Targeted Small-Molecule Conjugates: the Future is Now

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Abstract: In recent years, novel classes of small heterobifunctional compounds have been developed as tools for the treatment of cancer and other diseases through different approaches, from radio/chemotherapy and imaging to immunotherapy and protein degradation. Within this growing research area, progresses in ligand screening procedures and hit-to-lead optimizations, together with advances in drug release technologies, are paving the way to the future treatment of a broad range of pathologies with of small targeted therapeutics.

Current pharmaceutical research is experiencing an increasing development of heterobifuncional constructs, which combine the individual properties of two different molecular entities by their conjugation through cleavable or non-cleavable bonds. Among these hybrid structures, Antibody-Drug Conjugates (ADCs) represent the most clinically-validated platform to improve the therapeutic index of bioactive ingredients. The marketing approval of three ADCs within the last months of 2019 testifies the renewed interest of pharmaceutical companies in strategies to promote selective drug release in diseased tissues.[1] In addition to the oncology field, ADC evaluations for the treatment of a wide range of indications have also started, and the first conjugates against autoimmune diseases and bacterial infections are now under clinical evaluation.[2]

Alongside with ADC investigations, the development of small-molecule conjugates has gained increasing attention, aimed at overcoming the pharmacokinetic limitations of large protein therapeutics.[3] Recent experimental evidences support the potential of small carriers over antibodies: the comparative evaluation of drug release properties of an antibody and a small ligand (both showing high affinity for the same tumor antigen) indicated that small-molecule ligands accumulate rapidly and homogenously within the tumor mass and release the cytotoxic payload with higher selectivity than antibodies.[4] Although the clinical evaluation of Small Molecule-Drug Conjugates (Figure 1) has been so far limited to a few examples,[5] the use of radioactive conjugates is widely established not only for imaging applications,[6] but also for therapy, as testified by the recent marketing approval of the first peptide conjugate for radiotherapy (^{177}Lu-DOTATATE).[7]

In addition to their role as drug carriers, ligands targeting disease-specific proteins can be coupled to several classes of bioactive compounds (Figure 1), to engage different effectors and trigger therapeutic responses. For instance, the highly-attracting PROTAC (proteolysis targeting chimeras) technology promotes proteasome-mediated degradation of disease-specific proteins upon ligand binding.[8] Moreover, recent immunotherapy strategies feature small ligands coupled to specific organic molecules (haptens) capable of recruiting either endogenous[9] or engineered[10] biotherapeutics at the diseased site.

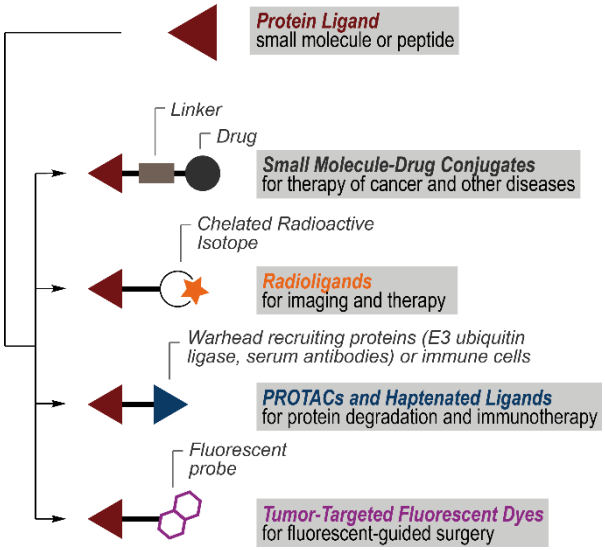

Figure 1. Schematic representation of heterobifunctional conjugates exploiting the targeting ability of small ligands/peptides and the biological properties of a second biologically-active compound.

Finally, stable conjugates of small targeting ligands with fluorescent dyes have been proposed to improve the visualization of residual tumor tissue during surgical intervention, allowing complete resection and minimizing the pathology recurrence.[11]

New strategies to improve the efficacy of all these classes of conjugates are being reported continuously. For instance, innovative strategies to control the activation of therapeutics will substantially advance drug delivery applications.[12] Moreover, new screening protocols will not only accelerate the identification of high-affinity ligands specific for validated clinical targets,[13] but they will also expand the ligand toolbox to probe the whole human proteome, i.e. a stated objective of worldwide research.[14] Finally, the development of general strategies to strengthen ligand-protein interactions may lead to small drugs with antibody-like affinities. Here, suitable approaches include the rationale design of multivalent binders[15] and the use of reactive tags to engage covalent interactions between the ligand and the target protein.[16] If successful, all these chemical upgrades will serve as a springboard to the advent of new-generation targeted therapies.

Keywords: Drug delivery • Fluorescence • Imaging Agents • Conjugates • Radiopharmaceuticals

Alberto Dal Corso studied Chemistry at Università degli Studi di Milano, where he obtained his Ph.D. in 2015 with Prof. Cesare Gennari. He then joined the group of Prof. Dario Neri at ETH Zürich as a postdoctoral fellow. In 2018 he returned to Milan for a postdoc and in 2019 he was awarded the Junior Prize “Organic Chemistry for Life Sciences” by the Italian Chemical Society. His research interests include the development of novel drug delivery strategies and the synthesis of ligands for clinically-relevant protein targets.

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