Antibody-Drug Conjugates (ADCs) Report

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INTRODUCTION

MabDesign is a French non-profit membership organization in the immunotherapy field, operational since September 2015, already with more than 80 companies' members, including immunotherapy developers, service providers, training organizations and suppliers of state-of-the-art equipment.

MabDesign federates and supports the industrial sector through the creation of a national directory of stakeholders, by developing specialized training solutions, and setting up high-level scientific events both regional and international thus promoting networking and innovation.

Moreover, MabDesign has developed a set of services for companies in order to optimize their marketing positioning, increase their knowledge of their market, maximize the protection and valorization of their innovations (Business Intelligence & IP analysis) and finally conquer new markets internationally through support in business development, thus supporting their economic growth.

MabDesign is support by a Scientific Advisory Board (*Comité d'orientation stratégique et scientifique de la filière* – COSSF) composed of 8 permanent experts, directed by its chairman, Alain Beck from Pierre-Fabre. The COSSF's mission is to contribute to the strategic scientific plans of action of MabDesign in the sector in order to foster innovation and economic development of companies as well as draft prospective reports on specific areas of the sector twice per year.

This document is a report on Antibody-Drug Conjugates drafted by the Scientific Advisory Board of MabDesign along with invited experts where you will able to find a summary on the lasted scientific progresses, clinical developments and stakeholders involved.

Scientific Advisory Board (COSSF)	Invited Experts	MabDesign
Alain Beck – Pierre Fabre	Anne Bousseau - GamamAbs	Nicolas Groux
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Table 0. Abbreviations used in this manuscript.

ABC	Adenosine triphosphate-binding cassette
Ab	Antibody
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADME	Absorption, distribution, metabolism and excretion
ALCL	Anaplastic large-cell lymphoma
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
CMO	Contract manufacturing organization
CRO	Contract research organization
CTLA-4	Cytotoxic T lymphocyte-associated protein-4
DAR	Drug to antibody ratio
DC	Dendritic cell
DLBCL	Diffuse large B-cell lymphoma
DM1	*N*(2')-deacetyl-*N*(2')-(3-mercapto-1-oxopropyl)-maytansine
DM4	N-methyl-N-(4-mercapto-4-methyl-1-oxopentyl)-L-alanine ester of maytansinol
EGFR	Epidermal growth factor receptor
EGFRvIII	Epidermal growth factor receptor mutant (exon deletion 2–7)
Fab	Fragment Antigen Binding
FDA	Food and Drug Administration
GPNMB	Glycoprotein-NMB
HER2	Human epidermal growth factor receptor 2
HL	Hodgkin lymphoma
HPAPI	Highly potent active pharmaceutical ingredient
IC_{50}	Concentration needed to achieve 50% inhibition
mAb	Monoclonal antibody
MC	Maleimidocaproyl
MCC	Maleimidomethyl cyclohexane-1-carboxylate
MDR	Multidrug resistance
MMAE	Monomethyl auristatin E
MMAF	Monomethyl auristatin F
NHL	Non-Hodgkin lymphoma
NSCLC	Non-small cell lung cancer
P-gp	P-glycoprotein
PBD	Pyrrolobenzodiazepine
PEG	Polyethylene Glycol
PD	Pharmacodynamics
PD-1	Programmed cell death protein-1
PDX	Patient-derived xenograft
PK	Pharmacokinetic
PL	Phenylalanine-lysine dipeptide linker
RCC	Renal cell cancer
sALCL	Systemic anaplastic large-cell lymphoma
SCLC	Small cell lung cancer
scFv	Single-chain fragment variable
SPDB	*N*-succinimidyl-4-(2-pyridyldithio) butanoate
Sulfo-SPBD	*N*-succinimidyl-4-(2-pyridyldithio)-2-sulfo butanoate
VA	Valine-alanine dipeptide linker
VC	Valine-citrulline dipeptide linker

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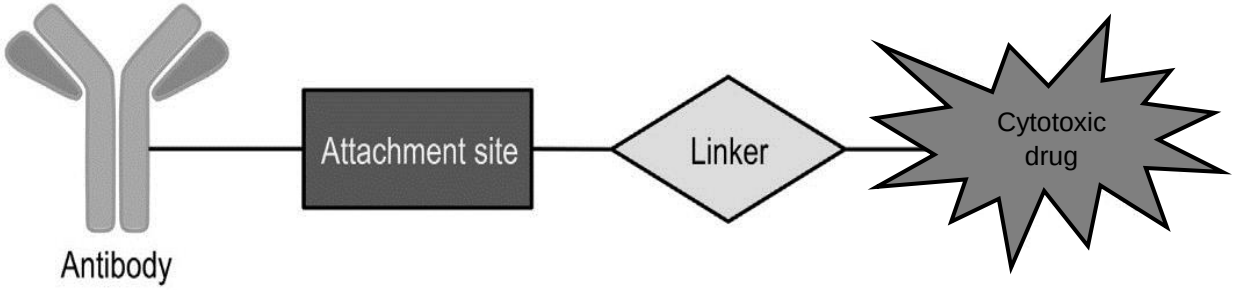
1. What is an ADC?

Antibody-drug conjugate (ADC) constitutes a novel class of highly potent biopharmaceutical drugs composed of an antibody (a whole monoclonal antibody-mAb, or an antibody fragment) conjugated to a cytotoxic drug through an appropriated linker (fig. 1). ADCs take advantage of the highly active cell-killing of cytotoxic molecules and their high binding specificity, while prolonging the half-life of cytotoxic molecules or decreasing their dose-limiting toxicity (Lu *et al.*, 2016).



- targets a well characterized and abundant tumor antigen associated with limited expression on healthy tissues - non-immunogenic - targets an antigen that is endocytosed after Ab binding - minimal non-specific binding - type of Ab format - FcγR-binding or not - FcRn binding affinity - Internalization & lysosomal trafficking	- conjugation to lysines, hinge cysteines, engineered cysteines, non-natural amino acids… - variable drug-to-antibody ratio (DAR)	- stable in systemic circulation - should efficiently release the cytotoxic drug inside the tumor cell - does not alter the Ab characteristics (PK) - selectively cleaved in or nearby the tumor cells - hydrazones, disulfides, peptides, non-cleavable	- highly potent with IC_{50} in subnanomolar range - non-toxic (dormant or inactive, prodrug) during systemic circulation - amenable to linker chemistry - define cell killing mechanism of action - tubulin inhibitors, DNA/RNA alkylators… - low off-target cytotoxity - bystander effect - multidrug resistance escape - drug-drug interactions

Fig.1 – Key components of an ADC (adapted from Gébleux et al., 2016).

2. Advantages of ADCs and how they work

The primary advantage of ADCs is that they can behave as prodrugs during systemic circulation and finally release the free drugs at the target tumor cells (fig. 2). Relying on highly targeted tumor antigen recognition and effective internalization, ADCs recognize and bind to specific tumor antigen on the cell surface, then the internalization is conducted through endocytosis. Once entering the tumor cells, ADCs are transferred to the endosome that fused to lysosome, allowing the digestion of the potential linkers or mAbs and actively release cytotoxic drugs (Lu *et al.*, 2016).

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Bien cordialement,

L'équipe MabDesign

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