Bispecific antibodies are capable of simultaneous binding of two different targets and thus also capable of delivering a great variety of payloads to the target tissues or cells. To date bispecific antibodies specific for certain cell targets have been described. However this methodology has a major disadvantage as it requires that antibodies be raised against every agent desired for diagnostic and therapeutic use.

US 7'429'381 discloses a two-step pretargeting method, wherein a bispecific antibody specific for a HSG hapten and a cell-surface protein is first administered to the cell and is then used to capture a HSG hapten to which a therapeutic or diagnostic cation or a therapeutic or diagnostic agent is chelated to. Haptens are small molecules, such as pesticides, drugs, hormones, and toxins, which are usually nonimmunogenic unless coupled with some macromolecules such as proteins. However the use of bispecific anti-HSG-hapten antibodies in a two-step pretargeting method has several limitations.

The major disadvantage is the complexity of the approach, which involves preparation and dosing of two separate reagents and consequential timing and ratio issues. In addition, it is not possible to analyse the resulting complex of the bispecific antibody and the therapeutic or diagnostic agent. It is therefore difficult to predict pharmacological properties, stoichiometry and possible degradation products of the therapeutic or diagnostic agent captured by the bispecific antibody.

In addition, currently used conjugates can not be applied for most therapeutic agents since conjugation often results in reduced or eliminated activity of the therapeutic agent or in undesired alterations of the binding capabilities of the antibody.

Therefore there is a need for a well-defined, efficient and specific delivery platform for therapeutic and diagnostic agents with effective release of the payload at the target that can be broadly applied.

The present ~~invention~~disclosure relates to a bi-specific antibody specific against a hapten and a target protein, comprising a first antigen-binding site that binds to a hapten and a second antigen-binding site that binds to a target protein, wherein the hapten is conjugated to a nucleic acid. Preferred haptens are digoxigenin, biotin and polyethyleneglycol (PEG).

In a first aspect, there is proivded a bi-specific antibody specific against digoxigenin (DIG) and a target protein for use in therapy or diagnostics, wherein a nucleic acid which has been conjugated to DIG is delivered to a target cell or tissue, wherein the bi-specific antibody comprises:

(a) a first antigen-binding site that binds to DIG comprising:

(i) a heavy chain variable domain selected from SEQ ID NO. 3, SEQ ID NO 3 with the mutations S49A, I58A and A61P or SEQ. ID NO. 2 and;

(ii) a light chain variable domain selected from SEQ ID NO 5 or SEQ. ID NO. 1; and

(b) a second antigen-binding site that binds to a target protein.

The ~~invention~~disclosure provides methods for producing the bispecific antibodies or antibody fragments, as well as methods for using them, in particular their use as a delivery platform for

therapeutic and diagnostic agents, as well as pharmaceutical compositions and diagnostic tools comprising said antibodies.

In a second aspect, there is provided a pharmaceutical composition comprising a bi-specific antibody specific against digoxigenin (DIG) and a target protein for delivery of a nucleic acid to a target cell or tissue, wherein the bi-specific antibody comprises: (a) a first antigen-binding site that binds to DIG comprising: (i) a heavy chain variable domain selected from SEQ ID. NO. 3, SEQ ID NO 3 with the mutations S49A, I58A and A61P or SEQ. ID NO. 2, and; (ii) a light chain variable domain selected from SEQ ID NO 5 or SEQ. ID NO. 1; and (b) a second antigen-binding site that binds to a target protein; wherein said antibody is coupled to a digoxigenated therapeutic or diagnostic nucleic acid.

In a third aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for targeted gene therapy.

In a fourth aspect, there is provided the pharmaceutical composition as defined above for use in targeted gene therapy.

Preferred embodiments include bi-specific antibodies or antibody fragments against a target protein and digoxigenin, comprising a first antigen-binding site that binds to digoxigenin (referred to as "Dig" or "DIG") and a second antigen-binding site that binds to a target protein. Said binding sites of the bi-specific antibodies or antibody fragments are referred to as "<target protein>" (or shortly, "<target>") and "<Dig>", respectively.

In other embodiments bi-specific antibodies or antibody fragments against a target protein and a hapten different from digoxigenin are envisaged. Preferred haptens are biotin and PEG.

Below embodiments are exemplified for bi-specific antibodies or antibody fragments against a target protein and digoxigenin, as well as methods for using them, in particular their application as a delivery platform. Even though digoxigenin is the most preferred hapten envisaged in this invention, these embodiments are also applicable for biotin and PEG.

Further this invention relates to monoclonal bi-specific antibodies and antibody fragments that comprise a first antigen-binding site that binds to digoxigenin and a second antigen-binding site that binds to a target protein, DNAs that encode such antibodies and antibody fragments, and vectors for expressing the DNAs. Preferably, said bi-specific antibodies are humanized and chimeric antibodies.

One embodiment of the invention is a bispecific antibody binding to digoxigenin and a target protein comprising a first antigen-binding site that binds to digoxigenin and a second antigen-binding site that binds to a target protein, comprising

a) a monospecific bivalent antibody consisting of two full length antibody heavy chains and two full length antibody light chains whereby each chain is comprising only one variable domain,

b) two peptide-linkers,

c) two monospecific monovalent single chain antibodies each consisting of an antibody heavy chain variable domain, an antibody light chain variable domain, and a single-chain-linker