Figure 1

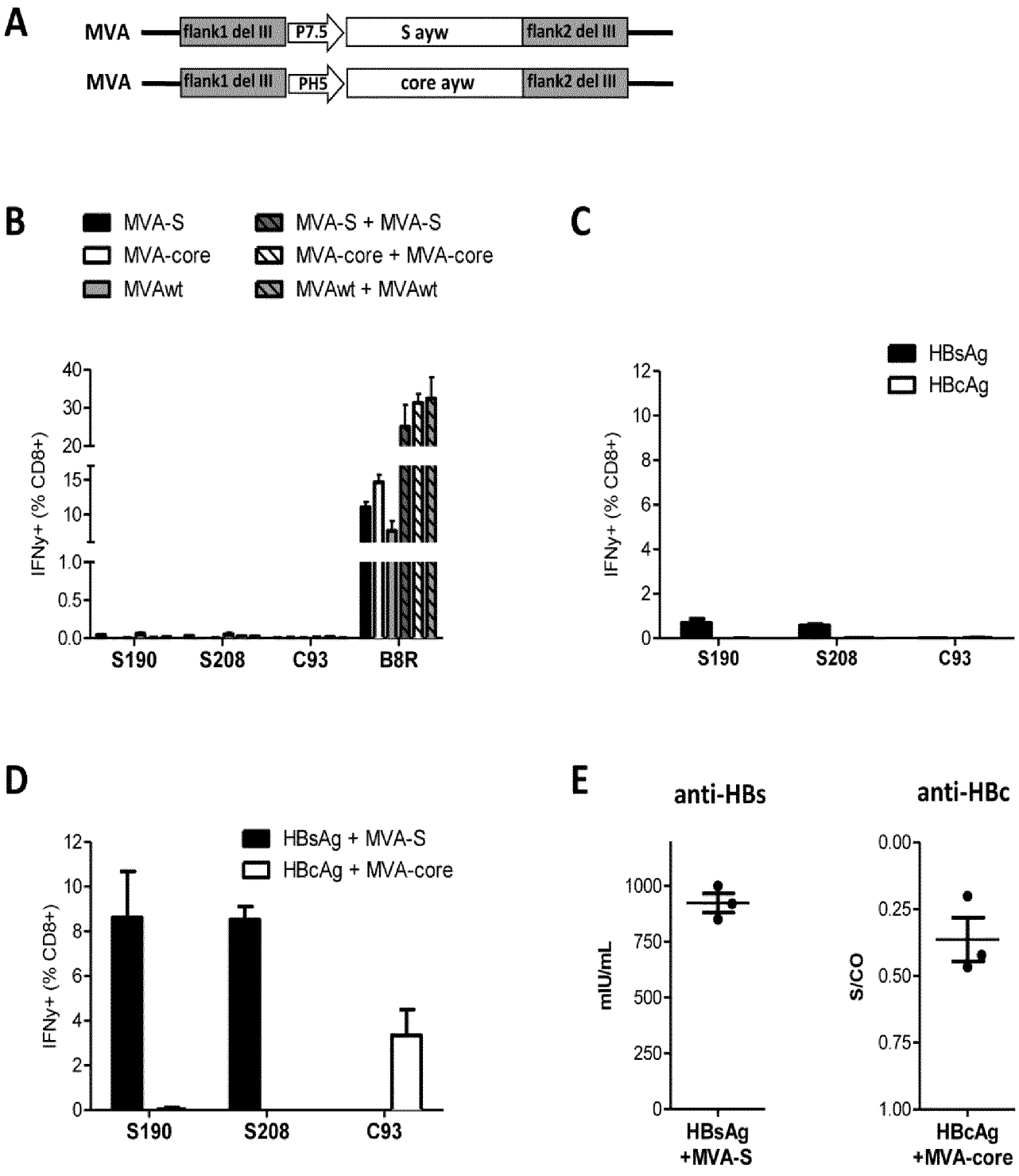

A
MVA
flank1 del III
P7.5
S ayw
flank2 del III
MVA
flank1 del III
PH5
core ayw
flank2 del III
B
MVA-S
MVA-core
MVAwt
MVA-S + MVA-S
MVA-core + MVA-core
MVAwt + MVAwt
IFNγ+ (% CD8+)
S190
S208
C93
B8R
C
HBsAg
HBcAg
IFNγ+ (% CD8+)
S190
S208
C93
D
HBsAg + MVA-S
HBcAg + MVA-core
IFNγ+ (% CD8+)
S190
S208
C93
E
anti-HBs
anti-HBc
mIU/mL
S/CO
HBsAg +MVA-S
HBcAg +MVA-core

Figure 2

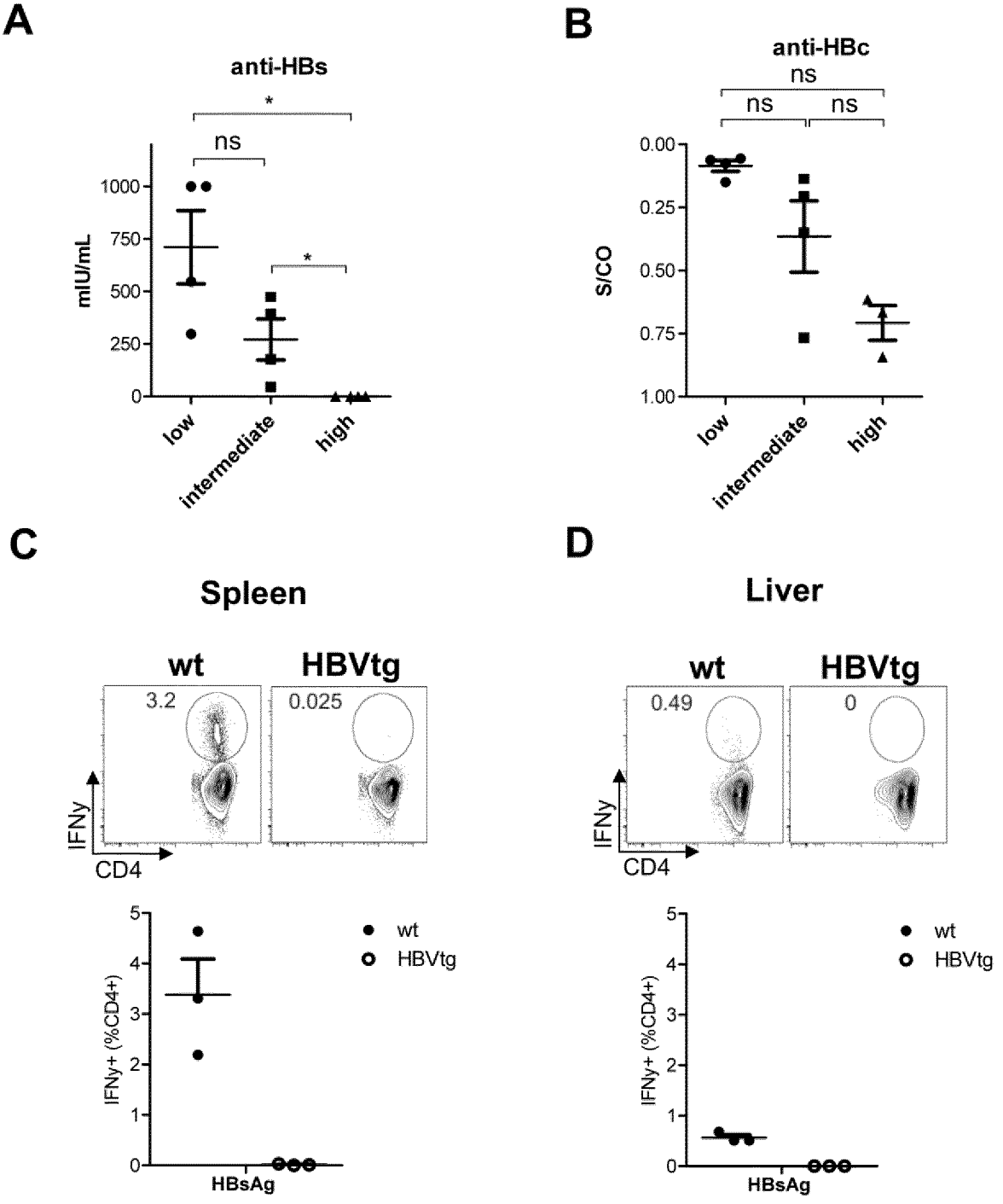

A
anti-HBs
*
ns
*
mIU/mL
1000
750
500
250
0
low
intermediate
high
B
anti-HBc
ns
ns
ns
S/CO
0.00
0.25
0.50
0.75
1.00
low
intermediate
high
C
Spleen
wt
HBVtg
3.2
0.025
IFNy
CD4
IFNy+ (%CD4+)
5
4
3
2
1
0
wt
HBVtg
HBsAg
D
Liver
wt
HBVtg
0.49
0
IFNy
CD4
IFNy+ (%CD4+)
5
4
3
2
1
0
wt
HBVtg
HBsAg

Figure 3

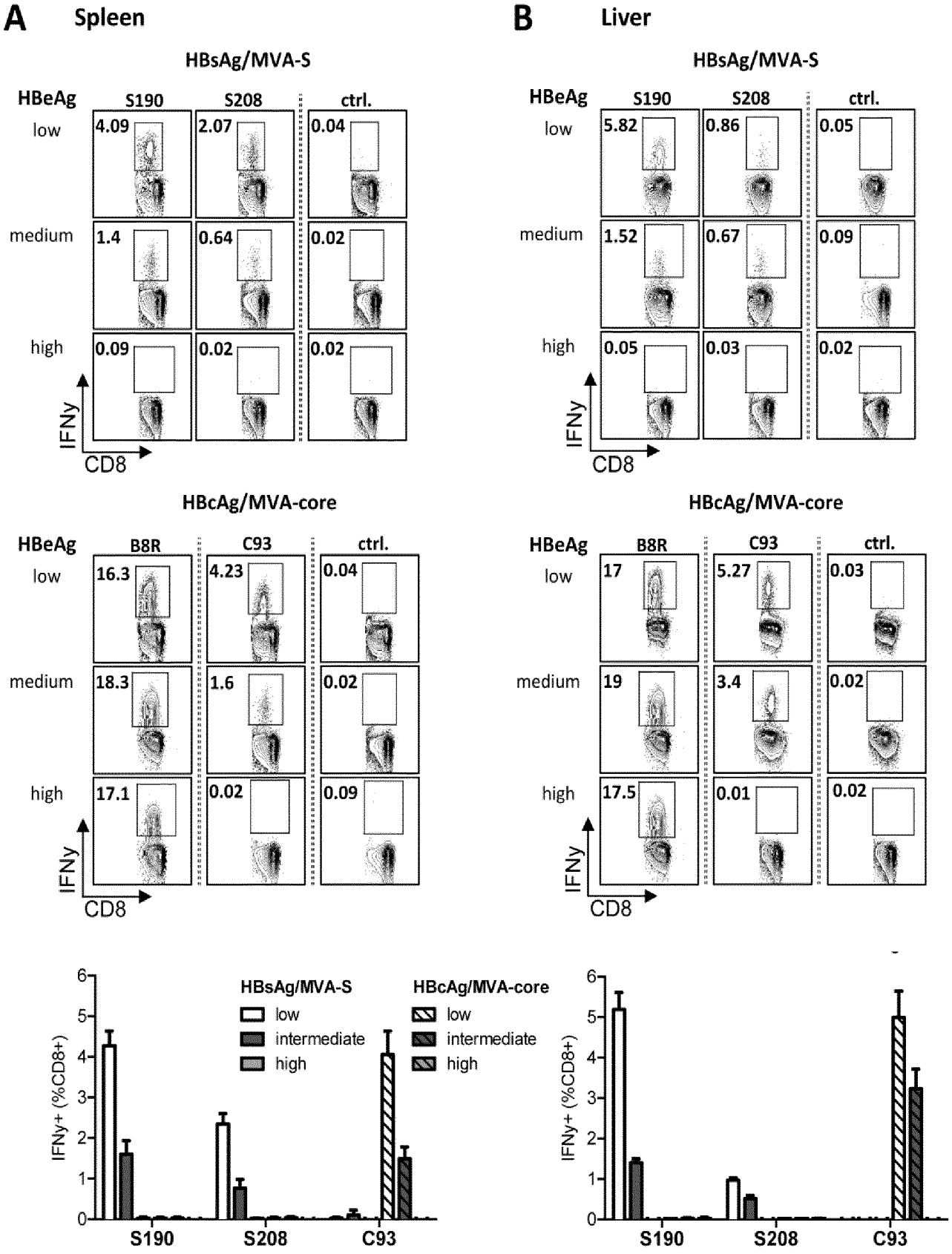

A
Spleen
HBsAg/MVA-S
HBeAg
S190
S208
ctrl.
low
medium
high
4.09
2.07
0.04
1.4
0.64
0.02
0.09
0.02
0.02
IFNy
CD8
HBcAg/MVA-core
B8R
C93
ctrl.
16.3
4.23
0.04
18.3
1.6
0.02
17.1
0.02
0.09
B
Liver
HBsAg/MVA-S
5.82
0.86
0.05
1.52
0.67
0.09
0.05
0.03
0.02
HBcAg/MVA-core
17
5.27
0.03
19
3.4
0.02
17.5
0.01
0.02
HBsAg/MVA-S
HBcAg/MVA-core
low
intermediate
high
IFNy+ (%CD8+)
S190
S208
C93

Figure 4

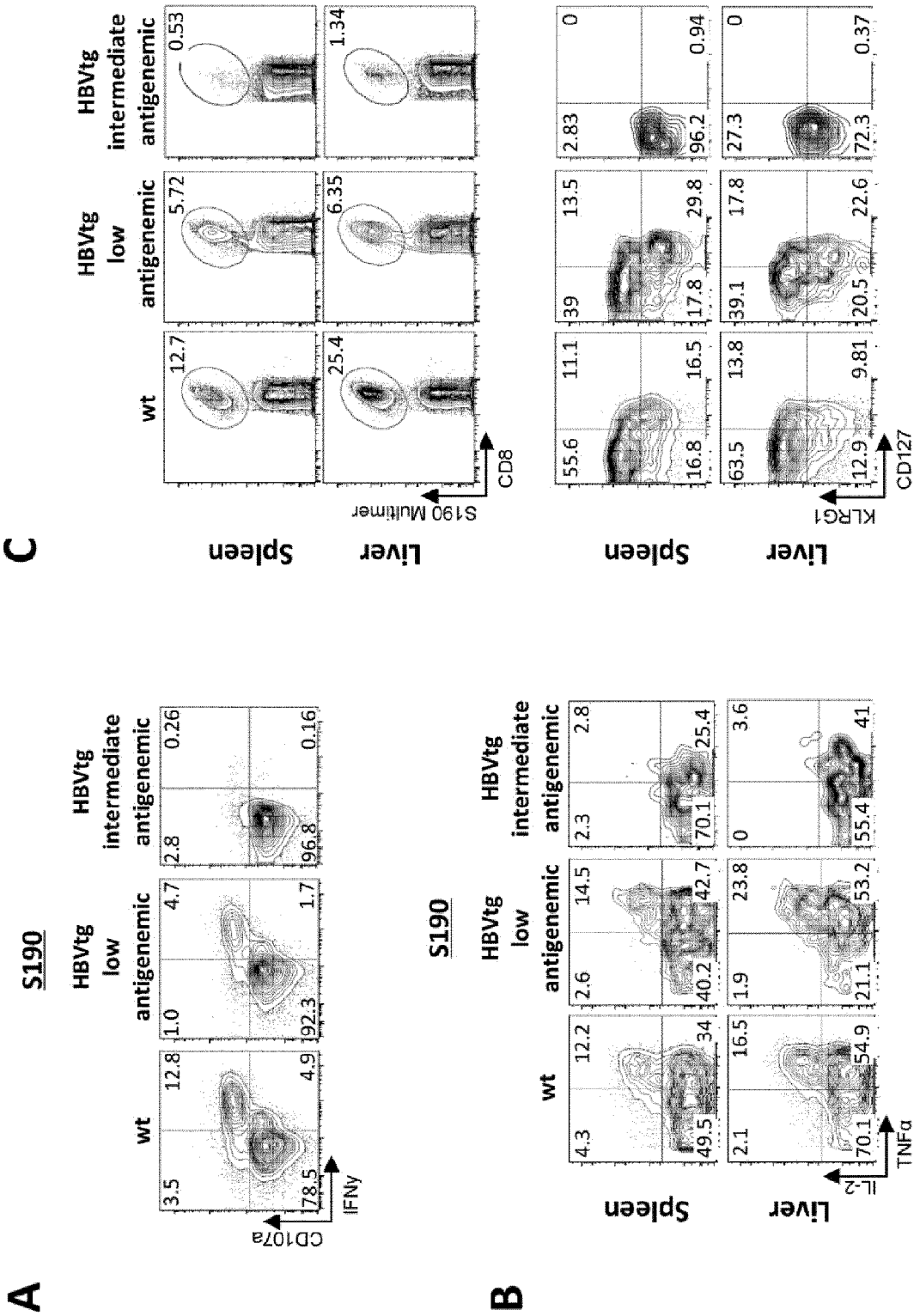

A
S190
wt
HBVtg low antigenemic
HBVtg intermediate antigenemic
3.5
12.8
4.9
78.5
1.0
4.7
92.3
1.7
2.8
0.26
96.8
0.16
CD107a
IFNγ
B
S190
wt
HBVtg low antigenemic
HBVtg intermediate antigenemic
4.3
12.2
49.5
34
2.6
14.5
40.2
42.7
2.3
2.8
70.1
25.4
2.1
16.5
70.1
54.9
1.9
23.8
21.1
53.2
0
3.6
55.4
41
Liver
Spleen
IL-2
TNFα
C
wt
HBVtg low antigenemic
HBVtg intermediate antigenemic
12.7
25.4
5.72
6.35
0.53
1.34
S190 Multimer
CD8
55.6
11.1
16.8
16.5
39
13.5
17.8
29.8
2.83
0
96.2
0.94
63.5
13.8
12.9
9.81
39.1
17.8
20.5
22.6
27.3
0
72.3
0.37
Liver
Spleen
KLRG1
CD127

Figure 5

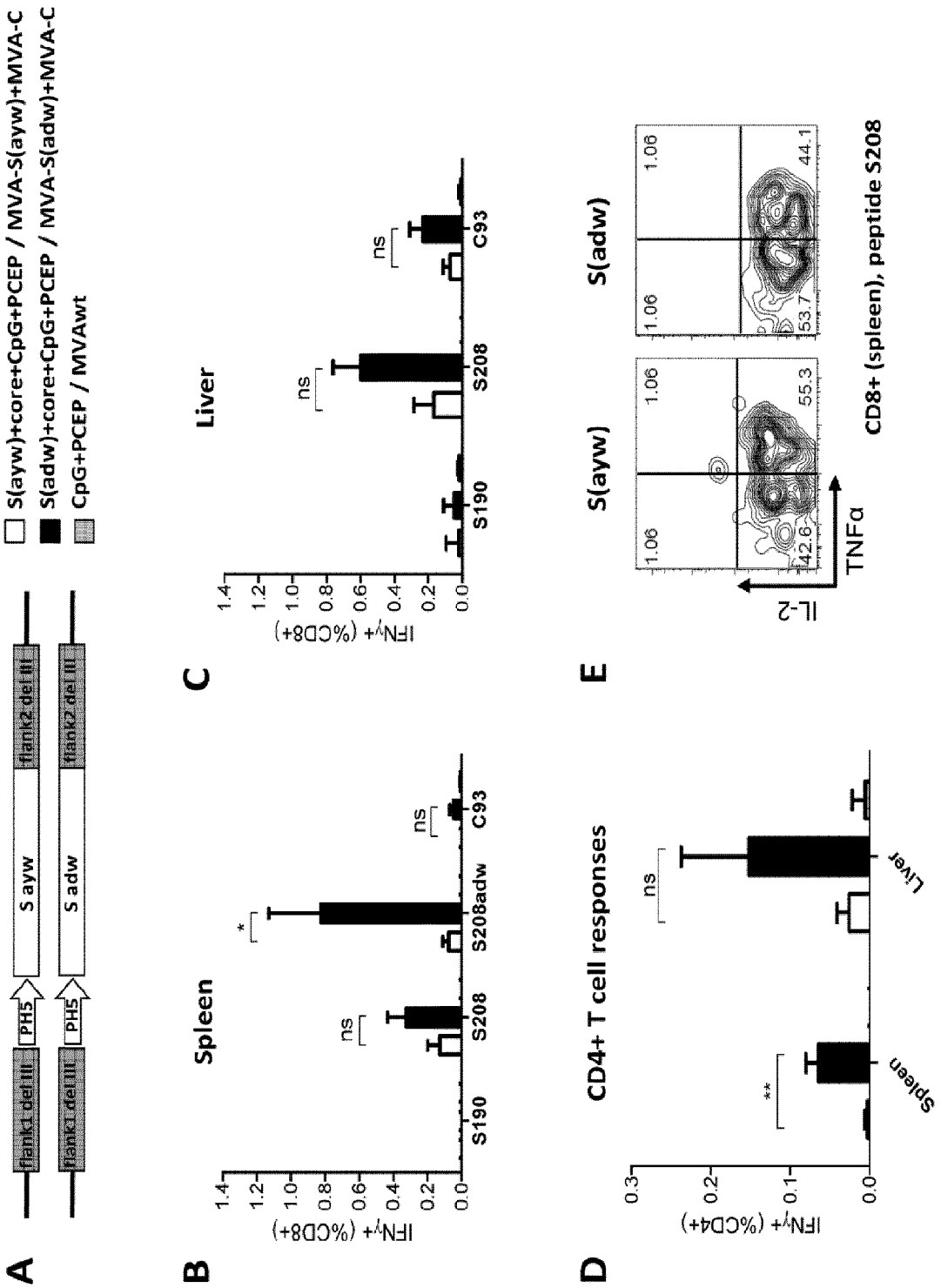
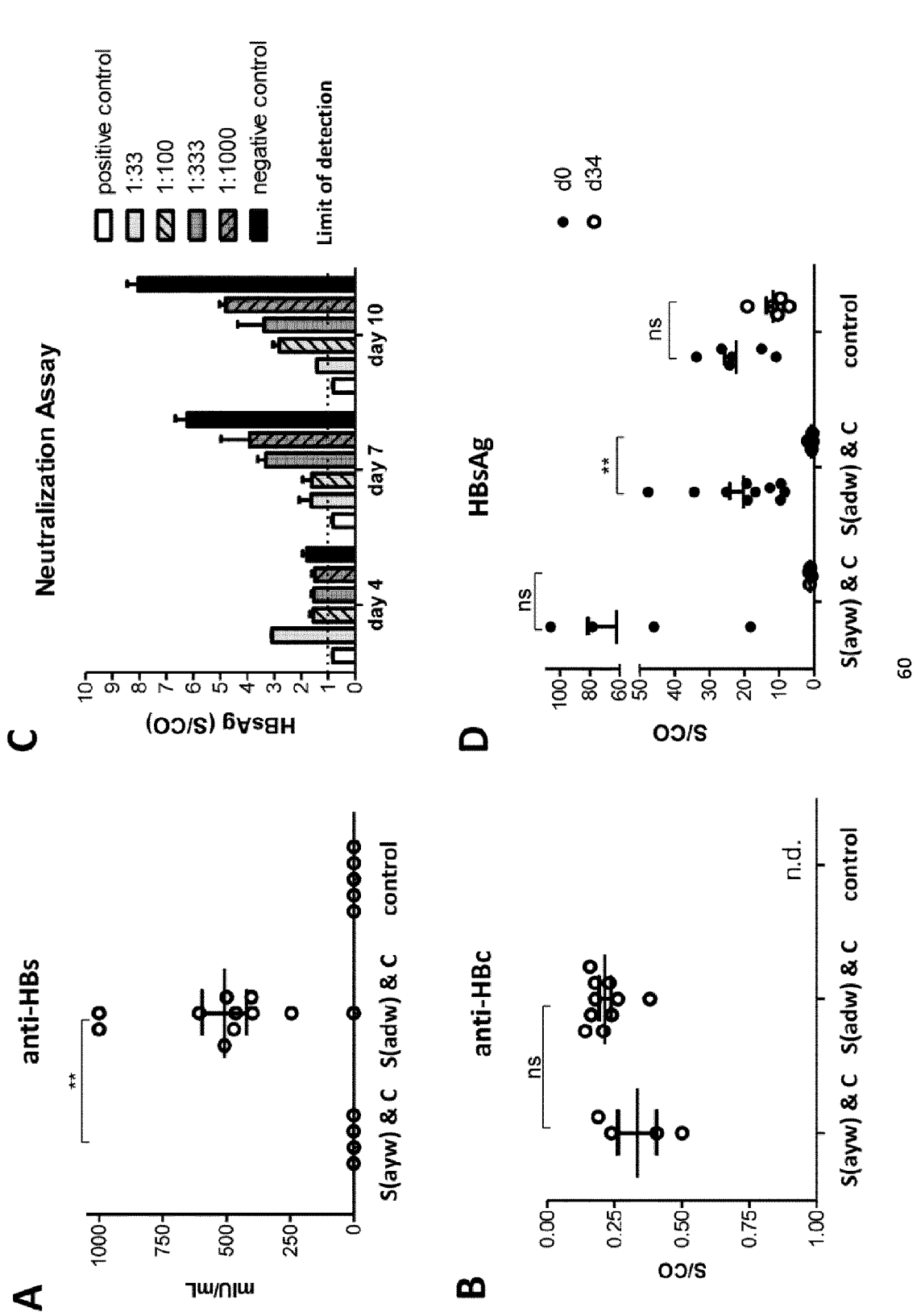

A
S(ayw)+core+CpG+PCEP / MVA-S(ayw)+MVA-C
S(adw)+core+CpG+PCEP / MVA-S(adw)+MVA-C
CpG+PCEP / MVAwt
flank1 del III
PH5
S ayw
flank2 del III
flank1 del III
PH5
S adw
flank2 del III
B
Spleen
IFNγ+ (%CD8+)
S190
S208
S208adw
C93
ns
*
C
Liver
IFNγ+ (%CD8+)
S190
S208
C93
ns
ns
D
CD4+ T cell responses
IFNγ+ (%CD4+)
Spleen
Liver
**
ns
E
S(ayw)
S(adw)
1.06
42.6
55.3
53.7
44.1
IL-2
TNFα
CD8+ (spleen), peptide S208

Figure 6


A
anti-HBs
**
mIU/mL
1000
750
500
250
0
S(ayw) & C
S(adw) & C
control
B
anti-HBc
ns
S/CO
0.00
0.25
0.50
0.75
1.00
n.d.
S(ayw) & C
S(adw) & C
control
C
Neutralization Assay
HBsAg (S/CO)
positive control
1:33
1:100
1:333
1:1000
negative control
Limit of detection
day 4
day 7
day 10
D
HBsAg
d0
d34
ns
**
ns
S/CO
S(ayw) & C
S(adw) & C
control

60

Figure 7

A
glycosylated
non-glycosylated
MVA-S
MVA-core
MVAwt
HBsAg
core
actin
B
S/CO
25
20
15
10
5
0
10
20
30
hours post infection
limit of detection
MVA-S
MVA-core
MVAwt

Figure 8

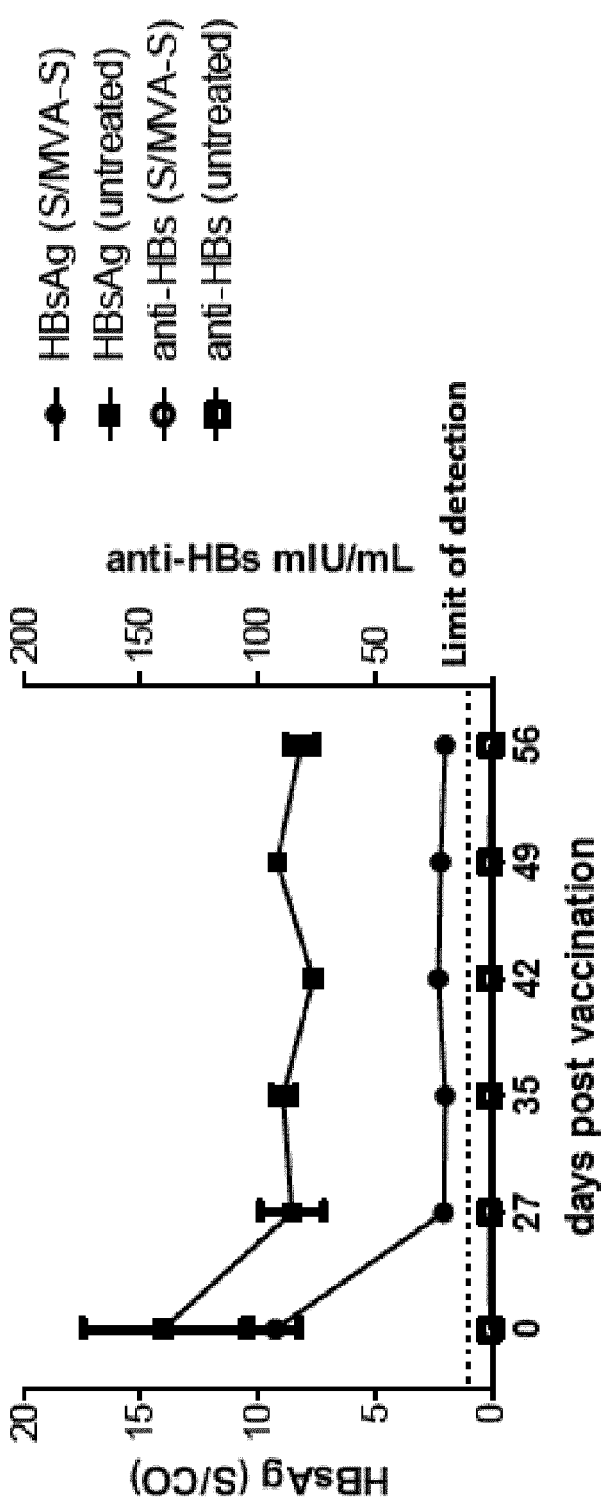
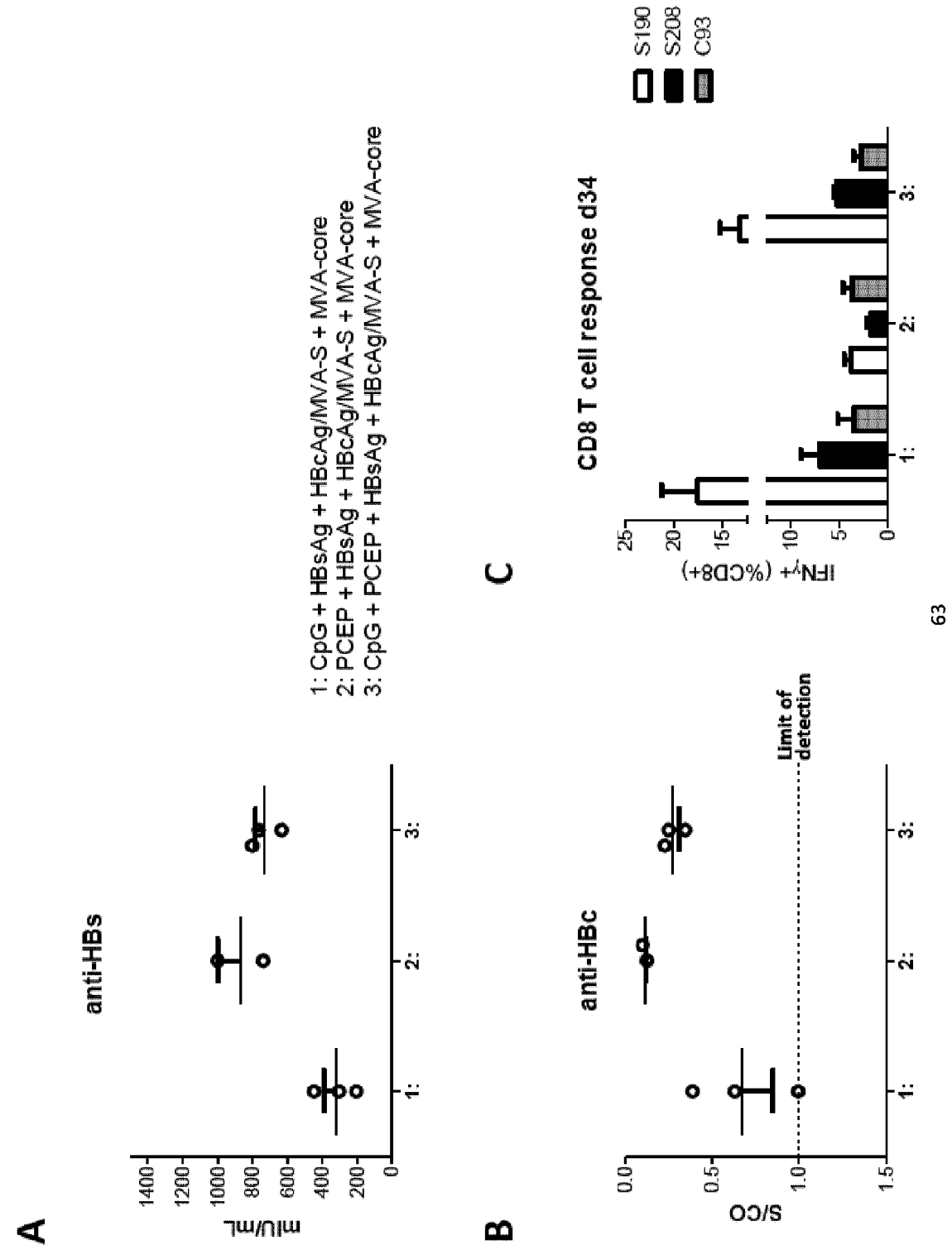

HBsAg (S/MVA-S)
HBsAg (untreated)
anti-HBs (S/MVA-S)
anti-HBs (untreated)
anti-HBs mIU/mL
200
150
100
50
Limit of detection
HBsAg (S/CO)
20
15
10
5
0
0
27
35
42
49
56
days post vaccination

Figure 9


A
anti-HBs
mIU/mL
1400
1200
1000
800
600
400
200
0
1:
2:
3:
1: CpG + HBsAg + HBcAg/MVA-S + MVA-core
2: PCEP + HBsAg + HBcAg/MVA-S + MVA-core
3: CpG + PCEP + HBsAg + HBcAg/MVA-S + MVA-core
B
anti-HBc
S/CO
0.0
0.5
1.0
1.5
Limit of detection
C
CD8 T cell response d34
S190
S208
C93
IFNγ+ (%CD8+)
25
20
15
10
5
0

63

Figure 10

Antigenemia	HBeAg (S/CO)	HBsAg (S/CO)	Serum HBV DNA copies/ml
Low	<2	neg.	$5x10^3$ to $5x10^4$
Intermediate	2-6	neg.	$1x10^4$ to $1x10^5$
High	7-60	5-45	$1x10^5$ to $1x10^6$

Figure 11

peptide	specificity	sequence	
S_{150}	HBsAg (ayw)	VWLSVIWM#	(SEQ ID NO: 19)
S_{208}	HBsAg (ayw)	ILSPFLPL	(SEQ ID NO: 21)
S_{208adw}	HBsAg (adw)	IVSPFIPL	(SEQ ID NO: 22)
S Pool	HBsAg (ayw)	15-mer peptides covering the C-terminus (aa 145-226) of S subtype ayw	(SEQ ID NO: 23)
C_{93}	HBcAg (ayw)	MGLKFRQL	(SEQ ID NO: 24)
$B8R_{20}$	MVA	TSYKFESV	(SEQ ID NO: 20)
β-Gal_{96}	β-galactosidase (negative control)	DAPIYTNV	(SEQ ID NO: 25)

#peptide is generated only from endogenously expressed antigen

Figure 12

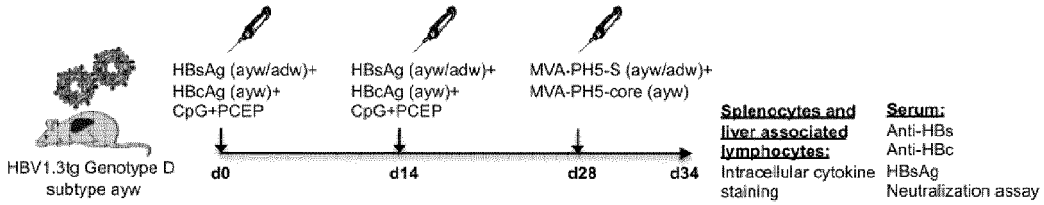


Figure 13

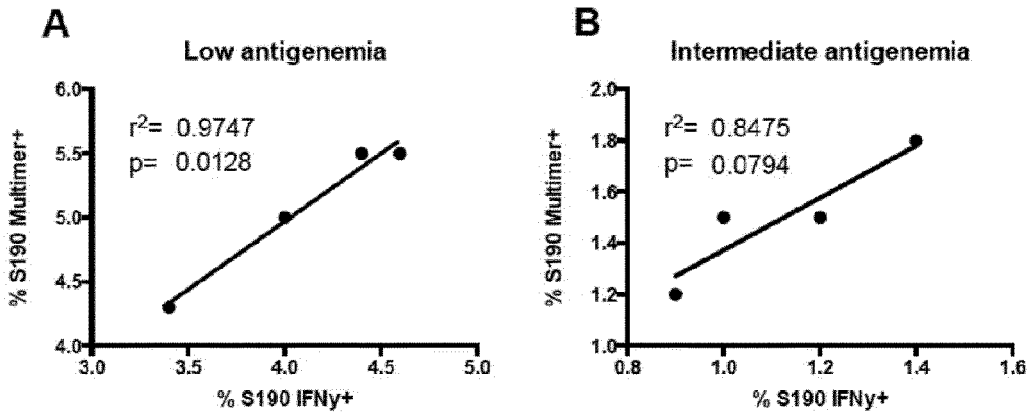


Figure 14

HBeAg	Serum anti-HBs [mIU/mL]	serum HBsAg [IU/ml]	HBsAg in precipitated immune complexes [IU/mL]
Mouse 1 High	nd	1160	7,6
Mouse 2 High	nd	85	5,7
Mouse 3 High	nd	24	6,4
Mouse 4 Intermediate	800	3	4,7
Mouse 1 Low	>10000	nd	0,8

Figure 15

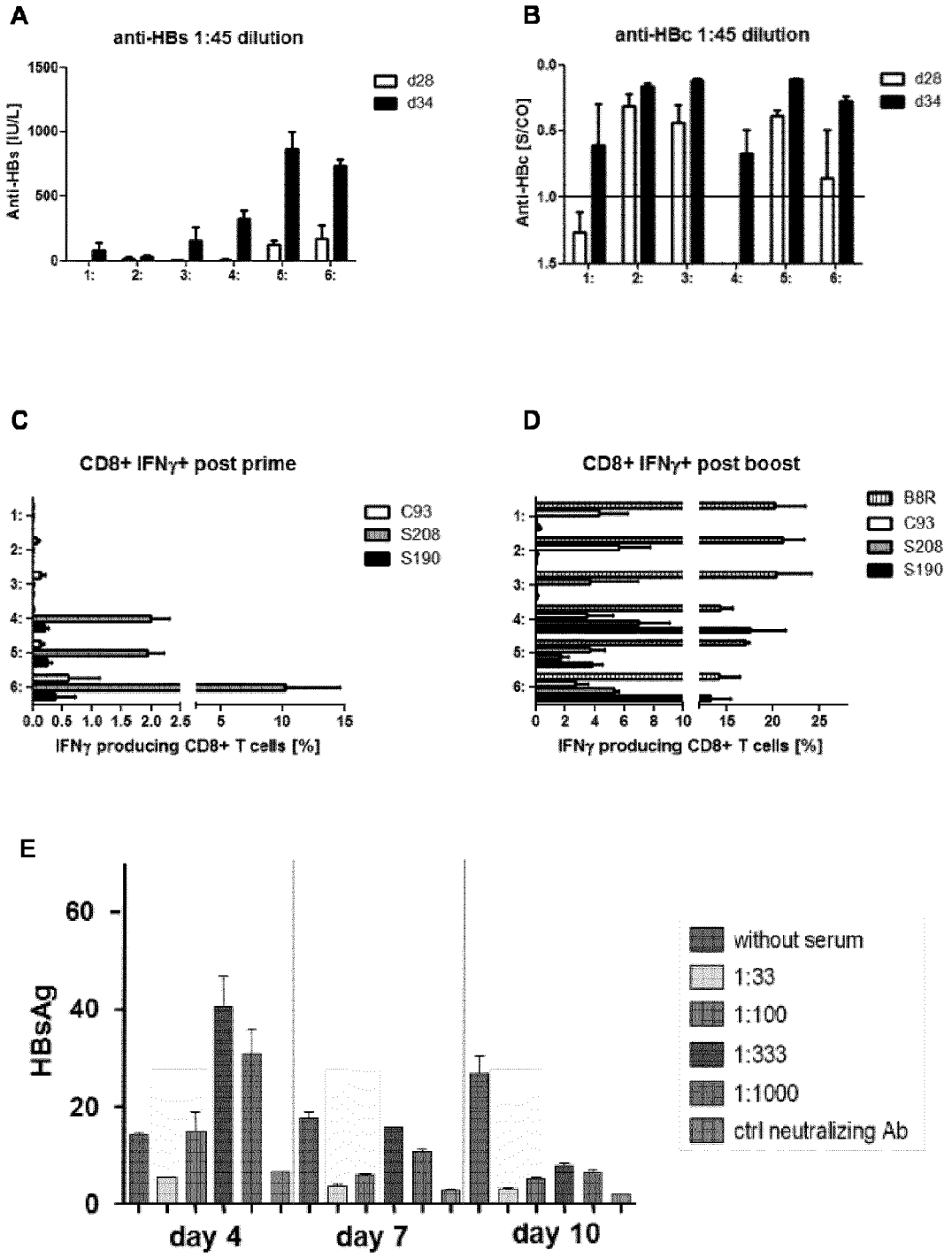

A
anti-HBs 1:45 dilution
Anti-HBs [IU/L]
1500
1000
500
0
d28
d34
1:
2:
3:
4:
5:
6:
B
anti-HBc 1:45 dilution
Anti-HBc [S/CO]
0.0
0.5
1.0
1.5
d28
d34
C
CD8+ IFNγ+ post prime
C93
S208
S190
0.0 0.5 1.0 1.5 2.0 2.5 5 10 15
IFNγ producing CD8+ T cells [%]
D
CD8+ IFNγ+ post boost
B8R
C93
S208
S190
0 2 4 6 8 10 15 20 25
IFNγ producing CD8+ T cells [%]
E
HBsAg
60
40
20
0
day 4
day 7
day 10
without serum
1:33
1:100
1:333
1:1000
ctrl neutralizing Ab

Figure 16

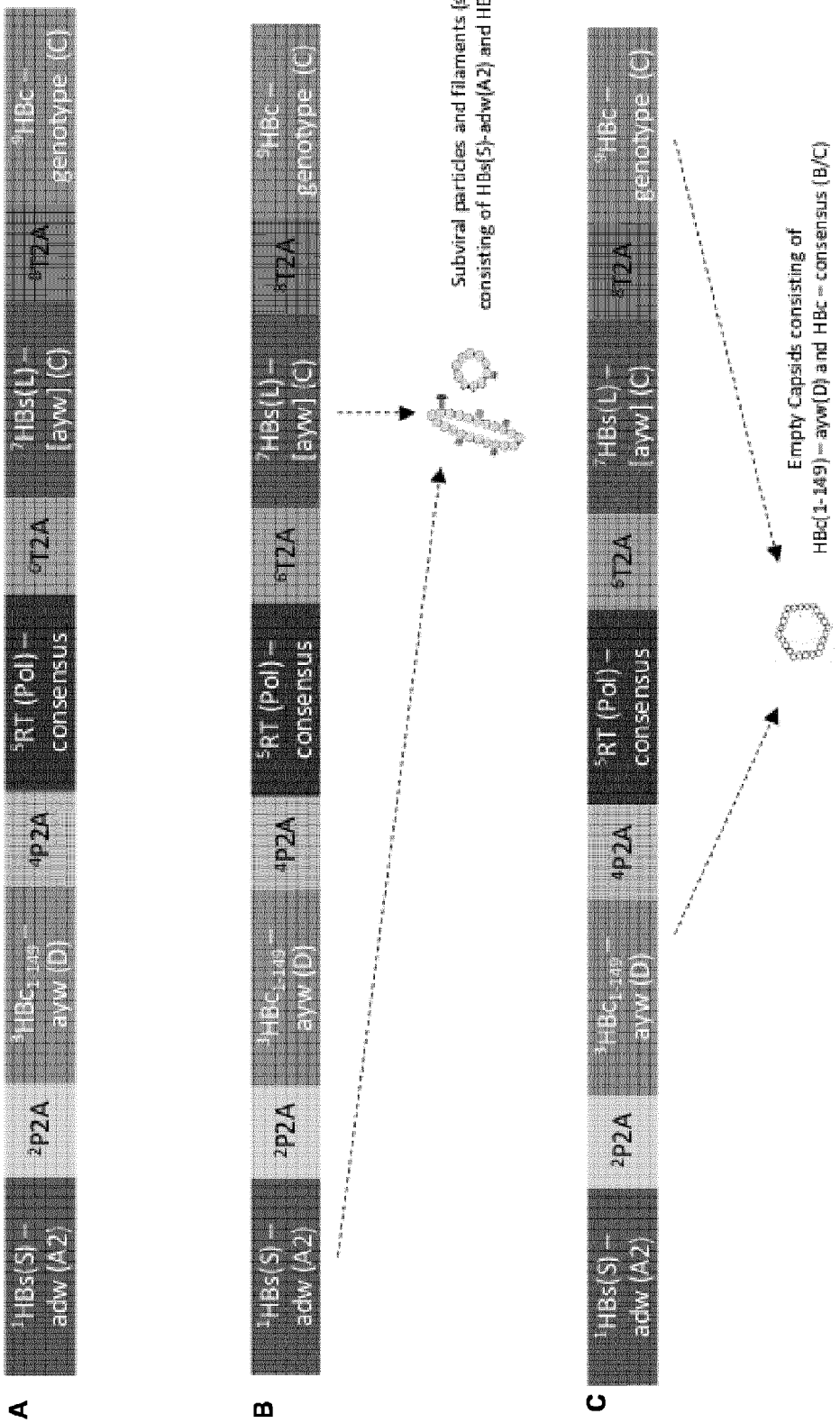

A
1HBs(S) – adw (A2)
2P2A
3HBc1-149 – ayw (D)
4P2A
5RT (Pol) – consensus
6T2A
7HBs(L) – [ayw] (C)
8T2A
9HBc – genotype (C)
B
1HBs(S) – adw (A2)
2P2A
3HBc1-149 – ayw (D)
4P2A
5RT (Pol) – consensus
6T2A
7HBs(L) – [ayw] (C)
8T2A
9HBc – genotype (C)
Subviral particles and filaments (secreted) consisting of HBs(S)-adw(A2) and HBs(L) ayw(C)
C
1HBs(S) – adw (A2)
2P2A
3HBc1-149 – ayw (D)
4P2A
5RT (Pol) – consensus
6T2A
7HBs(L) – [ayw] (C)
8T2A
9HBc – genotype (C)
Empty Capsids consisting of HBc(1-149) – ayw(D) and HBc – consensus (B/C)

Figure 17

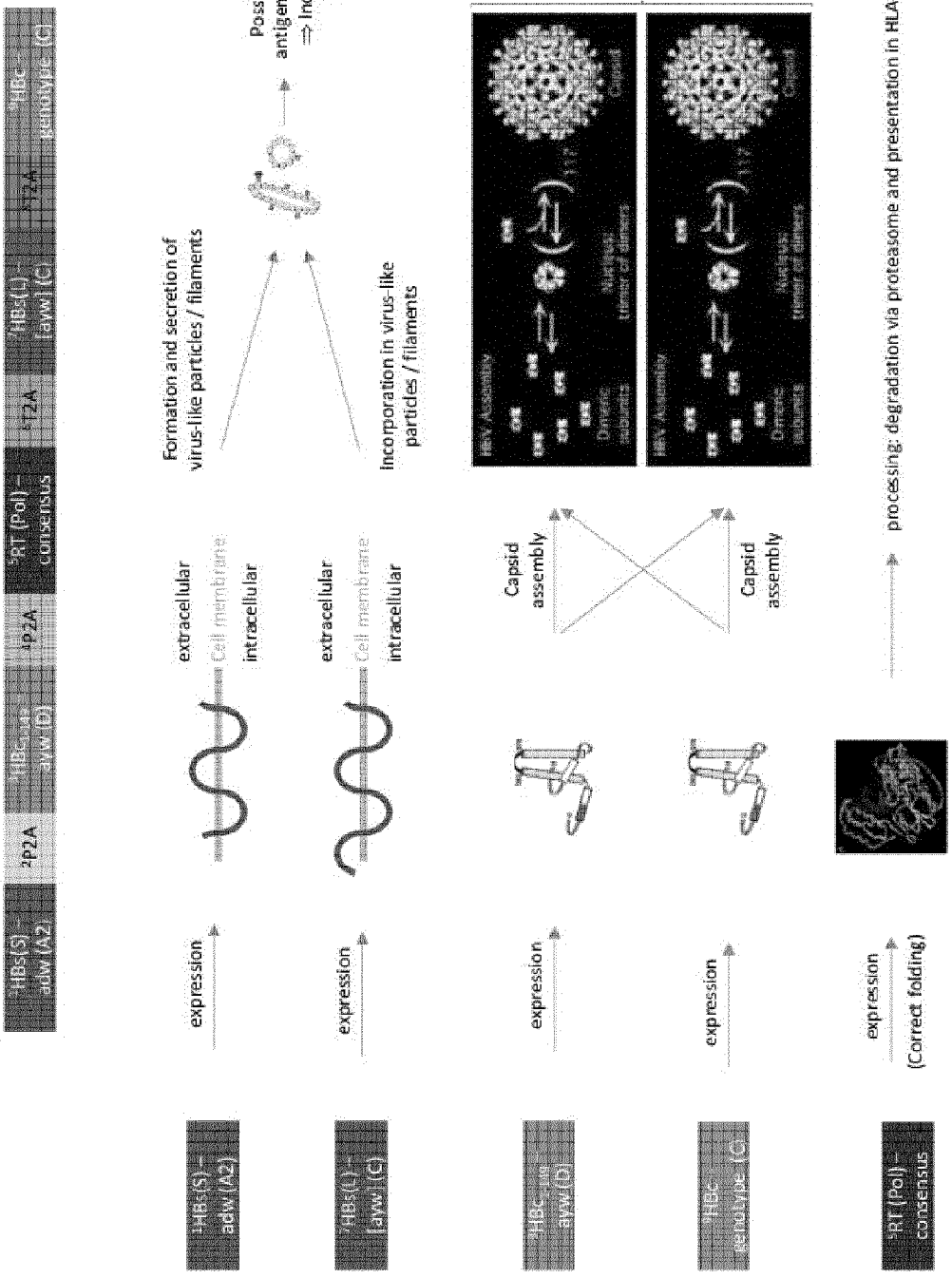

1HBs(S) – adw (A2)
2P2A
1HBc aa1-149 ayw (D)
3P2A
5RT (Pol) – consensus
4T2A
6HBs(L) – ayw1 (C)
5T2A
7HBc – genotype (C)
expression
extracellular
Cell membrane
intracellular
Formation and secretion of virus-like particles / filaments
Incorporation in virus-like particles / filaments
Possible uptake by antigen-presenting cells
⇒ Increase immune response
Capsid assembly
Trigger immune response
HBV Assembly
Dimers
subunits
Nucleus
trimer of dimers
Capsid
processing: degradation via proteasome and presentation in HLA-context
(Correct folding)

Figure 1B



Most of the partially unprocessed are assumed to increase the immune response (especially enhance and broaden the adaptive immune response) due to incorporation into secreted virus-like particles / filaments:

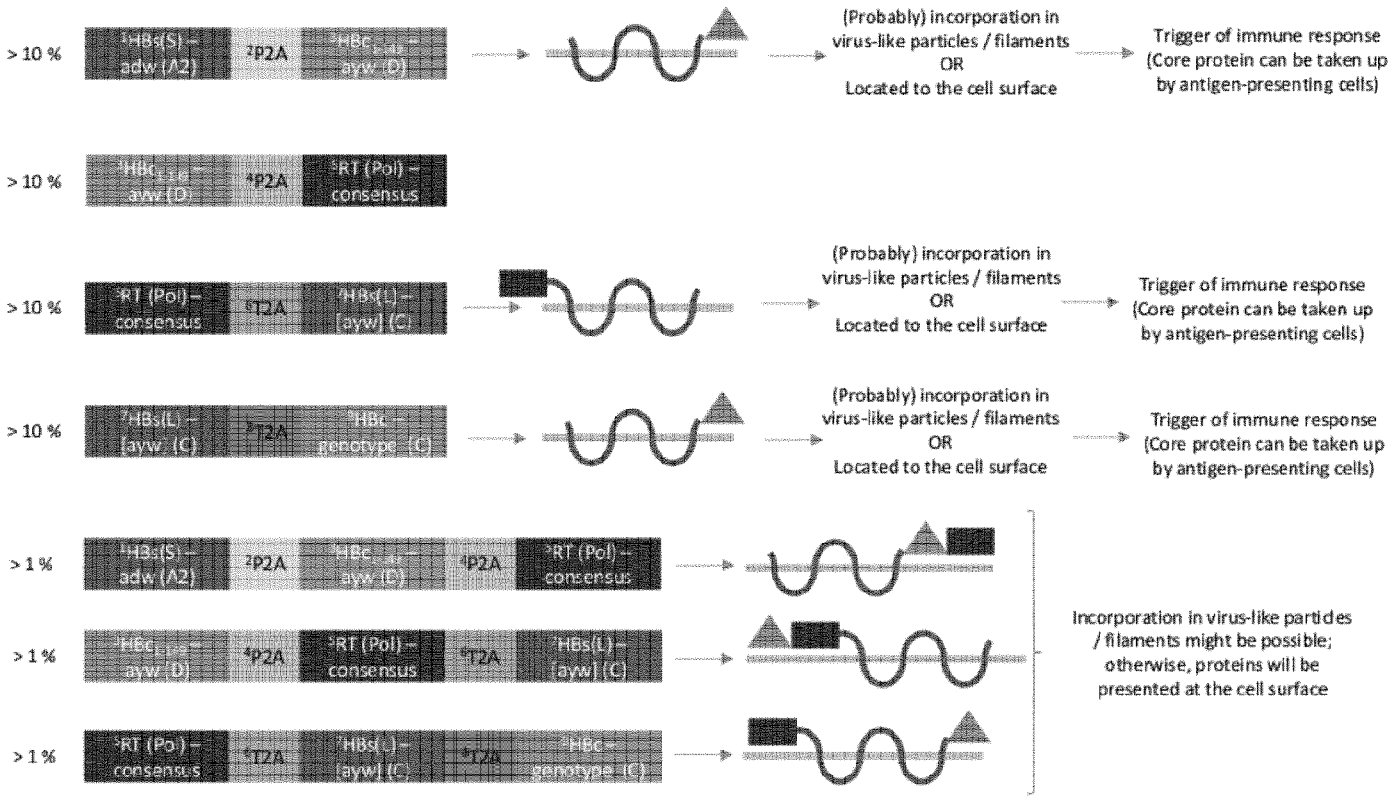


Figure 19

Small envelope protein of HBV A2/adw2 including C-terminal overhang

MENITSGFLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGSPVCLGQNSQSPTSNHSPTSCPPI
CPGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSTTTSTGPCKTCTTPAQGNSMFPS
CCCTKPTDGNCTCIPIPSSWAFAKYLWEWASVRFSWLSLLVPFVQWFVGLSPTVWLSAIWMMWYWGPS
LYSIVSPFIPLLPIFFCLWVYIGSGATNFSLLKQAGDVEENPG

(SEQ ID NO: 10)

Figure 20

Core protein fragment 1-149 of HBV D/ayw including N- and C-terminal overhangs

PMDIDPYKEFGATVELLSFLPSDFFPSVRDLLDTASALYREALESPEHCSPHHTALRQAILCWGELMT
LATWVGVNLEDPASRDLVVSYVNTNMGLKFRQLLWFHISCLTFGRETVIEYLVSFGVWIRTPPAYRPP
NAPILSTLPETTVVGSGATNFSLLKQAGDVEENPG

(SEQ ID NO: 12)

Figure 21

RT domain of HBV polymerase including N- and C-terminal overhangs

PEDWGPCAEHGEHHIRIPRTPARVTGGVFLVDKNPHNTAESRLVVDFSQFSRGKTRVSWPKFAVPNLQ
SLTNLLSSNLSWLSLDVSAAFYHIPLHPAAMPHLLVGSSGLSRYVARLSSNSRIFNHQHGNLQNLHDS
CSRNLYVSLLLLYKTFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAFPHCLAFSY
MDDVVLGAKSVQHLESLFTAVTNFLLSLGIHLNPNKTKRWGYSLNFMGYVIGSWGTLPQEHIVQKIKQ
CFRKLPVNRPIDWKVCQRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLNLY
PVARQGSGEGRGSLLTCGDVEENPG

(SEQ ID NO: 16)

Figure 22

Large envelope protein of HBV C/ayw including N- and C-terminal overhangs

PMGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWPEANQVGAGAFGPGF
TPPHGGLLGWSPQAQGILTTVPAAPPPASTNRQSGRQPTPISPPLRDSHPQAMQWNSTTFHQALLDPR
VRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPNMENTTSGFLGPLLVLQAGFLLLTRILTIP
QSLDSWWTSLNFLGGAPTCPGQNSQSPTSNHSPTSCPPICPGYRWMCLRRFIIFLFILLLCLIFLLVL
LDYQGMLPVCPLLPGTSTTSTGPCRTCTIPAQGTSMFPSCCCTKPSDGNCTCIPIPSSWAFAKFLWEW
ASVRFSWLSLLVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYNILSPFLPLLPIFFCLWVYIGSGEGRG
SLLTCGDVEENPG
(SEQ ID NO: 14)

Figure 23

Core protein of HBV C/ayw including N- terminal overhang

PMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALESPEHCSPHHTALRQAILCWGELMN
LATWVGSNLEDPASRELVVSYVNVNMGLKIRQLLWFHISCLTFGRETVLEYLVSFGVWIRTPPAYRPP
NAPILSTLPETTVVRRRGRSPRRRTPSPRRRRSQSPRRRRSQSRESQC
(SEQ ID NO: 15)

Figure 24

Consensus sequence of RT-domain of HBV polymerase:

EDWGPCTEHGEHHIRIPRTPARVTGGVFLVDKNPHNTAESRLVVDFSQFSRGNTRVSWPKFAVPNLQS
LTNLLSSNLSWLSLDVSAAFYHLPLHPAAMPHLLVGSSGLSRYVARLSSNSRIINHQHGTMQNLHDSC
SRNLYVSLLLLYKTFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAFPHCLAFSYM
DDVVLGAKSVQHLESLYTAVTNFLLSLGIHLNPNKTKRWGYSLNFMGYVIGSWGTLPQEHIVQKIKQC
FRKLPVNRPIDWKVCQRIVGLLGFAAPFTQCGYPALMPLYACIQAKQAFTFSPTYKAFLCKQYLNLYP
VAR
(SEQ ID NO: 03)

Figure 25

Consensus sequence of large envelope proteins of genotype C HBV strains

MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWPEANQVGAGAFGPGFT
PPHGGLLGWSPQAQGILTTVPAAPPPASTNRQSGRQPTPISPPLRDSHPQAMQWNSTTFHQALLDPRV
RGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPNMENTTSGFLGPLLVLQAGFFLLTRILTIPQ
SLDSWWTSLNFLGGAPTCPGQNSQSPTSNHSPTSCPPICPGYRWMCLRRFIIFLFILLLCLIFLLVLL
DYQGMLPVCPLLPGTSTTSTGPCKTCTIPAQGTSMFPSCCCTKPSDGNCTCIPIPSSWAFARFLWEWA
SVRFSWLSLLVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYNILSPFLPLLPIFFCLWVYI
(SEQ ID NO: 01)

Figure 26

Consensus sequence of core protein of genotype C HBV strains

MDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALESPEHCSPHHTALRQAILCWGELMNL
ATWVGSNLEDPASRELVVSYVNVNMGLKIRQLLWFHISCLTFGRETVLEYLVSFGVWIRTPPAYRPPN
APILSTLPETTVVRRRGRSPRRRTPSPRRRRSQSPRRRRSQSRESQC
(SEQ ID NO: 02)

Figure 27

A
siRNA
0
days
HBVxfs
Protein prime (2x)
57
71
MVA
85
91
Isolation of immune cells from spleen and liver
B
AAAAA
AAAAA
AAAAA
AAAAA
transcripts
siRNA/shRNA
HBV
3.2kb
polyA

Figure 28

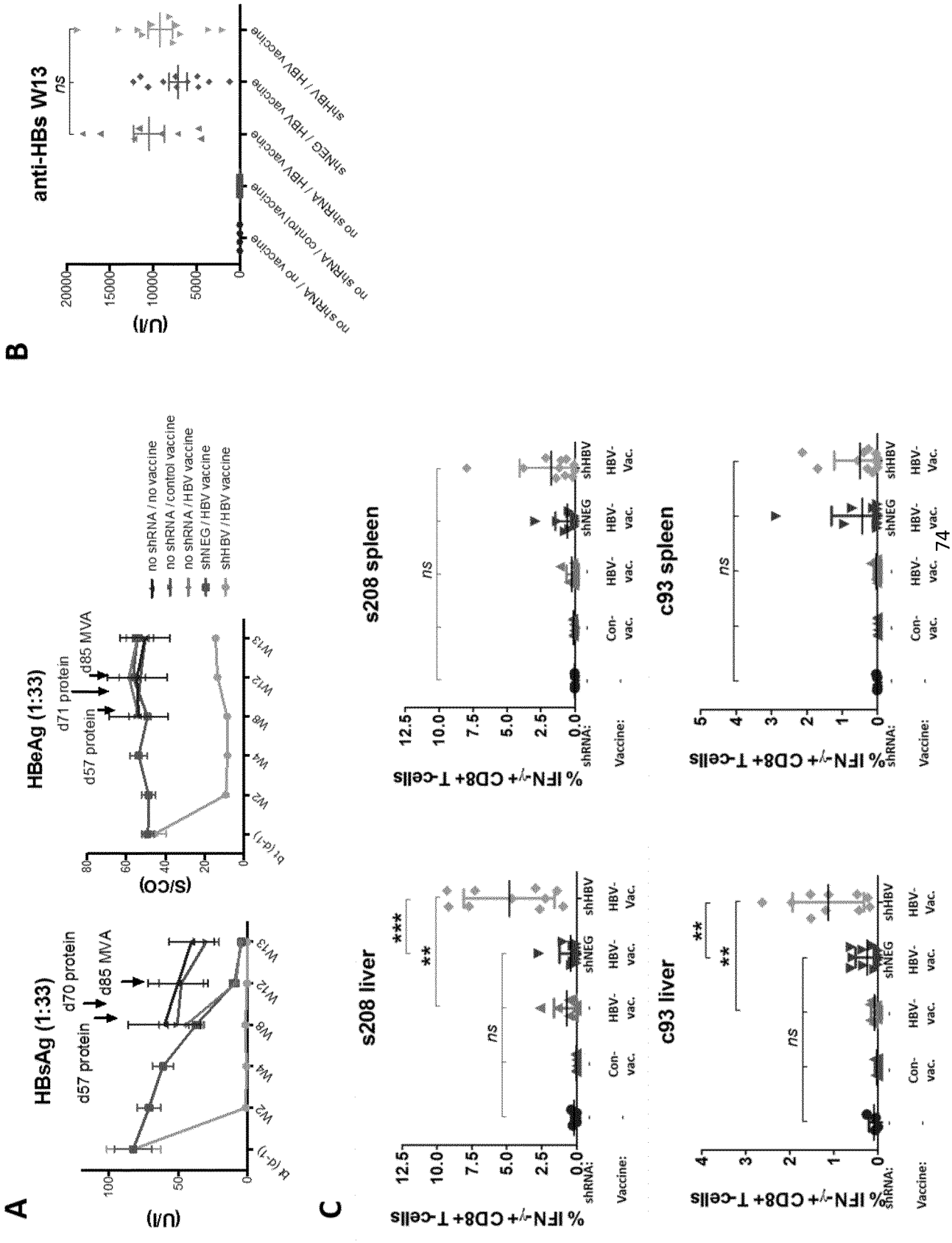
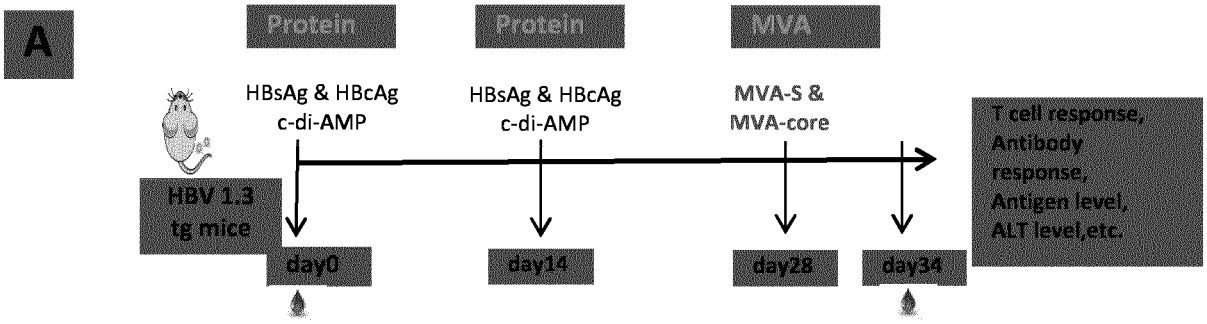

A
HBsAg (1:33)
d57 protein
d70 protein
d85 MVA
(U/l)
HBeAg (1:33)
d57 protein
d71 protein
d85 MVA
(S/CO)
no shRNA / no vaccine
no shRNA / control vaccine
no shRNA / HBV vaccine
shNEG / HBV vaccine
shHBV / HBV vaccine
B
anti-HBs W13
ns
(U/l)
no shRNA / no vaccine
no shRNA / control vaccine
no shRNA / HBV vaccine
shNEG / HBV vaccine
shHBV / HBV vaccine
C
s208 liver
s208 spleen
c93 liver
c93 spleen
% IFN-γ+ CD8+ T-cells
shRNA:
Vaccine:
Con-vac.
HBV-vac.
shNEG
shHBV
HBV-Vac.
ns
**
***

Figure 29



Group	Protein prime(2x)			MVA boost(1x)	
	vaccine	Adjuvant	Route	vaccine	Route
1	15ug HBcAg	c-di-AMP	i.m.	$3*10^6$ PFU MVA-core	i.m.
2	15ug HBcAg	c-di-AMP	i.m.	$1*10^7$ PFU MVA-core	i.m.
3	15ug HBcAg	c-di-AMP	i.m.	$3*10^7$ PFU MVA-core	i.m.
4	15ug HBcAg	c-di-AMP	i.m.	$1*10^8$ PFU MVA-core	i.m.

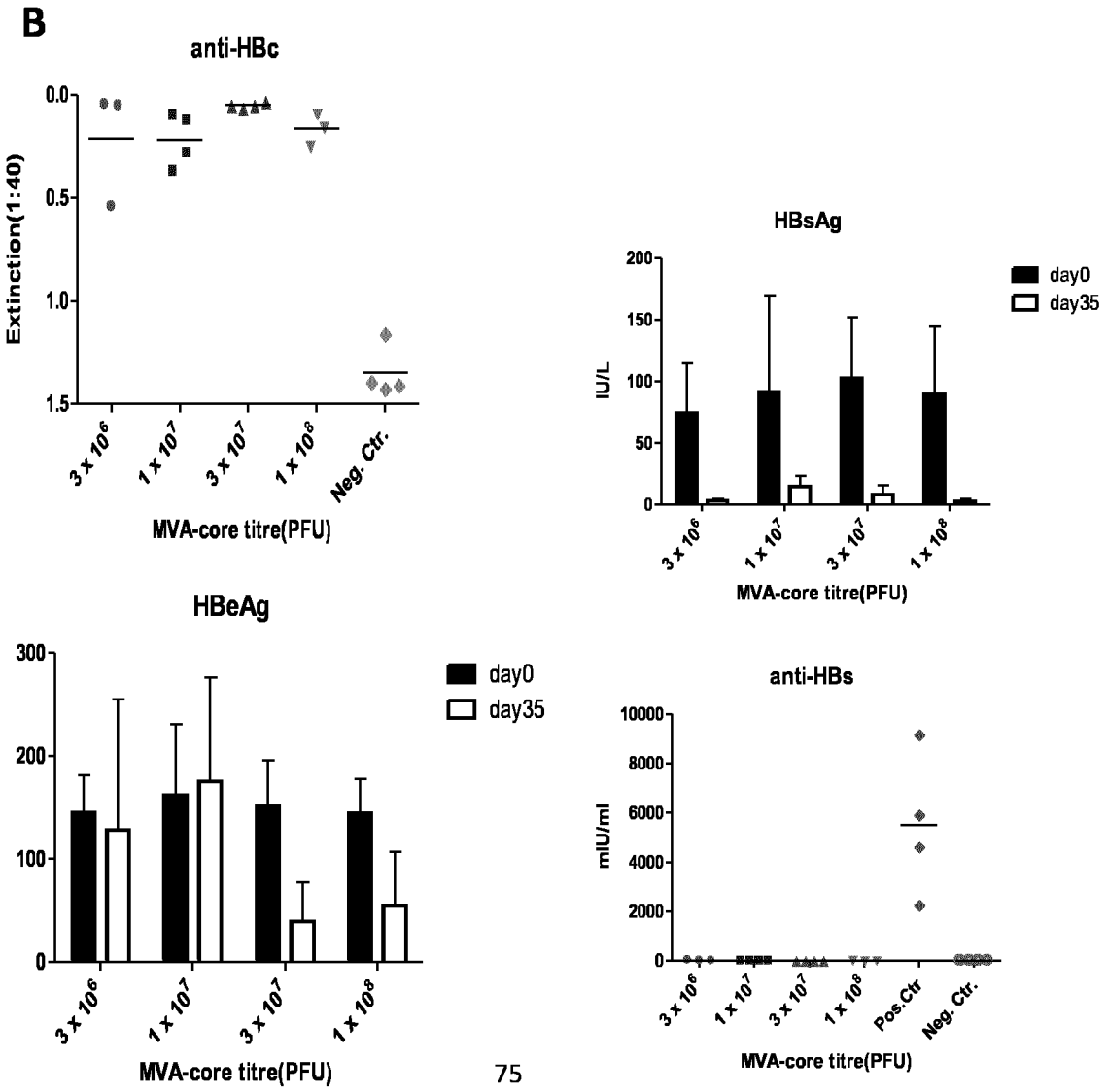


Figure 29 (cont.)

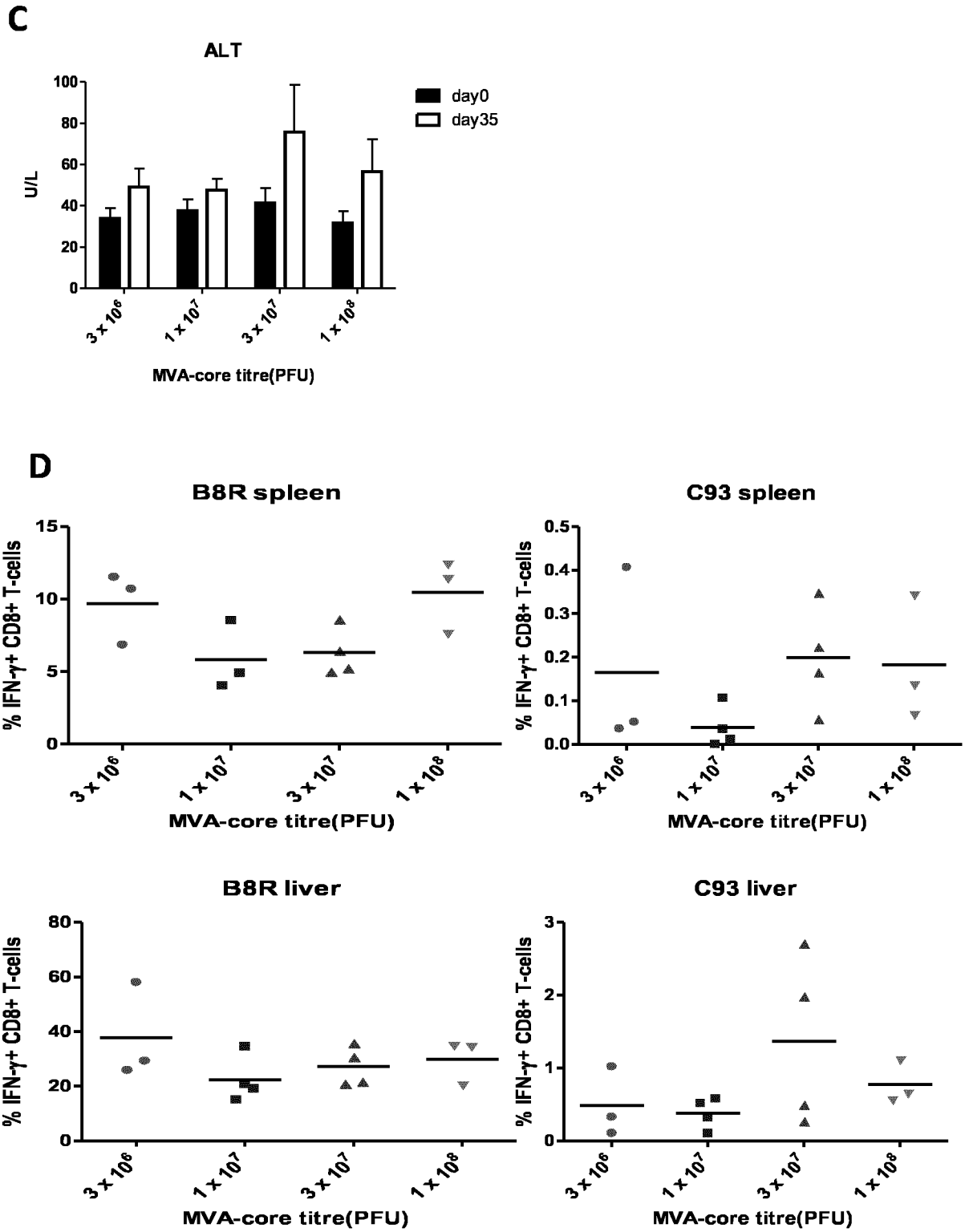
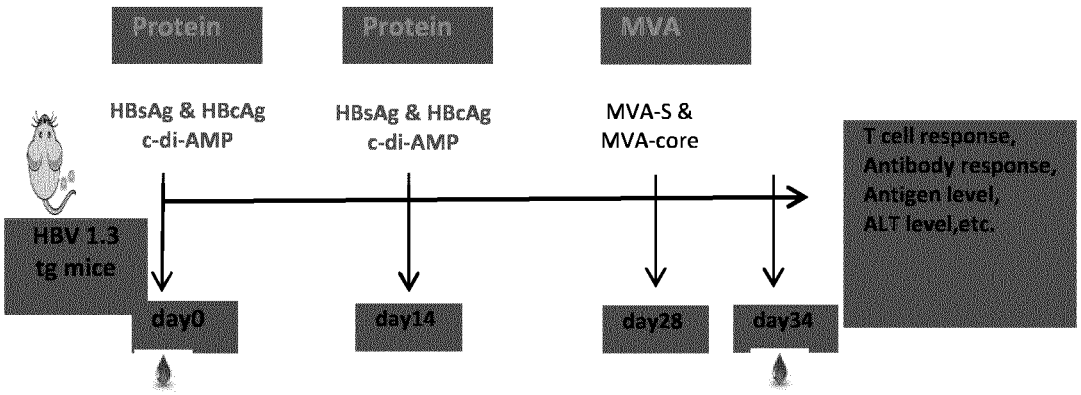


Figure 30

A



Group	Protein prime (2x)			MVA boost (1x)	
	vaccine	Adjuvant	Route	vaccine	Route
1	-	c-di-AMP	i.m.	$1*10^8$ PFU MVA-wt	i.m.
2	15ug cAg + 15ug sAg	c-di-AMP	i.m.	$5*10^7$ PFU MVA-cAg/-sAg	i.m.
3	15ug cAg + 15ug sAg	CpG/PCEP	i.m.	$5*10^7$ PFU MVA-cAg/-sAg	i.m.

B

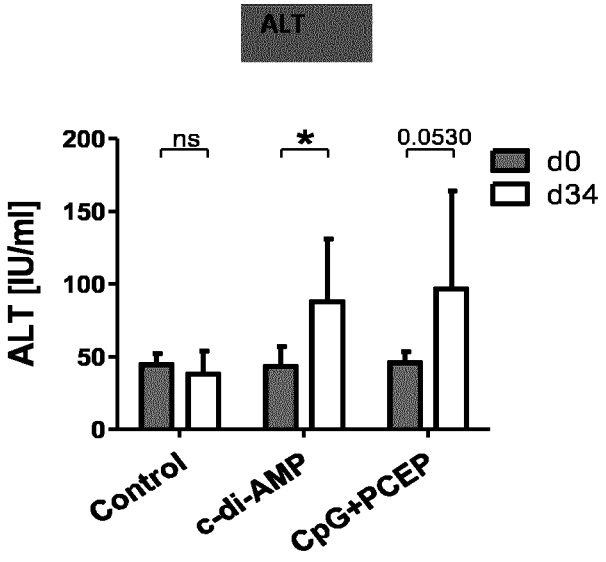


Figure 30 (cont.)

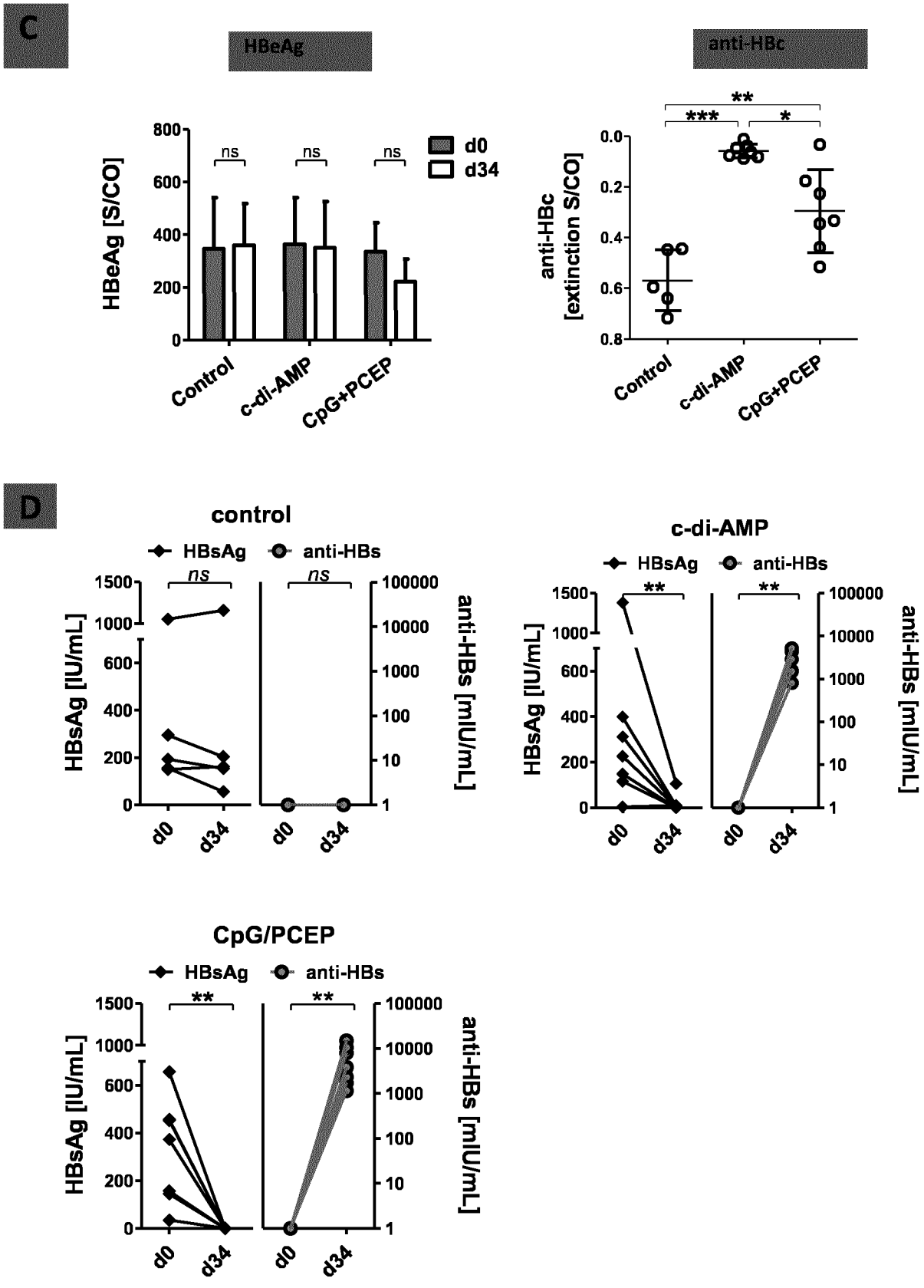


Figure 30 (cont.)

E

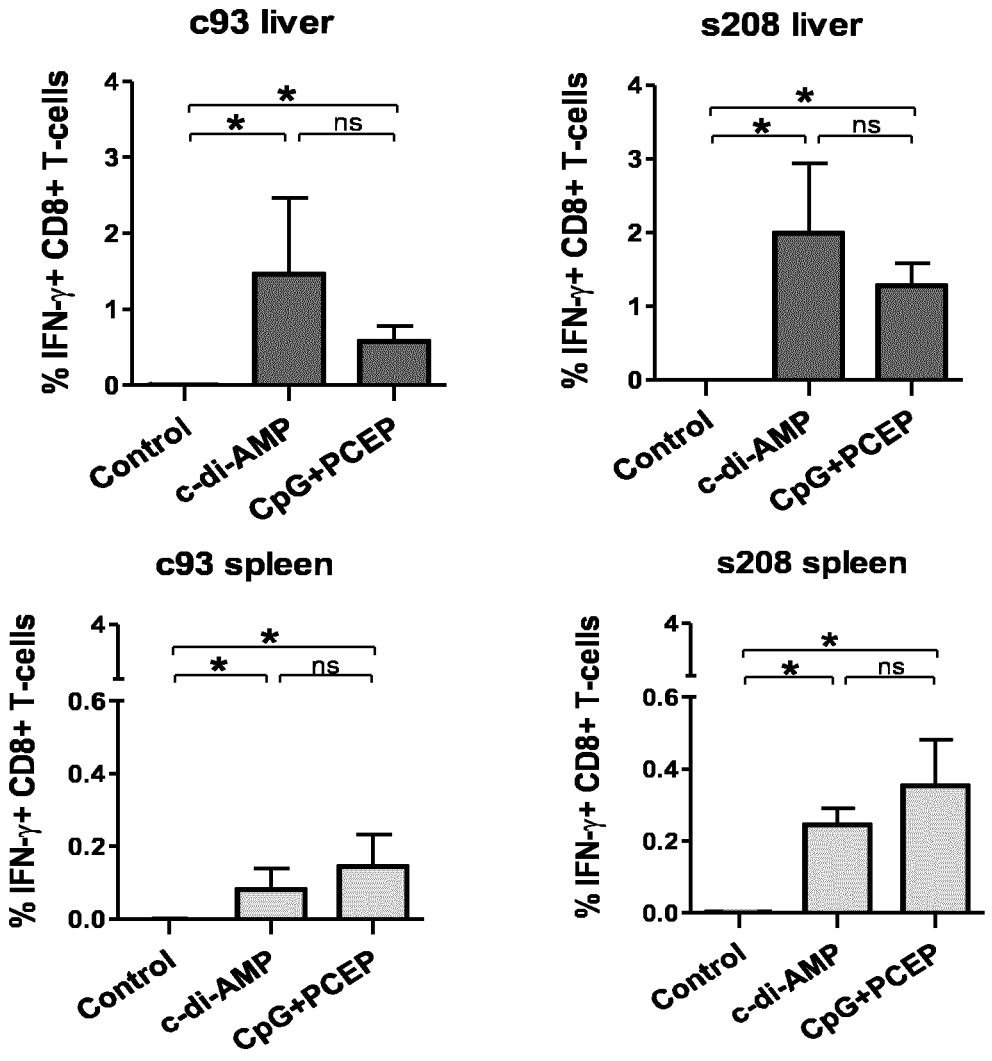


Figure 31

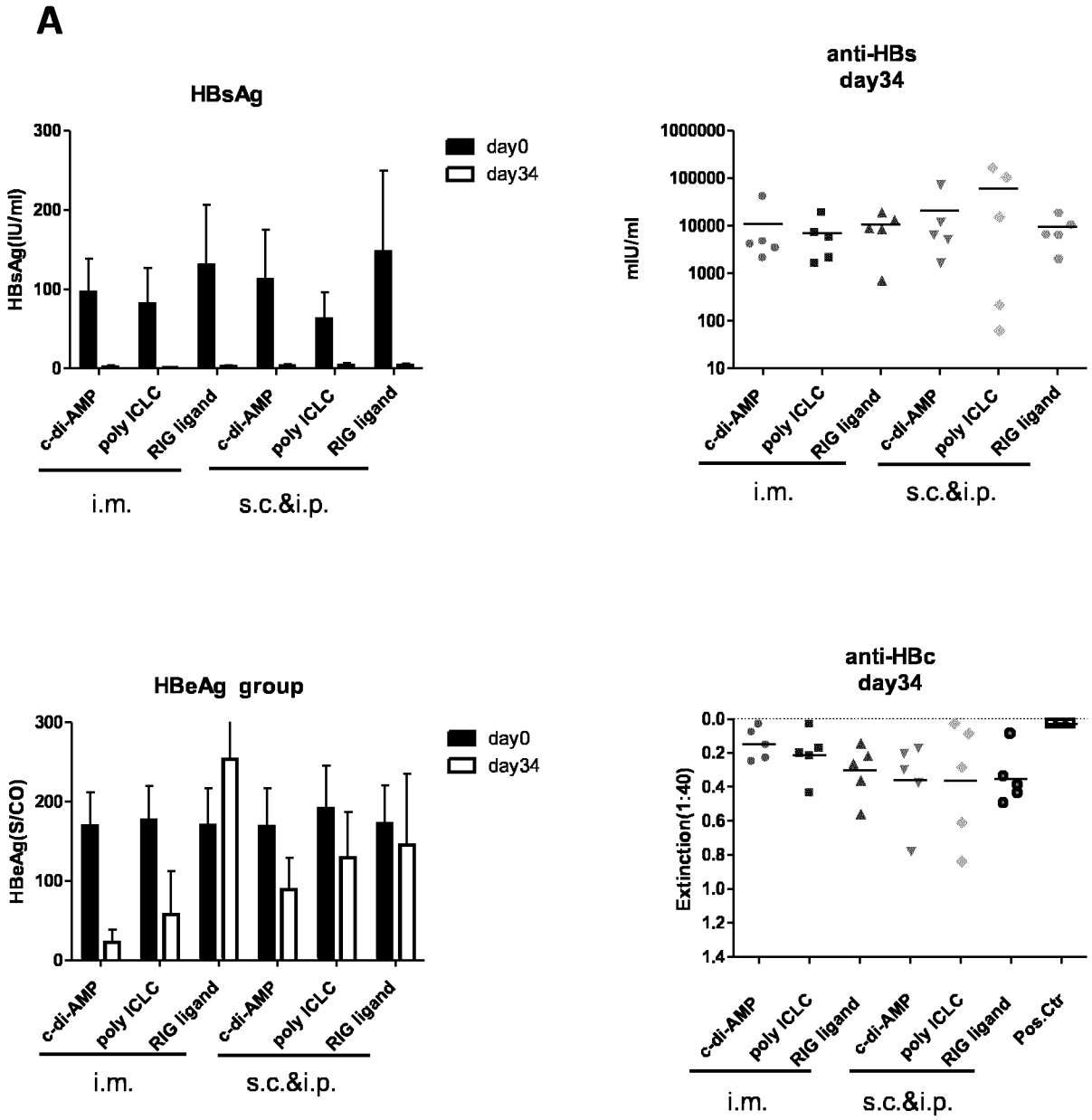

A
HBsAg
HBsAg(IU/ml)
300
200
100
0
day0
day34
c-di-AMP
poly ICLC
RIG ligand
c-di-AMP
poly ICLC
RIG ligand
i.m.
s.c.&i.p.
anti-HBs
day34
mIU/ml
1000000
100000
10000
1000
100
10
c-di-AMP
poly ICLC
RIG ligand
c-di-AMP
poly ICLC
RIG ligand
i.m.
s.c.&i.p.
HBeAg group
HBeAg(S/CO)
300
200
100
0
day0
day34
c-di-AMP
poly ICLC
RIG ligand
c-di-AMP
poly ICLC
RIG ligand
i.m.
s.c.&i.p.
anti-HBc
day34
Extinction(1:40)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
c-di-AMP
poly ICLC
RIG ligand
c-di-AMP
poly ICLC
RIG ligand
Pos.Ctr
i.m.
s.c.&i.p.

Figure 31 (cont.)

B

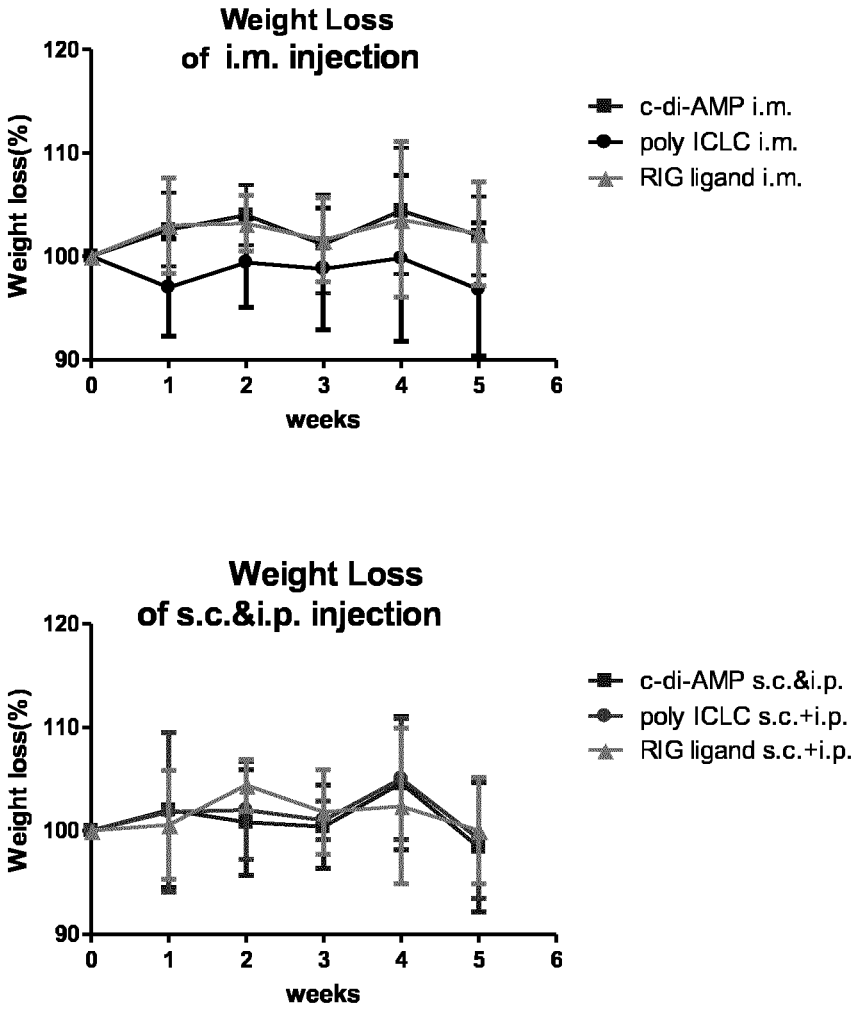
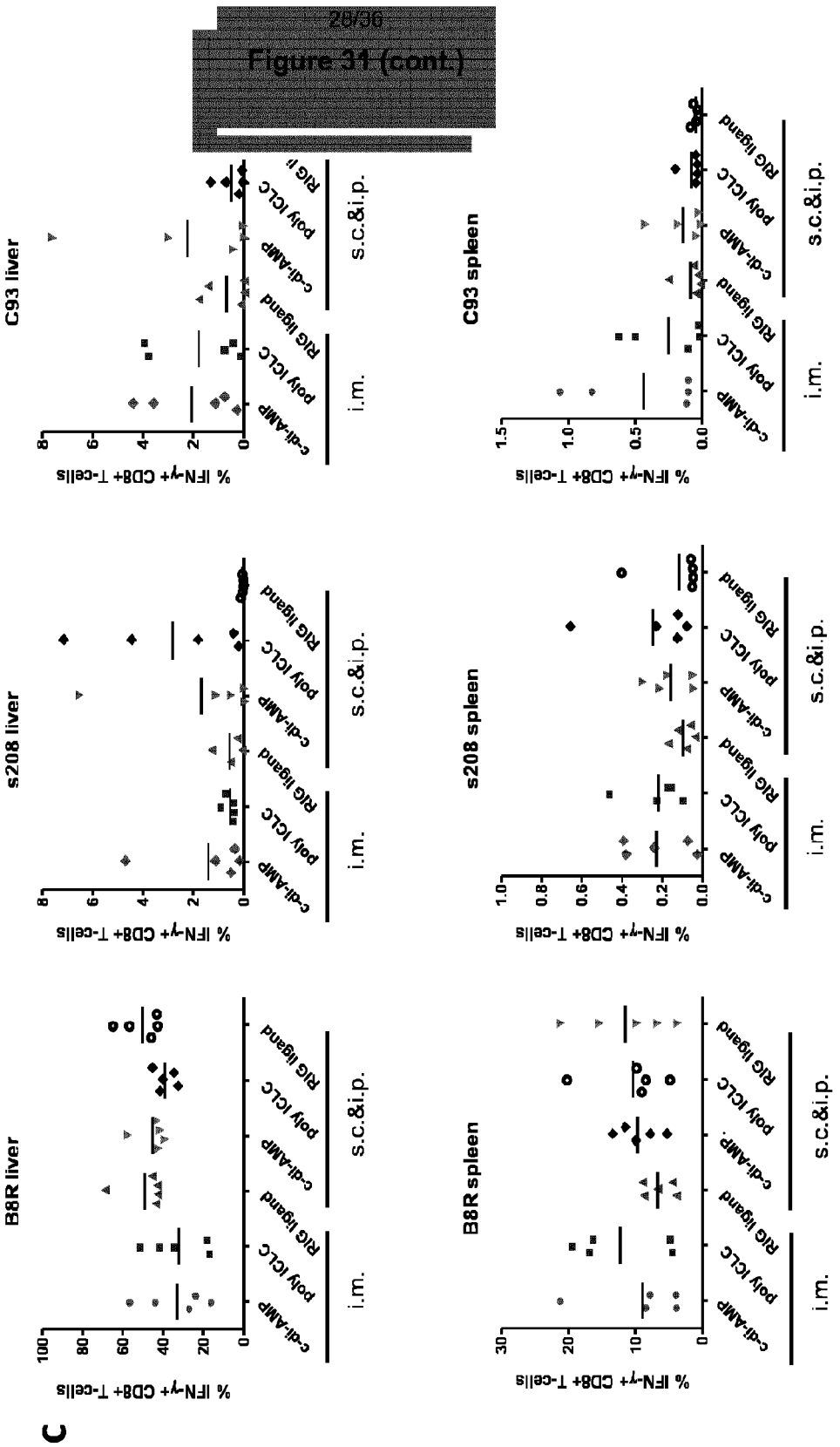
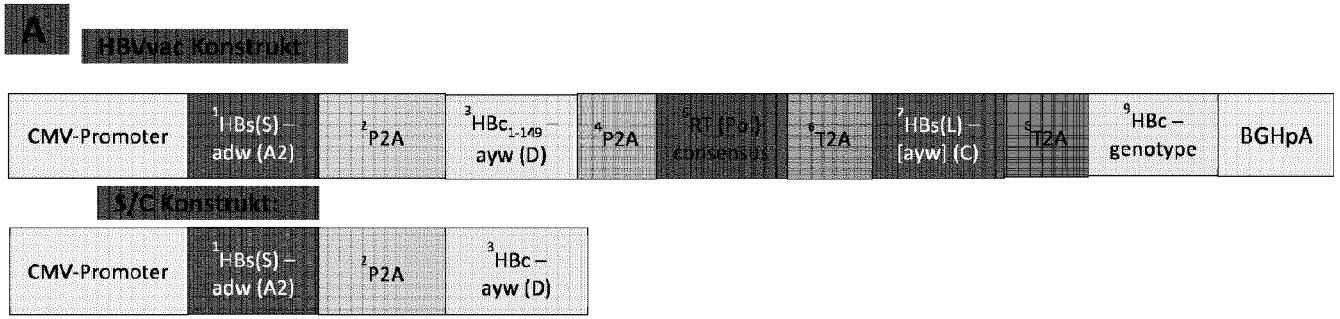
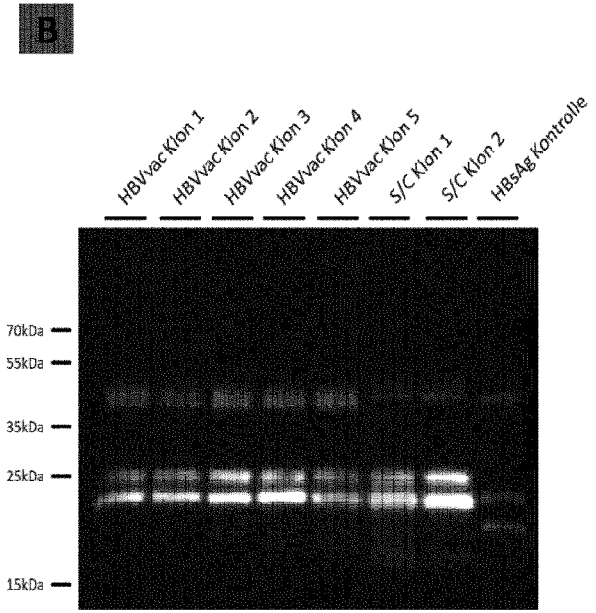
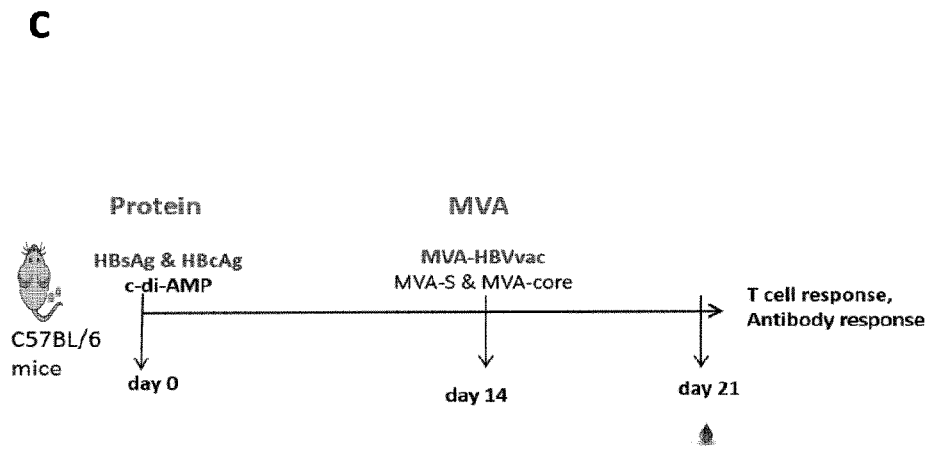


Figure 31 (cont.)



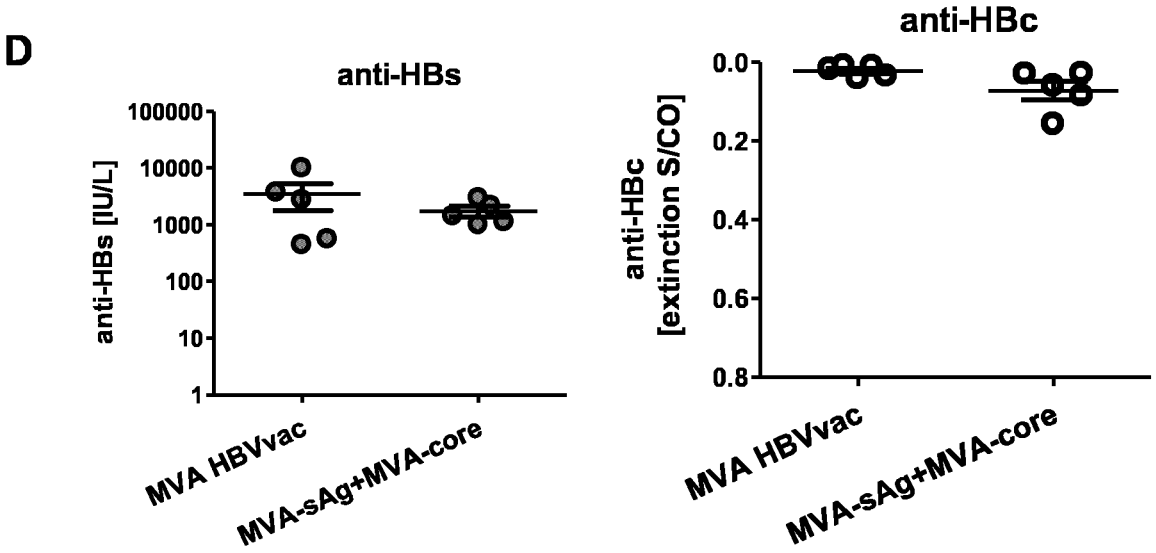


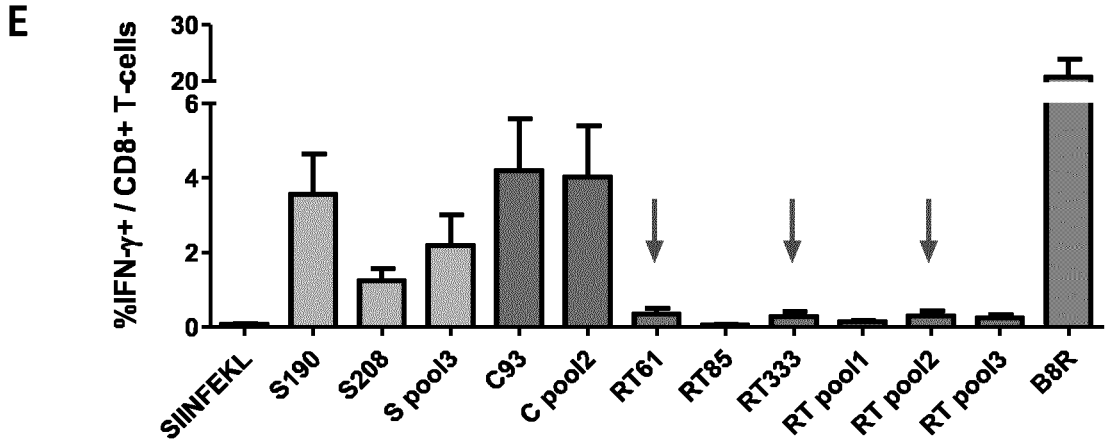




Group	Protein prime(1x)			MVA boost(1x)	
	vaccine	Adjuvant	Route	vaccine	Route
1	20ug cAg + 20ug sAg	c-di-AMP	i.m.	$6*10^7$ PFU MVA-HBVvac	i.m.
2	20ug cAg + 20ug sAg	c-di-AMP	i.m.	$53*10^7$ PFU MVA-cAg/-sAg	i.m.

Figure 32 (cont.)





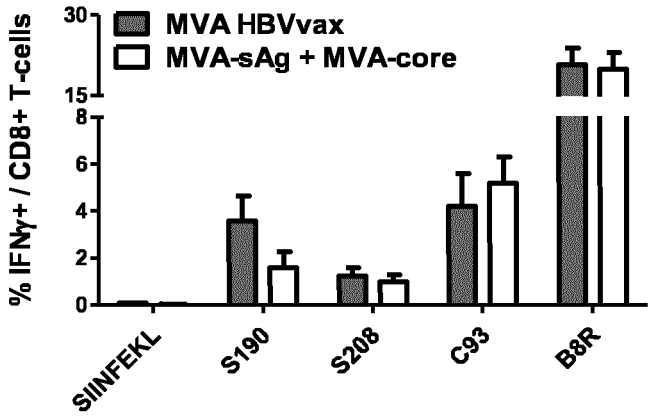


Figure 33

Construct of the recombinant vaccination vector (rMVA) further expressing CD70

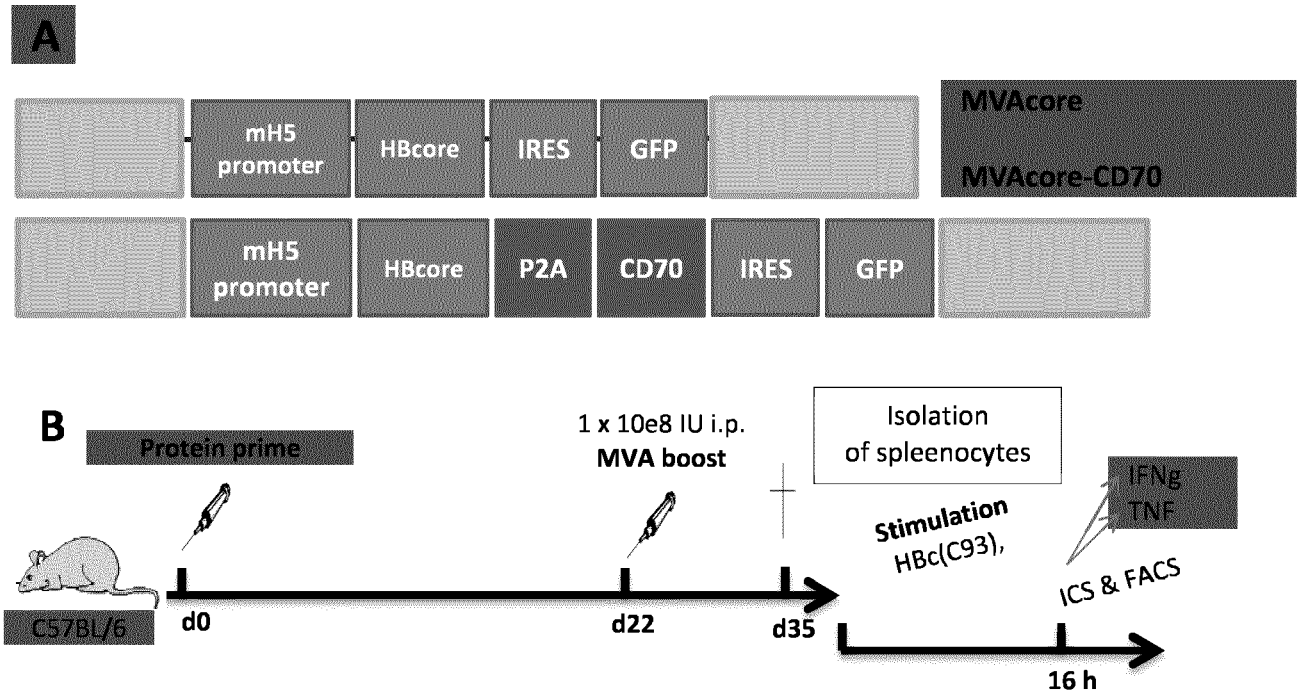
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Figure 33 (cont.)

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(SEQ ID NO: 27)

Figure 34



vaccination group		Protein prime	MVA boost
MVAwt	n=6	only adjuvants	MVAwt
MVAcore	n=7	HBcore protein (+PCEP, CpG)	MVAcore
MVAcore-CD70	n=7		MVAcore-CD70

Figure 34 (cont.)

C

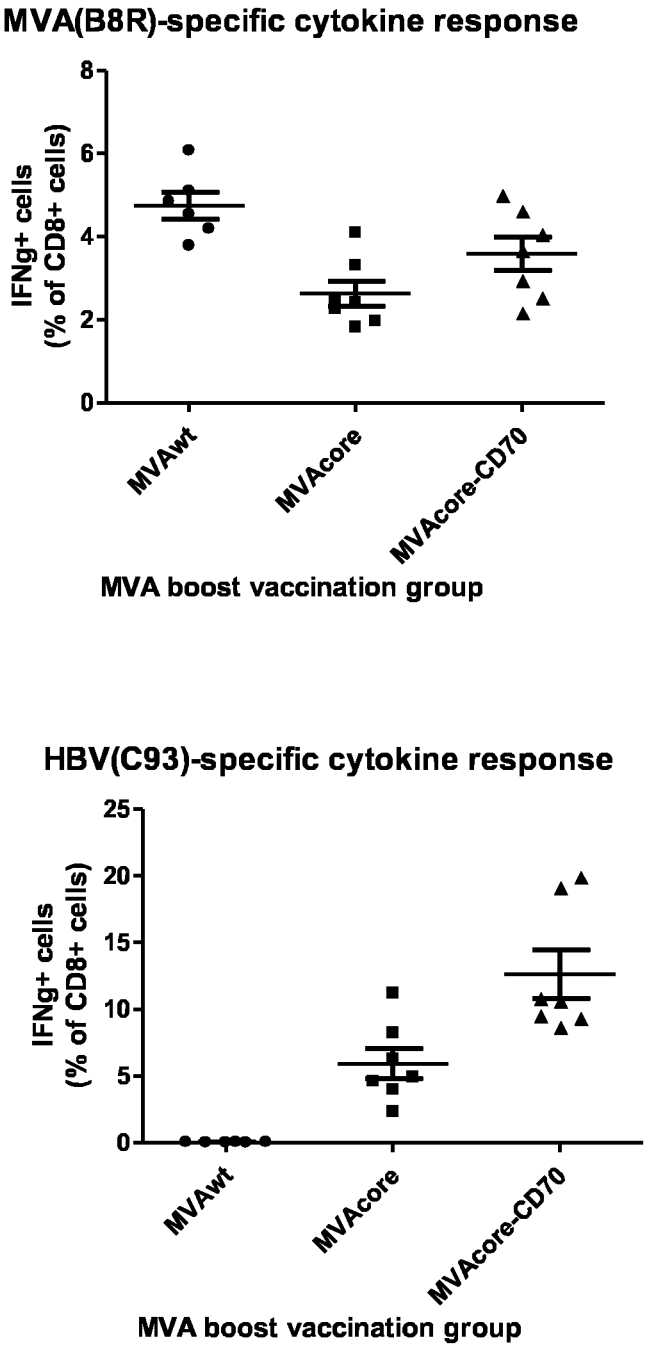
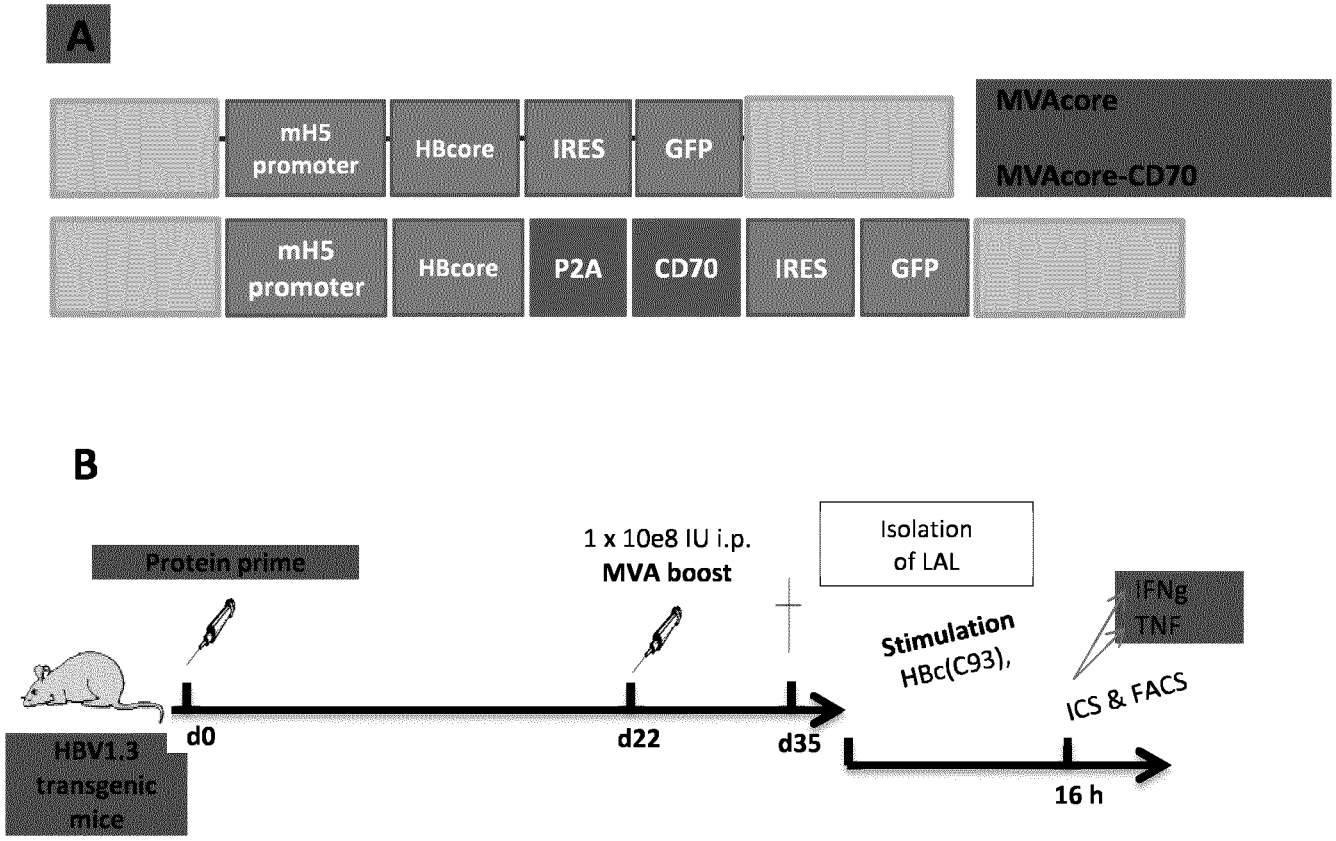


Figure 35



vaccination group		Protein prime	MVA boost
MVAwt	n=2	only adjuvants	MVAwt
MVAcore	n=5	HBcore protein (+PCEP, CpG)	MVAcore
MVAcore-CD70	n=6		MVAcore-CD70

Figure 35 (cont.)

C

