Universität Basel

Research Project

Engineering the Targeted Drugs of the Future: A General Approach

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Project title Engineering the Targeted Drugs of the Future: A General Approach
Principal Investigator(s) Gillingham, Dennis ; Neri, Dario ;
Organisation / Research unit
Departement Chemie / Organische Chemie (Gillingham)
Department
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We will build a general and broadly-applicable platform technology for the targeted delivery of drugs. In contrast to current approaches our targeting motifs will derive from libraries of modular small molecule macrocyclic scaffolds, opening the door to a variety of previously inaccessible targets. Our guided drugs will be designed to be released at the target through the development of smart linkers that respond to a disease microenvironment or cell receptor. The drugs themselves will derive from known compounds complemented by designs created in the Schneider group. Many pharmaceutical agents are unselective, causing toxicity to normal organs and preventing dose escalation to therapeutically active regimens. Selectively delivering and activating drugs at the site of disease holds great promise for dramatically increasing the therapeutic index of bioactive molecules, thus providing substantial benefits to patients. A successful general platform that exploits small ligands for pharmacodelivery applications would represent a transformative innovation for both academia and industry. Current strategies for targeted drug delivery rely mainly on antibodies as “vehicles”, but recent disappointments in Phase III clinical trials (>5 high-profile clinical failures) with antibody-drug conjugates call into question their real value. Moreover, because of their large size and unacceptably high cost, antibodies can only be used for delivering ultrapotent drugs, hindering development opportunities with conventional pharmaceutical agents and in areas outside oncology. A handful of naturally-occurring small organic ligands for common receptors (folate receptor, carbonic anhydrase IX) have been proposed as an alternative to antibodies for pharmacodelivery strategies, but a general approach that avoids large biomolecules has not been described due to limitations in ligand discovery and to the lack of suitable strategies for drug release at the site of disease. The ability to create “smart drugs” will emerge from advances made in each of the subgroups: Specifically, we will construct encoded chemical libraries of unprecedented size and quality (dozens of millions of compounds) and screen these libraries for ligands against at least ten validated accessible markers of cancer and chronic inflammation. In addition, we will develop and implement innovative technologies for the smart release and activation of bioactive payloads at the site of disease. The linker/release triggers for therapeutic payloads will be tailored to respond to the disease microenvironment and to selectively act on the target cells of choice. In addition to employing well-known cytotoxic agents like tubulin inhibitors (DM1, MMAE) as payloads, we will primarily explore the use of membrane-disruptive peptides. These designed cytotoxic peptides have the unique advantage of (i) directly addressing the plasma membrane of cancer cells as target without the involvement of proteins, which minimizes the risk of cancer cell escape by mutation or development of resistances; (ii) cancer cell-selective membrane targeting as a result of our molecular design aiming at custom-tailored highly potent cytotoxic peptide payloads; and (iii) rapid plasma clearance so that the peptides, once released from the carrier, will act only locally at the site of release, thereby minimizing unwanted off-target and side-effects. The proposal is bold, requiring expertise in chemical, biochemical, and computational technology – a combination beyond the

reach of any one research group. The synergy created through the participation of three complementary teams is essential. Prof. Neri (ETH Zürich) will be responsible for the production of target proteins, for the construction and screening of DNA-encoded libraries of chemically-modified cyclic peptides, for the development of small molecule-drug conjugates and for in vivo testing of the most promising compounds in mouse models of cancer and of rheumatoid arthritis. Prof. Gillingham (University of Basel) will be responsible for creating macrocycle libraries, importing them into the DNA encoded format, as well as developing new redox-responsive cleavable linkers. Prof. Schneider (ETH Zürich) will be responsible for the computational design, chemical synthesis, biochemical testing and engineering of novel peptide cytotoxins that kill target cells from the outside by direct cancer cell disruption.

Keywords DNA-encoded chemical libraries, Tumor targeting, Pharmacodelivery, Drug release, Macrocycles, Smart drugs
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