Logic-gated detection and drug delivery with DNA-drug conjugates

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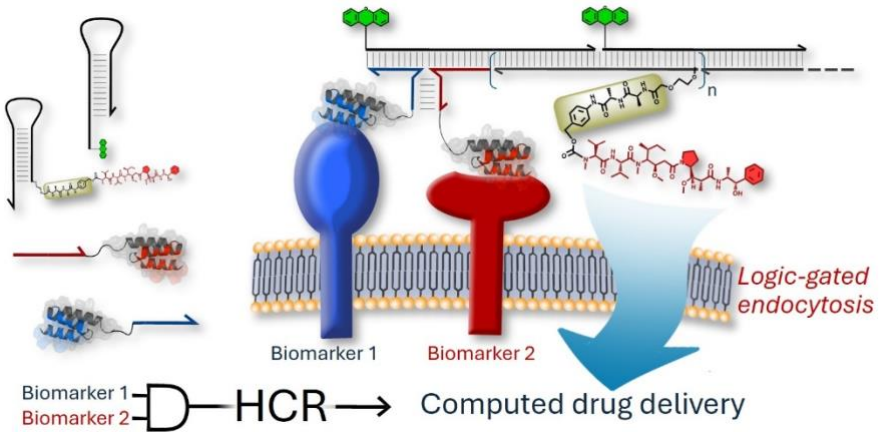
Antibody drug conjugates (ADCs) are a major breakthrough in cancer therapy offering increased selectivity and lower toxicity compared to traditional chemotherapy. While ADCs are a precious clinical tool, their use is limited to abundant cancer specific biomarkers, and their efficacy is restricted by the limited drug to antibody ratio (DAR). Cancer is increasingly recognised as heterogeneous and highly adaptable, showing the growing need for modular therapies, in contrast to rigid antigen-warhead system like ADCs[1]. In parallel, advancements in DNA nanotechnology and DNA-protein conjugates enabled precise control of input/output systems bridging the gap between protein recognition and molecular computing[2]. By integrating high affinity mini-proteins (affibodies) and aptamers with hybridization chain reaction (HCR), we developed a system responsive to a pair of membrane biomarkers. Upon recognition via a three-way junction, an HCR is initiated leading to > 100-fold amplification on the cell surface. By functionalising the HCR with fluorescent dyes, we could selectively detect cancer cells expressing two biomarkers. Modulation of the decorating molecules lipophilicity triggers efficient internalization of the HCR assemblies via endocytosis, enabling rapid AND-gated delivery of cytotoxics. Finally, we demonstrate that biomarker-triggered HCRs can recruit generic antibodies. This modular approach mitigates the on-target,off-tumor toxicity of ADCs. Moreover, robust HCR provides an alternative route to high DAR without of compromising ADC's physicochemical properties. Finally, the high modularity of this technology could be appealing for a field that is rapidly shifting towards personalized medicine.



References:

(1) Dumontet, C.; Reichert, J. M.; Senter, P. D.; Lambert, J. M.; Beck, A. *Nature Reviews Drug Discovery* **2023**, *22* (8), 641-661. DOI: 10.1038/s41573-023-00709-2.
(2) Ma, W.; Zhan, Y.; Zhang, Y.; Mao, C.; Xie, X.; Lin, Y. *Signal Transduction and Targeted Therapy* **2021**, *6* (1), 351. DOI: 10.1038/s41392-021-00727-9.