

## Accepted Manuscript

BMCL Digest

Antibody-drug conjugates—A new wave of cancer drugs

Herve Bouchard, Christian Viskov, Carlos Garcia-Echeverria

PII: S0960-894X(14)01066-X

DOI: <http://dx.doi.org/10.1016/j.bmcl.2014.10.021>

Reference: BMCL 22076

To appear in: *Bioorganic & Medicinal Chemistry Letters*

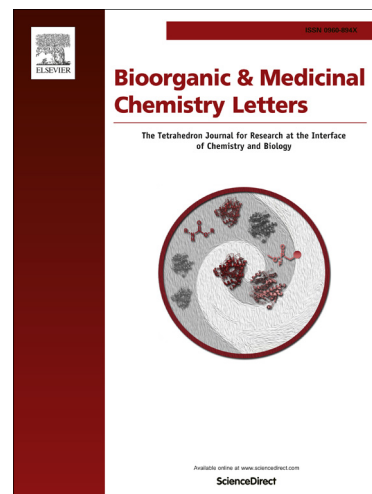
Received Date: 6 August 2014

Revised Date: 25 September 2014

Accepted Date: 1 October 2014

Please cite this article as: Bouchard, H., Viskov, C., Garcia-Echeverria, C., Antibody-drug conjugates—A new wave of cancer drugs, *Bioorganic & Medicinal Chemistry Letters* (2014), doi: <http://dx.doi.org/10.1016/j.bmcl.2014.10.021>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



## Antibody-drug conjugates – a new wave of cancer drugs

Herve Bouchard<sup>a,b</sup>, Christian Viskov<sup>a,b</sup> and Carlos Garcia-Echeverria<sup>b</sup>

<sup>a</sup>Natural Products and Protein Chemistry and <sup>b</sup>Lead Generation to Compound Realization,

Sanofi, 94403 Vitry-sur-Seine, France

*Abstract - Antibody-drug conjugates (ADCs) consist of cytotoxic drugs covalently linked to monoclonal antibodies directed to antigens differentially overexpressed in tumor cells. These loaded antibodies are expected to selectively deliver lethal cargoes to tumor cells and provide sustained clinical benefit to pre-selected cancer patients while, at the same time, minimizing systemic toxicity. Although on-target adverse events are not completely avoided and the true efficacy of these innovative agents still requires further clarification, proof-of-concept has already been achieved in clinical settings with immunoconjugates containing calicheamicin, auristatin or maytansine-based cytotoxic payloads. In this present article we review the characteristics of the preceding cytotoxic platforms and their chemical conjugation approaches.*

Cytotoxic drugs are broadly used to treat hematological malignancies and solid tumors and, under certain clinical conditions, have changed the natural course of some of these diseases. While effective, due to their intrinsic mode of action, they may also cause significant on-target adverse events that could preclude their full clinical efficacy, possibly resulting in early discontinuation of medication and a consequent increased risk of tumor relapse or recurrence. Efforts aimed at improving the quality of treatment of cancer patients have focused on alternative methods to both maintain the effectiveness of chemotherapeutic drugs and minimize systemic toxicity. Among these novel approaches, the conjugation of cytotoxic agents to humanized antibodies (also known as Antibody Drug Conjugates, ADCs) has begun to gain momentum among the scientific and clinical development cancer community. The durable clinical responses reported with brentuximab vedotin (SGN-35; Seattle Genetics/Takeda)<sup>1</sup> and trastuzumab emtansine (T-DM1; Roche in partnership with ImmunoGen),<sup>2</sup> which have recently obtained regulatory approval, have profoundly changed the outlook for this modality of cancer therapy (for recent review articles on this topic, see<sup>3</sup>).

Several aspects including the target, the antigen, the antibody, the linker and the cytotoxic payload, must be thoroughly investigated and balanced in the design and synthesis of an ADC drug, as well as evaluated within the context of the targeted cancer indication. The loaded-antibodies combine the unique targeting capabilities of monoclonal antibodies to discriminate between normal and tumoral cells with the cancer-killing ability of highly potent cytotoxic drugs (cellular IC<sub>50</sub> values in the pM range).

Download English Version:

<https://daneshyari.com/en/article/10586745>

Download Persian Version:

<https://daneshyari.com/article/10586745>

[Daneshyari.com](https://daneshyari.com)