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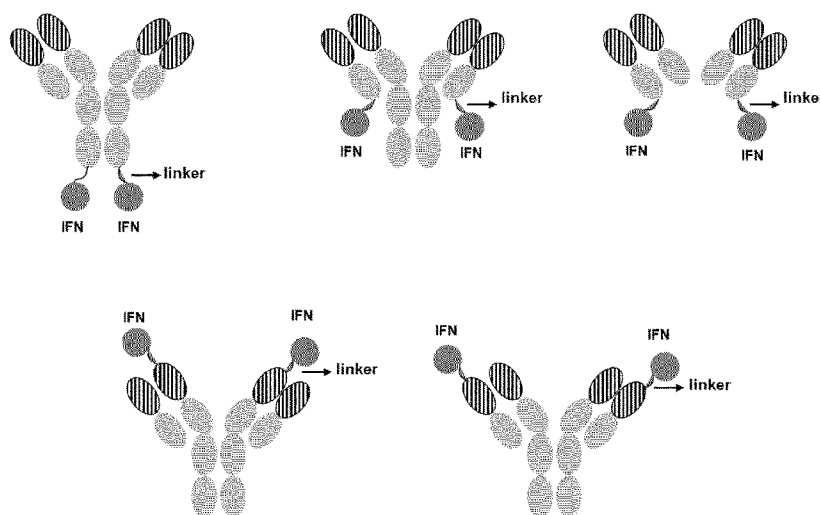
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(54) Title: INTERFERON-ASSOCIATED ANTIGEN BINDING PROTEINS FOR USE FOR THE TREATMENT OR PREVEN-
TION OF HEPATITIS DELTA VIRUS INFECTION

Fig.1



(57) Abstract: The present invention relates to methods for treating or preventing Hepatitis delta virus infection in a subject by administering a combination of a cluster of differentiation factor 40 (CD40) agonist and an interferon (IFN), for example an IFN-associated antigen binding protein, such as an IFN-fused antibody, or nucleic acids and expression vectors coding therefor. The present invention also relates to the use of corresponding pharmaceutical compositions for use in treating Hepatitis delta virus infection.



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Interferon-Associated Antigen Binding Proteins for Use for the Treatment or Prevention of Hepatitis delta virus Infection

FIELD OF THE INVENTION

[0001] The present invention relates to methods for treating or preventing Hepatitis delta virus infection in a subject. The present invention also relates to interferon-associated antigen binding proteins as well as nucleic acids and expression vectors encoding such interferon-associated antigen binding proteins for use in therapy, more particularly for use in treating or preventing Hepatitis delta virus infection. This includes interferon-fused antibodies or interferon-fused antigen binding fragments thereof, which are also referred to herein as “IFAs”. The present invention also relates to pharmaceutical compositions comprising such interferon-associated antigen binding proteins or nucleic acids or expression vectors for use in therapy, more particularly for use in treating Hepatitis delta virus infection. The present invention further provides methods of treatment using such interferon-associated antigen binding proteins or nucleic acids or expression vectors or pharmaceutical compositions. Said interferon-associated antigen binding proteins afford beneficial improvements over the current state of the art, for example in that they may effectively reduce viral burden in Hepatitis delta virus-infected cells and/or inhibit Hepatitis delta virus infection and/or rescue cells from Hepatitis delta virus-induced cell death and/or rescue cells from Hepatitis delta virus-induced cytopathic effect.

BACKGROUND

[0002] Hepatitis D is the most severe viral hepatitis known (Romeo et al., Gastroenterology 136: 1629-1638 (2009)). Unlike Hepatitis B virus (HBV) which is part of the Hepadnaviridae family (partial double strand DNA), the Hepatitis delta virus (HDV) genome is composed of a negative single strand RNA (He et al., J. Med. Virol. 27: 31-33 (1989)) and belongs to the Kolmioviridae family (Kuhn et al., Arch. Virol. 165: 3023-3072 (2020)). HDV as a viroid needs HBV surface proteins for secretion and entry into target liver cells (Branch et al., Science 223: 450-455

(1984)). Thus, during their life cycle, the two viruses share the same cellular receptor (NTCP) for their entry step.

[0003] The release from the cell after assembly is also similar for both viruses, as well as the ability to generate viral particles and virus-like particles (VLPs). However, the mechanisms involved for generating VLPs differ between the two viruses. In addition, HBV is dispensable for all remaining replication steps of HDV, as it relies almost exclusively on cellular host factors for viral replication (Chang et al., J. Virol. 82: 1118-1127 (2008)). First, due to the high GC content and self-complementarity, the HDV genome folds into an unbranched, rod-like structure which is a prerequisite for HDV replication to initiate a rolling circle mechanism using host RNA polymerases. Then, due to its small size and limited protein coding capacity, HDV also relies on the host machinery for its protein production with a specific RNA editing step to produce 2 proteins L-HDVAg and S-HDVAg from one RNA sequence. Finally, a prenylation step, involving the host enzyme Farnesyl-transferase, is also required for HDV and is essential for the HDV ribonucleoprotein to be able to interact with the HBs protein from HBV and to finalize the assembly and release from the cell (Goodrum et al, 2021). These specificities of each virus are not exhaustive and many host-factors, which are involved in the respective viral replication, differ and are not detailed here.

[0004] In addition, the host response to the infection is also different, in particular regarding the innate immune response. As an example, HBV virus employs active strategies to evade innate immune responses and induce immunosuppression in chronic HBV infection, while an HDV infection induces the type-1 and type-3 IFN pathways (Zhang et al, 2018). Paradoxically, HDV also shows some capabilities to escape immune responses and a certain degree of resistance to interferon activity. However, the IFN therapy, which demonstrates benefits in HBV-infected patients, remains one of the therapeutic approaches also used in HBV/HDV patients.

[0005] Chronic hepatitis delta (CHD) patients have a higher risk of developing cirrhosis and hepatocellular carcinoma (HCC) when compared to HBV mono-infected individuals (Yurdaydin et al., J. Viral. Hepat. 17: 749-756 (2010)). However, there is no accurate estimation of a total number of cases mainly due to the lack of

automatic HDV testing. Still, recent meta-analyses estimate that 13-14.6 % of HBsAg carriers are infected with HDV worldwide (15-50 million of people) (Stockdale et al., J. Hepatol. 73: 523-532 (2020) and Miao et al., J. Infect. Dis. 221:1677-1687 (2020)).

5 [0006] HBV/HDV infections are defined in two different categories:

[0007] On the one hand, acute hepatitis D caused by a simultaneous infection by both HBV and HDV is referred to as coinfection (Negro et al., Cold Spring Harb. Perspect. Med. 4: a021550 (2014)) while on the other hand, an HDV infection of an individual already chronically mono-infected with HBV is referred to as a
10 superinfection. While an HDV/HBV coinfection is mainly transient and usually self-limited in adults (i.e. less than 5% progression to chronicity) (Smedile et al., Prog. Clin. Biol Res. 143: 237-243 (1983)), an HDV superinfection of HBV chronically infected patients causes a severe acute hepatitis. In most cases superinfection progresses to chronicity (up to 80%) (Smedile et al., Lancet 2: 945-947 (1982)). HDV
15 superinfection accelerates disease progression compared to HBV mono-infection, regardless of the patient's age. Historical studies report that 70-80% of CHD patients develop cirrhosis within 5 to 10 years (Govindarajan et al., Hepatology 6: 640-44 (1986)) and 15% within 1-2 years (Saracco et al., J. Hepatol. 5: 274-281 (1987)), making CHD the most severe form of virus induced chronic liver disease (Romeo et al., Gastroenterology 136: 1629-1638 (2009)).
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[0008] The only therapy approved is pegylated interferon-IFN α (Peg-IFN α or Pegasys), which, however, has limited efficacy and is associated with side effects. Currently two molecules are under clinical trials. Bulevirtide (BLV, Hepcludex), previously known as Myrcludex B and acting as an entry inhibitor by preventing L-
25 HBsAg interaction with its cellular receptor (NTCP), is currently in phase 3 clinical trials (Blank et al., J. Hepatol. 65:483-489 (2016)). And Lonafarnib, which was initially developed to inhibit farnesylation of RAS for anti-cancer applications, is also currently in phase 3 clinical trials (Bordier et al., J. Virol. 76: 10465-10472 (2002)). Therefore, as there is to date no approved efficient treatment, that can cure
30 an active HDV infection, there is an urgent need to develop new antiviral therapies.

[0009] Novel methods for treating and preventing Hepatitis delta virus infection, are needed. In particular, methods for reducing viral burden in Hepatitis delta virus-infected cells, inhibiting Hepatitis delta virus infection, rescuing cells from Hepatitis delta virus-induced cell death and/or rescuing cells from Hepatitis delta virus-induced cytopathic effect, are needed.

SUMMARY OF THE INVENTION

[0010] In one aspect the invention relates to a cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof for use in the treatment or prevention of a Hepatitis delta virus infection, wherein the CD40 agonist or a functional fragment thereof is administered in combination with an interferon (IFN) or a functional fragment thereof.

[0011] In another aspect, the invention further relates to an interferon (IFN) or a functional fragment thereof for use in the treatment or prevention of a Hepatitis delta virus infection, wherein the IFN or a functional fragment thereof is administered in combination with a cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof.

[0012] In another aspect, the invention also relates to a combination of a cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof and an interferon (IFN) or a functional fragment thereof, for use in the treatment or prevention of a Hepatitis delta virus infection.

[0013] In another aspect the invention relates to an interferon-associated antigen binding protein comprising (I) an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and (II) an Interferon (IFN) or a functional fragment thereof for use in the treatment or prevention of a Hepatitis delta virus infection.

[0014] According to any of the aspects of the invention, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof may comprise (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 90% identical to SEQ ID NO 56, a CDRH2 that is at least

90% identical to SEQ ID NO 57, and a CDRH3 that is at least 90% identical to SEQ ID NO 58; and (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 90% identical to SEQ ID NO 52, a CDRL2 that is at least 90% identical to SEQ ID NO 53, and a CDRL3 that is at least 90% identical to SEQ ID NO 54.

5 Alternatively, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof may comprise (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to SEQ ID NO 58; and (b) a light chain or a fragment thereof comprising a CDRL1 that
10 is identical to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a CDRL3 that is identical to SEQ ID NO 54.

[0015] According to one embodiment, the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a light chain variable region V_L comprising the sequence as set forth in SEQ ID NO 51, or a sequence at least
15 90% identical thereto; and/or a heavy chain variable region V_H comprising the sequence as set forth in SEQ ID NO 55, or a sequence at least 90% identical thereto.

[0016] According to another embodiment, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%
20 identical thereto; and/or a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48, or a sequence at least 90% identical thereto.

[0017] According to a further embodiment, the IFN or the functional fragment thereof may be selected from the group consisting of a Type I IFN, a Type II IFN and a Type III IFN, or a functional fragment thereof. Preferably, the type I IFN or
25 the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.

[0018] According to another embodiment, the IFN or the functional fragment thereof is IFN α 2a, or a functional fragment thereof. According to a preferred embodiment, the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17, or a sequence at
30 least 90% identical thereto.

[0019] According to another embodiment, the IFN or the functional fragment thereof is IFN β , or a functional fragment thereof. In a preferred embodiment, the IFN β comprises the sequence as set forth in SEQ ID NO 14, or a sequence at least 90% identical thereto.

5 [0020] According to another embodiment, the IFN or the functional fragment thereof is fused to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, preferably to the C-terminus.

10 [0021] According to a further embodiment, the IFN or the functional fragment thereof is fused to a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, preferably to the C-terminus.

15 [0022] According to another embodiment, the agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and the IFN or the functional fragment thereof, are fused to each other via a linker. In a preferred embodiment, the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.

20 [0023] According to another embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising one of the sequence combinations disclosed in Table 9, in particular Table 9A or Table 9B, more particularly Table 9A.

25 [0024] According to another embodiment, the use comprises administering the interferon-associated antigen binding protein to a subject in need thereof by means of genetic delivery with RNA or DNA sequences encoding the interferon-associated antigen binding protein, or a vector or vector system encoding the interferon-associated antigen binding protein.

[0025] According to yet another embodiment, the interferon-associated antigen binding protein is comprised in a pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] **Fig. 1:** This schematic drawing depicts exemplary interferon-associated antigen binding protein formats. The interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof. IFNs are associated via linkers to different positions on the antibody or the antigen binding fragment thereof: N-terminal or C-terminal part of the light chain (LC) or the heavy chain (HC). In particular, IFNs are chosen from Type I, Type II and Type III interferon families.

[0027] **Fig. 2A** depicts an exemplary map of a pcDNA3.1 plasmid encoding SEQ ID NO 32 under the control of the pCMV promoter. The nucleic acid sequence encoding for SEQ ID NO 32 (= SEQ ID NO 78) is also shown at the bottom. *Italic*: signal peptide sequence; **black color**: CP870,893 heavy chain coding sequence; underlined: HL linker coding sequence; **bold**: IFN β coding sequence.

[0028] **Fig. 2B** shows examples of SDS PAGE in reduced conditions of some IFAs, with IFN α or IFN β fused either at the heavy chain or the light chain. Migration of the parental CP870,893 is also shown on the left.

[0029] **Fig. 3A-3B** graphically depict a dose dependent effect of a number of IFA molecules with IFN β fusions on activating the CD40-mediated NF κ B pathway reporter assay in HEK-Blue™ CD40L cells. **Fig. 3A** shows examples of anti-CD40 activities for IFAs with IFN β fused to the C-terminal part of the heavy chain (HC). **Fig. 3B** shows examples of anti-CD40 activities for IFAs with IFN β fused to the N-terminal part of the LC (IFA34) or the HC (IFA36) and the corresponding fusions on the C-terminal part (IFA35 and IFA37). Purification yield of the latter group of IFAs was very low, thus to test their activity, the supernatants from HEK transfected cells were used and serially diluted to evaluate the anti-CD40 activity on HEK-Blue™ CD40L cells.

[0030] **Figs. 3C-3D** graphically depict a dose dependent effect of a number of IFA molecules with IFN β fusions on activating the Type I IFN- pathway in reporter HEK-Blue-IFN- α/β cells. **Fig. 3C** shows examples of IFN activity for IFAs with IFN β fused to the C-terminal part of the HC. **Fig. 3D** shows examples of IFN activity for IFAs with IFN β fused to the N-terminal part of the LC (IFA34) or the HC (IFA36)

and the corresponding fusions on the C-terminal part (IFA35 and IFA37). The same supernatants from HEK transfected cells as in Fig. 3B were used and serially diluted to evaluate the IFN activity. Parental antibody CP870,893 was used as negative control and recombinant human IFN β was used as positive control. NS: Non Stimulated.

[0031] **Fig. 4A** graphically depicts a dose effect of a number of IFA molecules with IFN α fusions on activating the CD40-mediated NF κ B pathway reporter assay in HEK-BlueTM CD40L cells.

[0032] **Fig. 4B** graphically depicts a dose effect of a number of IFA molecules with IFN α fusions on activating the Type I IFN-mediated pathway in reporter HEK-Blue-IFN- α/β cells. The activity of Pegasys is indicated in the insert in the lower right corner.

[0033] **Fig. 4C** graphically depicts the effect of IFA molecules with IFN α fusions and HL linker on HC (IFA38) or LC (IFA39) on activating the CD40-mediated NF κ B pathway reporter assay in HEK-BlueTM CD40L cells.

[0034] **Fig. 4D** graphically depicts the effect of IFA38 and IFA39 on activation of the Type I IFN-pathway in reporter HEK-Blue-IFN α/β cells.

[0035] **Figs. 5A-5C** graphically depict a dose dependent effect of Pegasys on freshly isolated primary human hepatocytes (PHH) after HBV/HDV co-infection. Briefly, at the day of co-infection, cells were infected both with HBV and HDV for 4 days and incubated at 37°C, 5% CO₂. Then, all media was replaced with fresh media containing Pegasys in a 10-fold serial dilution at days 4 and 7, respectively. Finally, at day 10 post infection (p.i.) secreted HBsAg was measured with CLIA assay (**Fig. 5A**). Relative intracellular HBV RNA (**Fig. 5B**) and HDV RNA (**Fig. 5C**) expression was quantified by specific qRT-PCR reactions.

[0036] **Fig. 5D** graphically depicts a propagation assessment in Huh7.5-hNTCP with Pegasys conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the co-infection (day 10) as described in Fig. 5A-5C were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0037] **Figs. 5E-5G** graphically depict a dose dependent effect of IFA44 on freshly isolated primary human hepatocytes (PHH) after HBV/HDV co-infection. Briefly, at the day of co-infection, cells were infected both with HBV and HDV for 4 days and incubated at 37°C, 5% CO₂. Then, all media was replaced with fresh media containing IFA44 in a 10-fold serial dilution at days 4 and 7, respectively. Finally, at day 10 p.i. secreted HBsAg was measured with CLIA assay (**Fig. 5E**). Relative Intracellular HBV RNA (**Fig. 5F**) and HDV RNA (**Fig. 5G**) expression was quantified by specific qRT-PCR reactions.

[0038] **Fig. 5H** graphically depicts a propagation assessment in Huh7.5-hNTCP with IFA44 conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the co-infection (day 10) as described in Figs. 5E-5G were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0039] **Figs. 5I-5K** graphically depict a dose dependent effect of IFA25 on freshly isolated primary human hepatocytes (PHH) after HBV/HDV co-infection. Briefly, at the day of co-infection, cells were infected both with HBV and HDV for 4 days and incubated at 37°C, 5% CO₂. Then, all media was replaced with fresh media containing IFA25 in a 10-fold serial dilution at days 4 and 7, respectively. Finally, at day 10 p.i. secreted HBsAg was measured with CLIA assay (**Fig. 5I**). Relative Intracellular HBV RNA (**Fig. 5J**) and HDV RNA (**Fig. 5K**) expression was quantified by specific qRT-PCR reactions.

[0040] **Fig. 5L** graphically depicts a propagation assessment in Huh7.5-hNTCP with IFA25 conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the co-infection (day 10) as described in Figs. 5I-5K were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0041] **Figs. 5M-5O** graphically depict a dose dependent effect of IFA25 on freshly isolated primary human hepatocyte after HBV/HDV co-infection with a different kinetic. Briefly, at the day of co-infection, cells were infected both with HBV and

HDV for 3 days and incubated at 37°C, 5% CO₂. Then, all media was replaced with fresh media containing IFA25 in a 10-fold serial dilution at days 3 and 6 respectively. Finally, at day 9 p.i. secreted HBsAg was measured with CLIA assay (**Fig. 5M**). Relative Intracellular HBV RNA (**Fig. 5N**) and HDV RNA (**Fig. 5O**) expression was quantified by specific qRT-PCR reactions.

[0042] **Fig. 5P** graphically depicts a propagation assessment in Huh7.5-hNTCP with IFA25 conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the co-infection (day 9) as described in Figs. 5M-5O were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0043] **Figs. 5Q-5S** graphically depict antiviral effects of IFA25 compared to reference controls on freshly isolated primary human hepatocytes (PHH) after HBV/HDV co-infection. Briefly, at the day of co-infection, cells were infected for 3 days and incubated at 37°C, 5% CO₂. Then, all media was replaced with fresh media containing EVI5 (1 µg/ml), IFA25 (0.1 and 1 µg/ml), IFA202 (1µg/ml), Roferon-A (1000UI/ml), Myrcludex-B (MyrB; 100nM) and FTI-277 (10µM) (in that order from left to right as shown in Figs. 5Q - 5T) at days 3 and 6, respectively. Finally, at day 9 p.i. secreted HBsAg was measured with CLIA assay (**Fig. 5Q**). Relative Intracellular HBV RNA (**Fig. 5R**) and HDV RNA (**Fig. 5S**) expression was quantified by specific qRT-PCR reactions.

[0044] **Fig. 5T** graphically depicts a propagation assessment in Huh7.5-hNTCP with IFA25 conditioned PHH medium or reference controls conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the co-infection (day 9) as described in Figs. 5Q-5S were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0045] **Figs. 6A-6C** graphically depict a dose dependent effect of IFA25 on freshly isolated primary human hepatocytes (PHH) after HBV/HDV super-infection. Briefly, at the day of infection, cells were infected for 5 days with HBV only and incubated

at 37°C, 5% CO₂. Then, cells were super-infected by HDV for 3 extra days and incubated at 37°C, 5% CO₂. All media was replaced with fresh media containing IFA25 in a 10-fold serial dilution at days 8 and 11 respectively. Finally, at day 14 p.i. secreted HBsAg was measured with CLIA assay (**Fig. 6A**). Relative Intracellular HBV RNA (**Fig. 6B**) and HDV RNA (**Fig. 6C**) expression was quantified by specific qRT-PCR reactions.

[0046] **Fig. 6D** graphically depicts a propagation assessment in Huh7.5-hNTCP with IFA25 conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the super-infection (day 14) as described in Figs. 6A-6C were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0047] **Figs. 6E-6G** graphically depict a dose dependent effect of IFA25 compared to reference controls on freshly isolated primary human hepatocytes (PHH) after HBV/HDV super-infection. Briefly, at the day of infection, cells were infected for 5 days with HBV only and incubated at 37°C, 5% CO₂. Then, cells were super-infected by HDV for 3 extra days and incubated at 37°C, 5% CO₂. All media was replaced with fresh media containing EVI5 (1 µg/ml), IFA25 (0.1 and 1 µg/ml), IFA202 (1µg/ml), Roferon-A (1000UI/ml), Myrcludex-B (MyrB; 100nM) and FTI-277 (10µM) (in that order from left to right as shown in Figs. 6E – 6H) at D8 and D11 p.i., respectively. Finally, at day 14 p.i. secreted HBsAg was measured with CLIA assay (**Fig. 6E**). Relative Intracellular HBV RNA (**Fig. 6F**) and HDV RNA (**Fig. 6G**) expression was quantified by specific qRT-PCR reactions.

[0048] **Fig. 6H** graphically depicts propagation assessment in Huh7.5-hNTCP with IFA25 conditioned PHH medium or reference controls conditioned PHH medium. Briefly, supernatants collected at the end of the kinetic of the infection (day 14) were directly transferred to non-infected Huh7.5-hNTCP growing cell line for 6 days. At the end of the kinetic of the infection total RNA was extracted and the relative intracellular HDV RNA expression was quantified by a specific qRT-PCR reaction.

[0049] **Fig. 7** depicts results from an *in vitro* Cytokines Release Assay of Human Whole Blood Cells (WBCs): Example of data obtained after stimulation of WBCs

from 4 healthy volunteer donors. WBC were left Non-Stimulated (NS), treated with LPS (10 ng/mL) or with IFA1 (1 µg/mL) for 24 h. Supernatants were collected and submitted to cytokines release quantification using the MSD u-Plex kit for human cytokines. Results represent the mean of two independent stimulations from each donor. The profile of CXCL10 (IP10), IL6, IL1β and TNFα are shown.

[0050] Tables 11a-b: These tables summarize data obtained after in vitro stimulation of whole blood cells (WBCs) obtained from healthy volunteers. Each IFA was tested on WBCs from four different donors. WBCs were left Non-Treated (NT), treated with LPS (10 ng/mL) or with IFAs (1 µg/mL) for 24 h. Supernatants were collected and submitted to cytokines release quantification using the MSD u-Plex kit for human cytokines. Results represent the mean of two independent stimulations from each donor and are expressed in pg/mL (nd: not detected).

[0051] Fig. 8: Pharmacokinetic profile of IFA25, IFA26, IFA27, IFA28, IFA29, and IFA30 after 0.5 mg/kg (IFAs) or 0.3 mg/kg (Pegasys) intravenous bolus injection to mice. Data expressed as mean +/- SD on semi-logarithmic scale. Samples were collected up to 10 days after administration. ELISA assay using anti-IFNα as secondary antibody for quantification method was used for IFA27, IFA29 and IFA30 (**Fig. 8A**) and for IFA25, IFA26 and IFA28 (**Fig. 8B**). ELISA assay using anti-IgG2 as secondary antibody for quantification method was used for IFA25 and IFA27 (**Fig. 8C**). **Fig. 8D:** Pegasys quantification was done using human IFNα matched antibody pairs. The marked line (LLOQ) denotes the limit of detection for the Pegasys assay.

[0052] Table 12A: PK Report Summary: PK parameters for CP870,893, IFA27, IFA29 and IFA30 following single intravenous administration of 0.5 mg/kg to male CD1 Swiss mice. PK parameters for CP870,893 were explored in a 7-day experiment and those for IFA27, IFA29 and IFA30 in 10-day experiments (quantification for IFA27 was performed using 2 different ELISA approaches).

[0053] Table 12B: PK Report Summary: PK parameters for CP870,893, Pegasys and for three different IFAs (IFA25, IFA26 and IFA28) following single intravenous bolus administration of 0.5 mg/kg to male CD1 Swiss mice. PK parameters for CP870,893 and IFA25, IFA26, IFA28 and Pegasys were explored in 21-day

experiments (quantification for IFA25 was performed using 2 different ELISA approaches).

5 [0054] **Fig. 9A** depicts CD40 agonistic activity in a dose dependent manner of IFA50 and IFA51 with no Fc region in comparison to the parental anti-CD40 antibody in reporter HEK-Blue™ CD40L cells. **Fig. 9B** depicts the IFN α activity in a dose dependent manner of IFA50 and IFA51 in reporter HEK-Blue™ hIFN- α/β cells.

10 [0055] **Fig. 10A** depicts CD40 agonistic activity in a dose dependent manner of IFN ϵ based IFA49, in comparison to parental anti-CD40 antibody, in HEK-Blue™ CD40L reporter cells. IFA49 corresponds to fusion of IFN ϵ to the HC via a peptide linker. **Fig. 10B** depicts the IFN activity in a dose dependent manner of IFA49 on reporter HEK-Blue™ hIFN- α/β reporter cells which are activated by Type I interferons.

15 [0056] **Fig. 11A** depicts CD40 agonistic activity in a dose dependent manner of IFN ω based IFA46, in comparison to parental anti-CD40 antibody, in HEK-Blue™ CD40L reporter cells. IFA46 correspond to fusion of IFN ω to the LC via a peptide linker. **Fig. 11B** depicts the IFN activity in a dose dependent manner of IFA46 on reporter HEK-Blue™ hIFN- α/β reporter cells which are activated by Type I interferons.

20 [0057] **Fig. 12A** depicts CD40 agonistic activity in a dose dependent manner of IFN γ based IFAs (IFA42 and IFA43), in comparison to parental anti-CD40 antibody, in HEK-Blue™ CD40L reporter cells. IFA42 corresponds to fusion of IFN γ to the LC via a peptide linker and IFA43 corresponds to fusion of IFN γ to the HC via a peptide linker. **Fig. 12B** depicts the IFN activity in a dose dependent manner of IFA42 and IFA43 in reporter HEK-Blue-hIFN γ cells.

25 [0058] **Fig. 13A** depicts CD40 agonistic activity in a dose dependent manner of IFN λ based IFAs (IFA44 and IFA45), in comparison to parental anti-CD40 antibody, in HEK-Blue™ CD40L reporter cells. IFA44 corresponds to fusion of IFN λ to the LC via a peptide linker and IFA45 correspond to fusion of IFN λ to the HC via a peptide linker. **Fig. 13B** depicts the IFN activity in a dose dependent manner of IFA44 and IFA45 in reporter HEK-Blue-hIFN λ cells.

[0059] **Fig. 14** shows examples of SDS PAGE in reduced conditions of some IFAs, with IFN α or IFN β fused on the heavy chain of 3G5-antiCD40 antibody. Migration of the parental 3G5 antiCD40 antibody is also shown on the left.

[0060] **Figs. 15A-B** graphically show a dose dependent effect of a number of 3G5-based IFA molecules with IFN β fusions on activating the CD40-mediated NF κ B pathway reporter assay in HEK-Blue™ CD40L cells. Comparison to the parental antibody 3G5 (designated in this figure as CDX-3G5) is likewise shown. **Fig. 15A** shows examples of anti-CD40 activities for IFAs with fusion of IFN β to the C-terminal part of the heavy chain (HC). Purification yield of IFAs with fusions of IFN β on the light chain was very low, thus to test their activity, supernatants from HEK transfected cells were used and serially diluted to evaluate the anti-CD40 activity on HEK-Blue™ CD40L cells; an example of activity is shown in **Fig. 15B** and 3G5 containing supernatant was used as control.

[0061] **Figs. 15C-D** graphically show a dose dependent effect of a number of IFA molecules with IFN β fusions on activating the Type I IFN-pathway in reporter HEK-Blue-IFN- α/β cells. **Fig. 15C** shows examples of IFN activity for IFAs with fusion of IFN β to the C-terminal part of the HC. **Fig. 15D** shows IFN activity of IFAs with IFN β fused on the light chain; the production level of these proteins was very low and thus an example of activity for two IFAs is shown in **Fig. 15D** using the same supernatant as in Fig. 15B.

[0062] **Fig. 16A** graphically shows a dose effect of four IFAs molecules with IFN α fusions on activating the CD40-mediated NF κ B pathway reporter assay in HEK-Blue™ CD40L cells. Comparison to the parental antibody 3G5 (designated in this figure as CDX-3G5) is likewise shown.

[0063] **Fig. 16B** graphically shows a dose effect of a number of IFAs molecules with IFN α fusions on activating the Type I IFN-mediated pathway in reporter HEK-Blue-IFN- α/β cells.

[0064] **Fig. 17:** In vitro Cytokines Release Assay of Human Whole Blood Cells (WBCs): Example of data obtained after stimulation of WBCs from 4 healthy volunteer donors. WBCs were left non-treated (NT), treated with LPS (10 ng/mL) or with IFA109 (1 μ g/mL) for 24 h. Supernatants were collected and submitted to

cytokines release quantification using the MSD u-Plex kit for human cytokines. Results represent the mean of two independent stimulations from each donor. The profile of CXCL10 (IP10), IL6, IL1 β and TNF α are shown.

5 [0065] **Table 13:** This table summarizes data obtained after in vitro stimulation of whole blood cells obtained from healthy volunteers. IFA109 was tested on WBCs from four different donors. WBCs were left Non-Treated (NT), treated with LPS (10 ng/mL) or with IFA109 (1 μ g/mL) for 24 h. Supernatants were collected and submitted to cytokines release quantification using the MSD u-Plex kit for human cytokines. Results represent the mean of two independent stimulations from each
10 donor and are expressed in pg/mL (nd: not detected).

[0066] **Figs. 18A-C** graphically depict viral parameters monitored at day 7 following HBV/HDV Coinfection in Cryo-PHH after compounds treatment in primary infection. **Fig. 18A** depicts HDV RNA viremia quantification by qRT-PCR. **Fig. 18B** depicts HBsAg secretion quantification by CLIA assay. **Fig. 18C** depicts Tubulin
15 (upper band) and HD-Ag (lower bands) protein expression in western blot from intracellular cryo-PHH.

[0067] **Fig. 19** depicts relative intracellular HDV RNA expression measurement by qRT-PCR at day 7 in cryo-PHH after the secondary infection from conditioned-supernatants at fixed-volume (**Fig. 19A**) and fixed-Vge/cell (**Fig. 19B**).

20 [0068] **Figs. 20A-D** graphically depict viral parameters monitored at day 7 following HBV/HDV Coinfection with two different treatment modalities (Concomitant or 1-day post-Coinfection). **Fig. 20A** depicts HDV RNA viremia quantification by qRT-PCR after treatments given at the time of infection. **Fig. 20B** depicts HDV RNA viremia quantification by qRT-PCR after treatments given at 1-day post-Coinfection.
25 **Fig. 20C** depicts effect of treatments given at the time of Coinfection on HBsAg secretion quantification by CLIA. **Fig. 20D** depicts effect of treatments given at 1-day post-Coinfection on HBsAg secretion quantification by CLIA assay.

[0069] **Figs. 21A-E** graphically depict viral parameters monitored at day 7 following HBV/HDV genotype-3 Coinfection in Cryo-PHH after IFA25 and Pegasys treatment. **Fig. 21A** depicts HDV RNA viremia quantification by qRT-PCR.
30 **Fig. 21B** depicts HD-Ag expression in western blot from intracellular cryo-PHH.

Fig. 21C depicts HBsAg secretion quantification by CLIA assay. **Fig. 21D** depicts HBeAg secretion quantification by CLIA assay. **Fig. 21E** HBV DNA viremia quantification by ddPCR.

[0070] **Figs. 22A-G** graphically depict the assessment of Myrcludex-B compatibility with IFA25 and Pegasys (control) on viral parameters monitored at day 7 following HBV/HDV Coinfection. **Fig. 22A** depicts inhibitory concentration estimation from a dose range effect of Myrcludex-B given at the time of infection on HDV RNA viremia quantification by qRT-PCR. **Fig. 22B** depicts effect of IFA25 dose range given in addition to Myrcludex-B on HDV RNA viremia quantification by qRT-PCR. **Fig. 22C** depicts effect of Pegasys dose range given in addition to Myrcludex-B on HDV RNA viremia quantification by qRT-PCR. **Fig. 22D** depicts effect of IFA25 dose range given in addition to Myrcludex-B on HBsAg secretion quantified by CLIA assay. **Fig. 22E** depicts effect of Pegasys dose range given in addition to Myrcludex-B on HBsAg secretion quantification by CLIA assay. **Fig. 22F** depicts effect of IFA25 dose range given in addition to Myrcludex-B on cell viability assessed by Cell TiterGlo assay. **Fig. 22G** depicts effect of Pegasys dose range given in addition to Myrcludex-B on cell viability assessed by Cell TiterGlo assay.

[0071] **Figs. 23A-I** graphically depict the assessment of Tenofovir compatibility with IFA25 and Pegasys (control) on viral parameters monitored at day 7 following HBV/HDV Coinfection. **Fig. 23A** depicts inhibitory concentration estimation from a dose range effect of Tenofovir given at the time of infection on HBV DNA viremia quantification by qRT-PCR. **Fig. 23B** depicts effect of IFA25 dose range given in addition to tenofovir on HBV DNA viremia quantification by qRT-PCR. **Fig. 23C** depicts effect of Pegasys dose range given in addition to Tenofovir on HBV DNA viremia quantification by qRT-PCR. **Fig. 23D** depicts effect of IFA25 dose range given in addition to Tenofovir on HBsAg secretion quantified by CLIA assay. **Fig. 23E** depicts effect of Pegasys dose range given in addition to Tenofovir on HBsAg secretion quantification by CLIA assay. **Fig. 23F** depicts effect of IFA25 dose range given in addition to tenofovir on HDV RNA viremia quantification by qRT-PCR. **Fig. 23G** depicts effect of Pegasys dose range given in addition to tenofovir on HDV RNA viremia quantification by qRT-PCR. **Fig. 23H** depicts effect of IFA25 dose range given in addition to Tenofovir on cell viability assessed by Cell

TiterGlo assay. **Fig. 23I** depicts effect of Pegasys dose range given in addition to Tenofovir on cell viability assessed by Cell TiterGlo assay.

[0072] The foregoing and other features and advantages of the present invention will be more fully understood from the following detailed description of illustrative
5 embodiments taken in conjunction with the accompanying drawings.

DETAILED DESCRIPTION

[0073] It will be understood that any of the definitions and embodiments described and/or claimed herein are intended to be definitions and embodiments applicable to all aspects, embodiments, items and matters of the invention. For example, it will be
10 understood that the teaching and explanations provided herein in respect of suitable ways or embodiments of preparing, formulating and administering the interferon-associated antigen binding proteins of the invention, or nucleic acids encoding or expressing same, and routes of their administration, suitable dosages and administration regimens therefor, apply *mutatis mutandis* to the cluster of
15 differentiation factor 40 (CD40) agonists or functional fragments thereof, the interferons (IFNs) or functional fragments thereof, or nucleic acids encoding or expressing same, or the combinations thereof as described or claimed herein.

[0074] The present invention is based in part on the discovery of a therapy that is based on the use of “interferon-associated antigen-binding proteins”, variants or
20 derivatives thereof comprising (I) an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and (II) an interferon (IFN) or a functional fragment thereof in Hepatitis delta virus therapy. Said interferon-associated antigen-binding proteins reduce viral burden in Hepatitis delta virus-infected cells, inhibit Hepatitis delta virus infection, rescue cells from Hepatitis delta virus-induced cell
25 death and from Hepatitis delta virus-induced cytopathic effect and enhance the IFN pathway in uninfected and infected cells, and may even act in a synergistic fashion. Hepatitis delta virus therapy comprising administering an interferon-associated antigen-binding protein to a Hepatitis delta virus-infected cell, or a subject infected with Hepatitis delta virus, is provided.

[0075] The invention may be more readily understood in the light of the selected terms defined below.

[0076] As used herein, the term “**CD40**” refers to “Cluster of differentiation 40”, a member of the tumor necrosis factor receptor (TNFR) superfamily. A concordance list of CD40 nomenclature is recited in Table B, which is derived from the HUGO Gene Nomenclature Committee (HGNC) (see, Gray et al. Nucleic Acids Res. 43: D1079-1085 (2015); HGNC Database, HUGO Gene Nomenclature Committee (HGNC), EMBL Outstation - Hinxton, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK www.genenames.org) . The Approved Symbol denotes the HGNC symbol applied to a particular gene and the Approved Name corresponds to the full spelling of the gene. Previous Symbols denotes any previous symbol used by HGNC or refer to a particular gene. Synonyms refer to alternative, synonymous names for a particular gene. CD40 is a costimulatory protein found on antigen presenting cells (e.g., B cells, dendritic cells, monocytes), hematopoietic precursors, endothelial cells, smooth muscle cells, epithelial cells, as well as the majority of human tumors (Grewal & Flavell, Ann. Rev. Immunol., 1996, 16: 111-35; Toes & Schoenberger, Seminars in Immunology, 1998, 10(6): 443-8).

[0077] The binding of the natural ligand CD154 (CD40L) on T_H cells to CD40 activates antigen presenting cells and induces a variety of downstream effects. The TNF-receptor associated factor adaptor proteins TRAF1, TRAF2, TRAF6 and TRAF5 interact with CD40 and serve as mediators of the signal transduction. Ultimately, CD40 signaling activates both the canonical and the noncanonical NF- κ B pathways.

[0078] A concordance list of CD40 ligand nomenclature is recited below in Table A, derived from the HUGO Gene Nomenclature Committee (HGNC) (see, Gray et al. Nucleic Acids Res. 43: D1079-1085 (2015); HGNC Database, HUGO Gene Nomenclature Committee (HGNC), EMBL Outstation - Hinxton, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK www.genenames.org). The Approved Symbol denotes the HGNC symbol applied to a particular gene and the Approved Name

corresponds to the full spelling of the gene. Previous Symbols denotes any previous symbol used by HGNC or refer to a particular gene. Synonyms refer to alternative, synonymous names for a particular gene.

Table A. *Concordance list of CD40 ligand nomenclature*

Approved Symbol	Approved Name	Previous Symbols	Synonyms
CD40LG	CD40 ligand	TNFSF5, HIGM1, IMD3	CD40L, TRAP, gp39, hCD40L, CD154

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Table B. *Concordance list of CD40 nomenclature*

Approved Symbol	Approved Name	Previous Symbols	Synonyms
CD40	CD40 molecule	TNFRSF5	p50, Bp50

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[0079] As used herein, a "**CD40 agonist**" refers to a compound (e.g., protein, a fusion protein, a polypeptide, an antibody, an antigen-binding fragment of an antibody or the like) that activates CD40. For example, a CD40 agonist may be an agonistic antibody directed against CD40 or a functional fragment thereof, or a soluble CD40 agonist including but not limited to its natural ligand or a functional fragment thereof.

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[0080] In certain exemplary embodiments, a CD40 agonist is an agonistic antibody directed against CD40. In other certain exemplary embodiments, a CD40 agonist is CD40L.

[0081] As used herein, the term "**functional fragment**" refers to a fragment of a substance that retains one or more functional activities of the original substance, preferably all of the functional activities. For example, a functional fragment of a

CD40 agonist refers to a fragment of a CD40 agonist that retains a function of the CD40 agonist as described and/or claimed herein, e.g., it activates a target CD40.

[0082] As used herein, the term “**ligand**” refers to any substance capable of binding, or of being bound, to another substance. A ligand may be a peptide, a polypeptide, a protein, an aptamer, a polysaccharide, a sugar molecule, a carbohydrate, a lipid, an oligonucleotide, a polynucleotide, a synthetic molecule, an inorganic molecule, an organic molecule, and any combination thereof. Preferably, the ligand is a polypeptide.

Agonistic anti-CD40 antibodies and antigen binding fragments thereof

[0083] As used herein, the term “**antibody**” refers to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated VH or V_H) and a heavy chain constant region (CH or C_H). The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated VL or V_L) and a light chain constant region (CL or C_L). The light chain constant region comprises one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed “**complementarity determining regions (CDRs)**”, interspersed with regions that are more conserved, termed “**framework regions**” (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Framework regions can aid in maintaining the proper conformation of the CDRs to promote binding between the antigen binding region and an antigen.

[0084] The most commonly used immunoglobulin for therapeutic applications is immunoglobulin G (or IgG), a tetrameric glycoprotein. In a naturally-occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one light (about 25 kDa) and one heavy chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The

carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Immunoglobulins can be assigned to different classes depending on the amino acid sequence of the constant domain of their heavy chains.

- 5 **[0085]** Heavy chains are classified as mu (μ), delta (δ), gamma (γ), alpha (α), and epsilon (ϵ), and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Several of these may be further divided into subclasses or isotypes, e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. Different isotypes have different effector functions; for example, IgG1 and IgG3 isotypes have antibody-dependent cellular
- 10 cytotoxicity (ADCC) activity. In preferred embodiments, the agonistic antiCD40 antibodies or agonistic antigen binding fragments thereof comprised in the interferon-associated antigen binding proteins according to the invention are of the IgG class. In more preferred embodiments, the agonistic antiCD40 antibodies or agonistic antigen binding fragments thereof comprised in the interferon-associated
- 15 antigen binding proteins according to the invention are of the IgG1 or IgG3 subclasses. In specifically preferred embodiments, the agonistic antiCD40 antibodies or agonistic antigen binding fragments thereof comprised in the interferon-associated antigen binding proteins according to the invention are of the IgG1 subclass. In other more preferred embodiments, the agonistic antiCD40 antibodies or agonistic antigen
- 20 binding fragments thereof comprised in the interferon-associated antigen binding proteins according to the invention are of the IgG2 or IgG4 subclasses. In specifically preferred embodiments, the agonistic antiCD40 antibodies or agonistic antigen binding fragments thereof comprised in the interferon-associated antigen binding proteins according to the invention are of the IgG2 subclass.
- 25 **[0086]** Human light chains are classified as kappa (κ) and lambda (λ) light chains. Accordingly, in some embodiments, the agonistic antiCD40 antibodies or agonistic antigen binding fragments thereof comprised in the interferon-associated antigen binding proteins according to the invention comprise a light chain of the κ class. In other embodiments, the agonistic antiCD40 antibodies or agonistic antigen binding
- 30 fragments thereof comprised in the interferon-associated antigen binding proteins according to the invention comprise a light chain of the λ class. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12

or more amino acids, wherein the heavy chain additionally includes a "D" region of about 10 more amino acids. See generally, Fundamental Immunology, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)).

5 [0087] The term “**antibody**” further includes, but is not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to as “antibody mimetics”), chimeric antibodies, humanized antibodies, human antibodies, and fragments thereof, respectively. Unless otherwise indicated, the term “antibody” includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, 10 variants, antigen binding fragments, and muteins thereof, examples of which are described below.

[0088] As used herein, the term “**agonistic CD40 antibody**” or “**agonistic anti-CD40 antibody**” refers to an antibody that binds to CD40 and mediates CD40 signaling. In a preferred embodiment, it binds to human CD40. As described below, 15 binding to CD40 may be determined using surface plasmon resonance, preferably using the BIAcore® system. The agonistic anti-CD40 antibody may increase one or more CD40 activities by at least about 20% when added to a cell, tissue or organism expressing CD40. In some embodiments, the antibody activates CD40 activity by at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 85%. 20 **CD40 activity** of the agonistic anti-CD40 antibody may be measured using a whole blood surface molecule upregulation assay or using an *in vitro* reporter cell assay, e.g., using HEK-Blue™ CD40L cells (InvivoGen Cat. #: hkb-cd40), as described in greater detail in Example I. These reporter cells were generated by stable transfection of HEK293 cells with the human CD40 gene and an NFκB-inducible secreted embryonic alkaline phosphatase (SEAP) construct to measure the activity of CD40 25 agonists. Stimulation of CD40 leads to NFκB activation and thus to production of SEAP, which can be detected in the supernatant using chromogenic substrates such as QUANTI-Blue™.

30 [0089] In the context of the present invention, the interferon-associated antigen binding proteins activate both the CD40 and an IFN pathway. In certain embodiments, the interferon-associated antigen binding protein activates the CD40

pathway with an EC₅₀ of less than 400, 300, 200, 150, 100, 70, 60, 50, 40, 30, 25, 20, or 15 ng/mL, wherein CD40 activity is preferably determined using an in vitro reporter cell assay, optionally using HEK-Blue™ CD40L cells, as described for instance in Example I.

5 In more specific embodiments, the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ ranging from 10 to 200 ng/mL. In even more specific embodiments, the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ ranging from 10 to 50 ng/mL, preferably 10 to 30 ng/mL.

10 **[0090]** Examples of suitable agonistic anti-CD40 antibodies include, but are not limited to, CP870,893 (Pfizer / Roche), SGN-40 (Seattle Genetics), ADC-1013 (Janssen / Alligator BioSciences), Chi Lob 7/4 (University of Southampton), dacetumumab (Seattle Genetics), APX005M (Apexigen, Inc.), 3G5 (Celldex) and CDX-1140 (Celldex). Exemplary light and heavy chain sequences of the agonistic anti-CD40 antibody CP870,893 are shown in **Table 7**. Exemplary light and heavy chain sequences of the agonistic anti-CD40 antibody 3G5 are shown in **Table 8**.

15 **[0091]** As used herein, the term “**agonistic antigen binding fragment**” of an agonistic anti-CD40 antibody refers to a fragment of an agonistic anti-CD40 antibody that retains one or more functional activities of the original antibody, such as the ability to bind to and act as an agonist of CD40 signaling in a cell, e.g., it mediates CD40 pathway signaling. Such fragment may compete with the intact antibody for binding to CD40.

20 **[0092]** Agonistic antigen binding fragments of an agonistic anti-CD40 antibody can be produced by recombinant DNA techniques, or can be produced by enzymatic or chemical cleavage of an anti-CD40 antibody. Agonistic antigen binding fragments include, but are not limited to, a Fab fragment, a diabody (heavy chain variable domain on the same polypeptide as a light chain variable domain, connected via a short peptide linker that is too short to permit pairing between the two domains on the same chain), a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, domain antibodies and single-chain antibodies, and can be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit.

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[0093] The term “**variable region**” or “**variable domain**” refers to a portion of the light and/or heavy chains of an antibody, typically including approximately the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino terminal amino acids in the light chain. Variable regions of different antibodies differ extensively in amino acid sequence even among antibodies derived from the same species or of the same class. Exemplary V_L and V_H domain sequences of the agonistic anti-CD40 antibody CP870,893 are shown in **Table 1**. The variable region of an antibody typically determines specificity of a particular antibody for its target as it contains the CDRs. **Table 1** also shows exemplary CDR sequences of the agonistic anti-CD40 antibody CP870,893.

Table 1. *Anti-CD40 antibody heavy/light chain variable regions and CDRs of the agonistic anti-CD40 antibody CP870,893. Bold italicized sequences correspond to CDR regions according to the Kabat definition.*

Anti-CD40 antibody regions	Sequence
antiCD40 Antibody V _L domain (SEQ ID NO 51)	DIQMTQSPSSVSASVGDRVTITCRAS <i>QGIYSWLA</i> WYQQKPGKAPNLLIY <i>TASTLQ</i> SGVPSRFSGSGS GTDFTLTISSLQPEDFATYYC <i>QQANIFPLT</i> FGGG TKVEIK
antiCD40 Antibody CDRL1 (SEQ ID NO 52)	RAS <i>QGIYSWLA</i>
antiCD40 Antibody CDRL2 (SEQ ID NO 53)	<i>TASTLQ</i> S
antiCD40 Antibody CDRL3 (SEQ ID NO 54)	<i>QQANIFPLT</i>

antiCD40 Antibody V _H domain (SEQ ID NO 55)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGY YMHWRQAPGQGLEWMGWINPDSGGTNYAQ KFQGRVTMTRDTSISTAYMELNRLRSDDTAVY YCARDQPLGYCTNGVCSYFDYWGQGTLVTVSS
antiCD40 Antibody CDRH1 (SEQ ID NO 56)	TGYMH
antiCD40 Antibody CDRH2 (SEQ ID NO 57)	WINPDSGGTNYAQKFQG
antiCD40 Antibody CDRH3 (SEQ ID NO 58)	DQPLGYCTNGVCSYFDY

[0094] Delineation of a CDR and identification of residues comprising the binding site of an antibody may be accomplished by solving the structure of the antibody and/or solving the structure of the antibody-ligand complex. This can be accomplished by any of a variety of techniques known to those skilled in the art, such as X-ray crystallography. Various methods of analysis can be employed to identify or approximate the CDR regions. Examples of such methods include, but are not limited to, the Kabat definition, the Chothia definition, the AbM definition and the contact definition.

[0095] The Kabat definition is a standard for numbering the residues in an antibody and is typically used to identify CDR regions. *See, e.g.,* Johnson & Wu, *Nucleic Acids Res.*, 28: 214-8 (2000). The Chothia definition is similar to the Kabat definition, but the Chothia definition takes into account positions of certain structural loop regions. *See, e.g.,* Chothia *et al.*, *J. Mol. Biol.*, 196: 901-17 (1986); Chothia *et al.*, *Nature*, 342: 877-83 (1989). The AbM definition uses an integrated suite of computer programs produced by Oxford Molecular Group that model antibody structure. *See, e.g.,* Martin *et al.*, *Proc Natl Acad Sci (USA)*, 86:9268-9272 (1989); "AbMTM, A Computer Program for Modeling Variable Regions of Antibodies,"

Oxford, UK; Oxford Molecular, Ltd. The AbM definition models the tertiary structure of an antibody from primary sequence using a combination of knowledge databases and *ab initio* methods, such as those described by Samudrala *et al.*, “*Ab Initio* Protein Structure Prediction Using a Combined Hierarchical Approach,” in PROTEINS, Structure, Function and Genetics Suppl., 3:194-198 (1999). The contact definition is based on an analysis of the available complex crystal structures. *See, e.g.,* MacCallum *et al.*, J. Mol. Biol., 5:732-45 (1996).

[0096] In certain embodiments, the complementarity determining regions (CDRs) of the light and heavy chain variable regions of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof, can be grafted to framework regions (FRs) from the same, or another, species. In certain embodiments, the CDRs of the light and heavy chain variable regions of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof, can be grafted to consensus human FRs. To create consensus human FRs, in certain embodiments, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. In certain embodiments, the FRs of the heavy chain or light chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof, are replaced with the FRs from a different heavy chain or light chain. In certain embodiments, rare amino acids in the FRs of the heavy and light chains of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof, are not replaced, while the rest of the FR amino acids are replaced. Rare amino acids are specific amino acids that are in positions in which they are not usually found in FRs. In certain embodiments, the grafted variable regions from an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof, can be used with a constant region that is different from the constant region of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof. In certain embodiments, the grafted variable regions are part of a single chain Fv antibody. CDR grafting is described, e.g., in U.S. Patent Nos. 6,180,370, 6,054,297, 5,693,762, 5,859,205, 5,693,761, 5,565,332, 5,585,089, and 5,530,101, and in Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-327 (1988); Verhoeyen *et al.*, Science, 239:1534-1536 (1988), Winter, FEBS Letts., 430:92-94 (1998), which are hereby incorporated by reference for any purpose.

[0097] An “Fc” region typically comprises two heavy chain fragments comprising the C_{H2} and C_{H3} domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_{H3} domains.

5 [0098] A “**Fab fragment**” comprises one full-length light chain as well as the C_{H1} and variable regions of one heavy chain (the combination of the V_H and C_{H1} regions is referred to herein as “**fab region heavy chain**”).

[0099] A “**Fab’ fragment**” comprises one light chain and a portion of one heavy chain that contains the V_H domain and the C_{H1} domain and also the region between
10 the C_{H1} and C_{H2} domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab’ fragments to form an F(ab’)₂ molecule.

[00100] A “**F(ab’)₂ fragment**” contains two light chains and two heavy chains containing a portion of the constant region between the C_{H1} and C_{H2} domains, such that an interchain disulfide bond is formed between the two heavy chains. A F(ab’)₂
15 fragment thus is composed of two Fab’ fragments that are held together by a disulfide bond between the two heavy chains.

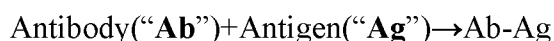
[00101] The “**Fv region**” comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

[00102] “**Single-chain antibodies**” are Fv molecules in which the heavy and light chain variable regions have been connected by a flexible linker to form a single polypeptide chain, which forms an antigen binding region. Single chain antibodies are discussed in detail in International Patent Application Publication No. WO 88/01649 and United States Patent Nos. 4,946,778 and No. 5,260,203, the disclosures of which are incorporated by reference.
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25 [00103] A “**domain antibody**” is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody can target the same or different antigens.

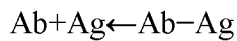
[00104] An antibody or antigen binding protein, such as an interferon-associated antigen binding protein according to the invention, preferably binds to its target antigen with a dissociation constant (K_d) of $\leq 10^{-7}$ M. The antibody or antigen binding protein binds its antigen with “high affinity” when the K_d is $\leq 5 \times 10^{-9}$ M, and with “very high affinity” when the K_d is $\leq 5 \times 10^{-10}$ M. More preferably, the antibody or antigen binding protein has a K_d of $\leq 10^{-9}$ M. In some embodiment, the off-rate is $< 1 \times 10^{-5}$. In other embodiments, the antibody or antigen binding protein will bind to human CD40 with a K_d of between about 10^{-9} M and 10^{-13} M, and in yet another embodiment the antibody or antigen binding protein will bind with a $K_d \leq 5 \times 10^{-10}$. As will be appreciated by one of skill in the art, in some embodiments, any or all of the antigen binding fragments can bind to CD40. Preferably, said constants are determined using surface plasmon resonance, more preferably using the BIAcore® system.

[00105] The term “**surface plasmon resonance**” means an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore® system (BIAcore International AB, a GE Healthcare company, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jönsson et al. (1993) Ann. Biol. Clin. 51:19-26. The term “ **K_{on}** ” means the on rate constant for association of a binding protein (e.g., an antibody or antigen binding protein) to the antigen to form the, e.g., antigen binding protein/antigen complex. The term “ **K_{on}** ”, or “**on-rate**” also means “**association rate constant**”, or “**ka**”, as is used interchangeably herein. This value indicating the binding rate of a binding protein to its target antigen or the rate of complex formation between a binding protein, e.g., an antibody or an antigen binding protein, and antigen also is shown by the equation below:



[00106] The term “ **K_{off}** ”, or “**off-rate**”, means the off rate constant for dissociation, or “**dissociation rate constant**”, of a binding protein (e.g., an antibody or antigen binding protein) from the, e.g., antigen binding protein/antigen complex as is known in the art. This value indicates the dissociation rate of a binding protein, e.g., an antibody or an antigen binding protein, from its target antigen or separation of Ab-

Ag complex over time into free antibody and antigen as shown by the equation below:



[00107] The terms “**K_d**” and “**equilibrium dissociation constant**” means the value obtained in a titration measurement at equilibrium, or by dividing the dissociation rate constant (K_{off}) by the association rate constant (K_{on}). The association rate constant, the dissociation rate constant and the equilibrium dissociation constant, are used to represent the binding affinity of a binding protein (e.g., an antibody or an antigen binding protein) to an antigen. Methods for determining association and dissociation rate constants are well known in the art. Using fluorescence-based techniques offers high sensitivity and the ability to examine samples in physiological buffers at equilibrium. Other experimental approaches and instruments such as a BIAcore® (biomolecular interaction analysis) assay, can be used (e.g., instrument available from BIAcore International AB, a GE Healthcare company, Uppsala, Sweden). Additionally, a KinExA® (Kinetic Exclusion Assay) assay, available from Sapidne Instruments (Boise, Id.), can also be used.

[00108] An antigen binding protein according to the invention may bind to one target with an affinity at least one order of magnitude, preferably at least two orders of magnitude higher than for a second target.

[00109] The term “**target**” refers to a molecule or a portion of a molecule capable of being bound by an antigen binding protein. In certain embodiments, a target can have one or more epitopes. It will therefore be understood that the target may serve as “antigen” for the “antigen binding protein” of the present invention.

[00110] The term “**epitope**” includes any determinant capable of being bound by an antigen binding protein, such as an antibody. An epitope is a region of an antigen that is bound by an antigen binding protein that targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antigen binding protein. Most often, epitopes reside on proteins, but in some instances can reside on other kinds of molecules, such as nucleic acids. Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three-dimensional

structural characteristics, and/or specific charge characteristics. Generally, antibodies specific for a particular target antigen will preferentially/specifically recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

5 [00111] In exemplary embodiments, the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof forming part (I) of the interferon-associated antigen binding proteins of the invention comprises three light chain complementarity determining regions (CDRs) that are at least 90% identical to the CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain
10 CDRs that are at least 90% identical to the CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6. The agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, may also comprise three light chain complementarity determining regions (CDRs) that are identical to the CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs that are identical to the
15 CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6. In such embodiments, each CDR is defined in accordance with the Kabat definition, the Chothia definition, the AbM definition, or the contact definition of CDR; preferably wherein each CDR is defined in accordance with the CDR definition of Kabat or the CDR definition of Chothia. In particular embodiments, each CDR is defined in
20 accordance with the Kabat definition. In other particular embodiments, each CDR is defined in accordance with the Chothia definition.

[00112] Alternatively, the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof forming part (I) of the interferon-associated antigen binding proteins of the invention may comprise (a) a heavy chain or a fragment thereof
25 comprising a complementarity determining region (CDR) CDRH1 that is at least 90%, at least 95%, at least 98% or at least 99% identical to SEQ ID NO 56, a CDRH2 that is at least 90%, at least 95%, at least 98% or at least 99% identical to SEQ ID NO 57, and a CDRH3 that is at least 90%, at least 95%, at least 98% or at least 99% identical to SEQ ID NO 58; and (b) a light chain or a fragment thereof comprising a
30 CDRL1 that is at least 90%, at least 95%, at least 98% or at least 99% identical to SEQ ID NO 52, a CDRL2 that is at least 90%, at least 95%, at least 98% or at least

99% identical to SEQ ID NO 53, and a CDRL3 that is at least 90%, at least 95%, at least 98% or at least 99% identical to SEQ ID NO 54.

5 [00113] In some embodiments, the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to SEQ ID NO 58; and (b) a light chain or a fragment thereof comprising a CDRL1 that is identical to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a CDRL3 that is identical to SEQ ID NO 54.

10 [00114] More specifically the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a light chain variable region V_L comprising the sequence as set forth in SEQ ID NO 51, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain variable region V_H comprising the sequence as set forth in SEQ ID NO 55, or a sequence at least 90%,
15 at least 95%, at least 98% or at least 99% identical thereto.

[00115] The interferon-associated antigen binding proteins of the invention may also comprise an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, comprising a Fab region heavy chain comprising an amino acid sequence as set forth in SEQ ID NO 12, or a sequence at least 90%, at least 95%, at least 98% or
20 at least 99% identical thereto.

[00116] In some embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises
25 a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 12 and SEQ ID NO 50, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

[00117] In more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that
30 comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC)

that comprises a sequence as set forth in SEQ ID NO 6, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

5 [00118] In more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises a sequence as set forth in SEQ ID NO 9, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

10 [00119] In other more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises a sequence as set forth in SEQ ID NO 49, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

15 [00120] In other more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises a sequence as set forth in SEQ ID NO 12, or a sequence at least 90%,
20 at least 95%, at least 98% or at least 99% identical thereto.

[00121] In other more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC)
25 that comprises a sequence as set forth in SEQ ID NO 50, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

[00122] In some embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 59, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises
30 a sequence selected from the group consisting of SEQ ID NO 61, SEQ ID NO 63 and

SEQ ID NO 65, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

5 [00123] In more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 59, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises a sequence as set forth in SEQ ID NO 61, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

10 [00124] In other more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 59, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises a sequence as set forth in SEQ ID NO 63, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto.

15 [00125] In other more specific embodiments, the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 59, or a sequence at least 90%, at least 95%, at least 98% or at least 99% identical thereto; and/or a heavy chain (HC) that comprises a sequence as set forth in SEQ ID NO 65, or a sequence at least 90%,
20 at least 95%, at least 98% or at least 99% identical thereto.

Variants and derivatives of interferon-associated antigen binding protein or components thereof

[00126] A “variant” of a polypeptide (*e.g.*, an interferon-associated antigen binding protein, an interferon-fused agonistic anti-CD40 antibody or an interferon-fused
25 agonistic antigen binding fragment thereof, an antibody, an antigen binding protein, or an IFN, or components thereof) comprises an amino acid sequence wherein one, two, three, four, five or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Preferably, the variant comprises up to ten insertions, deletions and/or
30 substitutions, more preferably up to eight insertions, deletions and/or substitutions.

More specifically, the variant may comprise up to ten, more preferably up to eight insertions. The variant may also comprise up to ten, more preferably up to eight deletions. In even more preferred embodiments, the variant comprises up to ten substitutions, most preferably up to eight substitutions. In some embodiments, these
5 substitutions are conservative amino acid substitution as described below.

[00127] A "**variant**" of a polynucleotide sequence (e.g., RNA or DNA) comprises one or more mutations within the polynucleotide sequence relative to another polynucleotide sequence, wherein one, two, three, four, five or more nucleic acid residues are inserted into, deleted from and/or substituted into the nucleic acid
10 sequence. Preferably, the variant comprises up to ten insertions, deletions and/or substitutions, more preferably up to eight insertions, deletions and/or substitutions. More specifically, the variant may comprise up to ten, more preferably up to eight insertions. The variant may also comprise up to ten, more preferably up to eight deletions. In even more preferred embodiments, the variant comprises up to ten
15 substitutions, most preferably up to eight substitutions. Said one, two, three, four, five or more mutations can cause one, two, three, four, five or more amino acid exchanges within the amino acid sequence the variant encodes for as compared to another amino acid sequence (i.e. a "*non-silent mutation*"). Variants also include nucleic acid sequences wherein one, two, three, four, five or more codons have been
20 replaced by their synonyms which does not cause an amino acid exchange and is thus called a "*silent mutation*".

[00128] The term "**identity**" or "**homology**", in the context of variants of polypeptide or nucleotide sequences, refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined
25 by aligning and comparing the sequences. "**Percent identity**" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. Preferably, identity is determined over the full length of a sequence. It is understood that the expression "at least 80% identical", includes embodiments wherein the
30 described or claimed sequence is at least 85%, preferably at least 90%, more preferably at least 95%, more preferably at least 98% or still more preferably at least 99% identical to the reference sequence. The expression "at least 90% identical"

includes embodiments wherein the described or claimed sequence is at least 90%, preferably at least 91%, more preferably at least 92%, more preferably at least 93%, more preferably at least 94%, more preferably at least 95%, more preferably at least 96%, more preferably at least 97%, more preferably at least 98% or still more preferably at least 99% identical to the reference sequence.

[00129] For the calculation of percent identity, gaps in alignments (if any) are preferably addressed by a particular mathematical model or computer program (*i.e.*, an “algorithm”). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in *Computational Molecular Biology*, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; *Biocomputing Informatics and Genome Projects*, (Smith, D. W., ed.), 1993, New York: Academic Press; *Computer Analysis of Sequence Data, Part I*, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., 1987, *Sequence Analysis in Molecular Biology*, New York: Academic Press; *Sequence Analysis Primer*, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo *et al.*, 1988, *SIAM J. Applied Math.* 48:1073.

[00130] In calculating percent identity, the sequences being compared are typically aligned in a way that gives the largest match between the sequences. One example of a computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux *et al.*, 1984, *Nucl. Acid Res.* 12:387; Genetics Computer Group, University of Wisconsin, Madison, WI). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span”, as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the “average diagonal” is the average of the diagonal of the comparison matrix being used; the “diagonal” is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSum 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (*see*, Dayhoff *et al.*, 1978, *Atlas of Protein Sequence and Structure* 5:345-352

for the PAM 250 comparison matrix; Henikoff *et al.*, 1992, *Proc. Natl. Acad. Sci. U.S.A.* 89:10915-10919 for the BLOSum 62 comparison matrix) is also used by the algorithm.

5 [00131] Examples of parameters that can be employed in determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

- Algorithm: Needleman *et al.*, 1970, *J. Mol. Biol.* 48:443-453
- Comparison matrix: BLOSum 62 from Henikoff *et al.*, 1992, *supra*
- Gap Penalty: 12 (but with no penalty for end gaps)
- Gap Length Penalty: 4
- 10 • Threshold of Similarity: 0

[00132] Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method
15 (GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 or at least 100, preferably the entire length, of contiguous amino acids of the target polypeptide.

[00133] Conservative amino acid substitutions can encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide
20 synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

[00134] Naturally occurring residues can be divided into classes based on common side chain properties:

- 25 1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;
- 2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
- 3) acidic: Asp, Glu;
- 4) basic: His, Lys, Arg;
- 5) residues that influence chain orientation: Gly, Pro; and
- 6) aromatic: Trp, Tyr, Phe.

5 [00135] For example, non-conservative substitutions can involve the exchange of a member of one of these classes for a member from another class. Such substituted residues can be introduced, for example, into regions of a human antibody that are homologous with non-human antibodies, or into the non-homologous regions of the molecule.

[00136] In making changes to the interferon-associated antigen binding protein, according to certain embodiments, the hydrophathic index of amino acids can be considered. Each amino acid has been assigned a hydrophathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

15 [00137] The importance of the hydrophathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte *et al.*, J. Mol. Biol., 157:105-131 (1982). It is known that certain amino acids can be substituted for other amino acids having a similar hydrophathic index or score and still retain a similar biological activity. In making changes based upon the hydrophathic index, in certain embodiments, the substitution of amino acids whose hydrophathic indices are within ± 2 is included. In certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included.

25 [00138] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

30 [00139] The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 $\pm$ 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5)

and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2 is included, in certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included.

5 [00140] Exemplary amino acid substitutions are set forth in **Table 2**.

Table 2. *Amino Acid Substitutions.*

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala, Gly	Ala
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe

Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu
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5 [00141] In light of the present invention, a skilled artisan will be able to determine suitable variants of the interferon-associated antigen binding proteins as set forth herein using well-known techniques. In certain embodiments, one skilled in the art can identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. In certain
10 embodiments, one can identify residues and portions of the molecules that are conserved among similar polypeptides. In certain embodiments, even areas that can be important for biological activity or for structure can be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[00142] Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important
15 for activity or structure in similar proteins. One skilled in the art can opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

[00143] One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar proteins or protein
20 domains. In view of such information, one skilled in the art can predict the alignment of amino acid residues of interferon-associated antigen binding protein, an antibody or an antigen binding fragment thereof or an interferon or a functional fragment thereof as described herein with respect to its three dimensional structure. In certain
25 embodiments, one skilled in the art can choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues can be involved in important interactions with other molecules. Moreover, one skilled in the art can generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such variants can be used to gather information

about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change can be avoided. In other words, based on information gathered from such experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

[00144] According to certain embodiments, amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and/or (5) confer or modify other physicochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) can be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). In certain embodiments, a conservative amino acid substitution typically may not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden & J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et al.*, Nature, 354:105 (1991), which are each incorporated herein by reference.

[00145] The term “**derivative**” refers to a molecule that includes a chemical modification other than an insertion, deletion, or substitution of amino acids (or nucleic acids). In certain embodiments, derivatives comprise covalent modifications, including, but not limited to, chemical bonding with polymers, lipids, or other organic or inorganic moieties. In certain embodiments, a chemically modified interferon-associated antigen binding protein can have a greater circulating half-life than an interferon-associated antigen binding protein that is not chemically modified. In certain embodiments, a chemically modified interferon-associated antigen binding

protein can have improved targeting capacity for desired cells, tissues, and/or organs. In some embodiments, a derivative interferon-associated antigen binding protein is covalently modified to include one or more water-soluble polymer attachments, including, but not limited to, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. *See, e.g.*, U.S. Patent Nos: 4,640,835, 4,496,689, 4,301,144, 4,670,417, 4,791,192 and 4,179,337. In certain embodiments, a derivative interferon-associated antigen binding protein comprises one or more polymer, including, but not limited to, monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of such polymers.

[00146] In certain embodiments, a derivative of an interferon-associated antigen binding protein as described herein is covalently modified with polyethylene glycol (PEG) subunits. In certain embodiments, one or more water-soluble polymer is bonded at one or more specific position, for example at the amino terminus, of a derivative. In certain embodiments, one or more water-soluble polymer is randomly attached to one or more side chains of a derivative. In certain embodiments, PEG is used to improve the therapeutic capacity of the interferon-associated antigen binding protein. Certain such methods are discussed, for example, in U.S. Patent No. 6,133,426, which is hereby incorporated by reference for any purpose.

[00147] In certain embodiments, interferon-associated antigen binding protein variants include glycosylation variants wherein the number and/or type of glycosylation site has been altered compared to the amino acid sequences of a parent polypeptide. In certain embodiments, protein variants comprise a greater number of N-linked glycosylation sites than the native protein. In other embodiments, protein variants comprise a lesser number of N-linked glycosylation sites than the native protein. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X can be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-

linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one, two, three, four, five or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. Additional preferred variants include

5 cysteine variants wherein one or more cysteine residues are deleted from or substituted for another amino acid (e.g., serine) as compared to the parent amino acid sequence. Cysteine variants can be useful when antibodies must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion

10 bodies. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

Hepatitis delta virus infection

[00148] The interferon-associated antigen binding proteins, the nucleic acids, vectors, vector systems, methods and compositions described herein can be used to treat

15 Hepatitis delta virus infection. Hepatitis delta virus (HDV) belongs to the *Kolmioviridae* family. The Hepatitis delta virus genome is composed of a negative single strand RNA. As used herein, “**treat Hepatitis delta virus infection**” and “**treatment of Hepatitis delta virus infection**” refers to one or more of: (i) reducing viral burden in Hepatitis delta virus-infected cells; (ii) inhibiting Hepatitis delta virus

20 infection; (iii) rescuing cells from Hepatitis delta virus-induced cell death; (iv) rescuing cells from Hepatitis delta virus-induced cytopathic effect; (v) decreasing one or more Hepatitis delta virus-related disorders; and (vi) decreasing one or more Hepatitis delta virus-related symptoms in a subject.

[00149] The terms “**viral load**”, “**viral titer**” and “**viral burden**” refer to the number

25 of viral particles in a cell, an organ or a bodily fluid such as blood or serum. Viral load or viral titer is often expressed as viral particles, or infectious particles per mL depending on the type of assay. Today, viral load is usually measured using international units per milliliter (IU/mL). Viral load or viral titer may alternatively be determined as so-called viral genome equivalent. A higher viral burden, titer, or

30 viral load often correlates with the severity of an active viral infection. Accordingly, reducing the viral load or viral titer correlates with a reduced number of infectious

viral particles, e.g., in the serum. Viral load is usually determined using nucleic acid amplification based tests (NATs or NAATs). NAT/NAAT tests utilize, for example, PCR, (quantitative) reverse transcription polymerase chain reaction (RT-PCR or qRT-PCR), nucleic acid sequence based amplification (NASBA) or probe-based assays. Due to the ease of detection of viral nucleic acids using nucleic acid amplification based tests, the viral load is useful in clinical settings to monitor success during treatment.

[00150] The terms “**patient**” and “**subject**” are used interchangeably and include human and non-human animal subjects, preferably human subjects, as well as those with formally diagnosed disorders, those without formally recognized disorders, those receiving medical attention, those at risk of developing the disorders, etc.

[00151] As used herein, a “**Hepatitis delta virus-related disorder**”, refers to a disorder that results from infection of a subject by Hepatitis delta virus.

[00152] As used herein, a “**Hepatitis delta virus-related symptom**,” a “**symptom of Hepatitis delta virus infection**” or a “**Hepatitis delta virus-related complication**” includes one or more physical dysfunctions related to Hepatitis delta virus infection.

[00153] On the one hand, “**acute hepatitis D**” caused by a simultaneous infection by both HBV and HDV is referred to as “**coinfection**” (Negro et al., Cold Spring Harb. Perspect. Med. 4: a021550 (2014)) while on the other hand, an HDV infection of an individual already chronically mono-infected with HBV is referred to as a HDV/HBV “**superinfection**”.

[00154] In **acute hepatitis**, simultaneous infection with HBV and HDV can lead to a mild-to-severe hepatitis. Symptoms include fever, fatigue, loss of appetite nausea, vomiting, dark urine, pale-colored stools, jaundice (yellow eyes) and even fulminant hepatitis. In a **superinfection**, HDV can infect a person already chronically infected with HBV. The superinfection of HDV on chronic hepatitis B accelerates progression to a more severe disease in all ages and in 70–90% of persons. HDV superinfection accelerates progression to cirrhosis almost a decade earlier than HBV mono-infected persons. (Source: WHO)

Interferons

- [00155] As used herein, an “**interferon**” or “**IFN**” refers to a cytokine, or derivative thereof, that is typically produced and released by cells in response to the presence of a pathogen or a tumor cell. IFNs include type I IFNs (e.g., IFN α , IFN β , IFN ϵ , IFN κ , IFN τ , IFN ζ and IFN ω), type II IFNs (e.g., IFN γ) and type III IFNs (e.g., IFN λ 1, IFN λ 2 and IFN λ 3). The term “interferon” or “IFN” includes without limitation full-length IFN, a variant or a derivative thereof (e.g., a chemically (e.g., PEGylated) modified derivative or mutein), or a functionally active fragment thereof, that retains one or more signaling activities of a full-length IFN.
- [00156] As used herein, the term “**functional fragment**” refers to a fragment of a substance that retains one or more functional activities of the original substance. For example, a functional fragment of an interferon refers to a fragment of an interferon that retains an IFN function as described herein, e.g., it mediates IFN pathway signaling.
- [00157] The IFN may increase one or more IFN receptor activities by at least about 20% when added to a cell, tissue or organism expressing a cognate IFN receptor (IFNAR for IFN α , IFNBR for IFN β , etc). In some embodiments, the interferon activates IFN receptor activity by at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 85%. The activity of the IFN (i.e., the “**IFN activity**”) may be measured, e.g., using an *in vitro* reporter cell assay, e.g., using HEK-Blue™ IFN- α/β cells (InvivoGen, Cat. #: hkb-ifn $\alpha\beta$), HEK-Blue™ IFN- λ (InvivoGen, Cat. #: hkb-ifnl) or HEK-Blue™ Dual IFN- γ cells (InvivoGen, Cat. #: hkb-ifng), as described in greater detail in Example I. These reporter cells were generated by stable transfection of HEK293 cells with human IFN receptor genes and an *IFN-stimulated response element*-controlled secreted embryonic alkaline phosphatase (SEAP) construct to measure the activity of IFNs. HEK-Blue™ IFN-cells are designed to monitor the activation of the JAK/STAT/ISGF3 pathways induced by type I, type II or type III interferons. Activation of these pathways induces the production and release of SEAP.
- [00158] In the context of the present invention, the interferon-associated antigen binding proteins activate both the CD40 and an IFN pathway. In certain

embodiments, the interferon-associated antigen binding protein activates the IFN pathway with an EC₅₀ of less than 100, 60, 50, 40, 30, 20, 10, or 1 ng/mL, preferably with an EC₅₀ of less than 11 ng/mL, more preferably with an EC₅₀ of less than 6 ng/mL, wherein IFN activity is preferably determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN-cells, as described for instance in Example I.

[00159] In some of these embodiments, the IFN pathway is the IFN α (interferon alpha), IFN β (interferon beta), IFN ϵ (interferon epsilon), IFN ω (interferon omega), IFN γ (interferon gamma), or IFN λ (interferon lambda) pathway.

10 [00160] According to certain exemplary embodiments, an interferon-associated antigen binding protein as described herein comprises full-length IFN, a variant or a derivative thereof (e.g., a chemically (e.g., PEGylated) modified derivative or mutein), or a functionally active fragment thereof, that retains one or more signaling activities of a full-length IFN. In certain embodiments, the IFN is a human IFN.

15 [00161] In certain embodiments, an interferon-associated antigen binding protein as described herein comprises an IFN or a functional fragment thereof selected from the group consisting of a Type I IFN, a Type II IFN and a Type III IFN, or a functional fragment thereof.

20 [00162] In particular embodiments, the IFN or the functional fragment thereof is a Type I IFN, or a functional fragment thereof. In specific embodiments, the type I IFN or the functional fragment thereof is IFN α , IFN β , IFN ω or IFN ϵ , or a functional fragment thereof. In more specific embodiments, the type I IFN or the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof. In other more specific embodiments, the type I IFN or the functional fragment thereof is IFN α , or
25 a functional fragment thereof. In other more specific embodiments, the type I IFN or the functional fragment thereof is IFN β , or a functional fragment thereof. In other more specific embodiments, the type I IFN or the functional fragment thereof is IFN ω , or a functional fragment thereof. In other more specific embodiments, the type I IFN or the functional fragment thereof is IFN ϵ , or a functional fragment thereof.

30 [00163] In particular embodiments, the IFN or the functional fragment thereof is IFN α , IFN β , IFN γ , IFN λ , IFN ϵ or IFN ω , or a functional fragment thereof. In specific

embodiments, the IFN or a functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.

[00164] In some embodiments, the IFN or the functional fragment thereof is IFN α , or a functional fragment thereof. In more specific embodiments, the IFN or functional
5 fragment thereof is IFN α 2a, or a functional fragment thereof. The IFN α 2a may comprise the sequence as set forth in SEQ ID NO 17, or a sequence at least 90% identical thereto.

[00165] In some embodiments, the IFN or the functional fragment thereof is IFN β , or a functional fragment thereof. The IFN β may comprise the sequence as set forth in
10 SEQ ID NO 14, or a sequence at least 90% identical thereto. The IFN β or the functional fragment thereof may comprise one or two amino acid substitution(s) relative to SEQ ID NO 14, selected from C17S and N80Q. In some embodiments, the IFN β or the functional fragment thereof comprises the amino acid substitution C17S relative to SEQ ID NO 14. In some embodiments, the IFN β comprises the
15 amino acid sequence as set forth in SEQ ID NO 15. In other embodiments, the IFN β comprises the amino acid substitutions C17S and N80Q relative to SEQ ID NO 14. In yet other embodiments, the IFN β comprises the amino acid sequence as set forth in SEQ ID NO 16.

[00166] In some embodiments, the IFN or the functional fragment thereof is IFN γ or
20 IFN λ , or a functional fragment thereof. In specific embodiments, the IFN or functional fragment thereof is IFN γ , or a functional fragment thereof. In more specific embodiments, the IFN γ comprises the sequence as set forth in SEQ ID NO 19, or a sequence at least 90% identical thereto. In other specific embodiments, the IFN or functional fragment thereof is IFN λ , or a functional fragment thereof. In more
25 specific embodiments, the IFN λ or the functional fragment thereof is IFN λ 2, or a functional fragment thereof. The IFN λ 2 may comprise the sequence as set forth in SEQ ID NO 18, or a sequence at least 90% identical thereto.

[00167] In some embodiments, the IFN or the functional fragment thereof is IFN ϵ , or a functional fragment thereof. The IFN ϵ may comprise the sequence as set forth in
30 SEQ ID NO 80, or a sequence at least 90% identical thereto.

[00168] In some embodiments, the IFN or the functional fragment thereof is IFN ω , or a functional fragment thereof. The IFN ω may comprise the sequence as set forth in SEQ ID NO 79, or a sequence at least 90% identical thereto.

5 [00169] In certain embodiments, the expression level of one or more IFN signaling pathway biomarkers is altered, i.e., upregulated or downregulated, in a Hepatitis delta virus-infected cell **treated** with an interferon-associated antigen binding protein described herein. According to certain exemplary embodiments, the expression level of one or more IFN pathway biomarkers is upregulated in a Hepatitis delta virus-infected cell treated with an interferon-associated antigen binding protein described
10 herein. In this context, a “**biomarker**” is to be understood as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

[00170] According to certain embodiments, a suitable IFN pathway biomarker featured herein is a chemokine, e.g., a C-X-C chemokine, selected from the group
15 consisting of CXCL9, CXCL10 and CXCL11. In certain exemplary embodiments, a suitable biomarker induced by the IFN pathway is CXCL9, CXCL10 and/or CXCL11, and also the interferon stimulated gene ISG20. Cytokine induction or release may be quantified using techniques known in the art, such as ELISA. Alternatively, induction may also be determined using RNA-based assays such as
20 RNAseq or qRT-PCR. In certain embodiments, upregulation may refer to an at least at 1.5-fold, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold or at least 10-fold increased expression or secretion of these cytokines.

[00171] In these or in other exemplary embodiments, the expression level of pro-inflammatory cytokines, e.g., IL10, IL1 β and/or IL2 is not significantly upregulated
25 in human Whole Blood cells upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression level of IL10 is not significantly upregulated in human Whole Blood cells upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression level of IL1 β is not significantly upregulated in human Whole Blood
30 cells upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression level of IL2 is not significantly

upregulated in a Hepatitis delta virus-infected cell upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression levels of IL10 and IL1 β are not significantly upregulated in a Hepatitis delta virus-infected cell upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression levels of IL10 and IL2 are not significantly upregulated in a Hepatitis delta virus-infected cell upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression levels of IL1 β and IL2 are not significantly upregulated in a Hepatitis delta virus-infected cell upon treatment with an interferon-associated antigen binding protein of the invention. In some embodiments, the expression levels of IL10, IL1 β and IL2 are not significantly upregulated in a Hepatitis delta virus-infected cell upon treatment with an interferon-associated antigen binding protein of the invention.

Interferon-associated antigen binding proteins

[00172] The term “**associated**”, as used herein, generally refers to a covalent or non-covalent linkage of two (or more) molecules. Associated proteins are created by joining two or more distinct peptides or proteins, resulting in a protein with one or more functional properties derived from each of the original proteins. In the context of the present invention, the interferon-associated antigen binding proteins activate both the CD40 and an IFN pathway. An associated protein encompasses monomeric and multimeric, e.g., dimeric, trimeric, tetrameric or the like, complexes of distinct associated or fused proteins. In this context, non-covalent linkage results from strong interactions between two protein surface regions, usually via ionic, Van-der-Waals, and/or hydrogen bond interactions. Covalent linkage, on the other hand, requires the presence of actual chemical bonds, such as peptide bonds, disulphide bridges, etc. The term “**fused**” as used herein, generally refers to the joining of two or more distinct peptides or proteins in a covalent fashion via a peptide bond. Thus, a “**fused protein**” refers to single protein created by joining two or more distinct peptides or proteins via a peptide bond with one or more functional properties derived from each of the original proteins. In certain embodiments, two or more distinct peptides or proteins may be fused to one another via one or more peptide linkers (“L”).

[00173] In a certain aspect of the invention, an interferon-associated antigen binding protein is a protein comprising an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof and an IFN or a functional fragment thereof.

5 [00174] In some embodiments, the IFN or the functional fragment thereof is non-covalently associated with the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In more specific embodiments, the IFN or the functional fragment thereof is non-covalently associated with the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof via ionic, Van-der-Waals, and/or hydrogen bond interactions.

10 [00175] In other embodiments, the IFN or the functional fragment thereof is covalently associated with the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In preferred embodiments, the IFN or the functional fragment thereof is fused to the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. The IFN or the functional fragment thereof may be fused
15 to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In some embodiments, the IFN or the functional fragment thereof is fused to the N-terminus of a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In other embodiments, the IFN or the functional fragment thereof is fused to the C-terminus of a light chain of the agonistic
20 anti-CD40 antibody or the agonistic antigen binding fragment thereof. The IFN or the functional fragment thereof may be also be fused to a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In some embodiments, the IFN or the functional fragment thereof is fused to the N-terminus of a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In other embodiments, the IFN or the functional fragment thereof
25 is fused to the C-terminus of a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In any of these embodiments, the agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and the IFN or the functional fragment thereof may be fused to each other via a linker.

30 [00176] The term **“linker”** or **“L,”** as used herein, refers to any moiety that covalently joins one or more agonistic anti-CD40 antibody or an agonistic antigen

binding fragment thereof to one or more interferon, or a functional fragment thereof. In exemplary embodiments, a linker is a peptide linker. The term “**peptide linker**”, as used herein, refers to a peptide adapted to link two or more moieties. A peptide linker referred to herein may have one or more of the properties outlined in the following. The sequences of peptide linker according to certain exemplary
5 embodiments are set forth in **Table 7**.

[00177] A peptide linker may have any length, i.e., comprise any number of amino acid residues. In exemplary embodiments, the linker comprises at least 1, at least 2, at least 3, at least 4, at least 5 amino acids. The linker may comprise at least 4 amino
10 acids. The linker may comprise at least 11 amino acids. The linker may comprise at least 12 amino acids. The linker may comprise at least 13 amino acids. The linker may comprise at least 15 amino acids. The linker may comprise at least 20 amino acids. The linker may comprise at least 21 amino acids. The linker may comprise at least 24 amino acids.

[00178] A linker is typically long enough to provide an adequate degree of flexibility to prevent the linked moieties from interfering with each other’s activity, e.g., the ability of a moiety to bind to a receptor. In exemplary embodiments, the linker comprises up to 10, up to 20, up to 30, up to 40, up to 50, up to 60, up to 70, up to
15 80, up to 90, or up to 100 amino acids. The linker may comprise up to 80 amino acids. The linker may comprise up to 40 amino acids. The linker may comprise up to 24 amino acids. The linker may comprise up to 21 amino acids. The linker may comprise up to 20 amino acids. The linker may comprise up to 15 amino acids. The linker may comprise up to 13 amino acids. The linker may comprise up to 12 amino
20 acids. The linker may comprise up to 11 amino acids. The linker may comprise up to 4 amino acids.
25

[00179] In some embodiments, the linker is selected from the group comprising rigid, flexible and/or helix-forming linkers. It is understood that helix-forming linkers can also be rigid linkers, since an α -helix has less degrees of freedom than a peptide assuming a more random-coil conformation. In some embodiments, the linker is a
30 rigid linker. An exemplary rigid linker comprises a sequence as set forth in SEQ ID NO 20. Further exemplary rigid linkers comprise a sequence as set forth in SEQ ID

NO 22 or SEQ ID NO 23. In related embodiments, the linker is a helix-forming linker. Exemplary helix-forming linkers comprise a sequence as set forth in SEQ ID NO 22 or SEQ ID NO 23. In other embodiments, the linker is a flexible linker. Exemplary flexible linkers comprise a sequence as set forth in SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.

[00180] The linker can also have different chemical properties. A linker can be selected from acidic, basic or neutral linkers. Typically, acidic linkers contain one or more acidic amino acid, such as Asp or Glu. Basic linkers typically contain one or more basic amino acids, such as Arg, His and Lys. Both types of amino acids are very hydrophilic. In some embodiments, the linker is an acidic linker. Exemplary acidic linkers comprise a sequence as set forth in SEQ ID NO 22 or SEQ ID NO 23. In other embodiments, the linker is a basic linker. In yet other embodiments, the linker is a neutral linker. Exemplary neutral linkers comprise a sequence as set forth in SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.

[00181] In preferred embodiments, the linker is Gly-Ser or a Gly-Ser-Thr linker composed of multiple glycine, serine and, where applicable, threonine residues. In some of these embodiments, the linker comprises the amino acids glycine and serine. In more specific embodiments, the linker comprises the sequence as set forth in SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25, SEQ ID NO 26. In some embodiments, the linker further comprises the amino acid threonine. In a more specific embodiment, the linker comprises the sequence as set forth in SEQ ID NO 21.

[00182] In exemplary embodiments of the present invention, the interferon-associated antigen binding protein comprises a linker comprising a sequence selected from the sequences as set forth in SEQ ID NOs 20 to 26, preferably from the sequences as set forth in SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26. In a preferred embodiment, the linker comprises a sequence as set forth in SEQ ID NO 24. In another preferred embodiment, the linker comprises a sequence as set forth in SEQ ID NO 25. In another preferred embodiment, the linker comprises a sequence as set forth in SEQ ID NO 26.

[00183] In various embodiments of any one of the aspects of the invention, the interferon-associated antigen binding protein comprises no amino acids other than those forming (I) said agonistic anti-CD40 antibody, or agonistic antigen binding fragment thereof and (II) said IFN or functional fragment thereof. In related
5 embodiments, the interferon-associated antigen binding protein comprises no amino acids other than those forming (I) said agonistic anti-CD40 antibody, or agonistic antigen binding fragment thereof, (II) said IFN or functional fragment thereof and (III) said linker.

[00184] Exemplary embodiments representing the various different configurations of
10 (I) the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, (II) the interferon (IFN) or the functional fragment thereof and (III) the linker are outlined in the following.

[00185] In certain preferred embodiments, the IFN or a functional fragment thereof is fused to the C-terminus of a heavy chain of the agonistic anti-CD40 antibody, or the
15 agonistic antigen binding fragment thereof, via the linker, as set forth in **Table 3A or Table 3B**. In these embodiments, the heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, may comprise a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 48 or SEQ ID NO 49, SEQ ID NO 61, or SEQ ID NO 63. The IFN α 2a may comprise
20 the sequence as set forth in SEQ ID NO 17. The IFN β may comprise the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16. The IFN β may comprise the sequence as set forth in SEQ ID NO 14. The IFN β _C17S may comprise the sequence as set forth in SEQ ID NO 15. The IFN β _C17S,N80Q may comprise the sequence as set forth in SEQ ID NO 16. The IFN γ may comprise the sequence as
25 set forth in SEQ ID NO 19. The IFN λ 2 may comprise the sequence as set forth in SEQ ID NO 18. The IFN ϵ may comprise the sequence as set forth in SEQ ID NO 80. The IFN ω may comprise the sequence as set forth in SEQ ID NO 79. The linkers referred to are those listed in **Table 7**.

[00186] In the embodiments where the IFN is fused to the C-terminus of the heavy
30 chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, the interferon-associated antigen binding protein further comprises a light

chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof. In more specific embodiments, a heavy chain comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 48, or SEQ ID NO 49 and a light chain comprises a sequence as set forth in SEQ ID NO 3. In other more specific embodiments, a heavy chain comprises a sequence as set forth in SEQ ID NO 61 or SEQ ID NO 63 and a light chain comprises a sequence as set forth in SEQ ID NO 59.

Table 3. *Interferon or a functional fragment thereof fused to the C-terminus of a heavy chain of the anti-CD40 antibody or an agonistic antigen binding fragment thereof.*

A	IFNα2a	IFNβ	IFNβ_C17S	IFNβ_C17S,N80Q	IFNγ	IFNλ2
RL linker	antiCD40_HC--RL--IFN α 2a	antiCD40_HC--RL--IFN β	antiCD40_HC--RL--IFN β _C17S	antiCD40_HC--RL--IFN β _C17S,N80Q	antiCD40_HC--RL--IFN γ	antiCD40_HC--RL--IFN λ 2
GST linker	antiCD40_HC--GST--IFN α 2a	antiCD40_HC--GST--IFN β	antiCD40_HC--GST--IFN β _C17S	antiCD40_HC--GST--IFN β _C17S,N80Q	antiCD40_HC--GST--IFN γ	antiCD40_HC--GST--IFN λ 2
HL linker	antiCD40_HC--HL--IFN α 2a	antiCD40_HC--HL--IFN β	antiCD40_HC--HL--IFN β _C17S	antiCD40_HC--HL--IFN β _C17S,N80Q	antiCD40_HC--HL--IFN γ	antiCD40_HC--HL--IFN λ 2
HL2 linker	antiCD40_HC--HL2--IFN α 2a	antiCD40_HC--HL2--IFN β	antiCD40_HC--HL2--IFN β _C17S	antiCD40_HC--HL2--IFN β _C17S,N80Q	antiCD40_HC--HL2--IFN γ	antiCD40_HC--HL2--IFN λ 2
(G4S)2 linker	antiCD40_HC--(G4S)2--IFN α 2a	antiCD40_HC--(G4S)2--IFN β	antiCD40_HC--(G4S)2--IFN β _C17S	antiCD40_HC--(G4S)2--IFN β _C17S,N80Q	antiCD40_HC--(G4S)2--IFN γ	antiCD40_HC--(G4S)2--IFN λ 2
(G4S)3 linker	antiCD40_HC--(G4S)3--IFN α 2a	antiCD40_HC--(G4S)3--IFN β	antiCD40_HC--(G4S)3--IFN β _C17S	antiCD40_HC--(G4S)3--IFN β _C17S,N80Q	antiCD40_HC--(G4S)3--IFN γ	antiCD40_HC--(G4S)3--IFN λ 2
(G4S)4 linker	antiCD40_HC--(G4S)4--IFN α 2a	antiCD40_HC--(G4S)4--IFN β	antiCD40_HC--(G4S)4--IFN β _C17S	antiCD40_HC--(G4S)4--IFN β _C17S,N80Q	antiCD40_HC--(G4S)4--IFN γ	antiCD40_HC--(G4S)4--IFN λ 2

10

B	IFNϵ	IFNω
RL linker	antiCD40_HC--RL--IFN ϵ	antiCD40_HC--RL--IFN ω
GST linker	antiCD40_HC--GST--IFN ϵ	antiCD40_HC--GST--IFN ω
HL linker	antiCD40_HC--HL--IFN ϵ	antiCD40_HC--HL--IFN ω
HL2 linker	antiCD40_HC--HL2--IFN ϵ	antiCD40_HC--HL2--IFN ω
(G4S)2 linker	antiCD40_HC--(G4S)2--IFN ϵ	antiCD40_HC--(G4S)2--IFN ω
(G4S)3 linker	antiCD40_HC--(G4S)3--IFN ϵ	antiCD40_HC--(G4S)3--IFN ω
(G4S)4 linker	antiCD40_HC--(G4S)4--IFN ϵ	antiCD40_HC--(G4S)4--IFN ω

[00187] In certain preferred embodiments, the IFN or a functional fragment thereof is fused to the N-terminus of a heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker, as set forth in **Table 4A** or **Table 4B**. In these embodiments, the heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, may comprise a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 48, SEQ ID NO 49, SEQ ID NO 50, SEQ ID NO 61, SEQ ID NO 63 or SEQ ID NO 65. The IFN α 2a may comprise the sequence as set forth in SEQ ID NO 17. The IFN β may comprise the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16. The IFN β may comprise the sequence as set forth in SEQ ID NO 14. The IFN β _C17S may comprise the sequence as set forth in SEQ ID NO 15. The IFN β _C17S,N80Q may comprise the sequence as set forth in SEQ ID NO 16. The IFN γ may comprise the sequence as set forth in SEQ ID NO 19. The IFN λ 2 may comprise the sequence as set forth in SEQ ID NO 18. The IFN ϵ may comprise the sequence as set forth in SEQ ID NO 80. The IFN ω may comprise the sequence as set forth in SEQ ID NO 79. The linkers referred to are those listed in **Table 7**.

[00188] In the embodiments where the IFN is fused to the N-terminus of a heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, the interferon-associated antigen binding protein further comprises a light chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof. In more specific embodiments, a heavy chain comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 48, SEQ ID NO 49 or SEQ ID NO 50 and a light chain comprises a sequence as set forth in SEQ ID NO 3. In other more specific embodiments, a heavy chain comprises a sequence as set forth in SEQ ID 61, SEQ ID 63 or SEQ ID 65 and a light chain comprises a sequence as set forth in SEQ ID NO 59.

Table 4. *Interferon or a functional fragment thereof fused to the N-terminus of a heavy chain of the anti-CD40 antibody or an agonistic antigen binding fragment thereof.*

<u>A</u>	IFN α 2a	IFN β	IFN β _C17S	IFN β _C17S,N80Q	IFN γ	IFN λ 2
RL linker	IFN α 2a--RL--antiCD40_HC	IFN β --RL--antiCD40_HC	IFN β _C17S--RL--antiCD40_HC	IFN β _C17S,N80Q--RL--antiCD40_HC	IFN γ --RL--antiCD40_HC	IFN λ 2--RL--antiCD40_HC

GST linker	IFN α 2a--GST-- antiCD40_HC	IFN β --GST-- antiCD40_HC	IFN β _C17S-- GST-- antiCD40_HC	IFN β _C17S,N80Q-- GST--antiCD40_HC	IFN γ --GST-- antiCD40_HC	IFN λ 2--GST-- antiCD40_HC
HL linker	IFN α 2a--HL-- antiCD40_HC	IFN β --HL-- antiCD40_HC	IFN β _C17S-- HL-- antiCD40_HC	IFN β _C17S,N80Q-- HL--antiCD40_HC	IFN γ --HL-- antiCD40_HC	IFN λ 2--HL-- antiCD40_HC
HL2 linker	IFN α 2a--HL2-- antiCD40_HC	IFN β --HL2-- antiCD40_HC	IFN β _C17S-- HL2-- antiCD40_HC	IFN β _C17S,N80Q-- HL2--antiCD40_HC	IFN γ --HL2-- antiCD40_HC	IFN λ 2--HL2-- antiCD40_HC
(G4S)2 linker	IFN α 2a-- (G4S)2-- antiCD40_HC	IFN β --(G4S)2-- antiCD40_HC	IFN β _C17S-- (G4S)2-- antiCD40_HC	IFN β _C17S,N80Q-- (G4S)2-- antiCD40_HC	IFN γ --(G4S)2-- antiCD40_HC	IFN λ 2--(G4S)2-- antiCD40_HC
(G4S)3 linker	IFN α 2a-- (G4S)3-- antiCD40_HC	IFN β --(G4S)3-- antiCD40_HC	IFN β _C17S-- (G4S)3-- antiCD40_HC	IFN β _C17S,N80Q-- (G4S)3-- antiCD40_HC	IFN γ --(G4S)3-- antiCD40_HC	IFN λ 2--(G4S)3-- antiCD40_HC
(G4S)4 linker	IFN α 2a-- (G4S)4-- antiCD40_HC	IFN β --(G4S)4-- antiCD40_HC	IFN β _C17S-- (G4S)4-- antiCD40_HC	IFN β _C17S,N80Q-- (G4S)4-- antiCD40_HC	IFN γ --(G4S)4-- antiCD40_HC	IFN λ 2--(G4S)4-- antiCD40_HC

<u>B</u>	IFNϵ	IFNω
RL linker	IFN ϵ --RL-- antiCD40_HC	IFN ω --RL-- antiCD40_HC
GST linker	IFN ϵ --GST-- antiCD40_HC	IFN ω --GST-- antiCD40_HC
HL linker	IFN ϵ --HL-- antiCD40_HC	IFN ω --HL-- antiCD40_HC
HL2 linker	IFN ϵ --HL2-- antiCD40_HC	IFN ω --HL2-- antiCD40_HC
(G4S)2 linker	IFN ϵ --(G4S)2-- antiCD40_HC	IFN ω --(G4S)2-- antiCD40_HC
(G4S)3 linker	IFN ϵ --(G4S)3-- antiCD40_HC	IFN ω --(G4S)3-- antiCD40_HC
(G4S)4 linker	IFN ϵ --(G4S)4-- antiCD40_HC	IFN ω --(G4S)4-- antiCD40_HC

[00189] In certain preferred embodiments, the IFN is fused to the C-terminus of a light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker, as set forth in **Table 5A** or **Table 5B**. In these

5 embodiments, the light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, may comprise a sequence as set forth in SEQ ID NO 3. In other embodiments, the light chain may comprise a sequence as set forth in SEQ ID NO 59. The IFN α 2a may comprise the sequence as set forth in SEQ ID NO 17. The IFN β may comprise the sequence as set forth in SEQ ID NO 14, SEQ ID NO

10 15 or SEQ ID NO 16. The IFN β may comprise the sequence as set forth in SEQ ID NO 14. The IFN β _C17S may comprise the sequence as set forth in SEQ ID NO 15. The IFN β _C17S,N80Q may comprise the sequence as set forth in SEQ ID NO 16. The IFN γ may comprise the sequence as set forth in SEQ ID NO 19. The IFN λ 2 may

comprise the sequence as set forth in SEQ ID NO 18. The IFN ϵ may comprise the sequence as set forth in SEQ ID NO 80. The IFN ω may comprise the sequence as set forth in SEQ ID NO 79. The linkers referred to are those listed in **Table 7**.

[00190] In the embodiments where the IFN is fused to the C-terminus of a light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, the interferon-associated antigen binding protein further comprises a heavy chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof. In more specific embodiments, a light chain comprises a sequence as set forth in SEQ ID NO 3 and a heavy chain comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, SEQ ID NO 50 or SEQ ID NO 12. In other more specific embodiments, a light chain comprises a sequence as set forth in SEQ ID NO 59 and a heavy chain comprises a sequence as set forth in SEQ ID NO 61, SEQ ID NO 63 or SEQ ID NO 65.

Table 5. *Interferon or a functional fragment thereof fused to the C-terminus of a light chain of the anti-CD40 antibody or an agonistic antigen binding fragment thereof.*

A	IFNα2a	IFNβ	IFNβ_C17S	IFNβ_C17S,N80Q	IFNγ	IFNλ2
RL linker	antiCD40_LC--RL--IFN α 2a	antiCD40_LC--RL--IFN β	antiCD40_LC--RL--IFN β _C17S	antiCD40_LC--RL--IFN β _C17S,N80Q	antiCD40_LC--RL--IFN γ	antiCD40_LC--RL--IFN λ 2
GST linker	antiCD40_LC--GST--IFN α 2a	antiCD40_LC--GST--IFN β	antiCD40_LC--GST--IFN β _C17S	antiCD40_LC--GST--IFN β _C17S,N80Q	antiCD40_LC--GST--IFN γ	antiCD40_LC--GST--IFN λ 2
HL linker	antiCD40_LC--HL--IFN α 2a	antiCD40_LC--HL--IFN β	antiCD40_LC--HL--IFN β _C17S	antiCD40_LC--HL--IFN β _C17S,N80Q	antiCD40_LC--HL--IFN γ	antiCD40_LC--HL--IFN λ 2
HL2 linker	antiCD40_LC--HL2--IFN α 2a	antiCD40_LC--HL2--IFN β	antiCD40_LC--HL2--IFN β _C17S	antiCD40_LC--HL2--IFN β _C17S,N80Q	antiCD40_LC--HL2--IFN γ	antiCD40_LC--HL2--IFN λ 2
(G4S)2 linker	antiCD40_LC--(G4S)2--IFN α 2a	antiCD40_LC--(G4S)2--IFN β	antiCD40_LC--(G4S)2--IFN β _C17S	antiCD40_LC--(G4S)2--IFN β _C17S,N80Q	antiCD40_LC--(G4S)2--IFN γ	antiCD40_LC--(G4S)2--IFN λ 2
(G4S)3 linker	antiCD40_LC--(G4S)3--IFN α 2a	antiCD40_LC--(G4S)3--IFN β	antiCD40_LC--(G4S)3--IFN β _C17S	antiCD40_LC--(G4S)3--IFN β _C17S,N80Q	antiCD40_LC--(G4S)3--IFN γ	antiCD40_LC--(G4S)3--IFN λ 2
(G4S)4 linker	antiCD40_LC--(G4S)4--IFN α 2a	antiCD40_LC--(G4S)4--IFN β	antiCD40_LC--(G4S)4--IFN β _C17S	antiCD40_LC--(G4S)4--IFN β _C17S,N80Q	antiCD40_LC--(G4S)4--IFN γ	antiCD40_LC--(G4S)4--IFN λ 2

B	IFNϵ	IFNω
RL linker	antiCD40_LC--RL--IFN ϵ	antiCD40_LC--RL--IFN ω
GST linker	antiCD40_LC--GST--IFN ϵ	antiCD40_LC--GST--IFN ω

HL linker	antiCD40_LC-- HL--IFN ϵ	antiCD40_LC-- HL--IFN ω
HL2 linker	antiCD40_LC-- HL2--IFN ϵ	antiCD40_LC-- HL2--IFN ω
(G4S)2 linker	antiCD40_LC-- (G4S)2--IFN ϵ	antiCD40_LC-- (G4S)2--IFN ω
(G4S)3 linker	antiCD40_LC-- (G4S)3--IFN ϵ	antiCD40_LC-- (G4S)3--IFN ω
(G4S)4 linker	antiCD40_LC-- (G4S)4--IFN ϵ	antiCD40_LC-- (G4S)4--IFN ω

[00191] In certain preferred embodiments, the IFN is fused to the N-terminus of a light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker, as set forth in **Table 6A** or **Table 6B**. In these embodiments, the light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, may comprise a sequence as set forth in SEQ ID NO 3 or SEQ ID NO 59. The IFN α 2a may comprise the sequence as set forth in SEQ ID NO 17. The IFN β may comprise the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16. The IFN β may comprise the sequence as set forth in SEQ ID NO 14. The IFN β _C17S may comprise the sequence as set forth in SEQ ID NO 15. The IFN β _C17S,N80Q may comprise the sequence as set forth in SEQ ID NO 16. The IFN γ may comprise the sequence as set forth in SEQ ID NO 19. The IFN λ 2 may comprise the sequence as set forth in SEQ ID NO 18. The IFN ϵ may comprise the sequence as set forth in SEQ ID NO 80. The IFN ω may comprise the sequence as set forth in SEQ ID NO 79. The linkers referred to are those listed in **Table 7**.

[00192] In the embodiments where the IFN is fused to the N-terminus of a light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, the interferon-associated antigen binding protein further comprises a heavy chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof. In more specific embodiments, a light chain comprises a sequence as set forth in SEQ ID NO 3 and a heavy chain comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, SEQ ID NO 12 or SEQ ID NO 50. In other more specific embodiments, a light chain comprises a sequence as set forth in SEQ ID NO 59 and a heavy chain comprises a sequence as set forth in SEQ ID NO 61, SEQ ID NO 63 or SEQ ID NO 65.

Table 6. *Interferon or a functional fragment thereof fused to the N-terminus of a light chain of the anti-CD40 antibody or an agonistic antigen binding fragment thereof.*

A	IFNα2a	IFNβ	IFNβ_C17S	IFNβ_C17S,N80Q	IFNγ	IFNλ2
RL linker	IFN α 2a--RL-- antiCD40_LC	IFN β --RL-- antiCD40_LC	IFN β _C17S-- RL-- antiCD40_LC	IFN β _C17S,N80Q-- RL--antiCD40_LC	IFN γ --RL-- antiCD40_LC	IFN λ 2--RL-- antiCD40_LC
GST linker	IFN α 2a--GST-- antiCD40_LC	IFN β --GST-- antiCD40_LC	IFN β _C17S-- GST-- antiCD40_LC	IFN β _C17S,N80Q-- GST--antiCD40_LC	IFN γ --GST-- antiCD40_LC	IFN λ 2--GST-- antiCD40_LC
HL linker	IFN α 2a--HL-- antiCD40_LC	IFN β --HL-- antiCD40_LC	IFN β _C17S-- HL-- antiCD40_LC	IFN β _C17S,N80Q-- HL--antiCD40_LC	IFN γ --HL-- antiCD40_LC	IFN λ 2--HL-- antiCD40_LC
HL2 linker	IFN α 2a--HL2-- antiCD40_LC	IFN β --HL2-- antiCD40_LC	IFN β _C17S-- HL2-- antiCD40_LC	IFN β _C17S,N80Q-- HL2--antiCD40_LC	IFN γ --HL2-- antiCD40_LC	IFN λ 2--HL2-- antiCD40_LC
(G4S)2 linker	IFN α 2a-- (G4S)2-- antiCD40_LC	IFN β --(G4S)2-- antiCD40_LC	IFN β _C17S-- (G4S)2-- antiCD40_LC	IFN β _C17S,N80Q-- (G4S)2-- antiCD40_LC	IFN γ --(G4S)2-- antiCD40_LC	IFN λ 2--(G4S)2-- antiCD40_LC
(G4S)3 linker	IFN α 2a-- (G4S)3-- antiCD40_LC	IFN β --(G4S)3-- antiCD40_LC	IFN β _C17S-- (G4S)3-- antiCD40_LC	IFN β _C17S,N80Q-- (G4S)3-- antiCD40_LC	IFN γ --(G4S)3-- antiCD40_LC	IFN λ 2--(G4S)3-- antiCD40_LC
(G4S)4 linker	IFN α 2a-- (G4S)4-- antiCD40_LC	IFN β --(G4S)4-- antiCD40_LC	IFN β _C17S-- (G4S)4-- antiCD40_LC	IFN β _C17S,N80Q-- (G4S)4-- antiCD40_LC	IFN γ --(G4S)4-- antiCD40_LC	IFN λ 2--(G4S)4-- antiCD40_LC

B	IFNϵ	IFNω
RL linker	IFN ϵ --RL-- antiCD40_LC	IFN ω --RL-- antiCD40_LC
GST linker	IFN ϵ --GST-- antiCD40_LC	IFN ω --GST-- antiCD40_LC
HL linker	IFN ϵ --HL-- antiCD40_LC	IFN ω --HL-- antiCD40_LC
HL2 linker	IFN ϵ --HL2-- antiCD40_LC	IFN ω --HL2-- antiCD40_LC
(G4S)2 linker	IFN ϵ --(G4S)2-- antiCD40_LC	IFN ω --(G4S)2-- antiCD40_LC
(G4S)3 linker	IFN ϵ --(G4S)3-- antiCD40_LC	IFN ω --(G4S)3-- antiCD40_LC
(G4S)4 linker	IFN ϵ --(G4S)4-- antiCD40_LC	IFN ω --(G4S)4-- antiCD40_LC

[00193] Exemplary sequences comprised in interferon-associated antigen binding proteins of the invention or precursors thereof are listed in **Table 7**.

[00194] In exemplary preferred embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NOs 28-47 or SEQ ID NOs 66-75. In other exemplary embodiments, the interferon-associated antigen binding protein comprises an

interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NOs 81-88. In exemplary preferred embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an
5 interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NOs 89-90. In exemplary preferred embodiments, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NOs 28-47 or SEQ ID NOs 66-75. In
10 other exemplary embodiments, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NOs 81-88. In other exemplary embodiments, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused
15 agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NOs 89-90.

[00195] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ
20 ID NO 89. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 89.

[00196] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ
25 ID NO 90. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ
30 ID NO 90.

[00197] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 81. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 81.

[00198] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 82. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 82.

[00199] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 83. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 83.

[00200] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 84. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 84.

[00201] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ

ID NO 85. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 85.

5 **[00202]** In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 86. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ
10 ID NO 86.

[00203] In certain exemplary embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ
15 ID NO 87. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 87.

[00204] In certain exemplary embodiments, the interferon-associated antigen binding
20 protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 88. In another exemplary embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ
25 ID NO 88.

[00205] In more preferred embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO
30 42 or SEQ ID NO 43. In more preferred embodiments, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an

interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42 or SEQ ID NO 43. In other more preferred embodiments, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NO 72, SEQ ID NO 73, SEQ ID NO 74 and SEQ ID NO 75. In still other more preferred embodiments, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising a sequence selected from SEQ ID NO 72, SEQ ID NO 73, SEQ ID NO 74 and SEQ ID NO 75.

[00206] In an even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 38. In still another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 38.

[00207] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 39. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 39.

[00208] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 40. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-

CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 40.

5 [00209] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 41. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 41.

10 [00210] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 42. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 42.

20 [00211] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 43. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 43.

25 [00212] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 72. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 72.

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[00213] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 73. In another even more preferred embodiment, the
5 interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 73.

[00214] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as
10 set forth in SEQ ID NO 74. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as set forth in SEQ ID NO 74.

[00215] In another even more preferred embodiment, the interferon-associated antigen binding protein comprises an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising a sequence as
15 set forth in SEQ ID NO 75. In another even more preferred embodiment, the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic binding fragment thereof comprising
20 a sequence as set forth in SEQ ID NO 75.

Table 7. Sequences of exemplary interferon-associated antigen binding protein and components thereof based on the antiCD40 antibody CP870,893. *Italic sequences correspond to signal peptides. Bold italic sequences in SEQ ID NOs 3 and 6 correspond to CDR regions. Bold non-italic sequences correspond to linkers. Mutated amino acids are 5 underlined.*

Name / SEQ ID Number	Sequence
Signal peptide 1 (SEQ ID NO 1)	<i>MGWSCII⁵FLVATATGVHS</i>
Signal peptide 2 (SEQ ID NO 2)	<i>MDMRVPAQLLGLLLLWLRGARC</i>
antiCD40 antibody light chain (SEQ ID NO 3)	DIQMTQSPSSVSASVGDRVTITCR <i>ASQGIYSWLAWYQQKPG</i> KAPNLLIY <i>TASTLQ</i> SGVPSRFSGSGSGTDFTLTIS ⁵ SLQPEDFAT YYC <i>QQANIFPL</i> TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSF NRGEC
antiCD40 antibody light chain with signal peptide 1 (SEQ ID NO 4)	<i>MGWSCII⁵FLVATATGVHSD</i> IQMTQSPSSVSASVGDRVTITCR ASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGS GSGTDFTLTIS ⁵ SLQPEDFATYYCQQANIFPLTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEEKHK VYACEVTHQGLSSPVTKSFNRGEC
antiCD40 antibody light chain	<i>MDMRVPAQLLGLLLLWLRGARCD</i> IQMTQSPSSVSASVGDRVT ITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRF SGSGSGTDFTLTIS ⁵ SLQPEDFATYYCQQANIFPLTFGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ

with signal peptide 2 (SEQ ID NO 5)	WKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
antiCD40 antibody heavy chain hIgG2 dK (SEQ ID NO 6)	QVQLVQSGAEVKKPGASVKVSCKASGYTF <i>TGYIMHW</i> VVRQ APGQGLEWMGWINPDSGGTNYA <i>QKFQ</i> GRVTMTRDTSISTA YMELNRLRSDDTAVYYCARD <i>QPLGYCTNGVCSYFDY</i> WGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDHKPSNTKVDKTVRKCCVECPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSVMSHEALHNHYTQKSLS LSPG
antiCD40 antibody heavy chain hIgG2 dK with signal peptide 1 (SEQ ID NO 7)	<i>MGWSCILFLVATATGVHSQ</i> VQLVQSGAEVKKPGASVKVSCK ASGYTFTGYIMHWVRQAPGQGLEWMGWINPDSGGTNYA QKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQP LGICTNGVCSYFDYWGQGTLVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTV ERKCCVECPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRV VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSV MSHEALHNHYTQKSLSLSPG
antiCD40 antibody heavy chain hIgG2 dK	<i>MDMRVPAQLLGLLLLWLRGARCQ</i> VQLVQSGAEVKKPGASVK VSCKASGYTFTGYIMHWVRQAPGQGLEWMGWINPDSGGT NYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCAR

with signal peptide 2 (SEQ ID NO 8)	DQPLGYCTNGVCSYFDYWGGTLVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPG
antiCD40 antibody heavy chain hIgG2 (SEQ ID NO 9)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGG GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPHKPSNTKVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
antiCD40 antibody heavy chain hIgG2 with signal peptide 1 (SEQ ID NO 10)	<i>MGWSCIIIFLVATATGVHS</i> QVQLVQSGAEVKKPGASVKVSCK ASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSSGGTNYA QKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQP LGYCTNGVCSYFDYWGGTLVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDKTV ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRV VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN

	GQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
antiCD40 antibody heavy chain hIgG2 with signal peptide 2 (SEQ ID NO 11)	<i>MDMRVPAQLLGLLLLWLRGARCQVQLVQSGAEVKKPGASVK</i> VSCKASGYTFTGYMHWRQAPGQGLEWMGWINPDSSGGT NYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCAR DQPLGYCTNGVCSYFDYWGGTLTVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDPHKPSNTKVDK TVERKCCVECPAPVAGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
antiCD40 antibody hIgG1 heavy chain - NNAS (SEQ ID NO 48)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQ APGQGLEWMGWINPDSSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGG GTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNNASRVVSVLTVLHQDWLNL GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK
antiCD40 antibody hIgG1 heavy chain - NNAS-dK	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQ APGQGLEWMGWINPDSSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGG GTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

(SEQ ID NO 49)	EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNNASRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQ KSLSLSPG
antiCD40 antibody hIgG2 Fab region heavy chain (SEQ ID NO 12)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHVVRQ APGQGLEWMGWINPDSSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDHKPSNTKVDKTVERKCCVE
antiCD40 antibody hIgG2 Fab region heavy chain with signal peptide 1 (SEQ ID NO 13)	<i>MGWSCII</i> FLVATATGVHSQVQLVQSGAEVKKPGASVKVSCK ASGYTFTGYMHVVRQAPGQGLEWMGWINPDSSGGTNYA QKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQP LGCTNGVCSYFDYWGGTLVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTV ERKCCVE
antiCD40 antibody hIgG2 Fab region heavy chain --TEV--6His tag (SEQ ID NO 50)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHVVRQ APGQGLEWMGWINPDSSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDHKPSNTKVDKTVERKCCVEENLYFQSHHHH HH

IFN β dM (SEQ ID NO 76)	SYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPE EIKQLQQFQKEDAALTIYEMLQNIFAIQRQDSSSTGWNATIVE NLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRY GRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGILRN
IFN β dM C17S (SEQ ID NO 77)	SYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLKDRMNFDIPE EIKQLQQFQKEDAALTIYEMLQNIFAIQRQDSSSTGWNATIVE NLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRY GRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGILRN
IFN β (SEQ ID NO 14)	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDI PEEIKQLQQFQKEDAALTIYEMLQNIFAIQRQDSSSTGWNATI VENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKR YYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGILRN
IFN β C17S (SEQ ID NO 15)	MSYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLKDRMNFDIP EEIKQLQQFQKEDAALTIYEMLQNIFAIQRQDSSSTGWNATIV ENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRY YGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGILRN
IFN β C17S,N80Q (SEQ ID NO 16)	MSYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLKDRMNFDIP EEIKQLQQFQKEDAALTIYEMLQNIFAIQRQDSSSTGWQETIV ENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRY YGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGILRN
IFN α 2a (SEQ ID NO 17)	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEE FGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKF YTELYQQNLNDEACVIQGVGVTTETPLMKEDSILAVRKYFQR ITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE
IFN λ 2 (SEQ ID NO 18)	VPVARLHGALPDARGCHIAQFKSLSPQELQAFKRAKDALEE SLLKDCRCHSRLFPRTWDLRQLQVRERPMALEAELATLK VLEATADTDPALVDVLDQPLHTLHHILSQFRACIQPQPTAGP

	RTRGRLHHWL YRLQEAPKKESPGCLEASVTFNLFRLLTRDL NCVASGDLCV
IFN γ (SEQ ID NO 19)	QDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEES DRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFF NSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPA AKTGKRKRSQMLFRGRRASQ
IFN ω (SEQ ID NO 79)	LGCDLPQNHGLLSRNTLVLLHQMRRISPFLCLKDRRDFRFPQ EMVKGSQQLQKAHVMSVLHEMLQQIFSLFHTERSSAAWNMT LLDQLHTGLHQQQLQHLETCLLQVVGESESAGAISSPALTLR RYFQGIRVYLKEKKYSDCAWEVVRMEIMKSLFLSTNMQER LRSKDRDLGSS
IFN ϵ (SEQ ID NO 80)	LDLKLIFQQRQVNQESLKLLNKLQTL SIQQCLPHRKNFLLPQ KSLSPQQYQKGHTLAILHEMLQQIFSLFRANISLDGWEENHT EKFLIQLHQQLEYLEALMGLEAEKLSGTLGSDNLRQLQVKMY FRRIH DYLENQDYSTCAWAIVQVEISRCLFFVFSLTEKLSKQ GRPLNDMKQELTTEFRSPR
RL linker (SEQ ID NO 20)	PAPA
GST linker (SEQ ID NO 21)	SGGTSGSTSGTG S
HL linker (SEQ ID NO 22)	AEAAAKEAAAKA
HL2 linker (SEQ ID NO 23)	AEAAAKEAAAKAAEAAAKEAAAKA
(G4S) ₂ linker	GGGGSGGGGS

(SEQ ID NO 24)	
(G4S)3 linker (SEQ ID NO 25)	GGGGS GGGGS GGGGS
(G4S)4 linker (SEQ ID NO 26)	GGGGS GGGGS GGGGS GGGGS
TEV-6His tag (SEQ ID NO 27)	ENLYFQSHHHHHH
antiCD40_LC-- HL--IFN β (SEQ ID NO 28)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTA ST LQSGVPSRFSGSGSGTDFTLTIS SL QPEDFAT YYCQQANIFPLTFGGG TK VEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSS TL TL SK ADY E KKVYACEVTHQGLSSPVTKSF NRGEC A E A A A K E A A A K AMSYNLLGFLQRSSNFQCQKLLW QLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEML QNIFAI FR QDSSSTGWN E TIVENLLANVYHQINHLKTVLEEK LEKEDFTRGKLMSSLHLKRY Y GRILHYLK A KEYSHCAWTIV RVEILRN F YFINRLTGYLRN
antiCD40_LC-- HL--IFN β _C17S (SEQ ID NO 29)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTA ST LQSGVPSRFSGSGSGTDFTLTIS SL QPEDFAT YYCQQANIFPLTFGGG TK VEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSS TL TL SK ADY E KKVYACEVTHQGLSSPVTKSF NRGEC A E A A A K E A A A K AMSYNLLGFLQRSSNF Q SQKLLW QLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEML QNIFAI FR QDSSSTGWN E TIVENLLANVYHQINHLKTVLEEK LEKEDFTRGKLMSSLHLKRY Y GRILHYLK A KEYSHCAWTIV RVEILRN F YFINRLTGYLRN

antiCD40_hIgG2_ dK_HC--RL-- IFN β (SEQ ID NO 30)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPHKPSNTKVDKTVKCCVECPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSVMSHEALHNHYTQKSLS LSPGPAPAMSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLK DRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSS TGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLM SSLHLKRYYYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINR LTGYLRN
antiCD40_hIgG2_ dK_HC--RL-- IFN β _C17S (SEQ ID NO 31)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPHKPSNTKVDKTVKCCVECPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSVMSHEALHNHYTQKSLS LSPGPAPAMSYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLK DRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSS TGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLM

	SSLHLKRYYYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGYLRN
antiCD40_hIgG2_ dK_HC--HL-- IFN β (SEQ ID NO 32)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPKPSNTKVDKTVERKCCVECPAPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSVMSVMEALHNHYTQKSLS LSPGAEEAAAKEAAAKAMSYNLLGFLQRSSNFQCQKLLWQL NGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNI FAIFRQDSSSTGWNENITIVENLLANVYHQINHLKTVLEEKLEK EDFTRGKLMSSLHLKRYYYGRILHYLKAKEYSHCAWTIVRVE ILRNIFYFINRLTGYLRN
antiCD40_hIgG2_ dK_HC--HL-- IFN β _C17S (SEQ ID NO 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPKPSNTKVDKTVERKCCVECPAPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSVMSVMEALHNHYTQKSLS LSPGAEEAAAKEAAAKAMSYNLLGFLQRSSNFQSQKLLWQL NGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNI

	FAIFRQDSSSTGWNENLLANVYHQINHLKTVLEEKLEK EDFTRGKLMSSLHLKRYYGRIHLHYLKAKEYSHCAWTIVRVE ILRNIFYFINRLTGYLRN
antiCD40_LC-- RL--IFN β (SEQ ID NO 34)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC PAP AMSYNLLGFLQRSSNFQCQKLLWQLNGRLEYC LKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQD SSSTGWNENLLANVYHQINHLKTVLEEKLEKEDFTRG KLMSSLHLKRYYGRIHLHYLKAKEYSHCAWTIVRVEILRNIFY FINRLTGYLRN
antiCD40_LC-- RL--IFN β _C17S (SEQ ID NO 35)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC PAP AMSYNLLGFLQRSSNFQSQKLLWQLNGRLEYC LKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQD SSSTGWNENLLANVYHQINHLKTVLEEKLEKEDFTRG KLMSSLHLKRYYGRIHLHYLKAKEYSHCAWTIVRVEILRNIFY FINRLTGYLRN
antiCD40_LC-- GST--IFN β _C17S (SEQ ID NO 36)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC SGGTSGTSGTGS MSYNLLGFLQRSSNFQSQKLLW QLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEML

	QNIFAI FRQDSSSTGWN ETIVENLLANVYHQINHLKTVLEEK LEKEDFTRGKLMSSLHLK RYYGRILHYLKAKEYSHCAWTIV RVEILRN FYFINRLTGYLRN
antiCD40_LC-- HL2--IFN β _C17S (SEQ ID NO 37)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGG TKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC A E A A A K E A A A K A A E A A A K E A A A K A M S Y N L L G F L QRSSNFQSQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQF QKEDAALTIYEMLQNIFAI FRQDSSSTGWN ETIVENLLANVY HQINHLKTVLEEKLEKEDFTRGKLMSSLHLK RYYGRILHYL KAKEYSHCAWTIVRVEILRN FYFINRLTGYLRN
antiCD40_hIgG2_ dK_HC--(G4S)2-- IFN α 2a (SEQ ID NO 38)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHWRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNV DHKPSNTKVDKTVERKCCVECP PCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVS VLT VVH QDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNV FSC SVMHEALHNHYTQKSLS LSPGGGGGSGGGGSCDLPQTHSLGSRRTLMLLAQMRKISLF SCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK DSSAAWDETLLDKFYTEL YQQLNDLEACVIQGVGVTTETPL MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKE

antiCD40_hIgG2_ dK_HC--(G4S)3-- IFN α 2a (SEQ ID NO 39)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNV DHKPSNTKVDKTVERKCCVECP PCP APPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNV FSC SVMHEALHNHYTQKSLS LSPGGGGGSGGGGSGGGGSGCDLPQTHSLGSRRTLMLLAQ MRKISLFSCLKDRHDFGFPQE EFGNQFQKAETIPVLHEMIQQI FNLFSTKDSSAAWDETLLDKFYTELYQQ LNDLEACVIQGVG VTETPLMKEDSILAVRK YFQRITLYLKEKKYSPCAWEVVRA EIMRSFSLSTNLQESLRSKE
antiCD40_hIgG2_ dK_HC--(G4S)4-- IFN α 2a (SEQ ID NO 40)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNV DHKPSNTKVDKTVERKCCVECP PCP APPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNV FSC SVMHEALHNHYTQKSLS LSPGGGGGSGGGGSGGGGSGGGGSGCDLPQTHSLGSRRTL MLLAQMRKISLFSCLKDRHDFGFPQE EFGNQFQKAETIPVLH EMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQ LNDLEAC

	VIQGVGVTTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE
antiCD40_LC-- (G4S)2--IFN α 2a (SEQ ID NO 41)	DIQMTQSPSSVSASVGDRVTTITCRASQGIYSWLAWYQQKPGKAPNLLIYTA ASTLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANIFPLTFGGG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC GGGGSGGGG SCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTEL YQQLNDLEACVIQGVGVTTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE
antiCD40_LC-- (G4S)3--IFN α 2a (SEQ ID NO 42)	DIQMTQSPSSVSASVGDRVTTITCRASQGIYSWLAWYQQKPGKAPNLLIYTA ASTLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANIFPLTFGGG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC GGGGSGGGGSGGGG SCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTEL YQQLNDLEACVIQGVGVTTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE
antiCD40_LC-- (G4S)4--IFN α 2a (SEQ ID NO 43)	DIQMTQSPSSVSASVGDRVTTITCRASQGIYSWLAWYQQKPGKAPNLLIYTA ASTLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQANIFPLTFGGG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDST YLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC GGGGSGGGGSGGGGSGGGG SCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTEL YQQLNDLEA

	CVIQGVGVTTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCA WEVVRAEIMRSFSLSTNLQESLRSKE
IFN β --(G4S)3-- antiCD40_LC) (SEQ ID NO 44)	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDI PEEIKQLQQFQKEDAALTIYEMLQNIFAIQRDSSSTGWNETI VENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKR YYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGYLRLN GGGGS GGGGS GGGGS DIQMTQSPSSVSASVGDRVITTCRA SQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGS GTDFTLTISLQPEDFATYYCQQANIFPLTFGGG TK VEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFY P REAKVQWKVD NALQSGNSQESVTEQDSKDSTYSL S STLTLSKADY E KHKVY ACEVTHQGLSSPVTKSFNRGEC
antiCD40_LC-- (G4S)4--IFN β (SEQ ID NO 45)	DIQMTQSPSSVSASVGDRVITTCRASQGIYSWLAWYQQKPG KAPNLLIYTASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFAT YYCQQANIFPLTFGGG TK VEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFY P REAKVQWKVDNALQSGNSQESVTEQDS KDSTYSL S STLTLSKADY E KHKVYACEVTHQGLSSPVTKSF NRGEC GGGGS GGGGS GGGGS GGGGS GGGGS MSYNLLGFLQRSSN FQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDA ALTIYEMLQNIFAIQRDSSSTGWNETIVENLLANVYHQINH LKTVLEEKLEKEDFTRGKLMSSLHLKRYYGRILHYLKAKEY SHCAWTIVRVEILRNIFYFINRLTGYLRLN
IFN β --(G4S)3-- antiCD40_HC_Ig G1_NNAS_dK (SEQ ID NO 46)	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDI PEEIKQLQQFQKEDAALTIYEMLQNIFAIQRDSSSTGWNETI VENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKR YYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGYLRLN GGGGS GGGGS GGGGS SQVQLVQSGAEVKKPGASVKV S CK ASGYTFTGYMHVWRQAPGGGLEWMGWINPD S GGTNYA QKFQGRVTMT R DTSISTAYMELNRLRSDDTAVYYCARDQP LGYCTNGVCSYFDYWGGGT L VTVSSASTKGPSVFPLAPSSK

	STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNN <u>ASRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA</u> KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG
antiCD40_HC_Ig G1_NNAS_dK-- (G4S)4--IFNβ (SEQ ID NO 47)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNN<u>ASRVVSVLTVLHQDWLNG</u> KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQ KSLSLSPGGGGGSGGGGSGGGGSGGGGSSMSYNLLGFLQR SSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQK EDAALTIYEMLNIFAIQRDSSSTGWNENIVENLLANVYHQ INHLKTVLEEKLEKEDFTRGKLMSSLHLKRYYGRILHYLKA KEYSHCAWTIVRVEILRNIFYFINRLTGYLRLN
antiCD40_hIgG2 dK_HC--HL-- IFNα2A (SEQ ID NO 81)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDHKPSNTKVDKTVRKCCVECPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV

	DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPMLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGAEEAAAKEAAAKACDLPQTHSLGSRRTLMLLAQMRKI SLFSLCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLF STKDSSAAWDETLLDKFYTELYQQLNDEACVIQGVGVGTET PLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMR SFSLSLSTNLQESLRSKE
antiCD40_LC- derivative--HL-- IFNα2A (SEQ ID NO 82)	DIQMTQSPSSVSASVGDRVITITCRASQGIYSWLAWYQQKPG KAPNLLIYTA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEKSLSLSPGAEEAAAKEAAAKACDLPQTHSLGSRRTLML LLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDEACVI QGVGVGTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWE VVRAEIMRSFSLSLSTNLQESLRSKE
antiCD40_LC-- (G4S)4--IFNγ (SEQ ID NO 83)	DIQMTQSPSSVSASVGDRVITITCRASQGIYSWLAWYQQKPG KAPNLLIYTA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECGGGGSGGGGSGGGGSGGGGSQDPYVKEAENLKK YFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYF KLFKNFKDDQSIQKS VETIKEDMNVKFFNSNKKKRDDFEKL TNYSVTDLNVQRKAIHELIQVMAELSPA AKTGKRKRSQMLF RGRRASQ

antiCD40_hIgG2 dK_HC--(G4S)4-- IFN γ (SEQ ID NO 84)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPHKPSNTKVDKTVKCCVECPPCAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLS LSPGGGGGSGGGGSGGGGSGGGGSGQDPYVKEAENLKKYF NAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKL FKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTN YSVTDLNVQRKAIHELIQVMAELSPAAGTKGRKRSQMLFRG RRASQ
antiCD40_LC-- (G4S)4--IFN λ 2 (SEQ ID NO 85)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTAATLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECGGGGSGGGGSGGGGSGGGGSGVPVARLHGALPDA RGCHIAQFKSLSPQELQAFKRAKDALEESLLLKDCRCHSRLF PRTWDLRQLQVRERPMALEAELALTLKVLEATADTDPALV DVLDQPLHTLHHILSQFRACIQPQPTAGPRTGRLLHHWLRYR LQEAPKKESPGCLEASVTFNLFRLLTRDLNLCVASGDLCV

antiCD40_hIgG2 dK_HC--(G4S)4-- IFN λ 2 (SEQ ID NO 86)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDPHKPSNTKVDKTVRKCCVECPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSQSVMHENHNTQKSL LSPGGGGGSGGGGSGGGGSGGGGSPVVARLHGALPDARG CHIAQFKSLSPQELQAFKRAKDALEESLLLKDCRCHSRLFPR TWDLRQLQVRERPMALAEALATLKVLEATADTDPALVDV LDQPLHTLHHILSQFRACIQPQPTAGPRTRGRLHHWLYRLQE APKKESPGCLEASVTFNLFRLLTRDLNCVASGDLCV
antiCD40_LC-- (G4S)4--IFN ω (SEQ ID NO 87)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPG KAPNLLIYTAATLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECGGGGSGGGGSGGGGSGGGGSLGCDLPQNHGLLSR NTLVLLHQMRRISPFLCLKDRRDFRFPQEMVKGSQQLQKAHV MSVLHEMLQQIFSLFHTERSSAAWNMTLLDQLHTGLHQQ QHLETCLLQVVGEGESAGAISSPALTLRRYFQGIRVYLKEKK YSDCAWEVVRMEIMKSLFLSTNMQERLRKDRDLGSS

antiCD40_hIgG2 dK_HC--(G4S)4-- IFN ϵ (SEQ ID NO 88)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTA YMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNF GTQTYTCNVDHKPSNTKVDKTVRKCCVECPPCAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPM L DSDG SFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLS LSPGGGGGSGGGGSGGGGSGGGGSLDLKLIIFQQRQVNQE SLKLLNKLQTL SIQQCLPHRKNFLLPQKSLSPQQYQKGHTLA ILHEMLQQIFSLFRANISLDGWEENHTEKFLIQLHQQLEYLE ALMGLEAEKLSGTLGSDNLRLQVKMYFRRIHDYLENQDYS TCAWAIVQVEISRCLFFVFSLTEKLSKQGRPLNDMKQELTTE FRSPR
antiCD40_LC-- (G4S)3-- IFN β _C17S (SEQ ID NO 90)	DIQMTQSPSSVSASVGDRVITITCRASQGIYSWLAWYQQKPG KAPNLLIYTASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECGGGGSGGGGSGGGGSM SYNLLGFLQRSSNFQSQK LLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIY EMLQNIFAIFRQDSSSTGWN ETIVENLLANVYHQINHLKTVL EEKLEKEDFTRGKLMSSLHLKRY YGRILHYLKAKEYSHCA WTIVRVEILRN FYFINRLTG YLRN

Table 8. Sequences of exemplary interferon-associated antigen binding protein and components thereof based on the antiCD40 antibody 3G5. *Italic sequences correspond to signal peptides. Bold non-italic sequences correspond to linkers. Mutated amino acids are underlined.*

Name / SEQ ID Number	Sequence
antiCD40_light chain (SEQ ID NO 59)	EIVMTQSPATLSVSPGERATLSCRASQSVRSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTINSLQSEDF VYYCQQHNKWITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
antiCD40_light chain with signal peptide 1 (SEQ ID NO 60)	<i>MGWSCIIIFLVATATGVH</i> EIVMTQSPATLSVSPGERATLSCR ASQSVRSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGS GSGTEFTLTINSLQSEDFVYYCQQHNKWITFGQGTRLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC
antiCD40_heavy chain hIgG2 dK (SEQ ID NO 61)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYS KLTVDKSRWQQGNV FSC SVMHEALHNHYTQKSLSLSPG

antiCD40_heavy chain hIgG2 dK with Signal peptide 1 (SEQ ID NO 62)	<i>MGWSCILFLVATATGVHSQVQLVESGGGVVQPGKSLRLSCA ASGFTFSSNGIHWVRQAPGKGLEWVAVIWSDGSNKFYADS VKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARASGSGS YYNFFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVEC PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPMLDSDGSFFLYSKLTV DKS R WQQGNVFSCSVMHEA LHNHYTQKSLSLSPG</i>
antiCD40 antibody Fab region heavy chain hIgG2 (SEQ ID NO 63)	<i>QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NV DHKPSNTKVDKTVERKCCVE</i>
antiCD40 antibody Fab region heavy chain hIgG2 with signal peptide 1 (SEQ ID NO 64)	<i>MGWSCILFLVATATGVHSQVQLVESGGGVVQPGKSLRLSCA ASGFTFSSNGIHWVRQAPGKGLEWVAVIWSDGSNKFYADS VKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARASGSGS YYNFFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVE</i>
antiCD40 antibody Fab region heavy chain hIgG2 --TEV--6His tag	<i>QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW</i>

(SEQ ID NO 65)	NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVEENLYFQSHHHHHH
antiCD40_hIgG2 dK_HC--RL-- IFN β dM (SEQ ID NO 66)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG PA P ASYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDI PEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTGWN ETI VENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKR YYGRILHYLKAKEYSHCAWTIVRVEILRN FYFINRLTG YLRN
antiCD40_hIgG2 dK_HC--RL-- IFN β dM_C17S (SEQ ID NO 67)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG PA P ASYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLKDRMNFDI PEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTGWN ETI

	VENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKR YYGRILHYLKAKEYSHCAWTIVRVEILRNIFYFINRLTGYLRLN
antiCD40_hIgG2 dK_HC--HL-- IFN β dM (SEQ ID NO 68)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTVRKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGAE AAAKEAAAK ASYNLLGFLQRSSNFQCQKLLWQLNGRLEYC LKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIQRD SSSTGWN ETIVENLLANVYHQINHLKTVLEEKLEKEDFTRG KLMSSLHLKRYYYGRILHYLKAKEYSHCAWTIVRVEILRNIFY FINRLTGYLRLN
antiCD40_hIgG2 dK_HC--HL-- IFN β dM_C17S (SEQ ID NO 69)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTVRKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC

	LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSOSVMHEALHNHYTQKSLSLSPGAE AAAKEAAAKASYNLLGFLQRSSNFQSQKLLWQLNGRLEYC LKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIQRD SSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRG KLMSSLHLKRYYYGRILHYLKAKEYSHCAWTIVRVEILRNFY FINRLTGYLRN
antiCD40_LC-- HL2--IFN β _C17S (SEQ ID NO 70)	EIVMTQSPATLSVSPGERATLSCRASQSVRSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTINSLQSEDF VYYCQQHNKWITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECAAAKEAAAKAAEAAAKEAAAKAMSYNLLGFL QRSSNFQSQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQF QKEDAALTIYEMLQNIFAIQRDSSSTGWNETIVENLLANVY HQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRYYYGRILHYL KAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN
antiCD40_LC-- (G4S) ³ -- IFN β _C17S (SEQ ID NO 71)	EIVMTQSPATLSVSPGERATLSCRASQSVRSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTINSLQSEDF VYYCQQHNKWITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGECGGGGSGGGSGGGGSMSYNLLGFLQRSSNFQSQK LLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIY EMLQNIFAIQRDSSSTGWNETIVENLLANVYHQINHLKTVL EEKLEKEDFTRGKLMSSLHLKRYYYGRILHYLKAKEYSHCA WTIVRVEILRNFYFINRLTGYLRN

antiCD40_hIgG2 dK_HC--(G4S)2-- IFN α 2a (SEQ ID NO 72)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDR HDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAA WDETLLDKFYTEL YQQLNDLEACVIQGVGVTTETPLMKEDSI LAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNL QESLRSKE
antiCD40_hIgG2 dK_HC--(G4S)3-- IFN α 2a (SEQ ID NO 73)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSGGGGSCDLPQTHSLGSRRTLMLLAQMRKISLF SCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK DSSAAWDETLLDKFYTEL YQQLNDLEACVIQGVGVTTETPL

	MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKE
antiCD40_hIgG2 dK_HC--(G4S)4-- IFN α 2a (SEQ ID NO 74)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSGGGGSGGGGSCDLPQTHSLGSRRTLMLLAQM RKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIF NLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGV TETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEI MRSFSLSTNLQESLRSKE

antiCD40_hIgG2 dK_HC--HL-- IFN α 2a (SEQ ID NO 75)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSLSPGAE AAAKEAAAKACDLPQTHSLGSRRTLMLLAQMRKISLFSCL KDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSS AAWDETLLDKFYTEL YQQ LNDLEACVIQGVGVTTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLST NLQESLRSKE
antiCD40_hIgG2 dK_HC--(G4S)4-- IFN γ (SEQ ID NO 89)	QVQLVESGGGVVQPGKSLRLSCAASGFTFSSNGIHWVRQAP GKGLEWVAVIWSDGSNKFYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARASGSGSYYNFFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTC NVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSLSPGGG GGSGGGGSGGGGSGGGGSQDPYVKEAENLKKYFNAGHS DVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFK DDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTD LNVQRKAIHELIQVMAELSPA AKTGKRKRSQMLFRGRRASQ

[00216] In preferred embodiments, the interferon-associated antigen binding proteins described herein are interferon-fused antigen binding proteins comprising polypeptides derived from those specified in **Table 9**, in particular **Table 9A** or **Table 9B**, more particularly **Table 9A** below, and especially from the polypeptides of SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42 or SEQ ID NO 43 above. In preferred embodiments, the interferon-associated antigen binding proteins described herein are interferon-fused antigen binding proteins consisting of polypeptides derived from those specified in **Table 9**, in particular **Table 9A** or **Table 9B**, more particularly **Table 9A** below, and especially from the polypeptides of SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42 or SEQ ID NO 43 above. In more preferred embodiments, the interferon-fused antibody comprises the sequences as set forth in SEQ ID NO 38 and SEQ ID NO 3. In other more preferred embodiments, the interferon-fused antibody comprises the sequences as set forth in SEQ ID NO 39 and SEQ ID NO 3. In other more preferred embodiments, the interferon-fused antibody comprises the sequences as set forth in SEQ ID NO 40 and SEQ ID NO 3. In other more preferred embodiments, the interferon-fused antibody comprises the sequences as set forth in SEQ ID NO 41 and SEQ ID NO 9. In other more preferred embodiments, the interferon-fused antibody comprises the sequences as set forth in SEQ ID NO 42 and SEQ ID NO 9. In other more preferred embodiments, the interferon-fused antibody comprises the sequences as set forth in SEQ ID NO 43 and SEQ ID NO 9.

Table 9. *Polypeptide combinations found in preferred interferon-fused antigen binding proteins of the invention based on the antiCD40 antibody CP870,893, their mean EC₅₀ values with regard to the activation of CD40 and IFN-pathways and their productivity (i.e., yield per liter culture). Each sequence combination as indicated is comprised twice in the 5 respective IFA. SN: supernatant.*

A

Interferon-fused Antibody (IFA)	Sequence combination	CD40 EC₅₀ (ng/mL)	IFNβ EC₅₀ (ng/mL)	IFNα EC₅₀ (ng/mL)	Productivity (mg/L)
IFA1	(SEQ ID NO 28) + (SEQ ID NO 9)	74,1	1,64		16,7
IFA2	(SEQ ID NO 29) + (SEQ ID NO 9)	111	0,14		17,8
IFA8	(SEQ ID NO 30) + (SEQ ID NO 3)	39,7	2,9		6,45
IFA9	(SEQ ID NO 31) + (SEQ ID NO 3)	42,6	0,7		3,4
IFA10	(SEQ ID NO 32) + (SEQ ID NO 3)	26,5	4,5		6,9
IFA11	(SEQ ID NO 33) + (SEQ ID NO 3)	42,8	1,78		5,1
IFA12	(SEQ ID NO 34) + (SEQ ID NO 9)	105	3,64		21,2
IFA13	(SEQ ID NO 35) + (SEQ ID NO 9)	192	0,7		11,5
IFA19	(SEQ ID NO 36) + (SEQ ID NO 9)	110	1,3		5,6
IFA20	(SEQ ID NO 37) + (SEQ ID NO 9)	182	2,34		4,2
IFA25	(SEQ ID NO 38) + (SEQ ID NO 3)	13,3		5,1	21
IFA26	(SEQ ID NO 39) + (SEQ ID NO 3)	15,35		4	8,6
IFA27	(SEQ ID NO 40) + (SEQ ID NO 3)	17		2,4	9,3
IFA28	(SEQ ID NO 41) + (SEQ ID NO 9)	12,8		4,5	75
IFA29	(SEQ ID NO 42) + (SEQ ID NO 9)	11,1		2	56,6

IFA30	(SEQ ID NO 43) + (SEQ ID NO 9)	11,3		1,6	46,6
IFA34	(SEQ ID NO 44) + (SEQ ID NO 49)	active (SN)	active (SN)		no significant production
IFA35	(SEQ ID NO 45) + (SEQ ID NO 49)	active (SN)	active (SN)		no significant production
IFA36	(SEQ ID NO 46) + (SEQ ID NO 3)	active (SN)	active (SN)		no significant production
IFA37	(SEQ ID NO 47) + (SEQ ID NO 3)	active (SN)	active (SN)		no significant production
IFA126	(SEQ ID NO 90) + (SEQ ID NO 9)	364,05	2,075		not determined

B

Interferon -fused Antibody (IFA)	Sequence combination	CD40 EC ₅₀ (ng/mL)	IFN α EC ₅₀ (ng/mL)	IFN λ EC ₅₀ (ng/mL)	IFN γ EC ₅₀ (ng/mL)	IFN ϵ EC ₅₀ (ng/mL)	IFN ω EC ₅₀ (ng/mL)	Productivity (mg/L)
IFA38	(SEQ ID NO 81) + (SEQ ID NO 3)	22.7	3.77					1.32
IFA39	(SEQ ID NO 82) + (SEQ ID NO 9)	17.5	2.95					1.25
IFA42	(SEQ ID NO 83) + (SEQ ID NO 9)	65.6			15.4			0.72
IFA43	(SEQ ID NO 84) + (SEQ ID NO 3)	50.8			<0.001			0.55
IFA44	(SEQ ID NO 85) + (SEQ ID NO 9)	41.4		0.153				0.91
IFA45	(SEQ ID NO 86) + (SEQ ID NO 3)	25.8		<0.001				1.09
IFA46	(SEQ ID NO 87) + (SEQ ID NO 9)	86.3					0.493	0.89
IFA49	(SEQ ID NO 88) + (SEQ ID NO 3)	65.8				78.2		0.61
IFA50	(SEQ ID NO 41) + (SEQ ID NO 50)	128	1.36					0.57
IFA51	(SEQ ID NO 42) + (SEQ ID NO 50)	123	1.43					0.48

[00218] In other preferred embodiments, the interferon-associated antigen binding proteins described herein are interferon-fused antigen binding proteins comprising polypeptides derived from those specified in **Table 10** below. In preferred
5 interferon-fused antigen binding proteins consisting of polypeptides derived from those specified in **Table 10** below.

Table 10. *Polypeptide combinations found in preferred interferon-fused antigen binding proteins of the invention based on the antiCD40 antibody 3G5, their mean EC₅₀ values with 10 regard to the activation of CD40 and IFN-pathways. Each sequence combination as indicated is comprised twice in the respective IFA. SN: supernatant.*

A

Interferon - fused Antibody (IFA)	Sequence combination	CD40 EC ₅₀ (ng/mL)	IFN β EC ₅₀ (ng/mL)	IFN α EC ₅₀ (ng/mL)	Productivity mg/L
IFA106	(seq ID NO 66) + (seq ID NO 59)	190,5	10,30		0,36
IFA107	(seq ID NO 67) + (seq ID NO 59)	141,5	2,03		0,28
IFA108	(seq ID NO 68) + (seq ID NO 59)	37,3	1,27		0,59
IFA109	(seq ID NO 69) + (seq ID NO 59)	30	0,45		0,4
IFA114	(seq ID NO 70) + (seq ID NO 61)	active (SN)	active (SN)		no significant production
IFA115	(seq ID NO 71) + (seq ID NO 61)	active (SN)	active (SN)		no significant production
IFA121	(seq ID NO 72) + (seq ID NO 59)	14,2		0,12	22,6
IFA122	(seq ID NO 73) + (seq ID NO 59)	11,74		0,07	16,8
IFA123	(seq ID NO 74) + (seq ID NO 59)	12,85		0,05	17,2
IFA124	(seq ID NO 75) + (seq ID NO 59)	12,14		0,04	21,6

B

Interferon-fused Antibody (IFA)	Sequence combination	CD40 EC ₅₀ (ng/mL)	IFN α EC ₅₀ (ng/mL)	IFN λ EC ₅₀ (ng/mL)	IFN γ EC ₅₀ (ng/mL)	IFN ϵ EC ₅₀ (ng/mL)	IFN ω EC ₅₀ (ng/mL)	Productivity (mg/L)
IFA125	(seq ID NO 89) + (seq ID NO 59)	8,8			0,142			1,79

Nucleic Acids and Expression Vectors

[00219] In one aspect, a combination of polynucleotides encoding an interferon-associated antigen binding protein is provided. Methods of making an interferon-associated antigen binding protein comprising expressing these polynucleotides are also provided.

[00220] In some embodiments, a nucleic acid encoding an IFN or a functional fragment thereof being fused to an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, as disclosed herein is provided. In certain exemplary embodiments, the nucleic acid is encoding an IFN or a functional fragment thereof fused to an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof according to any of the sequences set forth in SEQ ID NOs 89 to 90, or a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In certain exemplary embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of SEQ ID NOs 89 to 90. In certain exemplary embodiments, the nucleic acid is encoding an IFN or a functional fragment thereof fused to an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof according to any of the sequences set forth in SEQ ID NOs 81 to 88, or a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In certain exemplary embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of SEQ ID NOs 81 to 88. In preferred embodiments, the nucleic acid is encoding an IFN or a functional fragment thereof fused to an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof according to any of the sequences set forth in SEQ

ID NOs 28 to 47, or a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In even more specific embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of SEQ ID NOs 28 to 47. In other preferred embodiments, the nucleic acid is encoding an IFN or a functional fragment thereof fused to an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof according to any of the sequences set forth in SEQ ID NOs 66 to 75, or a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In even more specific embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of SEQ ID NOs 66 to 75.

[00221] In those embodiments wherein a nucleic acid encodes an IFN or a functional fragment thereof being fused to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, the nucleic acid may further encode a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In more specific embodiments, the heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 48, SEQ ID NO 49, or SEQ ID NO 50, or a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In even more specific embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8, SEQ ID NO 9, SEQ ID NO 10, SEQ ID NO 11, SEQ ID NO 12, SEQ ID NO 13, SEQ ID NO 48, SEQ ID NO 49, or SEQ ID NO 50. In other more specific embodiments, the heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a sequence as set forth in SEQ ID NO 61, SEQ ID NO 62, SEQ ID NO 63, SEQ ID NO 64 or SEQ ID NO 65, or a nucleic acid sequence at least at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In such other even more specific

embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding SEQ ID NO 61, SEQ ID NO 62, SEQ ID NO 63, SEQ ID NO 64 or SEQ ID NO 65.

[00222] In those embodiments where a nucleic acid encodes an IFN or a functional
5 fragment thereof being fused to the heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, the nucleic acid may further encode a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. In more specific embodiments, the light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a
10 sequence as set forth in SEQ ID NO 3, SEQ ID NO 4 or SEQ ID NO 5, or a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In even more specific embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding SEQ ID NO 3, SEQ ID NO 4 or SEQ ID NO 5.
15 In other more specific embodiments, the light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a sequence as set forth in SEQ ID NO 59 or SEQ ID NO 60, or a nucleic acid sequence at least at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding any of these sequences. In even more specific
20 embodiments, said nucleic acid is at least 95%, at least 98% or at least 99% identical to a nucleic acid encoding SEQ ID NO 59 or SEQ ID NO 60.

[00223] In certain embodiments, the nucleic acids described herein may comprise a sequence encoding a sequence to increase the yield (e.g. a solubility tag) or facilitate purification of the expressed proteins (i.e., a purification tag). Purification tags are
25 known to a person skilled in the art and may be selected from glutathione *S*-transferase (GST) tags, maltose binding protein (MBP) tags, calmodulin binding peptide (CBP) tags, intein-chitin binding domain (intein-CBD) tags, Streptavidin/Biotin-based tags (such as biotinylation signal peptide (BCCP) tags, Streptavidin-binding peptide (SBP) tags, His-patch ThioFusion tags, tandem affinity
30 purification (TAP) tags, Small ubiquitin-like modifier (SUMO) tags, HaloTag® (Promega), Profinity eXact™ system (Bio-Rad). In some embodiments, the purification tag may be a polyhistidine tag (e.g., a His₆-, His₇-, His₈-, His₉- or His₁₀-

tag). In other embodiments, the purification tag may be a Strep-tag (e.g., a Strep-tag® or a Strep-tag II®; IBA Life Sciences). In yet other embodiments, the purification tag may be a maltose binding protein (MBP) tag.

5 [00224] In some embodiments, the nucleic acid sequence may further comprise a sequence encoding a cleavage site for removal of the purification tag. Such cleavage sequences are known to a person skilled in the art and may be selected from a sequence recognized and cleaved by an endoprotease or an exoprotease. In some
10 embodiments, an endoprotease for the removal of a purification tag may be selected from: Enteropeptidase, Thrombin, Factor Xa, TEV protease or Rhinovirus 3C protease. In some embodiments, an exoprotease for the removal of a purification tag may be selected from: Carboxypeptidase A, Carboxypeptidase B or DAPase. In preferred embodiments, the protease for the removal of a purification tag is TEV protease. In a more specific preferred embodiment, the nucleic acid comprises a
15 sequence encoding a His₆-tag and a TEV cleavage site. In an even more specific preferred embodiment, said nucleic acid comprises a sequence encoding a sequence as set forth in SEQ ID NO 27.

[00225] The nucleic acid molecules of the invention may also comprise a sequence encoding a signal peptide. The skilled person is aware of the various signal peptides available to direct the expressed protein to the desired site of folding, assembly and/or
20 maturation as well as to effect secretion of the final protein into the medium to facilitate downstream processing. Thus, in some embodiments, the signal peptide is a secretory signal peptide. The encoded signal peptide may comprise a sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2. In some embodiments, the signal peptide comprises the sequence as set forth in SEQ ID NO: 1. In other embodiments, the
25 signal peptide comprises the sequence as set forth in SEQ ID NO: 2.

[00226] Signal peptide 1 (SEQ ID NO 1) was used for synthesis of the polypeptide sequences as set forth in SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, SEQ ID
30 NO 47, SEQ ID NO 50, SEQ ID NO 65, SEQ ID NO 66, SEQ ID NO 67, SEQ ID NO 68, SEQ ID NO 69, SEQ ID NO 70, SEQ ID NO 71, SEQ ID NO 72, SEQ ID

NO 73, SEQ ID NO 74 and SEQ ID NO 75. Such signal peptide that is initially present at the N-terminus of the respective sequence of the polypeptide is cleaved during synthesis.

5 [00227] Signal peptide 2 (SEQ ID NO 2) was used for synthesis of the polypeptide sequences as set forth in SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42 and SEQ ID NO 43. Such signal peptide that is initially present at the N-terminus of the respective sequence of the polypeptide is cleaved during synthesis.

10 [00228] For the synthesis of the polypeptide sequences as set forth in SEQ ID NO 81, SEQ ID NO 82, SEQ ID NO 83, SEQ ID NO 84, SEQ ID NO 85, SEQ ID NO 86, SEQ ID NO 87 and SEQ ID NO 88 the signal peptide MGWSCIILFLVATATGVHS (SEQ ID NO 1) was used. Such signal peptide that is initially present at the N-terminus of the respective sequence of the polypeptide is cleaved during synthesis.

15 [00229] For the synthesis of the polypeptide sequences as set forth in SEQ ID NO 89 and SEQ ID NO 90 the signal peptide 1 (SEQ ID NO 1) was used. Such signal peptide that is initially present at the N-terminus of the respective sequence of the polypeptide is cleaved during synthesis.

20 [00230] Polynucleotides encoding an IFN or a functional fragment thereof being fused to the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof as disclosed herein are typically inserted in an expression vector for introduction into host cells that may be used to produce the desired quantity of the described or claimed interferon-associated antigen binding proteins. Accordingly, in certain aspects, the invention provides expression vectors comprising polynucleotides disclosed herein and host cells comprising these vectors and
25 polynucleotides.

30 [00231] The term “**vector**” or “**expression vector**” is used herein for the purposes of the specification and claims, to mean vectors used in accordance with the present invention as a vehicle for introducing into and expressing a desired gene in a cell. As known to those skilled in the art, such vectors may easily be selected from the group consisting of plasmids, phages, viruses and retroviruses. In general, vectors compatible with the present invention will comprise a selection marker, appropriate

restriction sites to facilitate cloning of the desired gene and the ability to enter and/or replicate in eukaryotic or prokaryotic cells.

[00232] Numerous expression **vector systems** may be employed for the purposes of this invention. For example, one class of vector utilizes DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (RSV, MMTV or MOMLV), or SV40 virus. Others involve the use of polycistronic systems with internal ribosome binding sites. Additionally, cells which have integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow selection of transfected host cells. The marker may provide for prototrophy to an auxotrophic host, biocide resistance (e.g., antibiotics) or resistance to heavy metals such as copper. The selectable marker gene can either be directly linked to the DNA sequences to be expressed, or introduced into the same cell by co-transformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include signal sequences, splice signals, as well as transcriptional promoters, enhancers, and termination signals. In some embodiments the cloned variable region genes, one of them fused with a gene encoding an IFN or a functional fragment thereof, are inserted into an expression vector along with the heavy and light chain constant region genes (such as human genes) synthesized as discussed above.

[00233] In other embodiments, a vector system of the invention may comprise more than one vector. In some embodiments, a vector system may comprise a first vector for the expression of an IFN or a functional fragment thereof fused to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof and a second vector for expression of a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof. Alternatively, such a vector system may comprise a first vector for the expression of an IFN or a functional fragment thereof fused to a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof and a second vector for expression of a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.

[00234] In other embodiments, an interferon-associated antigen binding protein as described herein may be expressed using polycistronic constructs. In such expression systems, multiple gene products of interest such as those encoding an IFN or a functional fragment thereof being fused to a heavy chain of an agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof and encoding a light chain of said antibody, or those encoding an IFN or a functional fragment thereof being fused to a light chain of an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof and encoding a heavy chain of said antibody or an agonistic antigen binding fragment thereof may be produced from a single polycistronic construct. These systems advantageously use an internal ribosome entry site (IRES) to provide relatively high levels of polypeptides in eukaryotic host cells. Compatible IRES sequences are disclosed in U.S. Pat. No. 6,193,980, which is incorporated by reference herein. Those skilled in the art will appreciate that such expression systems may be used to effectively produce the full range of polypeptides disclosed in the instant application.

[00235] More generally, once a vector or a DNA sequence encoding an interferon-associated antigen binding protein of the present invention has been prepared, the expression vector may be introduced into an appropriate host cell. That is, the host cell may be transformed. Introduction of a plasmid into the host cell can be accomplished by various techniques well known to those of skill in the art. These include, but are not limited to, transfection (including electrophoresis and electroporation), protoplast fusion, calcium phosphate precipitation, cell fusion with enveloped DNA, microinjection, and infection with intact virus. See, e.g., Ridgway, A. A. G. "Mammalian Expression Vectors" Chapter 24.2, pp. 470-472 Vectors, Rodriguez and Denhardt, Eds. (Butterworths, Boston, MA 1988). The transformed cells are grown under conditions appropriate to the production of the light chains and heavy chains, and assayed for heavy and/or light chain protein synthesis. Exemplary assay techniques include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or fluorescence-activated cell sorter analysis (FACS), immunohistochemistry and the like.

[00236] As used herein, the term “**transformation**” shall be used in a broad sense to refer to the introduction of DNA into a recipient host cell that changes the genotype and consequently results in a change in the recipient cell.

5 [00237] Along those same lines, “**host cells**” refer to cells that have been transformed with vectors constructed using recombinant DNA techniques and encoding at least one heterologous gene. In descriptions of processes for isolation of polypeptides from recombinant hosts, the terms “**cell**” and “**cell culture**” are used interchangeably to denote the source of the interferon-associated antigen binding protein unless it is clearly specified otherwise. In other words, recovery of polypeptide from the “**cells**”
10 may mean either from spun down whole cells, or from the cell culture containing both the medium and the suspended cells.

[00238] In one embodiment, the **host cell line** used for expression of an interferon-associated antigen binding protein is of eukaryotic or prokaryotic origin. As used herein, the term “expression” may include the transcription and translation of more
15 than one polypeptide chain (such as a heavy and a light chain of the antibody moiety of an interferon-associated antigen binding protein), which associate to form the final interferon-associated antigen binding protein. In one embodiment, the host cell line used for expression of an interferon-associated antigen binding protein is of bacterial origin. In one embodiment, the host cell line used for expression of an interferon-associated antigen binding protein is of mammalian origin; those skilled in the art can determine particular host cell lines which are best suited for the desired gene product to be expressed therein. Exemplary host cell lines include, but are not limited to, CHO K1 GS knockout from Horizon, DG44 and DUXB11 (Chinese Hamster Ovary lines, DHFR minus), HELA (human cervical carcinoma), CVI (monkey
20 kidney line), COS (a derivative of CVI with SV40 T antigen), R1610 (Chinese hamster fibroblast) BALBC/3T3 (mouse fibroblast), HAK (hamster kidney line), SP2/O (mouse myeloma), BFA-1c1BPT (bovine endothelial cells), RAJI (human lymphocyte), HEK 293 (human kidney). In a preferred embodiment, HEK FS S11/254 cells may be used. In another preferred embodiment, CHO K1 GS from Horizon
25 may be used. In one embodiment, the cell line provides for altered glycosylation, e.g., afucosylation, of the antibody expressed therefrom (e.g., PER.C6® (Crucell) or FUT8-knock-out CHO cell lines (POTELLIGENT™ cells) (Biowa, Princeton, NJ)).
30

In one embodiment NS0 cells may be used. Host cell lines are typically available from commercial services, the American Tissue Culture Collection or from published literature.

5 [00239] In one embodiment, the **host** used for expression of an interferon-associated antigen binding protein is a non-human transgenic animal or transgenic plant.

[00240] Interferon-associated antigen binding proteins of the invention can also be produced transgenically through the generation of a non-human animal (e.g., mammal) or plant that is transgenic for the sequences of interest and production of the interferon-associated antigen binding protein in a recoverable form therefrom. In
10 connection with the transgenic production in mammals, interferon-associated antigen binding proteins can be produced in, and recovered from, the milk of goats, cows, or other mammals. See, e.g., US. Patent Nos 5,827,690, 5,756,687, 5,750,172, and 5,741,957. Exemplary plant hosts are Nicotiana, Arabidopsis, duckweed, corn, wheat, potato, etc. Methods for expressing antibodies in plants, including a
15 description of promoters and vectors, as well as transformation of plants is known in the art. See, e.g., United States Patent 6,517,529, herein incorporated by reference. In some embodiments, non-human transgenic animals or plants are produced by introducing one or more nucleic acid molecules encoding an interferon-associated antigen binding protein of the invention into the animal or plant by standard
20 transgenic techniques. See Hogan and United States Patent 6,417,429. The transgenic cells used for making the transgenic animal can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. See, e.g., Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual 2nd ed., Cold Spring Harbor Press (1999); Jackson et al., Mouse Genetics and Transgenics: A Practical Approach, Oxford
25 University Press (2000); and Pinkert, Transgenic Animal Technology: A Laboratory Handbook, Academic Press (1999). In some embodiments, the transgenic non-human animals have a targeted disruption and replacement by a targeting construct that encodes the sequence(s) of interest. The interferon-associated antigen binding
30 proteins may be made in any transgenic animal. In a preferred embodiment, the non-human animals are mice, rats, sheep, pigs, goats, cattle or horses. The non-human

transgenic animal expresses said interferon-associated antigen binding proteins in blood, milk, urine, saliva, tears, mucus and other bodily fluids.

[00241] *In vitro* production allows scale-up to give large amounts of the desired interferon-associated antigen binding proteins. Techniques for mammalian cell cultivation under tissue culture conditions are known in the art and include homogeneous suspension culture, e.g., in an airlift reactor or in a continuous stirrer reactor, or immobilized or entrapped cell culture, e.g., in hollow fibers, microcapsules, on agarose microbeads or ceramic cartridges. If necessary and/or desired, a solution of an interferon-associated antigen binding protein, can be purified by the customary chromatography methods, for example gel filtration, ion-exchange chromatography, chromatography over DEAE-cellulose and/or (immuno-) affinity chromatography.

[00242] One or more genes encoding an interferon-associated antigen binding protein can also be expressed in non-mammalian cells such as bacteria or yeast or plant cells. In this regard it will be appreciated that various unicellular non-mammalian microorganisms such as bacteria can also be transformed; i.e. those capable of being grown in cultures or fermentation. Bacteria, which are susceptible to transformation, include members of the enterobacteriaceae, such as strains of *Escherichia coli* or *Salmonella*; *Bacillaceae*, such as *Bacillus subtilis*; *Pneumococcus*; *Streptococcus*, and *Haemophilus influenzae*. It will further be appreciated that, when expressed in bacteria, interferon-associated antigen binding proteins according to the invention or components thereof (i.e., agonistic anti-CD40 antibodies or agonistic antigen binding fragments thereof, and IFNs or functional fragments of IFNs) can become part of inclusion bodies. The desired interferon-associated antigen binding proteins may then need to be isolated, optionally also refolded, and purified.

[00243] In addition to prokaryotes, eukaryotic microbes may also be used. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among eukaryotic microorganisms although a number of other strains are commonly available. For expression in *Saccharomyces*, the plasmid YRp7, for example, (Stinchcomb *et al.*, Nature, 282:39 (1979); Kingsman *et al.*, Gene, 7:141 (1979); Tschemper *et al.*, Gene, 10:157 (1980)) is commonly used. This plasmid already

contains the TRP1 gene, which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example ATCC No. 44076 or PEP4-1 (Jones, Genetics, 85:12 (1977)). The presence of the trp1 lesion as a characteristic of the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

Therapeutic Vectors

[00244] A nucleic acid sequence encoding an interferon-associated antigen binding protein can be inserted into a vector and used as a therapeutic vector, e.g., a vector that expresses an interferon-associated antigen binding protein of the invention. The construction of suitable, functional expression constructs and therapeutic expression vectors is known to one of ordinary skill in the art. Thus, in certain embodiments, the interferon-associated antigen binding protein may be administered to a subject by means of genetic delivery with RNA or DNA sequences, a vector or vector system encoding the interferon-associated antigen binding protein.

[00245] Therapeutic vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Pat. No. 5,328,470) or by stereotactic injection (see, e.g., Chen et al., PNAS 91:3054-3057 (1994)). The pharmaceutical preparation of a therapeutic vector can include the vector in an acceptable diluent.

[00246] An interferon-associated antigen binding protein encoding nucleic acid, or nucleic acids, can be incorporated into a gene construct to be used as a part of a therapy protocol to deliver nucleic acids encoding an interferon-associated antigen binding protein. Expression vectors for *in vivo* transfection and expression of an interferon-associated antigen binding protein are provided.

[00247] Expression constructs of such components may be administered in any biologically effective carrier, e.g., any formulation or composition capable of effectively delivering the component nucleic acid sequence to cells *in vivo*, as are known to one of ordinary skill in the art. Approaches include, but are not limited to, insertion of the subject nucleic acid sequence(s) in viral vectors including, but not limited to, recombinant retroviruses, adenovirus, adeno-associated virus and herpes simplex virus-1, recombinant bacterial or eukaryotic plasmids and the like.

[00248] Retrovirus vectors and adeno-associated viral vectors can be used as a recombinant delivery system for the transfer of exogenous nucleic acid sequences *in vivo*, particularly into humans. Such vectors provide efficient delivery of genes into cells, and the transferred nucleic acids can be stably integrated into the chromosomal DNA of the host.

[00249] The development of specialized cell lines (termed “**packaging cells**”) which produce only replication-defective retroviruses has increased the utility of retroviruses for gene therapy, and defective retroviruses are characterized for use in gene transfer for gene therapy purposes (for a review see, e.g., Miller, Blood 76:271-78 (1990)). A replication-defective retrovirus can be packaged into virions, which can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells in vitro or in vivo with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, et al., (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14, and other standard laboratory manuals. Non-limiting examples of suitable retroviruses include pLJ, pZIP, pWE and pEM, which are known to those of ordinary skill in the art. Examples of suitable packaging virus lines include *Crip, *Cre, *2 and *Am. (See, for example, Eglitis, et al., Science 230:1395-1398 (1985); Danos and Mulligan, Proc. Natl. Acad. Sci. USA 85:6460-6464 (1988); Wilson, et al., Proc. Natl. Acad. Sci. USA 85:3014-3018 (1988); Armentano, et al., Proc. Natl. Acad. Sci. USA 87:6141-6145 (1990); Huber, et al., Proc. Natl. Acad. Sci. USA 88:8039-8043 (1991); Ferry, et al., Proc. Natl. Acad. Sci. USA 88:8377-8381 (1991); Chowdhury, et al., Science 254:1802-1805 (1991); van Beusechem, et al., Proc. Natl. Acad. Sci. USA 89:7640-7644 (1992); Kay, et al., Human Gene Therapy 3:641-647 (1992); Dai, et al., Proc. Natl. Acad. Sci. USA 89:10892-10895 (1992); Hwu, et al., J. Immunol. 150:4104-4115 (1993); U.S. Pat. No. 4,868,116; U.S. Pat. No. 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573).

[00250] In another embodiment, adenovirus-derived delivery vectors are provided. The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner, et al., BioTechniques 6:616

(1988); Rosenfeld, et al., Science 252:431-434 (1991); and Rosenfeld, et al., Cell 68:143-155 (1992). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are known to those of ordinary skill in the art. Recombinant adenoviruses can be advantageous in certain circumstances in that they are not capable of infecting non-dividing cells and can be used to infect a wide variety of cell types, including epithelial cells (Rosenfeld, et al. (1992), supra). Furthermore, the virus particle is relatively stable and amenable to purification and concentration and, as above, can be modified so as to affect the spectrum of infectivity. Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell, but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis *in situ* where introduced DNA becomes integrated into the host genome (e.g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other delivery vectors (Berkner, et al. (1998), supra; Haj-Ahmand and Graham, J. Virol. 57:267 (1986)).

[00251] Yet another viral vector system useful for delivery of a nucleic acid sequence encoding an interferon-associated antigen binding protein, is the adeno-associated virus (AAV). AAV is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka, et al., Curr. Topics in Micro. and Immunol. 158:97-129 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte, et al., Am. J. Respir. Cell. Mol. Biol. 7:349-356 (1992); Samulski, et al., J. Virol. 63:3822-3828 (1989); and McLaughlin, et al., J. Virol. 62:1963-1973 (1989)). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin, et al., Mol. Cell. Biol. 5:3251-3260 (1985) can be used to introduce DNA into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors (see for example Hermonat, et al., Proc. Natl. Acad. Sci. USA 81:6466-6470 (1984); Tratschin, et al., Mol. Cell. Biol. 4:2072-2081 (1985); Wondisford, et al., Mol. Endocrinol. 2:32-39 (1988);

Tratschin, et al., J. Virol. 51:611-619 (1984); and Flotte, et al., J. Biol. Chem. 268:3781-3790 (1993)).

[00252] In addition to viral transfer methods, non-viral methods can also be employed to cause expression of a nucleic acid sequence encoding an interferon-associated antigen binding protein in the tissue of a subject. Most non-viral methods of gene transfer rely on normal mechanisms used by mammalian cells for the uptake and intracellular transport of macromolecules. In some embodiments, non-viral delivery systems rely on endocytic pathways for the uptake of the subject gene by the targeted cell. Exemplary delivery systems of this type include liposomal derived systems, poly-lysine conjugates, and artificial viral envelopes. Other embodiments include plasmid injection systems such as are described in Meuli, et al., J. Invest. Dermatol. 116 (1):131-135 (2001); Cohen, et al., Gene Ther 7 (22):1896-905 (2000); or Tam, et al., Gene Ther. 7 (21):1867-74 (2000).

[00253] In clinical settings, the delivery systems can be introduced into a subject by any of a number of methods, each of which is familiar in the art. For instance, a pharmaceutical preparation of the delivery system can be introduced systemically, e.g., by intravenous injection. Specific transduction of the protein in the target cells occurs predominantly from specificity of transfection provided by the delivery vehicle, cell-type or tissue-type expression due to the transcriptional regulatory sequences controlling expression of the receptor gene, or a combination thereof. In other embodiments, initial delivery of the recombinant gene is more limited with introduction into the animal being quite localized. For example, the delivery vehicle can be introduced by catheter (see, U.S. Pat. No. 5,328,470) or by stereotactic injection (e.g., Chen, et al., PNAS 91: 3054-3057 (1994)).

[00254] The pharmaceutical preparation of the **therapeutic construct** can consist essentially of the delivery system in an acceptable diluent, or can comprise a slow release matrix in which the delivery vehicle is imbedded. Alternatively, where the complete delivery system can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can comprise one or more cells, which produce the delivery system.

Methods of Treatment and Corresponding Uses

[00255] In one aspect, the invention provides methods of treating a patient in need thereof (e.g., a patient infected with Hepatitis delta virus) comprising administering an effective amount of an interferon-associated antigen binding protein, or a nucleic acid sequence (e.g., mRNA) that encodes an interferon-associated antigen binding protein, as disclosed herein. The invention also provides for a use of an interferon-associated antigen binding protein, or a nucleic acid sequence (e.g., mRNA) that encodes an interferon-associated antigen binding protein, as disclosed herein, in the preparation of a medicament for the treatment of Hepatitis delta virus infection. In certain embodiments, the present invention provides kits and methods for the treatment of disorders and/or symptoms, e.g., Hepatitis delta virus-related disorders and/or Hepatitis delta virus-related symptoms, in a mammalian subject in need of such treatment. In certain exemplary embodiments, the subject is a human.

The interferon-associated antigen binding proteins, or nucleic acid sequences that encode them, of the present invention are useful in a number of different applications. For example, in one embodiment, the subject interferon-associated antigen binding proteins, or nucleic acid sequences that encode them, are useful for reducing viral burden in Hepatitis delta virus-infected cells, inhibiting Hepatitis delta virus infection, rescuing Hepatitis delta virus-infected cells from cell death and/or from Hepatitis delta virus-induced cytopathic effect.

[00256] In another embodiment, the subject interferon-associated antigen binding proteins, or nucleic acid sequences that encode them, are useful for reducing one or more symptoms and/or complications associated with Hepatitis delta virus infection, as described herein (*infra*).

[00257] Accordingly, this invention also relates to a method of treating one or more disorders, symptoms and/or complications associated with Hepatitis delta virus infection in a human or other animal by administering to such human or animal an effective, non-toxic amount of an interferon-associated antigen binding protein, or a nucleic acid sequence that encodes it. One skilled in the art would be able, by routine experimentation, to determine what an effective, non-toxic amount of an interferon-

associated antigen binding protein, or a nucleic acid sequence that encodes it, would be for the purpose of treating Hepatitis delta virus infection.

5 [00258] For example, a “**therapeutically active amount**” of an interferon-associated antigen binding protein of the present invention may vary according to factors such as the disease stage (e.g., acute vs. chronic), age, sex, medical complications (e.g., HIV co-infection, immunosuppressed conditions or diseases) and weight of the subject, and the ability of the interferon-associated antigen binding protein to elicit a desired response in the subject. The dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be
10 administered daily, or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

15 [00259] In general, the compositions provided in the current invention may be used to prophylactically treat non-infected cells or therapeutically treat any Hepatitis delta virus-infected cells comprising an antigenic marker that allows for the targeting of the Hepatitis delta virus-infected cells by an interferon-associated antigen binding protein.

20 [00260] The treatment or prevention of a Hepatitis delta virus infection according to the methods and uses described and claimed herein may entail administering a CD40 agonist or a functional fragment thereof e.g., “**in combination**” with an IFN or a functional fragment thereof, and *vice versa*. If the CD40 agonist or the functional fragment thereof and the IFN or the functional fragment thereof are present in distinct pharmaceutical compositions, such administration in combination may be performed by simultaneous administration. Alternatively, the combined administration may be achieved in that case via sequential administration. For example, the CD40 agonist
25 or the functional fragment thereof may be administered prior to the IFN or the functional fragment thereof. Alternatively, the IFN or the functional fragment thereof may be administered prior to the CD40 agonist or the functional fragment thereof. In the case of sequential administration, the administration will be performed in such a manner that the combined administration will lead to an enhancement of the
30 beneficial effects of the treatment on, e.g., reducing viral burden in Hepatitis delta virus-infected cells, inhibiting Hepatitis delta virus infection, rescuing cells from

Hepatitis delta virus-induced cell death and/or from Hepatitis delta virus-induced cytopathic effect preferably compared to the administration of the IFN or the functional fragment thereof alone. A skilled artisan will be readily able to determine suitable administration regimens, associated dosages, administration intervals, and, where sequential administration of distinct pharmaceutical compositions is chosen, intervals between the administration of said distinct pharmaceutical compositions, where such enhancement is achieved.

Pharmaceutical Compositions and Administration Thereof

[00261] In certain embodiments, the interferon-associated antigen binding proteins of the invention or nucleic acid sequences (including vectors or vector systems) that encode them are comprised in a pharmaceutical composition. Methods of preparing and administering interferon-associated antigen binding proteins, or nucleic acid sequences that encode them, of the current invention to a subject are well known to or can be readily determined by those skilled in the art using this specification and the knowledge in the art as a guide. The route of administration of the interferon-associated antigen binding proteins, or nucleic acid sequences that encode them, of the current invention may be oral, parenteral, by inhalation or topical. The term “**parenteral**”, as used herein, includes intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal or vaginal administration. While all these forms of administration are clearly contemplated as being within the scope of the current invention, a form for administration would be a solution for injection, in particular for intravenous or intraarterial injection or drip. Usually, a suitable pharmaceutical composition for injection may comprise a buffering agent (e.g. acetate, phosphate or citrate buffer), a surfactant (e.g. polysorbate), optionally a stabilizing agent (e.g. human albumin), etc. In some embodiments, the buffering agent is acetate. In another embodiment, the buffering agent is formate. In yet another embodiment, the buffering agent is citrate. In related embodiments, the surfactant may be selected from the list comprising pluronics, PEG, sorbitan esters, polysorbates, triton, tromethamine, lecithin, cholesterol and tyloxapal. In preferred embodiments, the surfactant is polysorbate. In more preferred embodiments, the surfactant is

polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 or polysorbate 100, preferably polysorbate 20 or polysorbate 80.

5 [00262] In some embodiments, the interferon-associated antigen binding proteins, or nucleic acid sequences that encode them, can be delivered directly to the site of the adverse cellular population (e.g., the liver) thereby increasing the exposure of the diseased tissue to the therapeutic agent.

10 [00263] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. In the compositions and methods of the current invention, pharmaceutically acceptable carriers include, but are not limited to, 0.01-0.1 M, e.g., 0.05 M phosphate buffer, or 0.8% saline. Other common parenteral vehicles include sodium phosphate solutions, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present such as for example, antimicrobials, antioxidants, chelating agents, and inert gases and the like. More particularly, 20 pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water-soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In such cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and will typically be preserved against the contaminating action of 25 microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as 30 lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[00264] Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal and the like. In many cases, isotonic agents will be included, for example, sugars, polyalcohols, such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00265] In any case, sterile injectable solutions can be prepared by incorporating an active compound such as an interferon-associated antigen binding protein, or a nucleic acid sequence encoding said interferon-associated antigen binding protein, of the present invention by itself or in combination with other active agents in the required amount in an appropriate solvent with one or a combination of ingredients enumerated herein, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, exemplary methods of preparation include vacuum drying and freeze-drying, which yields a powder of an active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparations for injections are processed, filled into containers such as ampules, bags, bottles, syringes or vials, and sealed under aseptic conditions according to methods known in the art. Further, the preparations may be packaged and sold in the form of a kit. Such articles of manufacture will typically have labels or package inserts indicating that the associated compositions are useful for treating a subject suffering from Hepatitis delta virus infection.

[00266] Effective doses of the compositions of the present invention, for the treatment of the above described Hepatitis delta virus infection-related conditions vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but non-human mammals including transgenic mammals, in particular non-human primates, can also be treated. Treatment dosages

may be titrated using routine methods known to those of skill in the art to optimize safety and efficacy.

[00267] For treatment with an interferon-associated antigen binding protein, the dosage can range, e.g., from about 0.0001 to about 100 mg/kg, and more usually about 0.01 to about 5 mg/kg (e.g., about 0.02 mg/kg, about 0.25 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 2 mg/kg, etc.), of the host body weight. For example, dosages can be about 1 mg/kg body weight or about 10 mg/kg body weight or within the range of about 1 to about 10 mg/kg, e.g., at least about 1 mg/kg. Doses intermediate in the above ranges are also intended to be within the scope of the current invention. Subjects can be administered such doses daily, on alternative days, weekly or according to any other schedule determined by empirical analysis. An exemplary treatment entails administration in multiple dosages over a prolonged period, for example, of at least six months. Additional exemplary treatment regimens entail administration about once per every two weeks or about once a month or about once every 3 to 6 months. Exemplary dosage schedules include about 1 to about 10 mg/kg or about 15 mg/kg on consecutive days, about 30 mg/kg on alternate days or about 60 mg/kg weekly.

[00268] Interferon-associated antigen binding proteins, or nucleic acid sequences expressing any of these, can be administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of interferon-associated antigen binding proteins of components thereof in the patient. Alternatively, interferon-associated antigen binding proteins, or nucleic acid sequences expressing any of these can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the interferon-associated antigen binding proteins in the patient.

[00269] The term “**half-life**” or “ $t_{1/2}$ ”, as referred to herein, relates to the stability and/or the rate of excretion of a compound, such as the interferon-associated antigen binding proteins of the invention. In practice, the half-life of a compound is usually measured in the serum and denotes the time after administration that the serum concentration is 50% of the serum concentration at the time of administration. The

interferon-associated antigen binding proteins of the invention are characterized by a long serum half-life in mice. In some embodiments, the half-life of the interferon-associated antigen binding protein is at least 50 h, at least 60 h, at least 70 h, at least 80 h, at least 90 h or at least 100 h. In some embodiments, the half-life of the
5 interferon-associated antigen binding protein is at least 100 h. In preferred embodiments, the half-life of the interferon-associated antigen binding protein in mice ranges from 116 to 158 h.

[00270] The half-life of a protein is related to its clearance. The term “**clearance**” or “**clearance rate**”, as used herein, refers to the volume of plasma cleared of the
10 protein per unit time. Clearance of the interferon-associated antigen binding proteins of the invention is low. In some embodiments, clearance of the interferon-associated antigen binding protein is below 10 mL/h/kg, below 5 mL/h/kg, below 2.5 mL/h/kg, below 1 mL/h/kg, or below 0.5 mL/h/kg. In some embodiments, clearance of the
15 interferon-associated antigen binding protein is below 5 mL/h/kg. In some embodiments, clearance of the interferon-associated antigen binding protein is below 1 mL/h/kg. In some embodiments, clearance of the interferon-associated antigen binding protein in mice ranges from 0.28 to 0.49 mL/h/kg.

[00271] The terms “**volume of distribution**”, “**V_D**”, “**V_{ss}**” or “**apparent volume of distribution**” as used herein refer to the theoretical volume that would be necessary
20 to contain the total amount of an administered compound such as the interferon-associated antigen binding protein of the invention at the same concentration that it is observed in the blood plasma and relates to the distribution of said compound between plasma and the rest of the body after oral or parenteral dosing. In certain
25 embodiments, the volume of distribution V_{ss} of the interferon-associated antigen binding protein is below 500 mL/kg, below 400 mL/kg, below 300 mL/kg, below 200 mL/kg, or below 100 mL/kg. In some embodiments, the volume of distribution V_{ss} of the interferon-associated antigen binding protein is below 100 mL/kg. In some
embodiments, the volume of distribution V_{ss} of the interferon-associated antigen binding protein in mice ranges from 50 to 98 mL/kg.

[00272] Another related pharmacokinetic parameter is the systemic exposure. As used
30 herein, the terms “**systemic exposure**”, “**AUC**” or “**area under the curve**” refer to

the integral of the concentration-time curve. Systemic exposure might be represented by plasma (serum or blood) concentrations or the AUCs of parent compound and/or metabolite(s). The interferon-associated antigen binding proteins of the invention circulate in the blood with higher systemic exposure (AUC (0-inf)) than their parental antibody. In some embodiments, the parental antibody is CP870,893. In other
5 embodiments, the parental antibody is 3G5. In some embodiments, the systemic exposure of the interferon-associated antigen binding protein is at least 600 $\mu\text{g}\cdot\text{h}/\text{mL}$, at least 700 $\mu\text{g}\cdot\text{h}/\text{mL}$, at least 800 $\mu\text{g}\cdot\text{h}/\text{mL}$, at least 900 $\mu\text{g}\cdot\text{h}/\text{mL}$ or at least 1000 $\mu\text{g}\cdot\text{h}/\text{mL}$, preferably at least 1000 $\mu\text{g}\cdot\text{h}/\text{mL}$. In some embodiments, the systemic
10 exposure of the interferon-associated antigen binding protein in mice ranges from 1033 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 1793 $\mu\text{g}\cdot\text{h}/\text{mL}$.

[00273] As previously discussed, an interferon-associated antigen binding protein of the present invention may be administered in a pharmaceutically effective amount for the *in vivo* treatment of mammalian disorders. In this regard, it will be appreciated
15 that as disclosed an interferon-associated antigen binding protein, will be formulated to facilitate administration and promote stability of the active agent.

[00274] A pharmaceutical composition in accordance with the present invention can comprise a pharmaceutically acceptable, non-toxic, sterile carrier such as physiological saline, nontoxic buffers, preservatives and the like. A pharmaceutically
20 effective amount of an interferon-associated antigen binding protein typically is an amount sufficient to mediate one or more of: a reduction of Hepatitis delta virus-induced cell death and a stimulation of the IFN signaling pathway in an infected cell. Of course, the pharmaceutical compositions of the present invention may be administered in single or multiple doses to provide for a pharmaceutically effective
25 amount of the interferon-associated antigen binding protein.

[00275] In keeping with the scope of the present invention, interferon-associated antigen binding proteins, or nucleic acid sequences expressing any of them, may be administered to a human or other animal in accordance with the aforementioned methods of treatment in an amount sufficient to produce a therapeutic effect. The
30 interferon-associated antigen binding proteins, or nucleic acid sequences expressing any of them, can be administered to such human or other animal in a conventional

dosage form prepared by combining the interferon-associated antigen binding proteins, or nucleic acid sequences expressing any of them, with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. Those skilled in the art will further appreciate that a cocktail comprising one or more species of interferon-associated antigen binding proteins, or nucleic acid sequences expressing any of them, described in the current invention may prove to be effective.

[00276] It is to be understood that the methods described in this invention are not limited to particular methods and experimental conditions disclosed herein as such methods and conditions may 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.

[00277] Furthermore, the experiments described herein, unless otherwise indicated, use conventional molecular and cellular biological and immunological techniques within the skill of the art. Such techniques are well known to the skilled worker, and are explained fully in the literature. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, N.Y. (1987-2008), including all supplements, Molecular Cloning: A Laboratory Manual (Fourth Edition) by MR Green and J. Sambrook and Harlow et al., Antibodies: A Laboratory Manual, Chapter 14, Cold Spring Harbor Laboratory, Cold Spring Harbor (2013, 2nd edition).

[00278] Unless otherwise defined, scientific and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of “or” means “and/or” unless stated otherwise. The use of the term “including”, as well as other forms, such as “includes” and “included,” is not limiting. The use of the term “comprising” shall include the term “consisting of” unless stated otherwise.

[00279] Generally, nomenclature used in connection with cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein is well-known and commonly used in the art. The methods and techniques provided herein are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[00280] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. The contents of the articles, patents, and patent applications, and all other documents and electronically available information mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference. Applicants reserve the right to physically incorporate into this application any and all materials and information from any such articles, patents, patent applications, or other physical and electronic documents.

[00281] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention using this disclosure as a guide. Having now described certain embodiments in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting.

EXAMPLES

EXAMPLE I

Generation of Interferon-Fused Antibodies (IFA) based on agonistic anti-CD40 antibody CP870,893 and characterization on reporter cells

5 *I.a - IFA design*

[00282] The sequence combinations of exemplary IFAs, designed with CP870,893 agonistic anti-CD40 antibody as backbone antibody, with the location of IFNs and the nature of the linkers are listed in **Table 7** and **Table 9**. IFN was fused via a linker at the N- or the C-terminal part of the Light Chain (LC) or the Heavy Chain (HC), as indicated in **Table 7**. Nucleic acids encoding the HC, the LC or the fusions were synthesized with optimized mammalian expression codons and cloned into a eukaryotic expression vector such as pcDNA3.1 (Invitrogen). **Fig. 2A** depicts an exemplary map of a pcDNA3.1 plasmid encoding Seq ID NO 32 under the control of the pCMV promoter.

15 *I.b - IFA production*

[00283] The Freestyle 293-F cells (Invitrogen) were transiently cotransfected with plasmids encoding both HC and LC at a HC/LC ratio of 4/6. Six days after transfection, the supernatant was collected, centrifuged and filtered through 0.22 µm filters. Purification process was performed in two purification steps, on AktaExpress chromatography system (GE Healthcare) using Protein A MabSelect Sure 5mL 1.6/2.5 cm column (GE Healthcare) at a Flow rate of 5 mL/min. Sample binding was done in D-PBS1X pH 7.5 buffer, and elution with Glycine/HCl 0.1 M pH 3.0 buffer. Elution peak was stored in a loop then injected on HiTrap desalting 26/10 column (GE Healthcare) with a flow rate of 10 mL/min in D-PBS1XpH 7.5 buffer. Elution peak was collected on a 96-well microplate (2 mL fractions). Pool was performed according to the UV peak profile. After filtration on 0.22 µm filters (Sartorius MiniSart), quality control was performed including Bacterial Endotoxins using

Endosafe® nexgen-PTS™ (Charles River), size exclusion Chromatography: using SEC 200 Increase 10/300 column (GE Healthcare) to determine purity and oligomers and SDS-PAGE under reducing and non-reducing conditions on NuPAGE gel System (Invitrogen) in MES SDS running buffer. The production yield is indicated in **Table 9**. For some IFAs, the production yield was very low. In that case, the agonistic CD40 activity and the IFN activity were assessed directly using the supernatant containing IFAs without any further purification.

[00284] Reduced SDS-PAGE analysis of purified IFAs indicated the presence of two major bands corresponding to the HC and the LC. When the IFN (whatever the IFN family member) was fused to the HC, a shift of its molecular weight was observed and the same phenomenon was observed for the LCs fused with any IFN (**Fig. 2B**).

I.c - IFA characterization on reporter cells

[00285] HEK-Blue™ CD40L cells (InvivoGen Cat. #: hkb-cd40) or HEK-Blue™ IFN- α/β cells (InvivoGen, Cat. #: hkb-ifn $\alpha\beta$), were used to monitor, respectively, the activation of the NF κ B pathway by CD40 agonists or of the IFN pathway induced by type I-IFN.

[00286] HEK-Blue™ CD40L cells were generated by stable transfection of HEK293 cells with the human CD40 gene and a NF κ B-inducible Secreted Embryonic Alkaline Phosphatase (SEAP) construct (Invivogen) to measure the bioactivity of CD40 agonists. Stimulation of CD40 leads to NF κ B induction and then production of SEAP, which is detected in the supernatant using QUANTI-Blue™ (Invivogen, Cat. # rep-qbs2).

[00287] HEK-Blue™ IFN-cells are designed to monitor the activation of the JAK/STAT/ISGF3 pathways induced by type I-IFNs. Activation of this pathway induces the production and release of SEAP. Levels of SEAP are readily assessable in the supernatant using QUANTI-Blue™.

[00288] HEK-Blue™ IFN- α/β are used to monitor the activity of human IFN α or IFN β .

[00289] Cells were seeded in 96-well plates (50,000 cells per well) and stimulated with the indicated concentration for each IFA or controls and incubated at 37°C for

24h. Supernatants were then collected and levels of SEAP were quantified after incubation of the supernatant for about 30 min with QuantiBlue™ and Optical Density (O.D.) assessment at 620 nm on an Enight plate reader or PheraStar (Lab Biotech).

5 [00290] HEK-Blue™ Dual IFN- γ cells (InvivoGen, Cat. #: hkb-ifng) or HEK-Blue™ IFN- λ (InvivoGen, Cat. #: hkb-ifnl) may be used to respectively monitor the activity of type II- and type III-IFNs. HEK-Blue™ IFN- λ cells are designed to monitor the activity of IFN λ . HEK-Blue™ Dual IFN- γ cells allow the detection of bioactive human IFN γ .

10 *I.d - Functional activities of IFN α/β -based IFAs on reporter cells*

[00291] Fig. 3 shows examples of dose responses of IFAs, where IFN β or a mutated version thereof as specified in Table 7 was fused to the HC as indicated in Table 7, on HEK-Blue™ CD40L (Figs. 3A-3B) and HEK-Blue™ IFN- α/β cells (Figs. 3C-3D). Agonistic anti-CD40 activities of IFAs are summarized in Table 9 and
15 examples are shown in Fig. 3A and Fig. 3B. Results indicate that all tested IFAs are functional to activate both the CD40 pathway and the IFN- α/β pathway in a dose dependent manner. For fusions to the C-terminus of the HC or LC, the EC₅₀ values for agonistic CD40 are ranging from 11.1 ng/mL to 192 ng/mL (Table 9). The mean EC₅₀ value for the parental antibody is 48ng/mL and 57ng/mL in the experiment
20 shown in Fig. 3. IFAs with the IFN fused to the N-terminus of the HC or the LC were also able to activate the CD40 pathway, but the precise EC₅₀ values could not be determined for these IFAs since the activity was directly determined from the supernatant and not using purified proteins (Fig. 3B).

[00292] The IFN activity of various IFAs is summarized in Table 9 and examples are
25 shown in Figs. 3C to 3D. For fusions of IFN β or mutated IFN β (as specified in Table 7) to the C-terminus of the HC or LC, the IFN activity is variable depending on the linker sequence with EC₅₀ values ranging from 0.14 ng/mL to 4.5 ng/mL (Fig. 3C and Table 9). Fig. 3D shows that IFAs with IFN β fused to the N-terminal part exhibit high IFN activity. The parental antibody used as negative control did not show any
30 activity, whereas recombinant IFN β did show a strong dose-dependent response.

Altogether, these results demonstrate that fusion of IFN β or a mutated version thereof as specified in **Table 7** to an antibody, regardless the location, maintain both biological functions, although with differences in terms of potencies.

[00293] **Fig. 4** shows examples of dose responses of IFAs, where IFN α was fused to the HC or the LC as indicated in **Table 7**, on HEK-Blue™ CD40L (**Fig. 4A** and **Fig. 4C**) and HEK-Blue™ IFN- α/β cells (**Fig. 4B** and **Fig. 4D**). Results indicate that all tested IFAs are functional to activate both the CD40 pathway and the IFN α/β pathway in a dose-dependent manner. Surprisingly, for all the IFN α -based IFAs, the potency on CD40 pathway was reproducibly higher than that of the parental antibody. The EC₅₀ values for IFN α -based IFAs ranged from 11.1 ng/mL to 22.7 ng/mL and the EC₅₀ for CP870,893 ranged from 30 ng/mL to 80 ng/mL (mean EC₅₀ value: 48 ng/mL).

[00294] The IFN activity of IFAs is variable depending on the linker sequence with EC₅₀ values ranging from 1.6 ng/mL to 5.1 ng/mL. In the same assay, PEGylated IFN α 2a (Pegasys®) was also active in a dose-dependent manner with an EC₅₀ value of around 1 ng/mL.

I.e – Generation and characterization of IFAs without the Fc region

[00295] Suitable constructs according to the invention can also be interferon-associated antigen binding proteins without an Fc region. A construct encoding the heavy chain of the fab fragment of CP870,893 fused to a TEV-His tag was designed (SEQ ID NO 50) and cloned into the expression plasmid pcDNA3.1. This construct is cotransfected in HEK cells as described earlier, with LCs fused via different linkers to different IFNs such as SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, SEQ ID NO 41, SEQ ID NO 42, or SEQ ID NO 43. Proteins and/or supernatants are evaluated in reporter cells. It will be understood by one of skill in the art that constructs for use in therapy will no longer contain the TEV-His tag. These constructs are likewise embodiments of the invention. Interferon-associated antigen binding proteins without the Fc part will be active against Hepatitis delta virus infection. Two IFAs were then produced and their

functional characterization is described in Example V: IFA50: (SEQ ID NO 41) + (SEQ ID NO 50) and IFA51: (SEQ ID NO 42) + (SEQ ID NO 50).

EXAMPLE II

5 Effect of IFAs on HBV/HDV infected cells

II.a - Virus production

[00296] An HBV genotype D inoculum was prepared from the supernatant of HepAD38 cells, which were initially described in Ladner and colleagues (Antimicrob Agents Chemother, 41(8):1715-20, 1997; doi: 10.1128/AAC.41.8.1715). The 0.22-
10 micron filtrated supernatant of HepAD38 was precipitated with PEG8000 (8% final) to generate the viral stock.

[00297] An HDV genotype 1 inoculum was prepared from the supernatant of Huh7 cells co-transfected with pSVLD3 et pHB2.7 cells as described by C. Sureau (Methods Mol Biol, 640:463-73, 2010; doi: 10.1007/978-1-60761-688-7_25). This
15 0.22-micron filtrated supernatant was PEG8000 (8% final) precipitated to generate the HDV stock.

II.b - Virus quantification

[00298] The titers of these stocks, were determined by either qPCR (for HBV) or qRT-PCR (HDV) in virus genome equivalent per ml vge/mL, as described in
20 Michelet et al. (J Hep Report, 4(3):100415, 2021; doi: 10.1016/j.jhepr.2021.100415. PMID: 35141510).

II.c - Huh7.5-hNTCP cell line

[00299] Huh7.5-hNTCP cells were generated starting from Huh7.5 cells (described in Blight et al., J Virol., 77(5):3181-90, 2003; doi: 10.1128/jvi.77.5.3181-3190.2003)
25 that were stably transduced with a lentivirus encoding hNTCP gene (Gene ID: 6554).

Huh7.5-hNTCP cells were cultivated in the same medium as used for PHH (see *II.d* below), but without DMSO. Cells were seeded in 24-well plates at 0.1 million cells/well 24 hours before use.

II.d - Primary human hepatocytes (PHH) freshly isolated from liver resection

5 [00300] PHH were isolated from liver resection. The procedure of isolation of PHH and infection with HBV was essentially adapted after the work of Gripon and colleagues (J. Virol., 62(11):4136-43, 1988; doi: 10.1128/JVI.62.11.4136-4143.1988, and Virology, 192(2):534-40, 1993; doi: 10.1006/viro.1993.1069). In brief, after isolation from liver resection by a collagenase perfusion and differential
10 centrifugation procedure, PHH were seeded in 24-well plates (0.4 million cells/well) in Williams medium (Gibco) supplemented with 10% of HyCLone FetalClone II (Thermo Fisher Scientific), Glutamax (1x from a 100x stock; Gibco), Penicilin/Streptomycin (1x from 100x stock; Gibco), insulin (2,5 ng/mL; Sigma Aldrich), hydrocortisone hemisuccinate (50 µM; Sigma Aldrich), and 1,8% DMSO
15 (Hybrimax; Sigma Aldrich). Experiment 1 is composed of 2 independent donors (D1 and D2). Experiment 2 is composed of 3 independent donors (D1, D2 and D3). Overall, 5 different donors were used for infection experiments. Average percentage of inhibition of the viral parameters relates to average of all analyzed donors, unless indicated otherwise.

20 *II.e – Treatments used in HBV/HDV co-infection and superinfection experiments*

[00301] A serial 10-fold dilution from 1-0.00001 µg/ml of IFA25, IFA44 and Pegasys (lot B3030, 360µg/ml) was evaluated in a first set of experiment performed in HBV/HDV co-infection setting. The same serial 10-fold dilution with addition of one extra concentration at 5µg/ml was performed with IFA25 in a second round of
25 experiments in HBV/HDV coinfection and superinfection settings. In the comparative coinfection and superinfection treatment designs EVI5 (isotypic control antibody) was used at 1µg/ml and IFA202 (IFN alpha2A fused to EVI5) was used at 0.1 µg/ml, respectively. In addition, three reference inhibitors were used, including an entry inhibitor called Myrcludex-B, IFN alpha2A (Roferon-A) and FTI-277 a
30 farnesyl transferase inhibitor. Myrcludex-B consists of a myristoylated peptidic

sequence (Myristoyl-GTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNP NKDHWPEANKVG; SEQ ID NO 94) and was synthesized (with purity grade: >95%) on request by GenScript (Order No. 778876; Ref: SC1208). The peptide was diluted in water, stored at -20°C, and was used at a final concentration of 100 nM.

5 IFN alpha 2A (Roferon-A; 6 million UI Injectable in 0.5 mL pre-prepared syringe) was used at a final concentration of 1000 IU/mL. FTI-277 HCl was purchased from Selleckchem (catalog No. S7465, >99% purity). Stock solution was at 10mM in DMSO and the final working concentration was at 10 µM.

II.f – Sequences of control IFAs

10 **Table C.** Sequences of control interferon-associated antigen binding protein based on the isotypic control Evi5. *Italic sequences correspond to signal peptides. Bold non-italic sequences correspond to linkers.*

Name / SEQ ID Number	Sequence
eVi-5 D1.3-h1v2_hIgG2 dK_HC (SEQ ID NO 91)	<i>MGWSCIIILFLVATATGVHS</i> EVKLQESGPGLVAPSQSLSITCTVSGFSLTGYGVNWVRQPP GKGLEWLGMIWGDGNTDYN SALKSRLSISKDNSKSQVFLK MNSLHTDDTARYYCARERDYRLDYWGQGTLVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECPCAPPVAGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNK GLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSSFLYSK LTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPG
evi-5 D1.3-hk-LC (SEQ ID NO 92)	<i>MGWSCIIILFLVATATGVHS</i> IELTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQGK SPQLLVYYTTTLADGVPSRFSGSGSGTQYSLKINSLQPEDFG

	SYYCQHFVSTPRTFGGGTKLELKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
eVi-5 D1.3- h1v2_hIgG2 dK_HC--(G4S)2- -IFNα2A (SEQ ID NO 93)	MGWSCIIILFLVATATGVHS EVKLQESGPGLVAPSQSL SITCTVSGFSLTGYGVNWVRQPP GKGLEWLGMWGDGNTDYN SALKSRLSISKDNSKSQVFLK MNSLHTDDTARYYCARE RDYRLDYWGQGTLVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGA LTSGVHTFPAVLQSSGLYSLSSV VTPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECP PAPPVAGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNK GLPAPIEK TISKTKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK LTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGGG GGSGGGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKD RHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSA AWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKED SILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLST NLQESLRSKE

Table D. Polypeptide combinations found in control interferon-fused antigen binding proteins based on the isotypic control Evi5 (= (SEQ ID NO 89) + (SEQ ID NO 90); sequence combination comprised twice). Each sequence combination as indicated is comprised twice 5 in the respective IFA.

Interferon -fused Antibody (IFA)	Sequence combination
IFA202	(seq ID NO 92) + (seq ID NO 93)

II.g - Infection and treatment procedures in coinfection experiments

[00302] A multiplicity of infection of 250 HBV vge/cell and 25 HDV vge/cell were used to infect PHH. The day of coinfection cells were exposed overnight with an inoculum containing HBV and HDV virus in PEG8000 at 4% final concentration. At day one, cells were washed to remove viral inoculum and were kept for 3-4 days post-infection (p.i.) before receiving the treatments. IFAs and controls were extra-temporally diluted in complete medium from mother stocks. Treatments were repeated twice for each treatment kinetic, one treatment after 3 or 4 days p.i., respectively, and the second treatment after 6 or 7 days p.i., respectively. Analyses were performed on the supernatant and on cell extracts recovered at the end of the kinetic of the coinfection at 9 or 10 days, respectively.

II.h - Infection and treatment procedures of superinfection experiments

[00303] A multiplicity of infection of 250 HBV vge/cell and 25 HDV vge/cell were used to infect PHH. The day of infection, cells were first infected with HBV overnight and kept for 5 days post-infection to establish a long-lasting “chronic” HBV infection. Then, cells were super-infected by HDV for 3 extra days. IFAs and controls were extra-temporally diluted in complete medium from mother stocks. Treatments were done at 8 days and 11 days p.i.. Analyses were performed on the supernatant and on cell extracts recovered at the end of the kinetic of superinfection at 14 days.

II.i - Viral propagation assay

[00304] Huh7.5-hNTCP cells were used for a secondary infection as a surrogate test to assess viral propagation. Cells were infected with supernatants, which were recovered from PHH cultures at the end of the kinetic of co-infection or superinfection and adjusted to 4% final with PEG8000. The secondary infection was stopped at 6-day p.i. and intracellular HDV RNA quantification analyses were performed as described below.

II.j - Quantification of secreted HBsAg by CLIA Assay

[00305] Secreted HBsAg in the supernatants of infected non-treated (NT) and treated PHH cells were quantified with CLIA kits according to manufacturer's instructions (Autobio; ref: CL0310-2). The luminescence signals of calibration standards and samples were acquired with Luminoskan (Thermo Fischer Scientific). For HBsAg quantification, a calibration curve was generated using signals of the standards and a four-parameter logistic (4-PL) fitting curve. Sample concentrations were determined by interpolating the sample signal with the standard curve. The concentrations obtained were exported to GraphPad-Prism and percentages were calculated as compared to the non-treated (NT) infected condition of each cell culture plate, NT being defined at 100%. For each donor and each treatment, IC₅₀ [concentration of compound that gives a response halfway between Top and Bottom] was estimated using the four-parameter logistic model applied to [%HBsAg]. The adjustment was obtained by non-linear regression using GraphPad PRISM V9.1.0 software. For HBsAg, the top was constrained to 100 and the bottom was constrained to be positive if needed. The geometric mean of IC₅₀s of several donors and its 95% confidence interval were calculated for each experiment, each parameter and each treatment.

II.k - Quantification of intracellular HBV and HDV RNAs

[00306] Total RNA was extracted from cells with "NucleoSpin RNA Plus, Mini kit for RNA purification with DNA removal column" (Macherey-Nagel; ref: 740984), according to manufacturer's instructions, and the extracted RNA was reverse-transcribed with SuperScript III kit (Thermo Fisher Scientific; ref: 18080085), following manufacturer's instructions. Complementary DNA was quantified by qRT-PCR with either HBV or HDV specific primers and the "Luna[®] Universal qPCR Master Mix" reagent (BioLabs; ref: M3003E). HBV primers: HBV-F (5'-AGCTACTGTGGAGTTACTCTCGT-3'; SEQ ID NO 95) and HBV-R (5'-CAAAGAATTGCTTGCTGAGTG-3'; SEQ ID NO 96). HDV primers: HDV-F (5'-CGGGCCGGCTACTCTTCT-3'; SEQ ID NO 97) and HDV-R (5'-AAGGAAGGCCCTCGAGAACA-3'; SEQ ID NO 98). More details can be found in Michelet et al. (*J Hep Report*, 4(3):100415, 2021; doi: 10.1016/j.jhepr.2021.100415. PMID: 35141510).

[00307] For viral RNA quantification by qRT-PCR, results (CT values) were measured by the LightCycler LC480 (Roche) for the housekeeping gene (RPLP0) and the target genes (HBV and/or HDV). The delta of CTs was calculated as follows: $\Delta Ct = Ct \text{ (HBV or HDV)} - Ct \text{ (RPLP0)}$. Then a $2^{-\Delta Ct}$ was calculated for all conditions, including the non-treated conditions. For each donor and each treatment, IC_{50} [concentration of compound that gives a response halfway between Top and Bottom] was estimated using the four-parameter logistic model applied to $FC = 2^{-\Delta Ct / 2^{-\Delta Ct(NT)}}$ for HBV RNA, HDV RNA and HDV RNA re-infection (viral propagation) parameters in triplicate. The adjustment was obtained by non-linear regression using GraphPad PRISM V9.1.0 software. For HBV RNA, HDV RNA and HDV RNA re-infection parameters, the top was constrained to 0 (corresponding to 1 on the antilog scale). The geometric mean of IC_{50} s of several donors and its 95% confidence interval were calculated for each experiment, each parameter and each treatment.

15 *II.1 - Effect of IFA44 and IFA25 on HDV coinfection with HBV in freshly isolated PHH*

[00308] We evaluated the effect of Pegasys, IFA44 and IFA25 in HBV/HDV coinfection assay in freshly isolated human hepatocytes (PHH).

[00309] First, Pegasys treatment with doses ranging from 1-0.00001 $\mu\text{g/ml}$ was tested in biological triplicates and in two independent experiments, corresponding to 2 individual donors and coded Exp1_D1 and Exp1_D2. A trend toward virus inhibition was only observed at the highest concentration tested (1 $\mu\text{g/ml}$) with an effect on HbsAg (**Fig. 5A**), intracellular HBV RNA (**Fig. 5B**) and HDV viral propagation assay (**Fig. 5D**). No direct effect on intracellular HDV RNA was observed (**Fig. 5C**). However, the data obtained with Pegasys didn't allow to build a reliable analytical model to assess virological parameters inhibition. Thus, no IC_{50} value estimation was possible on data presented in **Figs. 5A-5D**.

[00310] IFA44 was tested at doses ranging from 1-0.00001 $\mu\text{g/ml}$ in biological triplicates and in two independent experiments, corresponding to 2 individual donors and coded Exp1_D1 and Exp1_D2. Data obtained with IFA44 treatment allowed a

reliable fitting model to assess virological parameters inhibition, as depicted with a black line for Exp1_D1 and with a dashed line for Exp1_D2 (**Figs. 5E-5H**).

[00311] HBsAg secretion was reduced by IFA44 treatment with IC₅₀ values of 505.54 pM and 51.94 pM for donor 1 and 2, respectively (**Fig. 5E**). IFA44 treatment resulted in a reduction of intracellular HBV RNA expression with estimated IC₅₀ values of 134.07 pM and 59.82 pM for donor 1 and 2, respectively, (**Fig. 5F**) and in a reduction of intracellular HDV RNA expression with estimated IC₅₀ values of 1844.49 pM and 386.22 pM for donor 1 and 2, respectively (**Fig. 5G**). Finally, for the reduction of intracellular HDV RNA expression in the viral propagation assay after IFA44 treatment, IC₅₀ values of 56.33 pM and 210.25 pM were estimated for donor 1 and 2, respectively (**Fig. 5H**).

[00312] The maximal effect of treatment with IFA44 occurred at the highest concentration tested (1 µg/ml) with an average of 69.72% inhibition of HBsAg secretion, 84.53% and 64.13% inhibition of both intracellular HBV and HDV RNA expression, and 66.46% inhibition of HDV reinfection compared to the co-infected nontreated condition.

[00313] IFA25 was tested at doses ranging from 1-0.00001 µg/ml in biological triplicates and in two independent experiments, corresponding to 2 individual donors and coded (Exp1_D1 and Exp1_D2). Data obtained with IFA25 treatment allowed a reliable fitting model to assess virological parameters inhibition, as depicted with a black line for Exp1_D1 and a grey dashed line for Exp1_D2 (**Figs. 5I-5L**).

[00314] HBsAg secretion was reduced by IFA25 treatment with IC₅₀ values of 20.63 pM and 11.50 pM for donor 1 and 2, respectively (**Fig. 5I**). IFA25 treatment resulted in a reduction of intracellular HBV RNA expression with estimated IC₅₀ values of 57.76 pM and 61.89 pM for donor 1 and 2, respectively (**Fig. 5J**), and in a reduction of intracellular HDV RNA expression with estimated IC₅₀ values of 219.34 pM and 344.70 pM for donor 1 and 2, respectively (**Fig. 5K**). Finally, for the reduction of intracellular HDV RNA expression in the viral propagation assay after IFA25 treatment, IC₅₀ values of 59.23 pM and 216.43 pM were estimated for donor 1 and 2, respectively (**Fig. 5L**).

[00315] The maximal effect of treatment with IFA25 occurred at the highest concentration tested (1µg/ml) with an average of 100% inhibition of HBsAg secretion, 91.07% and 70.88% inhibition of both intracellular HBV and HDV RNA expression, and 98.22% inhibition of HDV reinfection compared to the coinfecting nontreated condition.

[00316] A second round of experiments was carried out with IFA25 treatment in the context of coinfection with the following modalities:

[00317] IFA25 was tested at doses ranging from 5-0.00001 µg/ml in biological triplicates and in three independent experiments corresponding to three individual donors (Exp2_D1; Exp2_D2 and Exp2_D3). Data obtained by these experiments allowed a reliable fitting model to assess virological parameters inhibition, as depicted with a black line for Exp2_D1, a grey dashed line for Exp2_D2 and a light grey line for Exp2_D3 (**Figs. 5M-5P**).

[00318] HBsAg secretion was reduced by IFA25 treatment with IC₅₀ values of 7.76 pM, 14.51 pM and 15.05 pM for donor 1 to 3, respectively (**Fig. 5M**). IFA25 treatment resulted in a reduction of intracellular HBV RNA expression with estimated IC₅₀ values of 221.39 pM, 88.54 pM and 82.96 pM for donor 1-3, respectively (**Fig. 5N**), and in a reduction of intracellular HDV RNA expression with estimated IC₅₀ values of 143.56 pM, 523.55 pM and 854.04 pM for donor 1-3, respectively (**Fig. 5O**). Finally, for the reduction of intracellular HDV RNA expression in the viral propagation assay after IFA25 treatment IC₅₀ values of 111.79 pM, 236.18 pM and 93.56 pM were estimated for donor 1-3, respectively (**Fig. 5P**).

[00319] In this second round of experiments the maximal effect of treatment with IFA25 occurred at the highest concentration tested (5µg/ml) with an average of 98.47% inhibition of HBsAg secretion, 80.68% and 41.81% inhibition of both intracellular HBV and HDV RNA expression and 99.47% inhibition of HDV reinfection compared to the coinfecting non-treated condition.

II.m - Comparison of IFA25 and control molecules on HDV coinfection with HBV

[00320] Results are expressed in percentage of secreted HBsAg of the co-infected non-treated control for the CLIA assay or as fold change of RNA expression

compared to the co-infected nontreated control for RNA quantification (**Figs. 5Q-5T**). Treatment with the isotype control antibody EVI5 showed a similar profile as in the coinfecting non-treated condition for all tested viral parameters. IFA202, the isotype antibody with the same IFN alpha2A fusion as IFA25 (but without the anti-CD40 agonistic activity) demonstrated a limited antiviral effect with an average reduction of 25.13% of HBsAg secretion, 18.35% of intracellular HBV expression, no effect on intracellular HDV expression and a good reduction of 61.64% on HDV propagation. Roferon also demonstrated limited antiviral effects with an average of 59.83 % inhibition of HBsAg secretion, 29.01% and 3.64% inhibition of both intracellular HBV and HDV RNA expression and a strong inhibition of HDV reinfection with 91.55% compared to the coinfecting nontreated condition. In this tested conditions, FTI-277 and Myrcludex did not inhibit neither HDV nor HBV parameters but only HDV propagation with a reduction of 91.76% and 99.89% respectively. IFA25 is the most potent antiviral molecule evaluated in this experiment with a significant average reduction of HBsAg secretion of 88.79% at 0.1 µg/ml and 97.31% at 1 µg/ml compared to the co-infected non-treated control (**Fig. 5Q**), a significant average reduction of intracellular HBV RNA expression of 68.75% at 0.1 µg/ml and 79.93% at 1 µg/ml compared to the coinfecting non-treated control (**Fig. 5R**) as well as a significant average reduction of intracellular HDV RNA expression of 28.04% at 0.1 µg/ml and 43.68% at 1 µg/ml compared to the coinfecting non-treated control (**Fig. 5S**). Finally, IFA25 at 0.1 and 1 µg/ml is very potent to prevent HDV spreading in HuH7.5-hNTCP with a reduction of 98.21% and 99.56% respectively (**Fig. 5T**).

II.n – Effect of IFA25 on HDV superinfection with HBV in freshly isolated PHH

[00321] IFA25 was tested at doses ranging from 5-0.00001 µg/ml in biological triplicate and in three independent experiments (Exp2_D1; Exp2_D2 and Exp2_D3). Data obtained by these experiments allowed a reliable fitting model to assess virological parameters inhibition, as depicted with a black line for Exp2_D1, a grey dashed line for Exp2_D2 and a light grey line for Exp2_D3 (**Fig. 6A-6D**).

[00322] IFA25 treatment resulted in a reduction of HBsAg secretion with estimated IC₅₀ values of 23.43 pM, 35.63 pM and 31.40 pM for donor 1 to 3, respectively (**Fig.**

6A). IFA25 treatment also resulted in a reduction of intracellular HBV RNA expression with estimated IC₅₀ values of 157.13 pM, 92.64 pM and 317.65 pM for donor 1-3, respectively (**Fig. 6B**) and in a reduction of intracellular HDV RNA expression with estimated IC₅₀ values of 472.67 pM for donor 3 respectively (**Fig. 6C**, light grey line). No reliable fitting model for intracellular HDV RNA IC₅₀ determination could be applied for donors 1 and 2.

[00323] Finally, a reduction of intracellular HDV RNA expression in the viral propagation assay after IFA25 treatment could be detected with estimated IC₅₀ values of 1259.06 pM and 416.05 pM for donor 2 and 3 (**Fig. 6D**, dashed grey line and light grey line). No reliable fitting model for the determination of IC₅₀ values in the viral HDV propagation assay was found for donor 1.

[00324] The maximal effect of treatment with IFA25 occurred at the highest concentration tested (5µg/ml) with an average of 91.80% inhibition of HBsAg secretion, 72.99% inhibition of intracellular HBV RNA expression, 60.74% inhibition of intracellular HDV RNA expression (donor 3 only) and 93.06% inhibition of HDV reinfection (donor 2 and 3 only) compared to the co-infected non-treated condition.

II.o – Comparison of IFA25 and control molecules on HDV superinfection with HBV

[00325] Results are expressed in percentage of secreted HBsAg of the superinfected non-treated control for the CLIA assay or as fold change of RNA expression compared to the super-infected non-treated control for RNA quantification (**Fig. 6E-6H**). Treatment with the isotype control antibody EVI5 showed a similar profile as in the coinfecting non-treated condition for all tested viral parameters. IFA202, the isotype antibody with the same IFN alpha2A fusion as IFA25 (but without the anti-CD40 agonistic activity) demonstrated a limited antiviral effect with an average reduction of 21.39% of HBsAg secretion, 8.58% of intracellular HBV expression, no effect on intracellular HDV expression and an average reduction of 21.68% on HDV propagation. Roferon also demonstrated limited antiviral effects with an average of 40.75 % inhibition of HBsAg secretion, 24.68% inhibition of intracellular HBV and no effect on intracellular HDV RNA expression. However, a good inhibition of HDV

reinfection with 53.78% compared to the coinfecting nontreated condition was shown. In this tested conditions, FTI-277 and Myrcludex did not inhibit neither HDV nor HBV parameters but only HDV propagation with an average reduction of 85.04% and 99.26% respectively. IFA25 is the most potent antiviral molecule evaluated in this assay with a significant average reduction of HBsAg secretion of 74.21% at 0.1 µg/ml and 85.71% at 1 µg/ml compared to the super-infected nontreated control (**Fig. 6E**), a significant average reduction of intracellular HBV RNA expression of 63.64% at 1 µg/ml and 73.85% at 1 µg/ml compared to the super-infected nontreated control (**Fig. 6F**) as well as an average reduction of intracellular HDV RNA expression of 14.15% at 0.1 µg/ml and 30.03% at 1 µg/ml compared to the super-infected nontreated control (**Fig. 6G**). Finally, IFA25 at 0.1 and 1 µg/ml is very potent to prevent HDV spreading in HuH7.5-hNTCP with an average reduction of 73.01% and 91.49% respectively (**Fig. 6H**).

EXAMPLE III

Cytokine Release

III.a - Cytokine Release Assessment (CRA) from human Whole Blood Cells

[00326] Whole blood cells (WBC) *ex vivo* stimulation assay was used to investigate release of cytokines following IFA stimulation. WBC were collected from four healthy donors, diluted 1/3 in RPMI1640 (72400-021, Gibco) and distributed in sterile reaction tubes (300 µl). Cells were left unstimulated, stimulated with LPS (LipoPolySaccharide) K12 (tlrl-eklps, Invivogen) at 10 ng/mL as a positive control or with IFAs at 1 µg/mL and incubated for 24 h at 37 °C. Supernatants were then collected and frozen at -20 °C until the day of analysis.

[00327] Human pro-inflammatory cytokines were analyzed using multiplexing MSD assay (K15067L-4) which measures Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-12/IL-23p40 and IFNγ. MSD plates were analyzed on the 1300 MESO QuickPlex SQ120 apparatus (MSD).

[00328] Fig. 7 depicts exemplary results from an *in vitro* Cytokine Release Assessment of Human WBC either non-stimulated, treated with LPS or with IFA1.

[00329] Further results from testing IFN β - /mutated IFN β - and IFN α - based IFAs are summarized in **Tables 11a and 11b**. Results show that for all donors, LPS induces very high level of the inflammatory cytokines (IL-1 β , TNF- α , IL-6, IL-12p40 and IFN γ). It also induced IP10 (CXCL10) which is a biomarker of the IFN pathway and moderate level of IL-10. Two IFN β - (**Table 11a**) and six IFN α - (**Table 11b**) based IFAs were tested. All of them induced the biomarker IP10. However, they did not induce IL-10, IL-1 β and IL-2, and they induced only very low to moderate level of IFN γ , IL-6 and TNF- α , thus suggesting a favorable safety profile with regard to the induction of inflammatory cytokines.

EXAMPLE IV

Pharmacokinetic studies

IV.a - ELISA assay development for IFA quantifications

[00330] For the ELISA quantification 96-wells plates (PLATES 96 wells Maxisorp, THERMO Scientifique; 442404) were coated overnight at 4 C with 100 μ l of recombinant human CD40/TNFRSF5 Fc Chimera Protein, consisting of the extracellular domain of human CD40 fused to the Fc part of human IgG1 (CD40-Fc; R&D Systems; 1493-CDB-050) at 0.5 μ g/mL in Sodium Carbonate (0.05 M, pH 9.6, C-3041, Sigma). After emptying by flipping, plates were then incubated for 1 hour at 37 C with PBS - 0.05% Tween20 – 1% Milk (SIGMA; 70166-500g) followed by washing with PBS-0.05% Tween20. Samples and controls (100 μ l of 1/2 serial dilutions) were then incubated for 90 minutes at 37 C followed by three washes (PBS - 0.05% Tween20) and incubation with a secondary anti-IgG2-conjugate HRP (1/5000, ab99779, Abcam) antibody or anti-IFN α conjugate HRP (1/1000, eBIOSCIENCE/ Invitrogen; BMS216MST) in PBS - 0.05% Tween20 - 1% Milk. After three washes with PBS, 0.05% Tween2, TMB (Tetramethylbenzidin, Tebu Bio;

TMBW-1000-01) was added and the plates incubated for 20 minutes in the dark. The reaction was stopped by adding 1M HCl. Plates were read at 450-650 nm with an Ensign plate reader (Perkin Elmer). Quantification of Pegasys was assessed using similar protocol steps but using human IFN α matched antibody pairs from eBioscience/Invitrogen. Capture was performed using 100 μ L of human anti-IFN α antibody (eBioscience/Invitrogen; BMS216MST), at 1 μ g/mL in sodium carbonate (0.05 M, pH 9.6, C-3041, Sigma). For the detection, a secondary anti-IFN α conjugate HRP antibody (1/1000, Affymetrix eBioscience/BMS216MST; 15501707) in PBS - 0.05% Tween20 - 1% Milk was applied.

10 *IV.b - In vivo bioavailability in mice*

[00331] To determine the PK parameters, CP870,893, IFA25, IFA26, IFA27, IFA28, IFA29 and IFA30 were administrated at 0.5 mg/kg and Pegasys at 0.3 mg/kg i.v. bolus to male CD1-Swiss mice and blood samples were collected at different time points. Examples of quantification of circulating molecules using the ELISA approach described above and revealed with anti-IFN α -conjugated HRP are shown in **Fig. 8A** and **8B**, while examples of quantification revealed with anti-IgG2-conjugated HRP are shown in **Fig. 8C**; Pegasys quantification is shown in **Fig. 8D**. In one set of experiments summarized in **Table 12A**, PK parameters for CP870,893 were explored in a 7-day experiment and those for IFA27, IFA29 and IFA30 in 10-day experiments (quantification for IFA27 was performed using 2 different ELISA approaches). In another set of experiments summarized in **Table 12B**, the PK parameters for CP870,893 and IFA25, IFA26, IFA28 and Pegasys were explored in 21-day experiments (quantification for IFA25 was performed using 2 different ELISA approaches).

[00332] After a short distribution phase, the pharmacokinetic profiles of IFAs are characterized by a long serum half-life ranging from 116 to 218 h (**Table 12A** and **Table 12B**). Very similar PK profiles were obtained for the 6 tested IFAs with high circulating level even ten days after single dose administration. The pharmacokinetic parameters summarized in **Table 12A/B** indicate that these IFAs surprisingly circulate in the blood with higher systemic exposure (AUC (0-inf)) ranging from 1033 μ g.h/mL to 2552 μ g.h/mL for IFAs in comparison to 590 or 797 μ g.h/mL,

respectively, for the parental antibody CP870,893 (up to 3.2 fold), also reflecting lower clearance values for IFAs. The volume of distribution V_{ss} was low and ranked from 50 to 105 mL/kg, slightly higher than the plasma vascular volume (50 mL/kg) in this species. For all IFAs, the clearance was ranked as low (0.28 to 0.49 mL/h/kg).
5 Interestingly, the clearance of Pegasys (1.4 mL/hr/kg) is up to 7 fold higher than clearance of IFAs (e.g., 0.2 mL/hr/kg for IFA27) demonstrating a higher systemic exposure of IFAs.

EXAMPLE V

10 *V.a - Functional activities of IFAs without Fc region on reporter cells*

[00333] To determine whether the Fc part of IFAs is needed for activity, fusions of IFN α to the C-terminal part of the LC associated with a Fab fragment of the HC were designed and produced. IFN α was linked to the LC part with a (G4S)₂ (IFA50) or (G4S)₃ (IFA51) linker.

15 [00334] Evaluation on HEK-Blue™ CD40L cells demonstrated that such IFAs still exhibit agonistic CD40 activity (**Fig. 9A**) and activate the CD40 pathway with an EC_{50} value of about 128 ng/ml (IFA 50) and 123 ng/mL (IFA51), respectively.

[00335] Evaluation of the IFN activity on HEK-Blue™ IFN- α/β cells showed that both tested IFAs exhibit IFN activity (**Fig. 9B**). EC_{50} values are reported in **Table**
20 **9B** and are about 1.36 ng/ml for IFA50 and 1.43 ng/mL for IFA51.

V.b - Functional activities of IFN ϵ based IFAs on reporter cells

[00336] Fusions of CP870,893 to a third type I interferon (IFN epsilon; IFN ϵ) have also been designed and produced. Such IFAs were tested on HEK-Blue™ CD40L cells and it could be demonstrated that they maintain agonistic CD40 activity. Results
25 for one such IFA (IFA49) are shown in **Fig. 10A**. Evaluation on HEK-Blue™ hIFN- α/β cells (which are in fact activated by any type I interferon) showed that IFA49 is also able to activate the IFN-I-pathways (**Fig. 10B**). EC_{50} values are reported in **Table 9B**.

[00337] These results demonstrate that IFAs with IFN ϵ maintain both IFN and agonistic CD40 activity (i.e., are bifunctional).

V.c - Functional activities of IFN ω based IFAs on reporter cells

5 [00338] Fusions of CP870,893 to a fourth type I interferon (IFN omega; IFN ω) have also been designed and produced. Such IFAs were tested on HEK-Blue™ CD40L cells and results demonstrated that they maintain agonistic CD40 activity. Results for one such IFA (IFA46) are shown in **Fig. 11A**. Evaluation on HEK-Blue™ hIFN- α/β cells (which are in fact activated by any type I interferon) showed that IFA46 is also able to activate the IFN-I-pathways (**Fig. 11B**). EC₅₀ values are reported in **Table**
10 **9B**.

[00339] These results demonstrate that IFAs with IFN ω maintain both IFN and agonistic CD40 activity (i.e., are bifunctional).

V.d - Functional activities of IFN γ based IFAs on reporter cells

15 [00340] Fusions of CP870,893 to type II Interferon (IFN gamma; IFN γ) have also been designed and produced. Evaluation of these IFAs on HEK-Blue™ CD40L cells demonstrate that they maintain agonistic CD40 activity, regardless of whether IFN γ is linked to the C-terminal part of the LC (IFA42) or of the HC (IFA43) (**Fig. 12A**). Evaluation of these IFAs on HEK-Blue™-IFN γ cells (**Fig. 12B**) showed that they are also able to activate the IFN γ -pathway. IFN γ activity differed somewhat between
20 IFA42 (EC₅₀: 15 ng/ml) and IFA43 (EC₅₀: < 0.01 ng/ml). EC₅₀ values are reported in **Table 9B**.

[00341] Taken together, these results demonstrate that IFAs with IFN γ maintain both IFN and agonistic CD40 activity (i.e., are bifunctional).

V.e - Functional activities of IFN λ based IFAs on reporter cells

25 [00342] Fusions of CP870,893 to type III Interferon (IFN lambda; IFN λ) have also been designed and produced. These IFAs were tested on HEK-Blue™ CD40L cells and results demonstrated that they also maintain agonistic CD40 activity, regardless of whether IFN λ is linked to the C-terminal part of the LC (IFA44) or of the HC

(IFA45) (**Fig. 13A**). Evaluation of these IFAs on HEK-Blue™-IFN λ cells showed that they are also able to activate the IFN λ -pathway (**Fig. 13B**). EC₅₀ values are reported in **Table 9B**. These results also demonstrate that IFAs with IFN λ maintain both IFN and agonistic CD40 activity (i.e., are bifunctional).

5

EXAMPLE VI

Generation of Interferon-Fused Antibodies (IFA) based on anti-CD40 antibody 3G5 and characterization on reporter cells

VI.a - IFA design

10 **[00343]** The sequence combinations of exemplary IFAs, designed with 3G5 anti-CD40 antibody (Celldex) as backbone antibody, with the location of IFNs and the nature of the linkers are listed in **Table 8** and **Table 10**. IFN was fused via a linker at the C-terminal part of the Light Chain (LC) or the Heavy Chain (HC), as indicated in **Table 8**. Nucleic acids encoding the HC, the LC or the fusions were
15 synthesized with optimized mammalian expression codons and cloned into a eukaryotic expression vector such as pcDNA3.1 (Invitrogen).

VI.b - IFA production

20 **[00344]** IFA production was performed as described earlier and the production yield is indicated in **Table 10**. For some IFAs, the production yield was very low, mainly for the fusion of IFN β to the C-terminal part of the LC. For these IFAs, the agonistic CD40 and the IFN activities were assessed directly using the supernatant containing IFAs without any further purification. Reduced SDS-PAGE analysis of purified IFAs indicated the presence of two major bands corresponding to the HC and LC. When IFN was fused to the HC, a shift of its molecular weight was observed. (**Fig. 14**).

VI.c - Functional activities of IFN α/β -based IFAs on reporter cells

[00345] Characterization of 3G5 IFAs on reporter cells was done on HEK-Blue™ CD40L (**Fig. 15A-B, and Fig. 16A**) and HEK-Blue™ IFN- α/β cells (**Fig. 15C-D, and Fig. 16B**) as previously described (see I.c).

5 *VI.c.1. IFN β based IFAs*

[00346] **Fig. 15-** shows examples of dose responses of IFAs, where IFN β was fused to the HC or the LC of 3G5, on HEK-Blue™ CD40L and HEK-Blue™ IFN- α/β cells (**Fig. 15**). Results summarized in **Table 10** indicate that all tested IFN β -based IFAs are functional and able to activate both the CD40 pathway and the IFN α/β pathway in a dose-dependent manner.

10 [00347] Examples of CD40 activity are shown in **Fig. 15A and Fig. 15B**. Fusion of IFN β to the C-terminal part of the HC demonstrates high variable anti-CD40 activity and in all cases lower than the parental antibody with EC₅₀ values ranging from 30 ng/mL to 190.5 ng/mL (**Fig. 15A and Table 10**). The mean EC₅₀ value for the parental 3G5 antibody is 9.3 ng/mL.

15 [00348] For fusions on the C-terminal part the LC, the production yield was very low and the activity was assessed using supernatant-containing IFAs after overexpression in HEK-cells. Evaluation of these supernatants on HEK-Blue™ CD40L (**Fig. 15B**) demonstrates that these IFAs are active on CD40 pathway. For 3G5, the agonistic anti-CD40 activity is still detected when supernatant was diluted 300 times. Conversely, a 1/10 dilution was needed for the IFAs-containing supernatants to observe an activity (**Fig. 15B**).

20 [00349] The IFN activity of IFAs were tested on HEK-Blue™ IFN- α/β cells and results are summarized in **Table 10**. Examples are shown in **Fig. 15C-D**. For fusions of IFN β at the C-terminal part of the HC, the IFN activity is variable depending on the linker sequence with EC₅₀ values ranging from 0.45 ng/mL to 10,3 ng/mL (**Fig. 15C**). For IFAs with IFN β fusion at C-terminal part of the LC-containing supernatant, IFN activity is still detected even after a 10000-fold dilution of the supernatant (**Fig. 15D**).

VI.c.2. IFN α based IFAs

[00350] Figs. 16A-B show examples of dose responses of IFAs, where IFN α was fused to the HC of 3G5, on HEK-Blue™ CD40L (Fig. 16A) and HEK-Blue™ IFN α / β cells (Fig. 16B).

5 [00351] Results indicate that all IFAs display a functional activation of both the CD40 pathway and the IFN α / β pathway in a dose-dependent manner (mean EC₅₀ values are reported in Table 10).

10 [00352] For all the IFN α -based IFAs, the potency on CD40 pathway was similar to the parental antibody with the mean EC₅₀ values ranging from 11.74 ng/mL to 14.2 ng/mL (Fig. 16A and Table 10). The mean EC₅₀ value for the parental 3G5 antibody is 9.3ng/mL.

[00353] The IFN activities of IFN α -based IFAs were tested on HEK-Blue™ IFN- α / β cells and demonstrate very high activity. The mean EC₅₀ values for the IFN activity of these IFAs ranged from 0.04 ng/mL to 0.12 ng/mL (Fig. 16B and Table 10).

15 *VI.c.3. IFN γ based IFAs*

[00354] Evaluation of IFA125 on HEK-Blue™ CD40L and on HEK-Blue™-IFN γ cells as previously described (see I.c) showed that IFA 125 is functional and able to activate both the CD40 pathway and the IFN γ pathway (Table 10B).

VI.d – Generation and characterization of IFAs without the Fc region

20 [00355] Suitable constructs according to the invention can also be interferon-associated antigen binding proteins without an Fc region. A construct encoding the heavy chain of the Fab fragment of 3G5 fused to a TEV-His tag was designed (SEQ ID NO 65) and cloned into the expression plasmid pcDNA3.1. This construct is cotransfected in HEK cells as described earlier, with LCs fused via different linkers
25 to IFNs such as SEQ ID NO 70, or SEQ ID NO 71. Proteins and/or supernatants are evaluated in reporter cells and/or their effect on Hepatitis delta virus-infected cells. It will be understood by one of skill in the art that constructs for use in therapy will no longer contain the TEV-His tag. These constructs are likewise embodiments of

the invention. Interferon-associated antigen binding proteins without the Fc part will be active against Hepatitis delta virus infection.

EXAMPLE VII

5 Cytokine Release Assay (CRA) from human Whole blood cells

[00356] A WBC ex vivo stimulation assay was used to investigate release of cytokines following IFA stimulation as described previously (**see III.a**). An example with IFA109 is shown in **Fig. 17** and **Table 13**. The results indicate that all IFAs induce CXCL10 release. They did not induce IL-10, IL-1 β and IL-2, and they induced only
10 very low to moderate level of IFN γ , IL-6 and TNF- α , thus suggesting a favorable safety profile with regard to the induction of inflammatory cytokines.

EXAMPLE VIII

Effect of IFAs on HBV/HDV coinfecting cryopreserved PHH

15 *VIII.a - Virus production*

[00357] An HBV genotype D inoculum was prepared from the supernatant of HepAD38 cells, which were initially described in Ladner and colleagues (Antimicrob Agents Chemother, 41(8):1715-20, 1997; doi: 10.1128/AAC.41.8.1715). The 0.22-micron filtrated supernatant of HepAD38 was centrifuged with centricon for virus
20 concentration to generate the viral stock.

[00358] An HDV genotype 1 inoculum was prepared from the supernatant of Huh7 cells co-transfected with pSVLD3 and pHB2.7 cells as described by C. Sureau (Methods Mol Biol, 640:463-73, 2010; doi: 10.1007/978-1-60761-688-7_25). This 0.22-micron filtrated supernatant was used to generate the HDV stock.

VIII.b – Virus stocks quantification

[00359] The titers of these stocks were determined by ddPCR for HBV genotype D and by qRT-PCR for HDV genotype-1 and are expressed in viral genome equivalent (Vge in copy/mL).

5 *VIII.c – Coinfection protocol in Cryopreserved Primary human hepatocytes (PHH)*

[00360] Cryopreserved-PHH from Bioreclamation IVT (batch DSX; product number F00995-P) were used as *in vitro* cellular model for HBV/HDV Coinfection experiments. Cells were plated at least 24h before Coinfection in PHH plating medium [William's E glutaMAX (Gibco; 32551-020); 10% FBS (GE healthcare; SH30066.03); 5mg/ml Insulin (Sigma; I9278-5ML); 25mg/ml Hydrocortison (Sigma; H2270-100MG) and 1% Penicillin-streptomycin (Gibco; 15140122)]. At 4h post plating, PHH plating medium was changed for fresh one. From the time of Coinfection to the end of the experiments, PHH were maintained in PHH infection medium [invitrogro HI medium (BioIVT; Z99009); 5% FBS (GE healthcare; SH30066.03); 2% DMSO (Sigma; D2650-100ml) and 1% Penicillin-streptomycin (Gibco; 15140122)]. For the Coinfection step, a multiplicity of infection of 500 HBV genotype D Vge/cell and 5µl per well of 96-well plate or 20µl per well of 24-well plate for HDV genotype-1 were used. The day of Coinfection, cells were exposed overnight with an inoculum containing HBV and HDV virus in PEG8000 at 4% final in PHH infection medium. At day one, cells were washed to remove viral inoculum. Then, cells were kept 3 days. At day 4 post-Coinfection cell infection medium was changed and fresh one was added until end of the kinetic at day 7 post-Coinfection.

20 *VIII.d - Treatment with IFA25 and control molecules on HDV genotype-1 in HBV/HDV Coinfection experiments in cryopreserved PHH*

25 [00361] In this experiment, for the primary Coinfection IFA25 and control molecules were either added with viral inoculum at the time of Coinfection for Myrcludex-B (lipopeptide, entry inhibitor; Genscript U194RHD150_1) or at day 1 post-Coinfection for IFA25; EVI5 (Isotypic control antibody); IFA202 (IFN alpha2A fused to EVI5); CP870.893 (Agonist anti-CD40 antibody) and Lonafarnib

(farnesyltransferase inhibitor, HDV assembly inhibitor; selleckchem SCH66336). Two different concentrations were assessed, 1 and 10 nM for all molecules except for Lonafarnib at 1 and 10 μ M.

5 *VIII.e - Treatment with IFA25 and control molecules at different time points in HBV/HDV Coinfection experiments in cryopreserved PHH*

[00362] In this experiment, two different treatment time points of IFA25 and control molecules were assessed either at the time of Coinfection with viral inoculum (Co-treatment) or at day 1 post-Coinfection (post-treatment). For experiments when treatments were given at the time of infection the compounds were mixed with the viral inoculum and addressed to the cell simultaneously with HBV/HDV virus. For conditions when treatments were given at day one post-Coinfection compounds were added to the cells in fresh infection cell culture medium. A 10-fold serial dilution of Myrcludex-B and Pegasys starting from 10-0.001 nM was used. A 10-fold serial dilution of Tenofovir (nucleoside/nucleotide analog polymerase inhibitor) starting from 10-0.01 μ M was used and finally a 10-fold serial dilution of IFA25 starting from 1-0.001 nM was used.

VIII.f - Viral propagation assay in cryopreserved PHH

[00363] Following Coinfection experiment in cryopreserved-PHH, naïve cryopreserved-PHH were used for a second round of infection as a surrogate test to assess viral propagation. This second round of infection was performed either at fixed-volume (i.e. same volume of conditioned-supernatant from primary infection was used to infect the naïve PHH) or at fixed-Vge/cell (i.e. adjusted-volume of conditioned-supernatant from primary infection to have same HDV load to infect the naïve PHH). At 7 days post-reinfection, relative HDV intracellular RNA expression was measured by qRT-PCR and normalised to Coinfected nontreated condition.

VIII.g - Quantification of secreted HBsAg by CLIA Assay

[00364] HBs antigen (HBsAg) quantification in the supernatant was carried out according to commercial AutoBio CLIA kit protocol (#CL0310-2). First, the samples

were diluted 10 times in 96-well plate format or 20 times in 24-well plate format in infection cell culture medium solution. In the assay plate, 50 µl of standards, controls, and diluted samples were placed in the wells. Then, 50 µl of "Enzyme conjugate" solution was added to each well and the plate was incubated for one hour at 37° C.

5 Subsequently, the plate was washed 6 times with 300 µl of washing solution from the kit using an automated plate washer. Then, 50 µl of "Substrate Solution" (volume-to-volume mix in reagents A and B) was added in each well and, after an incubation period of 10 minutes in the dark, the plate was read for luminescence signal in relative light units (RLU) by an Envision apparatus. Using the calibrator's RLU values,

10 calibration curve was built, and a non-linear regression was applied. For each sample, RLU signal was interpolated using the calibration curve to obtain concentration in IU/mL for HBsAg. The final concentration was obtained by multiplying the concentration by the dilution factor.

VIII.h - Quantification of HBV Viremia

15 [00365] HBV DNA quantification in the supernatant was carried out by qPCR quantification with QuantStudio 7 Pro real-time PCR instrument, 96-Well 0.1 ml from ThermoFisher Scientific. Briefly viral DNA was first extracted from cell monolayer with NucleoSpin 96 Virus kit (Macherey-Nagel; 740691). Then, 5 µl of Eluted viral DNA was used as template for HBV DNA viremia quantification with

20 TaqMan fast universal PCR master Mix (Thermofisher scientific; 4366073) and Taqman-FAM-MGB assay with commercial set of HBV primers and Probe (Thermofisher scientific; Vi03453405_s1). For HBV viremia quantification a standard curve was built with HBV standard reference. For each sample, Ct quantification fluorescence was interpolated using the standard curve to obtain

25 concentration in HBV DNA copy/ml. The final concentration was obtained by multiplying the concentration by the dilution factor.

VIII.i - Quantification of HDV Viremia

[00366] HDV RNA quantification in the supernatant was carried out by qRT-PCR quantification with QuantStudio 7 Pro real-time PCR instrument, 96-Well 0.1 ml

30 from ThermoFisher Scientific. Briefly viral RNA was first extracted from cell

monolayer with NucleoSpin 96 Virus kit (Macherey-Nagel; 740691). Then, 5 µl of Eluted viral RNA was used as template for HDV RNA viremia quantification with TaqMan master mix fast virus 1-Step (Thermofisher scientific; 4444434) and Taqman-FAM-MGB assay with custom set of HDV primers and Probe (Thermofisher scientific; fwd 5'-TGGACGTGCGTCCTCCT-3', SEQ ID NO 99; rev 5'-TCTTCGGGTCGGCATGG-3', SEQ ID NO 100; and probe 5'-ATGCCCAGGTCGGAC-3'; SEQ ID NO 101). For HDV viremia quantification a standard curve was built with HDV standard reference. For each sample, Ct quantification fluorescence was interpolated using the standard curve to obtain concentration in HDV RNA copy/ml. The final concentration was obtained by multiplying the concentration by the dilution factor.

VIII.j - HDV antigens analysis by Western Blot

[00367] L-HDAg and S-HDAg proteins detection after Coinfection by Western blot analysis. Briefly, at the end of the kinetic cell monolayer was lysed with a combination of 1X RIPA (Millipore; 20188) and Protease inhibitor cocktail (Sigma Aldrich; P8340-5ml) to allow whole proteins extraction. Cell lysate was centrifuged at 4° C 15min at 14,000 g for clarification. Total protein quantification was performed with Pierce detergent compatible Bradford assay reagent following supplier instructions (Thermo; 1863028). A fixed protein quantity was loaded in LDS reducing reagent (Invitrogen; NP0007) in a presence of reducing agent (Invitrogen; NP0009) on Criterion gel 4-20% (Bio-rad; 5678094) with constant voltage. Then separating proteins were transferred to nitrocellulose membrane (Bio-rad, 5678094) following trans-blot Turbo protocol (Bio-rad; 1704155). L-HDAg and S-HDAg proteins were detected with FD3A7 primary mouse monoclonal antibody (Kerafast; EHD001) and secondary anti-mouse HRP antibody (Jackson Immuno Research; 111-035-146). For enhanced chemiluminescence (ECL) revelation, Clarity Western ECL substrate (Bio-rad; 1705060) was used. Chemiluminescent signal was captured with Chemidoc MP (Bio-rad). A loading protein control was always run in parallel (anti-beta Tubulin, Abcam; ab-6046).

VIII.k – Effect of IFA25 and control molecules on HDV genotype 1 Coinfection with HBV in cryopreserved-PHH

[00368] The effects of IFA25 and control molecules were evaluated in cryopreserved-PHH coinfecting with HDV genotype 1 and HBV genotype D. In this experiment, the treatments were given 1 day after the Coinfection, except for Myrcludex-B which was given at the time of infection. At 4 days post-Coinfection, the cell medium was changed to fresh medium without treatment. At 7 days post-Coinfection, the cell media were recovered for viral parameters analysis and were also used for a second round of infection of new cryopreserved-PHH, either using a fixed-volume or using a fixed Vge/Cell.

[00369] At 7 days post-Coinfection, EVI5, the isotype control antibody, and CP870.893 did not impact the HDV infection as shown by HDV RNA and the HBsAg levels respectively on **Fig. 18A** and **Fig. 18B**. IFA202 was able to decrease HDV infection compared to coinfecting non-treated condition, from 40 % and 60% on HDV RNA respectively at 1 and 10 nM. IFA202 effect on HBsAg was weaker compared to the one on HDV RNA. IFA25 induced a strong decrease of HDV parameters, with more than 80% decrease of HDV RNA level from 1nM dose level. IFA25 effect of HBsAg was also strong, already at the lowest dose. Myrcludex-B was able to strongly decrease HDV RNA level, by 60% at 1nM and more than 99% at 10nM. Similar profile was observed of HBsAg level. Finally, Lonafarnib induced a dose dependent decrease in HDV RNA level, from 20% at 1µM to 80% decrease at 10µM. On HBsAg level, the effect of Lonafarnib was detected, only at the highest dose of 10µM.

[00370] In addition to the HDV RNA level in supernatant, intracellular HDV antigens was evaluated by western blot analysis (**Fig. 18C**). HDV L and S antigens were detected, and Tubulin protein was used as loading control. No HDV Antigen was detected in non-infected condition whereas in the Coinfection condition, without treatment, the level of HDV antigens were high. Treatments with EVI5 and CP870.893 did not affect HDV antigen bands. IFA202 and Myrcludex-B demonstrated a dose dependent decrease of the HDV antigen bands intensity, with a higher potency for Myrcludex-B at highest dose which nearly abolished the HDV

antigen expression. IFA25 was able to abolish the HDV antigen bands intensity, at its 2 dose levels thus being the most potent treatment to decrease HDV antigen parameter in these experimental conditions. Finally, Lonafarnib showed a different pattern with an increase of the HDV Antigen bands intensity thus reflecting an intracellular accumulation of HDV antigen compared to the coinfecting non-treated condition.

[00371] Using supernatants from the primary Coinfection experiment, new cryopreserved PHH were infected with a fixed volume and intracellular HDV RNA level was measured at 7 days post-infection (**Fig. 19A**). In this experiment the data obtained confirmed absence or the very limited effect of EVI5 and CP870.893 treatments. IFA202 condition exhibited a decrease in intracellular HDV RNA level, 60% at highest dose of 10nM. IFA25 treatment was able to strongly decrease the HDV RNA level in the cells, more than 90% at the 2 dose levels. Myrcludex-B and Lonafarnib showed a dose dependent effect with 50% decrease at their lowest dose and below the limit of quantification (LOQ) at their highest dose.

[00372] Using their HDV titer measured by qRT-PCR, supernatants from the primary Coinfection experiment were used to infect new cryopreserved-PHH at fixed Vge/cell. After 7 days post-Coinfection, intracellular HDV RNA level was measured and is depicted in **Fig. 19B**. This protocol allowed for investigation of the specific infectivity of HDV virions produced during the primary Coinfection experiment. The data obtained demonstrated absence of effect of EVI5, CP870.893 and IFA202 treatments on HDV virions. A dose dependent effect was observed with IFA25, meaning that IFA25 treatment applied during the primary coinfection was able to strongly decrease the HDV RNA level in the cells following the second round of infection at fixed-Vge/cell. With Myrcludex-B treatment in the primary Coinfection, at lowest dose, it did not impact the HDV RNA level in the second round of infection at fixed Vge/cell. With Myrcludex-B at highest dose, the HDV RNA titer from the primary infection was too low to achieve the targeted Vge/cell, thus the data obtained at highest dose are not interpretable. Finally, Lonafarnib condition showed a dose dependent effect in the second round of infection at fixed-Vge/cell, with no effect at the lowest dose and below the LOQ at the highest dose. Overall, these fixed-volume and fixed-Vge/cell experiments demonstrated that IFA25 was able to decrease the

HDV RNA load from the primary Coinfection experiment and impacted the infectivity of the HDV virions produced. This was observed with IFA25 already at 1nM dose level. Lonafarnib exhibited a similar profile but only at the high dose of 10μM. The other treatments have either no effect on HDV (EVI5 and CP870.893) or
5 can decrease HDV load but not HDV infectivity (IFA202, Lonafarnib at 1 μM and Myrcludex-B at 1 nM).

VIII.1 – Effect of IFA25 and control molecules at different times following HDV Coinfection with HBV in cryopreserved-PHH

[00373] Similar HDV genotype 1 and HBV genotype D Coinfection protocol was
10 applied to cryopreserved PHH and the treatments were administered either at the time of the Coinfection (Co-treatment design) or 1 day after the Coinfection (post-treatment design). After 7 days, the viral parameters were analyzed and HDV RNA level is depicted in **Fig. 20A** and **Fig. 20B** and HBsAg level in **Fig. 20C** and **Fig. 20D**, respectively for the co-treatment and post-treatment designs. In these
15 various treatment settings, IFA25 induced a strong decrease in HDV RNA and HBsAg levels in the supernatant at 7 days whatever the treatment designs, in post-Coinfection and in co-treatment. Pegasys treatment was able to decrease the viral parameters in these different treatment designs, however its potency was always lower compared to IFA25. Myrcludex-B treatment induced a decrease in HDV RNA
20 and HBsAg level only in co-treatment design. When given after the time of infection, Myrcludex-B was not able to limit the HDV infection. Finally, Tenofovir treatment did not impact HDV RNA level whatever the treatment design, it was only able to slightly decrease the HBsAg level in the co-treatment setting.

EXAMPLE IXEffect of IFAs against HDV genotype-3 in HDV Coinfection with HBV in cryopreserved-PHH*IX.a - Virus production*

5 [00374] An HBV genotype D inoculum was prepared from the supernatant of HepAD38 cells, which were initially described in Ladner and colleagues (Antimicrob Agents Chemother, 41(8):1715-20, 1997; doi: 10.1128/AAC.41.8.1715). The 0.22-micron filtrated supernatant of HepAD38 was centrifuged with centricon for virus concentration to generate the viral stock.

10 [00375] An HDV genotype 3 inoculum was prepared from the supernatant of Huh-7 cells co-transfected with PL2032 (a 2-fold antigenome HDV-3) and pHB2.7. The 0.22-micron filtrated supernatant of Huh-7 was clarified by centrifugation to generate the HDV genotype 3 stock.

IX.b - Virus stocks quantification

15 [00376] The titers of these stocks of HBV genotype D and HDV genotype-3 were determined by ddPCR and expressed as viral genome equivalent per milliliter (Vge/mL).

IX.c - Coinfection protocol in Cryopreserved Primary human hepatocytes (PHH)

20 [00377] Cryopreserved PHH were coinfectd with the HBV genotype D and HDV genotype-3 according to the same protocol as described in section VIII.c.

IX.d - Treatment with IFA25 and control molecules on HDV genotype-3 in HBV/HDV Coinfection experiments in cryopreserved PHH

25 [00378] In this experiment, IFA25 and Pegasys (Peg-IFN α) were added at day 1 post-Coinfection at two different concentrations for IFA25 (0.1 and 1 nM) and at a single concentration for Pegasys (1 nM).

IX.e - Viral parameters analysis on HDV genotype-3 in HBV/HDV Coinfection experiments in cryopreserved PHH

[00379] Following the Coinfection protocol, viral parameters were assessed at 7-day post-infection. HBV DNA was quantified in the supernatant by qPCR analysis as described in section VIII.h. HDV antigen in cell lysate was analyzed by Western Blot as described in section VIII.j. Secreted HBsAg and HBeAg were quantified in the supernatant by CLIA Assay, respectively CLIA kit CL0310-2 and CL0312-2, as described in section VIII.g.

[00380] HDV-genotype 3 RNA viremia was quantified by ddPCR. In brief, after RNA extraction with Nucleospin 96 virus kit as described in section VIII.i. Eluted RNA was converted in cDNA in the presence of superscript VILO cDNA synthesis kit (Invitrogen; 11754-250) in PCR thermocycler (Bio-rad; T100) for 60 min at 42° C and 5 minutes at 85° C. Then, 5 µl of cDNA was subjected to droplet generation in a reaction mix of ddPCR Supermix for probes (Bio-rad, 1863010) and taqman custom primers and probe in autoDG instrument (Bio-rad; 773BR1339). Once, droplets generated, ddPCR plate move to PCR Thermocycler (Bio-rad; T100) for DNA amplification; 10 min. at 95° C; (30 sec. at 94°C and 1 min. at 58°C) 40 cycles and a final stage 10 min. at 98° C. Final quantification with Droplet Digital System (Bio-rad; QX-200). HDV viremia is expressed in copy/ml.

IX.f - Effect of IFA25 and control molecules on HDV genotype 3 coinfection with HBV in cryopreserved-PHH

[00381] The effects of IFA25 and Pegasys were evaluated in cryopreserved-PHH coinfecting with HDV genotype 3 and HBV genotype D. In this experiment, the treatments were given 1 day after the Coinfection. At 4 days post-Coinfection, the cell medium was changed to fresh medium without treatment. At 7 days post-Coinfection, the viral parameters were analyzed. IFA25 demonstrated a dose dependent effect in decreasing HDV RNA level in the supernatant (**Fig. 21A**). At the same concentration of 1nM, IFA25 was more potent than Pegasys to decrease this HDV RNA level. Furthermore, IFA25 was able to decrease the intracellular HDV antigens level (L- and S-HDAg) as shown by the western blot analysis (**Fig. 21B**).

The effect on the HDV antigens was also higher with IFA25 compared to Pegasys at the same dose level. In this Coinfection experiment with HDV genotype 3, although the level of HBsAg was high in the coinfecting non-treated condition (>3000 UI/mL; **Fig. 21C**), IFA25 demonstrated a strong and dose dependent decrease in HBsAg level, higher than Pegasys (**Fig. 21C**). Finally, HBV viral parameters were measured and were found high in the coinfecting non treated condition. IFA25 was able to decrease both the HBeAg level (**Fig. 21D**) and HBV DNA in supernatant (**Fig. 21E**), better than Pegasys treatment.

10 **EXAMPLE X**

Effect of IFAs given in addition to antiviral molecules on HDV Coinfection with HBV in cryopreserved-PHH

X.a - Virus production, titer and Coinfection protocol

[00382] HBV genotype D and HDV genotype-1 viruses used in example X were obtained and tittered as described in example VIII in section VIII.a and VIII.b respectively. Cryopreserved PHH were coinfecting with the viruses following the protocol described in section VIII.c.

X.b - IFA25 and Pegasys in addition to Myrcludex-B treatment

[00383] In this experiment, we first assessed the inhibitory concentration of Myrcludex-B added to the PHH at the time of Coinfection in a 10-fold serial dilution starting from $100-0.000001$ nM. Then, in a second independent experiment, we combined Myrcludex-B at a single inhibitory concentration with a dose range concentration of either IFA25 or Pegasys from a 10-fold serial dilution starting from $10-0.000001$ nM. All molecules were applied at the time of Coinfection.

X.c - IFA25 and Pegasys in addition to Tenofovir treatment

[00384] In this experiment, we first assessed the inhibitory concentration of Tenofovir added to the PHH at day 1 post-Coinfection in a 10-fold serial dilution starting from 100-0.000001 μ M. Then, in a second independent experiment, we combined
5 Tenofovir at a single inhibitory concentration with a dose range concentration of either IFA25 or Pegasys from a 10-fold serial dilution starting from 10-0.000001 nM. All molecules were applied at day 1 post-Coinfection.

X.d - Viral parameters and cell viability analysis in HBV/HDV coinfection experiments with IFA treatment in addition to antiviral molecules

10 [00385] Following the Coinfection protocol, viral parameters were assessed at 7-day post-infection. HBV Viremia was quantified in the supernatant by PCR analysis as described in section VIII.h. HDV Viremia was quantified in the supernatant by PCR analysis as described in section VIII.i. Secreted HBsAg was quantified in the supernatant by CLIA Assay as described in section VIII.g. Finally, Cell viability was
15 assessed at 7-day post-Coinfection by CellTiter-Glo assay (Promega; G8462). Briefly, supernatant was harvested and a volume-volume solution of CellTiter-Glo solution and PBS was added to the cell monolayer. The mixture was mixed in contact of the cells for at least 2 minutes on an orbital shaker to allow cell lysis. Then luminescence was recorded on Envision (Perkin). Results were expressed as
20 percentage of cell viability related to Coinfected nontreated control.

X.e - Effect of IFA25 and Pegasys in addition to Myrcludex-B in HDV Coinfection with HBV in cryopreserved-PHH

[00386] Effect of Myrcludex-B on HDV RNA in supernatant was evaluated in the HBV and HDV Coinfection protocol in cryopreserved PHH. As shown in **Fig. 22A**,
25 a dose dependent effect was observed and IC50 and IC90 were estimated respectively at 0.09 nM and 1.34 nM. In a separate HBV and HDV Coinfection experiment, Myrcludex-B treatment was set at 1.2 nM to target a dose between IC50 and IC90. In addition to such Myrcludex-B treatment, IFA25 or Pegasys were applied in dose range. As shown on **Fig. 22B and 22C**, the effect of Myrcludex-B alone was

consistent with previous findings as HDV RNA in supernatant decreased of approximately 80% in these experiments. IFA25 treatment given of top of Myrcludex-B induced a dose dependent further decrease of the HDV RNA in supernatant, reaching nearly 2.0LOG reduction at highest dose (**Fig. 22B**). Pegasys treatment in addition to Myrcludex-B tended to further decrease HDV RNA in supernatant, however it was less potent than IFA25 as it reached 1.3LOG decrease (**Fig. 22C**). On HBsAg parameter, the effect of Myrcludex-B alone was of 70% and treatment with IFA25 in addition to Myrcludex-B further decrease HBsAg secretion down to 95% at highest dose (**Fig. 22D**) whereas Pegasys decrease HBsAg to a lesser extent of 80% (**Fig. 22E**). Finally, the cell viability was assessed using a Cell TiterGlo assay which was normalized to the coinfecting non-treated condition. As shown on **Fig. 22F** and **Fig. 22G**, the level in Uninfected conditions were either similar or slightly lower compared to the coinfecting conditions thus showing that the Coinfection did not induce any cell toxicity. The CTG assay resulted in a slightly higher variability in the Pegasys experiment as shown by the greater error bars in **Fig. 22G** compared to the experiment with IFA25 in **Fig. 22F**. In addition, the conditions where no cytotoxicity is observed can range from about 85% to about 107%. In this assay, the treatment with Myrcludex-B alone also did not impact the cell viability. Finally, IFA25 or Pegasys in dose range, respectively on **Fig. 22F** and **Fig. 22G**, did not induce any or only minor cell cytotoxicity as shown by the cell viability above 80% even at the highest dose of 10nM.

X.f - Effect of IFA25 and Pegasys in addition to Tenofovir in HDV Coinfection with HBV in cryopreserved-PHH

[00387] Effect of Tenofovir, a nucleoside/nucleotide analog that inhibits HBV polymerase, on HBV DNA in supernatant was evaluated in the HBV and HDV Coinfection protocol in cryopreserved PHH. As shown in **Fig. 23A**, a dose dependent effect was observed and IC50 and IC90 were estimated respectively at 0.04 μ M and 1.72 μ M. In a separate HBV and HDV Coinfection experiment, Tenofovir treatment was set at 0.05 μ M to target a dose between IC50 and IC90. In addition to such Tenofovir treatment, IFA25 or Pegasys were applied in dose range. As shown on **Fig. 23B and 23C**, the effect of Tenofovir alone was consistent with previous

findings as HBV DNA in supernatant decreased by approximately 50% in these experiments. IFA25 treatment given in addition to Tenofovir induced a dose dependent further decrease of the HBV DNA in supernatant, reaching above 90% reduction from 0.1 nM dose (**Fig. 23B**). Pegasys treatment in addition to Tenofovir tended to further decrease HBV DNA in supernatant, however it was less potent than IFA25 as it reached 89% decrease at highest dose (**Fig. 23C**). On HBsAg parameter, Tenofovir alone has no effect and treatment with IFA25 in addition to Tenofovir decreases HBsAg secretion down to 96% at highest dose (**Fig. 23D**) whereas Pegasys decreases HBsAg to a lesser extent of 45% (**Fig. 23E**). On HDV RNA in supernatant, Tenofovir alone has no effect and treatment with IFA25 in addition to Tenofovir decrease HDV RNA in supernatant by more than 1LOG at 1nM dose (**Fig. 23F**) whereas Pegasys did not impacted HDV RNA parameter in these conditions (**Fig. 23G**). Finally, the cell viability was assessed using a Cell TiterGlo assay which was normalized to the coinfecting non-treated condition. As shown on **Fig. 23H** and **Fig. 23I**, the level in Uninfected conditions were either similar or slightly lower compared to the coinfecting conditions thus confirming that the Coinfection did not induce any cell toxicity. The treatment with Tenofovir alone did not impact the cell viability. For the conditions where no cytotoxicity is observed, in this experiment the CTG assay ranged from about 82% to about 106%. IFA25 in dose range in addition to Tenofovir did not induce cell cytotoxicity until including the 1nM dose. A mild decrease in cell viability was only observed at the highest dose of 10 nM with a viability at 70% (**Fig. 23H**), however, this remains very close to the uninfected condition and must likely be due to the cell culture protocol and/or the intrinsic variability applied to primary cells. Pegasys in dose range in addition to Tenofovir did not induce cell cytotoxicity until the highest dose of 10 nM (**Fig. 23I**).

[00388] Altogether, the viability data depicted in Fig. 22F, 22G and Fig. 23H and 23I demonstrated that, among the doses tested of IFA25 (from 0,001 nM to 10nM), 50% cytotoxicity concentrations (CC50), i.e. the concentration required to reduce cell viability by 50%, were reached in no experiment. Furthermore, in this dose range, the anti-HDV effects of IFA25, observed on HDV viremia and HBsAg already at low concentrations, were very potent (see Figs. 22B, 22D and 23B, 23D). Taken together, the demonstrated data confirm a favorable effective and safe profile of IFA treatment.

Equivalents

[00389] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting of the invention. The scope of the claimed invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are therefore intended to be embraced herein.

10

Items

[00390] In view of the above, it will be appreciated that the present invention also relates to the following **items**:

1. An interferon-associated antigen binding protein comprising
5 (I) an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and
(II) an Interferon (IFN) or a functional fragment thereof
for use in the treatment or prevention of Hepatitis delta virus infection.
- 10 2. The interferon-associated antigen binding protein for the use of item 1,
wherein the agonistic anti-CD40 antibody, or the agonistic antigen binding
fragment thereof, comprises three light chain complementarity determining
regions (CDRs) that are at least 90% identical to the CDRL1, CDRL2 and
CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs that
15 are at least 90% identical to the CDRH1, CDRH2 and CDRH3 sequences
within SEQ ID NO 6;
preferably wherein the agonistic anti-CD40 antibody, or the agonistic antigen
binding fragment thereof, comprises three light chain complementarity
determining regions (CDRs) that are at least 95% identical to the CDRL1,
CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain
20 CDRs that are at least 95% identical to the CDRH1, CDRH2 and CDRH3
sequences within SEQ ID NO 6;
more preferably wherein the agonistic anti-CD40 antibody, or the agonistic
antigen binding fragment thereof, comprises three light chain
complementarity determining regions (CDRs) that are at least 98% identical
25 to the CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and
three heavy chain CDRs that are at least 98% identical to the CDRH1,
CDRH2 and CDRH3 sequences within SEQ ID NO 6;
or still more preferably wherein the agonistic anti-CD40 antibody, or the
agonistic antigen binding fragment thereof, comprises three light chain
30 complementarity determining regions (CDRs) that are at least 99% identical
to the CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and
three heavy chain CDRs that are at least 99% identical to the CDRH1,
CDRH2 and CDRH3 sequences within SEQ ID NO 6.

3. The interferon-associated antigen binding protein for the use of item 1 or 2, wherein the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises three light chain complementarity determining regions (CDRs) that are identical to the CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs that are identical to the CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.
4. The interferon-associated antigen binding protein for the use of items 2 or 3, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the AbM definition, or the contact definition of CDR; preferably wherein each CDR is defined in accordance with the CDR definition of Kabat or the CDR definition of Chothia.
5. The interferon-associated antigen binding protein for the use of item 1, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises
- (I)
- (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 90% identical to SEQ ID NO 56, a CDRH2 that is at least 90% identical to SEQ ID NO 57, and a CDRH3 that is at least 90% identical to SEQ ID NO 58; and
- (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 90% identical to SEQ ID NO 52, a CDRL2 that is at least 90% identical to SEQ ID NO 53, and a CDRL3 that is at least 90% identical to SEQ ID NO 54;
- preferably (II)
- (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 95% identical to SEQ ID NO 56, a CDRH2 that is at least 95% identical to SEQ ID NO 57, and a CDRH3 that is at least 95% identical to SEQ ID NO 58; and
- (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 95% identical to SEQ ID NO 52, a CDRL2 that is at least 95% identical to SEQ ID NO 53, and a CDRL3 that is at least 95% identical to SEQ ID NO 54;
- more preferably (III)
- (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 98% identical to SEQ ID

- NO 56, a CDRH2 that is at least 98% identical to SEQ ID NO 57, and a CDRH3 that is at least 98% identical to SEQ ID NO 58; and
(b) a light chain or a fragment thereof comprising a CDRL1 that is at least 98% identical to SEQ ID NO 52, a CDRL2 that is at least 98% identical to
5 SEQ ID NO 53, and a CDRL3 that is at least 98% identical to SEQ ID NO 54; or
still more preferably (IV)
(a) a heavy chain or a fragment thereof comprising a complementarity
determining region (CDR) CDRH1 that is at least 99% identical to SEQ ID
10 NO 56, a CDRH2 that is at least 99% identical to SEQ ID NO 57, and a CDRH3 that is at least 99% identical to SEQ ID NO 58; and
(b) a light chain or a fragment thereof comprising a CDRL1 that is at least 99% identical to SEQ ID NO 52, a CDRL2 that is at least 99% identical to
SEQ ID NO 53, and a CDRL3 that is at least 99% identical to SEQ ID NO
15 54.
6. The interferon-associated antigen binding protein for the use of item 1,
wherein the agonistic anti-CD40 antibody or the agonistic antigen binding
fragment thereof comprises
(a) a heavy chain or a fragment thereof comprising a complementarity
20 determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to
SEQ ID NO 58; and
(b) a light chain or a fragment thereof comprising a CDRL1 that is identical
to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a
25 CDRL3 that is identical to SEQ ID NO 54.
7. The interferon-associated antigen binding protein for the use of any one of the
preceding items, wherein the agonistic anti-CD40 antibody, or the agonistic
antigen binding fragment thereof, comprises a light chain variable region V_L
comprising the sequence as set forth in SEQ ID NO 51, or a sequence at least
30 90% identical thereto; and/or a heavy chain variable region V_H comprising
the sequence as set forth in SEQ ID NO 55, or a sequence at least 90%
identical thereto;
preferably wherein the agonistic anti-CD40 antibody, or the agonistic antigen
binding fragment thereof, comprises a light chain variable region V_L
35 comprising a sequence that is at least 95% identical to the sequence as set

- forth in SEQ ID NO 51; and/or a heavy chain variable region V_H comprising a sequence that is at least 95% identical to the sequence as set forth in SEQ ID NO 55;
- more preferably wherein the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a light chain variable region V_L comprising a sequence that is at least 98% identical to the sequence as set forth in SEQ ID NO 51; and/or a heavy chain variable region V_H comprising a sequence that is at least 98% identical to the sequence as set forth in SEQ ID NO 55;
- still more preferably the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a light chain variable region V_L comprising a sequence that is at least 99% identical to the sequence as set forth in SEQ ID NO 51; and/or a heavy chain variable region V_H comprising a sequence that is at least 99% identical to the sequence as set forth in SEQ ID NO 55; or
- most preferably wherein the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a light chain variable region V_L comprising the sequence as set forth in SEQ ID NO 51 and a heavy chain variable region V_H comprising the sequence as set forth in SEQ ID NO 55.
8. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, comprises a Fab region heavy chain comprising an amino acid sequence as set forth in SEQ ID NO 12, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
9. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90% identical thereto; and/or a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48, or a sequence at least 90% identical thereto;
- preferably wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence that is at least 95% identical to the sequence as set forth in SEQ ID

- NO 3; and/or a heavy chain (HC) that comprises a sequence that is at least 95% identical to a sequence as set forth within the group of sequences consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48;
- 5 more preferably wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence that is at least 98% identical to the sequence as set forth in SEQ ID NO 3; and/or a heavy chain (HC) that comprises a sequence that is at least 98% identical to a sequence as set forth within the group of sequences
- 10 consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48;
- still more preferably wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence that is at least 99% identical to the sequence as set forth
- 15 in SEQ ID NO 3; and/or a heavy chain (HC) that comprises a sequence that is at least 99% identical to a sequence as set forth within the group of sequences consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48; or
- most preferably wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises
- 20 a sequence as set forth in SEQ ID NO 3; and a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48.
10. The interferon-associated antigen binding protein for the use of item 9,
- 25 wherein the HC comprises the sequence as set forth in SEQ ID NO 6, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
11. The interferon-associated antigen binding protein for the use of item 9,
- 30 wherein the HC comprises the sequence as set forth in SEQ ID NO 9, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
12. The interferon-associated antigen binding protein for the use of item 9,
- 35 wherein the HC comprises the sequence as set forth in SEQ ID NO 49, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.

13. The interferon-associated antigen binding protein for the use of item 9, wherein the HC comprises the sequence as set forth in SEQ ID NO 48, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 5 14. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the IFN or the functional fragment thereof is a human interferon.
- 15 15. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the IFN or the functional fragment thereof is selected from the group consisting of a Type I IFN, a Type II IFN and a Type III IFN, or a functional fragment thereof.
- 10 16. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the IFN or the functional fragment thereof is a Type I IFN, or a functional fragment thereof.
- 15 17. The interferon-associated antigen binding protein for the use of item 16, wherein the type I IFN or the functional fragment thereof is IFN α , IFN β , IFN ω , or IFN ϵ , or a functional fragment thereof.
- 20 18. The interferon-associated antigen binding protein for the use of item 16, wherein the type I IFN or the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.
19. The interferon-associated antigen binding protein for the use of item 16, wherein the type I IFN or the functional fragment thereof is IFN ω , or a functional fragment thereof.
- 25 20. The interferon-associated antigen binding protein for the use of item 16, wherein the type I IFN or the functional fragment thereof is IFN ϵ , or a functional fragment thereof.
21. The interferon-associated antigen binding protein for the use of any one of the items 1 to 14, wherein the IFN or the functional fragment thereof is IFN α , IFN β , IFN γ , IFN λ , IFN ω or IFN ϵ , or a functional fragment thereof.

22. The interferon-associated antigen binding protein for the use of item 21, wherein the IFN or the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.
- 5 23. The interferon-associated antigen binding protein for the use of item 22, wherein the IFN or the functional fragment thereof is IFN α , or a functional fragment thereof.
24. The interferon-associated antigen binding protein for the use of item 23, wherein the IFN or functional fragment thereof is IFN α 2a, or a functional fragment thereof.
- 10 25. The interferon-associated antigen binding protein for the use of item 24, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 15 26. The interferon-associated antigen binding protein for the use of item 22, wherein the IFN or the functional fragment thereof is IFN β , or a functional fragment thereof.
27. The interferon-associated antigen binding protein for the use of item 26, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 20 28. The interferon-associated antigen binding protein for the use of item 26, wherein the IFN β or the functional fragment thereof comprises one or two amino acid substitution(s) relative to SEQ ID NO 14, selected from C17S and N80Q.
- 25 29. The interferon-associated antigen binding protein for the use of item 28, wherein the IFN β or the functional fragment thereof comprises the amino acid substitution C17S relative to SEQ ID NO 14.
- 30 30. The interferon-associated antigen binding protein for the use of item 29, wherein the IFN β comprises the amino acid sequence as set forth in SEQ ID NO 15.

31. The interferon-associated antigen binding protein for the use of item 28, wherein the IFN β or the functional fragment thereof comprises the amino acid substitutions C17S and N80Q relative to SEQ ID NO 14.
- 5 32. The interferon-associated antigen binding protein for the use of item 31, wherein the IFN β comprises the amino acid sequence as set forth in SEQ ID NO 16.
33. The interferon-associated antigen binding protein for the use of item 21, wherein the IFN or a functional fragment thereof is IFN γ or IFN λ , or a functional fragment thereof.
- 10 34. The interferon-associated antigen binding protein for the use of item 33, wherein the IFN or a functional fragment thereof is IFN γ , or a functional fragment thereof.
- 15 35. The interferon-associated antigen binding protein for the use of item 34, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
36. The interferon-associated antigen binding protein for the use of item 33, wherein the IFN or a functional fragment thereof is IFN λ , or a functional fragment thereof.
- 20 37. The interferon-associated antigen binding protein for the use of item 36, wherein the IFN λ or the functional fragment thereof is IFN λ 2, or a functional fragment thereof.
- 25 38. The interferon-associated antigen binding protein for the use of item 37, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 30 39. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the IFN or the functional fragment thereof is non-covalently associated with the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.

- 5 40. The interferon-associated antigen binding protein for the use of item 39, wherein the IFN or the functional fragment thereof is non-covalently associated with the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof via ionic, Van-der-Waals, and/or hydrogen bond interactions.
41. The interferon-associated antigen binding protein for the use of any one of items 1 to 38, wherein the IFN or the functional fragment thereof is covalently associated with the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
- 10 42. The interferon-associated antigen binding protein for the use of item 41, wherein the IFN or the functional fragment thereof is fused to the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
43. The interferon-associated antigen binding protein for the use of item 42, wherein the IFN or the functional fragment thereof is fused to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
- 15 44. The interferon-associated antigen binding protein for the use of item 43, wherein the IFN or the functional fragment thereof is fused to the N-terminus of the light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
- 20 45. The interferon-associated antigen binding protein for the use of item 43, wherein the IFN or the functional fragment thereof is fused to the C-terminus of the light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
- 25 46. The interferon-associated antigen binding protein for the use of item 42, wherein the IFN or the functional fragment thereof is fused to a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
- 30 47. The interferon-associated antigen binding protein for the use of item 46, wherein the IFN or the functional fragment thereof is fused to the N-terminus of the heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.

48. The interferon-associated antigen binding protein for the use of item 46, wherein the IFN or the functional fragment thereof is fused to the C-terminus of the heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof.
- 5 49. The interferon-associated antigen binding protein for the use of any one of items 42 to 48, wherein the agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and the IFN or the functional fragment thereof are fused to each other via a linker.
- 10 50. The interferon-associated antigen binding protein for the use of item 49, wherein the interferon-associated antigen binding protein comprises no amino acids other than those forming (I) said agonistic anti-CD40 antibody, or agonistic antigen binding fragment thereof, (II) said IFN or functional fragment thereof and (III) said linker.
- 15 51. The interferon-associated antigen binding protein for the use of any one of items 1 to 49, wherein the interferon-associated antigen binding protein comprises no amino acids other than those forming (I) said agonistic anti-CD40 antibody, or agonistic antigen binding fragment thereof and (II) said IFN or functional fragment thereof.
- 20 52. The interferon-associated antigen binding protein for the use of any one of items 49 to 50, wherein the linker is a peptide linker.
53. The interferon-associated antigen binding protein for the use of item 52, wherein the linker comprises at least 1, at least 2, at least 3, at least 4, or at least 5 amino acids.
- 25 54. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 4 amino acids.
55. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 11 amino acids.
56. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 12 amino acids.
- 30 57. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 13 amino acids.

58. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 15 amino acids.
59. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 20 amino acids.
- 5 60. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 21 amino acids.
61. The interferon-associated antigen binding protein for the use of item 53, wherein the linker comprises at least 24 amino acids.
- 10 62. The interferon-associated antigen binding protein for the use of item 52, wherein the linker comprises up to 10, up to 20, up to 30, up to 40, up to 50, up to 60, up to 70, up to 80, up to 90, or up to 100 amino acids.
63. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 80 amino acids.
- 15 64. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 40 amino acids.
65. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 24 amino acids.
66. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 21 amino acids.
- 20 67. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 20 amino acids.
68. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 15 amino acids.
- 25 69. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 13 amino acids.
70. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 12 amino acids.

71. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 11 amino acids.
72. The interferon-associated antigen binding protein for the use of item 62, wherein the linker comprises up to 4 amino acids.
- 5 73. The interferon-associated antigen binding protein for the use of any one of items 52 to 72, wherein the linker is selected from the group comprising acidic, basic and neutral linkers.
74. The interferon-associated antigen binding protein for the use of item 73, wherein the linker is an acidic linker.
- 10 75. The interferon-associated antigen binding protein for the use of item 73 or 74, wherein the linker comprises a sequence as set forth in SEQ ID NO 22 or SEQ ID NO 23.
76. The interferon-associated antigen binding protein for the use of item 73, wherein the linker is a basic linker.
- 15 77. The interferon-associated antigen binding protein for the use of item 73, wherein the linker is a neutral linker.
78. The interferon-associated antigen binding protein for the use of item 73 or 77, wherein the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.
- 20 79. The interferon-associated antigen binding protein for the use of any one of items 52 to 78, wherein the linker is selected from the group comprising rigid, flexible and helix-forming linkers.
80. The interferon-associated antigen binding protein for the use of item 79, wherein the linker is a rigid linker.
- 25 81. The interferon-associated antigen binding protein for the use of item 79 or 80, wherein the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 22 or SEQ ID NO 23.
82. The interferon-associated antigen binding protein for the use of item 79, wherein the linker is a flexible linker.

83. The interferon-associated antigen binding protein for the use of item 79 or 82, wherein the linker comprises a sequence as set forth in SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.
- 5 84. The interferon-associated antigen binding protein for the use of item 79, wherein the linker is a helix-forming linker.
85. The interferon-associated antigen binding protein for the use of item 79 or 84, wherein the linker comprises a sequence as set forth in SEQ ID NO 22 or SEQ ID NO 23.
- 10 86. The interferon-associated antigen binding protein for the use of any one of items 52 to 74, 76, 77, 79, 80, 82 or 84, wherein the linker comprises the amino acids glycine and serine.
87. The interferon-associated antigen binding protein for the use of item 86, wherein the linker comprises the sequence as set forth in SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25, or SEQ ID NO 26.
- 15 88. The interferon-associated antigen binding protein for the use of item 86, wherein the linker further comprises the amino acid threonine.
89. The interferon-associated antigen binding protein for the use of item 88, wherein the linker comprises the sequence as set forth in SEQ ID NO 21.
- 20 90. The interferon-associated antigen binding protein for the use of item 52, wherein the linker comprises a sequence selected from the sequences as set forth in SEQ ID NOs 20 to 26.
91. The interferon-associated antigen binding protein for the use of item 90, wherein the linker comprises a sequence selected from the sequences as set forth in SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.
- 25 92. The interferon-associated antigen binding protein for the use of item 91, wherein the linker comprises a sequence as set forth in SEQ ID NO 24.
93. The interferon-associated antigen binding protein for the use of item 91, wherein the linker comprises a sequence as set forth in SEQ ID NO 25.

94. The interferon-associated antigen binding protein for the use of item 91, wherein the linker comprises a sequence as set forth in SEQ ID NO 26.
- 5 95. The interferon-associated antigen binding protein for the use of any one of items 49, 50 or 52 to 94, wherein the IFN or a functional fragment thereof is fused to the C-terminus of a heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker as set forth in Table 3, in particular Table 3A or Table 3B, more particularly Table 3A.
- 10 96. The interferon-associated antigen binding protein for the use of item 95, wherein the heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 48 or SEQ ID NO 49.
97. The interferon-associated antigen binding protein for the use of items 95 or 96, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
- 15 98. The interferon-associated antigen binding protein for the use of items 95 or 96, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.
99. The interferon-associated antigen binding protein for the use of item 98, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
- 20 100. The interferon-associated antigen binding protein for the use of item 98, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
101. The interferon-associated antigen binding protein for the use of item 98, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
- 25 102. The interferon-associated antigen binding protein for the use of item 95 or 96, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.
103. The interferon-associated antigen binding protein for the use of item 95 or 96, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.
104. The interferon-associated antigen binding protein for the use of any one of items 95 to 103, wherein the interferon-associated antigen binding protein

further comprises a light chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof.

105. The interferon-associated antigen binding protein for the use of item 104, wherein the light chain comprises a sequence as set forth in SEQ ID NO 3.
- 5 106. The interferon-associated antigen binding protein for the use of any one of items 49, 50 or 52 to 94, wherein the IFN or a functional fragment thereof is fused to the N-terminus of a heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker as set forth in Table 4, in particular Table 4A or Table 4B, more particularly Table 4A.
- 10 107. The interferon-associated antigen binding protein for the use of item 106, wherein the heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, or SEQ ID NO 12.
- 15 108. The interferon-associated antigen binding protein for the use of items 106 or 107, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
109. The interferon-associated antigen binding protein for the use of items 106 or 107, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.
- 20 110. The interferon-associated antigen binding protein for the use of item 109, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
111. The interferon-associated antigen binding protein for the use of item 109, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
- 25 112. The interferon-associated antigen binding protein for the use of item 109, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
113. The interferon-associated antigen binding protein for the use of items 106 or 107, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.
- 30 114. The interferon-associated antigen binding protein for the use of items 106 or 107, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.

115. The interferon-associated antigen binding protein for the use of any one of items 106 to 114, wherein the interferon-associated antigen binding protein further comprises a light chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof.
- 5 116. The interferon-associated antigen binding protein for the use of item 115, wherein the light chain comprises a sequence as set forth in SEQ ID NO 3.
- 10 117. The interferon-associated antigen binding protein for the use of any one of items 49, 50 or 52 to 94, wherein the IFN or a functional fragment thereof is fused to the C-terminus of a light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker as set forth in Table 5, in particular Table 5A or Table 5B, more particularly Table 5A.
- 15 118. The interferon-associated antigen binding protein for the use of item 117, wherein the light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 3.
119. The interferon-associated antigen binding protein for the use of items 117 or 118, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
- 20 120. The interferon-associated antigen binding protein for the use of items 117 or 118, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.
- 25 121. The interferon-associated antigen binding protein for the use of item 120, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
122. The interferon-associated antigen binding protein for the use of item 120, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
123. The interferon-associated antigen binding protein for the use of item 120, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
124. The interferon-associated antigen binding protein for the use of items 117 or 118, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.

125. The interferon-associated antigen binding protein for the use of items 117 or 118, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.
- 5 126. The interferon-associated antigen binding protein for the use of any one of items 117 to 125, wherein the interferon-associated antigen binding protein further comprises a heavy chain of an agonistic anti-CD40 antibody, or an agonistic antigen binding fragment thereof.
- 10 127. The interferon-associated antigen binding protein for the use of item 126, wherein the heavy chain of the agonistic anti-CD40 antibody comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, or SEQ ID NO 12.
- 15 128. The interferon-associated antigen binding protein for the use of any one of items 49, 50 or 52 to 94, wherein the IFN is fused to the N-terminus of a light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, via the linker as set forth in Table 6, in particular Table 6A or Table 6B, more particularly Table 6A.
- 20 129. The interferon-associated antigen binding protein for the use of item 128, wherein the light chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 3.
- 25 130. The interferon-associated antigen binding protein for the use of items 128 or 129, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
131. The interferon-associated antigen binding protein for the use of items 128 or 129, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.
- 30 132. The interferon-associated antigen binding protein for the use of item 131, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
133. The interferon-associated antigen binding protein for the use of item 131, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.

134. The interferon-associated antigen binding protein for the use of item 131, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
135. The interferon-associated antigen binding protein for the use of items 128 or 129, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.
- 5 136. The interferon-associated antigen binding protein for the use of items 128 or 129, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.
- 10 137. The interferon-associated antigen binding protein for the use of any one of items 128 to 136, wherein the interferon-associated antigen binding protein further comprises a heavy chain of an anti-CD40 antibody, or an agonistic antigen binding fragment thereof.
- 15 138. The interferon-associated antigen binding protein for the use of item 137, wherein the heavy chain of the agonistic anti-CD40 antibody comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, or SEQ ID NO 12.
- 20 139. The interferon-associated antigen binding protein for the use of any one of items 1 to 138, wherein the interferon-associated antigen binding protein comprises a sequence selected from SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 81, SEQ ID NO 82, SEQ ID NO 83, SEQ ID NO 84, SEQ ID NO 85, SEQ ID NO 86, SEQ ID NO 87, SEQ ID NO 88 and SEQ ID NO 90.
- 25 140. The interferon-associated antigen binding protein for the use of item 139, wherein the interferon-associated antigen binding protein comprises a sequence selected from SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42 or SEQ ID NO 43.
- 30 141. The interferon-associated antigen binding protein for the use of items 139 or 140, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising one of the sequence

combinations disclosed in Table 9, in particular Table 9A or Table 9B, more particularly Table 9A.

- 5 142. The interferon-associated antigen binding protein for the use of item 141, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 38 and SEQ ID NO 3.
- 10 143. The interferon-associated antigen binding protein for the use of item 141, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 39 and SEQ ID NO 3.
- 15 144. The interferon-associated antigen binding protein for the use of item 141, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 40 and SEQ ID NO 3.
- 20 145. The interferon-associated antigen binding protein for the use of item 141, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 41 and SEQ ID NO 9.
- 25 146. The interferon-associated antigen binding protein for the use of item 141, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 42 and SEQ ID NO 9.
- 30 147. The interferon-associated antigen binding protein for the use of item 141, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 43 and SEQ ID NO 9.

148. The interferon-associated antigen binding protein for the use of any one of items 1 to 147, wherein the interferon-associated antigen binding protein activates both the CD40 and an IFN pathway.
- 5 149. The interferon-associated antigen binding protein for the use of item 148, wherein CD40 activity is determined using a whole blood surface molecule upregulation assay or an in vitro reporter cell assay.
150. The interferon-associated antigen binding protein for the use of item 149, wherein CD40 activity is determined using an in vitro reporter cell assay, optionally using HEK-BlueTM CD40L cells.
- 10 151. The interferon-associated antigen binding protein for the use of any one of items 148 to 150, wherein the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ of less than 400, 300, 200, 150, 100, 70, 60, 50, 40, 30, 25, 20, or 15 ng/mL.
- 15 152. The interferon-associated antigen binding protein for the use of item 151, wherein the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ ranging from 10 to 200 ng/mL.
- 20 153. The interferon-associated antigen binding protein for the use of item 152, wherein the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ ranging from 10 to 50 ng/mL, preferably 10 to 30 ng/mL.
- 25 154. The interferon-associated antigen binding protein for the use of any one of items 148 to 153, wherein the interferon-associated antigen binding protein activates the IFN pathway with an EC₅₀ of less than 100, 60, 50, 40, 30, 20, 10, or 1 ng/mL.
- 30 155. The interferon-associated antigen binding protein for the use of any one of items 148 to 154, wherein the interferon-associated antigen binding protein activates the IFN pathway with an EC₅₀ of less than 11 ng/mL, preferably less than 6 ng/mL.
156. The interferon-associated antigen binding protein for the use of any one of items 148 to 155, wherein the IFN pathway is the IFN α , IFN β , IFN ϵ , IFN γ , IFN ω or IFN λ pathway.

157. The interferon-associated antigen binding protein for the use of item 156, wherein IFN β activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN- α/β cells.
- 5 158. The interferon-associated antigen binding protein for the use of item 156, wherein IFN α activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN- α/β cells.
159. The interferon-associated antigen binding protein for the use of item 156, wherein IFN γ activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ Dual IFN- γ cells.
- 10 160. The interferon-associated antigen binding protein for the use of item 156, wherein IFN λ activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN- λ cells.
- 15 161. The interferon-associated antigen binding protein for the use of any one of the preceding items, in particular items 148 to 160, wherein the expression level of one or more IFN pathway biomarkers is upregulated in a Hepatitis delta virus-infected cell upon treatment with the interferon-associated antigen binding protein, preferably at least 1.5-fold, more preferably at least 2-fold, most preferably at least 3-fold, as compared to the expression level of said biomarkers in said Hepatitis delta virus-infected cell that has not been treated
- 20 with the interferon-associated antigen binding protein..
162. The interferon-associated antigen binding protein for the use of item 161, wherein the IFN pathway biomarker is a chemokine.
163. The interferon-associated antigen binding protein for the use of item 162, wherein the IFN pathway biomarker is the interferon stimulated gene ISG20.
- 25 164. The interferon-associated antigen binding protein for the use of item 162, wherein the IFN pathway biomarker is a C-X-C chemokine, selected from the group consisting of CXCL9, CXCL10 and CXCL11.
165. The interferon-associated antigen binding protein for the use of item 164, wherein the IFN pathway biomarker is CXCL10.
- 30 166. The interferon-associated antigen binding protein for the use of any one of the preceding items, in particular items 148 to 165, wherein the expression level

- of one or more of IL10, IL1 β and IL2 is not significantly upregulated in a Hepatitis delta virus-infected cell upon treatment with the interferon-associated antigen binding protein, as compared to the expression level of said interleukins in said Hepatitis delta virus-infected cell that has not been treated with the interferon-associated antigen binding protein.
- 5
167. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the systemic exposure of the interferon-associated antigen binding protein is increased compared to antibody CP870,893, preferably by at least 10%, more preferably by at least 15%, most preferably by at least 25%.
- 10
168. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the systemic exposure of the interferon-associated antigen binding protein is at least 1000 $\mu\text{g}\cdot\text{h}/\text{mL}$.
169. The interferon-associated antigen binding protein for the use of item 168, wherein the systemic exposure of the interferon-associated antigen binding protein ranges from 1033 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 1793 $\mu\text{g}\cdot\text{h}/\text{mL}$.
- 15
170. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the half-life of the interferon-associated antigen binding protein is at least 100 h.
- 20
171. The interferon-associated antigen binding protein for the use of item 170, wherein the half-life of the interferon-associated antigen binding protein ranges from 116 to 158 h.
172. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the clearance rate of the interferon-associated antigen binding protein is below 0.5 $\text{mL}/\text{h}/\text{kg}$.
- 25
173. The interferon-associated antigen binding protein for the use of item 172, wherein the clearance of the interferon-associated antigen binding protein ranges from 0.28 to 0.49 $\text{mL}/\text{h}/\text{kg}$.
174. The interferon-associated antigen binding protein for the use of any one of items 1 to 173, wherein the volume of distribution V_{ss} of the interferon-associated antigen binding protein is below 100 mL/kg .
- 30

175. The interferon-associated antigen binding protein for the use of item 174, wherein the volume of distribution V_{ss} of the interferon-associated antigen binding protein ranges from 50 to 98 mL/kg.
- 5 176. The interferon-associated antigen binding protein for the use of any one of the preceding items, wherein the use comprises administering the interferon-associated antigen binding protein to a subject in need thereof by means of genetic delivery with RNA or DNA sequences encoding the interferon-associated antigen binding protein, or a vector or vector system encoding the interferon-associated antigen binding protein.
- 10 177. The interferon-associated antigen binding protein for the use of any one of items 1 to 176, wherein the interferon-associated antigen binding protein is comprised in a pharmaceutical composition.
- 15 178. The interferon-associated antigen binding protein for the use of item 177, wherein the pharmaceutical composition is suitable for oral, parenteral, or topical administration or for administration by inhalation.
179. The interferon-associated antigen binding protein for the use of item 178, wherein the pharmaceutical composition is suitable for oral administration.
180. The interferon-associated antigen binding protein for the use of item 178, wherein the pharmaceutical composition is suitable for topical administration.
- 20 181. The interferon-associated antigen binding protein for the use of item 178, wherein the pharmaceutical composition is suitable for administration by inhalation.
- 25 182. The interferon-associated antigen binding protein for the use of item 178, wherein the pharmaceutical composition is suitable for parenteral administration.
183. The interferon-associated antigen binding protein for the use of item 182, wherein the pharmaceutical composition is suitable for intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal or vaginal administration.

184. The interferon-associated antigen binding protein for the use of item 183, wherein the pharmaceutical composition is suitable for injection, preferably for intravenous or intraarterial injection or drip.
- 5 185. The interferon-associated antigen binding protein for the use of any one of items 177 to 184, wherein the pharmaceutical composition comprises at least one buffering agent.
186. The interferon-associated antigen binding protein for the use of item 185, wherein the buffering agent is acetate, formate or citrate.
- 10 187. The interferon-associated antigen binding protein for the use of item 186, wherein the buffering agent is acetate.
188. The interferon-associated antigen binding protein for the use of item 186, wherein the buffering agent is formate.
189. The interferon-associated antigen binding protein for the use of item 186, wherein the buffering agent is citrate.
- 15 190. The interferon-associated antigen binding protein for the use of any one of items 177 to 189, wherein the pharmaceutical composition comprises a surfactant.
- 20 191. The interferon-associated antigen binding protein for the use of item 190, wherein the surfactant is selected from the list comprising pluronics, PEG, sorbitan esters, polysorbates, triton, tromethamine, lecithin, cholesterol and tyloxapal.
- 25 192. The interferon-associated antigen binding protein for the use of item 191, wherein the surfactant is polysorbate.
193. The interferon-associated antigen binding protein for the use of item 192, wherein the surfactant is polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 or polysorbate 100.
194. The interferon-associated antigen binding protein for the use of item 193, wherein the surfactant is polysorbate 20.

195. The interferon-associated antigen binding protein for the use of item 193, wherein the surfactant is polysorbate 80.
196. The interferon-associated antigen binding protein for the use of any one of items 177 to 195, wherein the pharmaceutical composition comprises a stabilizing agent, optionally wherein the stabilizing agent is albumin.
197. The interferon-associated antigen binding protein for the use according to any one of items 1 to 196, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are at least 90% identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are at least 90% identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.
198. The interferon-associated antigen binding protein for the use according to any one of items 1 to 197, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.
199. The interferon-associated antigen binding protein for the use according to item 197 or item 198, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the AbM definition, or the contact definition of CDR; preferably wherein each CDR is defined in accordance with the CDR definition of Kabat or the CDR definition of Chothia.
200. The interferon-associated antigen binding protein for its use according to any one of items 2 to 199, wherein no amino acid substitutions, insertions or deletions are present within the complementarity determining regions of the

heavy chain and light chain variable regions of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof.

201. The interferon-associated antigen binding protein for its use according to any one of items 2 to 199, wherein no, one or two amino acid substitutions, insertions or deletions are independently present within each of the complementarity determining regions of the heavy chain and light chain variable regions of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof.
202. A polynucleotide or polynucleotides encoding the interferon-associated antigen binding protein as defined in any one of the preceding items for use in the treatment or prevention of a Hepatitis delta virus infection in a subject in need thereof, wherein the treatment comprises expression in said subject of said interferon-associated antigen binding protein, from a polynucleotide or polynucleotides administered to said subject.
203. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of the preceding items, wherein the Hepatitis delta virus infection is (i) a HDV/HBV coinfection, or (ii) a HDV/HBV superinfection.
204. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of the preceding items, wherein the Hepatitis delta virus infection is an HDV genotype-1 infection or an HDV genotype-3 infection.
205. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of items 2 to 204, wherein the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides are to be administered in addition to a host targeting agent.

206. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to item 205, wherein the host targeting agent is Myrcludex B.
- 5 207. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of items 2 to 204, wherein the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides are to be administered in addition to a direct acting antiviral agent.
- 10 208. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to item 207, wherein the direct acting antiviral agent is a nucleoside/nucleotide analog.
209. The interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to item 208, wherein the nucleoside/nucleotide analog is Tenofovir.

Matters

[00391] In view of the above, it will furthermore be appreciated that the present invention also relates to the following **matters**:

- 5 1. A cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof for use in the treatment or prevention of a Hepatitis delta virus infection, wherein the CD40 agonist or a functional fragment thereof is administered in combination with an interferon (IFN) or a functional fragment thereof.
- 10 2. An interferon (IFN) or a functional fragment thereof for use in the treatment or prevention of a Hepatitis delta virus infection, wherein the IFN or a functional fragment thereof is administered in combination with a cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof.
- 15 3. A combination of a cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof and an interferon (IFN) or a functional fragment thereof, for use in the treatment or prevention of a Hepatitis delta virus infection.
- 20 4. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of the preceding matters, wherein the CD40 agonist or functional fragment thereof is a polypeptide or functional fragment thereof, or an antibody or functional fragment thereof.
- 25 5. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 4, wherein the CD40 agonist or functional fragment thereof is CD40L or a functional fragment thereof.
6. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 4, wherein the CD40 agonist or functional fragment thereof is an

agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof.

7. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 6, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are at least 90% identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are at least 90% identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6;
- preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are at least 95% identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are at least 95% identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6;
- more preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are at least 98% identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are at least 98% identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6;
- or still more preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are at least 99% identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are at least 99% identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.

8. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 7, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are identical to the
5 respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.
- 10 9. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 7 or matter 8, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the AbM definition, or the contact definition of CDR; preferably wherein each CDR is defined in accordance
15 with the CDR definition of Kabat or the CDR definition of Chothia.
10. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 6, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises
20 (I)
(a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 90% identical to SEQ ID NO 56, a CDRH2 that is at least 90% identical to SEQ ID NO 57, and a CDRH3 that is at least 90% identical to SEQ ID NO 58; and
25 (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 90% identical to SEQ ID NO 52, a CDRL2 that is at least 90% identical to SEQ ID NO 53, and a CDRL3 that is at least 90% identical to SEQ ID NO 54;
preferably (II)
30 (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 95% identical to SEQ ID

- NO 56, a CDRH2 that is at least 95% identical to SEQ ID NO 57, and a CDRH3 that is at least 95% identical to SEQ ID NO 58; and
- (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 95% identical to SEQ ID NO 52, a CDRL2 that is at least 95% identical to SEQ ID NO 53, and a CDRL3 that is at least 95% identical to SEQ ID NO 54;
- more preferably (III)
- (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 98% identical to SEQ ID NO 56, a CDRH2 that is at least 98% identical to SEQ ID NO 57, and a CDRH3 that is at least 98% identical to SEQ ID NO 58; and
- (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 98% identical to SEQ ID NO 52, a CDRL2 that is at least 98% identical to SEQ ID NO 53, and a CDRL3 that is at least 98% identical to SEQ ID NO 54; or
- still more preferably (IV)
- (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 99% identical to SEQ ID NO 56, a CDRH2 that is at least 99% identical to SEQ ID NO 57, and a CDRH3 that is at least 99% identical to SEQ ID NO 58; and
- (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 99% identical to SEQ ID NO 52, a CDRL2 that is at least 99% identical to SEQ ID NO 53, and a CDRL3 that is at least 99% identical to SEQ ID NO 54.
11. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 10, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises
- a. a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a

CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to SEQ ID NO 58; and

- b. a light chain or a fragment thereof comprising a CDRL1 that is identical to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a CDRL3 that is identical to SEQ ID NO 54.

12. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 6 to 11, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain variable region VL comprising the sequence as set forth in SEQ ID NO 51, or a sequence at least 90% identical thereto; and/or a heavy chain variable region VH comprising the sequence as set forth in SEQ ID NO 55, or a sequence at least 90% identical thereto
preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain variable region VL comprising a sequence that is at least 95% identical to the sequence as set forth in SEQ ID NO 51; and/or a heavy chain variable region VH comprising a sequence that is at least 95% identical to the sequence as set forth in SEQ ID NO 55;
more preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain variable region VL comprising a sequence that is at least 98% identical to the sequence as set forth in SEQ ID NO 51; and/or a heavy chain variable region VH comprising a sequence that is at least 98% identical to the sequence as set forth in SEQ ID NO 55;
still more preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain variable region VL comprising a sequence that is at least 99% identical to the sequence as set forth in SEQ ID NO 51; and/or a heavy chain variable region VH comprising a sequence that is at least 99% identical to the sequence as set forth in SEQ ID NO 55; or

most preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain variable region VL comprising the sequence as set forth in SEQ ID NO 51 and a heavy chain variable region VH comprising the sequence as set forth in SEQ ID NO 55.

- 5 13. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 6 to 12, wherein the heavy chain of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a Fab region heavy chain comprising an amino acid sequence as set forth in SEQ ID NO 12, or a
- 10 sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
14. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 6 to 13, wherein the agonistic anti-CD40 antibody or agonistic
- 15 antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90% identical thereto; and/or a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48, or a sequence at least 90% identical thereto
- 20 preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence that is at least 95% identical to the sequence as set forth in SEQ ID NO 3; and/or a heavy chain (HC) that comprises a sequence that is at least 95% identical to a sequence as set forth within the group of sequences
- 25 consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48;
- more preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence that is at least 98% identical to the sequence as set forth in SEQ
- 30 ID NO 3; and/or a heavy chain (HC) that comprises a sequence that is at least 98% identical to a sequence as set forth within the group of sequences

- consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48;
- still more preferably wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises
- 5 a sequence that is at least 99% identical to the sequence as set forth in SEQ ID NO 3; and/or a heavy chain (HC) that comprises a sequence that is at least 99% identical to a sequence as set forth within the group of sequences consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48; or
- 10 most preferably wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3; and a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48.
- 15 15. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 14, wherein the HC comprises the sequence as set forth in SEQ ID NO 6, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 20 16. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 14, wherein the HC comprises the sequence as set forth in SEQ ID NO 9, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 25 17. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 14, wherein the HC comprises the sequence as set forth in SEQ ID NO 49, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.

18. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 14, wherein the HC comprises the sequence as set forth in SEQ ID NO 48, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
19. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 12 to 18, wherein no amino acid substitutions, insertions or deletions are present within the complementarity determining regions of the heavy chain and light chain variable regions of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof.
20. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 7 to 18, wherein no, one or two amino acid substitutions, insertions or deletions are independently present within each of the complementarity determining regions of the heavy chain and light chain variable regions of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof.
21. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of the preceding matters, wherein said IFN or functional fragment thereof is a human interferon.
22. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of the preceding matters, wherein the IFN or functional fragment thereof is selected from the group consisting of a Type I IFN, a Type II IFN and a Type III IFN, or functional fragments thereof.
23. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of the

preceding matters, wherein the IFN or the functional fragment thereof is a Type I IFN, or a functional fragment thereof.

24. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 23, wherein the type I IFN or the functional fragment thereof is IFN α , IFN β , IFN ω , or IFN ϵ , or a functional fragment thereof.
25. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 23, wherein the type I IFN or the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.
26. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 23, wherein the type I IFN or the functional fragment thereof is IFN ω , or a functional fragment thereof.
27. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 23, wherein the type I IFN or the functional fragment thereof is IFN ϵ , or a functional fragment thereof.
28. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 22, wherein the IFN or functional fragment thereof is IFN α , IFN β , IFN γ , IFN λ , IFN ω or IFN ϵ , or functional fragments thereof.
29. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 28, wherein the IFN or functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.
30. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 29,

wherein the IFN or functional fragment thereof is IFN α , or a functional fragment thereof.

31. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 30, wherein the IFN or functional fragment thereof is IFN α 2a, or a functional fragment thereof.
32. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 31, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
33. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 29, wherein the IFN or functional fragment thereof is IFN β , or a functional fragment thereof.
34. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 33, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
35. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 33, wherein the IFN β or functional fragment thereof comprises one or two amino acid substitution(s) relative to SEQ ID NO 14, selected from C17S and N80Q.
36. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 35, wherein the IFN β or functional fragment thereof comprises the amino acid substitution C17S relative to SEQ ID NO 14.

37. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 36, wherein the IFN β comprises the amino acid sequence as set forth in SEQ ID NO 15.
- 5 38. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 35, wherein the IFN β or functional fragment thereof comprises the amino acid substitutions C17S and N80Q relative to SEQ ID NO 14.
- 10 39. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 38, wherein the IFN β comprises the amino acid sequence as set forth in SEQ ID NO 16.
- 15 40. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 28, wherein the IFN or functional fragment thereof is IFN γ or IFN λ , or a functional fragment thereof.
- 20 41. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 40, wherein the IFN or functional fragment thereof is IFN γ , or a functional fragment thereof.
- 25 42. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 41, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
43. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 40, wherein the IFN or functional fragment thereof is IFN λ , or a functional fragment thereof.

44. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 43, wherein the IFN λ or functional fragment thereof is IFN λ 2, or a functional fragment thereof.
- 5 45. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 44, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18, or a sequence at least 90%, preferably 95%, more preferably 98%, or still more preferably 99% identical thereto.
- 10 46. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 45, wherein the IFN or functional fragment thereof is non-covalently associated with the CD40 agonist or functional fragment thereof.
- 15 47. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 46, wherein the IFN or functional fragment thereof is non-covalently associated with CD40 agonist or functional fragment thereof via ionic, Van-der-Waals, and/or hydrogen bond interactions.
- 20 48. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 45, wherein the IFN or functional fragment thereof is covalently associated with the CD40 agonist or functional fragment thereof.
- 25 49. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 45 or 48, wherein the IFN or functional fragment thereof is fused to the CD40 agonist or functional fragment thereof, preferably wherein the IFN or functional fragment thereof and the CD40 agonist or functional fragment thereof are fused to each other via a linker.

50. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 49, wherein the IFN or the functional fragment thereof is fused to an CD40 agonist or functional fragment thereof, wherein the CD40 agonist is CD40L or a functional fragment thereof.
51. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 49, wherein the CD40 agonist or functional fragment thereof and the IFN or functional fragment thereof are provided as an interferon-associated antigen binding protein, in which the CD40 agonist or functional fragment thereof is an antibody or antigen binding fragment thereof, preferably an agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof, more preferably an agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprising
- a. a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to SEQ ID NO 58; and
- b. a light chain or a fragment thereof comprising a CDRL1 that is identical to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a CDRL3 that is identical to SEQ ID NO 54;
- and wherein the IFN or a functional fragment thereof is fused to said antibody or antigen binding fragment thereof.
52. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 51, wherein the IFN or functional fragment thereof is fused to a light chain of the antibody or antigen binding fragment thereof.
53. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 52,

wherein the IFN or the functional fragment thereof is fused to the N-terminus of the light chain of the antibody or antigen binding fragment thereof.

54. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 52, wherein the IFN or the functional fragment thereof is fused to the C-terminus of the light chain of the antibody or antigen binding fragment thereof.
55. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 51, wherein the IFN or the functional fragment thereof is fused to a heavy chain of the antibody or antigen binding fragment thereof.
56. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 55, wherein the IFN or the functional fragment thereof is fused to the N-terminus of the heavy chain of the antibody or antigen binding fragment thereof.
57. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 55, wherein the IFN or the functional fragment thereof is fused to the C-terminus of the heavy chain of the antibody or antigen binding fragment thereof.
58. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 49 to 57, wherein the linker is a peptide linker.
59. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 58, wherein the linker comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 21 or at least 24 amino acids.
60. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 58,

wherein the linker comprises up to 4, up to 10, up to 11, up to 12, up to 13, up to 15, up to 20, up to 21, up to 24, up to 30, up to 40, up to 50, up to 60, up to 70, up to 80, up to 90, or up to 100 amino acids.

- 5 61. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 60, wherein the linker is selected from the group comprising acidic, basic and neutral linkers.
- 10 62. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 61, wherein the linker is an acidic linker.
63. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 61 or matter 62, wherein the linker comprises a sequence as set forth in SEQ ID NO 22 or SEQ ID NO 23.
- 15 64. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 61, wherein the linker is a basic linker.
65. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 61, wherein the linker is a neutral linker.
- 20 66. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 61 or matter 65, wherein the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.
- 25 67. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 66, wherein the linker is selected from the group comprising rigid, flexible and helix-forming linkers.

68. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 67, wherein the linker is a rigid linker.
- 5 69. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 67 or matter 68, wherein the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 22 or SEQ ID NO 23.
- 10 70. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 67, wherein the linker is a flexible linker.
71. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 67 or matter 70, wherein the linker comprises a sequence as set forth in SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.
- 15 72. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 67, wherein the linker is a helix-forming linker.
- 20 73. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 67 or matter 72, wherein the linker comprises a sequence as set forth in SEQ ID NO 22 or SEQ ID NO 23.
- 25 74. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 62, 64, 65, 67, 68, 70 or 72, wherein the linker comprises the amino acids glycine and serine.
75. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 74,

wherein the linker comprises the sequence as set forth in SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25, or SEQ ID NO 26.

- 5 76. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 74, wherein the linker further comprises the amino acid threonine.
77. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 76, wherein the linker comprises the sequence as set forth in SEQ ID NO 21.
- 10 78. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 58, wherein the linker comprises a sequence selected from the sequences as set forth in SEQ ID NOs 20 to 26.
79. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 78, wherein the linker comprises a sequence selected from the sequences as set forth in SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.
- 15 80. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 79, wherein the linker comprises a sequence as set forth in SEQ ID NO 24.
- 20 81. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 79, wherein the linker comprises a sequence as set forth in SEQ ID NO 25.
82. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 79, wherein the linker comprises a sequence as set forth in SEQ ID NO 26.
- 25 83. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 82, wherein the IFN or functional fragment thereof is fused to

the C-terminus of a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, via the linker as set forth in Table 3, in particular Table 3A or Table 3B, more particularly Table 3A.

- 5 84. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 83, wherein the heavy chain of the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 48 or SEQ ID NO 49.
- 10 85. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 83 or matter 84, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
- 15 86. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 83 or matter 84, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.
- 20 87. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 86, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
- 25 88. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 86, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
89. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 86, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
90. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 83 or

matter 84, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.

- 5 91. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 83 or matter 84, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.
- 10 92. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 83 to 91, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain, preferably wherein the light chain comprises a sequence as set forth in SEQ ID NO 3.
- 15 93. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 82, wherein the IFN or functional fragment thereof is fused to the N-terminus of a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, via the linker as set forth in Table 4, in particular Table 4A or Table 4B, more particularly Table 4A.
- 20 94. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 93, wherein the heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, or SEQ ID NO 12.
- 25 95. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 93 or matter 94, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
96. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 93 or

matter 94, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.

- 5 97. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 96, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
98. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 96, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
- 10 99. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 96, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
100. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 93 or matter 94, wherein the IFN γ comprises the sequence as set forth in SEQ ID
15 NO 19.
101. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 93 or matter 94, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID
 NO 18.
- 20 102. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 93 to 101, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises a light chain, preferably wherein the light chain comprises a sequence as set forth in SEQ ID NO 3.
- 25 103. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 82, wherein the IFN or functional fragment thereof is fused to the C-terminus of a light chain of the agonistic anti-CD40 antibody or the

agonistic antigen binding fragment thereof, via the linker as set forth in Table 5, in particular Table 5A or Table 5B, more particularly Table 5A.

- 5 104. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 103, wherein the light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 3.
- 10 105. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 103 or 104, wherein the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17.
- 15 106. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 103 or 104, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.
107. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 106, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
- 20 108. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 106, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
109. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 106, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
- 25 110. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 103 or 104, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.

111. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 103 or 104, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.
- 5 112. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 103 to 111, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a heavy chain, preferably wherein the heavy chain comprises a sequence as set forth in SEQ ID NO 6, 10 SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, or SEQ ID NO 12.
113. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 58 to 82, wherein the IFN or functional fragment thereof is fused to the N-terminus of a light chain of the agonistic anti-CD40 antibody or the 15 agonistic antigen binding fragment thereof, via the linker as set forth in Table 6, in particular Table 6A or Table 6B, more particularly Table 6A.
114. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 113, wherein the light chain of the agonistic anti-CD40 antibody or the agonistic 20 antigen binding fragment thereof, comprises a sequence as set forth in SEQ ID NO 3.
115. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 113 or matter 114, wherein the IFN α 2a comprises the sequence as set forth in SEQ 25 ID NO 17.
116. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 113 or matter 114, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14, SEQ ID NO 15 or SEQ ID NO 16.

117. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 116, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 14.
- 5 118. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 116, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 15.
119. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 116, wherein the IFN β comprises the sequence as set forth in SEQ ID NO 16.
- 10 120. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 113 or matter 114, wherein the IFN γ comprises the sequence as set forth in SEQ ID NO 19.
- 15 121. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to matter 113 or matter 114, wherein the IFN λ 2 comprises the sequence as set forth in SEQ ID NO 18.
- 20 122. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 113 to 121, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a heavy chain, preferably wherein the heavy chain comprises a sequence as set forth in SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49, SEQ ID NO 48, or SEQ ID NO 12.
- 25 123. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 51 to 122, wherein the interferon-associated antigen binding protein comprises a sequence selected from SEQ ID NO 28, SEQ ID NO 29, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 33, SEQ ID NO 34, SEQ ID NO 35, SEQ ID NO 36, SEQ ID NO 37, SEQ ID NO 38, SEQ ID

NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42, SEQ ID NO 43, SEQ ID NO 44, SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 81, SEQ ID NO 82, SEQ ID NO 83, SEQ ID NO 84, SEQ ID NO 85, SEQ ID NO 86, SEQ ID NO 87, SEQ ID NO 88 and SEQ ID NO 90.

- 5 124. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 123, wherein the interferon-associated antigen binding protein comprises a sequence selected from SEQ ID NO 38, SEQ ID NO 39, SEQ ID NO 40, SEQ ID NO 41, SEQ ID NO 42 or SEQ ID NO 43.
- 10 125. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 123 or matter 124, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising one of the sequence
- 15 combinations disclosed in Table 9, in particular Table 9A or Table 9B, more particularly Table 9A.
126. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 125, wherein the interferon-associated antigen binding protein is an interferon-
- 20 fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 38 and SEQ ID NO 3.
127. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 125,
- 25 wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 39 and SEQ ID NO 3.

128. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 125, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 40 and SEQ ID NO 3.
129. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 125, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 41 and SEQ ID NO 9.
130. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 125, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 42 and SEQ ID NO 9.
131. The CD40 agonist or functional fragment thereof, or the IFN or functional fragment thereof, or the combination for their use according to matter 125, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen binding fragment thereof comprising the sequences as set forth in SEQ ID NO 43 and SEQ ID NO 9.
132. An interferon-associated antigen binding protein comprising
- (I) an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and
 - (II) an Interferon (IFN) or a functional fragment thereof

for use in the treatment or prevention of a Hepatitis delta virus infection.

133. The interferon-associated antigen binding protein for the use of matter 132, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises
- 5 (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is at least 90% identical to SEQ ID NO 56, a CDRH2 that is at least 90% identical to SEQ ID NO 57, and a CDRH3 that is at least 90% identical to SEQ ID NO 58; and
- 10 (b) a light chain or a fragment thereof comprising a CDRL1 that is at least 90% identical to SEQ ID NO 52, a CDRL2 that is at least 90% identical to SEQ ID NO 53, and a CDRL3 that is at least 90% identical to SEQ ID NO 54.
134. The interferon-associated antigen binding protein for the use of matter 132, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding
- 15 fragment thereof comprises
- (a) a heavy chain or a fragment thereof comprising a complementarity determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to SEQ ID NO 58; and
- 20 (b) a light chain or a fragment thereof comprising a CDRL1 that is identical to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a CDRL3 that is identical to SEQ ID NO 54.
135. The interferon-associated antigen binding protein for the use of any one of matters 132 to 134, wherein the agonistic anti-CD40 antibody, or the
- 25 agonistic antigen binding fragment thereof, comprises a light chain variable region VL comprising the sequence as set forth in SEQ ID NO 51, or a sequence at least 90% identical thereto; and/or a heavy chain variable region VH comprising the sequence as set forth in SEQ ID NO 55, or a sequence at least 90% identical thereto.

136. The interferon-associated antigen binding protein for the use of any one of matters 132 to 135, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90% identical thereto; and/or a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 12, SEQ ID NO 49 and SEQ ID NO 48, or a sequence at least 90% identical thereto.
137. The interferon-associated antigen binding protein for the use of any one of matters 132 to 136, wherein the IFN or the functional fragment thereof is selected from the group consisting of a Type I IFN, a Type II IFN and a Type III IFN, or a functional fragment thereof.
138. The interferon-associated antigen binding protein for the use of matter 137, wherein the type I IFN or the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.
139. The interferon-associated antigen binding protein for the use of any one of matters 132 to 138, wherein the IFN or the functional fragment thereof is IFN α 2a, or a functional fragment thereof, and wherein preferably the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17, or a sequence at least 90% identical thereto.
140. The interferon-associated antigen binding protein for the use of any one of matters 132 to 138, wherein the IFN or the functional fragment thereof is IFN β or a functional fragment thereof, and wherein preferably the IFN β comprises the sequence as set forth in SEQ ID NO 14, or a sequence at least 90% identical thereto.
141. The interferon-associated antigen binding protein for the use of any one of matters 132 to 140, wherein the IFN or the functional fragment thereof is fused to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, preferably to the C-terminus.

142. The interferon-associated antigen binding protein for the use of any one of matters 132 to 140, wherein the IFN or the functional fragment thereof is fused to a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, preferably to the C-terminus.
- 5 143. The interferon-associated antigen binding protein for the use of any one of matters 132 to 142, wherein the agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and the IFN or the functional fragment thereof, are fused to each other via a linker, and wherein preferably the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 21, SEQ ID
10 NO 24, SEQ ID NO 25 or SEQ ID NO 26.
144. The interferon-associated antigen binding protein for the use of any one of matters 132 to 143, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising one of the sequence
15 combinations disclosed in Table 9, in particular Table 9A or Table 9B, more particularly Table 9A.
145. The interferon-associated antigen binding protein for the use of any one of matters 132 to 144, wherein the use comprises administering the interferon-associated antigen binding protein to a subject in need thereof by means of
20 genetic delivery with RNA or DNA sequences encoding the interferon-associated antigen binding protein, or a vector or vector system encoding the interferon-associated antigen binding protein.
146. The interferon-associated antigen binding protein for the use of
- 25 (a) any one of matters 132 to 144, wherein the interferon-associated antigen binding protein is comprised in a pharmaceutical composition;
or
(b) matter 145, wherein the RNA or DNA sequences encoding said interferon-associated antigen binding protein, or the vector or vector

system encoding said interferon-associated antigen binding protein are comprised in a pharmaceutical composition.

147. An interferon-associated antigen binding protein comprising an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen
5 binding fragment thereof comprising the amino acid sequences as set forth in SEQ ID NO 38 and SEQ ID NO 3, for use in the treatment or prevention of a Hepatitis delta virus infection.
148. An interferon-associated antigen binding protein comprising an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen
10 binding fragment thereof comprising the amino acid sequences as set forth in SEQ ID NO 39 and SEQ ID NO 3, for use in the treatment or prevention of a Hepatitis delta virus infection.
149. An interferon-associated antigen binding protein comprising an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen
15 binding fragment thereof comprising the amino acid sequences as set forth in SEQ ID NO 40 and SEQ ID NO 3, for use in the treatment or prevention of a Hepatitis delta virus infection.
150. An interferon-associated antigen binding protein comprising an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen
20 binding fragment thereof comprising the amino acid sequences as set forth in SEQ ID NO 41 and SEQ ID NO 9, for use in the treatment or prevention of a Hepatitis delta virus infection.
151. An interferon-associated antigen binding protein comprising an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen
25 binding fragment thereof comprising the amino acid sequences as set forth in SEQ ID NO 42 and SEQ ID NO 9, for use in the treatment or prevention of a Hepatitis delta virus infection.
152. An interferon-associated antigen binding protein comprising an interferon-fused agonistic anti-CD40 antibody or interferon-fused agonistic antigen

binding fragment thereof comprising the amino acid sequences as set forth in SEQ ID NO 43 and SEQ ID NO 9, for use in the treatment or prevention of a Hepatitis delta virus infection.

- 5 153. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination for its use according to any one of matters 1 to 131, or the interferon-associated antigen binding proteins for their use according to any one of matters 132 to 152, wherein the interferon-associated antigen binding protein activates both the CD40 and an IFN pathway.
- 10 154. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 153, wherein CD40 activity is determined using a whole blood surface molecule upregulation assay or an in vitro reporter cell assay.
- 15 155. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 154, wherein CD40 activity is determined using an in vitro reporter cell assay, optionally using HEK-BlueTM CD40L cells.
- 20 156. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 153 to 155, wherein the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ of less than 400, 300, 200, 150, 100, 70, 60, 50, 40, 30, 25, 20, or 15 ng/mL.
- 25 157. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 156, wherein the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ ranging from 10 to 200 ng/mL.

158. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 157, wherein the interferon-associated antigen binding protein activates the CD40 pathway with an EC₅₀ ranging from 10 to 50 ng/mL, preferably 10 to 30 ng/mL.
159. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 153 to 158, wherein the interferon-associated antigen binding protein activates the IFN pathway with an EC₅₀ of less than 100, 60, 50, 40, 30, 20, 10, or 1 ng/mL.
160. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 153 to 159, wherein the interferon-associated antigen binding protein activates the IFN pathway with an EC₅₀ of less than 11 ng/mL, preferably less than 6 ng/mL.
161. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 153 to 160, wherein the IFN pathway is the IFN α , IFN β , IFN ϵ , IFN γ , IFN ω or IFN λ pathway.
162. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 161, wherein IFN β activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN- α/β cells.
163. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 161, wherein IFN α activity is

determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN- α/β cells.

164. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 161, wherein IFN γ activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ Dual IFN- γ cells.
165. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 161, wherein IFN λ activity is determined using an in vitro reporter cell assay, optionally using HEK-Blue™ IFN- λ cells.
166. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 1 to 165, wherein the expression level of one or more IFN pathway biomarkers is upregulated in a Hepatitis delta virus-infected cell upon treatment with the interferon-associated antigen binding protein, preferably at least 1.5-fold, more preferably at least 2-fold, most preferably at least 3-fold, as compared to the expression level of said biomarkers in said Hepatitis delta virus-infected cell that has not been treated with the interferon-associated antigen binding protein.
167. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 166, wherein the IFN pathway biomarker is a chemokine.
168. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen

binding protein for their use according to matter 167, wherein the IFN pathway biomarker is the interferon stimulated gene ISG20.

169. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 167, wherein the IFN pathway biomarker is a C-X-C chemokine, selected from the group consisting of CXCL9, CXCL10 and CXCL11.
170. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 169, wherein the IFN pathway biomarker is CXCL10.
171. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 1 to 170, wherein the expression level of one or more of IL10, IL1 β and IL2 is not significantly upregulated in an Hepatitis delta virus-infected cell upon treatment with the interferon-associated antigen binding protein, as compared to the expression level of said interleukins in said Hepatitis delta virus-infected cell that has not been treated with the interferon-associated antigen binding protein.
172. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of the matters 1 to 171, wherein the systemic exposure of the interferon-associated antigen binding protein is increased compared to antibody CP870,893, preferably by at least 10%, more preferably by at least 15%, most preferably by at least 25%.
173. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 51 to 172,

wherein the systemic exposure of the interferon-associated antigen binding protein is at least 1000 $\mu\text{g}\cdot\text{h}/\text{mL}$.

174. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 173, wherein the systemic exposure of the interferon-associated antigen binding protein ranges from 1033 $\mu\text{g}\cdot\text{h}/\text{mL}$ to 1793 $\mu\text{g}\cdot\text{h}/\text{mL}$.
175. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 51 to 174, wherein the half-life of the interferon-associated antigen binding protein is at least 100 h.
176. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 175, wherein the half-life of the interferon-associated antigen binding protein ranges from 116 to 158 h.
177. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 51 to 176, wherein the clearance rate of the interferon-associated antigen binding protein is below 0.5 $\text{mL}/\text{h}/\text{kg}$.
178. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 177, wherein the clearance of the interferon-associated antigen binding protein ranges from 0.28 to 0.49 $\text{mL}/\text{h}/\text{kg}$.
179. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 1 to 178,

wherein the volume of distribution V_{ss} of the interferon-associated antigen binding protein is below 100 mL/kg.

180. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 179, wherein the volume of distribution V_{ss} of the interferon-associated antigen binding protein ranges from 50 to 98 mL/kg.
181. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of the preceding matters, wherein the use comprises administering said CD40 agonist or functional fragment thereof, said IFN or functional fragment thereof, said combination or said interferon-associated antigen binding protein to a subject in need thereof by means of
- a. genetic delivery with RNA or DNA sequences encoding said CD40 agonist or functional fragment thereof, said IFN or functional fragment thereof, said combination or said interferon-associated antigen binding protein; or
 - b. a vector or vector system encoding said CD40 agonist or functional fragment thereof, said IFN or functional fragment thereof, said combination or said interferon-associated antigen binding protein.
182. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 181, wherein said interferon-associated antigen binding protein is expressed in said subject from a polynucleotide or polynucleotides administered to said subject.
183. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 1 to 182,

wherein the interferon-associated antigen binding protein is comprised in a pharmaceutical composition.

- 5 184. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, or the combination for their use according to any one of matters 1 to 183, wherein the CD40 agonist or the functional fragment thereof and the IFN or the functional fragment thereof are comprised in the same pharmaceutical composition or in distinct pharmaceutical compositions.
- 10 185. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 183 or matter 184, wherein the pharmaceutical composition is suitable for oral, parenteral, or topical administration or for administration by inhalation.
- 15 186. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 185, wherein the pharmaceutical composition is suitable for oral administration.
- 20 187. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 185, wherein the pharmaceutical composition is suitable for topical administration.
- 25 188. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 185, wherein the pharmaceutical composition is suitable for administration by inhalation.
189. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 185, wherein the pharmaceutical composition is suitable for parenteral administration.

190. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 183 or matter 184, wherein the pharmaceutical composition is suitable for intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal or vaginal administration.
191. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 183 or matter 184, wherein the pharmaceutical composition is suitable for injection, preferably for intravenous or intraarterial injection or drip.
192. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 183 to 191, wherein the pharmaceutical composition comprises at least one buffering agent.
193. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 192, wherein the buffering agent is acetate, formate or citrate.
194. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 193, wherein the buffering agent is acetate.
195. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 193, wherein the buffering agent is formate.
196. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen

binding protein for their use according to matter 193, wherein the buffering agent is citrate.

197. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 183 to 196, wherein the pharmaceutical composition comprises a surfactant.
198. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 197, wherein the surfactant is selected from the list comprising pluronics, PEG, sorbitan esters, polysorbates, triton, tromethamine, lecithin, cholesterol and tyloxapal.
199. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 198, wherein the surfactant is polysorbate.
200. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 199, wherein the surfactant is polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 or polysorbate 100.
201. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 200, wherein the surfactant is polysorbate 20.
202. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to matter 200, wherein the surfactant is polysorbate 80.

203. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, or the interferon-associated antigen binding protein for their use according to any one of matters 183 to 202, wherein the pharmaceutical composition comprises a stabilizing agent, optionally wherein the stabilizing agent is albumin.
204. The interferon-associated antigen binding protein for its use according to any one of matters 132 to 203, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are at least 90% identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are at least 90% identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.
205. The interferon-associated antigen binding protein for its use according to any one of matters 132 to 204, wherein the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof comprises three light chain complementarity determining regions (CDRs) CDRL1, CDRL2 and CDRL3 that are identical to the respective CDRL1, CDRL2 and CDRL3 sequences within SEQ ID NO 3; and three heavy chain CDRs, CDRH1, CDRH2 and CDRH3, that are identical to the respective CDRH1, CDRH2 and CDRH3 sequences within SEQ ID NO 6.
206. The interferon-associated antigen binding protein for its use according to matter 204 or matter 205, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the AbM definition, or the contact definition of CDR; preferably wherein each CDR is defined in accordance with the CDR definition of Kabat or the CDR definition of Chothia.
207. The interferon-associated antigen binding protein for its use according to any one of matters 132 to 206, wherein no amino acid substitutions, insertions or deletions are present within the complementarity determining regions of the

heavy chain and light chain variable regions of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof.

208. The interferon-associated antigen binding protein for its use according to any one of matters 132 to 206, wherein no, one or two amino acid substitutions, insertions or deletions are independently present within each of the complementarity determining regions of the heavy chain and light chain variable regions of the agonistic anti-CD40 antibody or agonistic antigen binding fragment thereof.
209. A polynucleotide or polynucleotides encoding the CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof or the interferon-associated antigen binding protein as defined in any one of the preceding matters for use in the treatment or prevention of a Hepatitis delta virus infection in a subject in need thereof, wherein the treatment comprises expression in said subject of said CD40 agonist or functional fragment thereof and said IFN or functional fragment thereof, or expression in said subject of said interferon-associated antigen binding protein, from a polynucleotide or polynucleotides administered to said subject.
210. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of the preceding matters, wherein the Hepatitis delta virus infection is (i) a HDV/HBV coinfection, or (ii) a HDV/HBV superinfection.
211. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of the preceding matters, wherein the Hepatitis delta virus infection is an HDV genotype-1 infection or an HDV genotype-3 infection.
212. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding

protein, or the polynucleotide or polynucleotides for their use according to any one of matters 1 to 211, wherein the CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides are to be administered in addition to a host targeting agent.

213. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to matter 212, wherein the host targeting agent is Myrcludex B.
214. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to any one of matters 1 to 211, wherein the CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides are to be administered in addition to a direct acting antiviral agent.
215. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to matter 214, wherein the direct acting antiviral agent is a nucleoside/nucleotide analog.
216. The CD40 agonist or functional fragment thereof, the IFN or functional fragment thereof, the combination, the interferon-associated antigen binding protein, or the polynucleotide or polynucleotides for their use according to matter 215, wherein the nucleoside/nucleotide analog is Tenofovir.

5 [00392] It will be understood by one of skill in the art that the present invention is also directed to a CD40 agonist or functional fragment thereof, an IFN or functional fragment thereof, a combination of the two, an interferon-associated antigen binding protein or a polynucleotide or polynucleotides for their use according to any one of the matters or items identified herein, wherein the CD40 agonist comprises SEQ ID NO 59, SEQ ID NO 61 or SEQ ID NO 63 as disclosed in Table 8 and/or wherein the interferon-associated binding protein is an interferon-fused agonistic anti-CD40 antibody comprising one of the sequence combinations disclosed in Table 10, or an interferon-fused agonistic antigen binding fragment thereof.

10 [00393] Furthermore, it will be understood by one of skill in the art that the present invention is furthermore also directed to methods for the treatment or prevention of a Hepatitis delta virus infection in a subject, in particular a Hepatitis delta virus infection as identified in matters 210 and 211, wherein a therapeutically effective amount of the CD40 agonist or functional fragment thereof, the IFN or functional
15 fragment thereof, the combination of the two, the interferon-associated antigen binding protein or the polynucleotide or polynucleotides as referred to in any one of the aspects, embodiments, matters or items identified herein, or in the preceding paragraph, is administered to said subject.

20 [00394] It will be understood that in accordance with all aspects, embodiments, items and matters described and claimed herein, the subject to be treated is preferably a mammal, and most preferably a human subject.

[00395] Finally, it will be understood that all aspects, embodiments, items and matters described herein may be made the subject matter of further claims (in addition to the claims provided below).

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Table 11a: IFN- β -based IFAs		IFN- γ	IL10	IL12p40	IL1 β	IL2	IL6	IP10	TFN α
NT	donor 1	nd	nd	nd	nd	nd	nd	457,0	nd
	donor 2	nd	nd	101,4	nd	nd	nd	672,7	4,6
	donor 3	nd	nd	nd	nd	nd	nd	302,3	nd
	donor 4	nd	nd	104,0	nd	nd	nd	648,2	nd
LPS	donor 1	2023,0	148,0	7757,1	5116,0	nd	20709,6	6646,7	1706,3
	donor 2	4675,6	57,2	6265,6	6263,7	20,7	11070,1	39539,4	2987,1
	donor 3	1537,3	192,9	1750,0	3137,6	nd	16837,7	6141,0	944,9
	donor 4	2360,7	299,7	1676,5	6423,0	18,6	20654,0	22848,2	1107,2
IFA1	donor 1	98,1	nd	nd	nd	nd	16,3	46033,6	43,7
	donor 2	nd	nd	118,8	nd	nd	11,8	43545,5	36,6
	donor 3	nd	nd	nd	nd	nd	nd	23562,1	34,0
	donor 4	nd	nd	nd	nd	nd	nd	31922,5	57,1
IFA2	donor 1	nd	nd	nd	nd	nd	18,6	43382,3	41,0
	donor 2	nd	nd	114,2	nd	nd	17,4	43283,4	33,8
	donor 3	nd	nd	nd	nd	nd	nd	25961,4	32,2
	donor 4	109,4	nd	nd	nd	nd	nd	38445,0	66,0

Table 11b: IFN- α -based IFAs		IFN- γ	IL10	IL12p40	IL1 β	IL2	IL6	IP10	TFN α
NT	donor 5	12,6	0,6	91,6	0,9	0,9	3,9	270,3	2,1
	donor 6	5,0	1,1	129,9	19,9	#DIV/0!	423,2	1052,7	16,0
	donor 7	16,5	2,0	143,7	22,1	2,1	426,9	1025,0	12,6
	donor 8	9,7	0,1	58,3	1,8	#DIV/0!	2,6	594,2	2,2
LPS	donor 5	10848,1	46,6	8463,3	8712,3	10,5	30713,2	20538,9	1738,3
	donor 6	2467,1	175,6	5364,9	6557,9	3,3	31735,5	17262,6	2583,3
	donor 7	3310,1	248,6	6814,8	9123,9	16,6	39139,8	59939,2	6270,1
	donor 8	2555,6	138,5	2942,9	6767,5	9,6	31756,7	20062,7	1265,5
IFA25	donor 5	495,5	1,5	99,5	1,9	5,5	30,5	39637,5	30,4
	donor 6	312,2	2,0	129,8	16,5	4,0	51,8	61963,8	71,4
	donor 7	271,2	2,9	130,3	9,1	4,4	75,0	133442,5	30,3
	donor 8	441,6	1,9	74,8	6,8	3,2	44,3	95647,9	87,4
IFA26	donor 5	330,4	2,0	98,1	2,1	6,4	29,3	37880,2	32,1
	donor 6	303,7	3,3	150,8	17,1	3,1	53,0	72944,8	45,7
	donor 7	180,3	2,0	135,6	9,2	4,9	75,2	154696,3	29,7
	donor 8	421,4	2,8	95,7	6,8	4,1	42,1	79768,5	89,1
IFA27	donor 5	430,7	2,2	127,8	3,1	7,1	32,9	40214,1	61,3
	donor 6	286,5	2,0	148,5	16,8	2,1	66,0	83445,0	70,1
	donor 7	350,3	4,7	117,6	9,3	4,4	73,5	195844,6	105,6
	donor 8	440,1	2,6	68,6	8,9	0,6	46,9	102676,8	43,4
IFA28	donor 5	620,1	2,7	127,3	3,4	8,7	35,0	40958,5	24,6
	donor 6	264,7	2,0	170,3	13,6	2,4	45,7	62333,3	33,0
	donor 7	289,6	2,7	144,8	13,7	3,9	77,1	176521,8	59,6
	donor 8	436,2	2,5	74,4	4,9	2,3	36,8	79217,6	37,6
IFA29	donor 5	692,7	1,3	108,7	2,3	3,7	33,9	55062,8	30,3
	donor 6	183,1	2,2	158,8	11,6	0,4	44,4	58665,4	44,3
	donor 7	235,5	2,6	127,6	9,6	2,0	65,6	136893,2	90,5
	donor 8	301,1	3,0	77,7	5,8	0,6	33,8	69226,3	48,0
IFA30	donor 5	709,7	1,2	110,6	2,9	5,5	38,0	63040,7	36,5
	donor 6	122,9	2,0	153,0	14,9	1,7	46,1	67861,2	37,4
	donor 7	64,6	1,0	114,0	10,0	2,9	75,5	149093,0	32,7
	donor 8	206,0	1,9	71,1	6,8	1,8	37,9	85986,9	40,5

Table 12A

Matrix	Compound	Dose In-life period	Method	C ₀ (µg/mL)	AUC (0-last) (µg.h/mL)	T _{last} (h)	AUC (0-inf) (µg.h/mL)	% extrapolation	T _{1/2t} (h)	Cl (mL/hr/kg)	V _D (mL/kg)
Serum	CP870,893	0,5 mg/kg 168h	ELISA-IgG2	7,15	241	168	590	59	264 (long)	0,35 (Low)	296 (Low)
Serum	IFA27	0,5 mg/kg 240h	ELISA-IgG2	14,7	1501	240	2552	41	218 (long)	0,20 (Low)	55 (Low)
Serum	IFA27	0,5 mg/kg 240h	ELISA-IFN	16,9	1318	240	1793	26	125 (long)	0,28 (Low)	50 (Low)
Serum	IFA29	0,5 mg/kg 240h	ELISA-IFN	11,6	804	240	1033	22	116 (long)	0,49 (Low)	78 (Low)
Serum	IFA30	0,5 mg/kg 240h	ELISA-IFN	8,12	741	240	1089	31	158 (long)	0,46 (Low)	98 (Low)

Table 12B

Matrix	Compound	Dose In-life period	Method	C ₀ (µg/mL)	AUC (0-last) (µg.h/mL)	T _{last} (h)	AUC (0-inf) (µg.h/mL)	% extrapolation	T _{1/2t} (h)	Cl (mL/hr/kg)	V _D (mL/kg)
Serum	IFA25	0,5 mg/kg 504h	ELISA-IFN	7,45	1328	504	1500	11	154 (long)	0,34 (Low)	73 (Low)
Serum	IFA26	0,5 mg/kg 504h	ELISA-IFN	8,20	988	336	1027	3,8	59 (long)	0,49 (Low)	57 (Low)
Serum	IFA28	0,5 mg/kg 504h	ELISA-IFN	9,38	1048	504	1264	17	213 (long)	0,40 (Low)	105 (Low)
Serum	Pegasys	0,3 mg/kg 504h	ELISA-IFNα specific	8,3	210	168	215	2	30 (moderate)	1,4 (Low)	62 (Low)
Serum	CP870,893	0,5 mg/kg 504h	ELISA-IgG2	11,9	527	168	797	34	116 (long)	0,63 (Low)	96 (Low)
Serum	IFA25	0,5 mg/kg 504h	ELISA-IgG2	11,8	1292	240	1971	34	155 (long)	0,26 (Low)	56 (Low)

TABLE 13

Condition	Donor	IFNg	IL10	IL12p40	IL1b	IL2	IL6	IP10	TNFa
NT	D1	nd	nd	nd	nd	nd	nd	457,0	nd
	D2	nd	nd	101,4	nd	nd	nd	672,7	4,63
	D3	nd	nd	nd	nd	nd	nd	302,3	nd
	D4	nd	nd	104,0	nd	nd	nd	648,2	nd
LPS	D1	2023	148	7757	5116	nd	20710	6647	1706
	D2	4676	57	6266	6264	21	11070	39539	2987
	D3	1537	193	1750	3138	nd	16838	6141	945
	D4	2361	300	1677	6423	19	20654	22848	1107
IFA109	D1	nd	nd	nd	nd	nd	13,48	44495,49	43,63
	D2	nd	nd	116,29	nd	nd	10,6	44030,74	37,52
	D3	nd	nd	nd	nd	nd	nd	31506,88	62,17
	D4	nd	nd	103,45	nd	nd	nd	45005,31	133,02

CLAIMS

What is claimed is:

1. A combination of a cluster of differentiation factor 40 (CD40) agonist or a functional fragment thereof and an interferon (IFN) or a functional fragment thereof,
5 for use in the treatment or prevention of a Hepatitis delta virus infection.
2. An interferon-associated antigen binding protein comprising
 - (I) an agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and
 - (II) an Interferon (IFN) or a functional fragment thereof
10 for use in the treatment or prevention of a Hepatitis delta virus infection.
3. The interferon-associated antigen binding protein for the use of claim 2, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises
 - (a) a heavy chain or a fragment thereof comprising a complementarity
15 determining region (CDR) CDRH1 that is at least 90% identical to SEQ ID NO 56, a CDRH2 that is at least 90% identical to SEQ ID NO 57, and a CDRH3 that is at least 90% identical to SEQ ID NO 58; and
 - (b) a light chain or a fragment thereof comprising a CDRL1 that is at least
20 90% identical to SEQ ID NO 52, a CDRL2 that is at least 90% identical to SEQ ID NO 53, and a CDRL3 that is at least 90% identical to SEQ ID NO 54.
4. The interferon-associated antigen binding protein for the use of claim 2 or 3, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises
 - (a) a heavy chain or a fragment thereof comprising a complementarity
25 determining region (CDR) CDRH1 that is identical to SEQ ID NO 56, a

CDRH2 that is identical to SEQ ID NO 57, and a CDRH3 that is identical to SEQ ID NO 58; and

(b) a light chain or a fragment thereof comprising a CDRL1 that is identical to SEQ ID NO 52, a CDRL2 that is identical to SEQ ID NO 53, and a CDRL3 that is identical to SEQ ID NO 54.

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5. The interferon-associated antigen binding protein for the use of any one of claims 2 to 4, wherein the agonistic anti-CD40 antibody, or the agonistic antigen binding fragment thereof, comprises a light chain variable region V_L comprising the sequence as set forth in SEQ ID NO 51, or a sequence at least 90% identical thereto; and/or a heavy chain variable region V_H comprising the sequence as set forth in SEQ ID NO 55, or a sequence at least 90% identical thereto.

6. The interferon-associated antigen binding protein for the use of any one of claims 2 to 5, wherein the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof comprises a light chain (LC) that comprises a sequence as set forth in SEQ ID NO 3, or a sequence at least 90% identical thereto; and/or a heavy chain (HC) that comprises a sequence selected from the group consisting of SEQ ID NO 6, SEQ ID NO 9, SEQ ID NO 49 and SEQ ID NO 48, or a sequence at least 90% identical thereto.

7. The interferon-associated antigen binding protein for the use of any one of claims 2 to 6, wherein the IFN or the functional fragment thereof is selected from the group consisting of a Type I IFN, a Type II IFN and a Type III IFN, or a functional fragment thereof.

8. The interferon-associated antigen binding protein for the use of claim 7, wherein the type I IFN or the functional fragment thereof is IFN α or IFN β , or a functional fragment thereof.

9. The interferon-associated antigen binding protein for the use of any one of claims 2 to 8, wherein the IFN or the functional fragment thereof is IFN α 2a, or a functional fragment thereof, and wherein preferably the IFN α 2a comprises the sequence as set forth in SEQ ID NO 17, or a sequence at least 90% identical thereto.

10. The interferon-associated antigen binding protein for the use of any one of claims 2 to 8, wherein the IFN or the functional fragment thereof is IFN β , or a

functional fragment thereof, and wherein preferably the IFN β comprises the sequence as set forth in SEQ ID NO 14, or a sequence at least 90% identical thereto.

11. The interferon-associated antigen binding protein for the use of any one of claims 2 to 10, wherein the IFN or the functional fragment thereof is fused to a light chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, preferably to the C-terminus.

12. The interferon-associated antigen binding protein for the use of any one of claims 2 to 10, wherein the IFN or the functional fragment thereof is fused to a heavy chain of the agonistic anti-CD40 antibody or the agonistic antigen binding fragment thereof, preferably to the C-terminus.

13. The interferon-associated antigen binding protein for the use of any one of claims 2 to 12, wherein the agonistic anti-CD40 antibody or an agonistic antigen binding fragment thereof, and the IFN or the functional fragment thereof, are fused to each other via a linker, and wherein preferably the linker comprises a sequence as set forth in SEQ ID NO 20, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 25 or SEQ ID NO 26.

14. The interferon-associated antigen binding protein for the use of any one of claims 2 to 13, wherein the interferon-associated antigen binding protein is an interferon-fused agonistic anti-CD40 antibody or an interferon-fused agonistic antigen binding fragment thereof comprising one of the sequence combinations disclosed in Table 9, in particular Table 9A or Table 9B, more particularly Table 9A.

15. The interferon-associated antigen binding protein for the use of any one of claims 2 to 14, wherein the use comprises administering the interferon-associated antigen binding protein to a subject in need thereof by means of genetic delivery with RNA or DNA sequences encoding the interferon-associated antigen binding protein, or a vector or vector system encoding the interferon-associated antigen binding protein.

16. The interferon-associated antigen binding protein for the use of any one of claims 2 to 15, wherein the interferon-associated antigen binding protein is comprised in a pharmaceutical composition.

17. The interferon-associated antigen binding protein for the use of any one of claims 2 to 16, wherein the Hepatitis delta virus infection is (i) a HDV/HBV coinfection, or (ii) a HDV/HBV superinfection.

Fig.1

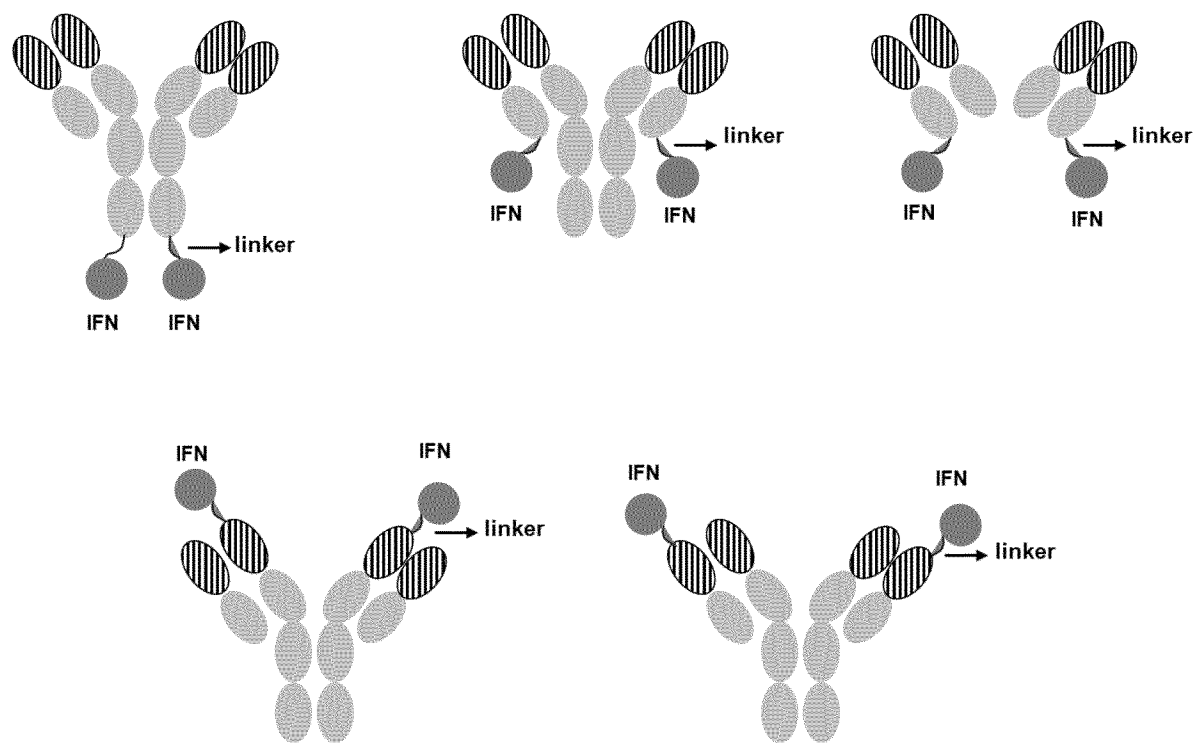
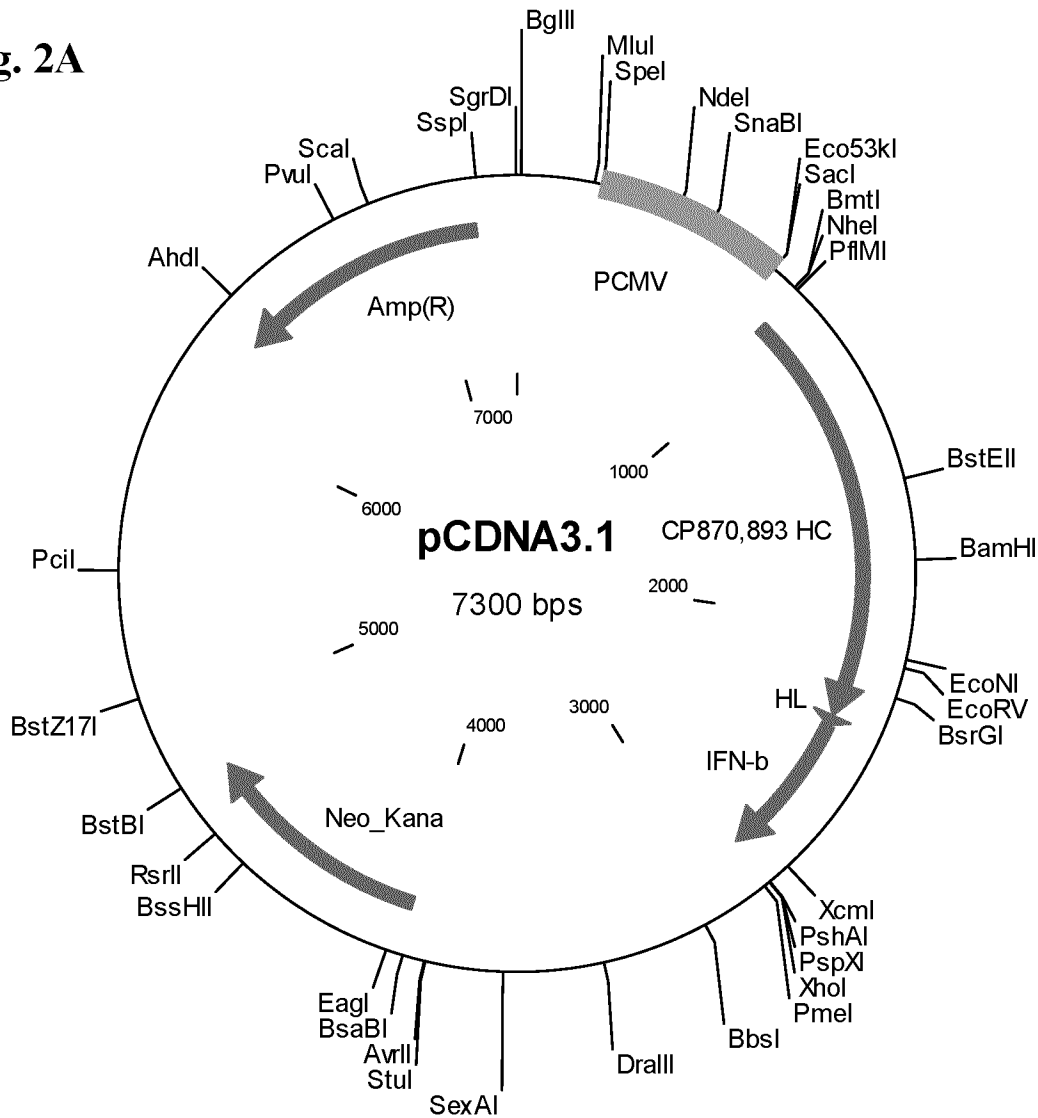


Fig. 2A

**Nucleic acid sequence encoding SEQ ID NO 32**

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Fig.2B

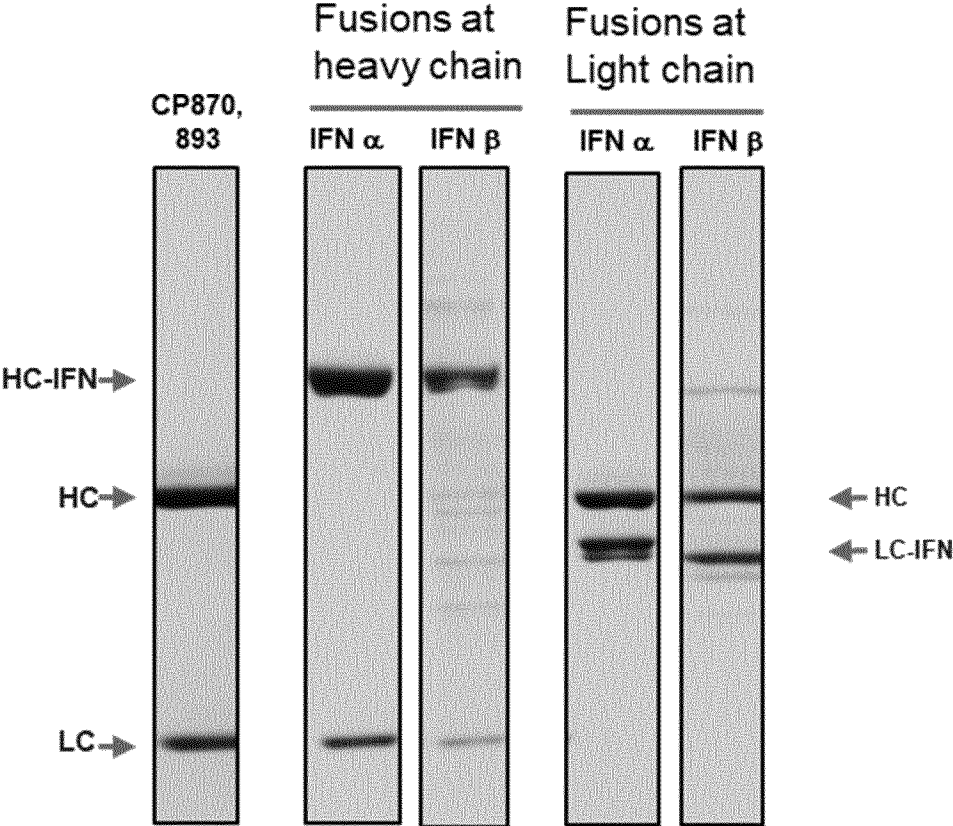


Fig. 3A

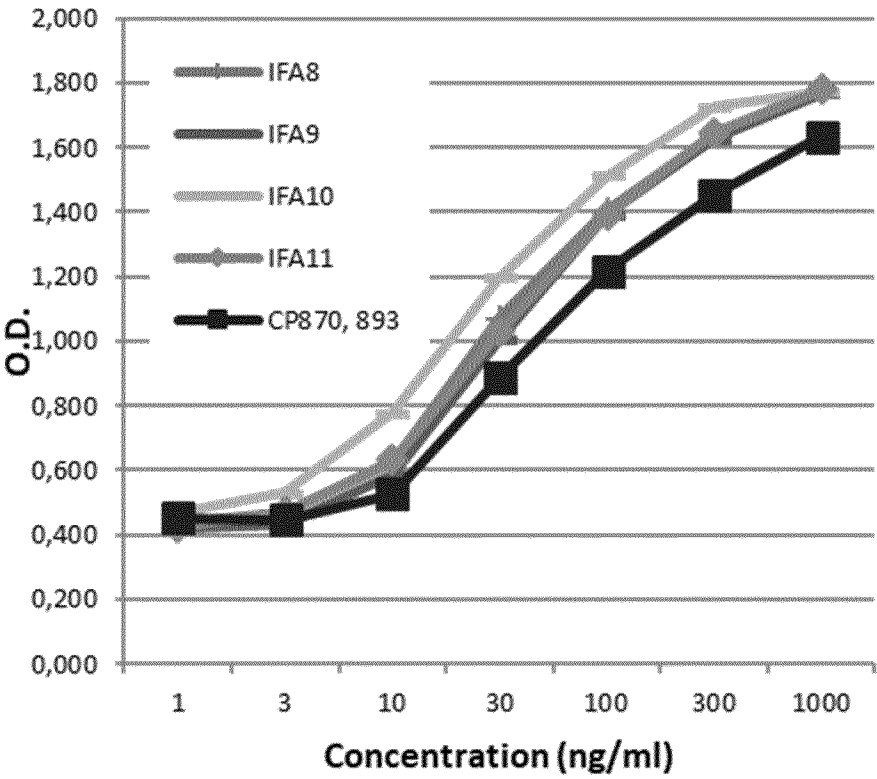


Fig. 3B

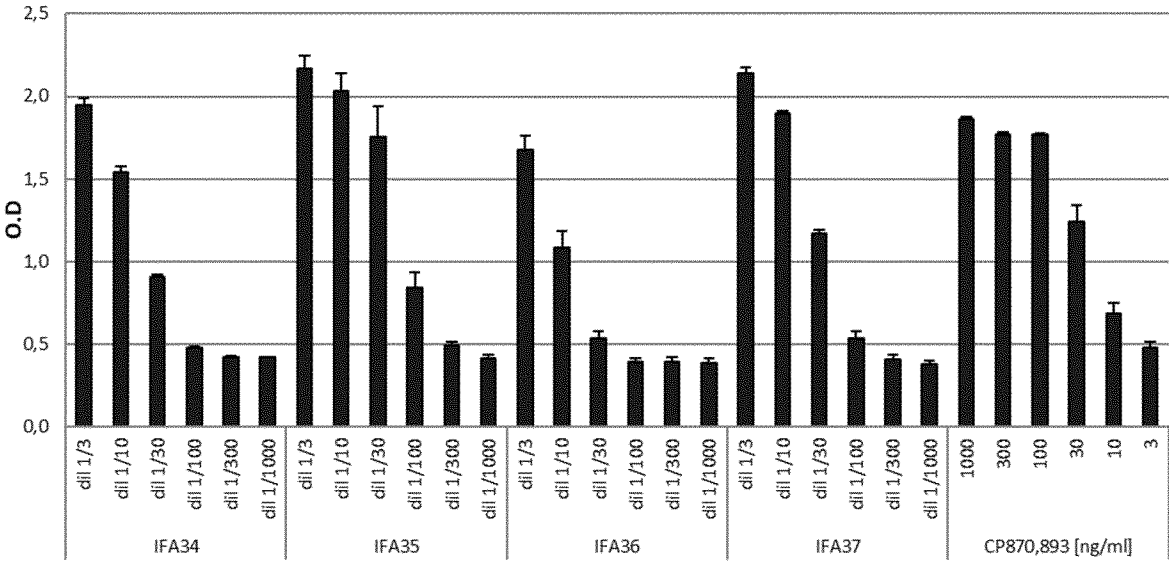


Fig. 3C

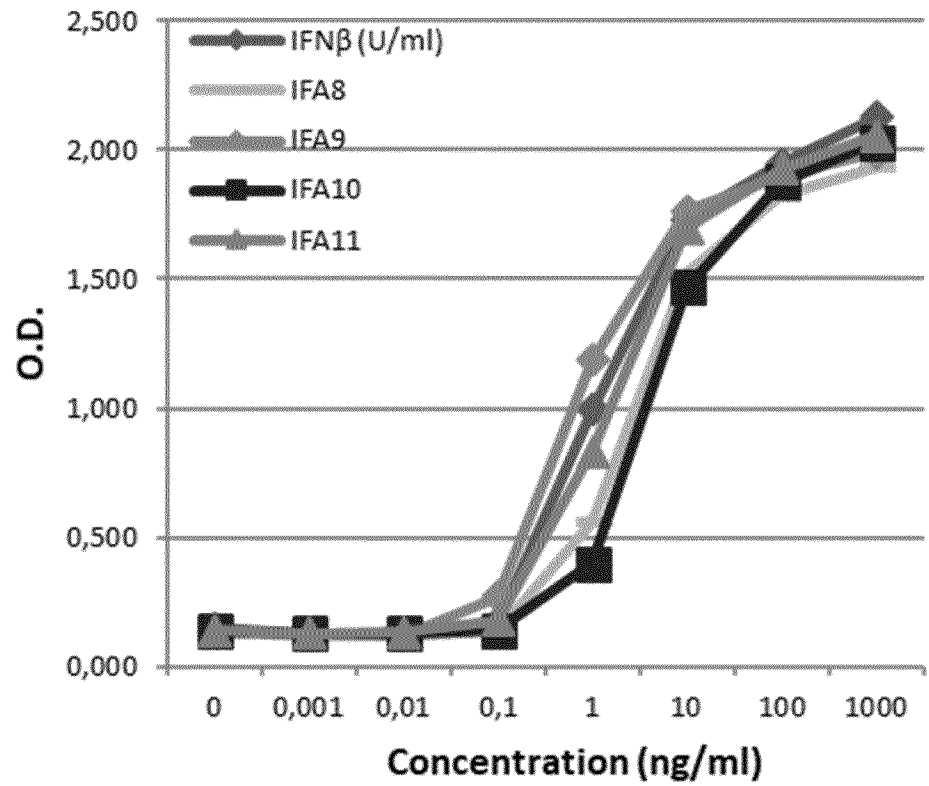


Fig. 3D

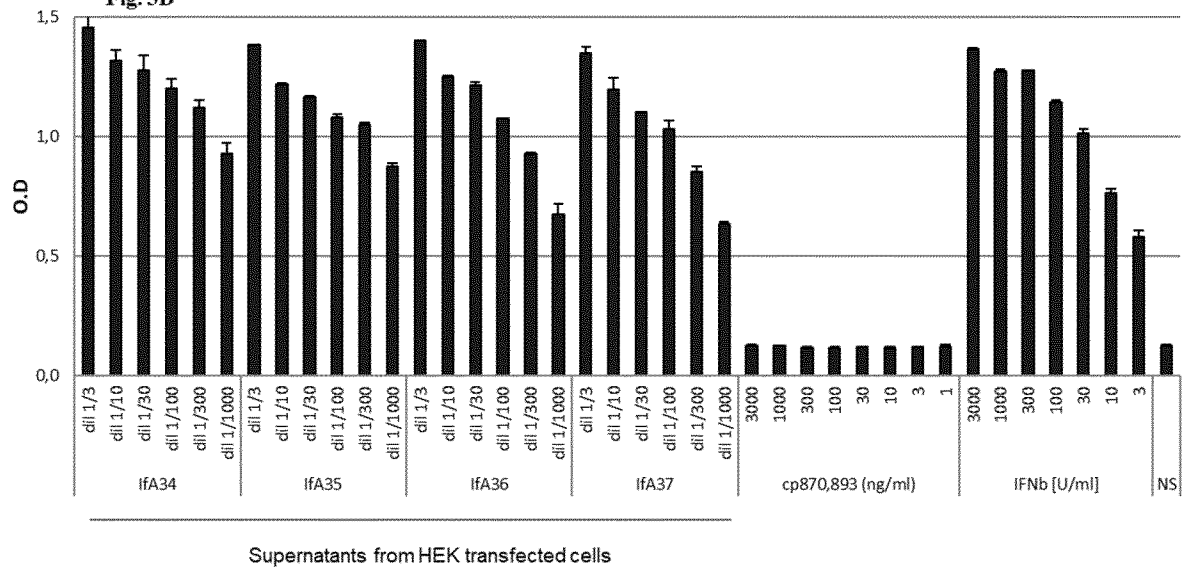


Fig. 4A

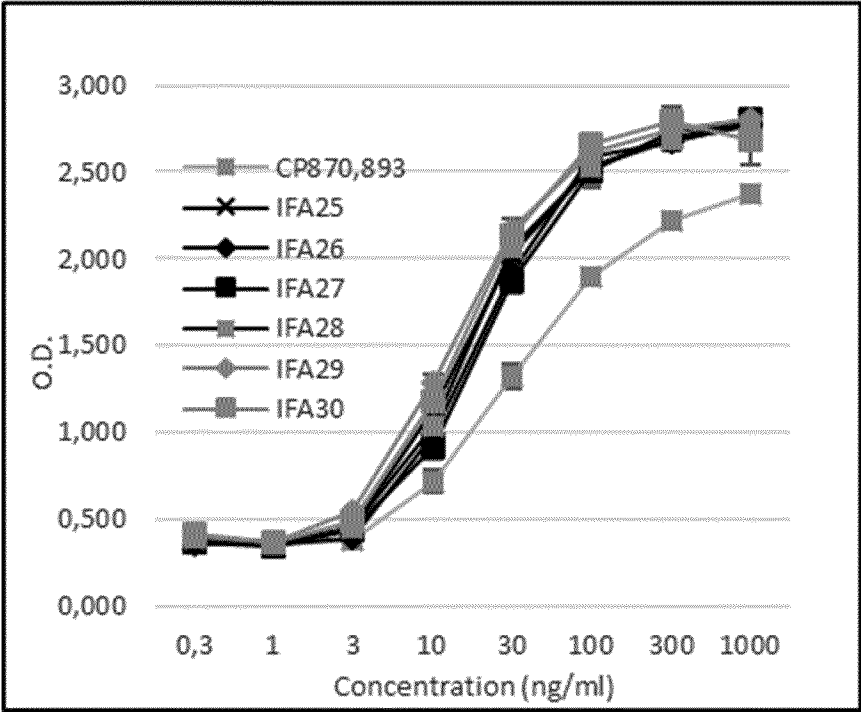


Fig. 4B

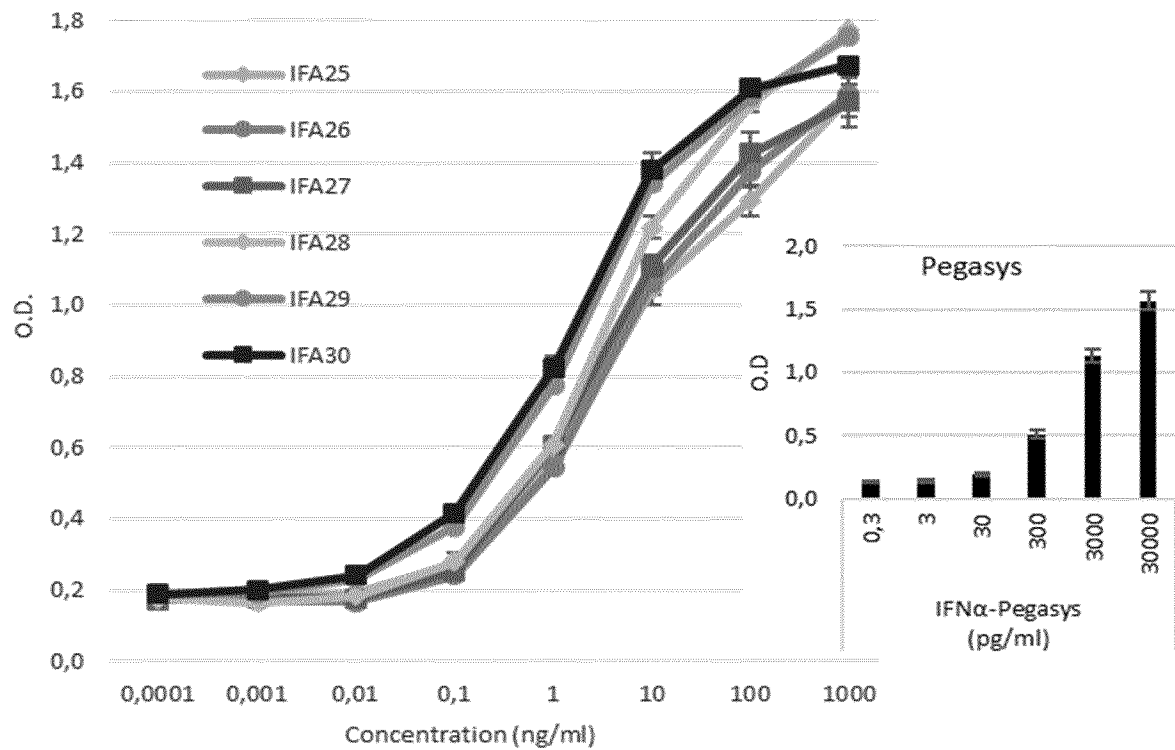


Fig. 4C

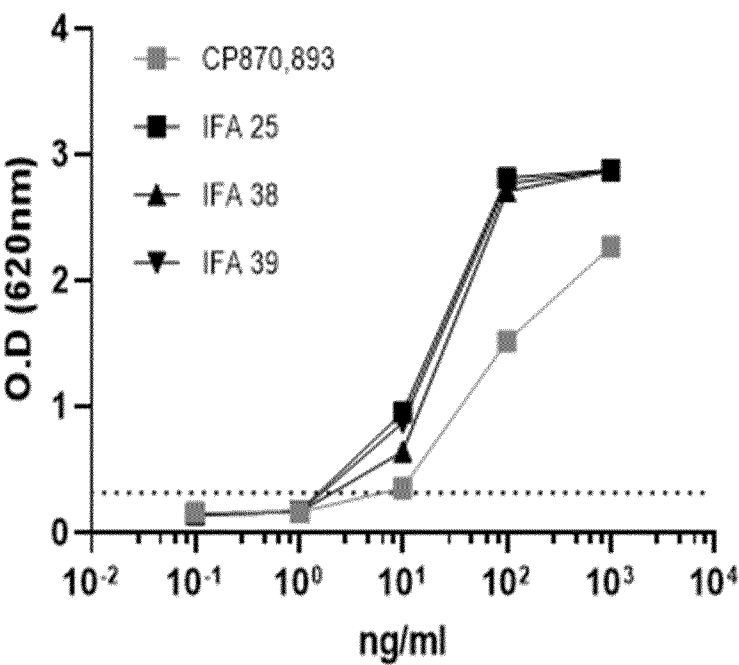


Fig. 4D

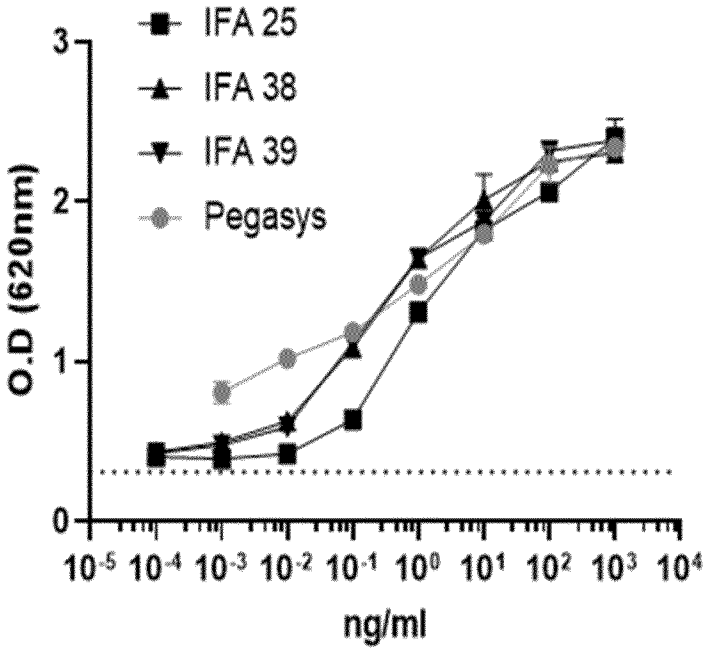


Fig. 5A

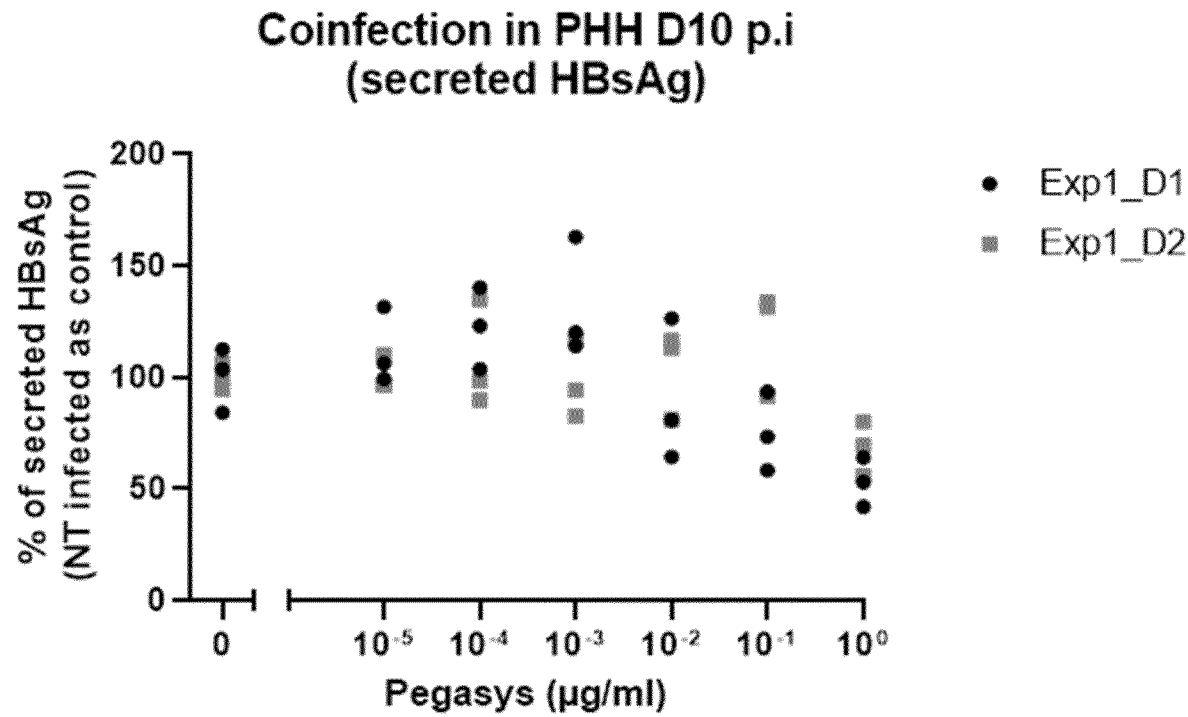


Fig. 5B

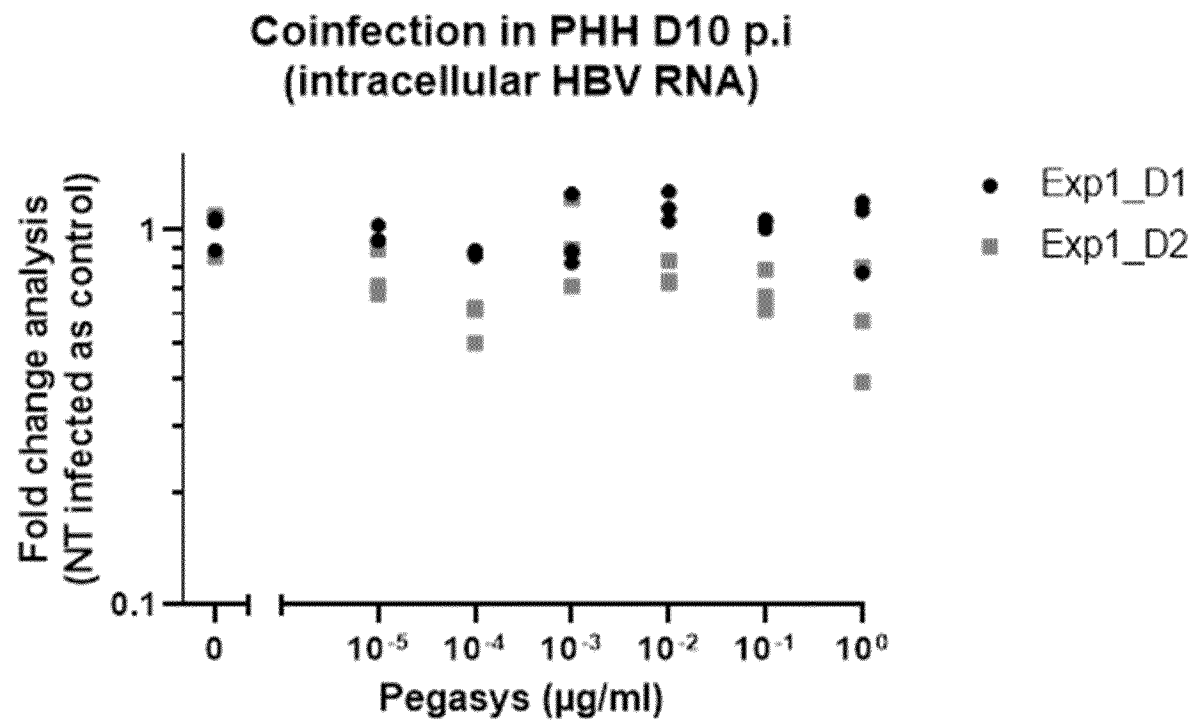


Fig. 5C

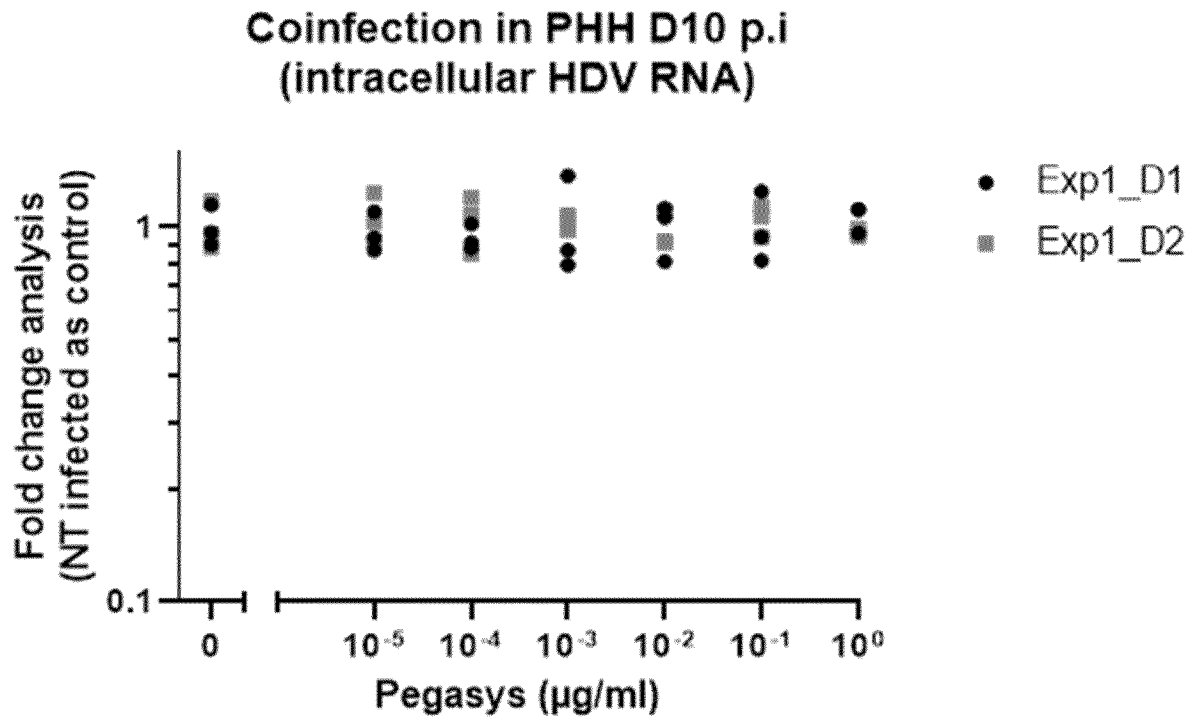


Fig. 5D

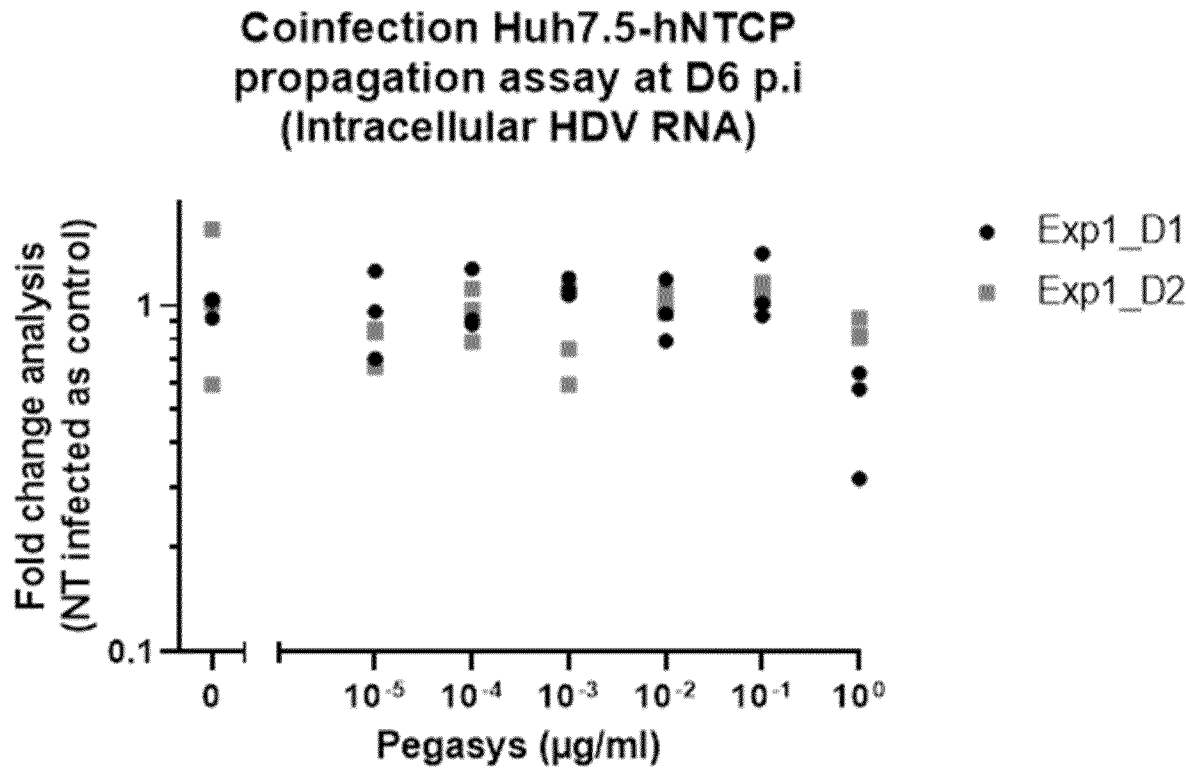


Fig. 5E

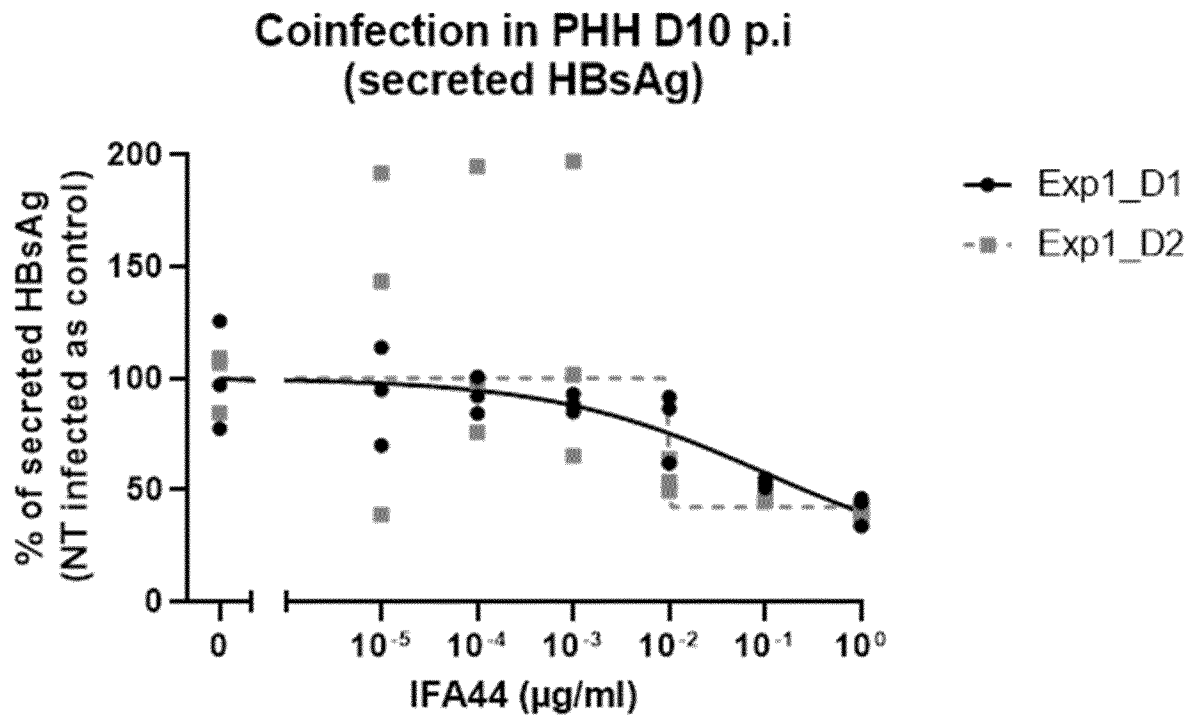


Fig. 5F

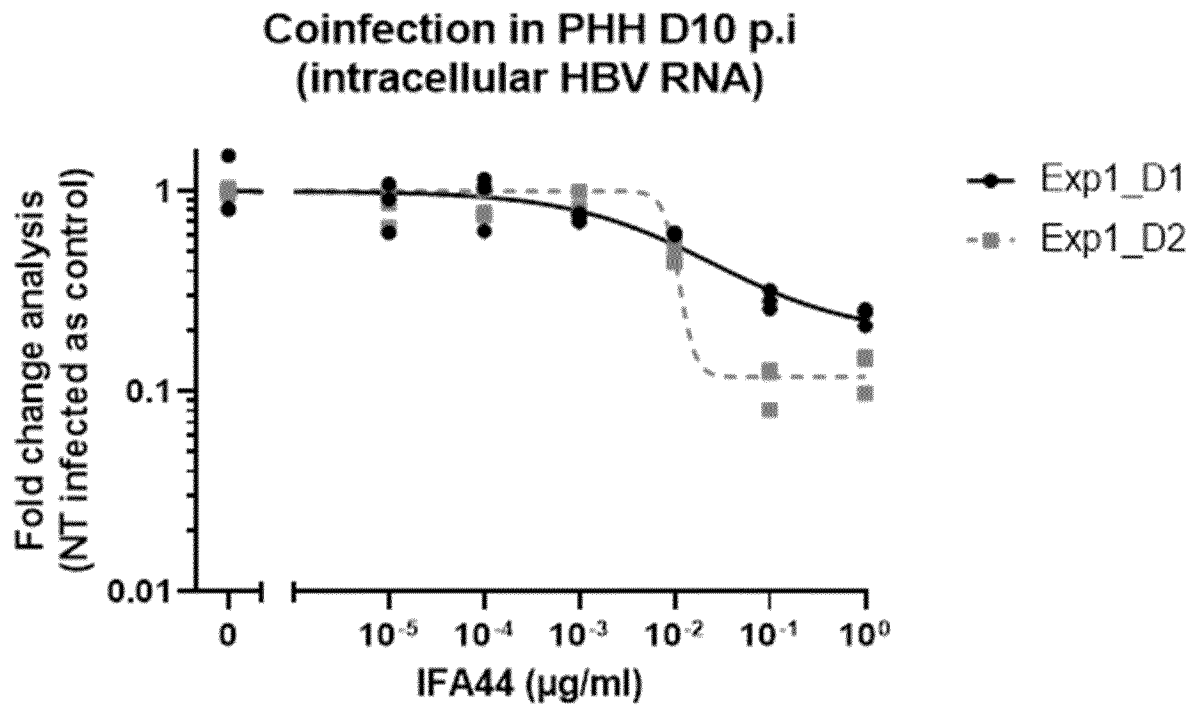


Fig. 5G

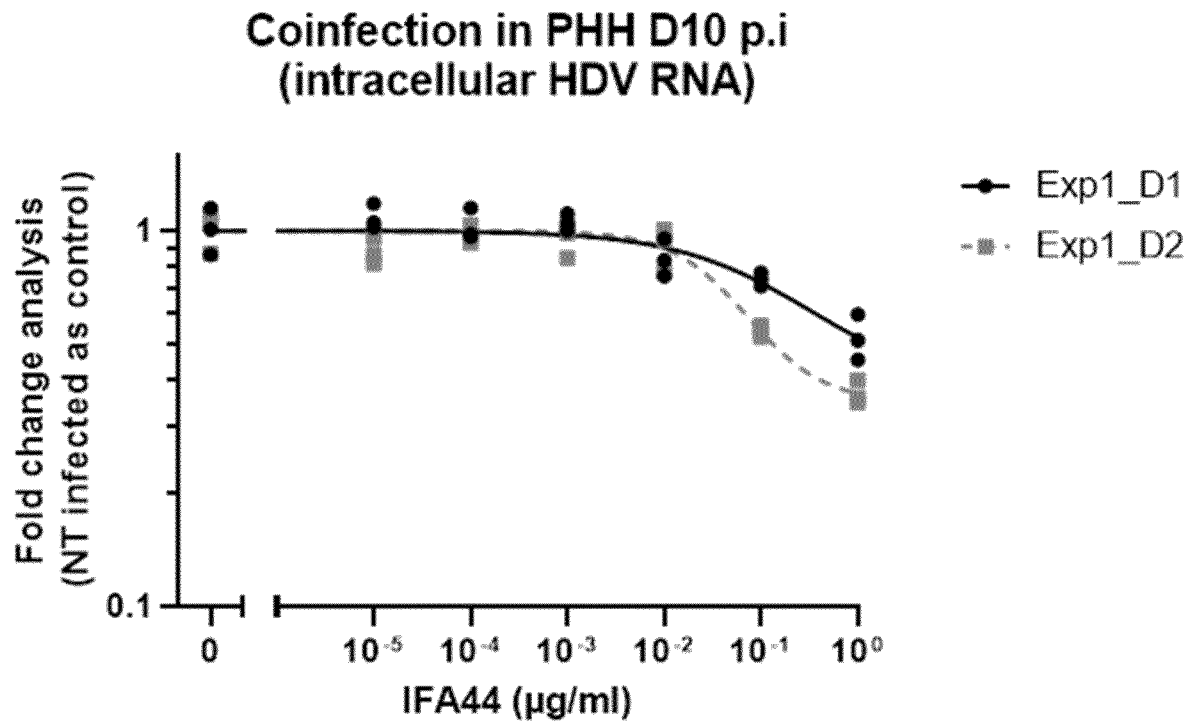


Fig. 5H

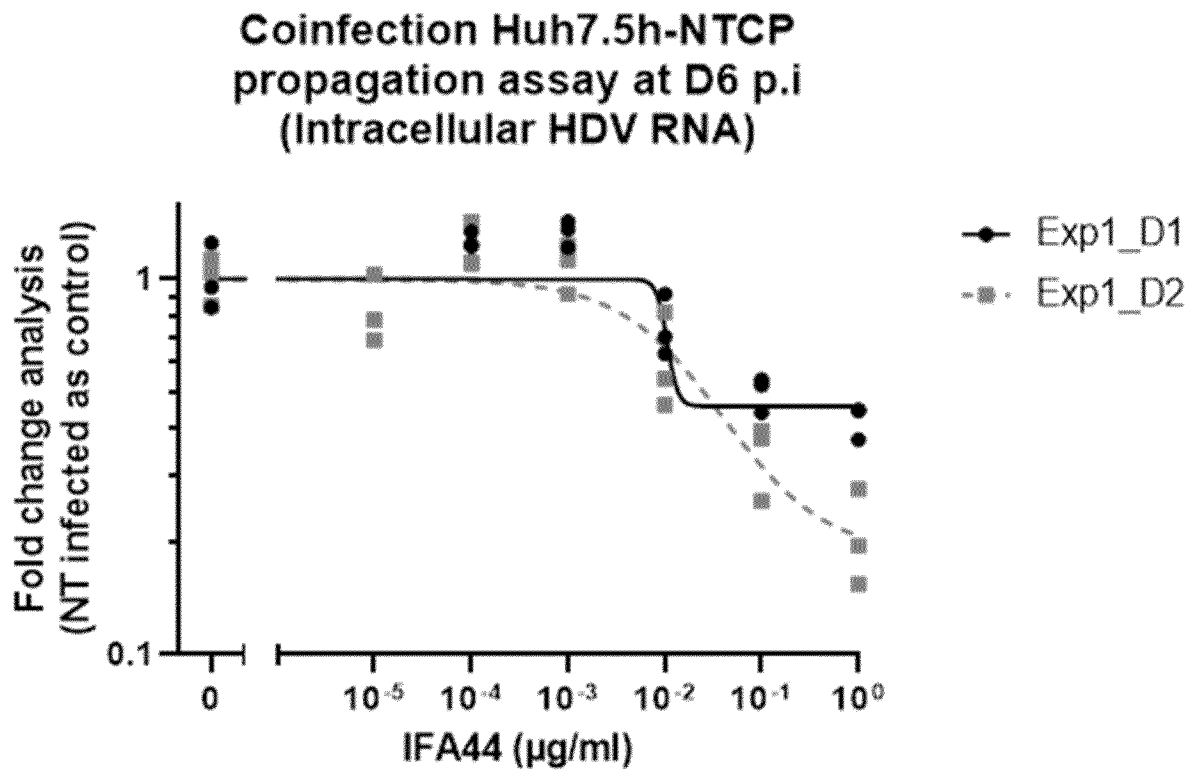


Fig. 5I

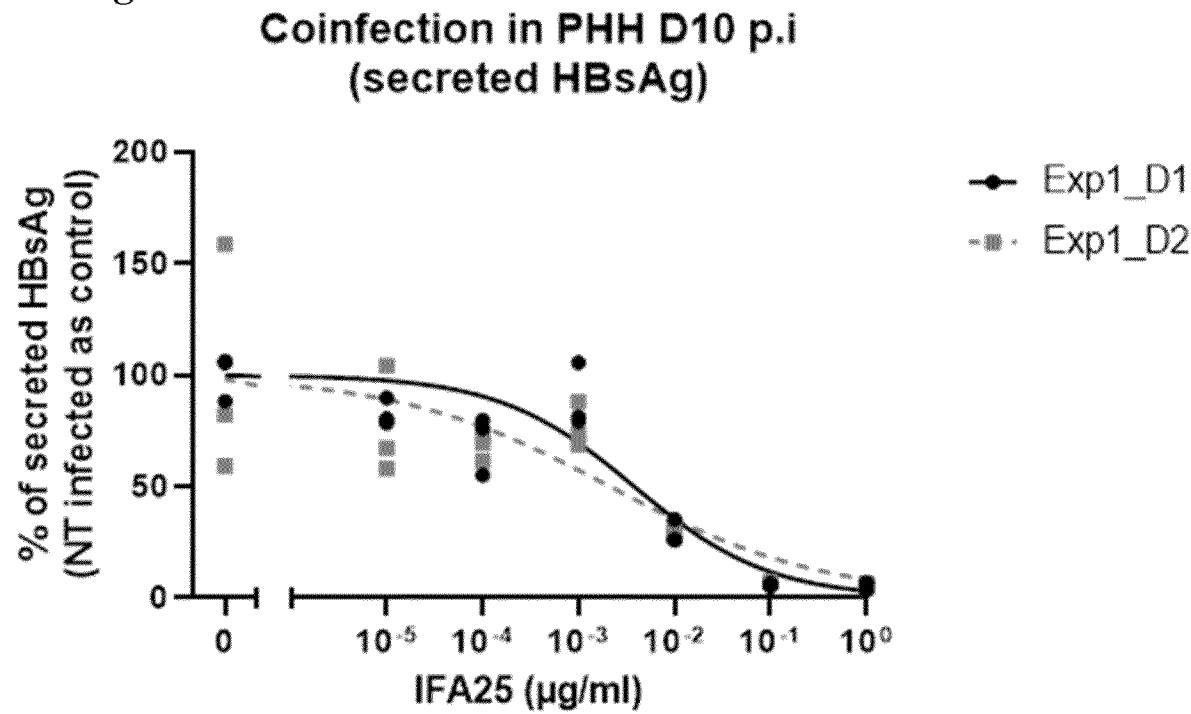


Fig. 5J

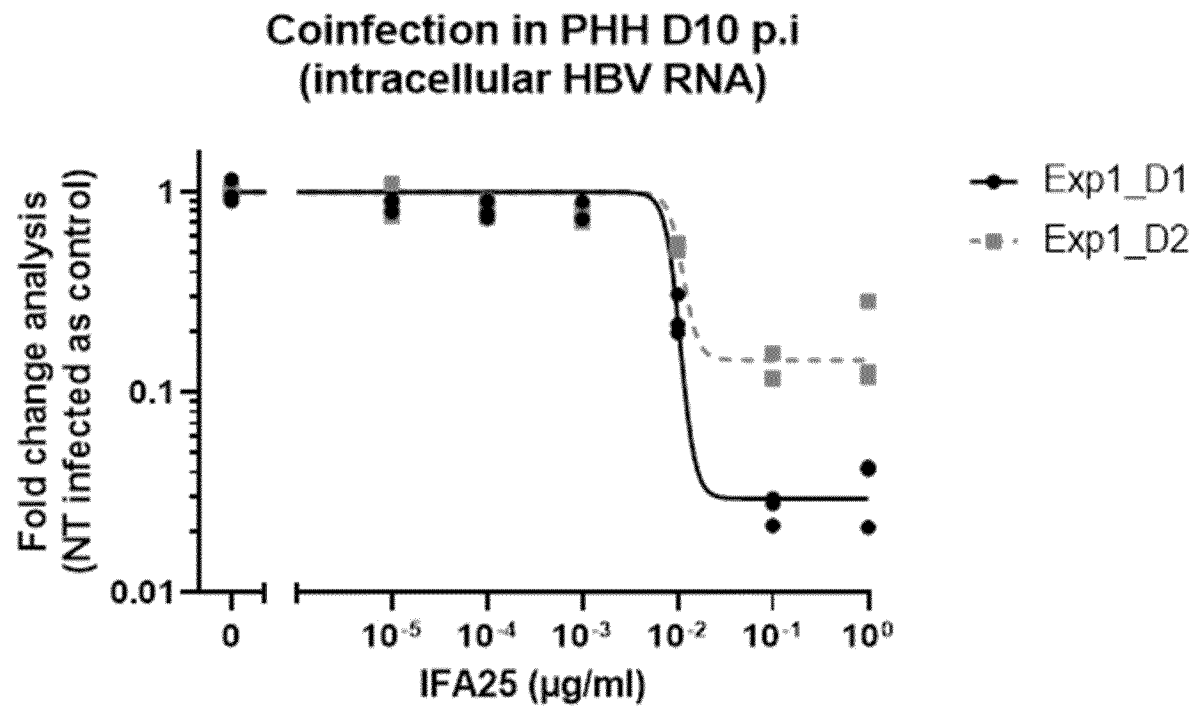


Fig. 5K

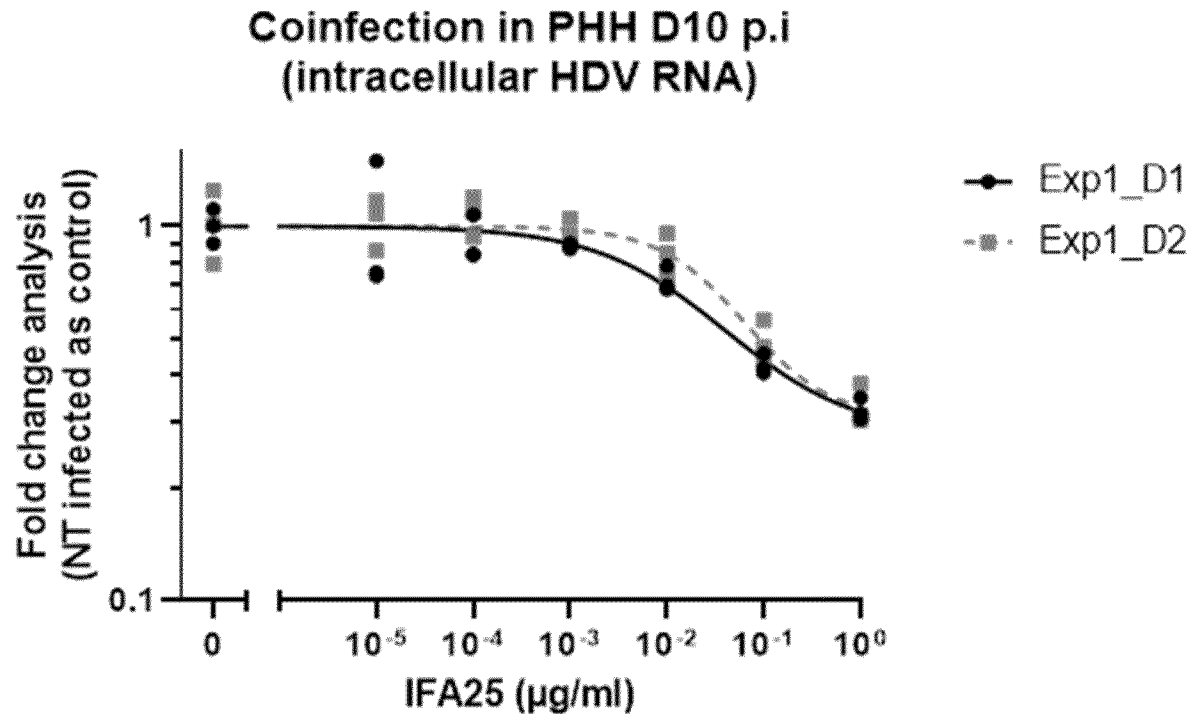


Fig. 5L

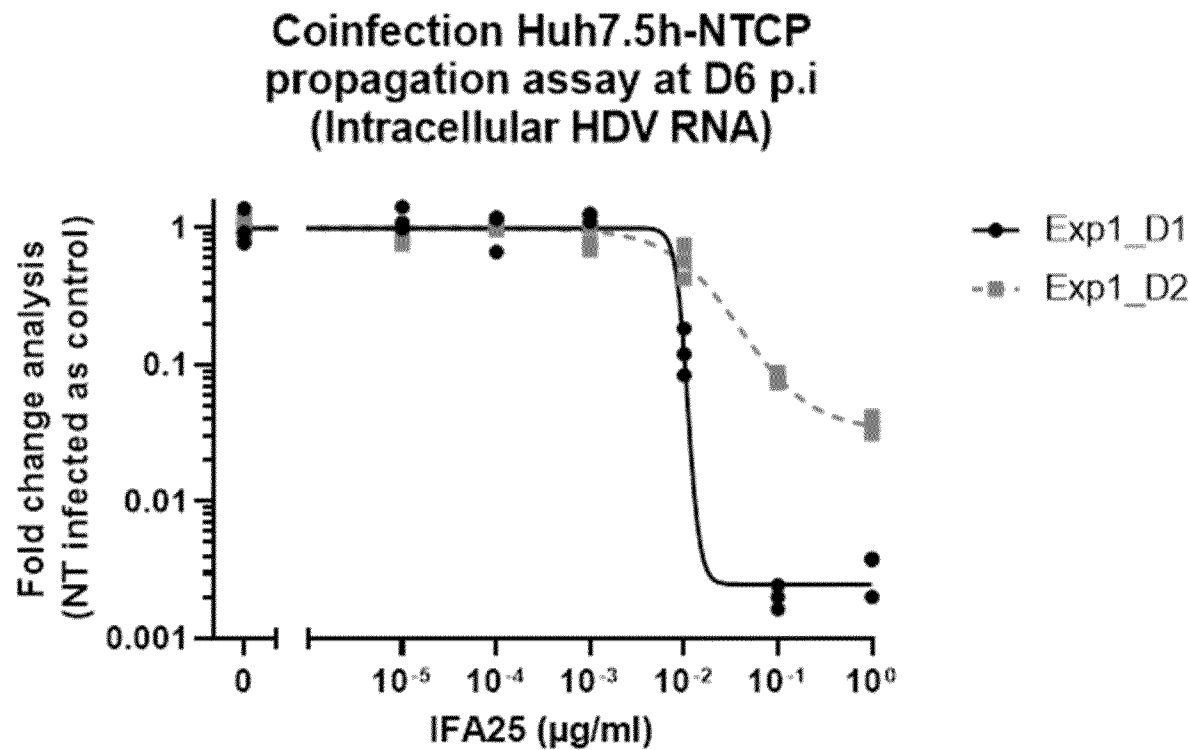


Fig. 5M

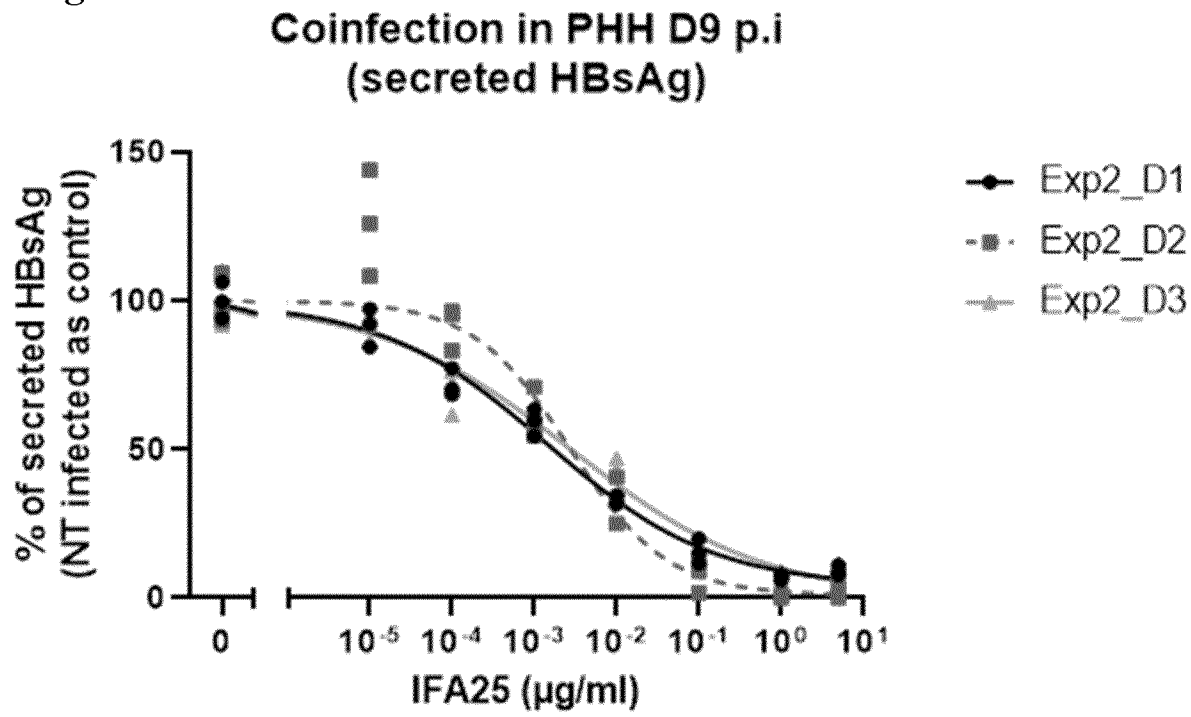


Fig. 5N

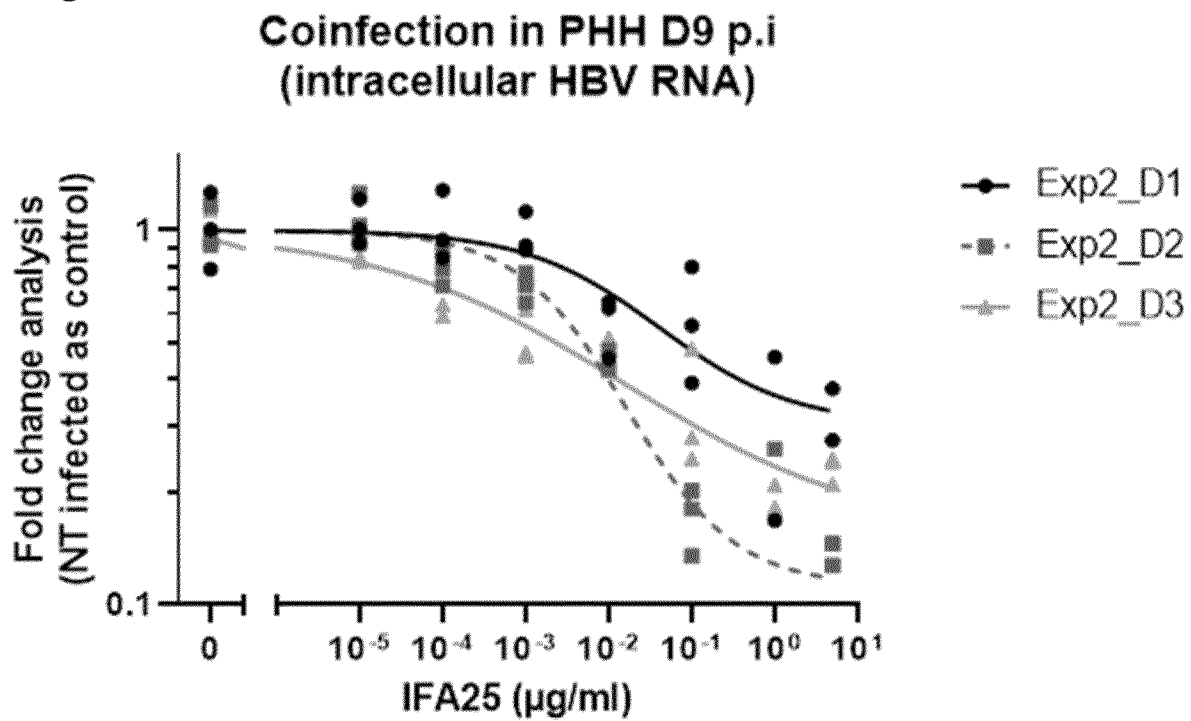


Fig. 5O

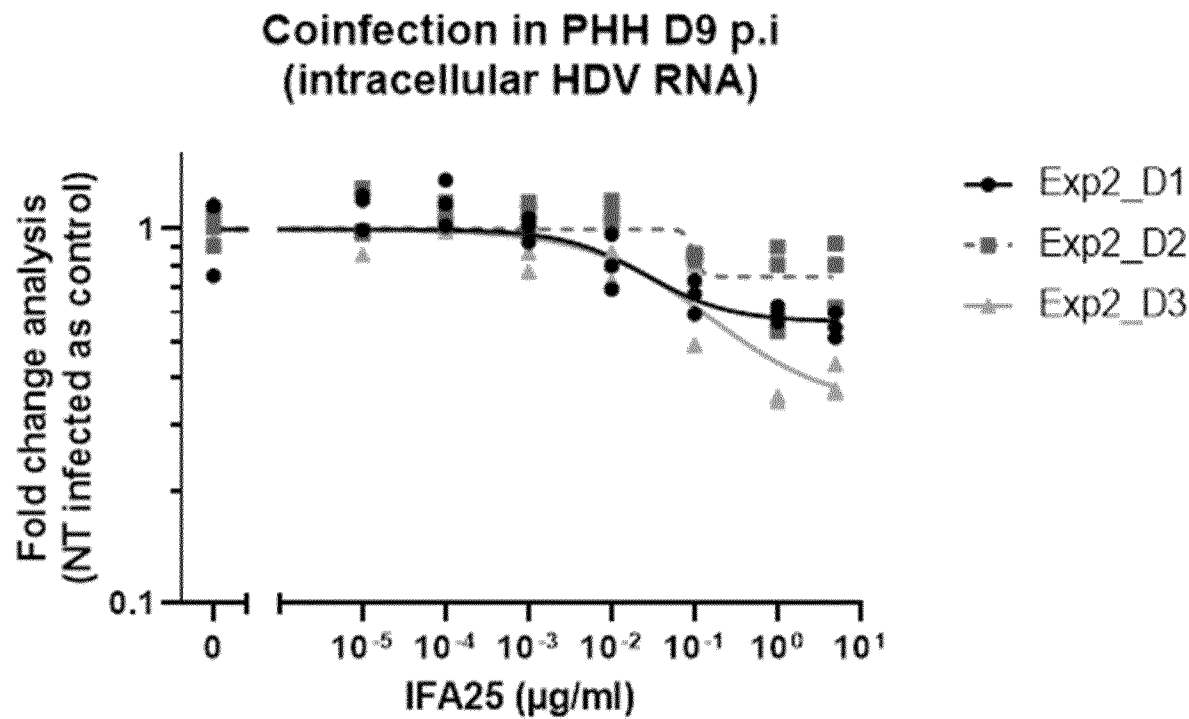


Fig. 5P

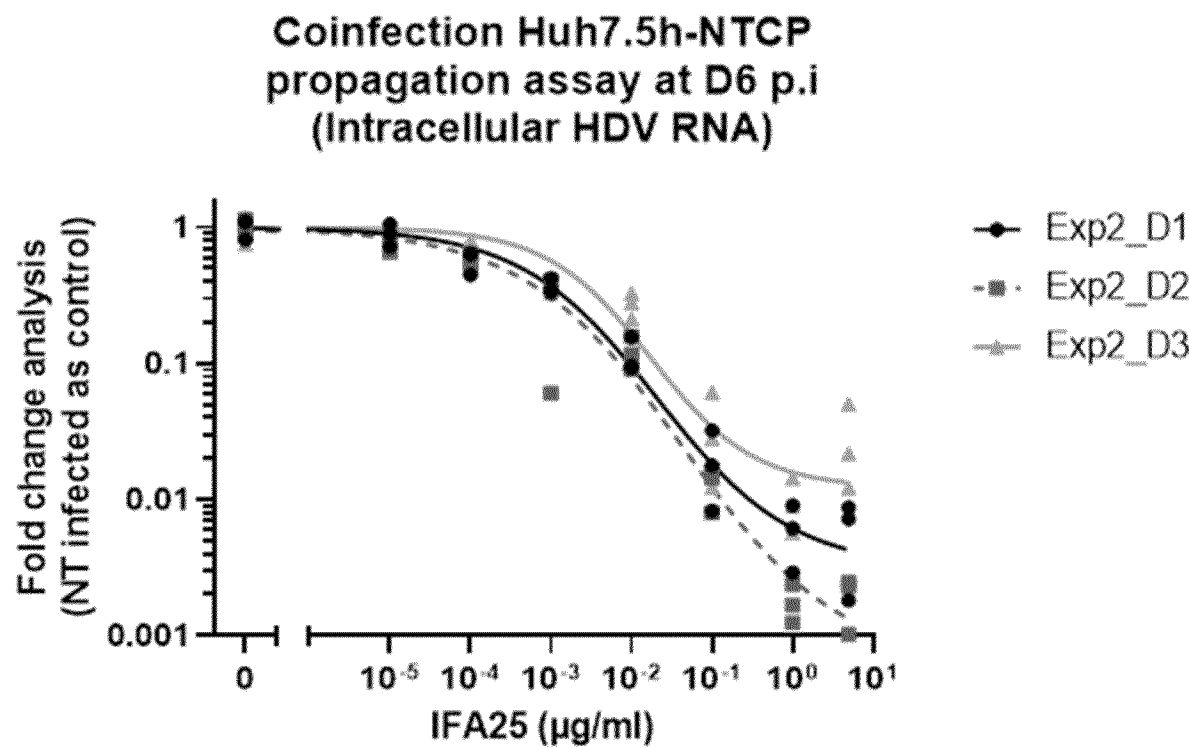


Fig. 5Q

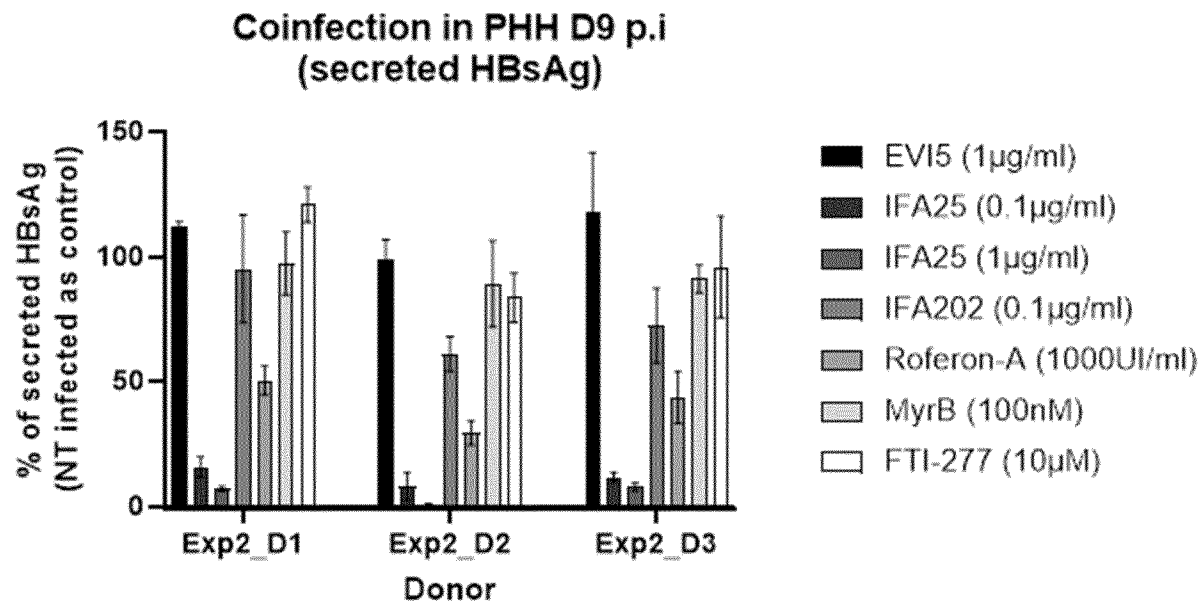


Fig. 5R

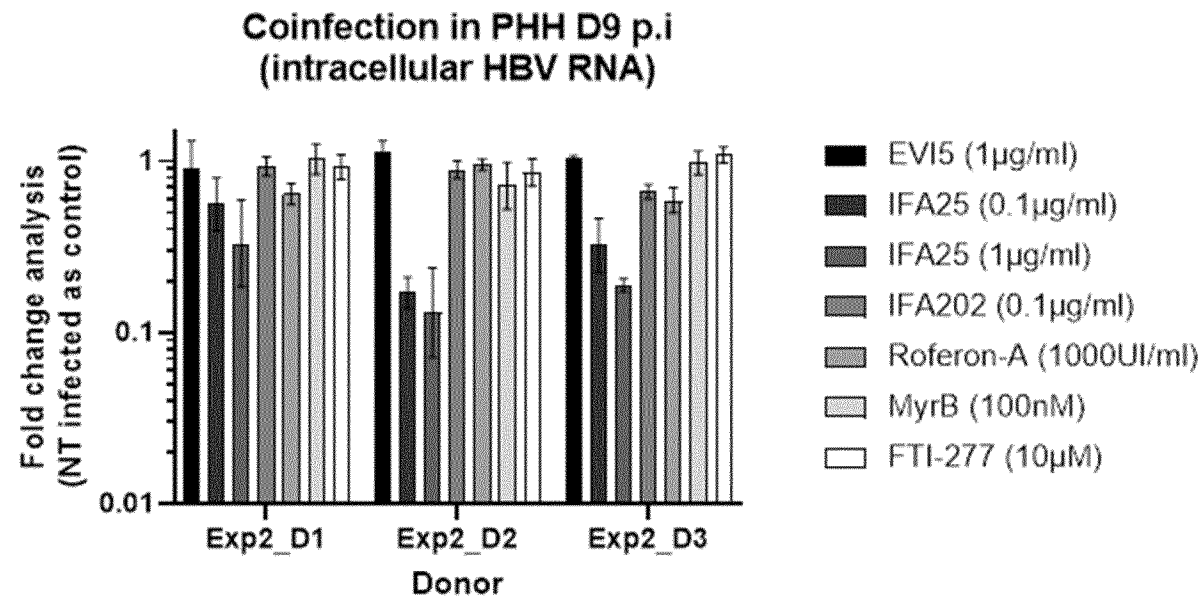


Fig. 5S

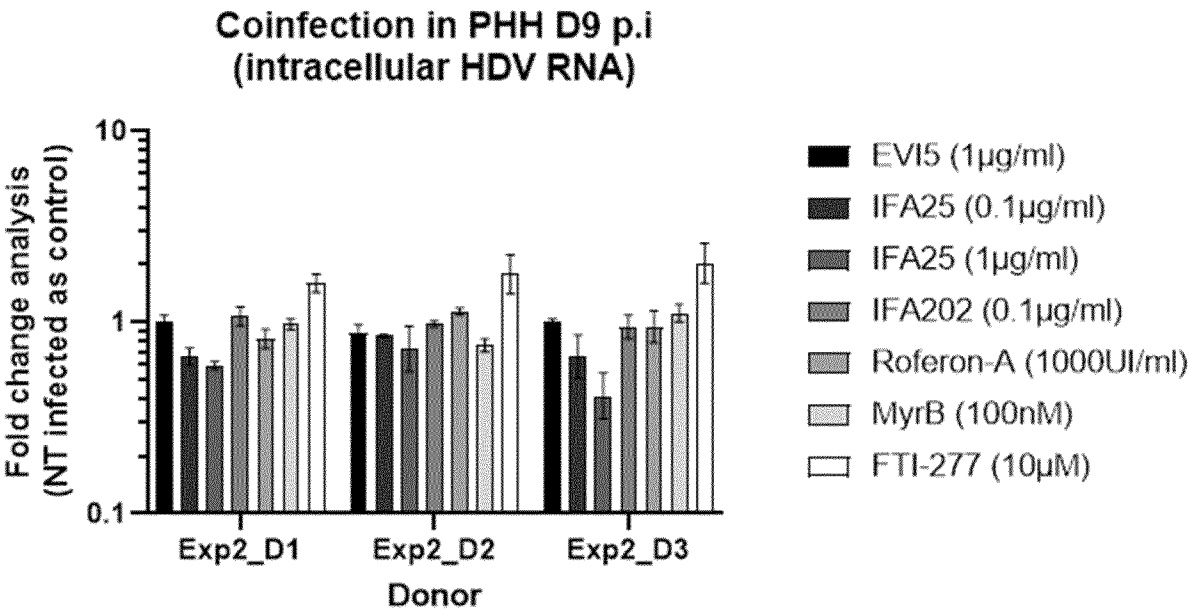


Fig. 5T

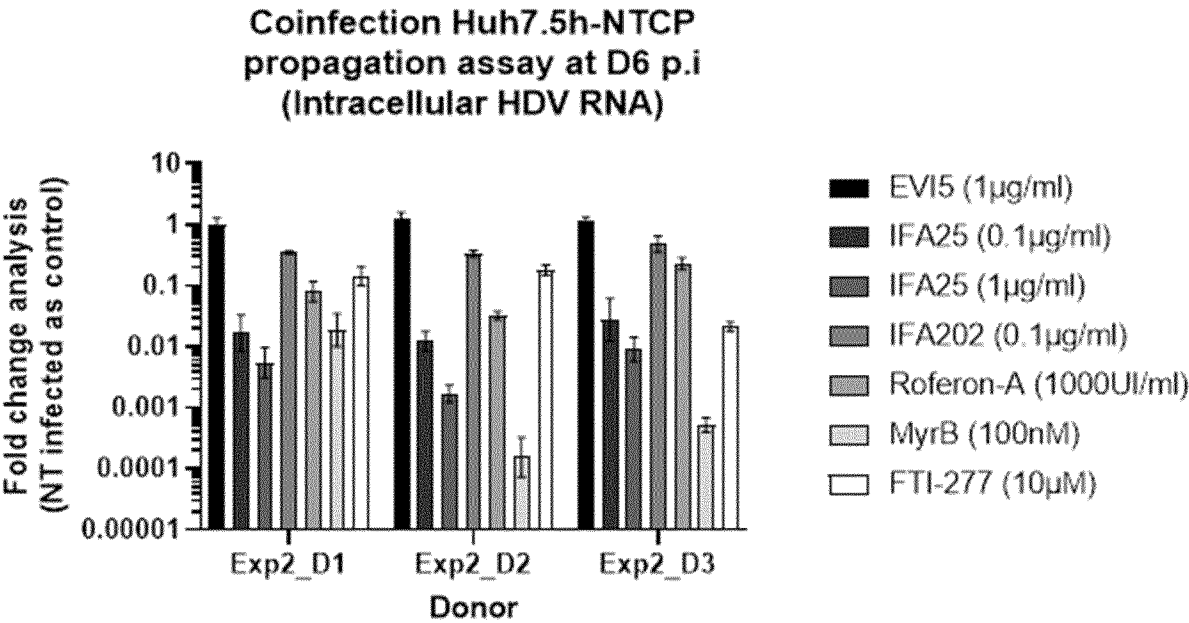


Fig. 6A

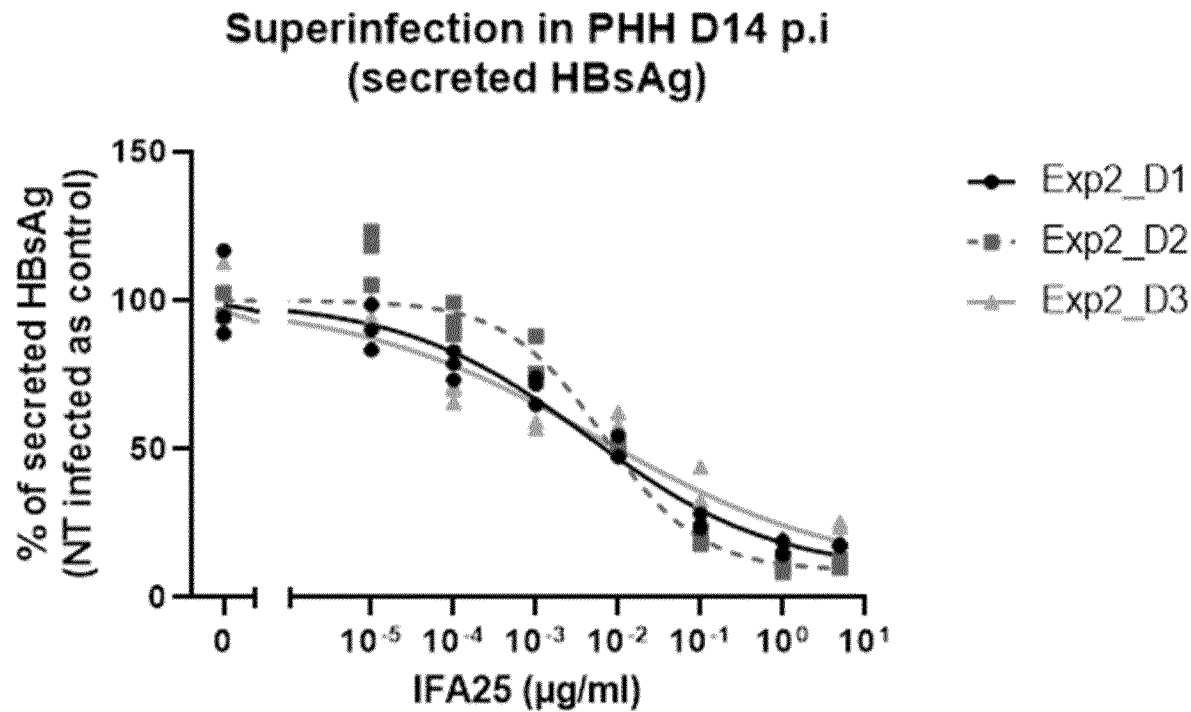


Fig. 6B

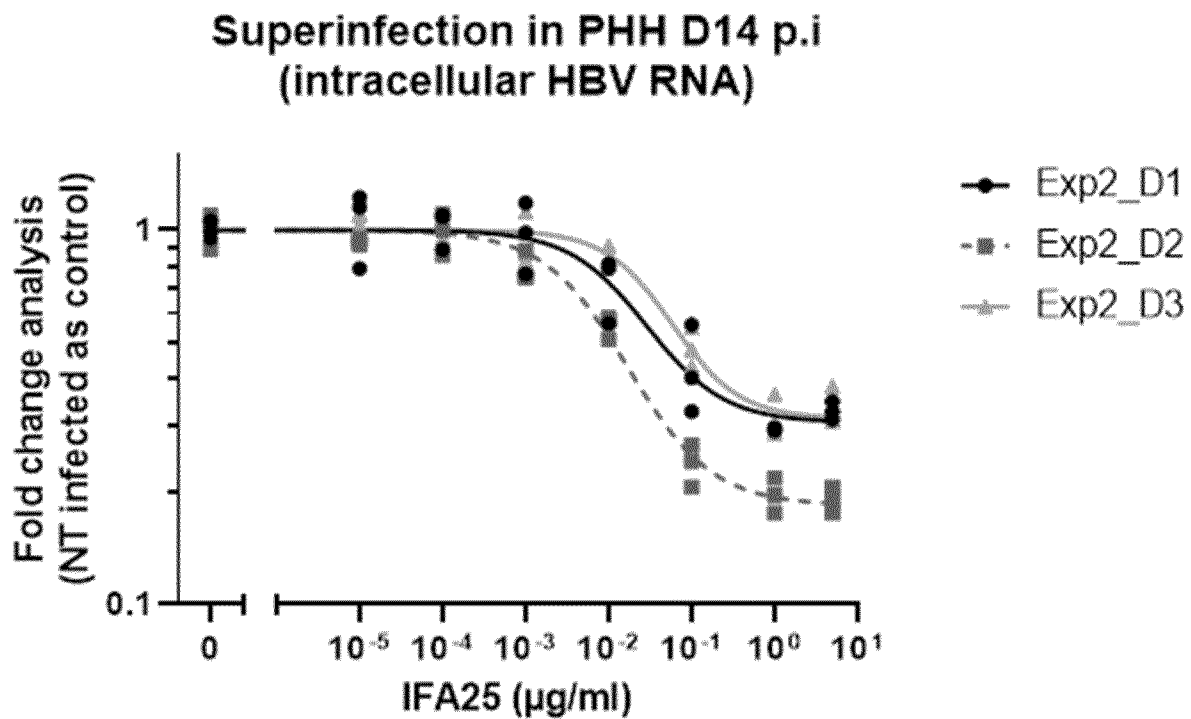


Fig. 6C

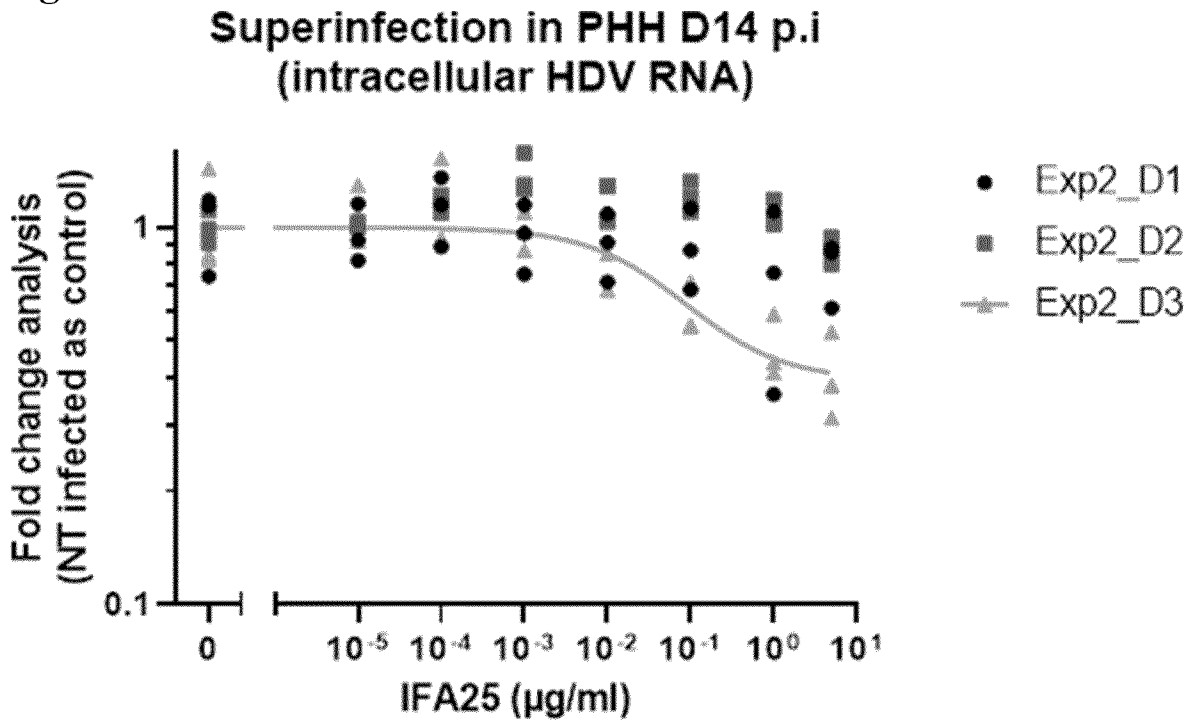


Fig. 6D

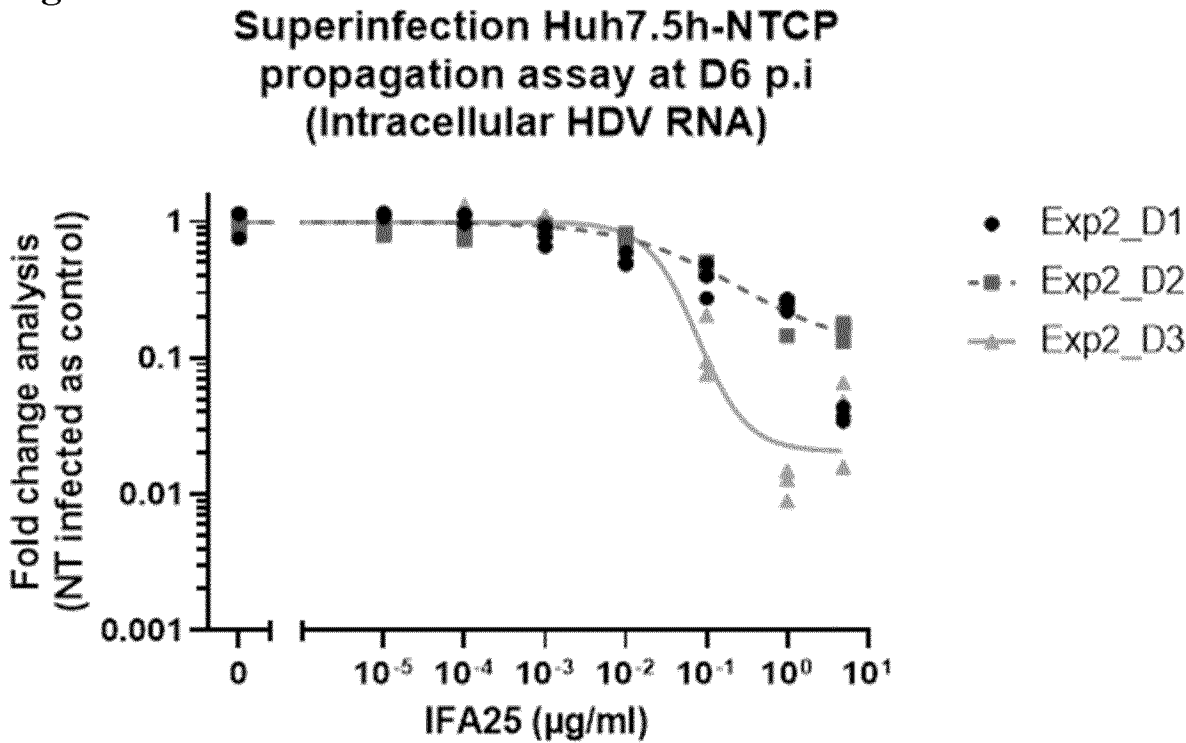


Fig. 6E

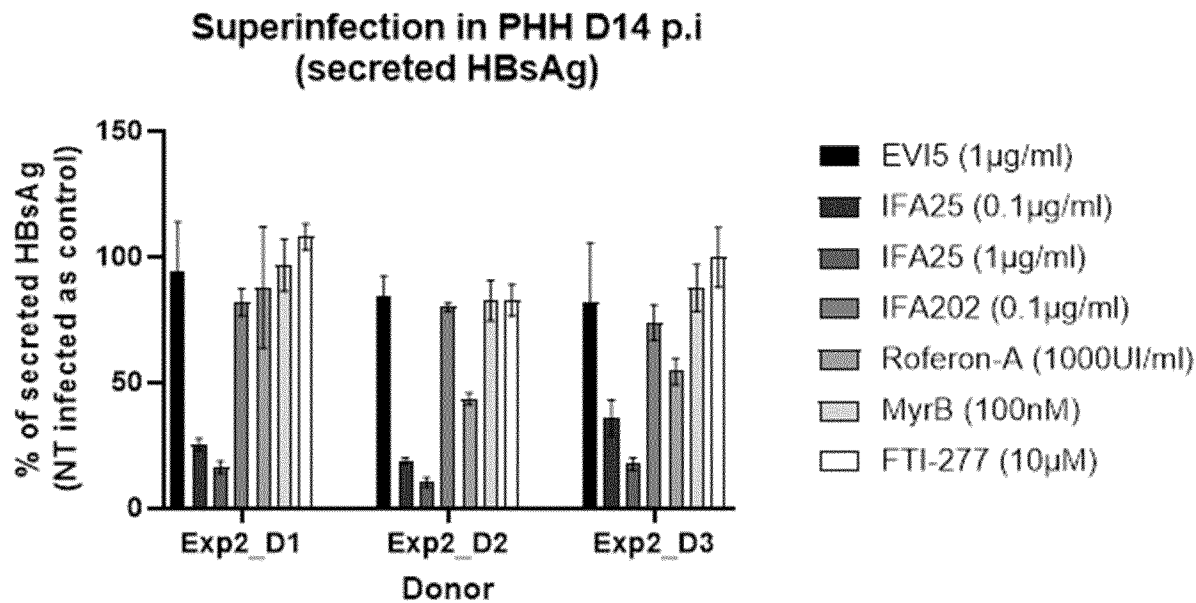


Fig. 6F

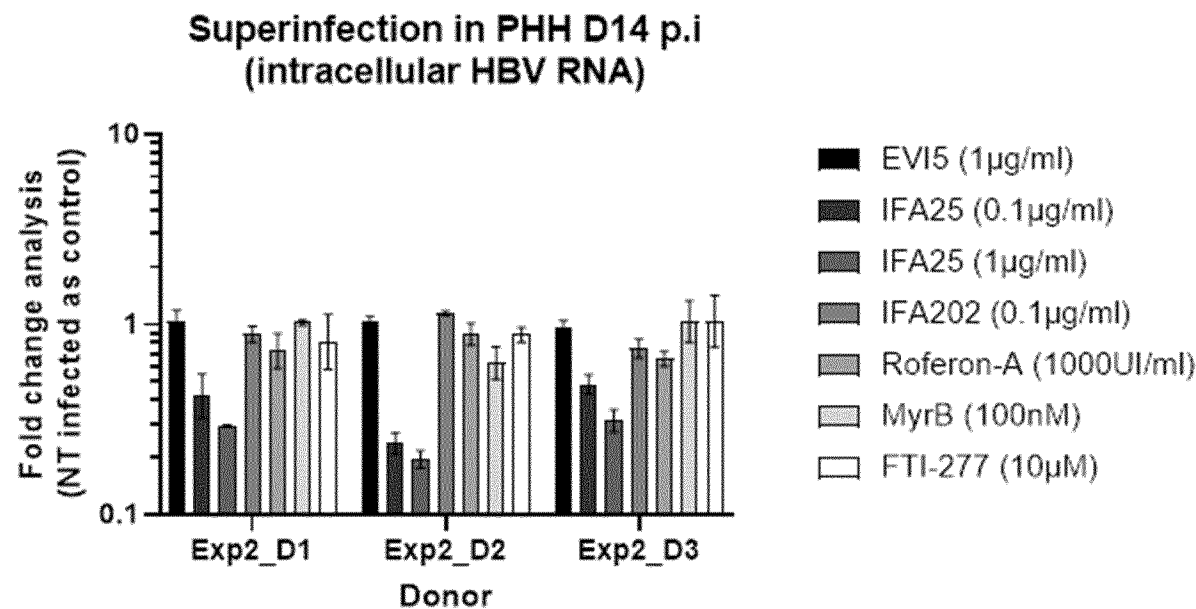


Fig. 6G

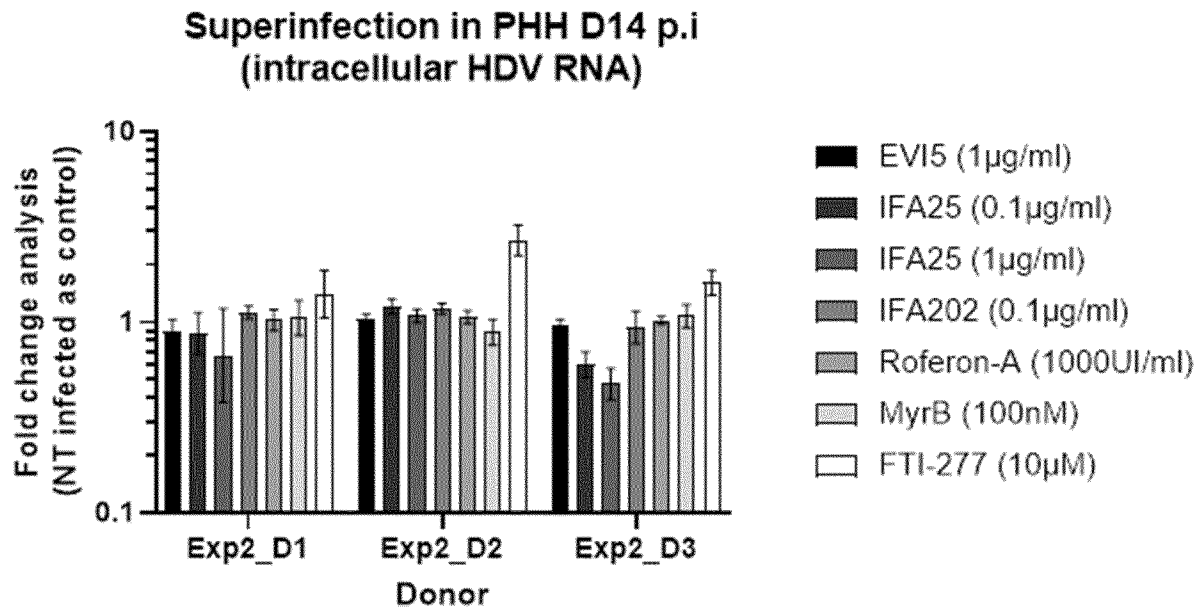


Fig. 6H

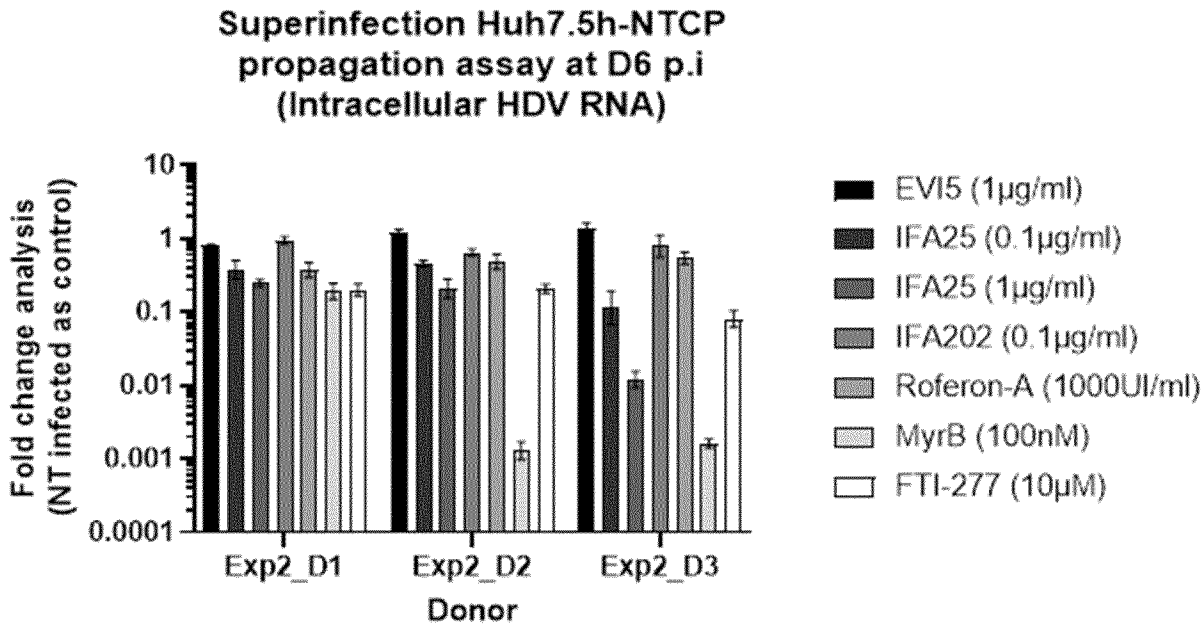
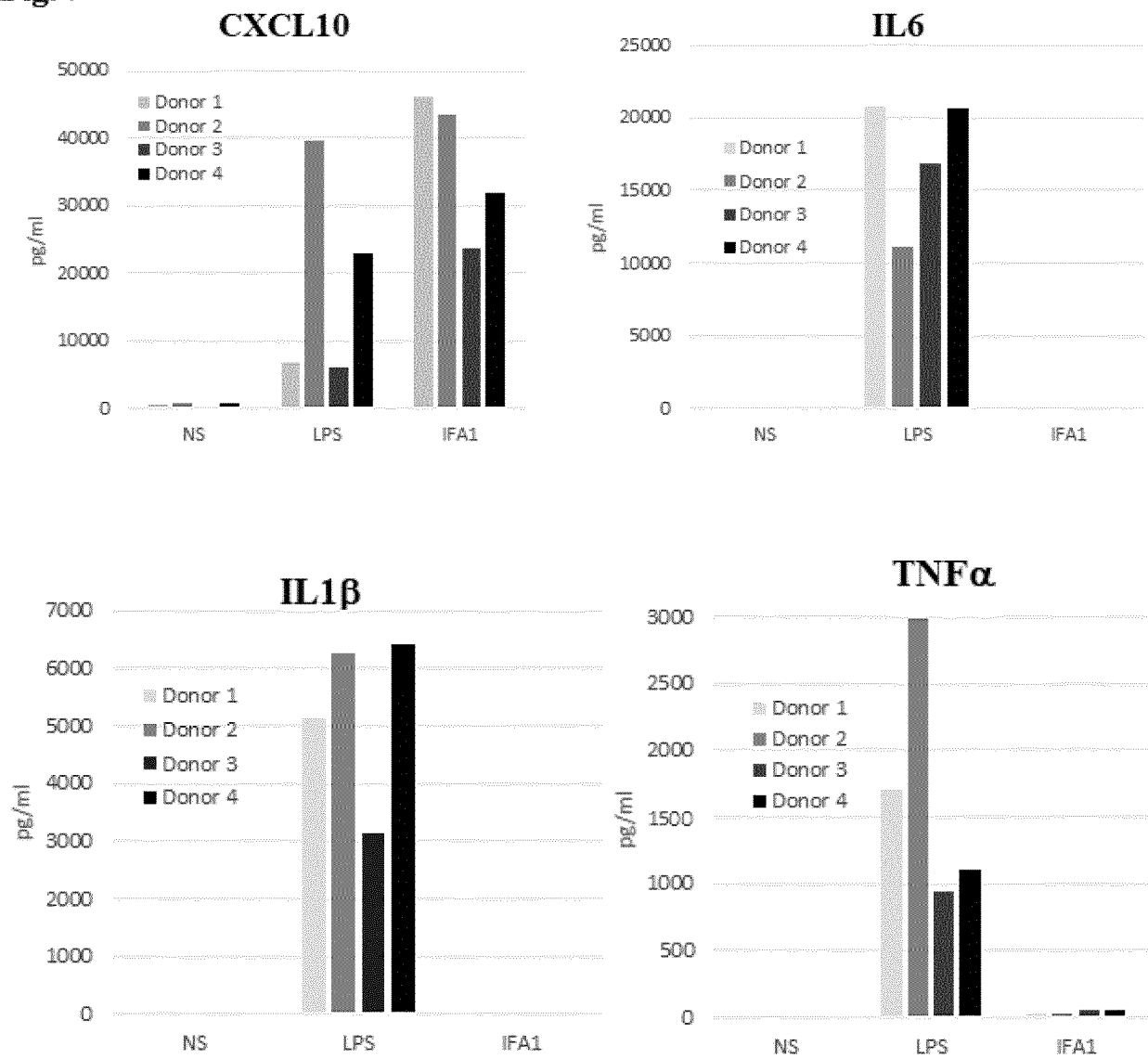


Fig. 7

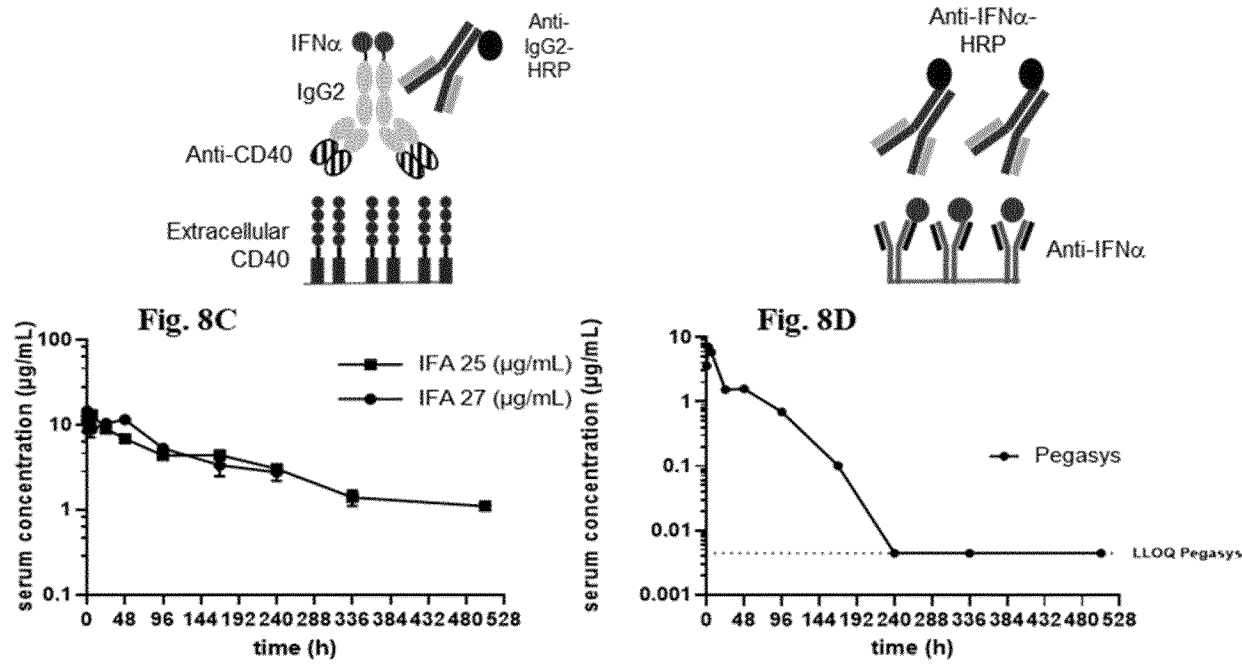
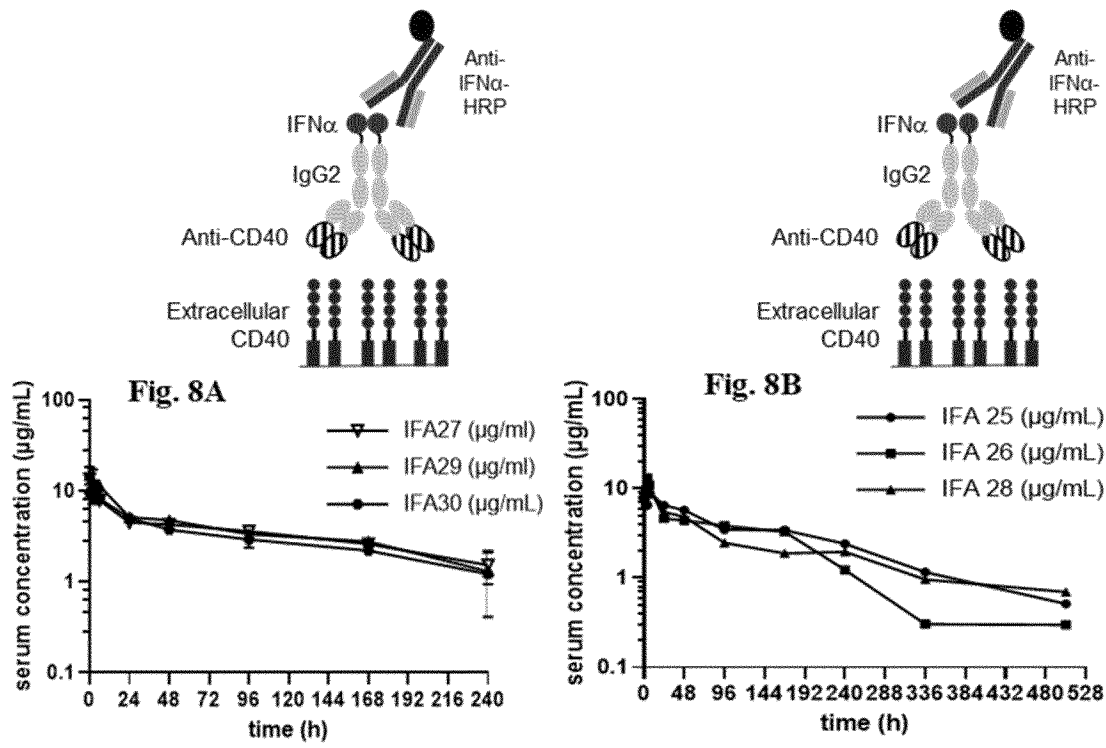


Fig. 9A

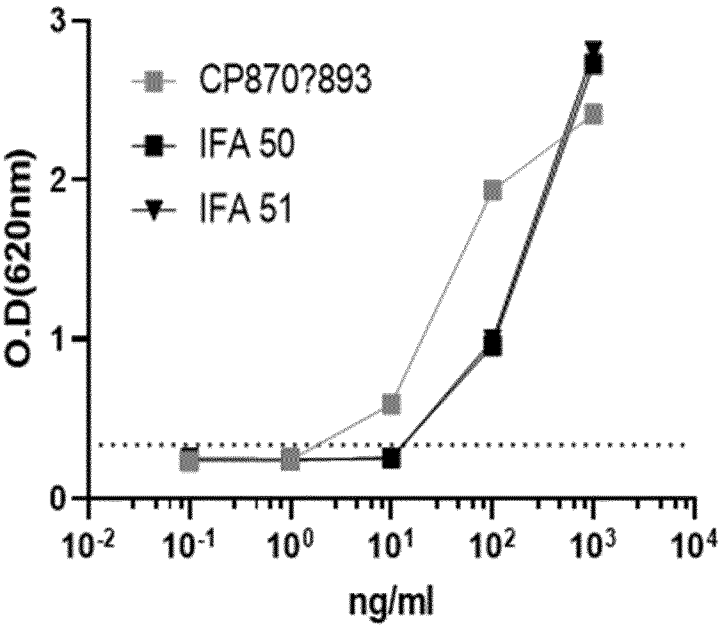


Fig. 9B

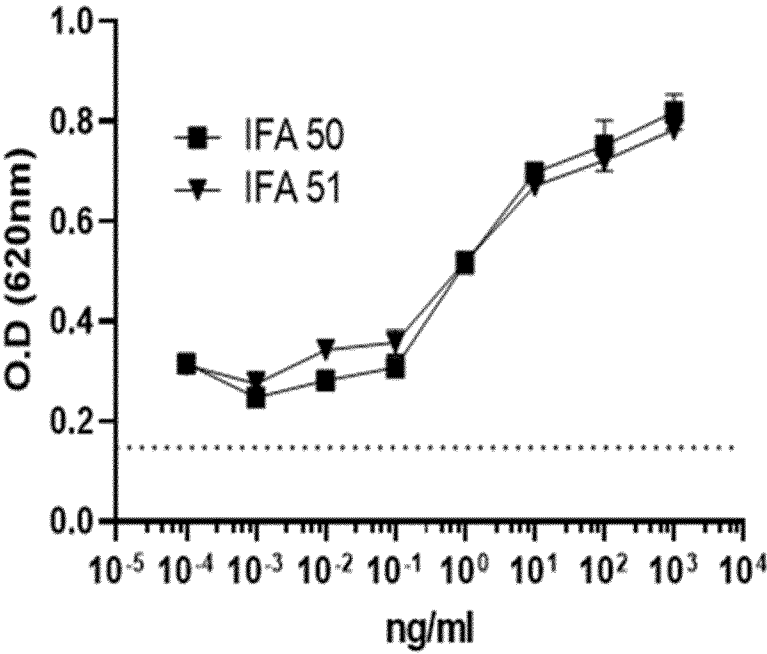


Fig. 10A

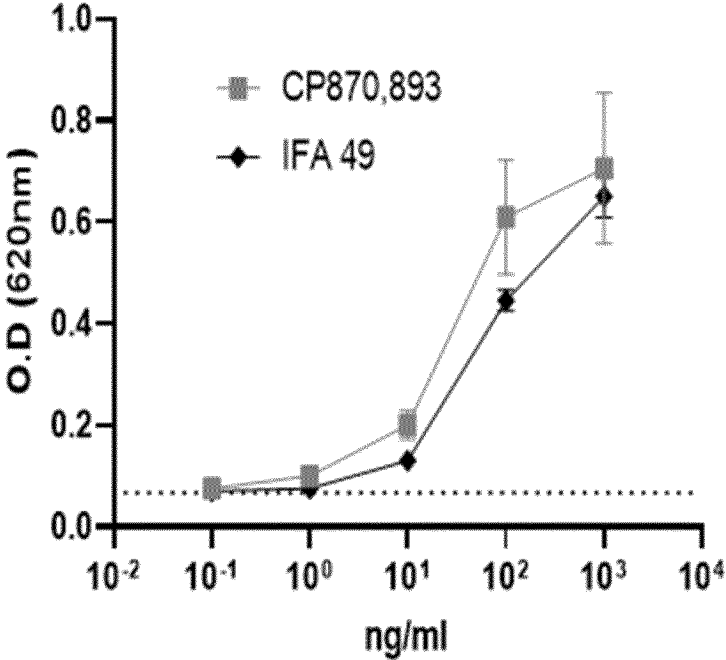


Fig. 10B

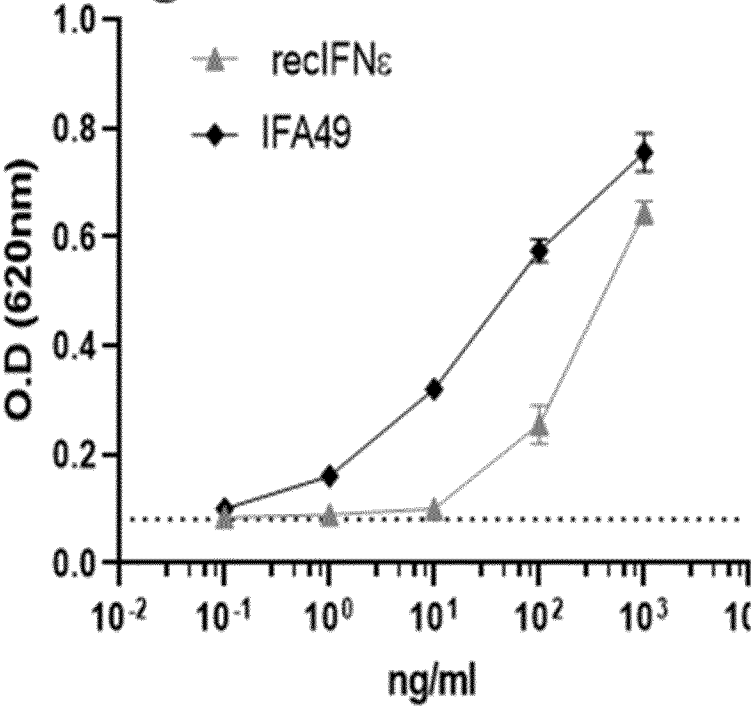


Fig. 11A

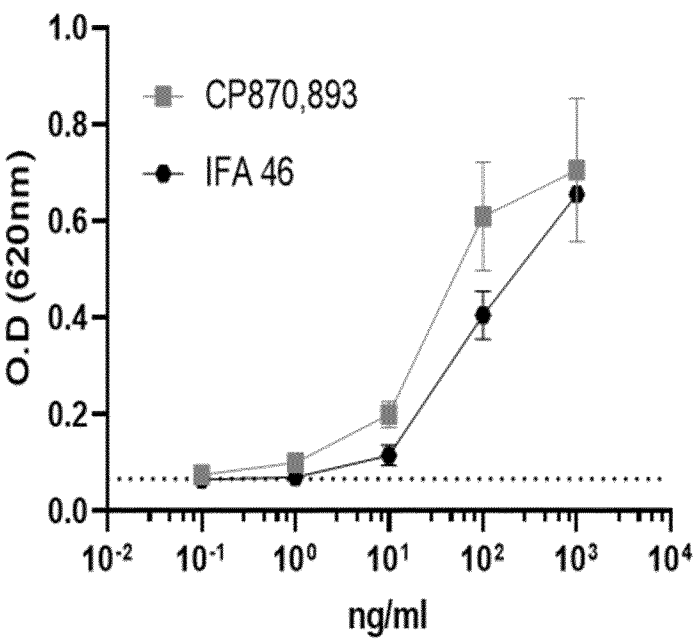


Fig. 11B

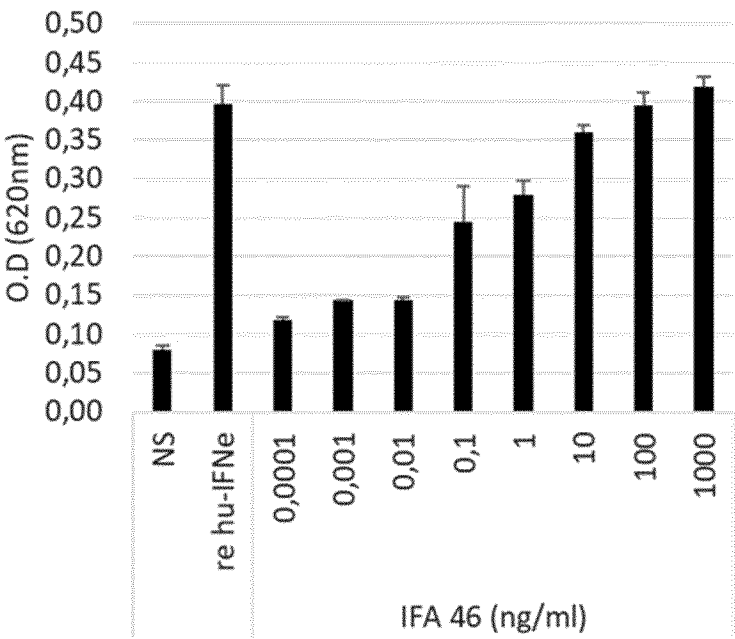


Fig. 12A

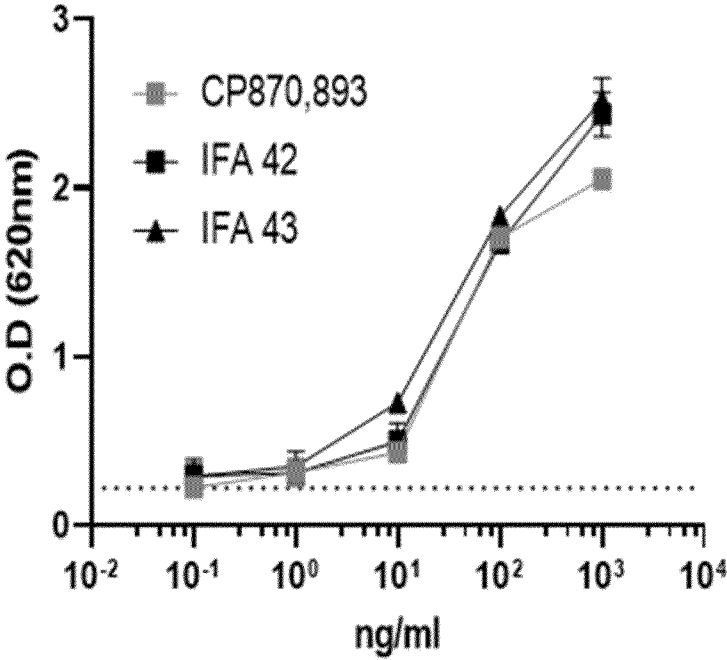


Fig. 12B

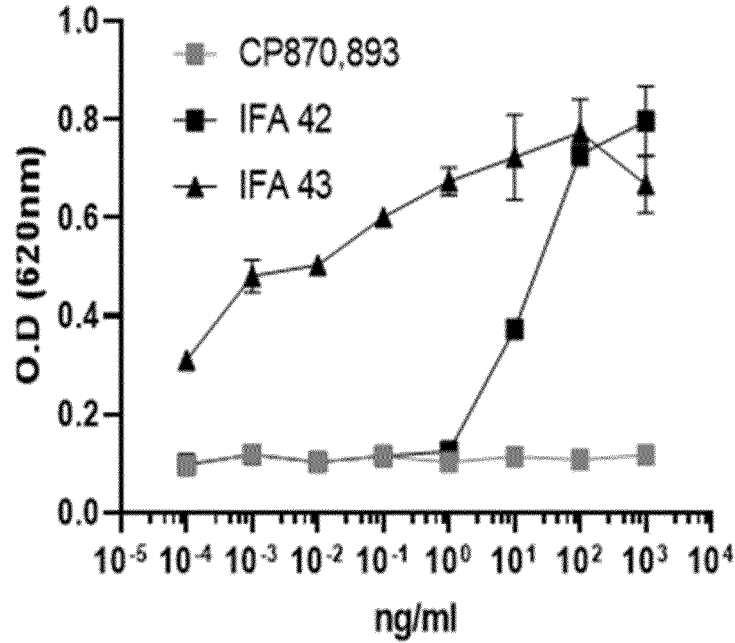


Fig. 13A

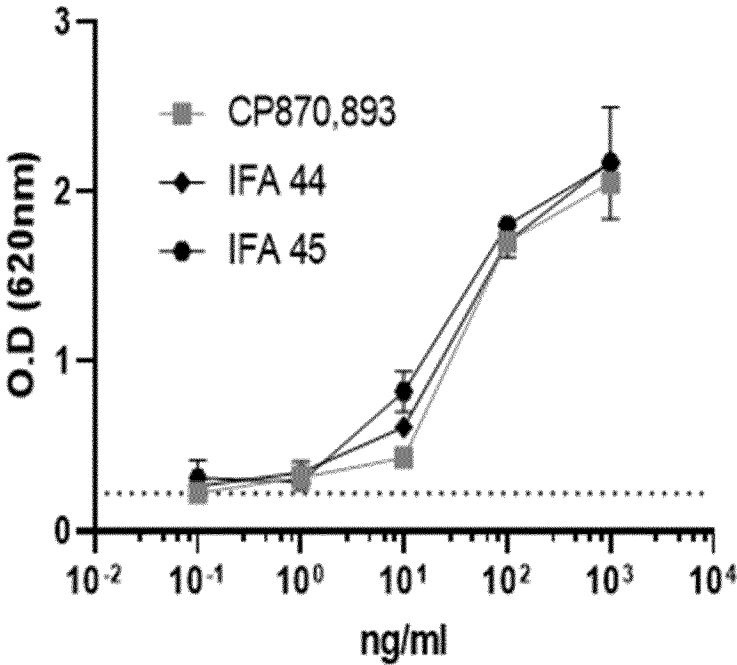


Fig. 13B

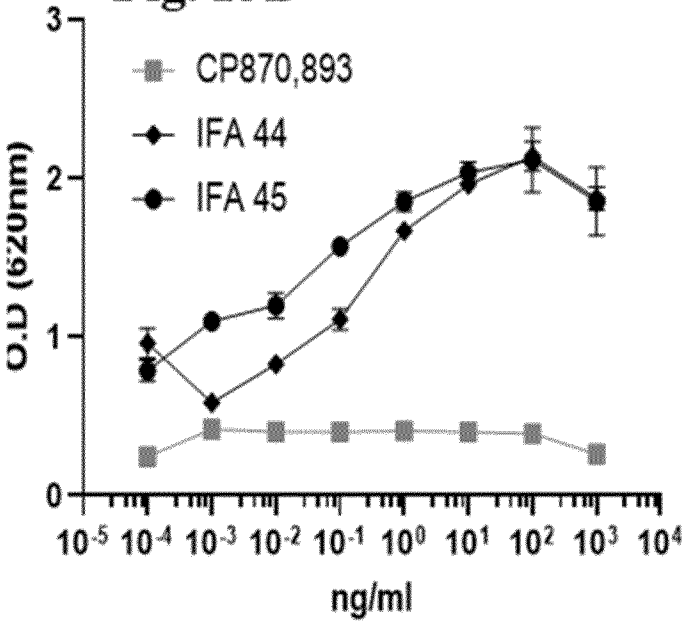


Fig. 14

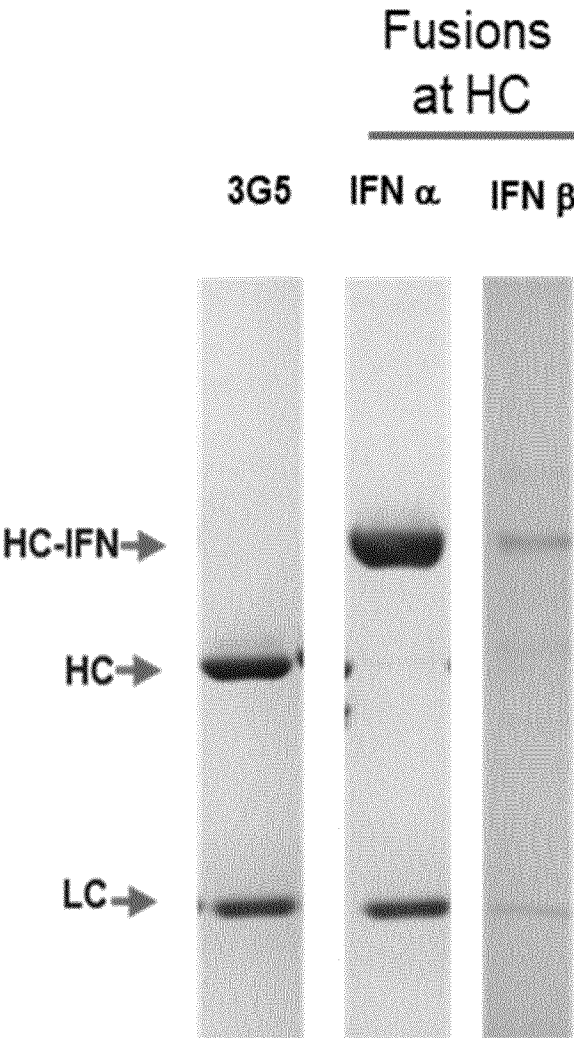


Fig. 15A

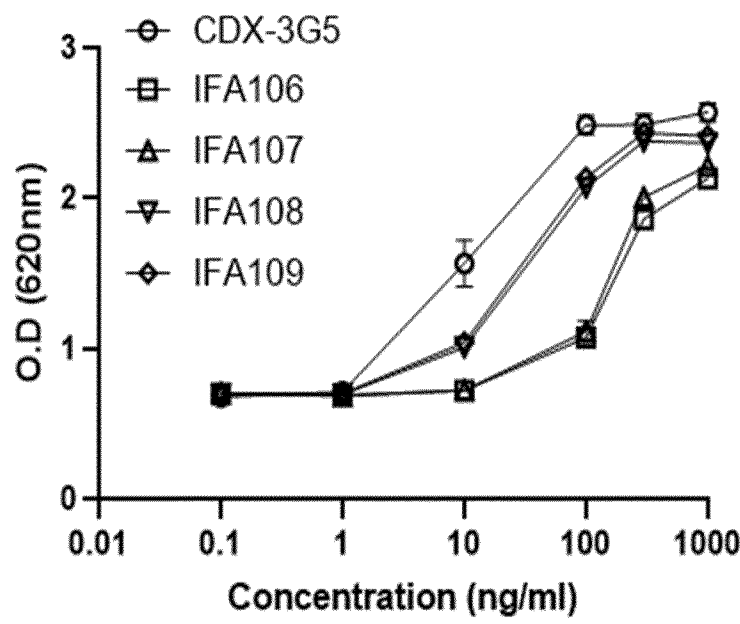


Fig. 15B

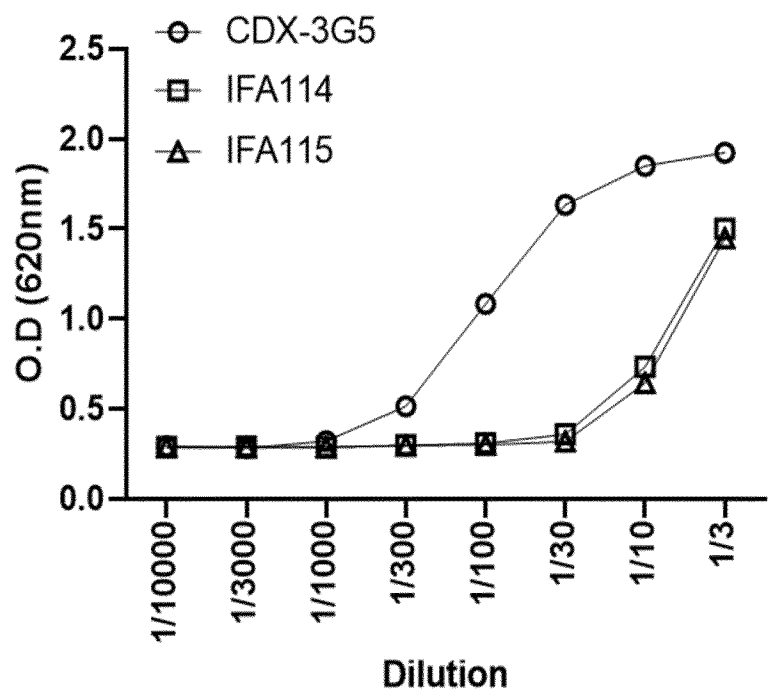


Fig. 15C

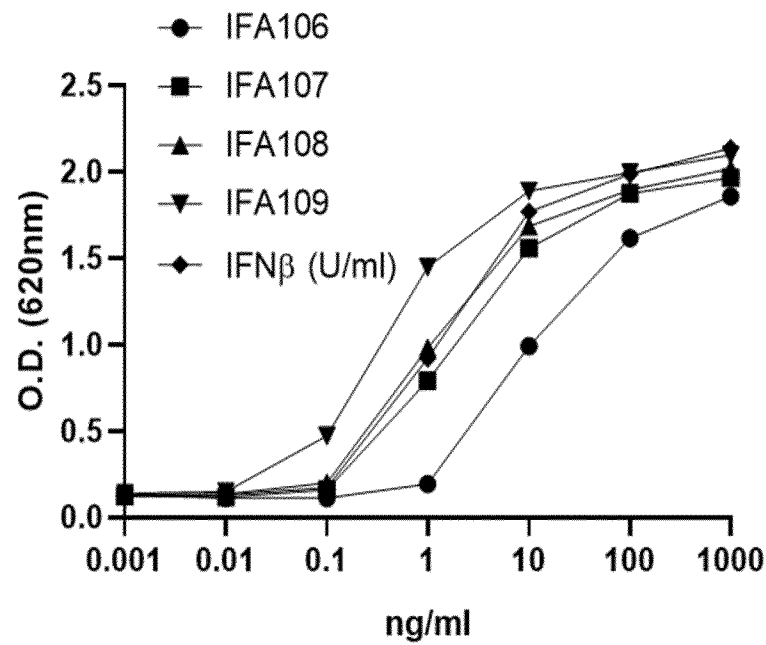


Fig. 15D

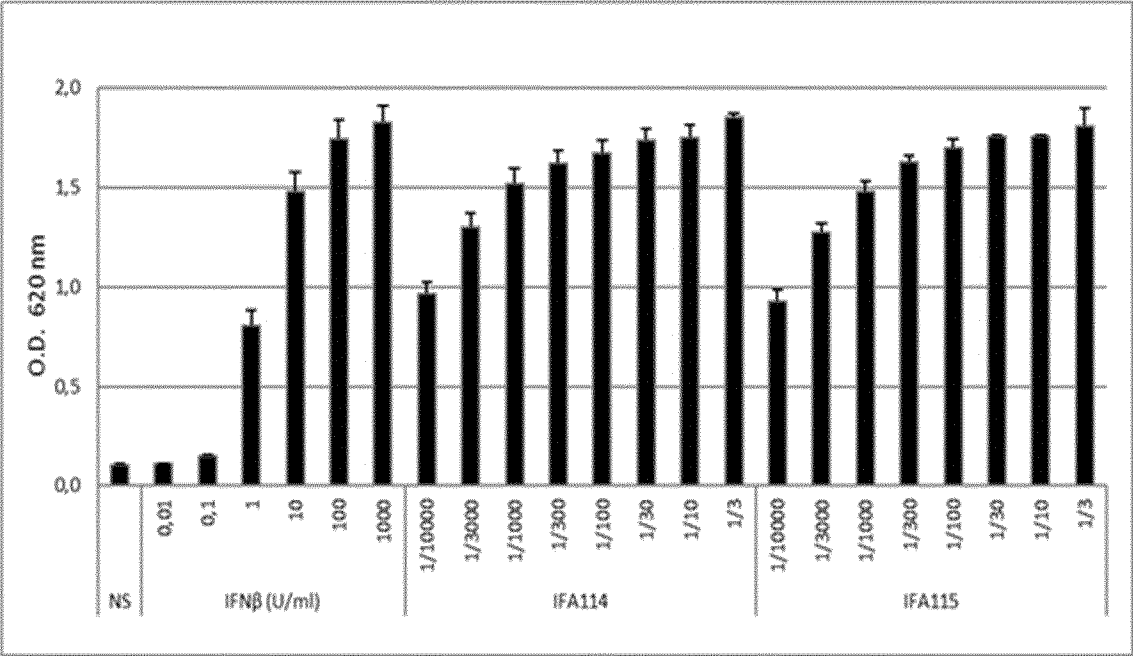


Fig. 16A

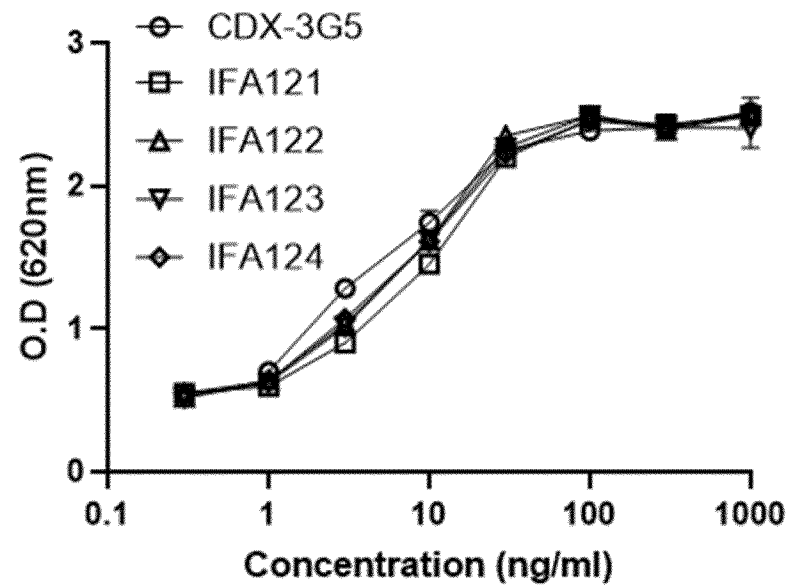


Fig. 16B

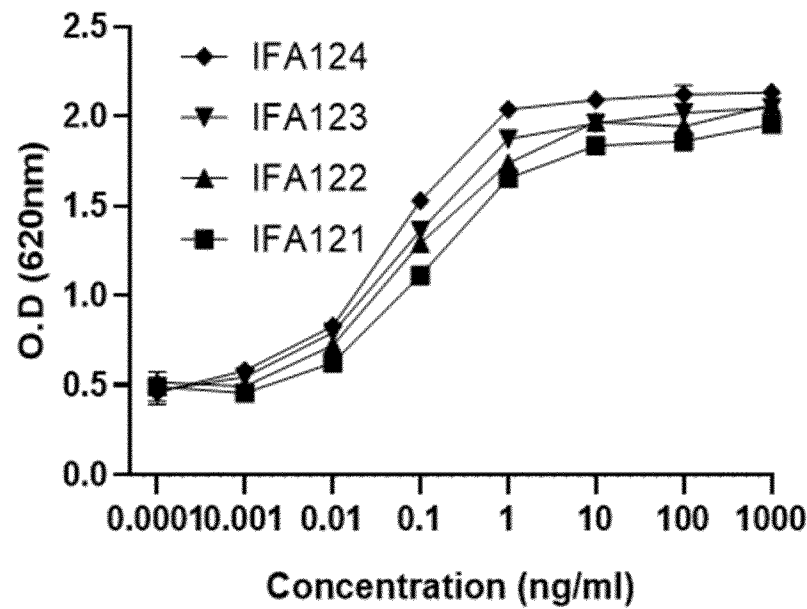


Fig. 17

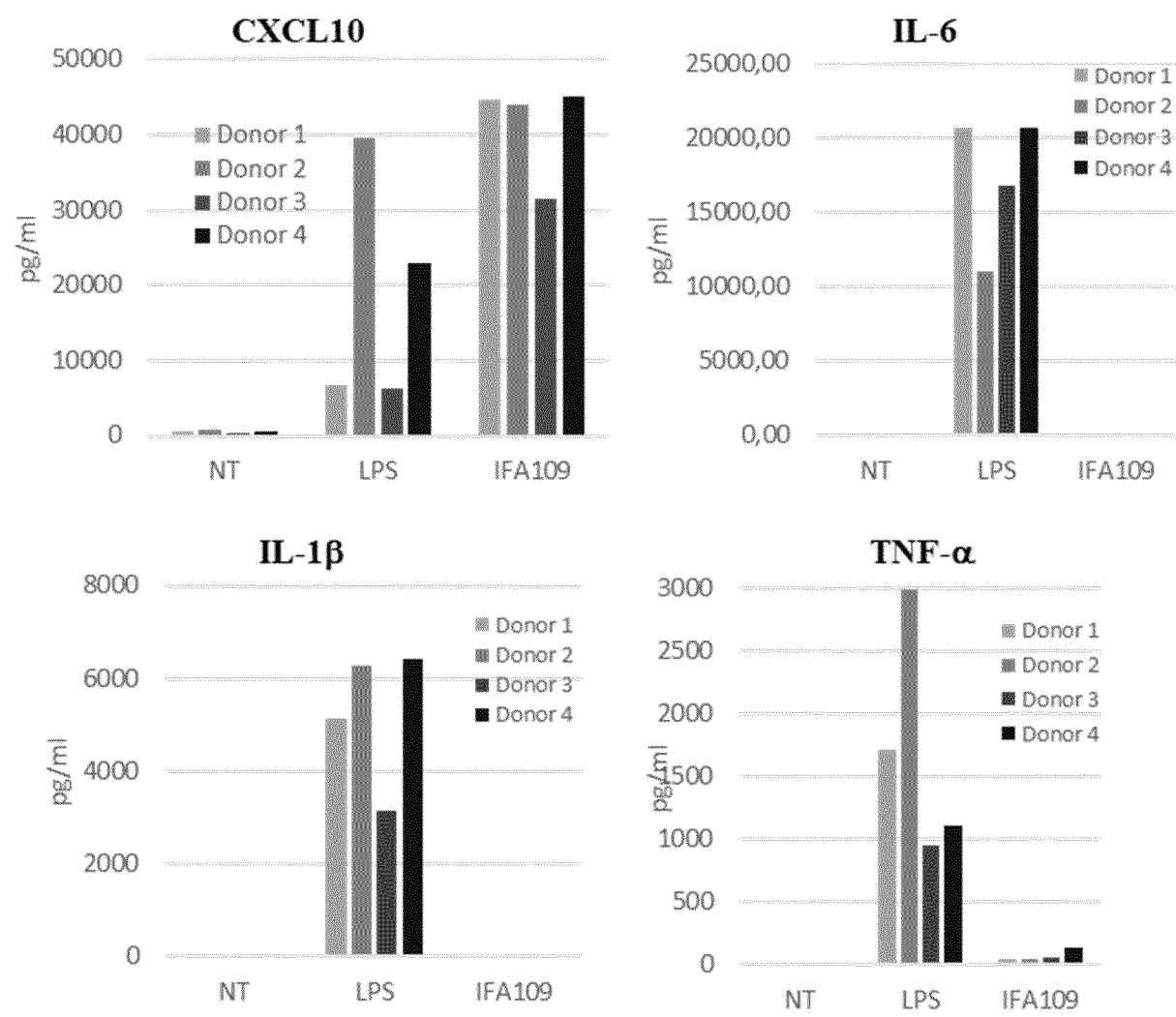


Fig. 18A

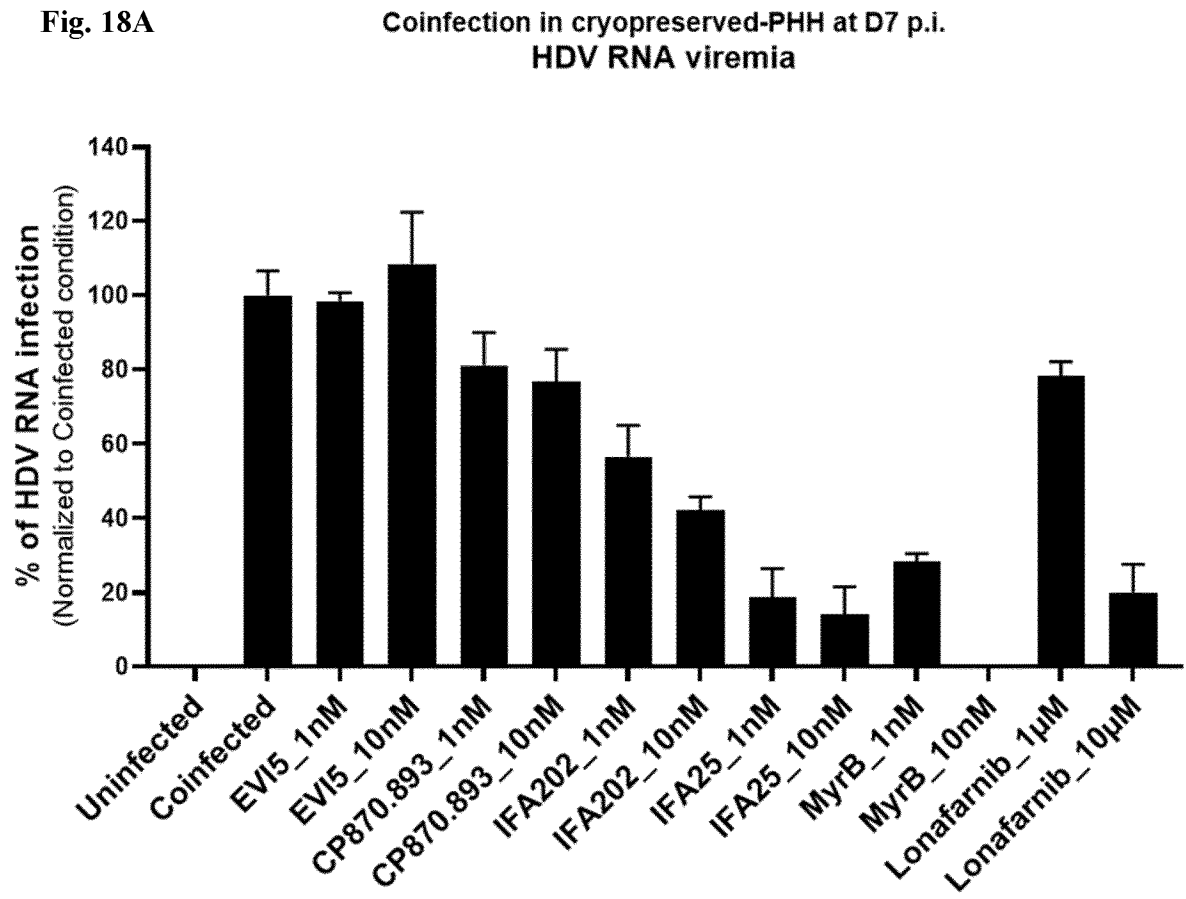


Fig. 18B

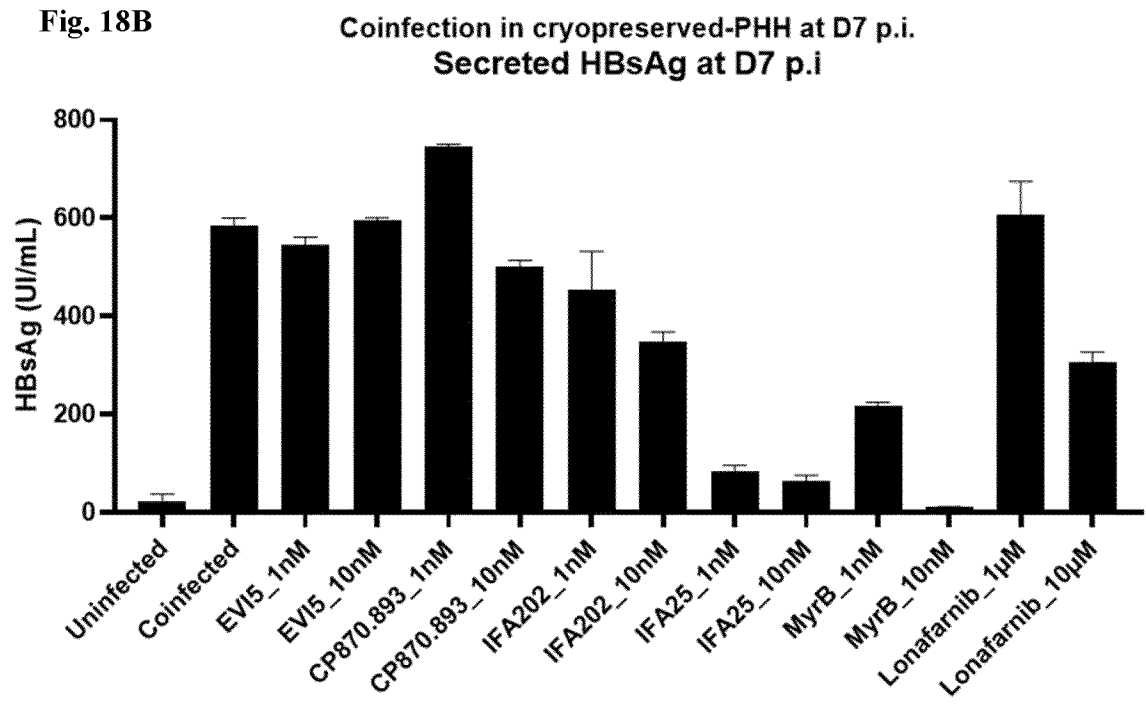


Fig. 18C

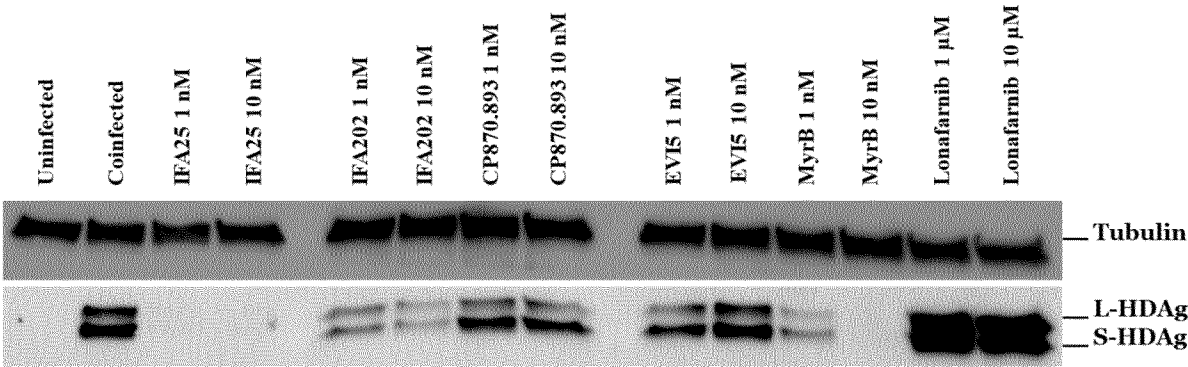


Fig. 19A

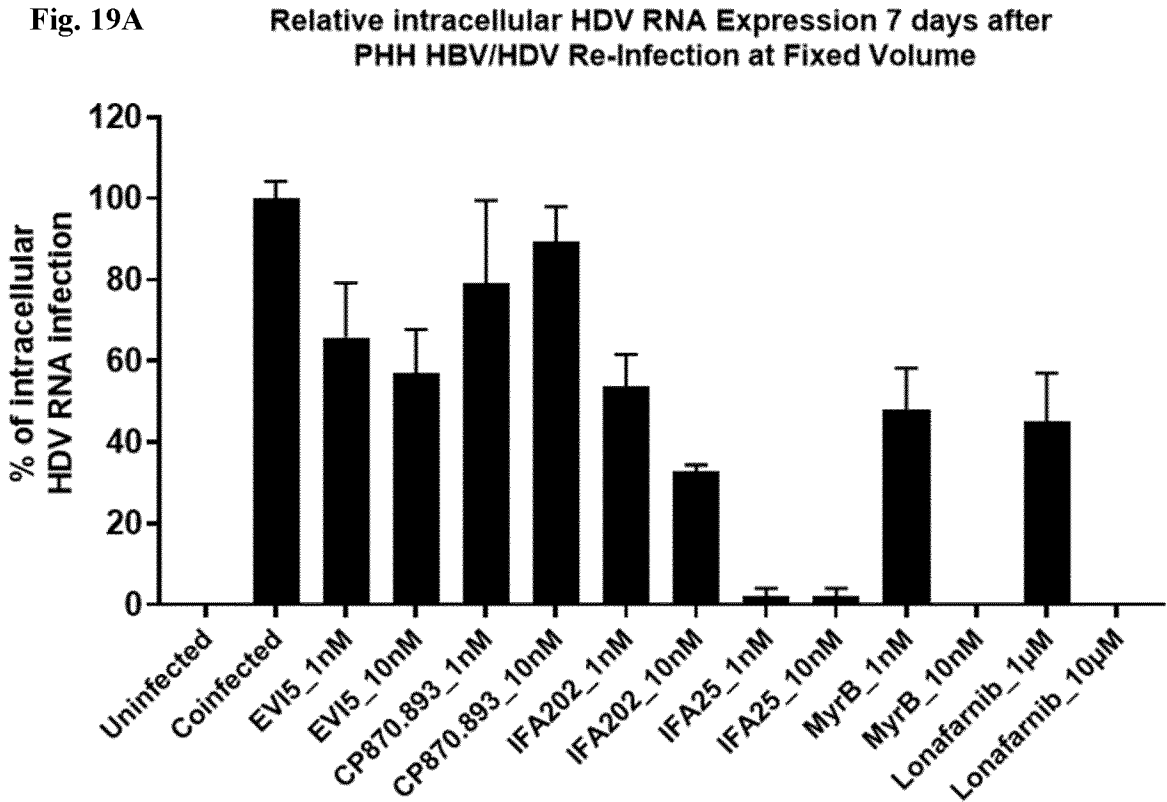
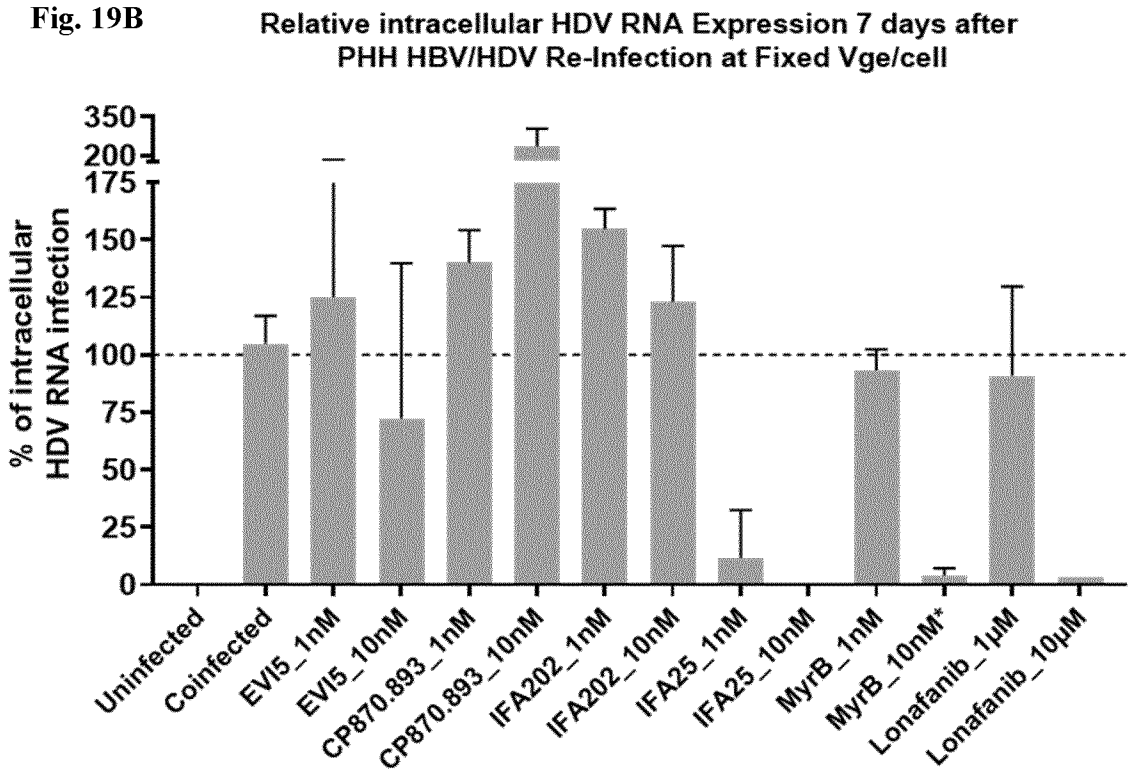


Fig. 19B



* For Myrcludex-B at 10nM condition, HDV RNA titer from the primary infection was too low to achieve the targeted Vge/cell, thus the data obtained at this dose are not interpretable.

Fig. 20A

Coinfection in cryopreserved-PHH at D7 p.i.

HDV RNA viremia

(treatments given at the time of the coinfection)

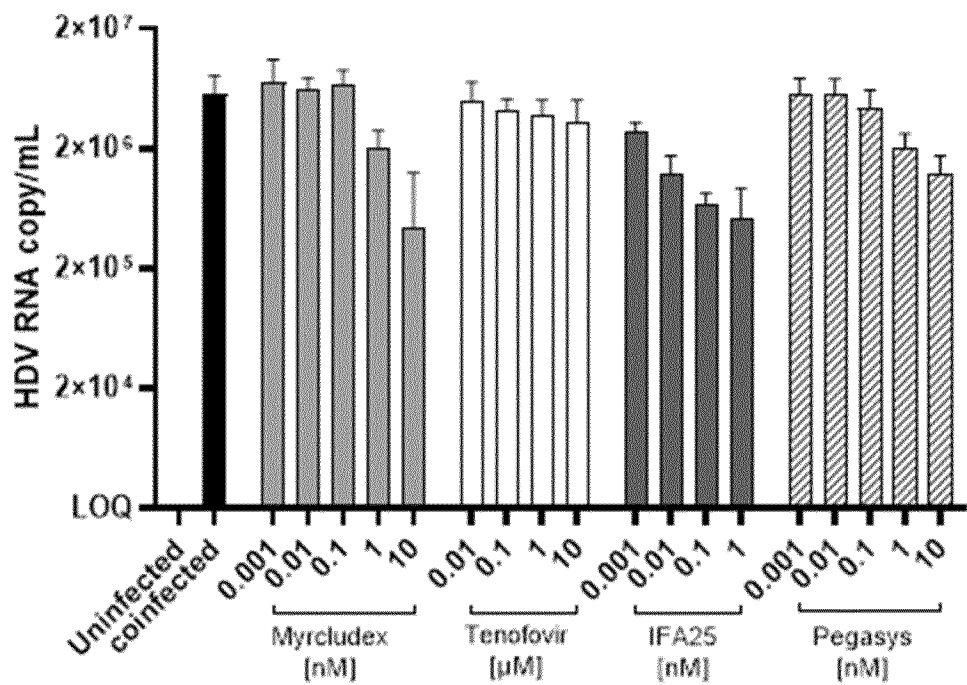


Fig. 20B

Coinfection in cryopreserved-PHH at D7 p.i.

HDV RNA viremia

(treatments given at D1 post-coinfection)

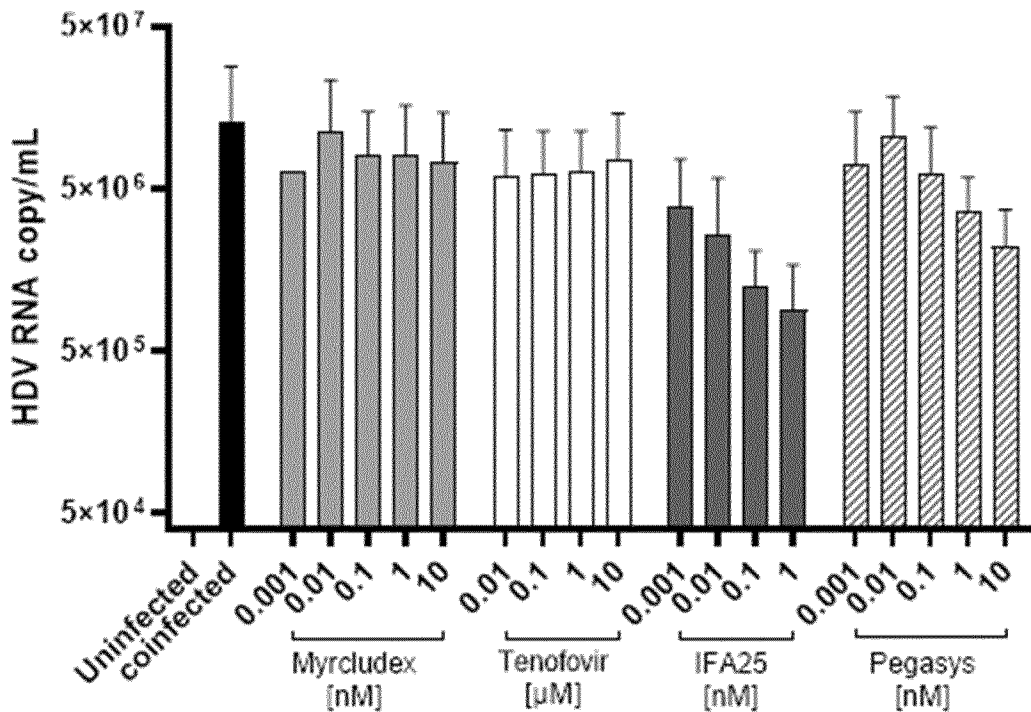


Fig. 20C
Coinfection in cryopreserved-PHH at D7 p.i.
Secreted HBsAg
(treatments given at the time of the coinfection)

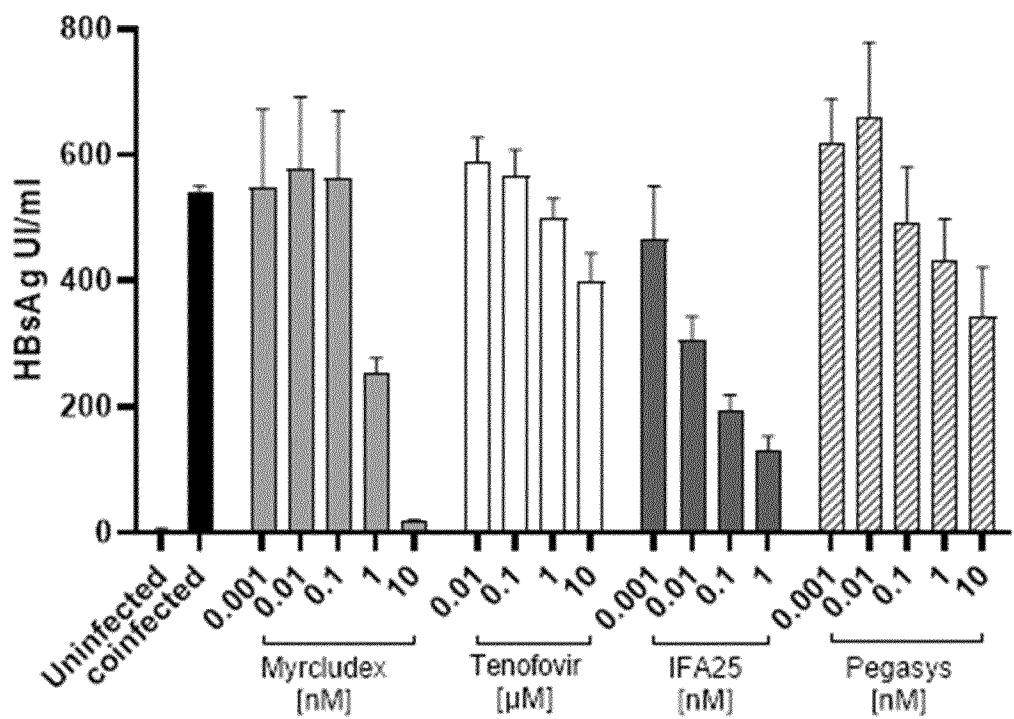


Fig. 20D
Coinfection in cryopreserved-PHH at D7 p.i.
Secreted HBsAg
(treatments given at D1 post-coinfection)

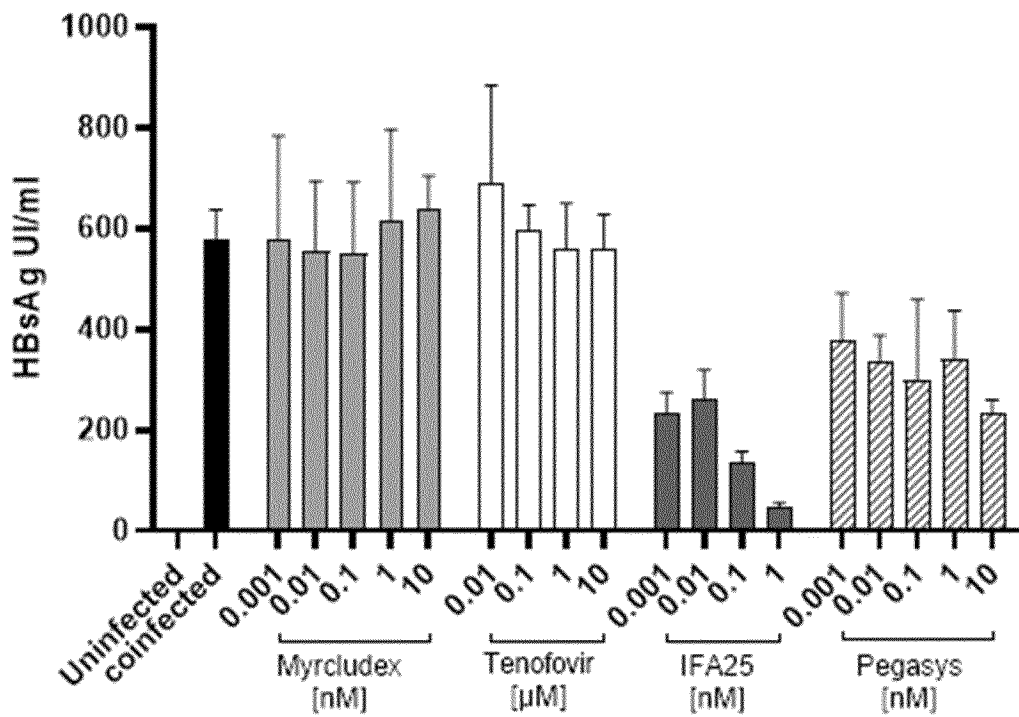


Fig. 21A

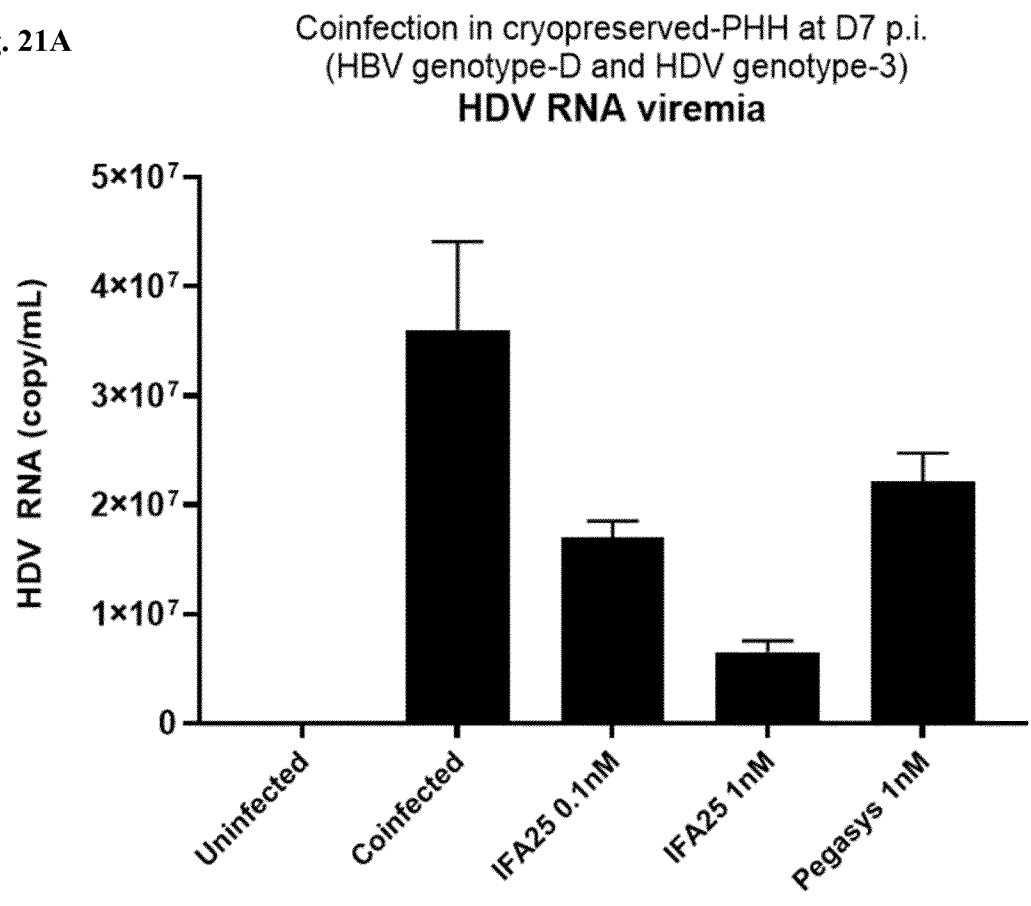


Fig. 21B

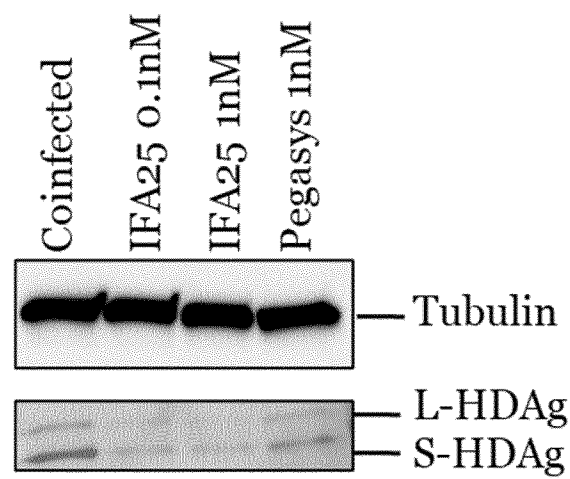


Fig. 21C

Coinfection in cryopreserved-PHH at D7 p.i.
(HBV genotype-D and HDV genotype-3)
Secreted HBsAg

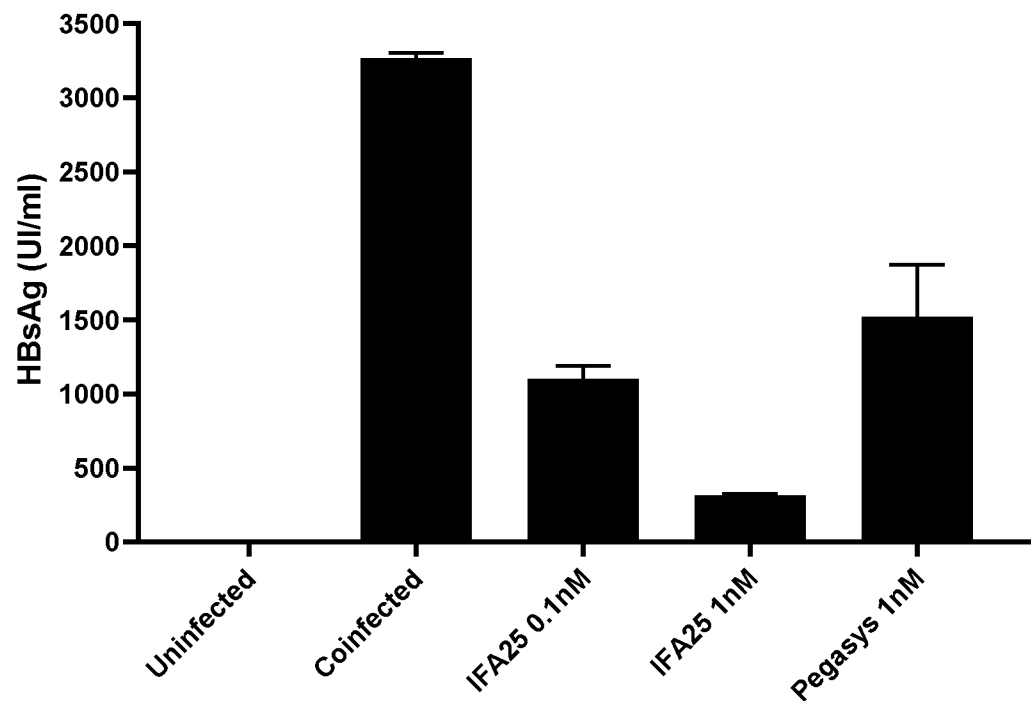


Fig. 21D

Coinfection in cryopreserved-PHH at D7 p.i.
(HBV genotype-D and HDV genotype-3)
Secreted HBeAg

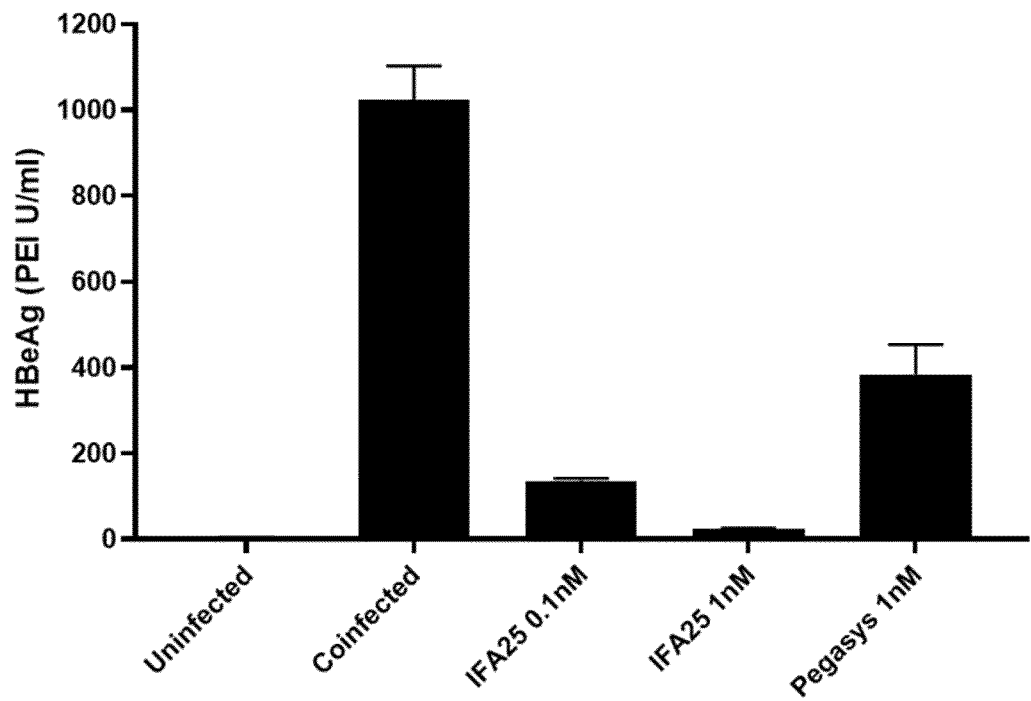


Fig. 21E Coinfection in cryopreserved-PHH at D7 p.i.
(HBV genotype-D and HDV genotype-3)
HBV DNA viremia

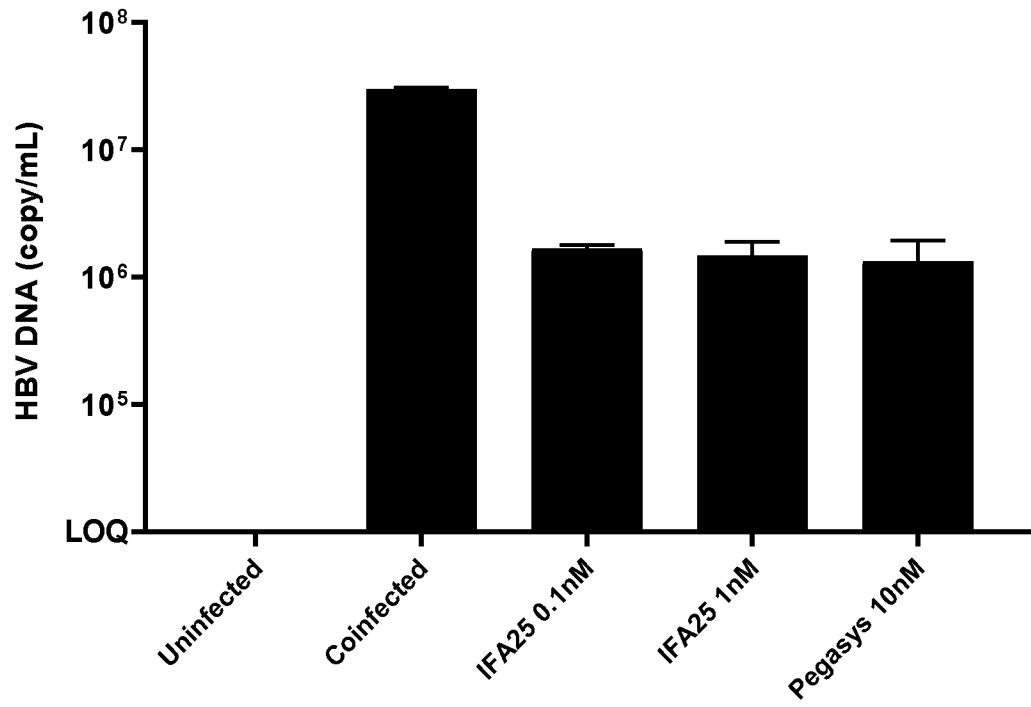


Fig. 22A Coinfection in cryopreserved-PHH at D7 p.i.
dose dependent effect of Myrcludex on
HDV RNA viremia

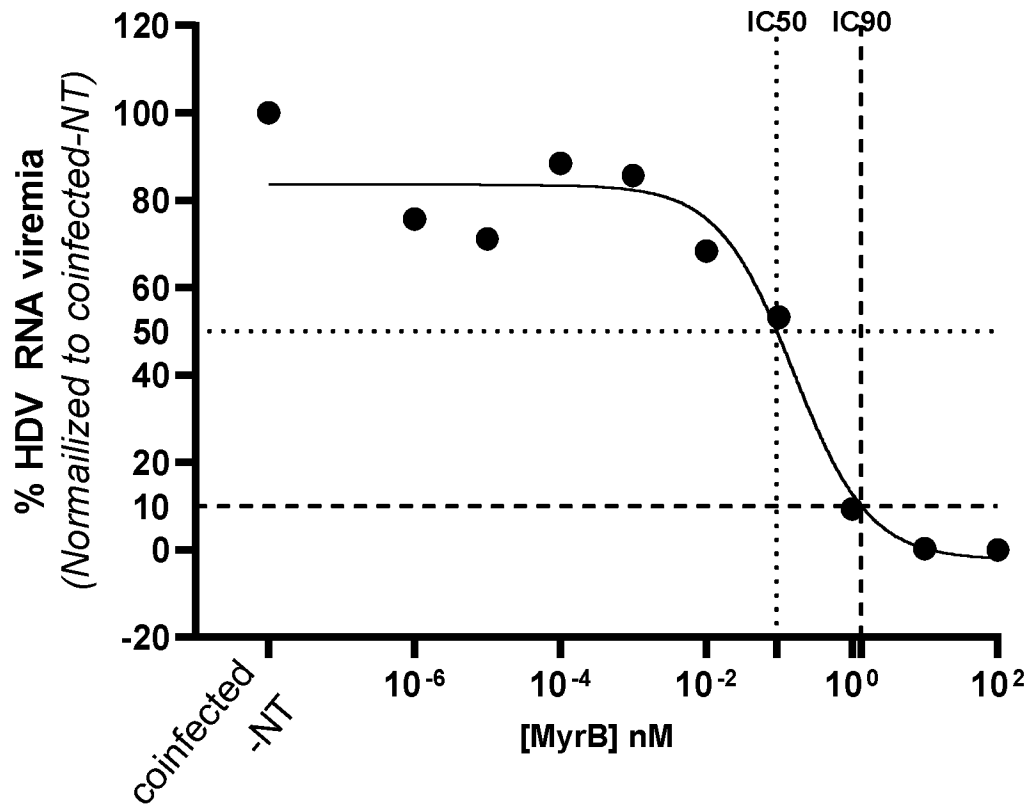


Fig. 22B

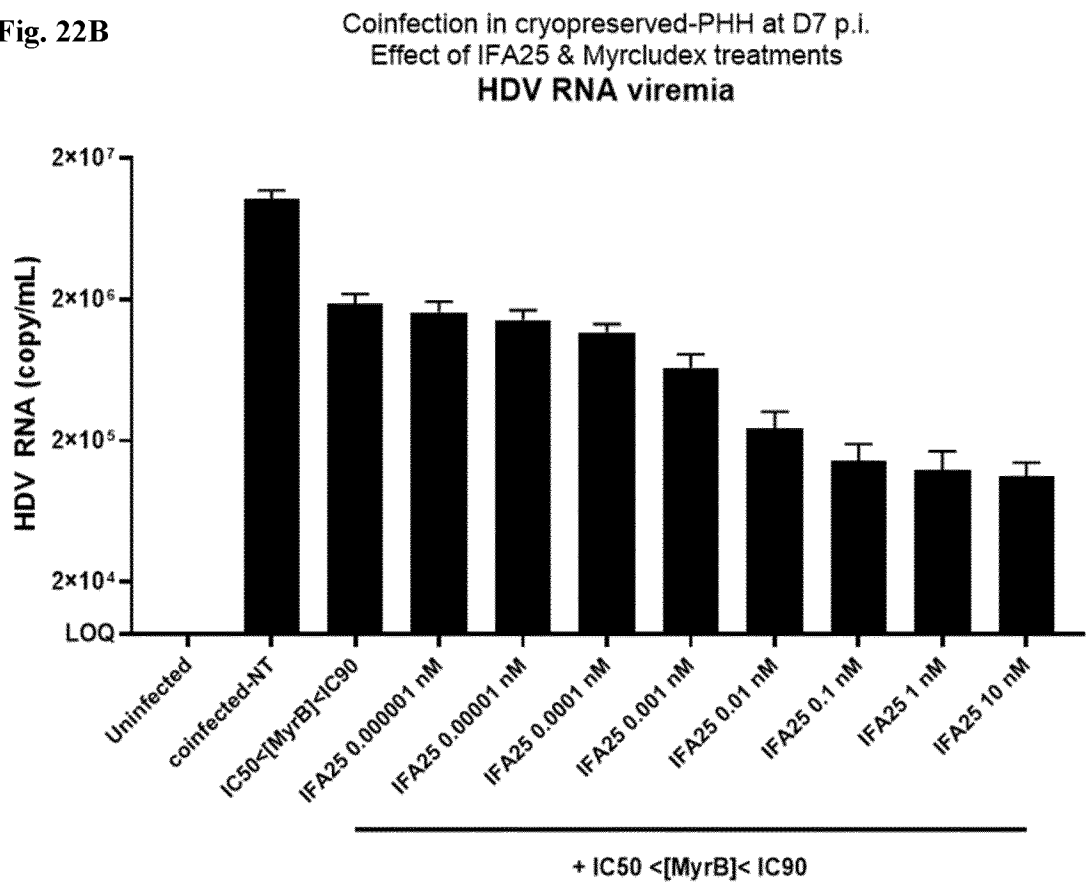


Fig. 22C

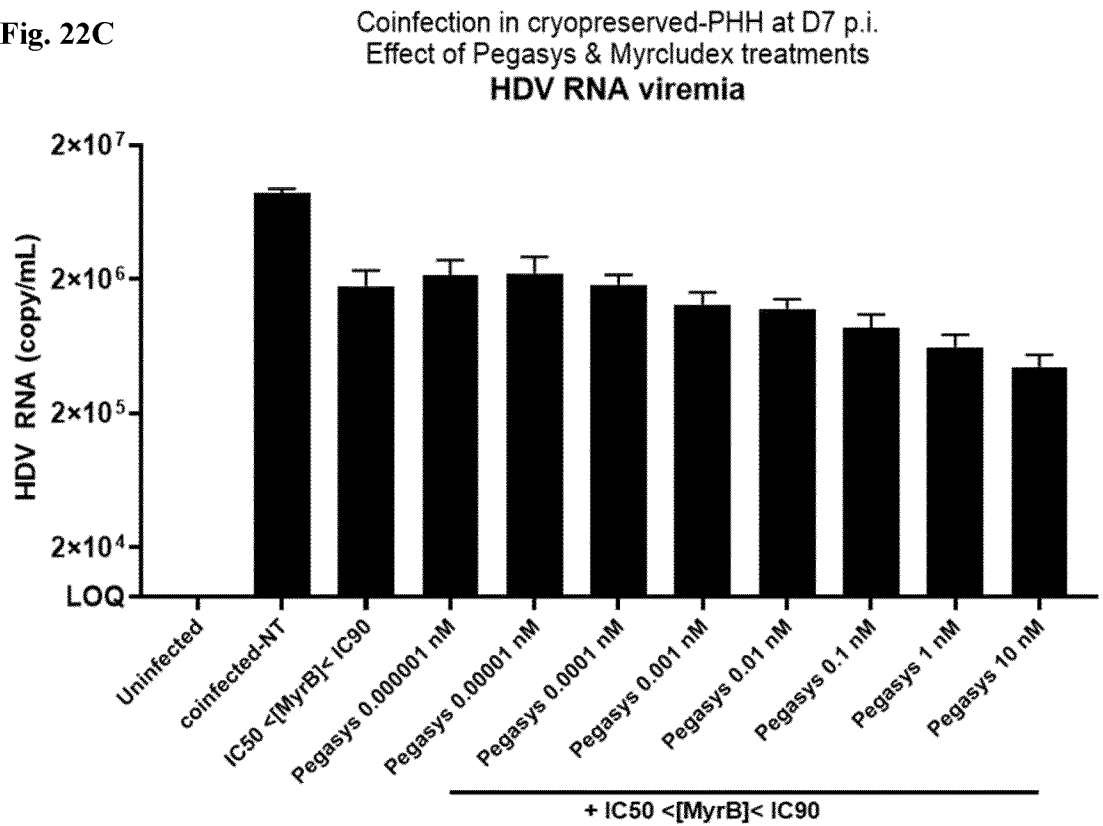


Fig. 22D
Coinfection in cryopreserved-PHH at D7 p.i.
Effect of IFA25 & Myrcludex treatments
Secreted HBsAg

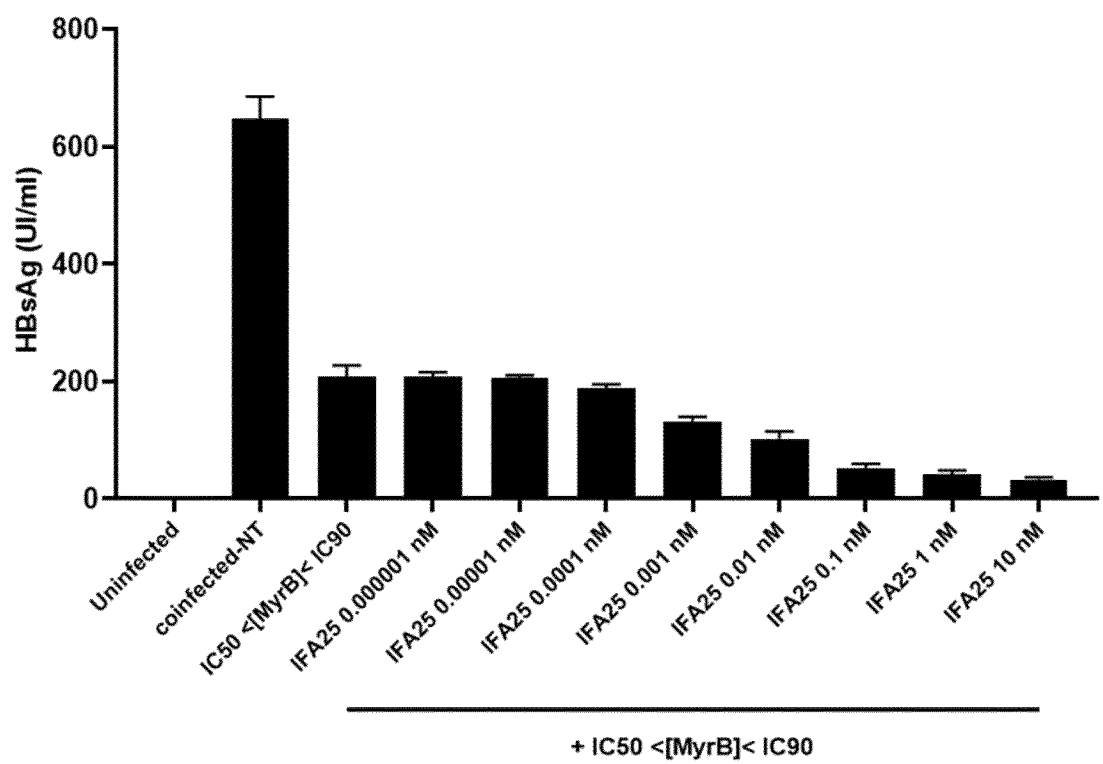


Fig. 22E
Coinfection in cryopreserved-PHH at D7 p.i.
Effect of Pegasys & Myrcludex treatments
Secreted HBsAg

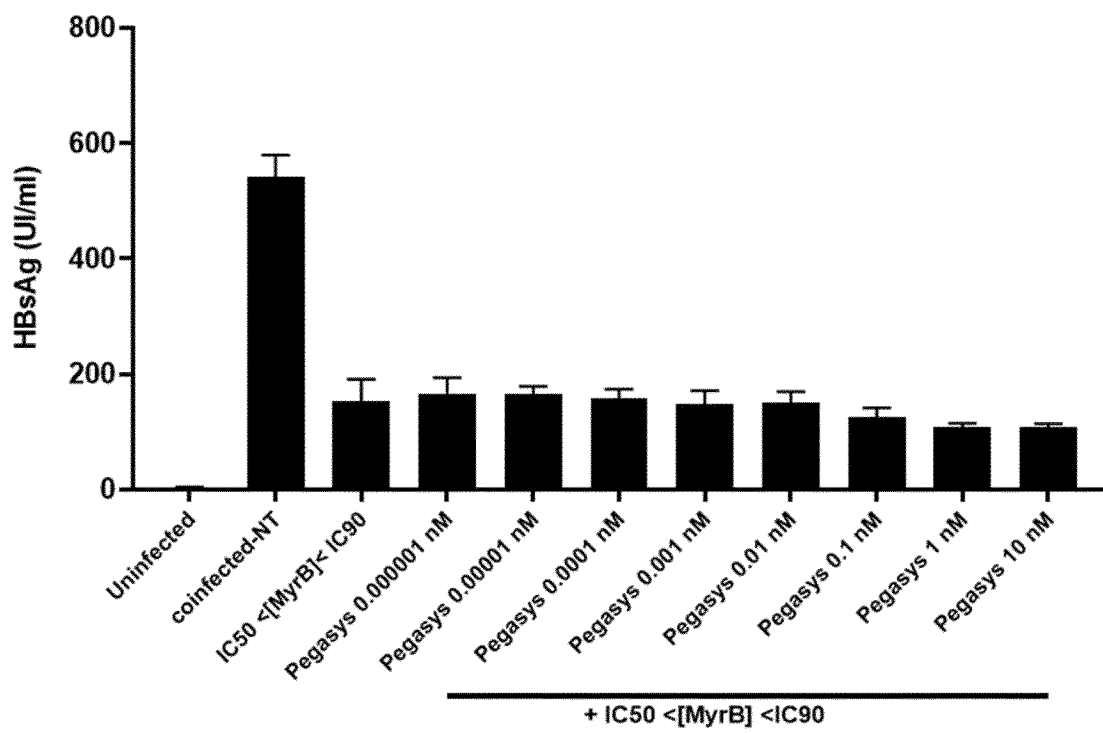


Fig. 22F

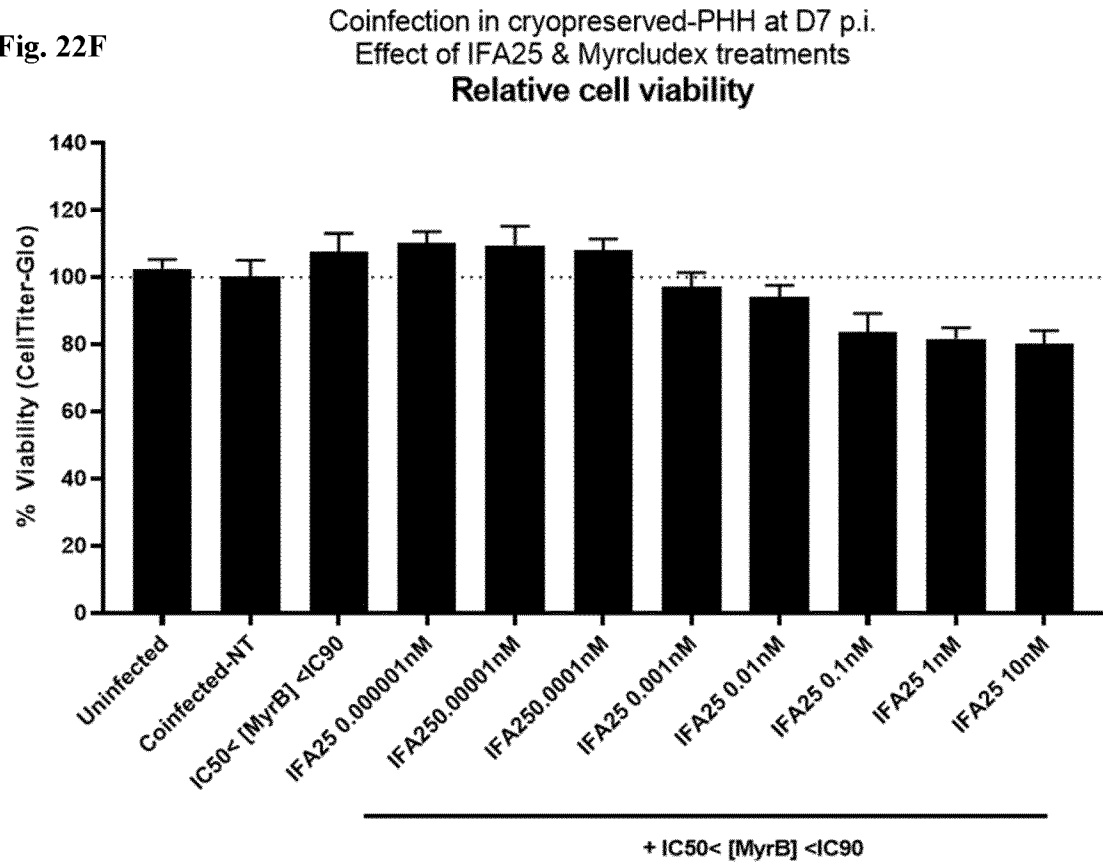
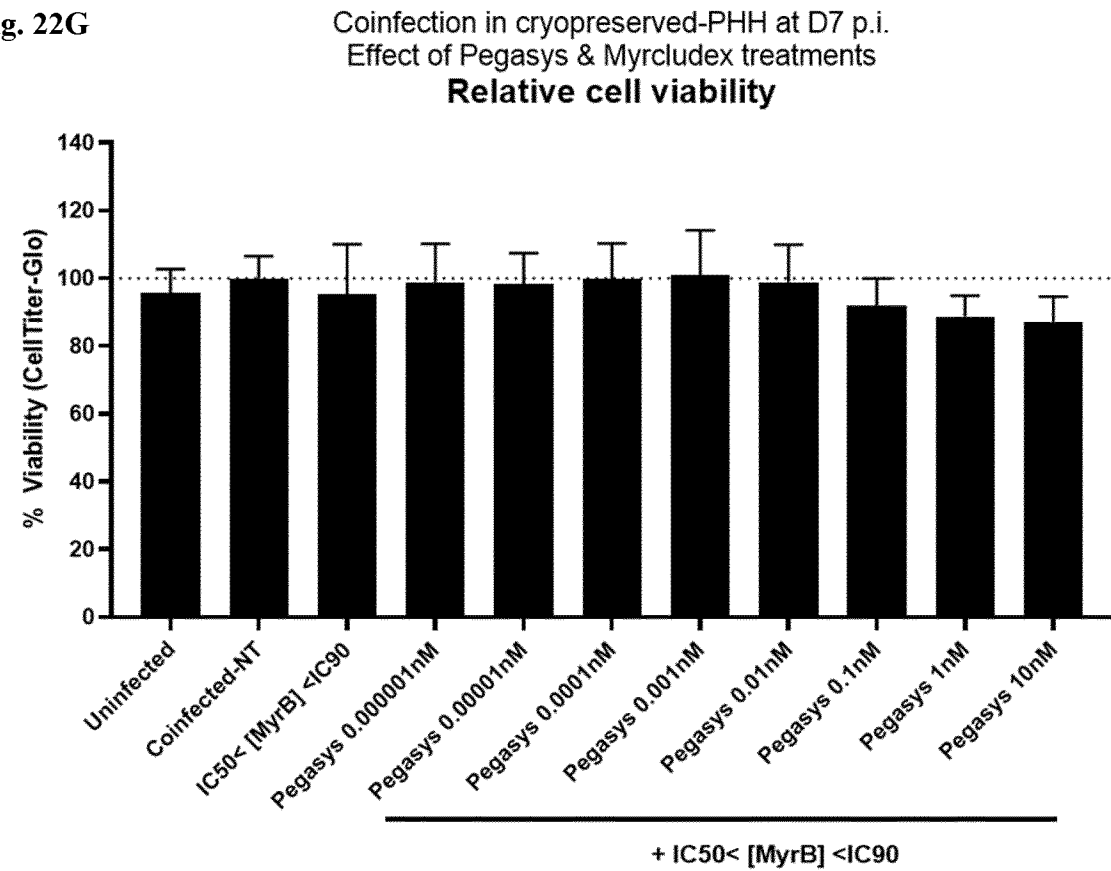


Fig. 22G



v

Fig. 23A

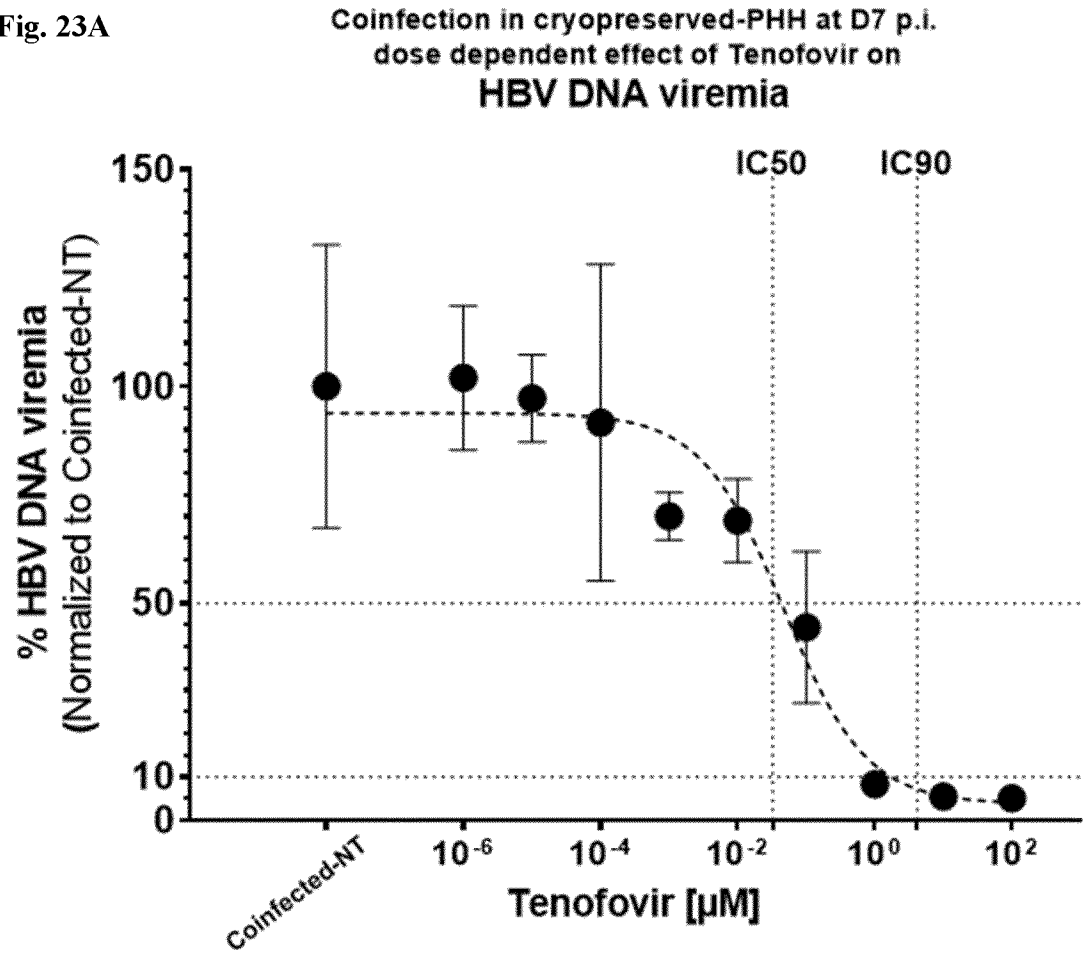


Fig. 23B

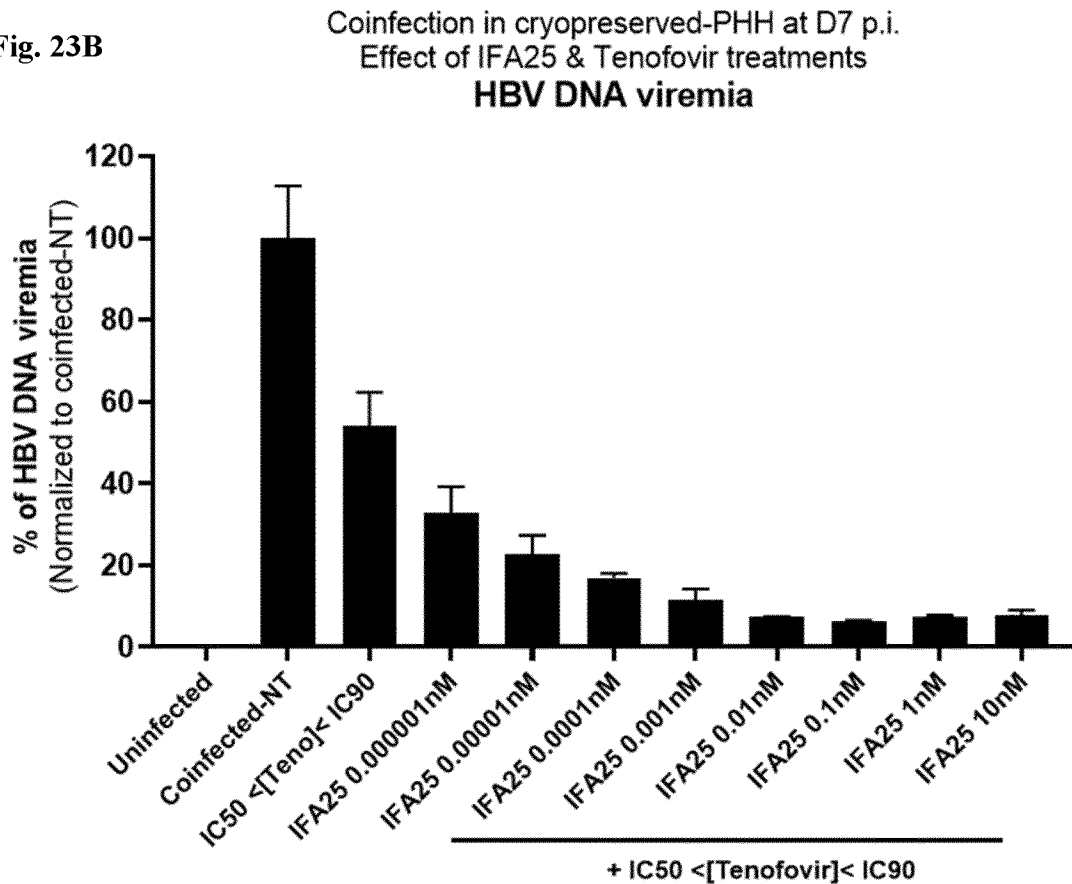


Fig. 23C

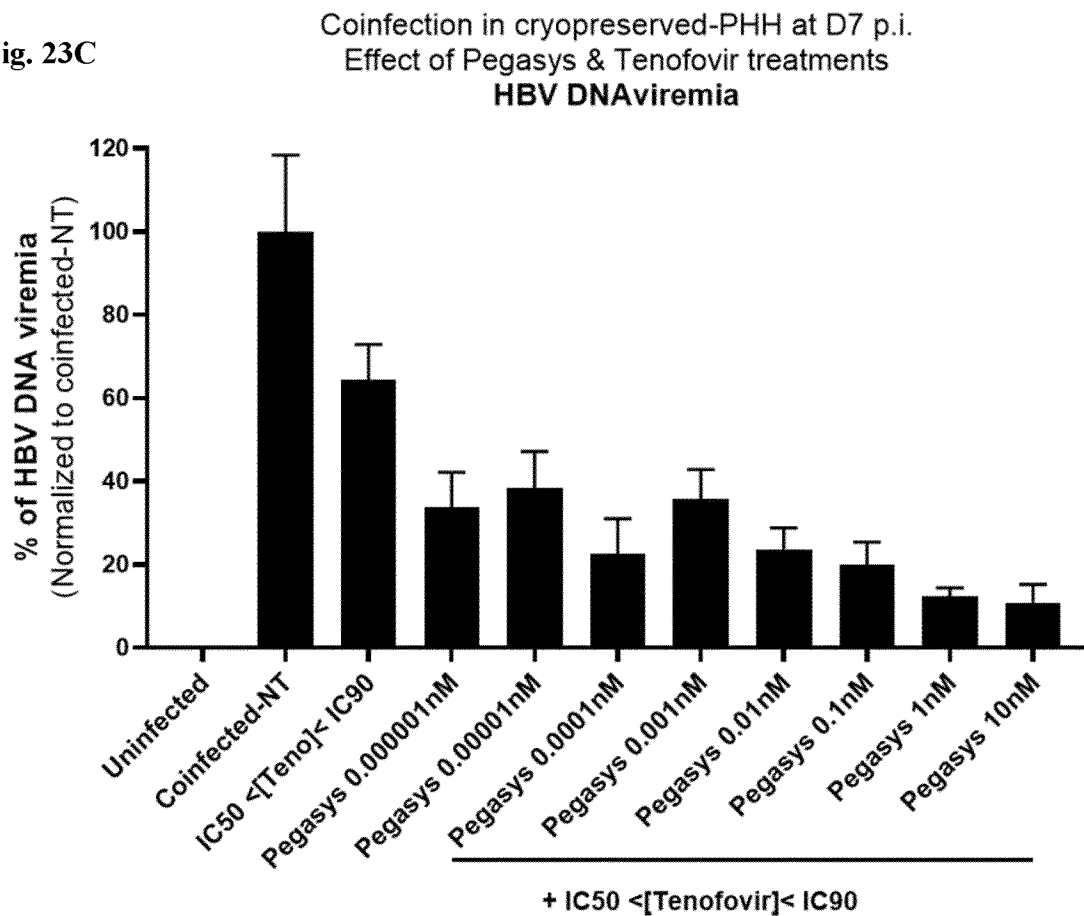


Fig. 23D
Coinfection in cryopreserved-PHH at D7 p.i.
Effect of IFA25 & Tenofovir treatments
Secreted HBsAg

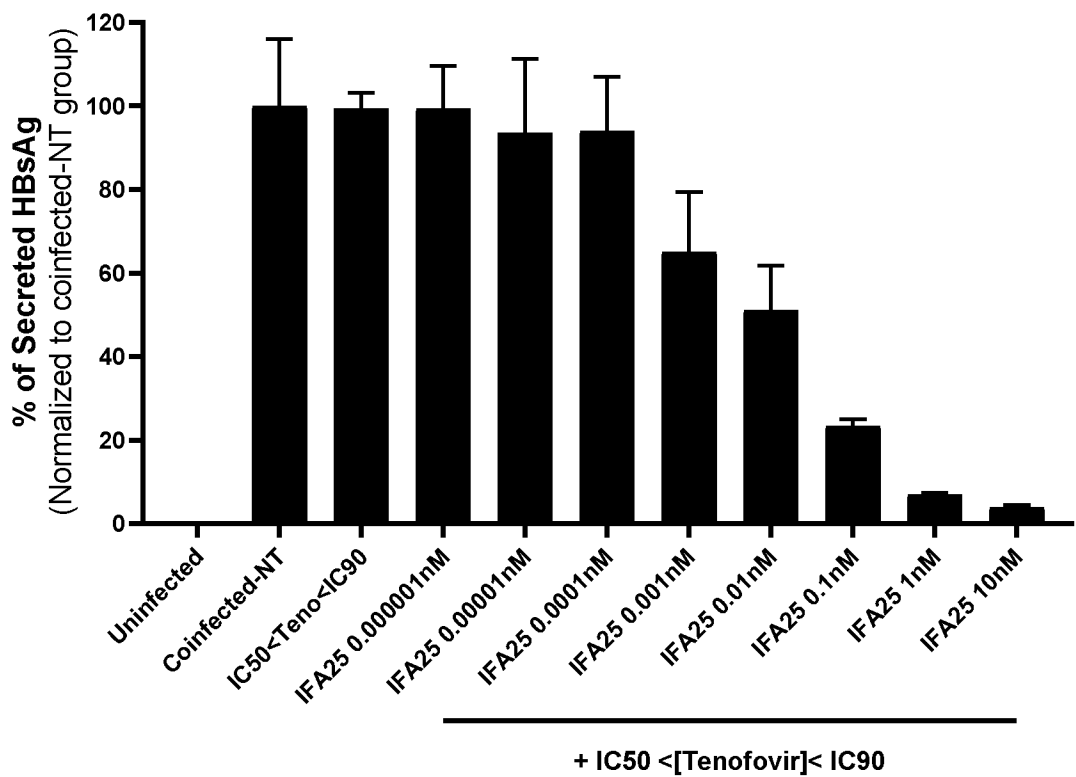


Fig. 23E
Coinfection in cryopreserved-PHH at D7 p.i.
Effect of Pegasys & Tenofovir treatments
Secreted HBsAg

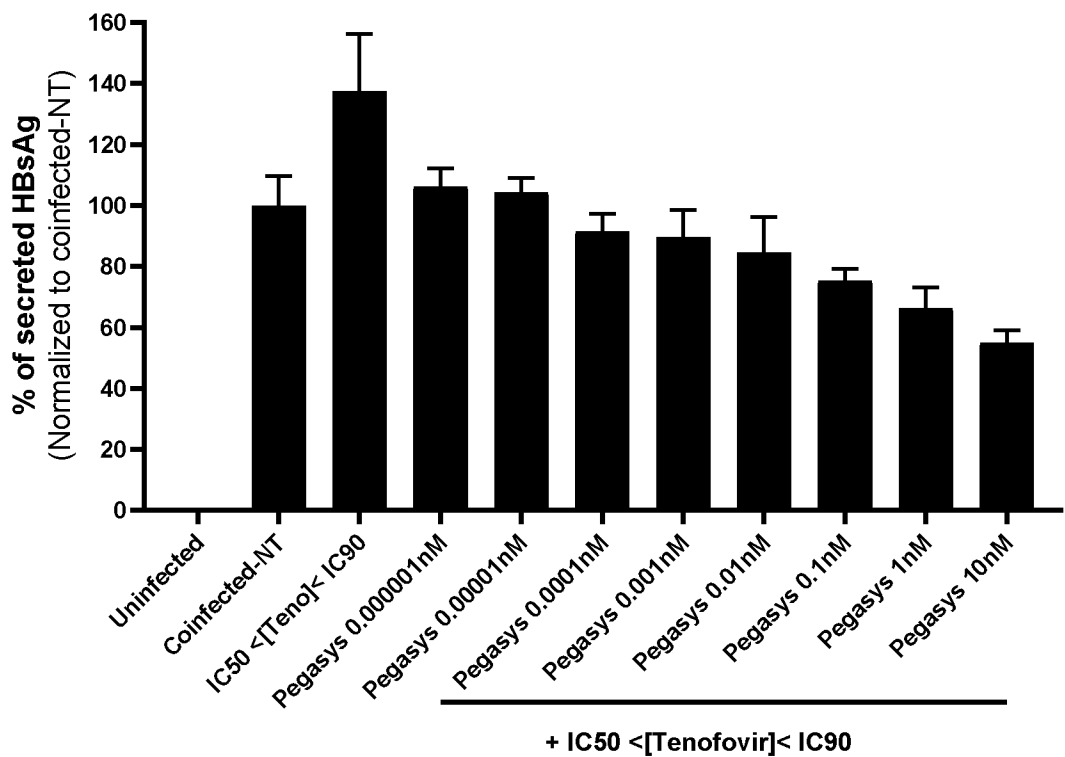


Fig. 23F

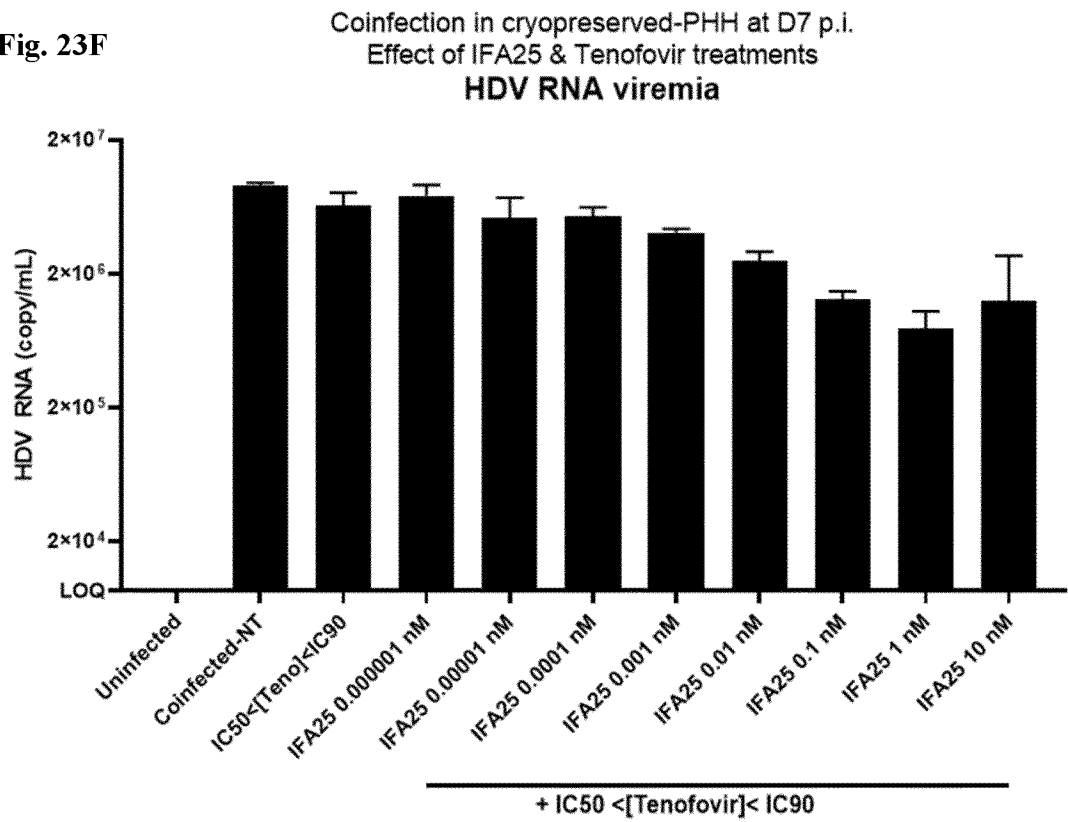
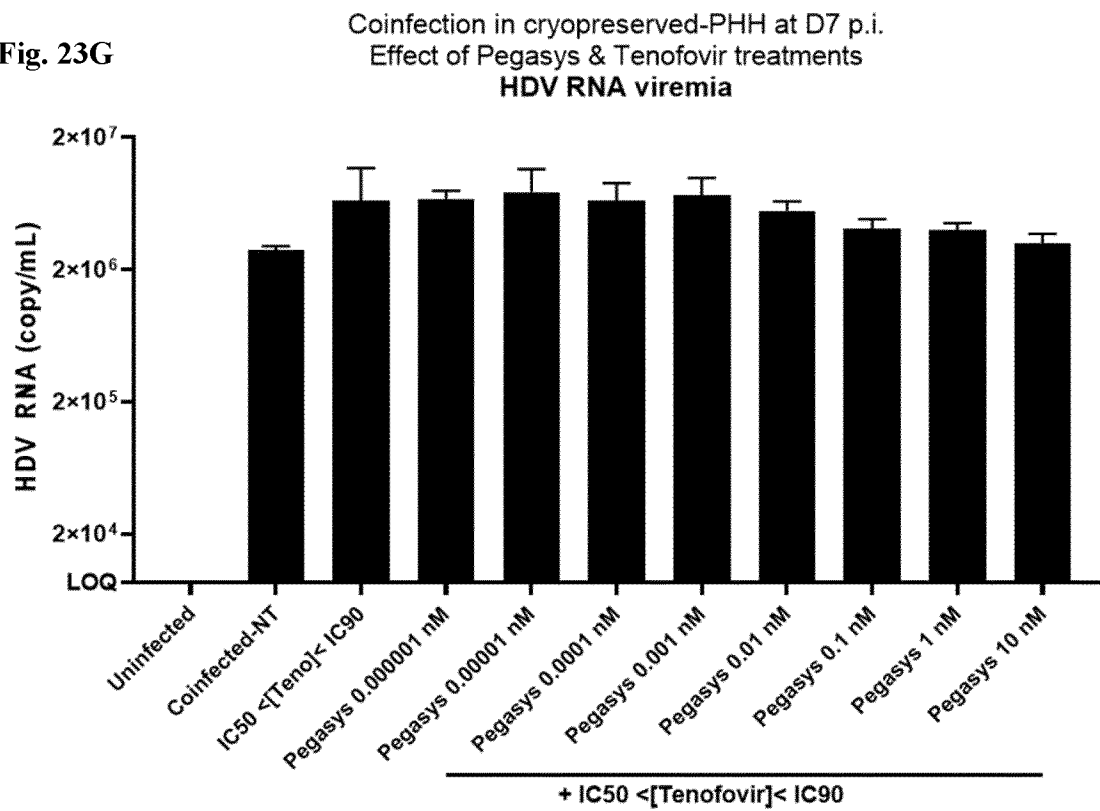
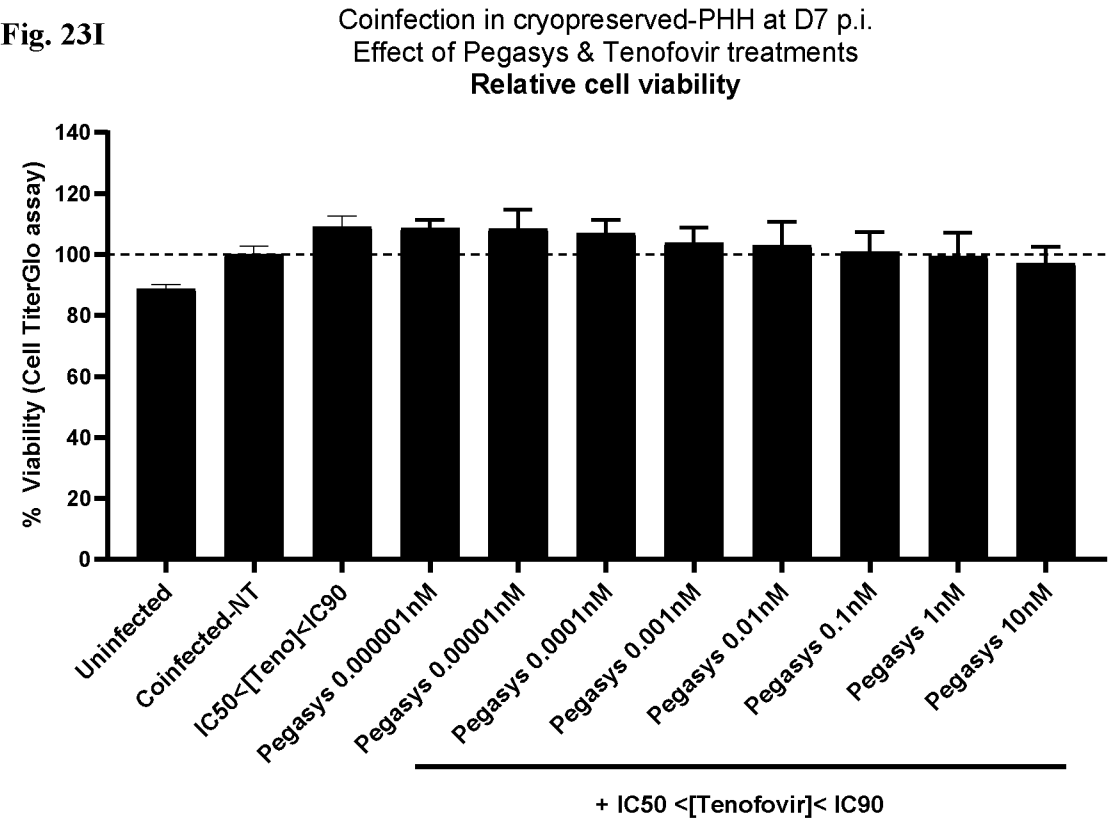
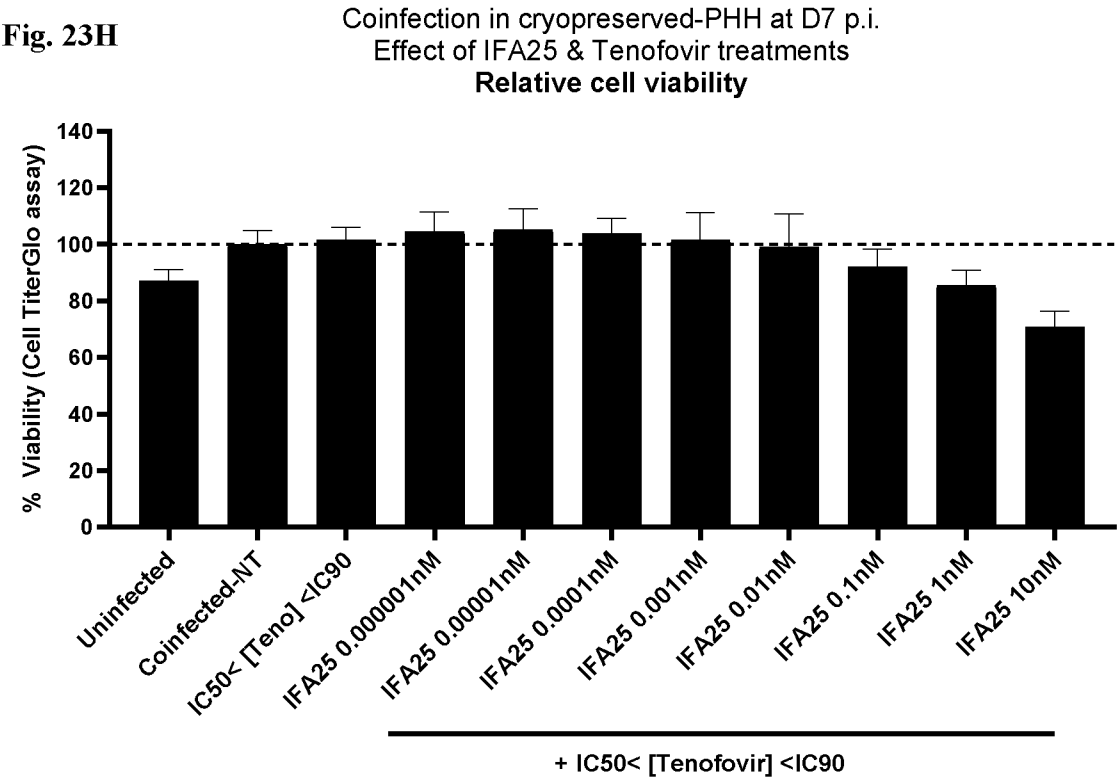


Fig. 23G





INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/059835

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/28 A61P31/14 A61K38/21 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) A61P A61K C07K 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, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2021/110561 A1 (EVOTEC INT GMBH [DE]; SANOFI SA [FR]) 10 June 2021 (2021-06-10) Figures, Tables, Examples; paragraph [0004] -----	1 - 17
Y	WO 2021/110562 A1 (EVOTEC INT GMBH [DE]; SANOFI SA [FR]) 10 June 2021 (2021-06-10) Figures, Tables, Examples -----	1 - 17
Y	WO 2007/130493 A2 (UNIV COLORADO [US]; KEDL ROSS [US] ET AL.) 15 November 2007 (2007-11-15) paragraphs [0001], [0018], [0144] claims 21, 60 ----- - / - -	1 - 17
☒ 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 6 June 2024		Date of mailing of the international search report 17/06/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Rojo Romeo, Elena

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2024/059835

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. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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/EP2024/059835

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUANG CHI-RUEI ET AL: "Hepatitis D virus infection, replication and cross-talk with the hepatitis B virus", WORLD JOURNAL OF GASTROENTEROLOGY, vol. 20, no. 40, 28 October 2014 (2014-10-28), page 14589, XP093082489, CN ISSN: 1007-9327, DOI: 10.3748/wjg.v20.i40.14589 the whole document -----	1-17
Y	WO 2018/036852 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 1 March 2018 (2018-03-01) Discloses anti-CD40 antibodies of SEQ ID NO: 56, 57, 58 and 52, 53, 54, and 51/55 -----	1-17
Y	WO 03/040170 A2 (PFIZER PROD INC [US]; ABGENIX INC [US] ET AL.) 15 May 2003 (2003-05-15) Discloses anti-CD40 antibodies of SEQ ID NO: 56, 57, 58 and 52, 53, 54, and 51/55 -----	1-17
A	WO 2022/258720 A1 (EVOTEC INT GMBH [DE]) 15 December 2022 (2022-12-15) the whole document -----	1-17

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