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Antibody drug conjugates: Progress, pitfalls, and promises

Anubhab Mukherjee[a,b], Ariana K. Waters[a,b], Ivan Babic[b], Elmar Nurmemmedov[b], Mark C. Glassy[c,d], Santosh Kesari[b] and Venkata Mahidhar Yenugonda[a,b,*]
[a]Drug Discovery and Nanomedicine Research Program, CA 90404, USA
[b]Department of Translational Neurosciences and Neurotherapeutics, John Wayne Cancer Institute, Pacific Neuroscience Institute, Providence Saint John's Health Center, Santa Monica, CA 90404, USA
[c]University of California San Diego, Moores Cancer Center La Jolla, CA, USA
[d]Nascent Biotech, Inc., San Diego, CA, USA

Abstract. Antibody drug conjugates (ADCs) represent a promising and an efficient strategy for targeted cancer therapy. Comprised of a monoclonal antibody, a cytotoxic drug, and a linker, ADCs offer tumor selectivity, reduced toxicity, and improved stability in systemic circulation. Recent approvals of two ADCs have led to a resurgence in ADC research, with more than 60 ADCs under various stages of clinical development. The therapeutic success of future ADCs is dependent on adherence to key requirements of their design and careful selection of the target antigen on cancer cells. Here we review the main components in the design of antibody drug conjugates, improvements made, and lessons learned over two decades of research, as well as the future of third generation ADCs.

Keywords: Monoclonal antibodies, target antigens, linker, cytotoxic drugs, site-specific drug conjugation, antibody drug conjugates

1. Introduction

For several decades, chemotherapy has remained the preeminent modality for the treatment of cancer [1,2]. The earliest category of chemotherapeutics tested in humans were chlorambucil and cyclophosphamide, which were reported to induce cellular cytotoxicity by DNA alkylation. The recognition that folic acid stimulates cancer cell growth led to the synthesis of antifolates, such as methotrexate, as antitumor agents. This was followed by nucleoside analogues, such as 5-fluorouracil, and cytosine arabinoside (ara-C), which essentially interfere with DNA synthesis. DNA inter-circulating agents such as cisplatin, actinomycin D, anthracyclines (e.g., Doxorubicin) and tubulin targeting molecules (Taxanes, Vinca alkaloids) subsequently came into play. The triumph of eliminating cancer cells was unfortunately retarded by a lack of tumor selectivity, in which chemotherapy ended up killing normal cells, eventually leading to unforeseen systemic toxicities. However, it was soon discovered that therapeutics with non-overlapping toxicity profiles and different mechanisms of action could be combined at different dose regimens to yield synergistic anticancer activity. Combinatorial chemotherapy thus emerged as a modality for the treatment of most cancers [3]. Clinicians worked with a plethora of individual drugs and their combinations to define the maximum tolerated dose (MTD), minimum effective dose (MED) and later, minimum dose (MET) in order to reach an improved therapeutic index.

In more recent decades, an increased understanding of cancer biology has spawned a new era of targeted cancer treatment by exploiting certain properties of tumor cells in contrast to normal cells [4]. These salient features, popularly coined the 'hallmarks of

*Corresponding author: Venkata Mahidhar Yenugonda, Drug Discovery and Nanomedicine Research Program, John Wayne Cancer Institute, Pacific Neuroscience Institute, Providence Saint John's Health Center, Santa Monica, CA 90404, USA. Tel.: +1 310 582 7899; E-mail: vmy@pnii.org.