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(71) Applicant: **THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Office of Technology Transfer, National Institutes of Health, 6701 Rockledge Drive, Suite 700, MSC 7788, Bethesda, Maryland 20892-7788 (US).

(72) Inventors: **YEWDELL, Jonathan Wilson**; NIAID, 5601 Fishers Lane, Bethesda, Maryland 20892 (US). **KOSIK, Ivan**; NIAID, 5601 Fishers Lane, Bethesda, Maryland 20892 (US).

(74) Agent: **SUSAN, Janine M.** et al.; Armstrong Teasdale LLP, 7700 Forsyth Blvd., Suite 1800, St. Louis, Missouri 63105-1847 (US).

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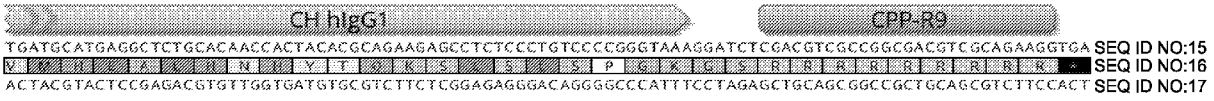

FIG. 1

(57) Abstract: Compounds for inhibiting the replication of intracellular microorganisms are described. More specifically, the present disclosure provides transbodies comprising a cell-penetrating moiety (CPM) and a binding moiety (BM). The CPM, which may be a cell-penetrating peptide (CPP), allows translocation of the entire transbody into a cell. The BM, which may comprise an antibody, binds a protein from an intracellular microorganism, thereby inhibiting replication of the intracellular microorganism. The disclosed transbodies may be used to inhibit replication of intracellular microorganisms in cells in culture, and/or they may be used to treat individuals infected with an intracellular microorganism.

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ENGINEERED CELL-PENETRATING ANTIVIRAL COMPOUND

[0001] PRIORITY PARAGRAPH

[0002] This application claims the benefit of priority under 35 U.S.C. § 119 of U.S. Provisional Application Serial No. 63/365841 filed on June 3, 2022, the content of which is incorporated herein by reference in its entirety.

[0003] STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH & DEVELOPMENT

[0004] This work was supported by the Division of Intramural Research of the National Institute of Allergy and Infectious Disease. The U.S. government has certain rights in this invention.

BACKGROUND

[0005] Viral infections are an intractable problem for human health. Recent events have highlighted the significant impact that viral infections can have on human health, medical systems, and economies. Efficient and early treatment may improve the prognosis, but current treatment of viral infections is not satisfactory. Many antiviral drugs and vaccines are inefficient due to frequent virus mutations and viruses escaping the host immune system. Moreover, many antiviral drugs have strong side effects, such as rashes, central nervous system disorders, or organ damage (Vcev, 2009; Frasca et al., 2012).

[0006] One example of a virus that has had a significant impact throughout human history is influenza virus. Influenza virus is a negative-sense RNA, respiratory virus from the family *Orthomyxoviridae*. Infection with influenza virus results in an acute, febrile respiratory disease referred to as influenza or "flu". Disease caused by influenza virus ranges from mild to severe and is sometimes fatal. In the United States, approximately 5-20% of the population is infected resulting in approximately 200,000 hospitalizations and 30,000-50,000 deaths. Thus, flu presents significant health care challenges.

[0007] Influenza viruses are classified into subtypes based on two viral glycoproteins, hemagglutinin (HA) and neuraminidase (NA) present on the surface of the virus. Each subtype is identified by the combination of HA and NA proteins carried by the virus. The HA protein is the principal surface antigen on influenza virus particles, and thus is the principal target for the immune system. Because the HA and NA proteins are exposed

to the host's immune system, they are subject to selection pressure and in fact, variants of these proteins frequently arise as the hosts immune system responds to the original protein. This well-known seasonal drift of influenza virus antigenicity accounts for the absence of long-term immune protection in previously infected individuals.

[0008] Influenza virus also produces several other proteins that remain on the interior of the virus particle, such as the nucleocapsid (NP), the RNA polymerase, and the matrix protein (M1). Functional constraints/low mutational plasticity, and inaccessibility of extracellular antibodies to NP limit the evolution of this protein. Consequently, the sequences of the NP are more highly conserved. Thus, therapeutic agents directed towards such protein should remain effective for longer periods of time, and also be effective against various subtypes of influenza virus.

[0009] Currently, the first line of defense against influenza virus is vaccines produced using inactivated influenza virus. However, for the reasons discussed above, vaccines remain effective for a short period of time and must be re-administered every year. Moreover, because vaccine production entails trying to identify the dominant subtype at least six months prior to outbreaks, current vaccines are often only partially effective. Recently, attempts have been made to produce vaccines using recombinant HA protein, and in particular, conserved portions of the HA protein. However, to date these attempts have not been successful at providing a robust, and reliable vaccine.

[0010] Thus, the need remains for therapeutic agents that can be used to treat pathogenic organisms, such as influenza virus infections. The present disclosure addresses this need.

SUMMARY

[0011] One aspect is a transbody comprising a cell penetrating peptide (CPP) joined to a binding moiety (BM), wherein the binding moiety specifically binds a protein from an intracellular microorganism. In some aspects, binding of the BM to the protein inhibits replication of the intracellular microorganism. The BM may comprise a polynucleotide and/or polypeptide that binds a protein from an intracellular microorganism. The CPP may be joined to the carboxyl-terminal end of the polypeptide, the amino-terminal end of the polypeptide, or to a side chain of an amino acid in the polypeptide. The CPP may be joined directly to the polypeptide or it may be joined to the polypeptide by a linker. In some aspects, the polypeptide may comprise a Fab, a single chain fragment variable (scFv),

a di-scFv, a single chain antibody (scab), or a single domain antibody (sdAb). The polypeptide may comprise an antibody light chain, or a portion thereof, comprising one, two or three CDR_Ls from an immunoglobulin that specifically binds a protein from an intracellular microorganism. At least one CDR_L may be selected from the group consisting of CDR_L1, CDR_L2, and CDR_L3, wherein CDR_L1, CDR_L2, and CDR_L3 are from the immunoglobulin that specifically binds a protein from an intracellular microorganism. In some aspects, the antibody light chain, or portion thereof, may comprise CDR_L1, CDR_L2, and CDR_L3 from the immunoglobulin that specifically binds a protein from an intracellular microorganism. CDR_L1 may comprise, or consist of, SEQ ID NO:4, CDR_L2 may comprise, or consist of, SEQ ID NO:5, and CDR_L3 may comprise, or consist of, SEQ ID NO:6. In some aspects, the light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, the light chain may comprise SEQ ID NO:7. The polypeptide may comprise an antibody heavy chain, or a portion thereof, comprising one, two or three CDR_Hs from an immunoglobulin that specifically binds a protein from an intracellular microorganism. At least one CDR_H may be selected from the group consisting of CDR_H1, CDR_H2, and CDR_H3, wherein CDR_H1, CDR_H2, and CDR_H3 are from the immunoglobulin that specifically binds a protein from an intracellular microorganism. In some aspects, the antibody heavy chain, or portion thereof, may comprise CDR_H1, CDR_H2, and CDR_H3 from an immunoglobulin that specifically binds a protein from an intracellular microorganism. CDR_H1 may comprise, or consist of, SEQ ID NO:8, CDR_H2 may comprise, or consist of, SEQ ID NO:9, and CDR_H3 may comprise, or consist of, SEQ ID NO:10. In some aspects, the heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein the heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the heavy chain may comprise SEQ ID NO:11 or 12. The BM may comprise an antibody, which may comprise a whole antibody, an antibody fragment, a synthetic antibody, a recombinantly produced antibody, a multispecific antibody, a human antibody, a non-human antibody, a humanized antibody, a chimeric antibody, intrabodies, a, Fab fragment, a Fab' fragment, a

$F(ab')_2$ fragment, an Fv fragment, a disulfide-linked Fvs (dsFv), a Fd fragment, a Fd' fragment, a single-chain fragment variant (Fvs) (scFv), a single-chain Fab (scFab), a single chain antibody, a diabody, an anti-idiotypic (anti-Id) antibody, or an antigen-binding fragment of any of the above. The antibody may be of any immunoglobulin type (e.g., IgG, IgM, IgD, IgE, IgA and IgY), and any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass (e.g., IgG2a and IgG2b. In some aspects, the CPP may be a cationic CPP, an amphipathic CPP, or a hydrophobic CPP. The CPP may comprise, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, or functional variants thereof. The intracellular, microorganism may be an intracellular bacterium, which may be selected from the group consisting of Mycobacterium, Legionella, Chlamydia, Coxiella, Rickettsia, Salmonella and Yersinia. The intracellular microorganism may be a virus, which may be selected from the group consisting of an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, and a coronavirus.

[0012] One aspect of the disclosure is a therapeutic composition comprising a transbody of the disclosure.

[0013] One aspect of the disclosure is a kit comprising a transbody of the disclosure or a therapeutic composition of the disclosure.

[0014] One aspect of the disclosure is a method of inhibiting replication of an intracellular microorganism in a cell, comprising contacting the cell with a transbody of the disclosure.

[0015] One aspect of the disclosure is a method of treating an individual for infection by an intracellular microorganism, comprising administering to the individual a transbody of the disclosure or a therapeutic composition of the disclosure.

[0016] One aspect of the disclosure is a method of preventing infection of an individual by an intracellular microorganism, comprising administering to the individual a transbody of the disclosure or a therapeutic composition of the disclosure.

[0017] In these methods, the intracellular, microorganism may be an intracellular bacterium, which may be selected from the group consisting of Mycobacterium, Legionella, Chlamydia, Coxiella, Rickettsia, Salmonella and Yersinia. In these methods, the intracellular microorganism may be a virus, which may be selected from the group consisting of an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, and a coronavirus. In some methods, the intracellular microorganism

may be an influenza virus and the transbody may comprise a BM that binds an influenza virus nonstructural protein, which may be an influenza NP.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 illustrates the design of the GS-CPP modification of the Ab Fc region. The bar labeled CH hIg1 represents the carboxyl end of constant chain of the human IgG1 heavy chain. The bar labeled CPP-R9 represents an example of a cell penetrating peptide. The amino acid sequence (middle sequence) shows sequence of the CH hIg1 joined to the CPP using a glycine-serine linker. The nucleotide sequences show the coding (top) and non-coding (bottom) sequences for the listed amino acid sequence.

[0019] FIG. 2 displays a heat map showing the avidity of wt H16-L10 (a-NP-wt) and the HL16-L10 transbody (a-NP-CP) for various antigenic influenza A and B virus variants.

[0020] FIG. 3 shows the result of immunofluorescence imaging demonstrating cellular uptake of a-NP-CP.

[0021] FIGS. 4A & B illustrate a flow-cytometry-based neutralization assay and results obtained using such an assay. FIG. 4A illustrates the general principle of a flow-cytometry-based assay. FIG. 4B shows the percent of cells infected by A/Puerto Rico/8/1934 (H1N1) (left panel), A/California/07/2016 (H1N1) (center panel), and A/North Carolina/13/2014 (H3N2) (right panel).

[0022] FIG. 5 shows the amount of A/Puerto Rico/9/1934 (H1N1) virus produced in cells treated with either wt H16-L10 (a-NP-wt) or HL16-L10 transbody (a-NP-CP), as determined by the level of neuraminidase activity in the supernatant of the infected cells.

[0023] FIGS.6A-C illustrate the ability of an H10-L16 transbody to provide prophylactic protection. FIG. 6A illustrates outlines the method of the study. FIG. 6B shows body weight lost over time following influenza infection of mice treated with wt H16-L10 (a-NP-wt) , HL16-L10 transbody (a-NP-CP), a-SARS1 NP-CP (an unrelated transbody), or PBS. FIG. 6C shows percent survival over time following influenza infection of mice treated with a-NP-wt, a-NP-CP, a-SARS1 NP-CP, or PBS.

[0024] FIGS. 7A-C illustrate the ability of an H10-L16 transbody to provide therapeutic protection. FIG. 7A illustrates outlines the method of the study. FIG. 7B shows body weight lost over time following influenza infection of mice treated with wt

H16-L10 (a-NP-wt) , HL16-L10 transbody (a-NP-CP), or PBS. FIG. 7C shows percent survival over time following influenza infection of mice treated with a-NP-wt, a-NP-CP, or PBS.

[0025] FIG. 8 show the results of an immunofluorescence analysis of influenza virus infected cells expressing NP protein and treated with either wt H16-L10 (WT; top row) or HL16-L10 transbody (CP; bottom row).

[0026] FIGS 9A & B. show analysis of NP expression on A549 cell line treated with WT or CP Ab and infected with IAV overnight. FIG. 9A shows a Western blot analysis of proteins isolated from the infected and treated cells. Beta-actin was used to normalize protein recovered from the different samples. FIG. 9B displays the results from FIG. 9A in graphical form.

[0027] FIGS. 10A-E show the results of flow cytometry analysis of H16-L10 internalization of A549 cell line.

DETAILED DESCRIPTION

[0028] The present disclosure relates to therapeutic agents, referred to as transbodies, that may be used to inhibit the replication of intracellular, microorganisms. Transbodies of the disclosure comprise a binding moiety (BM) that binds a molecule of interest, and a cell penetrating moiety (CPM) that catalyzes entry of the transbody into a cell. To illustrate, a transbody having a BM specific for a viral protein can translocate into cell and bind to the viral protein within the cell, thereby preventing the virus from producing new virions. Thus, the present disclosure generally provides a transbody comprising a BM joined to a CPM, wherein the CPM catalyzes entry of the transbody into a cell, and wherein the BM binds to a molecule from an infectious microorganism. Such transbodies may be used for preventing replication of intracellular microorganisms, such as bacteria or viruses within a cell.

[0029] One aspect of the disclosure is a transbody comprising a first CPM and a BM, wherein the first CPM is joined to the BM, wherein the CPM catalyzes entry of the transbody into a cell, and wherein the BM binds to a molecule from an intracellular microorganism and inhibits replication of the intracellular microorganism.

[0030] Before the present disclosure is further described, it is to be understood that this disclosure is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the

purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the claims.

[0031] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. For example, a nucleic acid molecule refers to one or more nucleic acid molecules. As such, the terms "a", "an", "one or more" and "at least one" can be used interchangeably. Similarly, the terms "comprising", "including" and "having" can be used interchangeably. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0032] Publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Terms and phrases, which are common to the various aspects disclosed herein, are defined below.

[0034] As used herein, a transbody refers to a molecule comprising a cell-penetrating moiety (CPM) (aka cell-penetrating portion) joined to a binding moiety (BM) (aka binding portion), wherein the CPM catalyzes translocation of the transbody into a cell. Translocation, translocates, and the like, mean the transbody moves from the exterior of a cell, through the cell membrane and into the interior of the cell. A transbody of the disclosure may comprise any kind of molecule that enables the transbody to function as intended. For example, a transbody may comprise an amino acid sequence (e.g., a polypeptide), a nucleic acid sequence (e.g., a polynucleotide), modified forms thereof, and/or combinations thereof.

In certain aspects, a transbody may comprise one or more polypeptide sequences and one or more nucleic acid sequences.

[0035] As used herein, a CPM refers to a molecule that can translocate through the outer membrane and into the interior of a cell. Many CPMs are also able to facilitate the delivery of other molecules to which they are joined, such as proteins, nucleic acid molecules, and organic compounds, such as imaging agents and anti-cancer compounds, into the interior of a cell. Thus, with regard to a transbody of the present disclosure, the CPM of a transbody refers to the portion of the transbody that enables the entire transbody to translocate through a cell membrane and into the cytoplasm, at least, of the cell. One example of a CPM is a cell-penetrating peptide (CPP) (aka protein transduction domain). Cell penetrating peptides comprise a large class of short amino acid sequences, generally between 6 and 50 amino acids in length, that possess the ability to translocate across the membrane of mammalian cells. A CPP useful for practicing methods of the disclosure is any CPP that when joined to a BM of the disclosure catalyzes (enables, facilitates) translocation of the transbody through the cell membrane and into the cytoplasm, and may, but need not, localize in one or more intracellular compartments, such as the nucleus, the nucleolus, lysosomes, peroxisomes, mitochondria, and endoplasmic reticulum.

[0036] In one aspect of the disclosure, the CPM may be a CPP. Any CPP may be used for producing a transbody of the disclosure, as long as the CPP catalyzes translocation of the transbody into the interior of the cell. Examples of CPPs suitable for producing transbodies of the disclosure are known in the art and may be found, for example, at the CPPsite 2.0 Database of Cell-Penetrating Peptides, which is a curated database of known CPPs (http://crdd.osdd.net/8cab8va/cppsite/). Examples of CPPs useful for practicing aspects of the disclosure are shown below in Table 1.

SEQ ID NO:	Sequence	Description
1	RRRRRRRRR	Exemplary cell penetrating peptide
2	CRRRRRRRRC	Exemplary cell penetrating peptide

3	GRRRRRRRRKCCKRRRRRRRRG	Exemplary cell penetrating peptide
4	QDVGTA	H16-L10 light chain CDR1
5	WAS	H16-L10 light chain CDR2
6	QQYNDYPLT	H16-L10 light chain CDR3
7	DIVMTQSHKFMSTSLGDRVDITYRASQDVGTAVAWY QQKPGQSPRLLISWASTRHAGVPDRFTGSGSGTDFT LTISNVQSEDLADYFCQQYNDYPLTFGPGTKLDLKR ADAAPTVSIFPPSSEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	H16-L10 light chain
8	GFIFSSYA	H16-L10 heavy chain CDR1
9	TSGGGTT	H16-L10 heavy chain CDR2
10	GRDGNWFTS	H16-L10 heavy chain CDR3
11	EVKLVESGGALVNPGGSLKLSCAASGFIFSSYAMSW IRQTPEKRLEWVASTSGGGTTYYLDSVRGRFTISRD NARRILYLQMTSLRSEDTAIYFCGRDGNWFTSWGQG TLVTVSIAKTTAPSVYPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGKG	H16—L10 heavy chain
12	EVKLVESGGALVNPGGSLKLSCAASGFIFSSYAMSW IRQTPEKRLEWVASTSGGGTTYYLDSVRGRFTISRD NARRILYLQMTSLRSEDTAIYFCGRDGNWFTSWGQG TLVTVSIAKTTAPSVYPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK	H16—L10 heavy chain minus terminal G

	PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	
13	EVKLVESGGALVNPGGSLKLSCAASGFIFSSYAMSW IRQTPEKRLEWVASTSGGGTTYYLDSVRGRFTISRD NARRILYLQMTSLRSEDTAIYFCGRDGNWFTSWGQG TLVTVSIAKTTAPSVYPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGKGSRRRRRRRRR	Exemplary transbody
14	EVKLVESGGALVNPGGSLKLSCAASGFIFSSYAMSW IRQTPEKRLEWVASTSGGGTTYYLDSVRGRFTISRD NARRILYLQMTSLRSEDTAIYFCGRDGNWFTSWGQG TLVTVSIAKTTAPSVYPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGKGSCRRRRRRRRC	Exemplary transbody
15	EVKLVESGGALVNPGGSLKLSCAASGFIFSSYAMSW IRQTPEKRLEWVASTSGGGTTYYLDSVRGRFTISRD NARRILYLQMTSLRSEDTAIYFCGRDGNWFTSWGQG TLVTVSIAKTTAPSVYPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGKGSGRRRRRRRRKCCKRRRRR RRRG	Exemplary transbody

16	TGATGCATGAGGCTCTGCACAACCACTACACGCAGA AGAGCCTCTCCCTGTCCCCGGGTAAAGGATCTCGAC GTCGCCGGCGACGTCGCAGAAGGTGA	
17	MHEALHNHYTQKSLSLSPGKGSRRRRRRRRR	
18	ACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCT TCTCGGAGAGGGACAGGGGCCCATTTCCTAGAGCTG CAGCGGCCGCTGCAGCGTCTTCCACT	

[0037] In some aspects, the CPP may be between 6 and 50 amino acids in length. In some aspects, the CPP may be between 6 and 15, 20, 25, 30, 35, or 40 amino acids in length. In some aspects, the CPP may comprise, consist essentially of, or consist of, the amino acid sequence RRRRRRRRR (SEQ ID NO:1), the amino acid sequence CRRRRRRRRC (SEQ ID NO:2), the amino acid sequence GRRRRRRRRKCCKRRRRRRRRRG (SEQ ID NO:3), or variants thereof that catalyze translocation of a transbody comprising the variant CPP into a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, an amino acid sequence at least 85%, at least 90%, at least 95%, at least 97%, or at least 99%, identical to SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the CPP catalyzes translocation of the transbody into the interior of a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

[0038] As used herein, a BM refers to the portion of the transbody that selectively binds to a molecule, such as a protein, from an intracellular microorganism. The BM may comprise any type of molecule capable of binding a protein from the intracellular microorganism. For example, the binding moiety may comprise a polynucleotide, a polypeptide, combinations thereof, and/or modified forms thereof.

[0039] In some aspects, the BM may comprise, consist essentially of, or consist of, a polynucleotide, one example of which is an aptamer. The aptamer may be joined to the CPM at any location in the CPM that allows the transbody to translocate into a cell, and that allows the aptamer to bind to a molecule from an intracellular, microorganism. If the CPM is a CPP, then the aptamer may be joined, at either its 5' or 3' end, to the amino-terminal end (N-terminus), the carboxyl terminal end (C-terminus), or to any of the side groups of the amino acids that make the CPP. Methods of producing and identifying suitable aptamers for practicing methods of the disclosure are known in the art, such as in US5,475,096, and US8,030,475, both of which are incorporated by reference in their entirety.

[0040] In some aspects, the BM may comprise a polypeptide that specifically binds a protein from an intracellular microorganism. As used herein, a polypeptide refers to a molecule composed of amino acid monomers (a.k.a. "amino acids"), or modified forms thereof, linked by amide bonds (a.k.a. peptide bonds). The term "polypeptide" indicates a chain of amino acids and unless otherwise stated, does not refer to a specific length of a chain of amino acids. The polypeptide may comprise any amino acid sequence, as long as it binds a protein from an intracellular microorganism. In some aspects, the polypeptide may comprise an antibody such as a Fab, a scFv, a di-scFV, a 12cab, and a sdAb.

[0041] In some aspects, the BM may comprise an antibody that binds a protein from an intracellular microorganism. As used herein, the term "antibody" refers to immunoglobulins, immunoglobulin fragments, and derivatives thereof, whether natural or partially or wholly synthetically, such as recombinantly, produced, including any fragment thereof containing at least a portion of the variable region of the immunoglobulin molecule that retains the binding specificity ability of the full-length immunoglobulin. Thus, an antibody may include any protein having a binding domain that is homologous or substantially homologous to an immunoglobulin antigen-binding domain (antibody combining site). Antibodies include whole antibodies (i.e., having an Fc portion and two Fab regions, each of which comprises at least one, two or three CDRs, held together by disulfide bonds), or antibody fragments, such as anti-bacterial or anti-viral (e.g. anti-influenza virus) antibody fragments. As used herein, the term antibody, thus, includes synthetic antibodies, recombinantly produced antibodies, multi-specific antibodies (e.g., bispecific antibodies), human antibodies, non-human antibodies, humanized antibodies, chimeric antibodies, intrabodies, and antibody fragments, such as, but not limited to, Fab fragments, Fab' fragments, $F(ab')_2$ fragments, Fv fragments, disulfide-linked Fvs (dsFv), Fd fragments, Fd' fragments, single-chain fragment variants (Fvs) (scFv), single-chain Fabs (scFab), single chain antibodies, diabodies, anti-idiotypic (anti-Id) antibodies, or antigen-binding fragments of any of the above. Antibodies hereof may include members of any immunoglobulin type (e.g., IgG, IgM, IgD, IgE, IgA and IgY), and any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass (e.g., IgG2a and IgG2b).

[0042] The general structure of antibodies used herein is as understood in the art. The classical pictures of an antibody (aka an immunoglobulin) is generally a complex molecule made from two full length heavy chains, each heavy chain having a constant region

and a variable region, and two light chains, each light chain comprising a constant region and a variable region. The variable region of a full-length heavy chain comprises three heavy chain complementarity-determining regions (CDR_HS), while the variable region of a full-length light chain comprises three light chain CDRs (CDR_LS). The light chain and heavy chain are joined through disulfide bonds such that the variable regions are in proximity, thereby forming an antigen binding site that specifically binds an antigen. The heavy chain CDRs may be referred to as CDR_H1, CDR_H2, and CDR_H3, while the light chain CDRs may be referred to as CDR_L1, CDR_L2, and CDR_L3. As used herein, the term "heavy chain" includes a full-length heavy chain and any portion of fragment thereof having sufficient variable region sequence to confer binding specificity. As used herein, the term "light chain" includes a full-length light chain and any portion of fragment thereof having sufficient variable region sequence to confer binding specificity.

[0043] A BM of the disclosure, such as an antibody, is considered to "specifically bind" its target when the dissociation constant (KD) is $<10^6$ M. The BM specifically binds the target antigen with "high affinity" when the KD is $\leq$lx 10^8 M.

[0044] In some aspects, the antibody that binds a protein from an intracellular microorganism may comprise a light chain, or at least a portion thereof, and/or a heavy chain, or at least a portion thereof. The light chain, or the at least a portion thereof, may comprise at least one, two or three CDR_Ls from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one CDR_L selected from the group consisting of CDR_L1, CDR_L2 and CDR_L3, wherein CDR_L1, CDR_L2 and CDR_L3 are from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise at least one, two, or three CDR_Hs from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise at least one CDR_H selected from the group consisting of CDR_H1, CDR_H2 and CDR_H3, wherein CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some

aspects, the heavy chain, or the at least a portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain may comprise the heavy chain of an antibody that binds to a protein from an intracellular, microorganism. In some aspects, the immunoglobulin that binds to a protein from an intracellular, microorganism, may comprise a H16-L10 mAb produced by the H16L10-4R5 hybridoma. In some aspects, CDR_L1, CDR_L2 and CDR_L3 may be from the light chain of the H16-L10 mAb. In some aspects, CDR_H1, CDR_H2 and CDR_H3 may be from the heavy chain of the H16-L10 mAb. In some aspects, the antibody may comprise a light chain, or at least a portion thereof, comprising: i) CDR_L1, comprising or consisting of SEQ ID NO:4; ii) CDR_L2, comprising or consisting of SEQ ID NO:5; and/or iii) CDR_L3, comprising or consisting of SEQ ID NO:6. In some aspects, the light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, the antibody may comprise a light chain comprising or consisting of SEQ ID NO:7. In some aspects, the antibody may comprise a heavy chain, or at least a portion thereof, comprising: i) CDR_H1, comprising or consisting of SEQ ID NO:8; ii) CDR_H2, comprising or consisting of SEQ ID NO:9; and/or, iii) CDR_H3, comprising or consisting of SEQ ID NO:10. In some aspects, the heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein the heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the heavy chain may comprise, or consist of, SEQ ID NO:11 or 12.

[0045] In some aspects, the BM may comprise an antibody comprising two light chains, or at least portions thereof, and two heavy chains, or at least portions thereof. In some aspects, each light chain, or each portion thereof, may comprise at least one, two or three CDR_Ls from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, each light chain, or each portion thereof, may comprise at least one CDR_L selected from the group consisting of CDR_L1, CDR_L2 and CDR_L3, wherein CDR_L1, CDR_L2 and CDR_L3 are from the light chain of an immunoglobulin that binds to a

protein from an intracellular, microorganism. In some aspects, each light chain, or each portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, each light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, each heavy chain, or each portion thereof, may comprise at least one, two, or three CDR_Hs from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, each heavy chain, or each portion thereof, may comprise at least one CDR_H selected from the group consisting of CDR_H1, CDR_H2 and CDR_H3, wherein CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, each heavy chain, or each portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, each heavy chain may comprise the heavy chain of an antibody that binds to a protein from an intracellular, microorganism. In some aspects, the immunoglobulin that binds to a protein from an intracellular, microorganism, may comprise a H16-L10 mAb produced by the H16L10-4R5 hybridoma. In some aspects, CDR_L1, CDR_L2 and CDR_L3 may be from the light chain of the H16-L10 mAb. In some aspects, CDR_H1, CDR_H2 and CDR_H3 may be from the heavy chain of the H16-L10 mAb. In some aspects, each light chain, or each portion thereof, may comprise: i) CDR_L1, comprising or consisting of SEQ ID NO:4; ii) CDR_L2, comprising or consisting of SEQ ID NO:5; and/or iii) CDR_L3, comprising or consisting of SEQ ID NO:6. In some aspects, each light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein each light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, each light chain may comprise or consist of SEQ ID NO:7. In some aspects, each heavy chain, or each portion thereof, may comprise: i) CDR_H1, comprising or consisting of SEQ ID NO:8; ii) CDR_H2, comprising or consisting of SEQ ID NO:9; and/or, iii) CDR_H3, comprising or consisting of SEQ ID NO:10. In some aspects, each heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein each heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID

NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, each heavy chain may comprise, or consist of, SEQ ID NO:11 or 12.

[0046] In some aspects, the antibody may comprise a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment, a Fv fragment, a dsFv, a Fd fragment, a Fd' fragment, a scFv, a single-chain Fab (scFab), a diabody, or a minibody. In some aspects, the antibody that binds to a protein from an intracellular, microorganism may be an anti-viral antibody (e.g., an anti-influenza antibody), such that the BM binds to a viral protein, such as an influenza virus protein. In some aspects, the antibody may comprise a CDR_L3, comprising or consisting of SEQ ID NO:6 and a CDR_H3 comprising, or consisting of, SEQ ID NO:10.

[0047] In some aspects, an antibody may be a neutralizing antibody. As used herein, a "neutralizing antibody" is an antibody that binds to a protein from an intracellular, microorganism and inhibits or prevents replication of the intracellular microorganism. With regard to viruses, it should be understood that while neutralizing antibodies are traditionally thought of as binding an intact virus and preventing the virus from binding to and/or entering a cell, as used herein, a neutralizing antibody may be an antibody that can bind to a viral protein within a cell and inhibit replication of the virus. Inhibition of viral replication by a BM of the disclosure may result from inhibition of any step of virus production, such as, nucleic acid replication, protein production, and/or virus assembly. Thus, binding of a BM to a viral protein may result in, for example, an inability of the virus to assemble viral particles, or inhibition by the BM of an enzyme necessary for genome synthesis, virus assembly, virus budding, and the like. In certain aspects, inhibition of replication means that binding of the BM to the protein from a intracellular microorganism may reduce replication of the microorganism by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 100%. In certain aspects, inhibition of replication may mean that binding of the BM to the protein from an intracellular, microorganism reduces replication of the microorganism by at least 0.5 logs, at least 1.0 logs, at least 2.0 logs, at least 3.0 logs, at least 4.0 logs, at least 5.0 logs, at least 6.0 logs, at least 8.0 logs, or at least 8.0 logs. In certain aspects, binding of the antibody to the protein from an intracellular, microorganism may completely inhibit replication of the microorganism. As used herein, the phrase "completely inhibits" means that binding of the antibody to the protein from the intracellular, microorganism may prevent the microorganism from producing a detectable level of progeny microorganisms.

[0048] As used herein, an intracellular, microorganism refers to a microorganism that can infect a cell and replicate therein. For convenience, an intracellular, microorganism may herein simply be referred to as "a microorganism" or "the microorganism". Examples of intracellular, microorganisms that may be inhibited by a transbody of the disclosure include, but are not limited to, bacteria, viruses, fungi, and protozoa. Examples of viruses, the replication of which may be inhibited by transbodies of the disclosure, include, but are not limited to Picornaviruses (such as Aphthoviridae [for example foot-and-mouth-disease virus (FMDV)]), Cardioviridae; Enteroviridae (such as Coxsackie viruses, Echoviruses, Enteroviruses, and Polioviruses); Rhinoviridae (Rhinoviruses)); Hepataviridae (Hepatitis A viruses); Togaviruses (examples of which include rubella; alphaviruses (such as Western equine encephalitis virus, Eastern equine encephalitis virus, and Venezuelan equine encephalitis virus)); Flaviviruses (examples of which include Dengue virus, West Nile virus, and Japanese encephalitis virus); and Coronaviruses (examples of which include Severe Acute Respiratory Syndrome corona virus (SARS or SARS-CoV), SARS-CoV-2, and Middle East Respiratory Syndrome coronavirus (MERS-CoV)). Examples of negative-strand RNA viruses include, but are not limited to: Orthomyxoviruses (such as influenza virus, including influenza virus Types A and B), Rhabdoviruses (such as Rabies virus), and Paramyxoviruses (examples of which include measles virus, respiratory syncytial virus, and parainfluenza viruses). Examples of bacteria, the replication of which may be inhibited by transbodies of the disclosure, include, but are not limited to, bacteria from the genera Mycobacterium (e.g., Mycobacterium tuberculosis), Legionella (e.g., Legionella Pneumophila), Chlamydia (e.g., Chlamydia trachomatis), Coxiella (e.g., Coxiella burnetiid), Rickettsia (e.g., Rickettsia rickettsia and Rickettsia prowazekii) Salmonella (e.g., Salmonella typhi), and Yersinia (e.g., and Yersinia pestis).

[0049] As previously stated, transbodies of the disclosure comprise a CPM joined to a BM. The CPM and the BM may be joined to one another by any method suitable that allows the transbody to function as intend (i.e., translocate into a cell and bind to a target molecule). In some aspects of the disclosure, the CPM and the BM are joined directly. The phrases "joined directly, "directly joined", and the like, mean that a terminal amino acid or an amino acid side group of the CPM shares a bond with an amino acid or nucleotide of the BM without any intervening nucleotides or amino acid residues. In some aspects, the CPM and the BM are joined by a linker sequence. As used herein, "linker sequence", "linker

molecule", "linker", and the like, refer to an amino acid, or nucleotide, sequence that joins the CPM to the BM, but need not directly function to facilitate translocation of the transbody into the cell or binding of the target molecule. The use of linker sequences is known to those in the art. For example, in the construction of fusion proteins, linker sequences (e.g., linker peptides) are often used to add some distance between different functional portions of the fusion protein. In such instances, it is common, but not necessary, to use short chains of amino acid residue (e.g., from 1-18 residues) having small and/or polar uncharged, or charged, side chains. Examples of such amino acid residues include, but are not limited to, alanine, glycine, and serine. In certain aspects, the linker may be a single amino acid, such as, a serine or a glycine. Additional examples of linkers includes, but are not limited to, a glycine-serine (GS) dipeptide, short glycine polypeptides, short serine polypeptides, short alanine polypeptides, and combinations thereof. In some aspects, the linker sequence may comprise an enzyme recognition site so that once the transbody is within the cell, a cellular enzyme cuts the transbody, thereby separating the CPM from the BM. In some aspects, the linker sequence may be a self-cleaving molecule, such that once the transbody is within the cell, the self-cleaving molecule cuts the link between the CPM and the BM.

[0050] The CPM may be joined to any portion of the BM that allows the transbody to pass through a cell membrane and enter the cell. For example, in aspects where the BM is a polypeptide, the CPM may be joined to the amino-terminal end (N-terminus), the carboxyl terminal end (C-terminus), or to any of the side groups of the amino acids of the CPP. Further, in aspects where the BM is an antibody, the CPM may be joined to the N-terminus, or the C-terminus of a heavy or light chain of the antibody. In some aspects, the CPM may be joined to a side group of an amino acid residue in a heavy or light chain of the antibody.

[0051] In some aspects, the transbody may comprise at least a second CPM. The at least a second CPM may be the same type, or a different type, of CPM. For example, a transbody of the disclosure may comprise more than one CPP, each of which has a different amino acid sequence.

[0052] One aspect of the disclosure is a transbody comprising a first cell-penetrating peptide (CPP) joined to a polypeptide that specifically binds a protein from an intracellular, microorganism. In some aspects, binding of the polypeptide to the protein inhibits replication of the intracellular microorganism. In some aspects, the CPP may be between 6 and 50 amino acids in length. In some aspects, the CPP may be between 6 and

15, 20, 25, 30, 35, or 40 amino acids in length. In some aspects, the CPP may comprise, consist essentially of, or consist of, the amino acid sequence RRRRRRRRR (SEQ ID NO:1), the amino acid sequence CRRRRRRRRC (SEQ ID NO:2), the amino acid sequence GRRRRRRRRKCCKRRRRRRRRRG (SEQ ID NO:3), or variants thereof that catalyze entry of the transbody into a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, an amino acid sequence at least 85%, at least 90%, at least 95%, at least 97%, or at least 99%, identical to SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the CPP catalyzes translocation of the transbody into the interior of a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3. In some aspects, the first CPP is joined to the amino terminal end of the polypeptide. In some aspects, the CPP is joined to the carboxyl-terminal end of the polypeptide. In some aspects, the CPP is joined to the side group of an amino acid residue in the polypeptide. In some aspects, the CPP is joined directly to the polypeptide. In some aspects, the CPP is joined to the polypeptide via a linker, which may be comprise one or more serine and/or glycine residues and which may comprise a glycine-serine dipeptide. In some aspects, the polypeptide may comprise an antibody selected from the group consisting of an scFV, a di-scFV, a scAb and a sdAb. In some aspects, the antibody may comprise a light chain, or at least a portion thereof, which may comprise at least one, two or three CDR_Ls from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one CDR_L selected from the group consisting of CDRL1, CDR_L2 and CDR_L3, wherein CDR_L1, CDR_L2 and CDR_L3 are from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the antibody may comprise a heavy chain, or at least a portion thereof, which may comprise at least one, two, or three CDR_Hs from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise at least one CDR_H selected from the group consisting of CDR_H1, CDR_H2 and CDR_H3, wherein CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some

aspects, the heavy chain, or the at least a portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain may comprise the heavy chain of an antibody that binds to a protein from an intracellular, microorganism. In some aspects, the antibody may comprise a light chain, or a portion thereof, comprising at least one CDR_L selected from the group consisting of CDR_L1, CDR_L2 and CDR_L3, wherein CDR_L1, CDR_L2 and CDR_L3 are from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism, and a heavy chain, or a portion thereof, comprising at least one CDR_H selected from the group consisting of CDR_H1, CDR_H2 and CDR_H3, wherein CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the immunoglobulin that binds to a protein from an intracellular, microorganism, may comprise a H16-L10 mAb produced by the H16L10-4R5 hybridoma. In some aspects, CDR_L1, CDR_L2 and CDR_L3 may be from the light chain of the H16-L10 mAb. In some aspects, CDR_H1, CDR_H2 and CDR_H3 may be from the heavy chain of the H16-L10 mAb. In some aspects, the antibody may comprise a CDR_L3, comprising or consisting of SEQ ID NO:6 and a CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, CDR_L1 may comprise, or consist of, SEQ ID NO:4. In some aspects, CDR_L2 may comprise, or consist of, SEQ ID NO:5. In some aspects, CDR_L3 may comprise, or consist of, SEQ ID NO:6. In some aspects, the light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, the light chain may comprise, or consist of, SEQ ID NO:7. In some aspects, CDR_H1 may comprise, or consist of, SEQ ID NO:8. In some aspects, CDR_H2 may comprise, or consist of, SEQ ID NO:9. In some aspects, CDR_H3 may comprise, or consist of, SEQ ID NO:10. In some aspects, the heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein the heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the heavy chain may comprise, or consist of, SEQ ID NO:11 or 12. In some aspects, the intracellular microorganism may be a virus,

which may be as described above, or in some preferred aspects, an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, or a coronavirus. In some aspects, the intracellular microorganism may be a bacterium, which may be Mycobacterium, Legionella, Chlamydia, Coxiella, Rickettsia, Salmonella or Yersinia. In some aspects, the protein from the intracellular organism may be a structural protein. In some aspects, the intracellular organism is influenza virus, and the protein from the intracellular organism is an influenza virus nonstructural protein. In some aspects, the protein from the intracellular organism may be the influenza virus NP protein.

[0053] One aspect of the disclosure is a transbody comprising a first cell-penetrating peptide (CPP) joined to an antibody that specifically binds a protein from an intracellular, microorganism. In some aspects, binding the antibody to the protein inhibits replication of the intracellular microorganism. In some aspects, the first CPP may be between 6 and 50 amino acids in length. In some aspects, the first CPP may be between 6 and 15, 20, 25, 30, 35, or 40 amino acids in length. In some aspects, the first CPP may comprise, consist essentially of, or consist of, the amino acid sequence RRRRRRRRR (SEQ ID NO:1), the amino acid sequence CRRRRRRRRC (SEQ ID NO:2), the amino acid sequence GRRRRRRRRKCCKRRRRRRRRRG (SEQ ID NO:3), or variants thereof that catalyze entry of the transbody into a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, an amino acid sequence at least 85%, at least 90%, at least 95%, at least 97%, or at least 99%, identical to SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the CPP catalyzes translocation of the transbody into the interior of a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3. In some aspects the antibody may comprise at least 1 light chain, or at least a portion thereof, and 1 heavy chain, or at least a portion thereof. In some aspects, the antibody may comprise 2 light chains, or at least portions thereof, and 2 heavy chains, or at least portions thereof. In some aspects, the first CPP may be joined to the amino terminal end of a light chain, or at least a portion thereof, or a heavy chain, or at least a portion thereof, of the antibody. In some aspects, the first CPP may be joined to the carboxyl-terminal end of a light chain, or at least a portion thereof, or a heavy chain, or at least a portion thereof, of the antibody. In some aspects, the first CPP may be joined to the side group of an amino acid residue in a light chain, or at least a portion thereof, or a heavy chain, or at least a portion thereof, of the antibody. In some aspects, the first CPP may be joined directly to a light chain, or at least a portion thereof, or a heavy chain, or at least a portion thereof, of the

antibody. In some aspects, the first CPP may be joined to the antibody via a linker, which may comprise one or more serine and/or glycine residues and which may comprise a glycine-serine dipeptide. In some aspects, the antibody may comprise a heavy chain, or at least a portion thereof, which may comprise at least one, two, or three CDR_Hs from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise at least one CDR_H selected from the group consisting of CDR_H1, CDR_H2 and CDR_H3, wherein CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain may comprise the heavy chain of an antibody that binds to a protein from an intracellular, microorganism. In some aspects, the antibody may comprise a nanobody. In some aspects, the antibody may comprise a light chain, or at least a portion thereof, which may comprise at least one, two or three CDR_Ls from an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one CDR_L selected from the group consisting of CDRL1, CDR_L2 and CDR_L3, wherein CDR_L1, CDR_L2 and CDR_L3 are from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the antibody may comprise a whole antibody. In some aspects, the antibody may comprise an immunoglobulin light chain, or at least a portion thereof; and, an immunoglobulin heavy chain, or at least a portion thereof, wherein the light chain, or the least a portion thereof, comprises at least one, two or three light chain CDRs (CDR_Ls) from an immunoglobulin known to specifically bind a protein from an intracellular, microorganism, and wherein the heavy chain, or the at least a portion thereof, comprises at least at least one, two, or three heavy chain CDRs (CDR_Hs) from the immunoglobulin that binds to the protein from the intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one of CDR_L1, CDR_L2 or CDR_L3 from the light chain of the immunoglobulin that binds a protein from an intracellular,

microorganism, and the heavy chain, or the at least a portion thereof, may comprise at least one of CDR_H1, CDR_H2 or CDR_H3 from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism, and the heavy chain, or at least a portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism and the heavy chain may comprise the heavy chain of an antibody that binds to a protein from an intracellular, microorganism. In some aspects, the immunoglobulin that binds to a protein from an intracellular, microorganism, may be monoclonal antibody (mAb) H16-L10 produced by the H16L10-4R5 hybridoma (ATCC HB65). In some aspects, CDR_L1, CDR_L2 and CDR_L3 may be from the light chain of the H16-L10 mAb. In some aspects, CDR_H1, CDR_H2 and CDR_H3 may be from the heavy chain of the H16-L10 mAb. In some aspects, CDR_L1 may comprise, or consist of, SEQ ID NO:4. In some aspects, CDR_L2 may comprise, or consist of, SEQ ID NO:5. In some aspects, CDR_L3 may comprise, or consist of, SEQ ID NO:6. In some aspects, the antibody may comprise a CDR_L3, comprising or consisting of SEQ ID NO:6 and a CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, the light chain may comprise, or consist of, SEQ ID NO:7. In some aspects, CDR_H1 may comprise, or consist of, SEQ ID NO:8. In some aspects, CDR_H2 may comprise, or consist of, SEQ ID NO:9. In some aspects, CDR_H3 may comprise, or consist of, SEQ ID NO:10. In some aspects, the heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein the heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the heavy chain may comprise, or consist of, SEQ ID NO:11 or 12. In some aspects, the antibody may comprise mAb H16-L10. In some aspects, the intracellular microorganism may be a virus, as

described above, or in some preferred aspects, may be an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, or a coronavirus. In some aspects, the intracellular microorganism may be a bacterium, which may be Mycobacterium, Legionella, Chlamydia, Coxiella, Rickettsia, Salmonella or Yersinia. In some aspects, the protein from the intracellular organism may be a structural protein. In some aspects, the protein from the intracellular organism may be a structural protein. In some aspects, the intracellular organism is influenza virus, and the protein from the intracellular organism is an influenza virus nonstructural protein. In some aspects, the protein from the intracellular organism may be the influenza virus NP protein.

[0054] One aspect of the disclosure is a transbody comprising a cell-penetrating peptide (CPP) joined to a whole antibody that specifically binds an influenza protein. In some aspects, binding of the whole antibody to the protein inhibits replication of the intracellular microorganism. In some aspects, the first CPP may be between 6 and 50 amino acids in length. In some aspects, the first CPP may be between 6 and 15, 20, 25, 30, 35, or 40 amino acids in length. In some aspects, the first CPP may comprise, consist essentially of, or consist of, the amino acid sequence RRRRRRRRR (SEQ ID NO:1) the amino acid sequence CRRRRRRRRC (SEQ ID NO:2), the amino acid sequence GRRRRRRRRKCCKRRRRRRRRG (SEQ ID NO:3), or variants thereof that catalyze entry of the transbody into a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, an amino acid sequence at least 85%, at least 90%, at least 95%, at least 97%, or at least 99%, identical to SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the CPP catalyzes translocation of the transbody into the interior of a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3. In some aspects, the CPP is joined to the carboxyl-terminal end of a light chain of the whole antibody. In some aspects, the CPP is joined to the carboxyl-terminal end of a heavy chain of the whole antibody. In some aspects, the CPP may be joined to the antibody via a linker. In some aspects, the linker comprises a glycine-serine dipeptide. In some aspects, the whole antibody may comprise:

[0055] i) an immunoglobulin light chain, or at least a portion thereof; and;

[0056] ii) an immunoglobulin heavy chain, or at least a portion thereof,

[0057] wherein the immunoglobulin light chain, or portion thereof, comprises at least one CDR_L from the light chain of mAb H16-L10; and,

[0058] wherein the immunoglobulin heavy chain, or portion thereof, comprises at least one CDR_H from the heavy chain of mAb H16L0.

[0059] In some aspects, the immunoglobulin light chain, or portion thereof, comprises at least two CDR_Ls from the light chain of mAb H16-L10. In some aspects, the immunoglobulin light chain, or portion thereof, comprises CDR_L1, CDR_L2, and CDR_L3 from mAb H216-L10. In some aspects, the immunoglobulin heavy chain, or portion thereof, comprises at least two CDR_Hs from the heavy chain of mAb H16-L10. In some aspects, the immunoglobulin heavy chain, or portion thereof, comprises CDR_H1, CDR_H2, and CDR_H3 from mAb H216-L10.

[0060] In one aspect, the whole antibody may comprise:

[0061] an immunoglobulin light chain, or at least a portion thereof; and,

[0062] b) an immunoglobulin heavy chain, or at least a portion thereof;

[0063] wherein the immunoglobulin light chain, or portion thereof, comprises at least one CDR_L selected from the group consisting of CDR_L1 consisting of SEQ ID NO:4, CDR_L2 consisting of SEQ ID NO:5, and CDR_L3 consisting of SEQ ID NO:6; and,

[0064] wherein the immunoglobulin heavy chain, or portion thereof, comprises at least one CDR_H selected from the group consisting of CDR_H1 consisting of SEQ ID NO:8, CDR_H2 consisting of SEQ ID NO:9, and CDR_H3 consisting of SEQ ID NO:10. In some aspects, the immunoglobulin light chain may comprise at least two CDRs selected from the group consisting of CDR_L1 consisting of SEQ ID NO:4, CDR_L2 consisting of SEQ ID NO:5, and CDR_L3 consisting of SEQ ID NO:6. In some aspects, the immunoglobulin light chain, or portion thereof, may comprise CDR_L1 consisting of SEQ ID NO:4, CDR_L2 consisting of SEQ ID NO:5, and CDR_L3 consisting of SEQ ID NO:6. In some aspects, the immunoglobulin heavy chain may comprise at least two CDRs selected from the group consisting of CDR_H1 consisting of SEQ ID NO:8, CDR_H2 consisting of SEQ ID NO:9, and CDR_H3 consisting of SEQ ID NO:10. In some aspects, the immunoglobulin heavy chain may comprise CDR_H1 consisting of SEQ ID NO:8, CDR_H2 consisting of SEQ ID NO:9, and CDR_H3 consisting of SEQ ID NO:10. In some aspects, the whole antibody may comprise mAb H16-L10. In some aspects, the influenza protein is a nonstructural protein. In some aspects, the influenza protein is the influenza virus NP protein.

[0065] One aspect of the disclosure is a transbody comprising a CPP comprising, or consisting of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, joined to a whole antibody comprising two heavy chains and two light chains, wherein each light chain

comprises CDR_L1 consisting of SEQ ID NO:4, CDR_L2 consisting of SEQ ID NO:5, and CDR_L3 consisting of SEQ ID NO:6, wherein each heavy chain comprises CDR_H1 consisting of SEQ ID NO:8, CDR_H2 consisting of SEQ ID NO:9, and CDR_H3 consisting of SEQ ID NO:10, and wherein the CPP is joined to the carboxyl terminal end of one of the heavy chains. In some aspects, each light chain comprises an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, each light chain comprises SEQ ID NO:7. In some aspects, each heavy chain comprises SEQ ID NO:9. In some aspects, the CPP is joined to the carboxyl terminal end of the heavy chains by a linker. In some aspects, the linker is a glycine-serine dipeptide. In some aspects, the whole antibody may comprise mAb H16-L10.

[0066] In some aspects, the transbody may comprise an amino acid sequence at least 85%, at least 95%, at least 95%, at least 97%, at least 99%, identical to SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15, wherein the transbody inhibits replication of an influenza virus. In some aspects, the transbody is capable oof translocating into a cell and inhibiting replication of an influenza virus. In some aspects, the transbody may comprise SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15,

[0067] One aspect of the disclosure is a therapeutic composition comprising a transbody of the disclosure. In some aspects, the therapeutic composition may comprise a pharmaceutically acceptable carrier, excipient, or stabilizer. Transbodies used in methods of the disclosure may be formulated in a therapeutic composition comprising a carrier. "Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. A "pharmaceutically acceptable carrier" is an excipient that does not interfere with the effectiveness of the biological activity of a transbody of the disclosure. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids, Hanks' solution, Ringer's solution, or physiological saline buffer; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine,

arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®. Additional agents, such as flavoring, coloring, sweetening, and/or thickening agents, may be added to compositions of the disclosure.

[0068] One aspect of the disclosure is a method for inhibiting replication of an intracellular microorganism, the method comprising contacting a cell infected with the intracellular microorganism with a transbody of the disclosure. In some aspects, the transbody comprises a first cell-penetrating peptide (CPP) joined to a polypeptide that specifically binds a protein from an intracellular, microorganism. In some aspects, binding the polypeptide to the protein inhibits replication of the intracellular microorganism. In some aspects, the first CPP is joined to the amino terminal end of the polypeptide. In some aspects, the CPP is joined to the carboxyl-terminal end of the polypeptide. In some aspects, the CPP is joined to the side group of an amino acid residue in the polypeptide. In some aspects, the CPP is joined directly to the polypeptide. In some aspects, the CPP is joined to the polypeptide via a linker, which may be comprise one or more serine and/or glycine residues and which may comprise a glycine-serine dipeptide. In some aspects, the polypeptide may comprise an antibody that specifically binds to the protein from the intracellular, microorganism. In some aspects, binding the antibody to the protein inhibits replication of the intracellular microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one of CDR_L1, CDR_L2 or CDR_L3, or may comprise CDR_L1, CDR_L2 and CDR_L3, from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise at least one of CDR_H1, CDR_H2 or CDR_H3, or may comprise CDR_H1, CDR_H2 and CDR_H3, from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain may comprise the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the antibody may comprise mAb H16-L10. In some aspects, the antibody may comprise a CDR_L3, comprising or consisting of SEQ ID NO:6 and a CDR_H3 comprising, or consisting of, SEQ ID NO:10.

[0069] In some aspects, the transbody comprises a first CPP joined to a whole antibody that specifically binds a protein from an intracellular, microorganism. In some aspects, binding the whole antibody to the protein inhibits replication of the intracellular microorganism. In some aspects the whole antibody may comprise at least 1 light chain and 1 heavy chain. In some aspects, the whole antibody may comprise 2 light chains and 2 heavy chains. In some aspects, first CPP may be joined to the amino terminal end or the carboxyl terminal end of a light chain or a heavy chain of the antibody. In some aspects, the first CPP may be joined to the side group of an amino acid residue in a light chain or a heavy chain of the antibody. The first CPP may be joined directly to a light chain or a heavy chain of the antibody, or it may be joined via a linker, which may comprise one or more serine and/or glycine residues and which may comprise a glycine-serine dipeptide. In some aspects, the whole antibody may comprise an immunoglobulin light chain, or at least a portion thereof; and, an immunoglobulin heavy chain, or at least a portion thereof, wherein the light chain comprises at least one, two or three light chain CDRs (CDR_LS) from an immunoglobulin known to specifically bind a protein from an intracellular, microorganism, and wherein the heavy chain comprises at least at least one, two, or three heavy chain CDRs (CDR_HS) from the immunoglobulin that binds to the protein from the intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one of CDR_L1, CDR_L2 or CDR_L3, or may comprise from the light chain of the immunoglobulin that binds a protein from an intracellular, microorganism, and the heavy chain, or the at least a portion thereof, may comprise at least one of CDR_H1, CDR_H2 or CDR_H3 from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism, and the heavy chain, or at least a portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism and the heavy chain may comprise the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the immunoglobulin that binds to a protein from an intracellular, microorganism, may be the H16-L10 mAb produced by the H16L10-4R5 hybridoma. In some aspects, CDR_L1, CDR_L2 and CDR_L3 are from the light chain of the

H16-L10 mAb. In some aspects, CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of the H16-L10 mAb. In some aspects, CDR_L1 may comprise, or consist of, SEQ ID NO:4. In some aspects, CDR_L2 may comprise, or consist of, SEQ ID NO:5. In some aspects, CDR_L3 may comprise, or consist of, SEQ ID NO:6. In some aspects, the light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, the light chain may comprise, or consist of, SEQ ID NO:7. In some aspects, CDR_H1 may comprise, or consist of, SEQ ID NO:8. In some aspects, CDR_H2 may comprise, or consist of, SEQ ID NO:9. In some aspects, CDR_H3 may comprise, or consist of, SEQ ID NO:10. In some aspects, the heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein the heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the heavy chain may comprise, or consist of, SEQ ID NO:11 or 12. In some aspects, the whole antibody may comprise mAb H16-L10. In some aspects, the CPP may be between 6 and 50 amino acids in length. In some aspects, the CPP may be between 6 and 15, 20, 25, 30, 35, or 40 amino acids in length. In some aspects, the CPP may comprise, consist essentially of, or consist of, the amino acid sequence RRRRRRRRR (SEQ ID NO:1), the amino acid sequence CRRRRRRRRC (SEQ ID NO:2), the amino acid sequence GRRRRRRRRKCCKRRRRRRRRG (SEQ ID NO:3), , or variants thereof that catalyze entry of the transbody into a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, an amino acid sequence at least 85%, at least 90%, at least 95%, at least 97%, or at least 99%, identical to SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the CPP catalyzes translocation of the transbody into the interior of a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3. In some aspects, the intracellular microorganism may be a virus, as described above, or in some preferred aspects in which the intracellular microorganism may be an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, or a coronavirus. In some aspects, the intracellular microorganism may be a bacterium, which may be Mycobacterium, Legionella, Chlamydia, Coxiella, Rickettsia,

Salmonella or Yersinia. In some aspects, the protein from the intracellular organism may be a structural protein. In some aspects, the intracellular organism is influenza virus, and the protein is a nonstructural protein. In some aspects, the protein is the influenza virus NP protein. In some aspects, the transbody may comprise an amino acid sequence at least 85%, at least 95%, at least 95%, at least 97%, at least 99%, identical to SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15, wherein the transbody inhibits replication of an influenza virus. In some aspects, the transbody is capable oof translocating into a cell and inhibiting replication of an influenza virus. In some aspects, the transbody may comprise SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15,

[0070] One aspect of the disclosure is a method of treating an individual for an infection by an intracellular microorganism, comprising administering to the individual a therapeutically effective amount of a transbody, or a therapeutic composition comprising a transbody, of the disclosure. The terms "individual", "subject", and "patient" are well-recognized in the art and are herein used interchangeably to refer to any animal susceptible to developing NAFLD and related conditions. Examples include, but are not limited to, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, seals, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The terms individual, subject, and patient by themselves, do not denote a particular age, sex, race, and the like. Thus, individuals of any age, whether male or female, are intended to be covered by the present disclosure and include, but are not limited to the elderly, adults, children, babies, infants, and toddlers.

[0071] As used herein, a therapeutically effective amount of a transbody disclosed herein means an amount, that when administered to an individual is sufficient to treat the individual for an infection by an intracellular, microorganism. Treating, treatment of, and the like, for infection by an intracellular, microorganism mean reducing the infectious load of the microorganism by at least 25%, at least 50%, at least 75%, at least 95%, reducing the incidence, severity, and/or duration of clinical signs of infection in a subject caused by the intracellular microorganism by at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 100% in comparison to a subject or individual that has not received the transbody disclosed herein.

In some forms, Treating, treatment of, and the like also refers to eliminating the intracellular microorganism from an individual.

[0072] The dose administered to an individual in a method of the disclosure may be any dose suitable for treating, preventing, inhibiting, and/or reducing infection by an intracellular microorganism. In conjunction with the present disclosure, those skilled in the art are capable of identifying a dose appropriate for the chosen formulation and method of delivery.

[0073] Transbodies, and compositions comprising transbodies, of the disclosure may be administered by any route suitable for the subject being treated. Such routes of administration include, but are not limited to, injection, including intravenous, intraperitoneal, intramuscular, and subcutaneous injection, oral administration, transmucosal administration, transdermal administration, topical administration, nasal administration, or ocular administration. The preferred method of administration can vary depending on various factors (e.g., the nature of the intracellular microorganism, the severity of the condition being treated, etc.).

[0074] A method of treating an individual for an infection by an intracellular microorganism may use any transbody of the disclosure, as long as the transbody comprises a BM that binds a protein from the intracellular microorganism. In some aspects, the transbody comprises a first cell-penetrating peptide (CPP) joined to a polypeptide that specifically binds a protein from an intracellular, microorganism. In some aspects, binding the polypeptide to the protein inhibits replication of the intracellular microorganism. In some aspects, the first CPP is joined to the amino terminal end of the polypeptide. In some aspects, the CPP is joined to the carboxyl-terminal end of the polypeptide. In some aspects, the CPP is joined to the side group of an amino acid residue in the polypeptide. In some aspects, the CPP is joined directly to the polypeptide. In some aspects, the CPP is joined to the polypeptide via a linker, which may be comprise one or more serine and/or glycine residues and which may comprise a glycine-serine dipeptide. In some aspects, the polypeptide may comprise an antibody that specifically binds to the protein from the intracellular, microorganism. In some aspects, binding the antibody to the protein inhibits replication of the intracellular microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one of CDR_L1, CDR_L2 or CDR_L3, or may comprise CDR_L1, CDR_L2 and CDR_L3, from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may

comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain, or the at least a portion thereof, may comprise at least one of CDR_H1, CDR_H2 or CDR_H3, or may comprise CDR_H1, CDR_H2 and CDR_H3, from the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the heavy chain may comprise the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the antibody may comprise a CDR_L3, comprising or consisting of SEQ ID NO:6 and a CDR_H3 comprising, or consisting of, SEQ ID NO:10.In some aspects, the antibody may comprise mAb H16-L10. In some aspects, the transbody comprises a first CPP joined to a whole antibody that specifically binds a protein from an intracellular, microorganism. In some aspects, binding the whole antibody to the protein inhibits replication of the intracellular microorganism. In some aspects the whole antibody may comprise at least 1 light chain and 1 heavy chain. In some aspects, the whole antibody may comprise 2 light chains and 2 heavy chains. In some aspects, first CPP may be joined to the amino terminal end or the carboxyl terminal end of a light chain or a heavy chain of the antibody. In some aspects, the first CPP may be joined to the side group of an amino acid residue in a light chain or a heavy chain of the antibody. The first CPP may be joined directly to a light chain or a heavy chain of the antibody, or it may be joined via a linker, which may comprise one or more serine and/or glycine residues and which may comprise a glycine-serine dipeptide. In some aspects, the whole antibody may comprise an immunoglobulin light chain, or at least a portion thereof; and, an immunoglobulin heavy chain, or at least a portion thereof, wherein the light chain comprises at least one, two or three light chain CDRs (CDR_LS) from an immunoglobulin known to specifically bind a protein from an intracellular, microorganism, and wherein the heavy chain comprises at least at least one, two, or three heavy chain CDRs (CDR_HS) from the immunoglobulin that binds to the protein from the intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise at least one of CDR_L1, CDR_L2 or CDR_L3, or may comprise from the light chain of the immunoglobulin that binds a protein from an intracellular, microorganism, and the heavy chain, or the at least a portion thereof, may comprise at least one of CDR_H1, CDR_H2 or CDR_H3 from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain, or the at least a portion thereof, may comprise CDR_L1, CDR_L2 and CDR_L3 from the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism, and the heavy

chain, or at least a portion thereof, may comprise CDR_H1, CDR_H2 and CDR_H3 from the heavy chain of the immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the light chain may comprise the light chain of an immunoglobulin that binds to a protein from an intracellular, microorganism and the heavy chain may comprise the heavy chain of an immunoglobulin that binds to a protein from an intracellular, microorganism. In some aspects, the immunoglobulin that binds to a protein from an intracellular, microorganism, may be the H16-L10 mAb produced by the H16L10-4R5 hybridoma. In some aspects, CDR_L1, CDR_L2 and CDR_L3 are from the light chain of the H16-L10 mAb. In some aspects, CDR_H1, CDR_H2 and CDR_H3 are from the heavy chain of the H16-L10 mAb. In some aspects, CDR_L1 may comprise, or consist of, SEQ ID NO:4. In some aspects, CDR_L2 may comprise, or consist of, SEQ ID NO:5. In some aspects, CDR_L3 may comprise, or consist of, SEQ ID NO:6. In some aspects, the light chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:7, wherein the light chain comprises CDR_L1 comprising, or consisting of, SEQ ID NO:4, CDR_L2 comprising, or consisting of, SEQ ID NO:5, and/or CDR_L3 comprising, or consisting of, SEQ ID NO:6. In some aspects, the light chain may comprise, or consist of, SEQ ID NO:7. In some aspects, CDR_H1 may comprise, or consist of, SEQ ID NO:8. In some aspects, CDR_H2 may comprise, or consist of, SEQ ID NO:9. In some aspects, CDR_H3 may comprise, or consist of, SEQ ID NO:10. In some aspects, the heavy chain may comprise an amino acid sequence at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical or at least 97% identical to SEQ ID NO:11 or 12, wherein the heavy chain comprises CDR_H1 comprising, or consisting of, SEQ ID NO:8, CDR_H2 comprising, or consisting of, SEQ ID NO:9, and CDR_H3 comprising, or consisting of, SEQ ID NO:10. In some aspects, the heavy chain may comprise, or consist of, SEQ ID NO:11 or 12. In some aspects, the antibody may comprise In some aspects, the whole antibody may comprise mAb H16-L10. In some aspects, the CPP may be between 6 and 50 amino acids in length. In some aspects, the CPP may be between 6 and 15, 20, 25, 30, 35, or 40 amino acids in length. In some aspects, the CPP may comprise, consist essentially of, or consist of, the amino acid sequence RRRRRRRRR (SEQ ID NO:1), the amino acid sequence CRRRRRRRRC (SEQ ID NO:2), the amino acid sequence GRRRRRRRRKCCKRRRRRRRRRG (SEQ ID NO:3), or variants thereof that catalyze entry of the transbody into a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, an amino acid sequence at least 85%, at least 90%, at least 95%, at least 97%,

or at least 99%, identical to SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the CPP catalyzes translocation of the transbody into the interior of a cell. In some aspects, the CPP may comprise, consist essentially of, or consist of, SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3. In some aspects, the intracellular microorganism may be a virus as described above. In some aspects, the intracellular microorganism may be an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, or a coronavirus. In some aspects, the intracellular microorganism may be a bacterium, which may be Mycobacterium, Legionella, Chlamydia, Coxiella, Rickettsia, Salmonella or Yersinia. In some aspects, the protein from the intracellular organism may be a structural protein. In some aspects, the intracellular organism is influenza virus, and the protein from the intracellular organism is an influenza virus nonstructural protein. In some aspects, the protein from the intracellular organism may be the influenza virus NP protein. In some aspects, the transbody may comprise an amino acid sequence at least 85%, at least 95%, at least 95%, at least 97%, at least 99%, identical to SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15, wherein the transbody inhibits replication of an influenza virus. In some aspects, the transbody is capable oof translocating into a cell and inhibiting replication of an influenza virus. In some aspects, the transbody may comprise SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15.

[0075] One aspect of the disclosure is a kit comprising a transbody of the disclosure or a therapeutic composition of the disclosure. In some aspects, the kit may comprise associated components, such as, but not limited to, buffers, labels, containers, inserts, tubing, vials, syringes, instructions for use, and the like.

[0076] This written description uses examples to disclose the disclosure, including the best mode, and to enable any person skilled in the art to practice the disclosure, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the disclosure is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have structural elements that do not differ from the literal language of the claims, or if they include equivalent structural elements with insubstantial differences from the literal languages of the claims.

[0077] EXAMPLES

[0078] Example 1. Production of a cell penetrating antibody

[0079] To produce an anti-influenza virus transbody, the variable heavy (VH) and light (VL) chains of the influenza virus NP-specific Ab produced by H16-L10 hybridoma (Yewdell et al., 1981), were cloned and expressed using the Expi293™ cell line (Thermo Fisher). In one instance, the wild-type chain was expressed. In a second instance, a polypeptide consisting of GSRRRRRRRRR was joined to the carboxy-terminus of one of the heavy chains using a glycine-serine linker. These mAbs are termed H16-L10Hu and H16-L10HuCPP, respectively. The details of the joining region of H16-L10HuCPP are shown in FIG. 1.

[0080] Example 2. Effect of CPP on antibody affinity

[0081] To determine whether the presence of a CPP affected binding of the antibody to influenza NP, the binding of H16-L10Hu and H16-L10HuCPP for NP from different influenza strains was tested. Whole virus, which was coated on ELISA plates, was used as the source of antigen in these experiments. H16-L10Hu and H16-L10HuCPP were also tested for their abilities to bind influenza B and parainfluenza virus (Sendai virus) proteins. The results, which are shown in FIG. 2, show that fusion of the CPP to H16-L10Hu, to produce H16-L10HuCPP, does not alter the binding of H16-L10Hu to influenza NP.

[0082] Example 3. Internalization of H16-L10HuCPP

[0083] This example demonstrates the ability of H16-L10HuCPP to enter cells. H16-L10Hu and H16-L10HuCPP were each conjugated to Cy5 dye to allow easy detection of the location of each antibody. Cultured MDCK SIAT1 cells were then incubated with 1 uM of each antibody for 24 hours at 37°C, after which the supernatant was removed, and the cells rinsed and fixed. The cells were then imaged using confocal microscopy. The results showed massive accumulation of the CP mAb in cytoplasmic vesicles, likely a site of Ab entry into the cytosol (FIG. 3, right panel). By contrast, little if any non-CP mAb was retained intracellularly (FIG. 3, left panel).

[0084] Example 4. Anti-viral activity of H16-L10HuCPP transbody

[0085] MDCK SIAT1 cells were incubated overnight at 37°C with either H16-L10Hu or H16-L10HuCPP, after which the cells were washed and then incubation overnight at 37 C with one of three different influenza A viruses: A/Puerto Rico/8/ 1934 (H1N1), A/California/07/2016 (H1N1), or A/North Carolina/13/2014 (H3N2). Following incubation, the supernatant was removed, and the cells washed and harvested. The harvested cells were then analyzed for influenza virus using flow cytometry. The fraction of infected cells was measured by flow cytometry, normalizing data by the fraction of cells to infected

cells. As shown in FIG. 4, non-CPP Ab (H16-L10Hu; a-NP-wt) did not exhibit measurable neutralization even at the highest concentration, while the CPP-containing Ab (H16-L10HuCPP; a-NP-CP) inhibited infection in a dose-dependent manner of all viruses tested.

[0086] The amount of neuraminidase in the supernatant of the infected cells from each group was then determined as a proxy for the relative amount of virus in the supernatant. As shown in FIG. 5 cells treated with H16-L10HuCPP (a-NP-CP) produced less virus than did cells treated with H16-L10Hu (a-NP-wt).

[0087] Example 5. H16-L10HuCPP confers prophylactic protection *in vivo*

[0088] This Example demonstrates the ability of the H16-L10HuCPP transbody to provide prophylactic protection from infection with influenza virus.

[0089] Mice (n=9-12) were treated intranasally with H16-L10Hu (a-NP-wt) or H16-L10HuCPP (a-NP-CP) mAb, an irrelevant anti-SARS1-NP-CP Ab, or PBS. Five hours later, the mice were intranasally infected with a lethal dose of an influenza A virus. The condition and body weight of each mouse was followed for 14 days. As shown in FIG. 6B, mice receiving H16-L10HuCPP (a-NP-CP) lost a significant amount of body weight, but 80% then recovered as determined by body mass. Mice receiving H16-L10Hu (a-NP-wt), the irrelevant mAB, or PBS, lost a significant amount of weight but did not recover. In fact, as shown in FIG. 6C, all mice in the PBS, irrelevant Ab or non-CP Ab groups succumbed to infection by day 8 post-infection. 80% of mice treated with H16-L10HuCPP recovered from infection as determined by body mass.

[0090] To measure therapeutic protection, mice were administered a lethal dose of an influenza A virus. 18 hours post-infection, each mouse was then given an IN administration of either H16-L10Hu, H16-L10HuCPP, an irrelevant anti-SARS1-NP-CP Ab, or PBS. The results, which are shown in FIG. 7, show that post-infection administration H16-L10HuCPP reduced mortality by 50%.

[0091] Example 6. H16-L10HuCPP confers therapeutic protection *in vivo*

[0092] This Example demonstrates the ability of the H16-L10HuCPP transbody to provide therapeutic protection from infection with influenza virus.

[0093] Mice were intranasally infected with a lethal dose of an influenza A virus. Eighteen hours later, each mouse was treated intranasally with H16-L10Hu (a-NP-wt) or H16-L10HuCPP (a-NP-CP) mAb, or PBS, and the condition and body weight of each mouse followed for 14 days. As shown in FIG. 7B, mice receiving H16-L10Hu (a-NP-wt) or H16-L10HuCPP (a-NP-CP) lost a significant amount of body weight. However, mice

receiving H16-L10HuCPP (a-NP-CP) recovered as determined by body mass. In contrast, mice receiving H16-L10Hu (a-NP-wt), or PBS, succumbed to infection by day 9 post-infection (FIG.7C). The results demonstrate that giving the H16-L10HuCPP transbody reduced mortality by 50%.

[0094] Example 7. Mechanism of protection

[0095] To dissect potential mechanisms of H16-L10HuCPP's ability to protect against infection, immunofluorescence analysis of infected and treated cells was conducted. Cells were infected with influenza A virus, and then treated with either H16-L10Hu (a-NP-wt) or H16-L10HuCPP (a-NP-CP), each of which had been conjugated to CyS5 fluorophore. Biosynthesized NP was localized in cells using rabbit NP-carboxy terminal-specific polyclonal sera combined with a-rabbit-488 secondary Ab. The results, which are shown in FIG. 8, revealed that treatment of cells with H16-L10HuCPP (a-NP-CP) reduced NP levels in the nucleus and cytoplasm (compare wt NP panel (top) with CP NO panel (bottom). Further, the small amounts of cytoplasmic NP detected colocalized with the CP Ab (Figure 8, bottom panel under "merge").

[0096] To quantify these observations, MDCK SIAT1 cells were incubated with influenza virus and either H16-L10HuCPP or H16-L10HuCPP, after which the cells were harvested, and the level of influenza NP protein quantitated by Western blow analysis. The results, which are shown in FIGS. 9 A & B, confirmed that treatment of cells with H16-L10HuCPP (a-NP-CP) reduce the total cellular amount of NP by 50%.

[0097] Example 8. Production of alternative transbodies

[0098] Additional anti-influenza virus transbodies were produced as described in Example 1, except that instead of using a CPP consisting of RRRRRRRRR, the -terminus of one of the H16-L10 heavy chains was joined to a CPP consisting of CRRRRRRRRC or GRRRRRRRRKCCKRRRRRRRRG using a glycine-serine linker. These mAbs were termed H16-L10-cycCP and H16-L10-BiArmCP, respectively.

[0099] Example 9. Internalization of H16-L10-cycCP and H16-L10-BiArmCP

[0100] The ability of H16-L10-cycCP and H16-L10-BiArmCP to translocate into cells was tested using A549 cells. Briefly, cells were treated for 16h with 500nM of either H16-L10, H16-L10-CP, H16-L10-cycCP, or H16-L10-BiArmCP indicated. Following incubation, the cells were washed extensively and fixed-permeabilized using a formaldehyde-saponin solution for 30 minutes. After the washing step, cells were incubated

for 30 minutes with the secondary goat anti-human IgG-AF488 and rewashed. Internalization of H16-L10 was analyzed using BD-celesta flow cytometer and FlowJo software. The results, which are shown in FIGS.10A-10E, showed that internalization of H16-L10-cycCP and H16-L10-BiArmCP was enhanced relative toH16-L10HuCP. The H16-L10-BiArm-CP enhanced uptake roughly 100-fold compared to H16-L10-CP.

[0101] The results demonstrate that joining a CPP to a whole antibody allows the antibody to access the cytoplasm where it can bind to intracellular influenza virus proteins. Moreover, the results demonstrate that the internalized antibodies (transbodies) exert anti-viral activity and may be used both prophylactically and therapeutically to protect an individual from infection by influenza virus.

WHAT IS CLAIMED IS:

1. A transbody comprising a cell penetrating peptide (CPP) joined to a binding moiety (BM), wherein the binding moiety specifically binds a protein from an intracellular microorganism.

2. The transbody of claim 1, wherein binding of the BM to the protein inhibits replication of the intracellular microorganism.

3. The transbody of claim 1 or 2, wherein the intracellular microorganism is a virus selected from the group consisting of an influenza virus, a rabies virus, a picornavirus, a rhinovirus, a hepatitis virus, an alphavirus, flavivirus, and a coronavirus.

4. The transbody of any one of claims 1-3, wherein the CPP comprises an amino acid sequence at last 85%, at least 90%, or at least 95%, or 100%, identical to a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3.

5. The transbody of any one of claims 1-4, wherein the BM comprises an antibody.

6. The transbody of claim 5, wherein the antibody comprises a CDR_L3 that comprises, or consists of, SEQ ID NO:6, or a CDR_H3 that comprises, or consists of, SEQ ID NO:8.

7. The transbody of claim 5 or 6, wherein the antibody comprises a light chain comprising a CDR_L1 comprise, or consists of, SEQ ID NO:4, a CDR_L2 comprises, or consists of, SEQ ID NO:5, and a CDR_L3 comprises, or consists of, SEQ ID NO:6.

8. The transbody of claim 7, wherein the light chain comprises an amino acid sequence at least 85% identical, optionally 90% identical, optionally 95% identical, optionally 100% identical, to SEQ ID NO:7.

9. The transbody of any one of claims 5-8, wherein the antibody comprises a heavy chain comprising a CDR_H1 comprise, or consists of, SEQ ID NO:8, a CDR_H2 comprises, or consists of, SEQ ID NO:9, and a CDR_H3 comprises, or consists of, SEQ ID NO:10.

10. The transbody of claim 9, wherein the heavy chain comprises at least 85% identical, optionally 90% identical, optionally 95% identical, optionally 100% identical SEQ ID NO:11 or SEQ ID NO:12.

11. A method of inhibiting replication of an intracellular microorganism in a cell, comprising contacting the cell with the transbody of any one of claims 1-10.

12. The transbody of any one of claims 1-10 for use in treating an individual for an infection by an intracellular microorganism.

13. The transbody of any one of claims 1-10 for use in preventing infection of an individual by an intracellular microorganism.

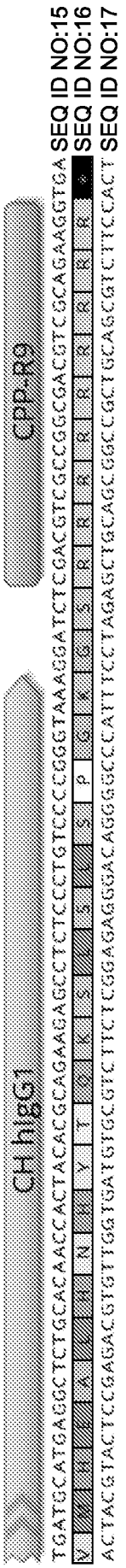


FIG. 1

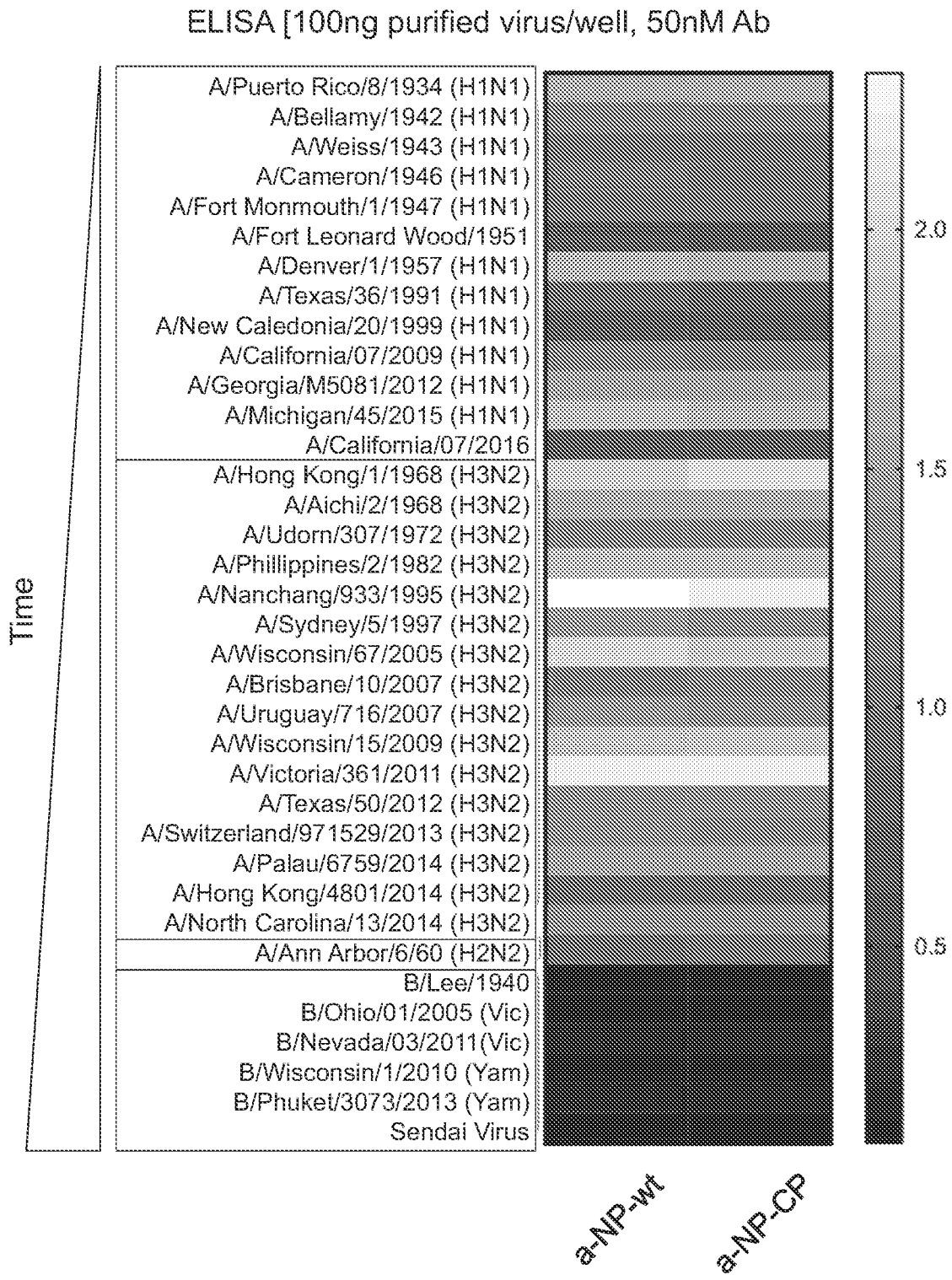

ELISA [100ng purified virus/well, 50nM Ab
Time
A/Puerto Rico/8/1934 (H1N1)
A/Bellamy/1942 (H1N1)
A/Weiss/1943 (H1N1)
A/Cameron/1946 (H1N1)
A/Fort Monmouth/1/1947 (H1N1)
A/Fort Leonard Wood/1951
A/Denver/1/1957 (H1N1)
A/Texas/36/1991 (H1N1)
A/New Caledonia/20/1999 (H1N1)
A/California/07/2009 (H1N1)
A/Georgia/M5081/2012 (H1N1)
A/Michigan/45/2015 (H1N1)
A/California/07/2016
A/Hong Kong/1/1968 (H3N2)
A/Aichi/2/1968 (H3N2)
A/Udorn/307/1972 (H3N2)
A/Phillippines/2/1982 (H3N2)
A/Nanchang/933/1995 (H3N2)
A/Sydney/5/1997 (H3N2)
A/Wisconsin/67/2005 (H3N2)
A/Brisbane/10/2007 (H3N2)
A/Uruguay/716/2007 (H3N2)
A/Wisconsin/15/2009 (H3N2)
A/Victoria/361/2011 (H3N2)
A/Texas/50/2012 (H3N2)
A/Switzerland/971529/2013 (H3N2)
A/Palau/6759/2014 (H3N2)
A/Hong Kong/4801/2014 (H3N2)
A/North Carolina/13/2014 (H3N2)
A/Ann Arbor/6/60 (H2N2)
B/Lee/1940
B/Ohio/01/2005 (Vic)
B/Nevada/03/2011(Vic)
B/Wisconsin/1/2010 (Yam)
B/Phuket/3073/2013 (Yam)
Sendai Virus
2.0
1.5
1.0
0.5
a-NP-wt
a-NP-CP

FIG. 2

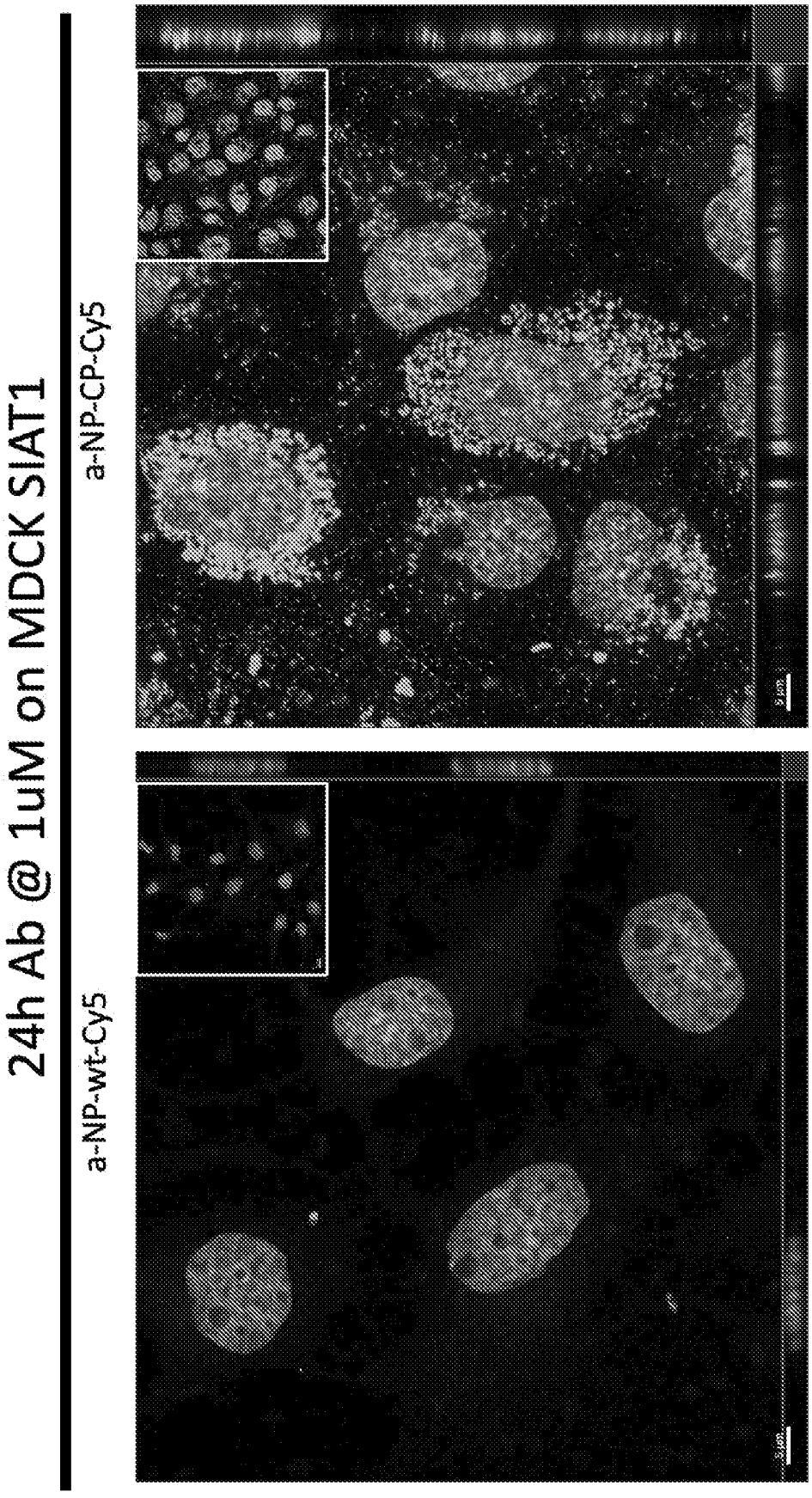


FIG. 3

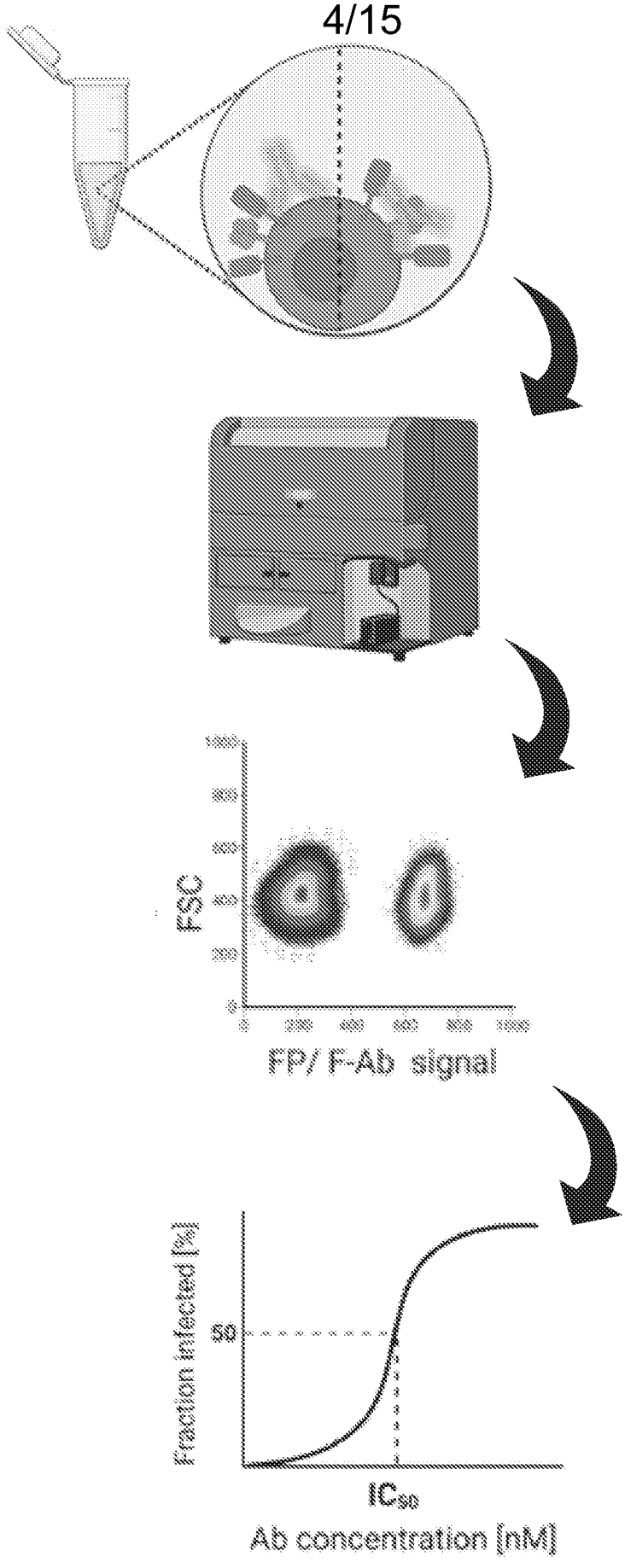

FSC
FP/ F-Ab signal
Fraction infected [%]
50
IC50
Ab concentration [nM]

FIG. 4A

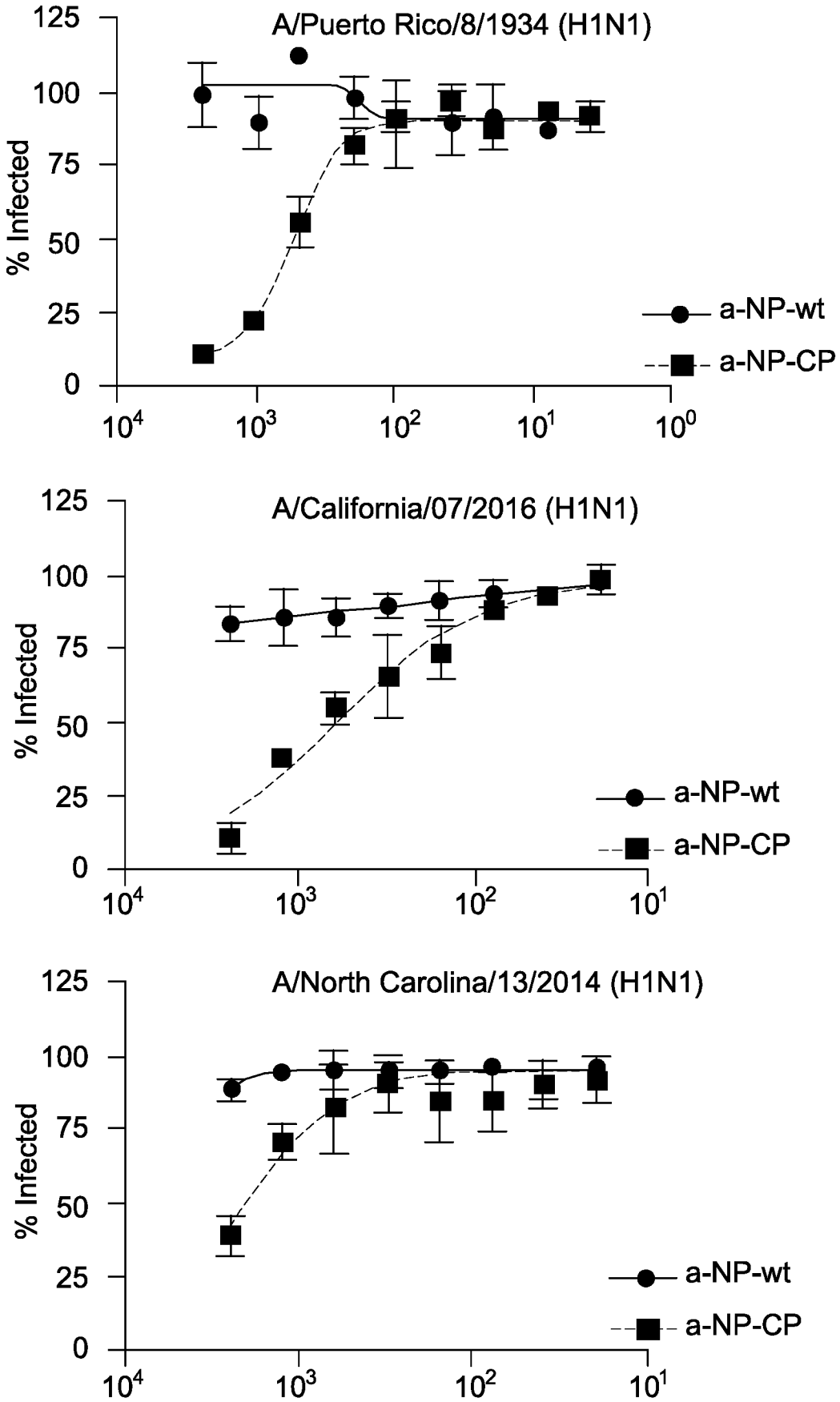

A/Puerto Rico/8/1934 (H1N1)
% Infected
125
100
75
50
25
0
10^4
10^3
10^2
10^1
10^0
a-NP-wt
a-NP-CP
A/California/07/2016 (H1N1)
% Infected
125
100
75
50
25
0
10^4
10^3
10^2
10^1
a-NP-wt
a-NP-CP
A/North Carolina/13/2014 (H1N1)
% Infected
125
100
75
50
25
0
10^4
10^3
10^2
10^1
a-NP-wt
a-NP-CP

FIG. 4B

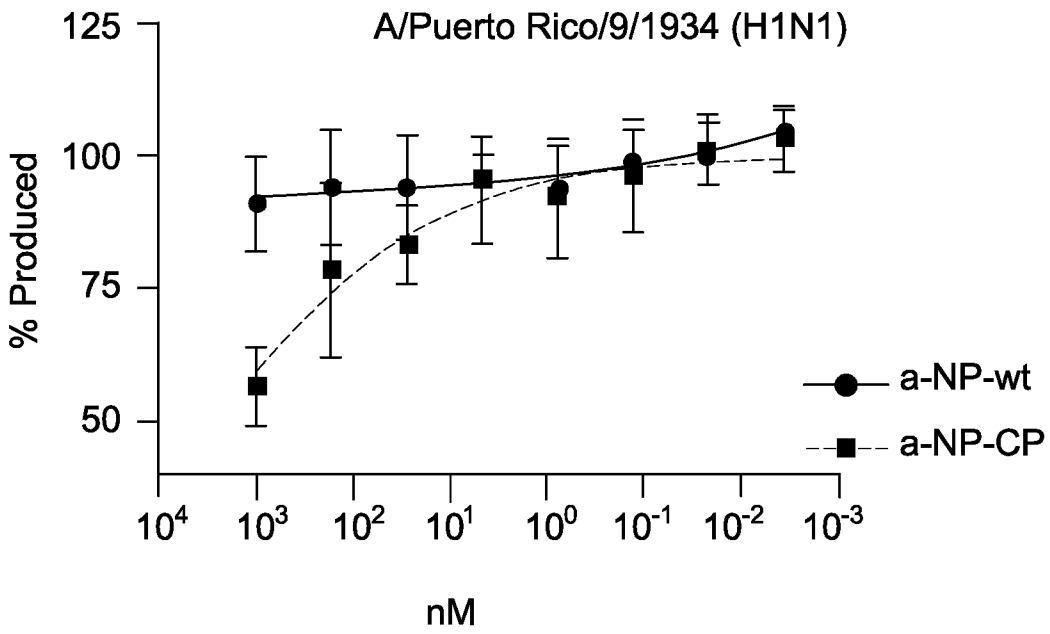
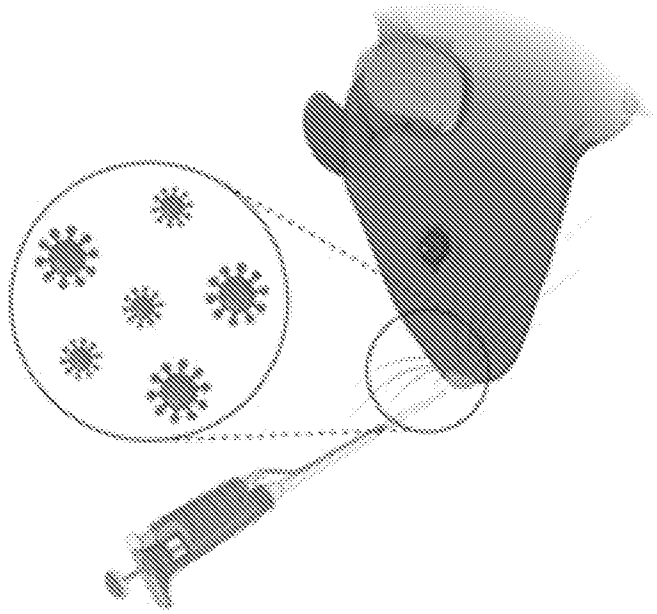

A/Puerto Rico/9/1934 (H1N1)
125
100
75
50
% Produced
10^4 10^3 10^2 10^1 10^0 10^{-1} 10^{-2} 10^{-3}
nM
a-NP-wt
a-NP-CP

FIG. 5



5H

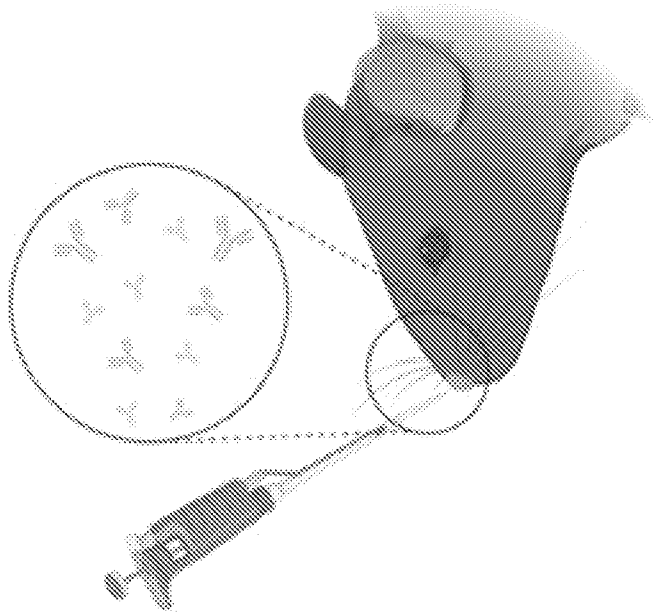


FIG. 6A

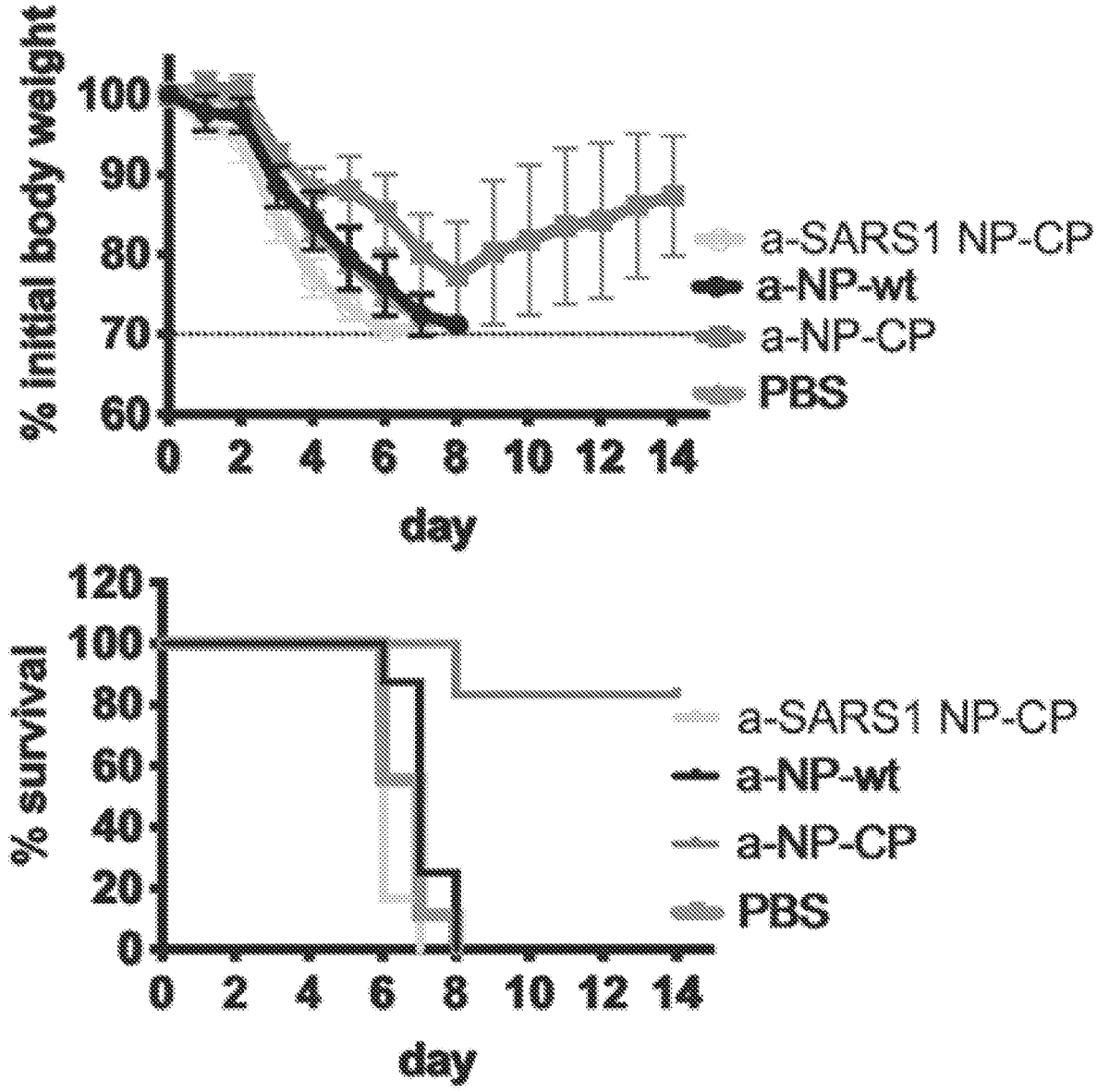

% initial body weight
100
90
80
70
60
0 2 4 6 8 10 12 14
day
a-SARS1 NP-CP
a-NP-wt
a-NP-CP
PBS
% survival
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14
day
a-SARS1 NP-CP
a-NP-wt
a-NP-CP
PBS

FIG. 6B

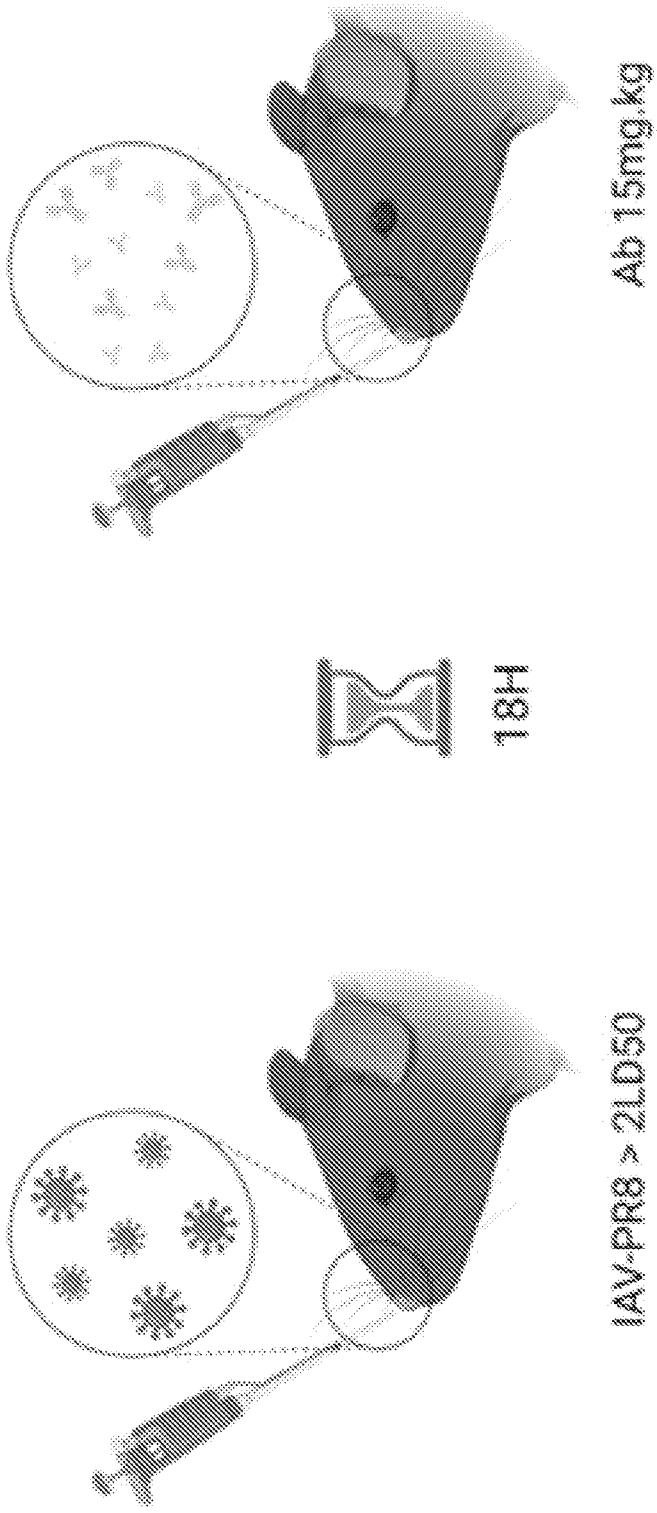


FIG. 7A

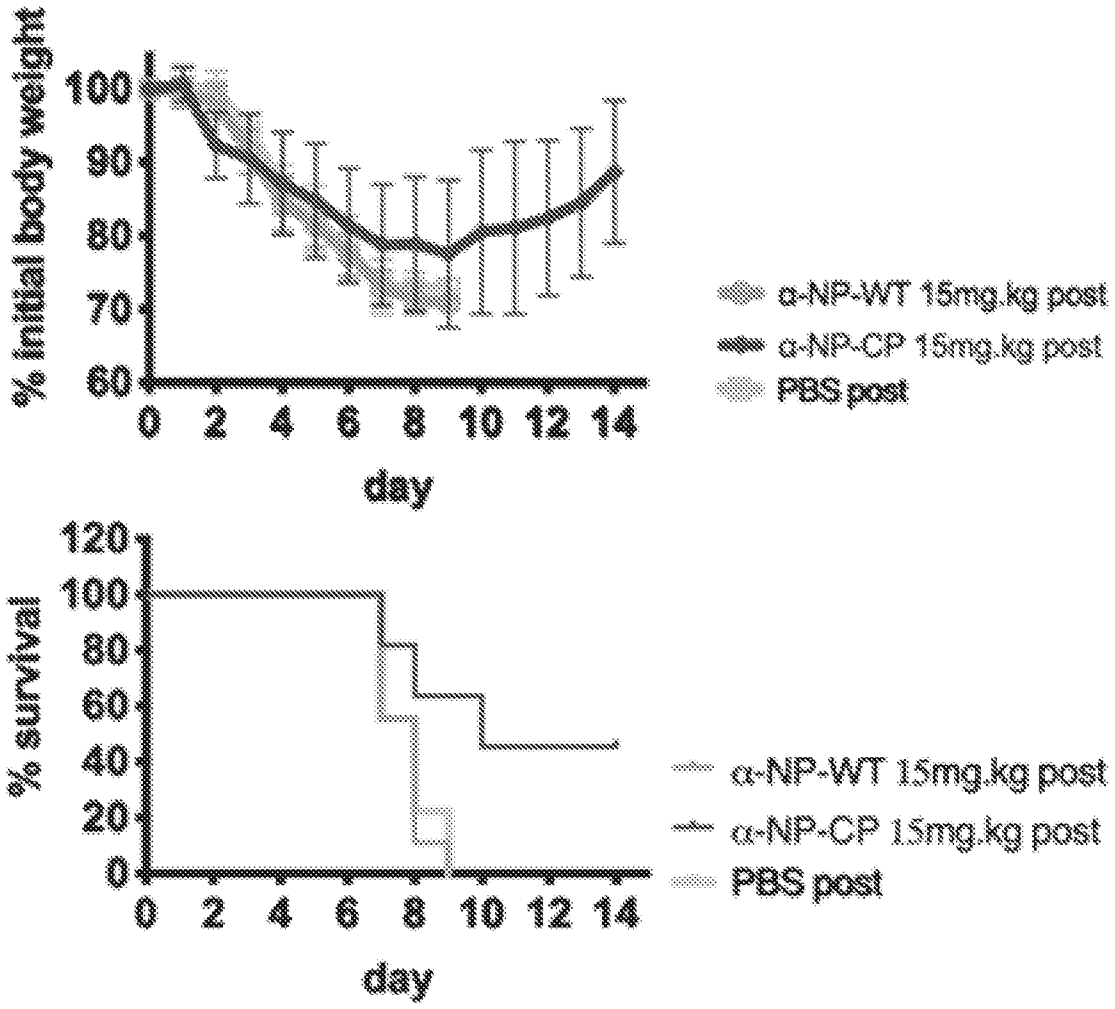

% initial body weight
100
90
80
70
60
0 2 4 6 8 10 12 14
day
α-NP-WT 15mg.kg post
α-NP-CP 15mg.kg post
PBS post
% survival
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14
day
α-NP-WT 15mg.kg post
α-NP-CP 15mg.kg post
PBS post

FIG. 7B

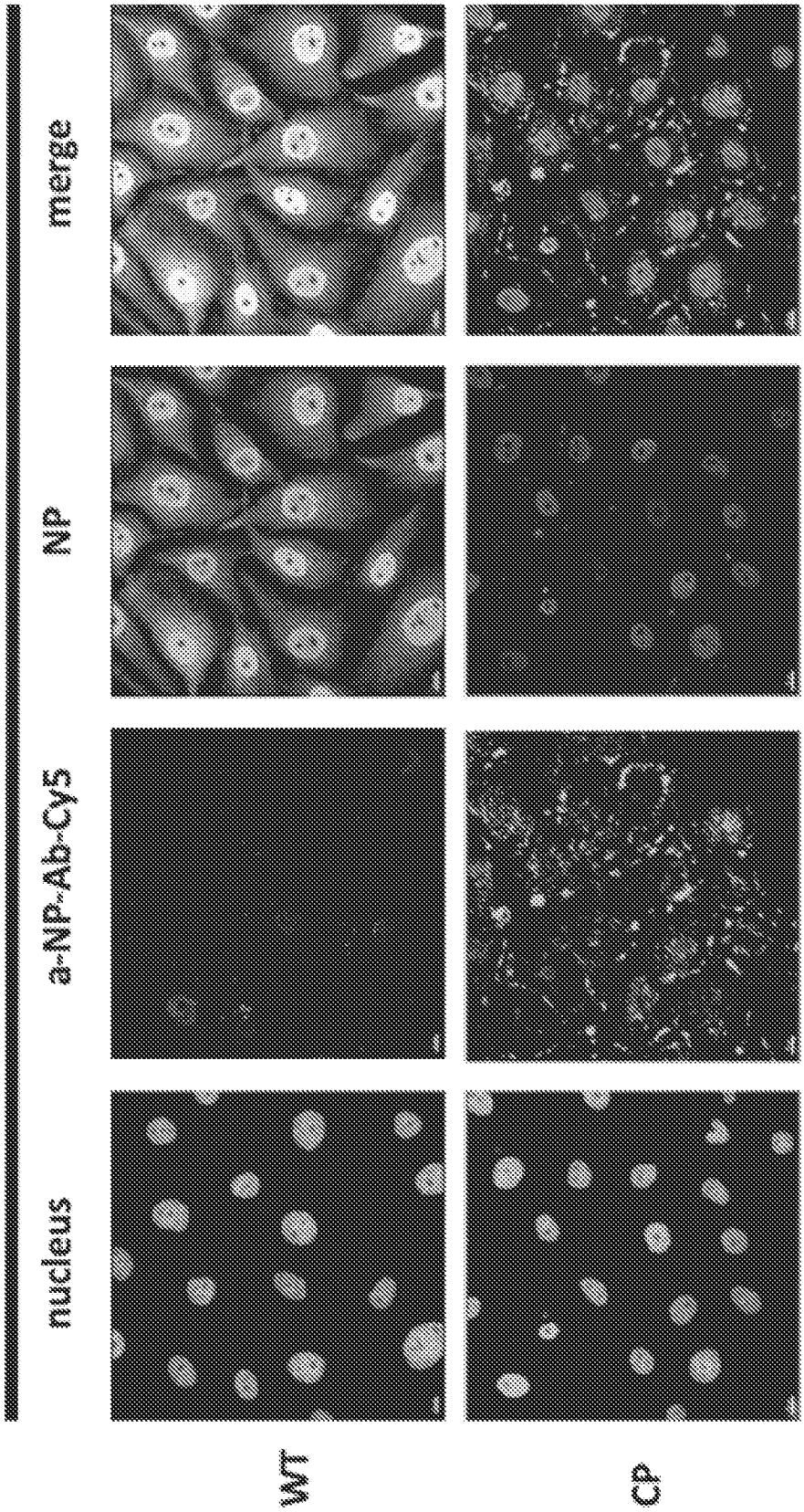


FIG. 8

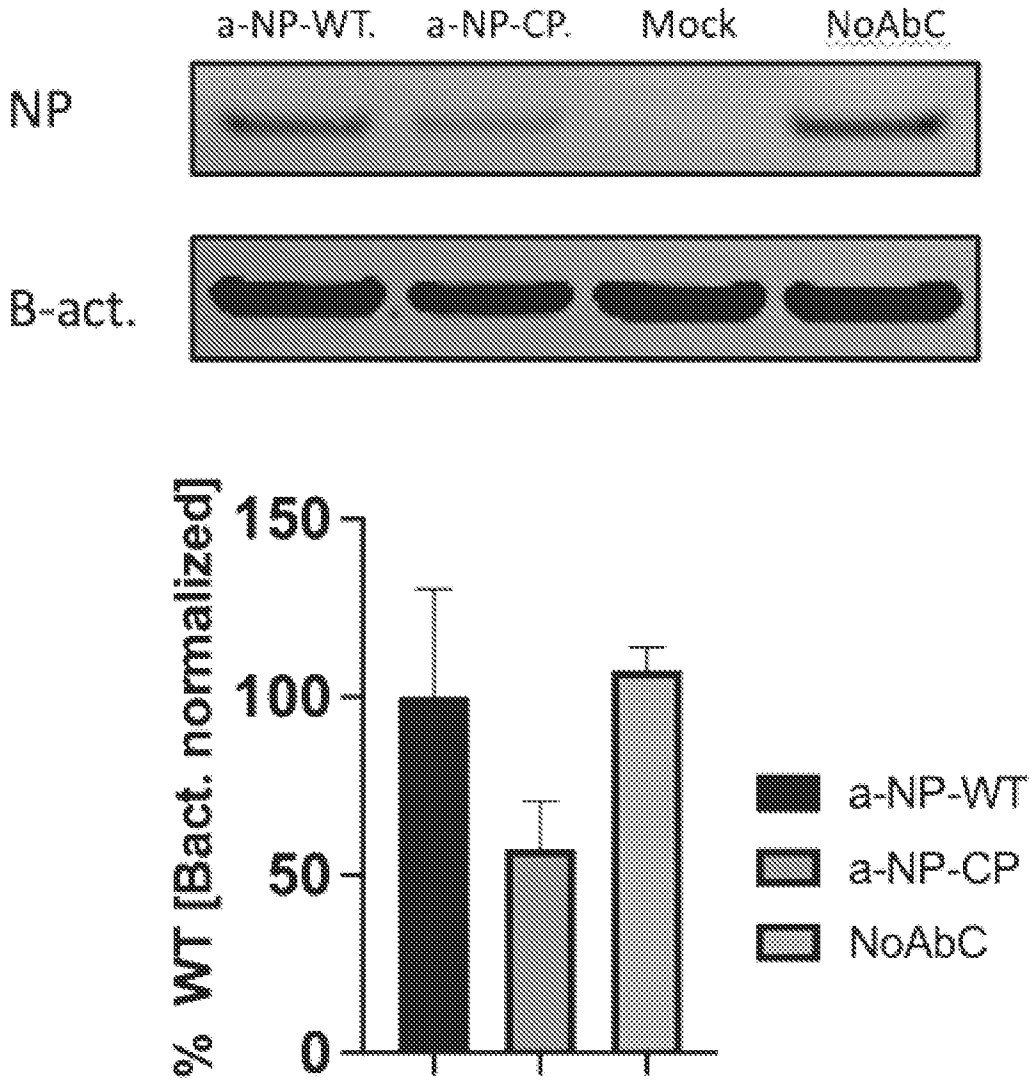

a-NP-WT.
a-NP-CP.
Mock
NoAbC
NP
B-act.
% WT [Bact. normalized]
150
100
50
0
a-NP-WT
a-NP-CP
NoAbC

FIG. 9

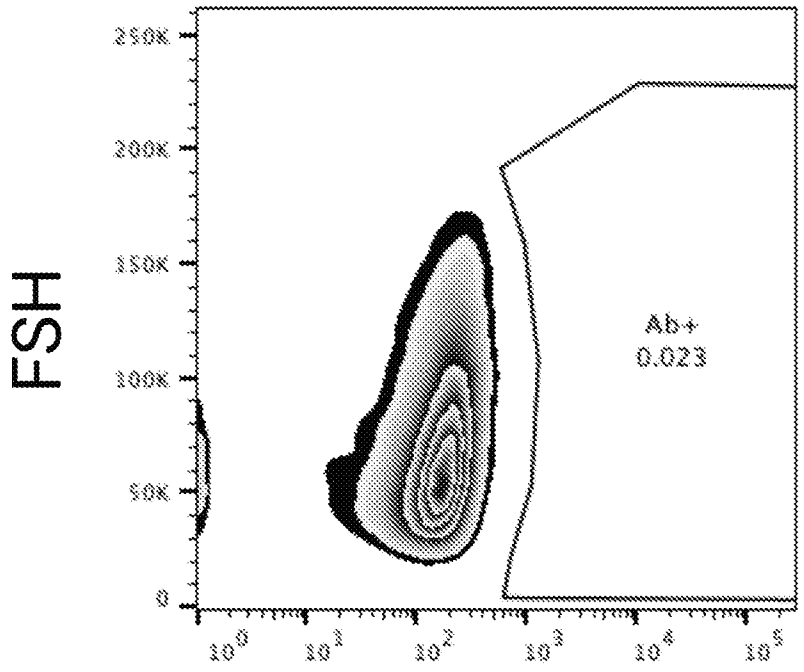


FIG. 10A

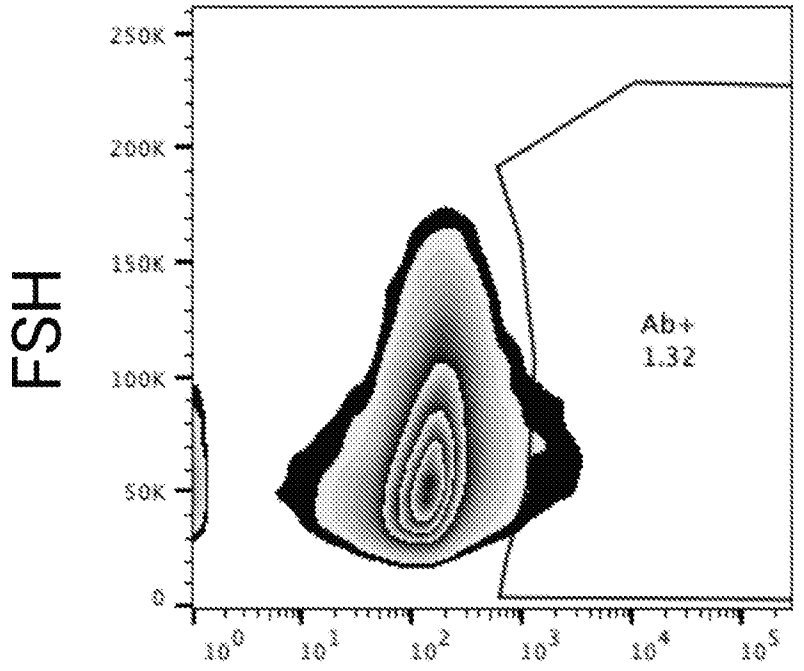


FIG. 10B

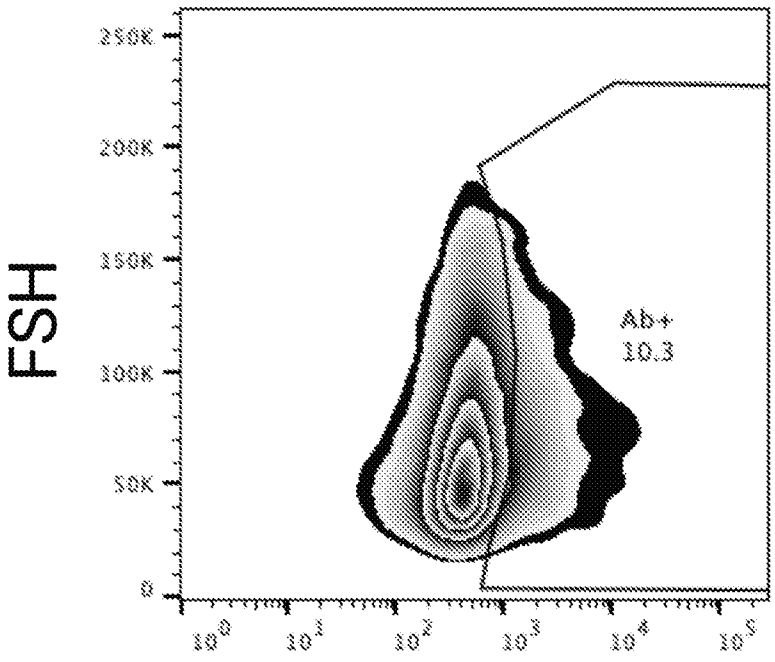


FIG. 10C

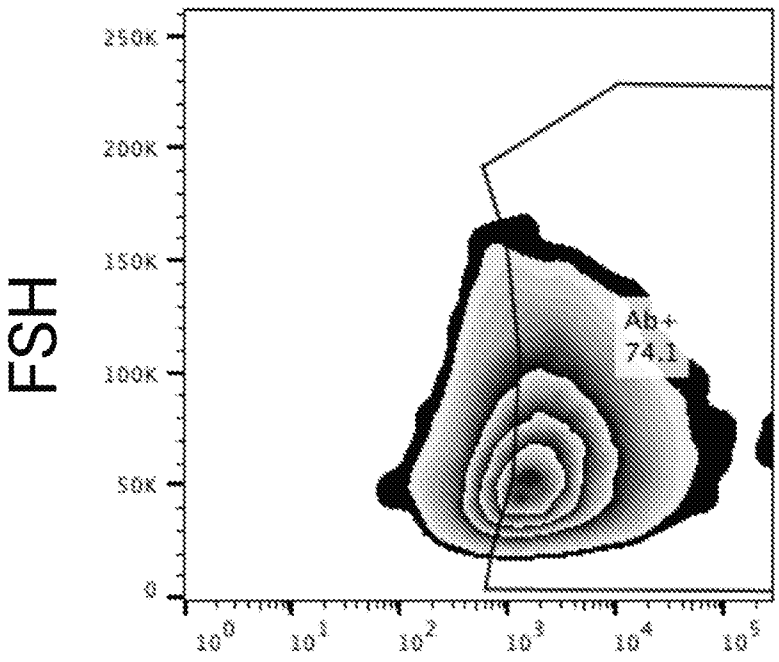


FIG. 10D

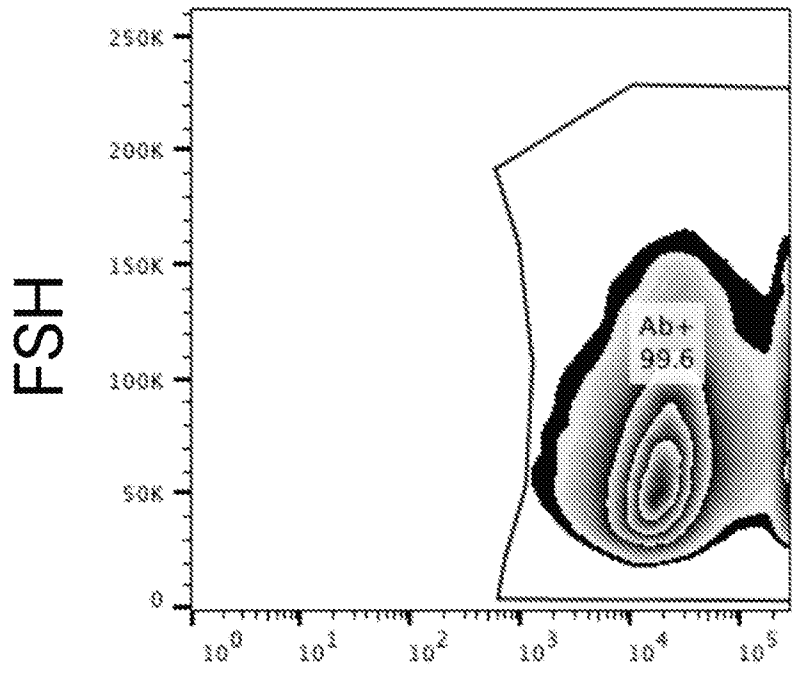

FSH
250K
200K
150K
100K
50K
0
Ab+
99.6
10^0
10^1
10^2
10^3
10^4
10^5
AF488-A
H16-L10-BiArmCP 500nM 17H

FIG. 10E

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/067856

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P31/16 C07K16/10 A61K39/395
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	POUNGPAIR ORNNUTHCHAR ET AL: "A Human Single Chain Transbody Specific to Matrix Protein (M1) Interferes with the Replication of Influenza A Virus", BIOCONJUGATE CHEMISTRY, vol. 21, no. 7, 21 July 2010 (2010-07-21), pages 1134-1141, XP93075457, US ISSN: 1043-1802, DOI: 10.1021/bc900251u abstract; figure 4 ----- -/--	1-13

[x] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2023	30/08/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fleitmann, J

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/067856

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	URAI CHAISRI ET AL: "Evolution of Therapeutic Antibodies, Influenza Virus Biology, Influenza, and Influenza Immunotherapy", BIOMED RESEARCH INTERNATIONAL, vol. 2018, 28 May 2018 (2018-05-28), pages 1-23, XP055723440, ISSN: 2314-6133, DOI: 10.1155/2018/9747549 page 14, right-hand column, last paragraph - page 15, left-hand column, paragraph frist ----- RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436, ISSN: 0027-8424, DOI: 10.1073/PNAS.79.6.1979 the whole document	1-13
A		1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/067856

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/067856

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-13(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-13(partially)

Claims 6-10 define the structure of the antibody by less than 6 CDR amino acid sequences.

The description discloses antibody H16-L10 defined by the amino acid sequence of the VH and VL as shown in table 1. No further antibody is exemplified in the application.

The claims hence relates to sequence combinations which may or may not generate an antibody with defined technical /functional properties. In view of the importance of the role played by each single amino acid in the binding of an antibody to its target, especially at the level of its CDRs (see Rudikoff AT AL) a claim to an antibody which is structurally characterized by less than the full sequence of all the CDRs, and their specific order, cannot be seen to sufficiently disclose an antibody with any particular properties. Thus, it is apparent that a search of all possible combinations of claimed sequences would not be useful, since only an antibody defined by at least 6 CDRs (HCDR1-3, LCDR1-3) has any defined technical properties of binding.

It is impossible to carry out a meaningful search regarding the state of the art on the basis of the of the subject-matter claimed. The search is thus restricted to the antibody which comprises a VL chain that comprises the CDRs of SEQ ID NO: 4-6 and a

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.