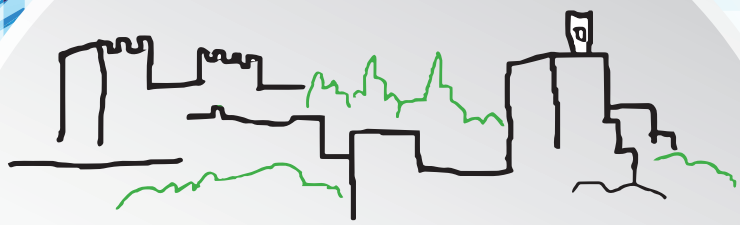
GRANADA

Book of Abstracts



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ACETALS AS ACID-SENSITIVE CLEAVABLE LINKERS FOR THE DESIGN OF ANTIBODY-DRUG CONJUGATES

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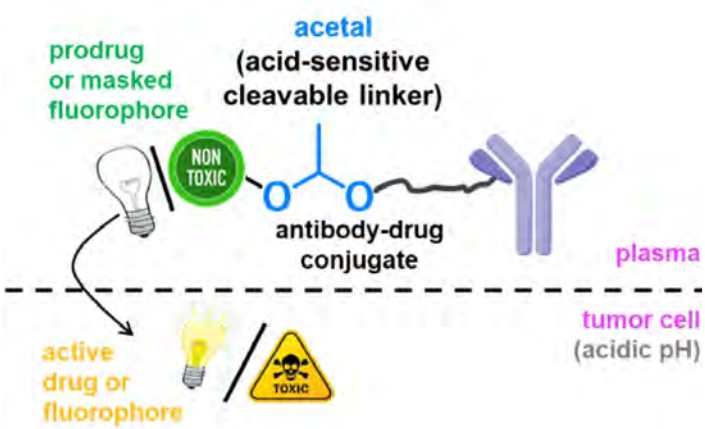

Several acid-cleavable linkers, based on an acetal group, that feature either a deactivated coumarin or a prodrug derived from the potent anti-cancer agent duocarmycin, have been designed. The linkers are stable in plasma and can rapidly break down in acidic pH to generate the free fluorophore or the toxic drug in situ. These scaffolds were conjugated to a Trastuzumab antibody that is specific for Her2, a receptor that is overexpressed in breast cancer cells. Interestingly, although the Trastuzumab-coumarin conjugate is stable in plasma, the analogue that carries the duocarmycin derivative slowly decomposes under similar conditions. Molecular dynamics (MD) simulations performed on these antibody-drug conjugates (ADCs) suggest that a lysine residue of the antibody nearby the conjugation site can act as an acid, which promotes hydrolysis of the acetal bearing the duocarmycin derivative. These data demonstrate that both the conjugation site of the antibody and the combination linker-payload can modulate the stability of the conjugate. Finally, we show that both ADCs retain their specificity to cancerous cell lines expressing Her2 and that the ADC bearing the prodrug efficiently kills antigen-positive cancer cells. Therefore, the straightforward synthesis combined with the possibility of incorporating different payloads, makes the use of acetals an innovative and competitive strategy for the design of targeted drug-delivery systems.

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