. Now, the internet has made all the latest papers from around the world available within seconds. AlphaFold is like the internet for structural biology - and for biology as a whole. It lets us see highly complex cell structures and play around with near-infinite perspectives and possibilities."