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DISSERTATION

"New Frontiers in Biological Information Transfer: Ligand-Directed CRISPR System Delivery with Phage-based Vectors and Conceptual Insights from Generative Artificial Intelligence"

By

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Friday, June 14th, 2024
1:30 P.M.
Cancer Center, G1196

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ABSTRACT

Biological information transfer, defined specifically as the residue-by-residue transfer of sequence information between nucleic acids and protein, is a fundamental aspect of molecular biology with extensive experimental and theoretical implications. The elucidation of this phenomenon over half a century ago has directly facilitated remarkable progression in basic science research, numerous applications in biotechnology and medicine, as well as emerging developments in artificial intelligence. This dissertation describes two paradigms which pertain to biological information transfer: (1) an experimental application of phage-based gene transfer for targeted delivery of a CRISPR gene editing system, and (2) a computational analysis exploring the capabilities of generative artificial intelligence to correctly process various aspects of biological information transfer. Early research on the flow of biological information often involved the use of bacteriophage (phage) as a central experimental subject, spurring the genetic and functional characterization of these bacterial viruses. Decades later, phage display technology was developed and refined, whereby phage is genetically manipulated to display unique peptides on the capsid surface for various applications, including protein binding interaction discovery and ligand-directed targeting. The latter was utilized here for the targeted delivery of a CRISPR gene editing system. Filamentous phage displaying the tumor-targeting RGD4C peptide was engineered to carry a CRISPR transgene consisting of a Cas9 nuclease and gRNA sequence. Proof-of-concept evaluation of the engineered vector was performed in vitro, including for cell-surface binding, cellular internalization, post-transduction CRISPR transgene expression, and post-transduction gene editing, collectively indicating CRISPR system delivery by targeted gene transfer. In parallel, gRNA screening with Cas9 protein co-transfection resulted in the identification of high editing efficiency gRNA candidates for various cancer target genes, one of which robustly inhibited cell proliferation. In addition to this experimental application, biological information transfer in the context of generative pre-trained transformer (GPT)-based artificial intelligence was explored. Particularly, GPT-4 was challenged with interpreting the genetic code and with performing rudimentary structural biology modeling. In terms of genetic code interpretation, GPT-4 was able to recognize biological information transfer between nucleic acid and proteins through a reasoning exercise. GPT-4 was also capable of modelling the 3D structures of the 20 standard amino acids as well as an alpha-helical polypeptide chain with atomic-scale accuracy. However, both genetic code interpretation and structural modeling were error-prone and molecular complexity was not well tolerated. Insights, both practical and conceptual, were gained from the assessment of phage-based CRISPR system delivery along with examining the capacity of generative artificial intelligence to process genetic code interpretation and structural modeling. Taken together, this work highlights the importance of biological information transfer as it pertains to experimental application and theoretical implementation.