Immunoconjugates and long circulating systems: Origins, current state of the art and future directions☆

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ABSTRACT

Significant progress has been made recently in the area of immunoconjugated drugs and drug delivery systems (DDS). The immuno-modification of either the drug or DDS has proven to be a very promising approach that has significantly improved the targeted accumulation in pathological sites while decreasing its undesirable side effects in healthy tissues. The arrangement for both prolonged life in the circulation and specific target recognition represents another potent strategy in the development of immuno-targeted systems. The longevity of immuno-targeted DDS such as immunoliposomes and immunomicelles improves their targetability even in the presence of the additional passive accumulation in areas with a compromised vasculature. The added use of the immuno-targeted systems takes advantage of the specific microenvironment of pathological sites including lowered pH, increased temperature, and variation in the enzymatic activity. "Smart" stimulus-responsive systems combine different valuable functionalities including PEG-protection, targeting antibody, cell-penetration, and stimulus-sensitive functions. In this review we examined the evolution, current status and future directions in the area of therapeutical immunoconjugates and long-circulating immuno-targeted DDS.

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1. Introduction

One of the main problems for effective drug delivery is to increase the therapeutic efficacy of toxic drugs while minimizing their non-specific side effects. Targeting of drugs towards disease sites can bring a solution to this problem. The idea of the "magic bullet" drug, which was introduced by Paul Ehrlich early in the twentieth century, considered that

one part should consist of a moiety recognizing and binding the target, while the second part should provide a therapeutic action at this target. With the discovery of antibodies, a targeting molecule with high specificity for the ligand, the concept of "magic bullet" was successfully implemented with a variety of immuno-target drugs (immunoconjugates) including immunotoxins, immunoisotopes, antibody-chemotherapeutic conjugates and immuno-targeted drug delivery systems (DDS).

To date, as many as 31 therapeutical antibodies and immunocojugates (Table 1) are clinically approved for a variety of applications, with many more under investigation [1]. Despite the recent clinical success of individual antibodies, they are still rarely curative. Conjugation of pharmaceutical agents with an antibody provides an opportunity to improve the therapeutic efficacy of the antibody itself or/and potency of the conjugated drug. Although, immunoconjugates are considered a very promising therapeutic tool, still, the problems associated with low drug/antibody ratios, complexity of the conjugation chemistry, the high cost of production and instability in the circulation remain.

On the other hand, nanosized DDS, such as liposomes and micelles, have certain advantages that might offer a solution to some of these problems. The obvious advantages of immuno-targeted DDS over other immunoconjugated systems include: 1) a high capacity of drug loading; 2) the relatively few mAbs necessary to achieve high levels of drug targeting; 3) protection of the encapsulated drug from degradation in the biological environment, and 4) the ability to provide stimulus-sensitive compositions for controlled and enhanced release of the drug in the targeting areas.

The concept of long-circulating immuno-targeted DDS requires an attempt to combine the capacity for prolonged circulation with specific target recognition by mobilized mAbs (or their fragments) in one preparation. The longevity of immuno-targeted DDS in the blood is routinely achieved by modification of their surface with flexible hydrophilic polymers, such as poly-ethylene glycol (PEG) [2] to protect them from the elimination by cells of the reticulo-endothelial

system (RES). The prolonged circulation can help to achieve a better targeting effect for immuno-targeted DDS by allowing more time for opportunities for their interaction with the target antigen [3]. In situations when the target has a diminished blood supply (ischemic or necrotic areas), or the expression of the targeting antigen is very low, the longevity of the immuno-targeted DDS becomes a critical parameter for their therapeutic efficiency. The other important aspect of longevity is the ability of many drugs and DDS to be accumulated passively in the areas with leaky vasculature (including tumors, infarcts, and inflammation sites) due to the Enhanced Permeability and Retention (EPR) effect [4]. In this case, the EPR effect additionally can contribute to the targeted accumulation of immunoconjugates and immuno-targeted DDS [5].

Recently the concept of "smart multifunctional" nanocarriers that gather various functionalities including PEG-protection, targeting ligand, cell-penetrating and stimulus-sensitive functions was introduced as a novel direction in the development of immuno-targeted DDS [6].

This review focuses on recent developments, design, applicability and future directions in the development of therapeutical immunoconjugates and long-circulating immuno-targeted DDS.

2. Immunoconjugates: past, present and future in targeted drug delivery

2.1. Evolution of therapeutical immunoglobulins

The invention of a hybridoma technique by Köhler and Milstein in 1975 [7], which allowed obtaining large quantities of monoclonal antibodies (mAbs) with a single specificity, accelerated the introduction of antibodies and immunoconjugates for therapy. However, the initial use of full-length mouse mAbs was restricted because of their low efficacy and rapid clearance due to the immune response initiated in human patients [8]. These limitations on the use of murine mAbs have largely been overcome by the development of the chimerization

Table 1
FDA-approved mAbs and immunoconjugates.

Antibody	Brand name/manufacturer	Approval date	Type of mAbs	Antigen	Indication
Muronomab-CD3[a]	OKT3/Johnson & Johnson	1986	Murine, IgG2a	CD3	Autoimmune
Abciximab	ReoPro/Johnson & Johnson	1997	Chimeric, IgG1, Fab	PIIb/IIIa	Homeostasis
Rituximab	Rituxan/Genentech	1997	Chimeric, IgG1	CD20	Cancer
Daclizumab[a]	Zenapax/Roche	1997	Humanized, IgG1	CD25	Autoimmune
Basiliximab	Simulect/Novartis	1998	Chimeric, IgG1	CD25	Autoimmune
Palivizuma	Synagis/MedImmune	1998	Humanized, IgG1	RSV	Infections
Infliximab	Remicade/Johnson & Johnson	1998	Chimeric, IgG1	TNFα	Autoimmune
Trastuzumab	Herceptin/Genentech, Roche	1998	Humanized, IgG1	HER2	Cancer
Gemtuzumab[a] ozogamicin	Mylotarg/Wyeth, Pfizer	2000	Humanized, IgG4, immunotoxin	CD33	Cancer
Alemtuzumab	Campath/Genzyme	2001	Humanized, IgG1	CD52	Cancer
Ibritumomab tiuxetan	Zevalin/Biogen Idec	2002	Murine, IgG1, radiolabeled (yttrium-90)	CD20	Cancer
Adalimumab	Humira/Abbott	2002	Human, IgG1		Autoimmune
Omalizumab	Xolair/Genentech, Roche	2003	Humanized, IgG1	IgE	Autoimmune
Tositumomab-I-131	Bexxar/Corixa, GSK	2003	Murine, IgG2a, radiolabeled (iodine-131)	CD20	Cancer
Efalizumab[a]	Raptiva/Genentech, Roche	2003	Humanized, IgG1	CD11a	Autoimmune
Cetuximab	Erbitux/Imclone, Lilly	2004	Chimeric, IgG1	EGFR	Cancer
Bevacizumab	Avastin/Genentech, Roche	2004	Humanized, IgG1	VEGF	Cancer
Tocilizumab	Actemra/Roche	2010	Humanized, IgG1	IL-6R	Autoimmune
Panitumumab	Vectibix/Amgen	2006	Human, IgG2	EGFR	Cancer
Ranibizumab	Lucentis/Genentech, Roche	2006	Humanized IgG1 Fab	VEGF	Macular degeneration
Eculizumab	Soliris/Alexion	2007	Humanized IgG2/4	C5	Hemoglobinuria
Certolizumab pegol	Cimzia/USB	2008	Humanized, pegylated Fab	TNFα	Autoimmune
Natalizumab	Tysabri/Biogen Idec	2008	Humanized, IgG4	VLA-4	Autoimmune
Golimumab	Simponi/Johnson & Johnson	2009	Human IgG1	TNFα	Autoimmune
Canakinumab	Ilaris/Novartis	2009	Human IgG1	IL-1ß	Inflammatory
Ustekinumab	Stelara/Johnson & Johnson	2009	Human IgG1	IL-12/23	Autoimmune
Ofatumumab	Arzerra/Genmab	2009	Human IgG1	CD20	Cancer
Denosumab	Prolia	2010	Human IgG1	RANKL	Osteoporosis
Ipilimumab	Yervoy/BMS	2011	Human IgG1	CTLA-4	Cancer
Belimumab	Benlysta/Human Genome Sciences	2011	Human IgG1	BLyS	Cancer
Brentuximab Vedotin	Adcetris/Seattle Genetics	2011	Chimeric IgG1 MMAE-conjugate	CD30	Cancer

[a] Withdrawn by the manufacturer.