ゲノム DNA を標的とした中分子創薬開発

Medium Molecule Drug Discovery targeting genome DNA

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While numerous studies have explored the possibility of directly targeting biomacromolecule responsible for the onset or progression of disease phenotypes, in many intractable and/or rare diseases clinically viable drugs against such targets have yet to become commercially available, for instance critical oncogenic proteins, such as p53, RAS and MYC, or amyloid-β (Aβ) peptides for Alzheimer's disease (AD). Complexities in three-dimensional protein surface topologies and binding pocket inaccessibility present major hurdles for protein-level inhibitors to overcome and hinder the development of successful therapeutics. Additional externalities, for example time, cost, and labor, can also delay rational design-based developments of new small-molecule therapeutics. As such, a new approach that can directly target critical driver genes may provide a more direct route to address unmet medical needs for the conquest of those unfavorable diseases.

Pyrrole-Imidazole (PI) polyamide specifically recognizes, binds and targets the minor groove of genomic DNA in a sequence-dependent manner. We have successfully synthesized various PI polyamide-drug conjugates (PDC) targeting driver genes in the disease genome, and subsequently evaluated those conjugates, both *in vitro* and *in vivo*, to confirm their anti-disease efficacy as well as genetic or epigenetic modification to the target genes.

PDCs against their gene-level frequently showed promising anti-disease effect and subsequent target modification in the unhealthy genome, and mouse models of various human diseases also confirmed the anti-disease efficacy of PDCs, simultaneously showing little adverse events. Intriguingly, pharmacokinetic studies also suggested PI polyamide conjugates to possess enhanced permeability and retention- (EPR) like effect, an additional advantage for PDC’s to restrictively localize in tumor and tumor environments, as expected of well-performing cancer therapeutics. We also confirmed that several modifications to a candidate PDC could alter its intracellular localization, for instance improved specific mitochondrial localization and the subsequent reduction of mutant mitochondrial DNA copy numbers. Druggability, synthesizability and modifiability of PDC, coupled with the capability of targeting disease genomes at specifically affected lesions/locations, prevent a new design strategy against difficult diseases. This approach should provide many PDC drug candidates for personalized medicine against a variety of unfavorable/rare diseases.