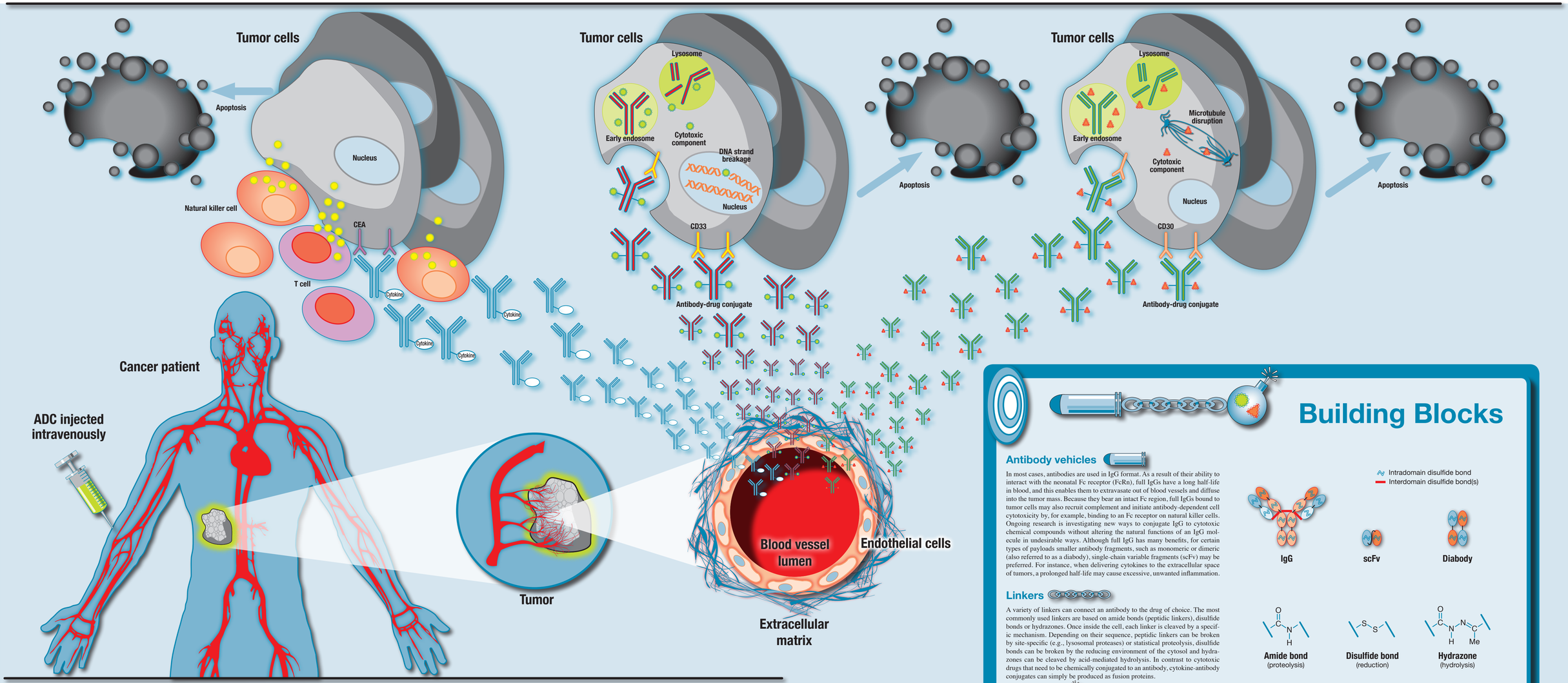
nature biotechnology

Antibody-drug conjugates for cancer therapy

Dario Neri

Conventional chemotherapeutic drugs do not selectively localize to tumors. And as their systemic drug distribution may result in damage to healthy tissue and organs, drug dose escalation to therapeutically active levels may be impossible. Because antibodies bind specifically to cells expressing their cognate antigen, they represent ideal 'vehicles' for applications that require delivery of a drug (e.g., a very toxic drug) specifically to the site of disease. Using various linker strategies, antibodies can be conjugated to a variety of cytotoxic drugs or 'payloads'. Once taken up into cognate antigen-expressing tumor cells, these drugs are released (through mechanisms that depend on which type of linker is used) from the antibody-drug conjugates. These drugs can then kill tumor cells through their established cytotoxic mechanisms. Alternatively, antibodies can be fused directly to cytokines; these antibody-drug conjugates can act extracellularly by recruiting cytotoxic immune cells to the tumor site, thereby indirectly killing tumor cells. Some antibody-drug conjugates have been approved for clinical use in a variety of solid and hematological tumors, and many more are in clinical trials. In general, antibody-drug conjugates may provide a way to repurpose tumor-specific antibodies, which on their own did not have therapeutic activity, or chemotherapeutic drugs, which when injected systemically, are too toxic for healthy tissues.



Building Blocks

Antibody vehicles

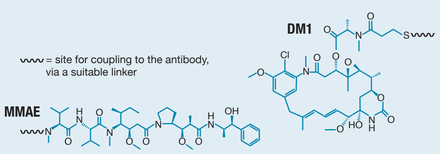
In most cases, antibodies are used in IgG format. As a result of their ability to interact with the neonatal Fc receptor (FcRn), full IgGs have a long half-life in blood, and this enables them to extravasate out of blood vessels and diffuse into the tumor mass. Because they bear an intact Fc region, full IgGs bound to tumor cells may also recruit complement and initiate antibody-dependent cell cytotoxicity by, for example, binding to an Fc receptor on natural killer cells. Ongoing research is investigating new ways to conjugate IgG to cytotoxic chemical compounds without altering the natural functions of an IgG molecule in undesirable ways. Although full IgG has many benefits, for certain types of payloads smaller antibody fragments, such as monomeric or dimeric (also referred to as a diabody), single-chain variable fragments (scFv) may be preferred. For instance, when delivering cytokines to the extracellular space of tumors, a prolonged half-life may cause excessive, unwanted inflammation.

Linkers

A variety of linkers can connect an antibody to the drug of choice. The most commonly used linkers are based on amide bonds (peptidic linkers), disulfide bonds or hydrazones. Once inside the cell, each linker is cleaved by a specific mechanism. Depending on their sequence, peptidic linkers can be broken by site-specific (e.g., lysosomal proteases) or statistical proteolysis, disulfide bonds can be broken by the reducing environment of the cytosol and hydrazones can be cleaved by acid-mediated hydrolysis. In contrast to cytotoxic drugs that need to be chemically conjugated to an antibody, cytokine-antibody conjugates can simply be produced as fusion proteins.

Payloads

To ensure that tumor cell killing can be mediated at acceptably low doses of antibody-drug conjugates (e.g., at antibody doses below those that would saturate all of the antigen binding sites on the tumor), very potent cytotoxic agents are typically used. For example, monomethyl auristatin E (MMAE) and the maytansinoid DM1 kill tumor cells by inhibiting microtubule polymerization. Alternative payloads include DNA damaging agents or cytokines; the latter typically act extracellularly and can modulate immune cell activity at picomolar concentrations.



Dario Neri, Department of Chemistry and Applied Biosciences Swiss Federal Institute of Technology (ETH Zürich)

Dario Neri is a co-founder and shareholder of Philogen, a Swiss-Italian biotech company which operates in the field of antibody-drug conjugates.

Edited by Christine Borowski; copyedited by Teresa Moogan; designed by Lewis Long.

Available online at:
www.nature.com/nbt/extra/adc/pdf/adc_poster.pdf