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Editorial
Nanobodies: Introduction to Third Generation Antibodies

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Abstract

Monoclonal antibody-based therapy has been a revolution in the therapy of both solid tumours and hematological malignancies. Continuous global efforts focusing on new strategies to improve therapeutic efficiency of antibodies by engineering second generation of antibodies fails to show much promise due to aggregation induced immunogenicity and their short half-life. Nanobodies are variable domain of heavy chain only antibodies. Conventional antibodies consist of two identical heavy (H) and two identical light (L) polypeptide chains (total four polypeptide chains) but camelids and some cartilaginous fish contains a unique form of immunoglobulin (IgG) without any light polypeptide chains and first constant domain (CH1) of heavy chain. Size of these unique antibodies ranges in nanometer therefore is popularly termed as nanobodies. The present article discussed the role of nanobodies in the therapy.

Key words: Antibodies, caplacizumab, nanobodies, therapy

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Monoclonal antibody based therapy has been a revolution in the therapy of both solid tumours and hematological malignancies[1]. First monoclonal antibody was approved in 1986 and till today this number of Food and Drug administration approved monoclonal antibodies has reached more than fifty[2]. However large size of monoclonal antibodies (150 KDa with four polypeptide chains) hampers their tissue penetration into tumour cells and high immunogenicity is detrimental to their efficacy[3]. Similarly, their stability, fragility, binding affinity and immunogenicity are other concerns for researchers working in the field of biotherapy. Continuous global efforts focusing on new strategies to improve therapeutic efficiency of antibodies by engineering second generation of antibodies (antigen binding fragments (Fab-50 KDa and short chain variable fragment (SCVF-30 KDa) fails to show much promise due to aggregation induced immunogenicity and their short half-life[4]. Recent approval of caplacizumab for treatment of acquired thrombotic thrombocytopenic purpura by FDA in 2019 has emerged as an important break through in efforts of scientific community to improve antibody therapy and has attracted the mind of clinicians and researchers towards so called third generation of antibodies known as nanobodies[5]. Caplacizumab is 28 KDa bivalent anti-von Willebrand factor (vWF) nanobody available in two forms viz ALX-0681 (Subcutaneous administration) and ALX-0081 (Intravenous administration) in the treatment of acquired thrombotic thrombocytopenic purpura[5]. Nanobodies are variable domain of heavy chain only antibodies[6]. They were serendipitously discovered from serum of camelid family in 1993. Conventional antibodies consist of two identical heavy (H) and two identical light (L) polypeptide chains (total four polypeptide chains) but camelids and some cartilaginous fish contains an unique form of immunoglobulin (IgG) without any light polypeptide chains and first constant domain (CH1) of heavy chain. Size of these unique antibodies ranges in nanometer therefore are popularly termed as nanobodies.

Small size and molecular weight (less than 15 KDa) impart many important characteristics to nanobodies over conventional antibodies viz better tissue penetration, stability, solubility, binding and renal clearance. By virtue of small size nanobodies can penetrate deeply in to tissues, within the tissue and even reach poorly vascularized sites in body, therefore, are excellent candidates for *in vivo* imaging and drug delivery to less vascularized organs and tissues of body. Large size of monoclonal antibodies has been a major limitation for long period in their use as molecular probes in imaging of tumorous tissue but nanobodies has emerged as suitable candidates to be used as molecular probes for *in vivo* imaging. Nanobodies have small half-life due to which they are rapidly cleared by kidneys following imaging. However, their short half-life becomes an important constrain in their therapeutic uses. Nanobodies possess stability at temperature and pH extremes therefore are suitable for oral, parental as well intratumour administration. Non-therapeutic nanobodies can be conjugated with chemotherapeutic agents to increase their penetration to specific tissue and can be used for drug delivery.

There are many nanobodies other than caplacizumab which had shown therapeutic potential for various malignancies, autoimmune and infectious diseases and are under intensive clinical trials. Such nanobodies include Vobarilizumab ALX-0061 for rheumatoid arthritis and systemic lupus erythematosus, Vobarilizumab ALX-0761 for psoriasis, Ozoralizumab ATN-103 for rheumatoid arthritis, biospecific nanobody derived CAR-T cells for B-cell lymphoma and ^{131}I SGMIB anti-HER2 VHH168 for breast cancer and 68-GANOTA anti-HER2 VHH168 for brain metastasis of brain cancer[5]. High sequence identity of VHH domain of nanobodies with human type 3 VH domain imparts low immunogenicity to them which can be further reduced by humanization of nanobodies. This low immunogenic nature of nanobody is an exclusive advantage of nanobodies over various other monoclonal and chimeric antibodies. Evidencing the rapid research in the field of nanobodies assures approval of many other nanobodies for *in vivo* imaging, immunotherapy and cancer biotherapy in coming future.

SIGNIFICANCE STATEMENT

Monoclonal antibodies are used for the therapy of cancer as well as hematological malignancies but due to less size of nanobodies, these are having potential in imaging and drug delivery and known as third generation antibodies.

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