

Figure 1
Alignment of IL6 sequences from human, macaque, mouse and rat
species (SEQ ID NOs: 227-230).

Human	MNSFSTSAFGPVAFSLGILLVLPAAFPAPVPPGEDSKDVAAPHRQPLTSSERIDKQ	-20	-10	1	10	20
Macaque	MNSFSTSAFGPVAFSLGILLVLPAAFPAPVPPGEDSKNVAAPHSQPLTSSERIDKH					
Mouse	MKFLSARDFHPVAF-LGLMLVTTTAFPTSQVRRGDFDTPNR-PVYTTSQVGGGL					
Rat	MKFLSARDFQPVAF-LGLMLLTATAFPTSQVRRGDFDTPNR-PVYTTSQVGGGL					
Human	IRYILDGISALRKETCNKSNMCESSKEALAENNINLPKMAEKDGCFFQSGFNEETCL	30	40	50	60	70
Macaque	IRYILDGISALRKETCNRSNMCESSKEALAENNINLPKMAEKDGCFFQSGFNEDTCL					
Mouse	ITHVLWEIVEMRKELCNGNSDCMNDDALAENNLKLEIQRNDGCGYQTGYNQEIICL					
Rat	ITYVLREIILEMRKELCNGNSDCMNSDDALSNNLKLPEIQRNDGCGYQTGYNQEIICL					
Human	VKIITGLLEFEVYLEYLQNRFEES-EEQARAVQMSTKVLIQFLQKKAKNLDAITTP	90	100	110	120	130
Macaque	VKIITGLLEFEVYLEYLQNRFEES-EEQARAVQMSTKVLIQFLQKKAKNLDAITTP					
Mouse	LKISSGLLEYSYLEYMKNNLKNKKDKARVLQRDTETLIHIFNQEVKDLHKIVLP					
Rat	LKICSGLLEFRFYLFVKNLQDNKKDKARVIQSNTEITLVHIFKQEIKDSYKIVLP					
Human	DPTTNASLLTKLQAAQ-NQWLQDMTTHLILRSFKEFLQSSLRALRQM (SEQ ID NO. 227)	140	150	160	170	180
Macaque	EPTTNASLLTKLQAAQ-NQWLQDMTTHLILRSFKEFLQSNLRALRQM (SEQ ID NO. 228)					
Mouse	TPISNALLTDKLESQ-KEWLRTKTIQILKSLEEFKVTLRSTRQT (SEQ ID NO. 229)					
Rat	TPTSNALLMEKLESQ-KEWLRTKTIQILKALEEFKVTMRSTRQT (SEQ ID NO. 230)					

Figure 2

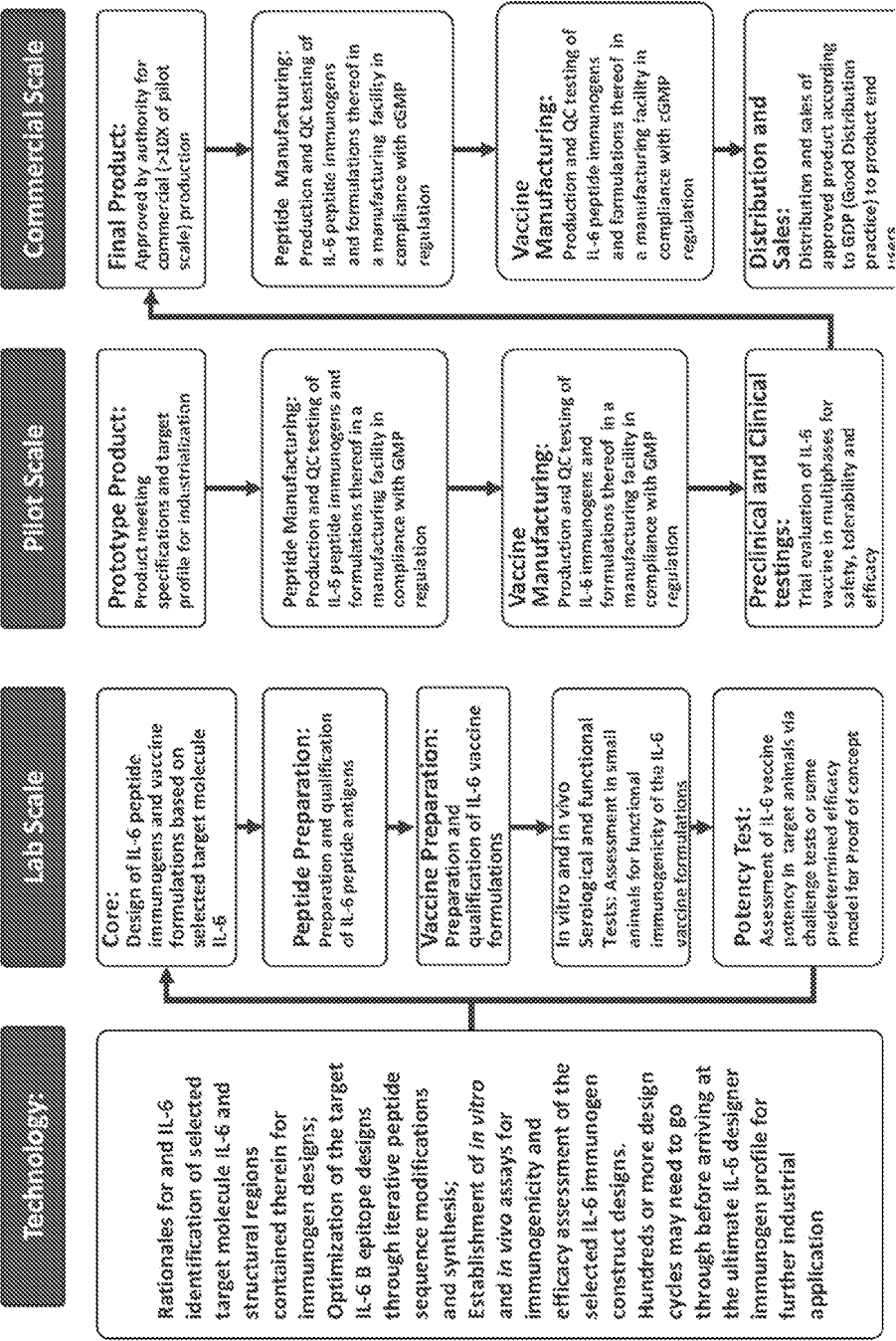


Figure 3
High immunogenicity of IL-6 immunogens in guinea pig

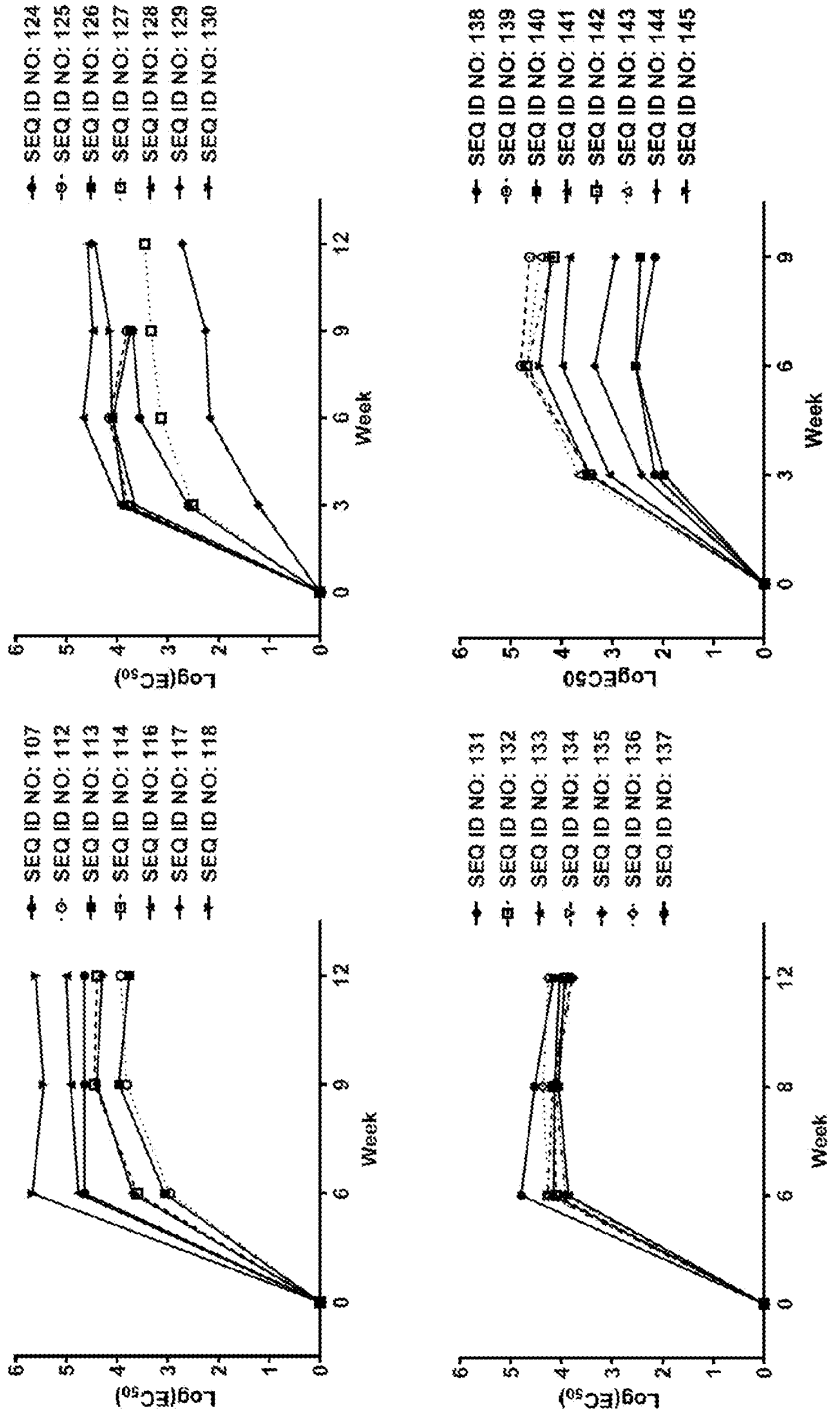


Figure 4A
IgGs raised by IL-6 peptide immunogens are crossreactive with
recombinant human, monkey and rodent IL-6 proteins

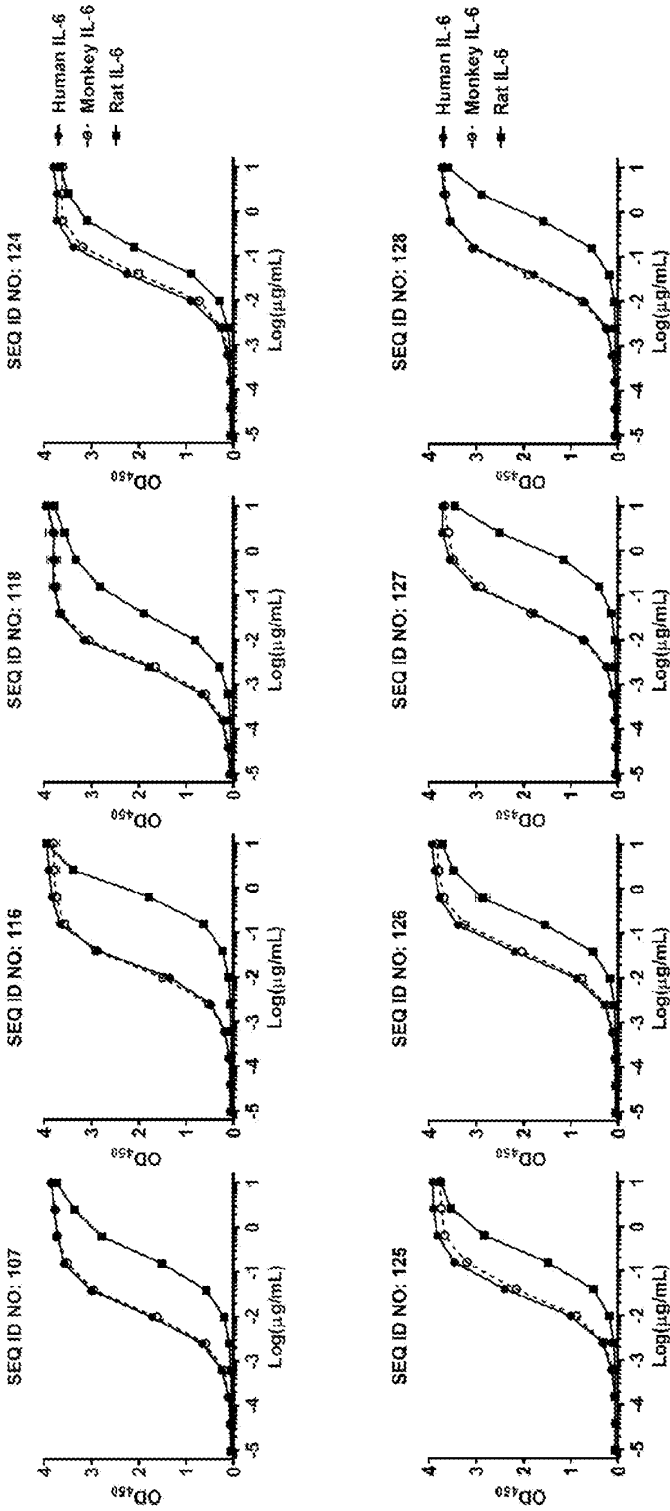


Figure 4B
IgGs raised by IL-6 peptide immunogens are crossreactive with
recombinant human, monkey and rodent IL-6 proteins

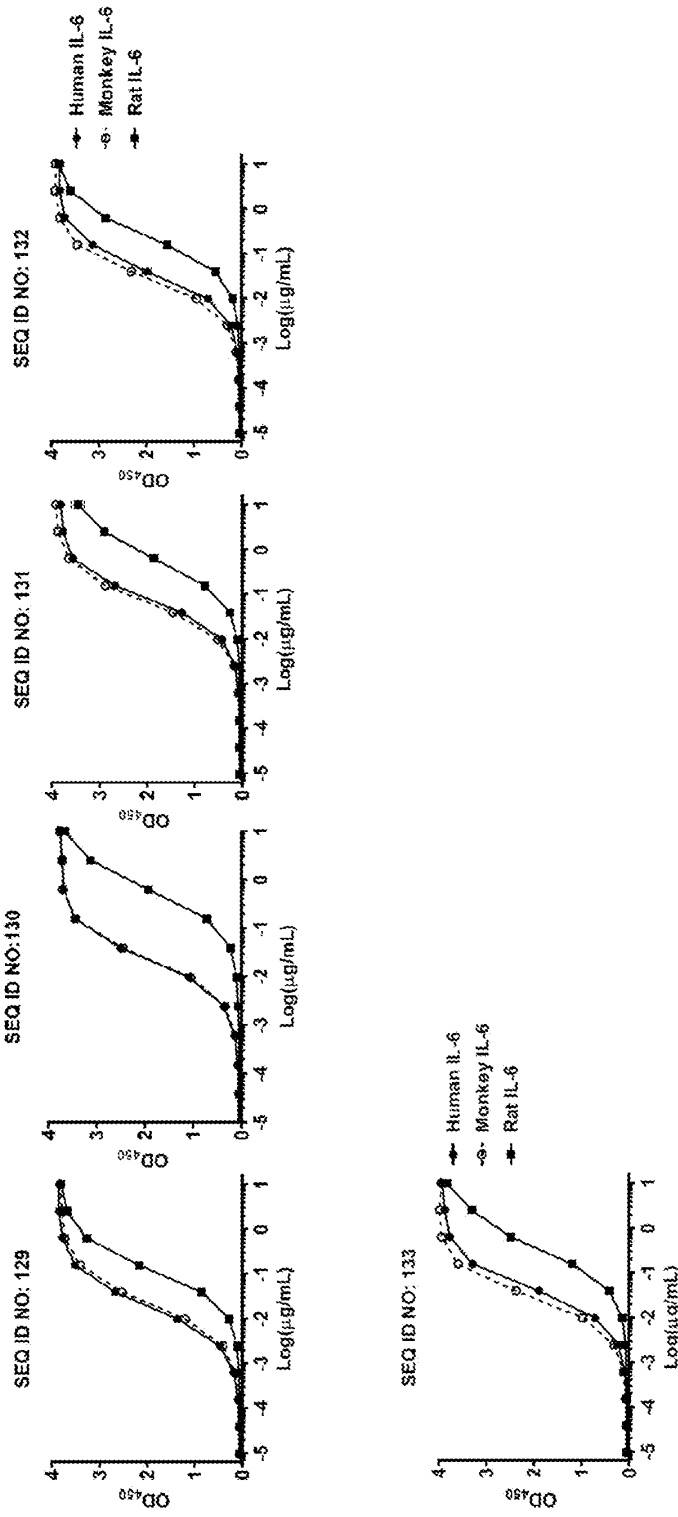


Figure 5A
IgGs elicited by IL-6 peptide immunogens were able to inhibit IL-6
and IL-6R interaction via cis-signaling mode

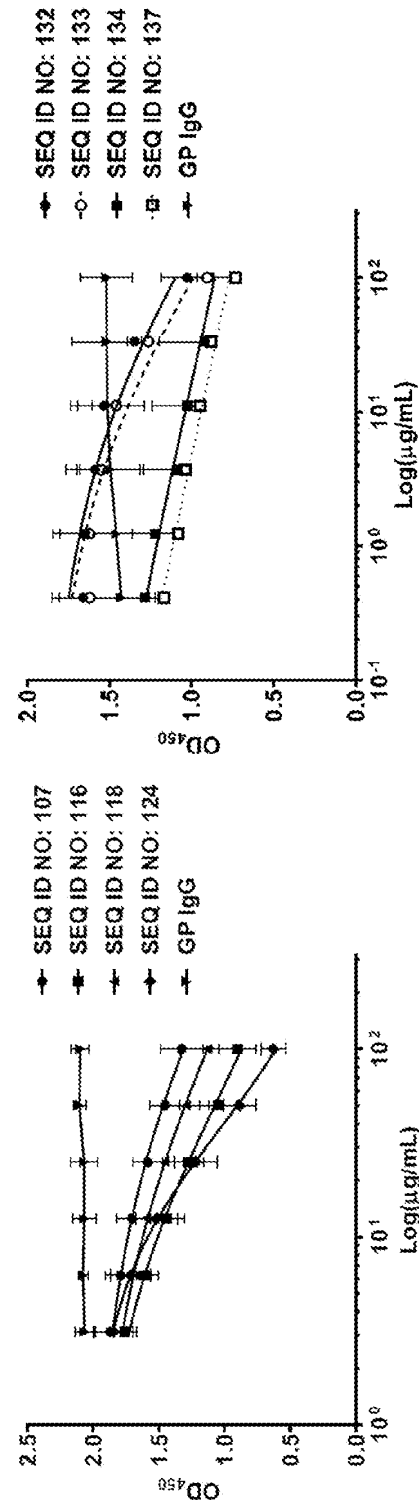


Figure 5B
IgGs elicited by IL-6 peptide immunogens were able to inhibit IL-6 and
IL-6R interaction via trans-signaling mode

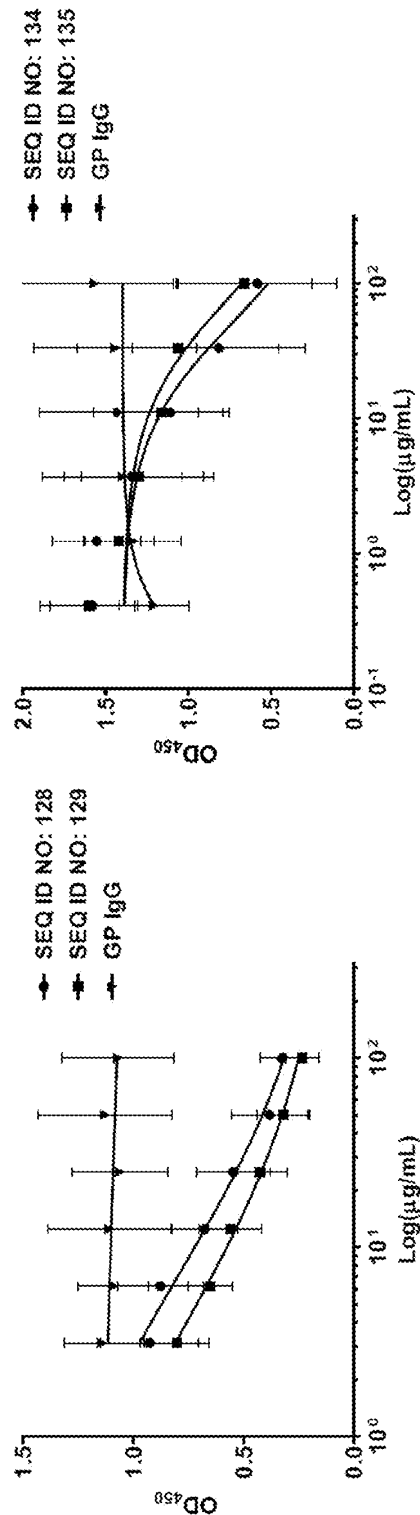


Figure 6
IgGs elicited by IL-6 peptide immunogens were able to suppress IL-6-induced STAT3 phosphorylation

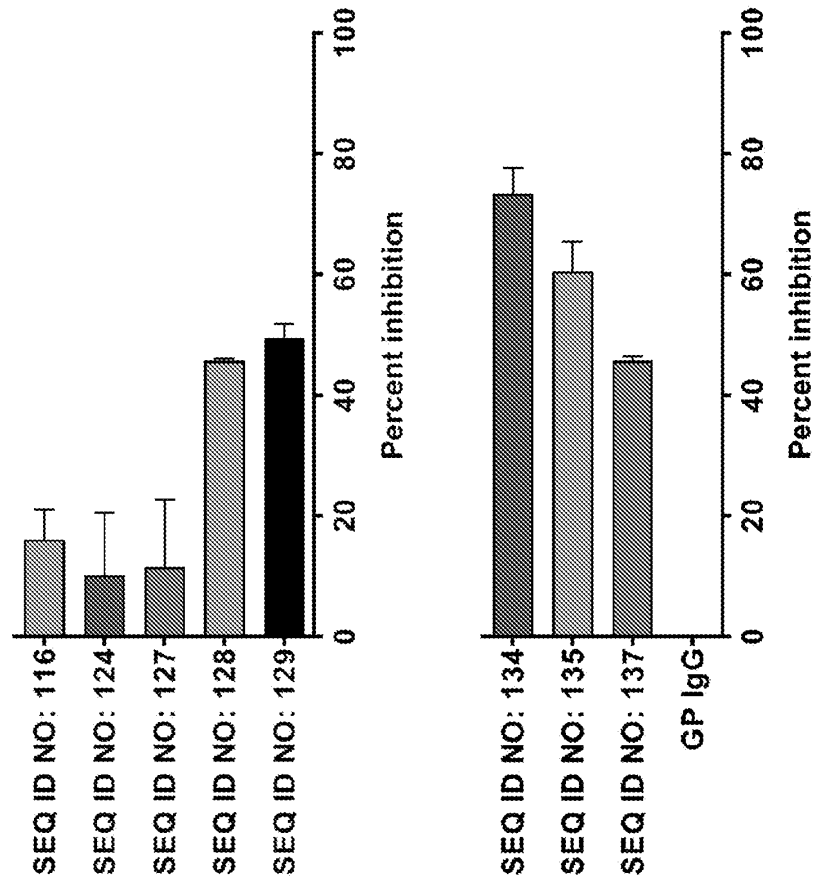


Figure 7A
IgGs elicited by IL-6 peptide immunogens were able to suppress IL-6-dependent cell growth of human TF-1 cells

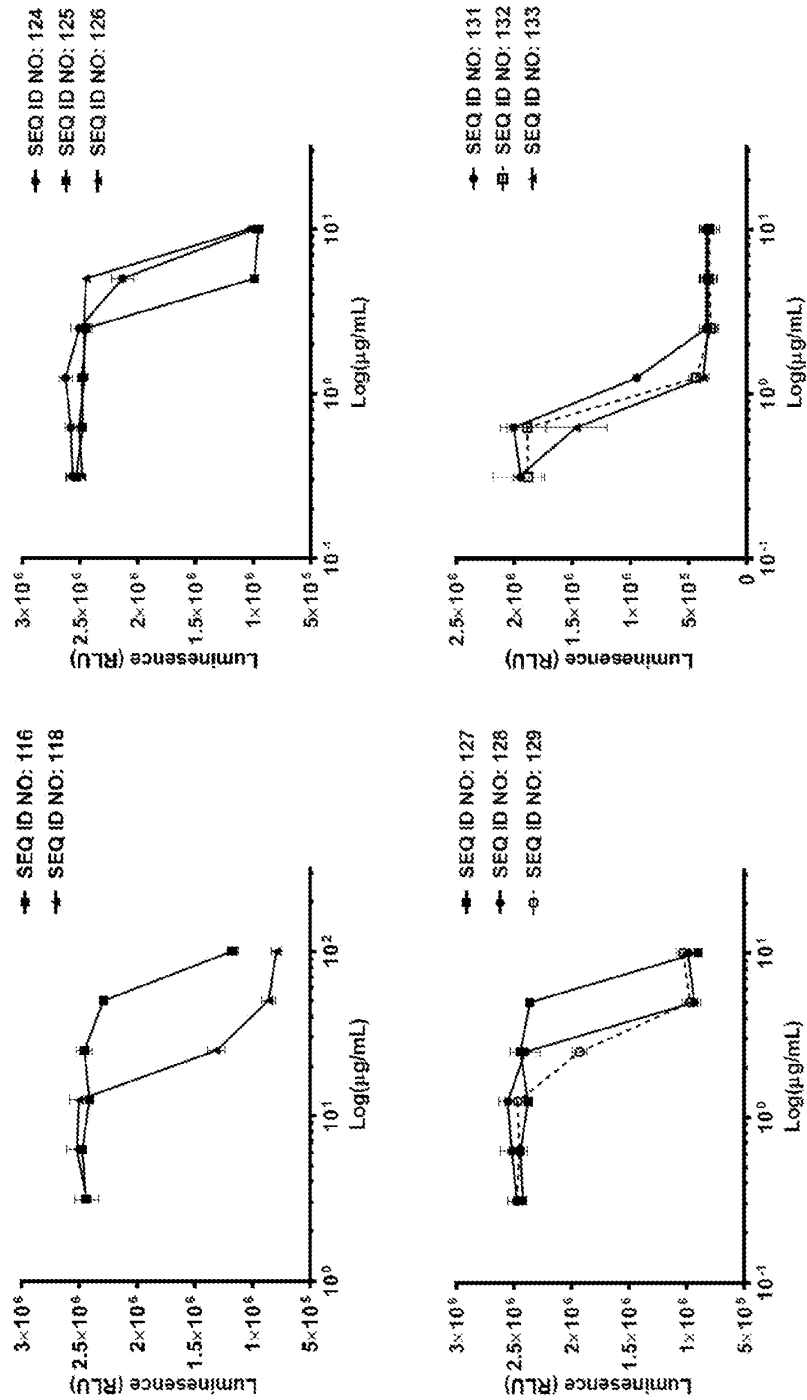


Figure 7B
IgGs elicited by IL-6 peptide immunogens were able to suppress IL-6-dependent cell growth of human TF-1 cells

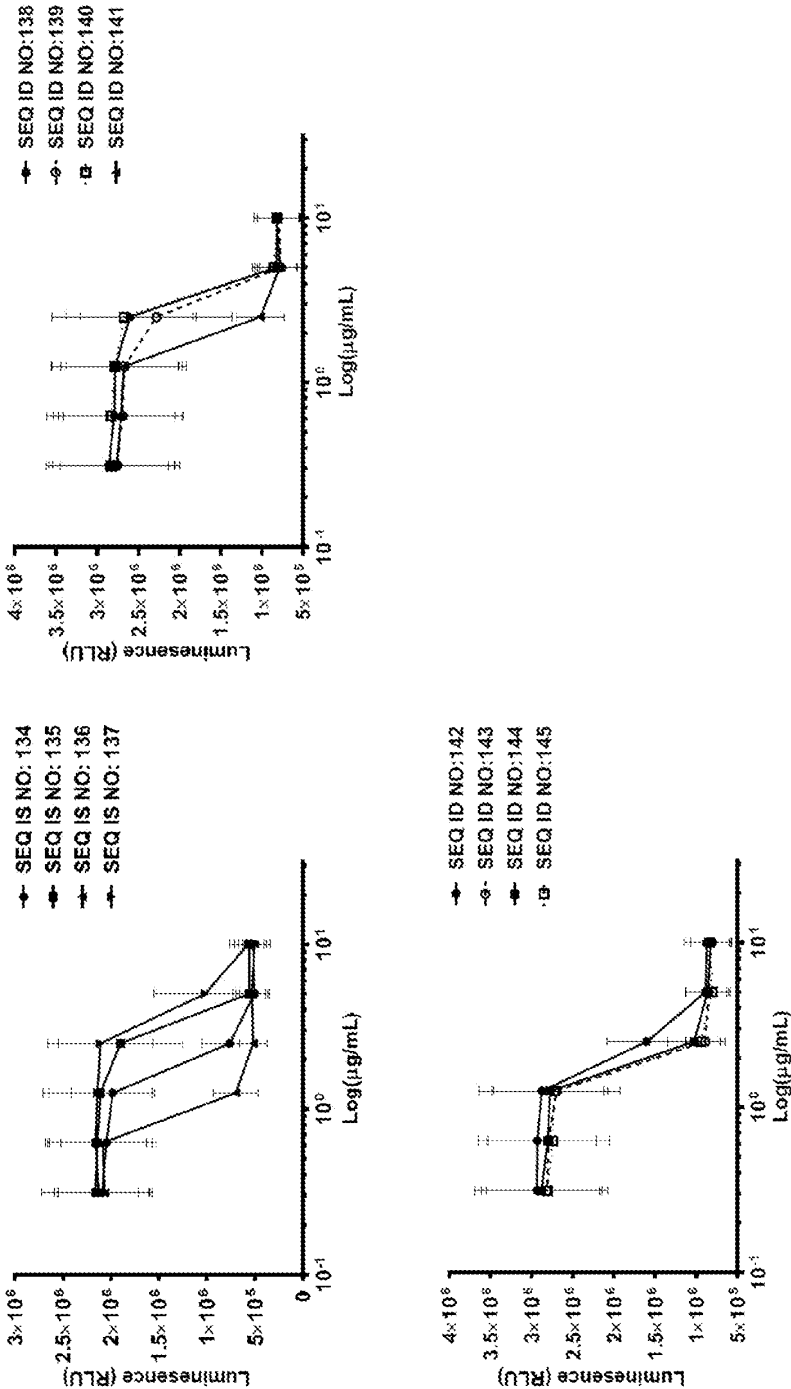


Figure 8A
IgGs elicited by IL-6 peptide immunogens were able to suppress IL-6-induced MCP-1 production of human U937 cells

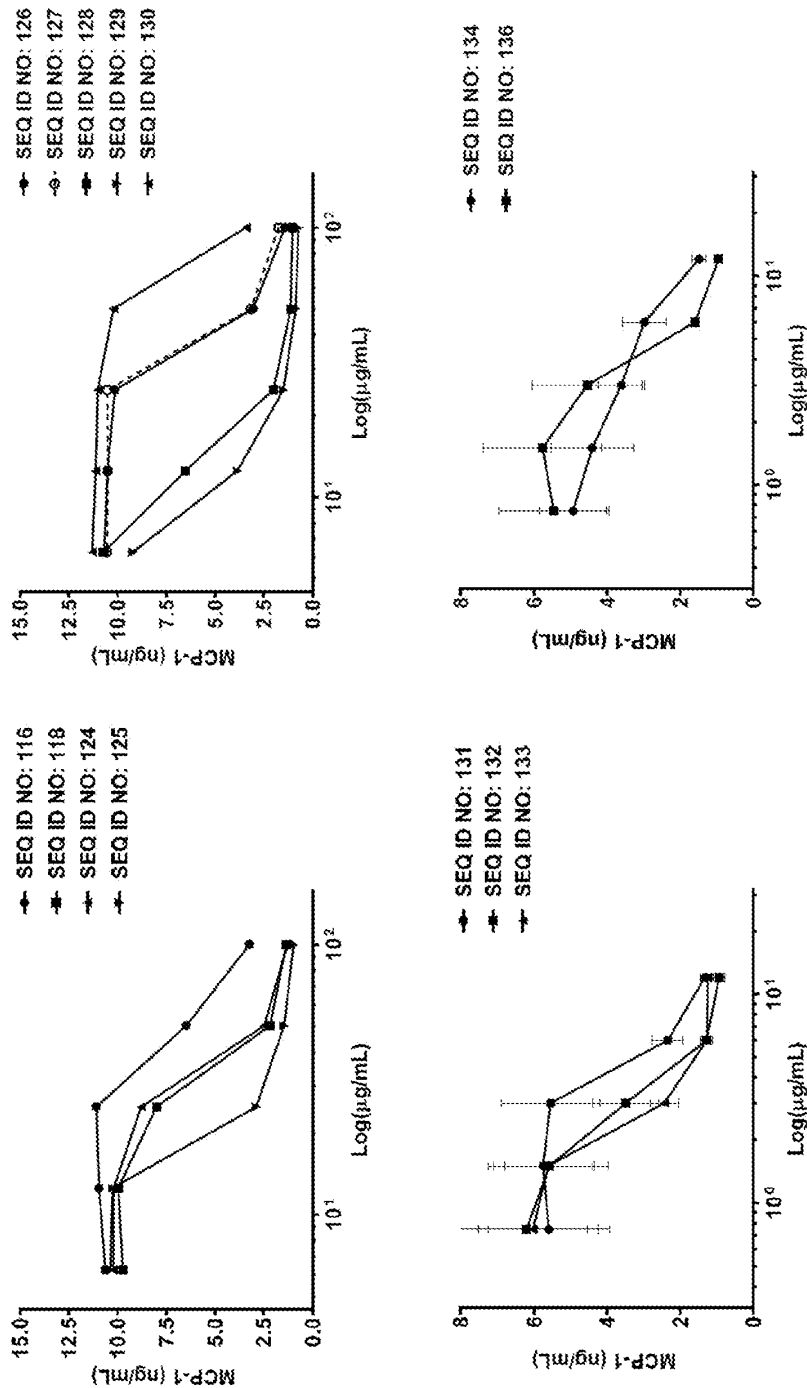


Figure 8B
IgGs elicited by IL-6 peptide immunogens were able to suppress IL-6-induced MCP-1 production of human U937 cells

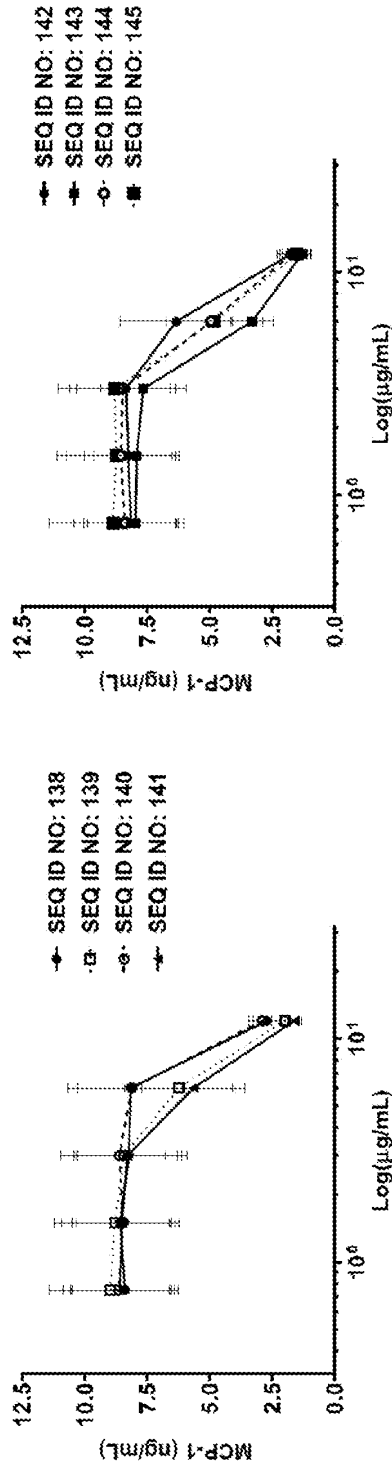
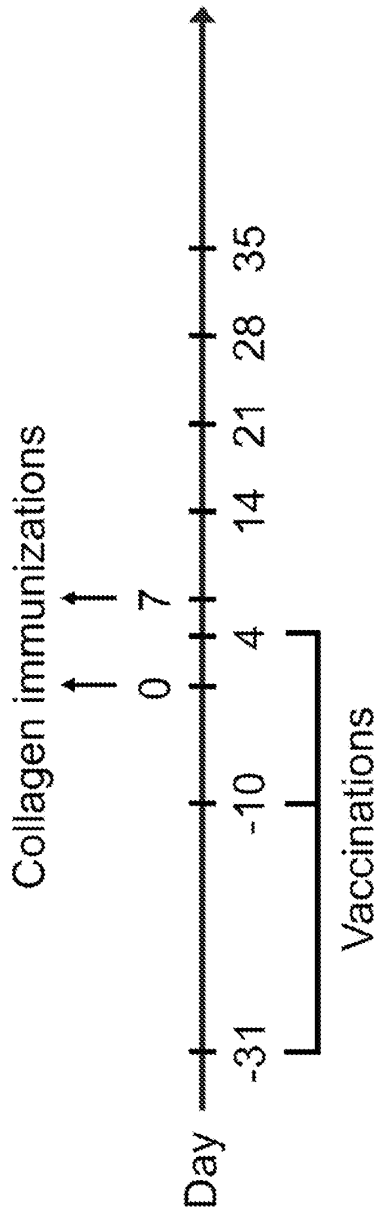


Figure 9
Experimental protocol for efficacy evaluation of rat IL-6 peptide constructs in rat collagen-induced arthritis (CIA) model



- Animals: Lewis rat
- Groups: Placebo and 2 vaccination groups
- Adjuvant: ISA 51 and CpG
- Vaccine dose: Immunize rats on day -31, -10 and 4 with 45 µg in 0.5 ml vaccine or adjuvant placebo by *i.m.* route.
- Collagen: Inject at the base of the tail (100 µg in 100 µL) on day 0 and 7 with bovine type II collagen/IFA emulsion by *i.d.* route.

Figure 10
Rat IL-6 peptide constructs (SEQ ID NOs: 148 and 157) elicited
anti-IL-6 Ab titers in Lewis rats

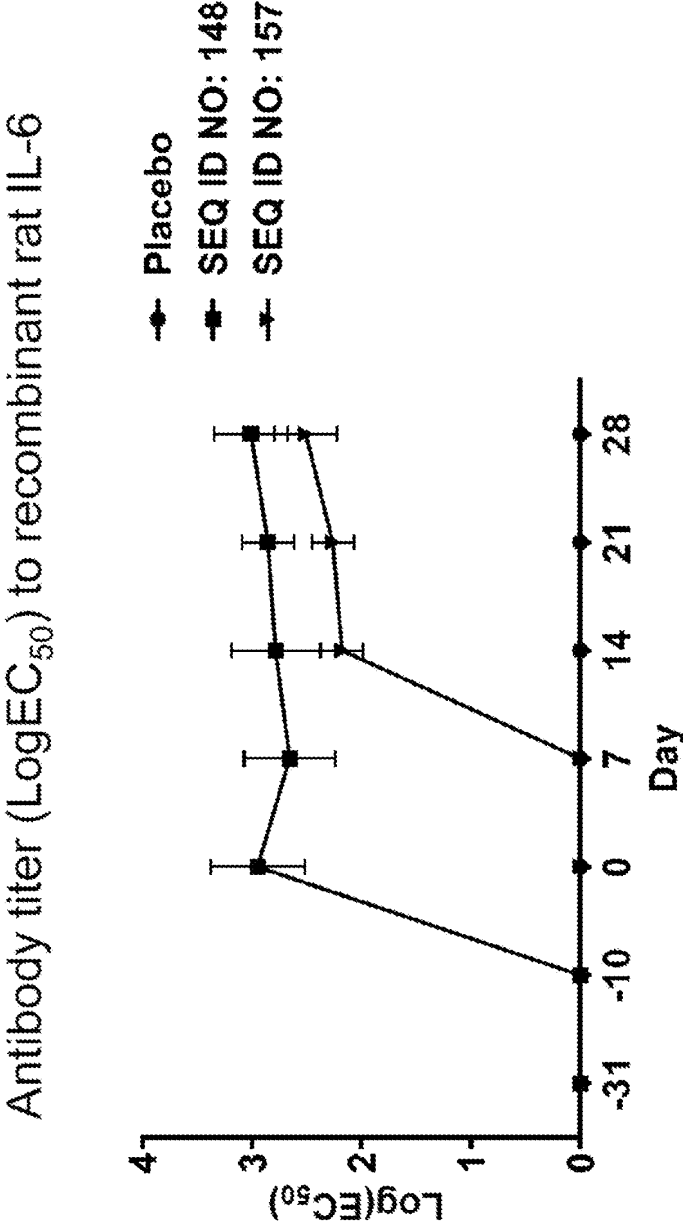


Figure 11
Rat vaccinated with rat IL-6 immunogens (SEQ ID NOs: 148 & 157)
showed low arthritis score in a CIA model

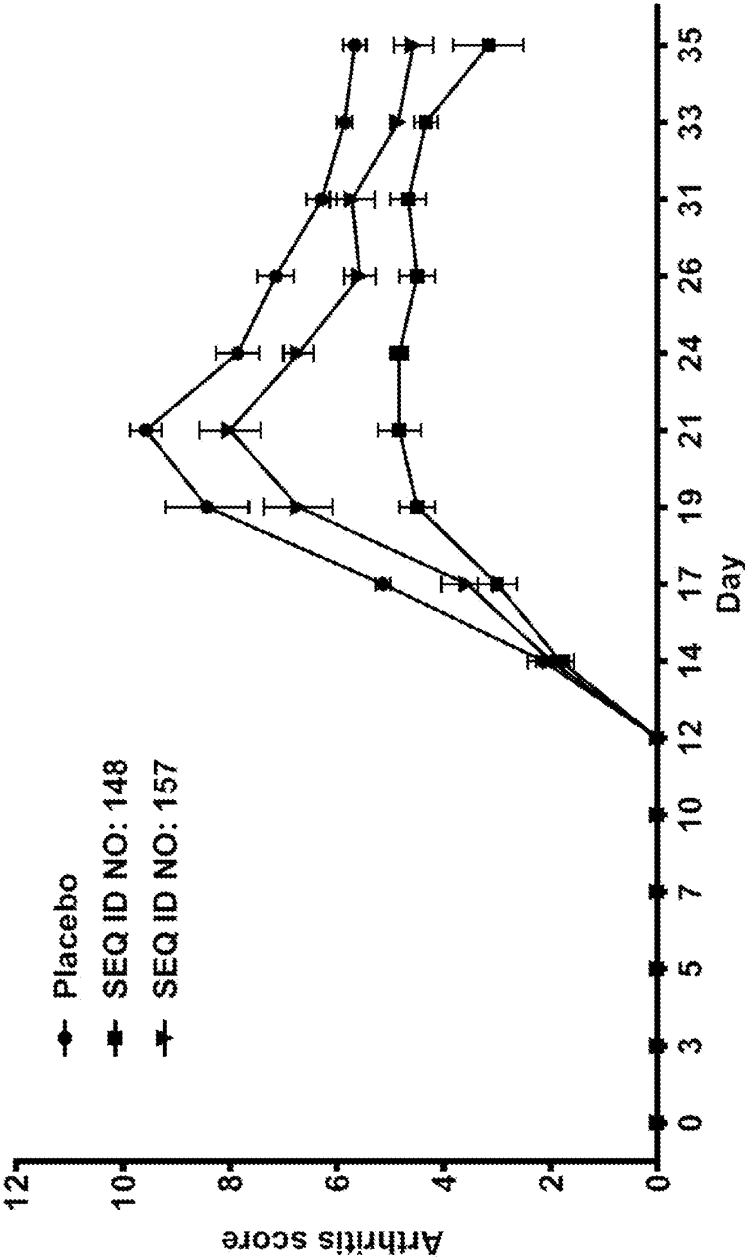


Figure 12
Rat vaccinated with rat IL-6 immunogens (SEQ ID NOs: 148 and 157)
showed mild-to-moderate paw swelling in a CIA model

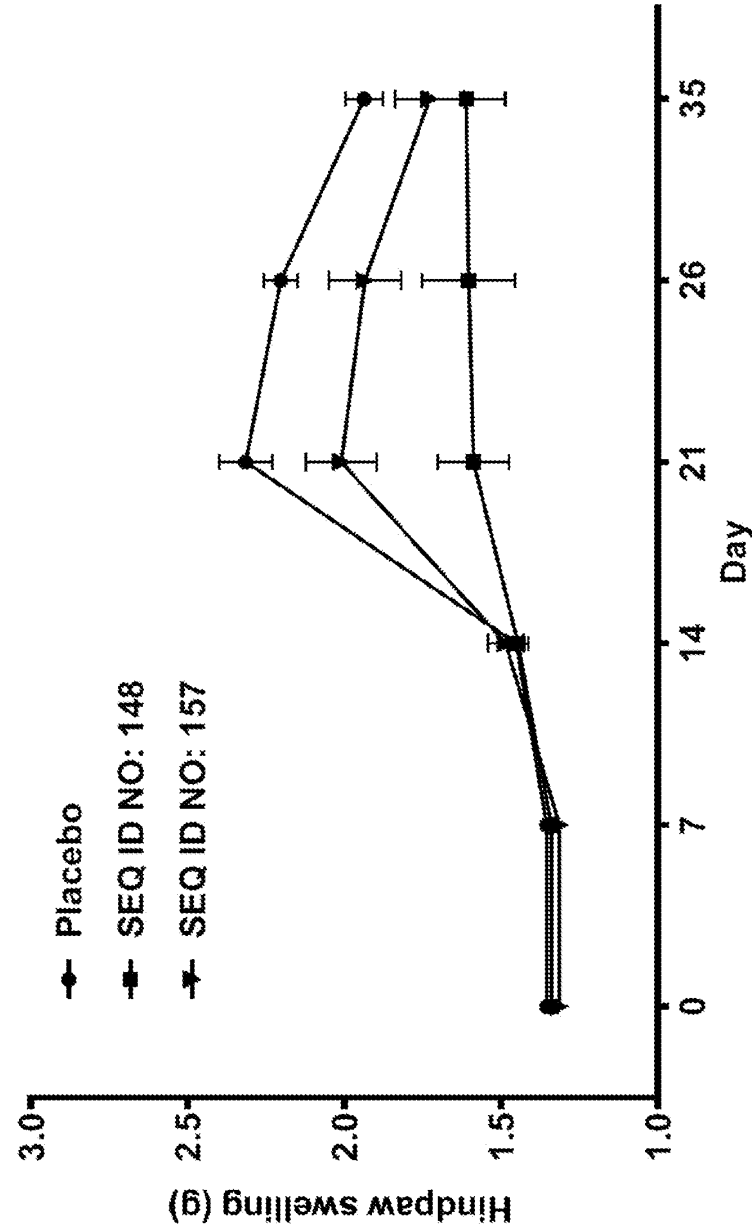


Figure 13
Rat IL-6 immunogens (SEQ ID NOs: 148 and 157) attenuated the release of neutrophils from bone marrow into circulation

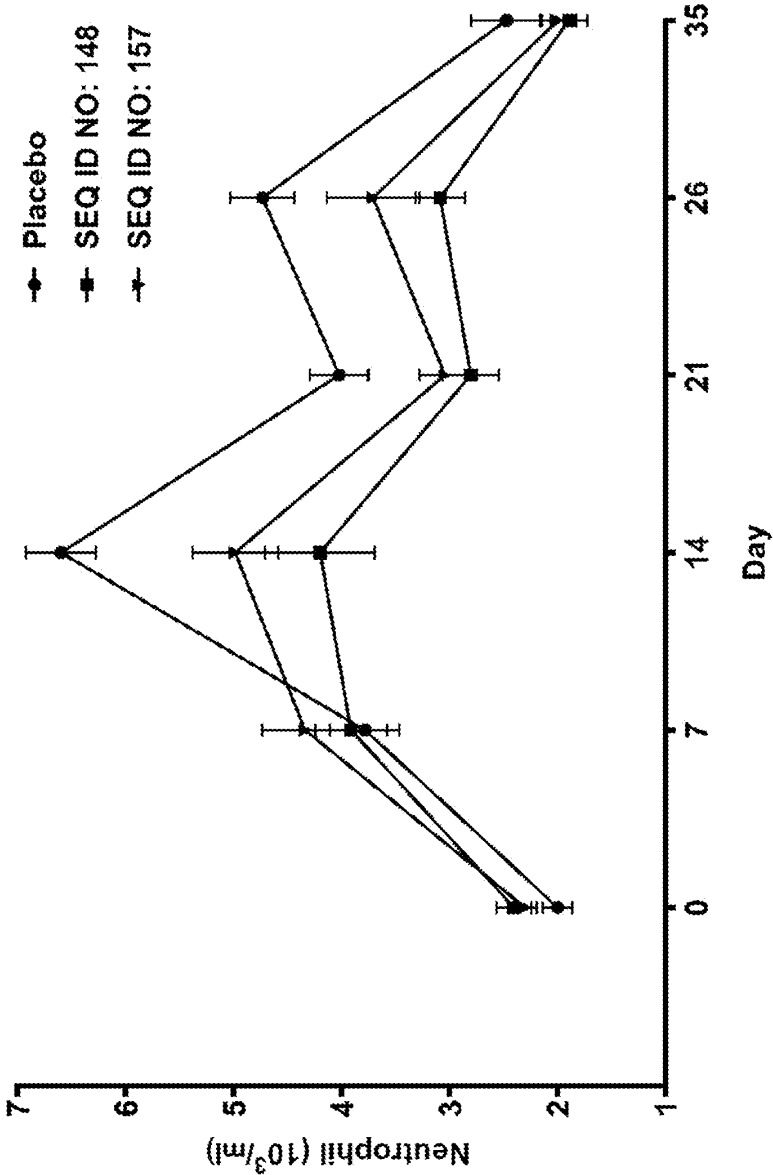
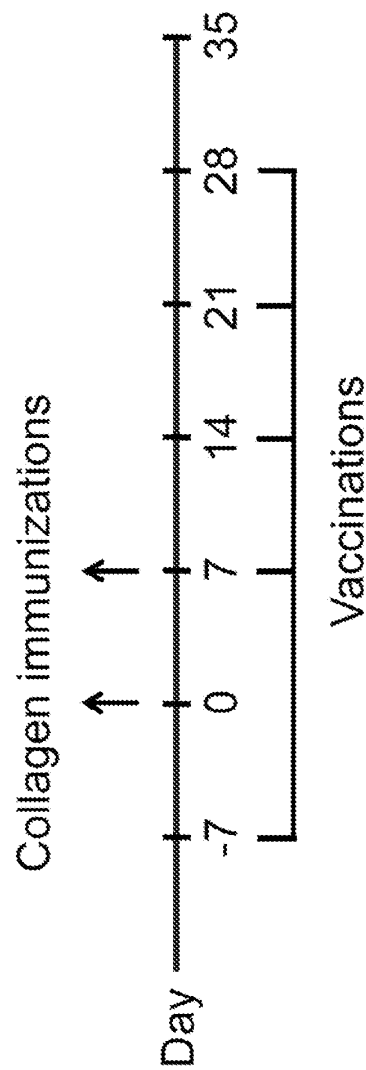


Figure 14
POC study protocol in a rat CIA model



- Animals: Lewis rat (female).
- Groups: Group 1 (placebo), Group 2 (SEQ NO: 148/ISA 51) and Group 3 (SEQ NO: 148/ISA 51/CpG).
- Vaccine dose: Immunize rats on day -7, 7, 14, 21 and 28 with 45 µg in 0.5 ml vaccine or adjuvant placebo by *i.m.* route.
- Collagen: Inject at the base of the tail (100 µg/100 µL) on day 0 and 7 with bovine type II collagen/IFA emulsion by *i.d.* route.

Figure 15
High immunogenicity of rat IL-6 peptide construct (SEQ ID NO: 148)
in rats

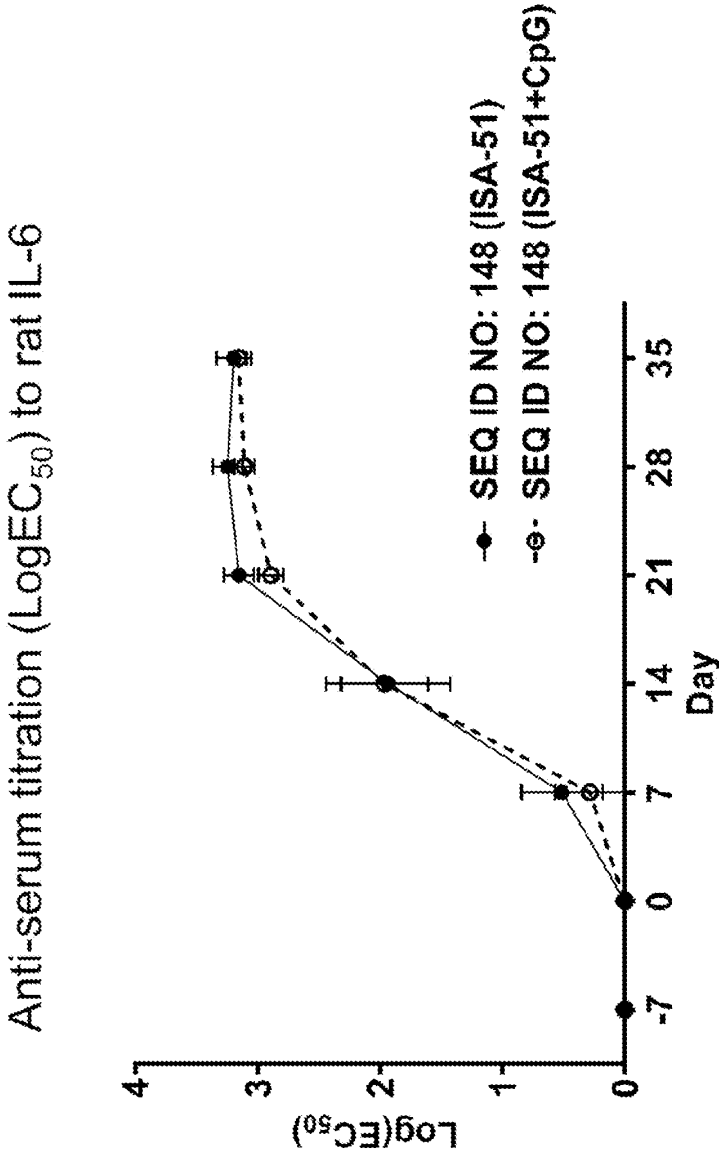


Figure 16
Arthritis symptoms were reduced significantly throughout the study

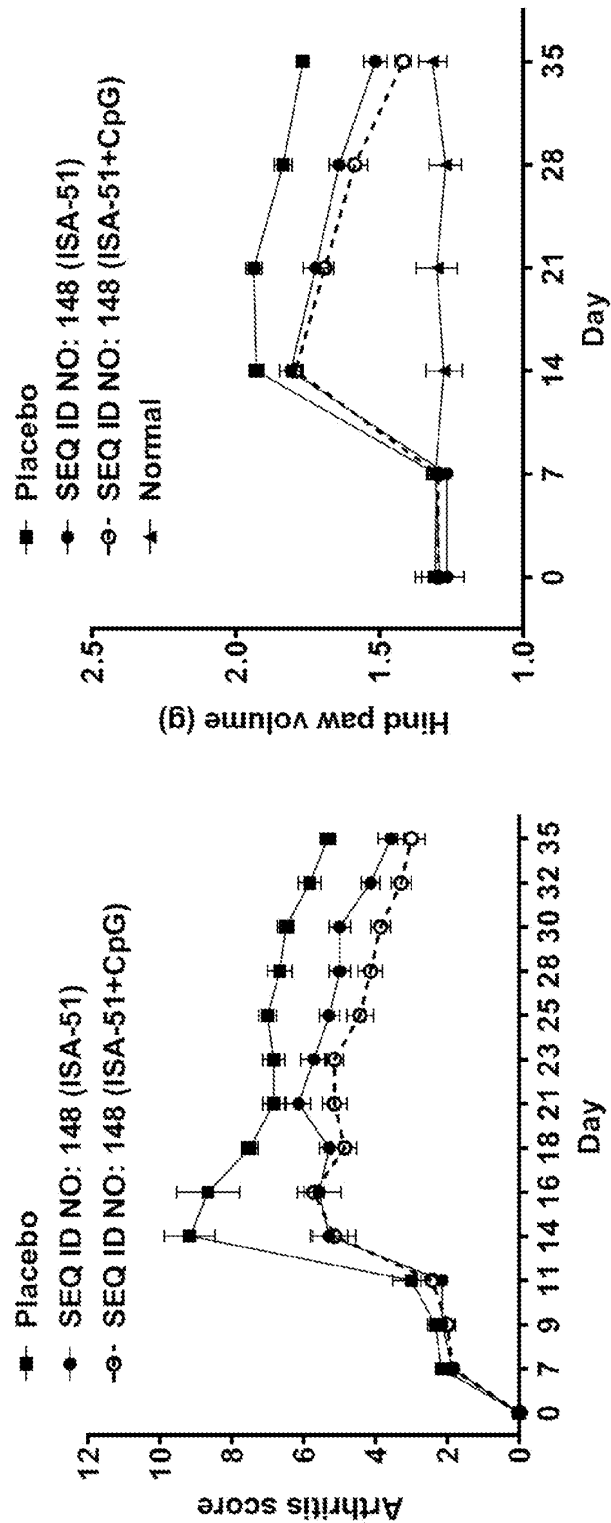
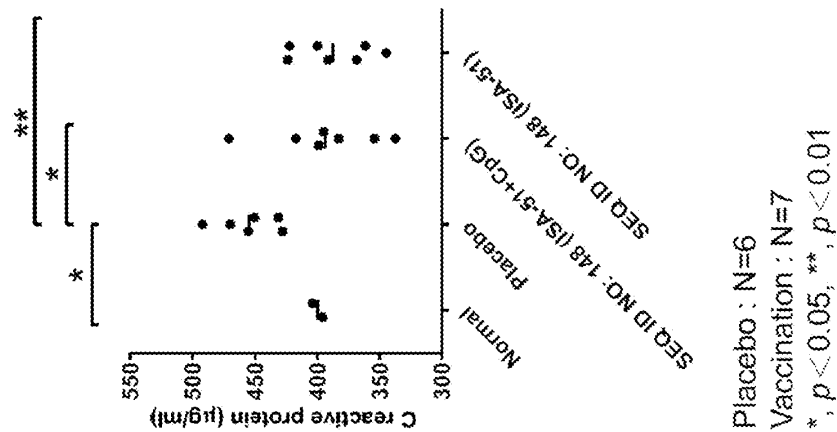


Figure 17
Inflammation-induced liver secretory proteins were reduced significantly



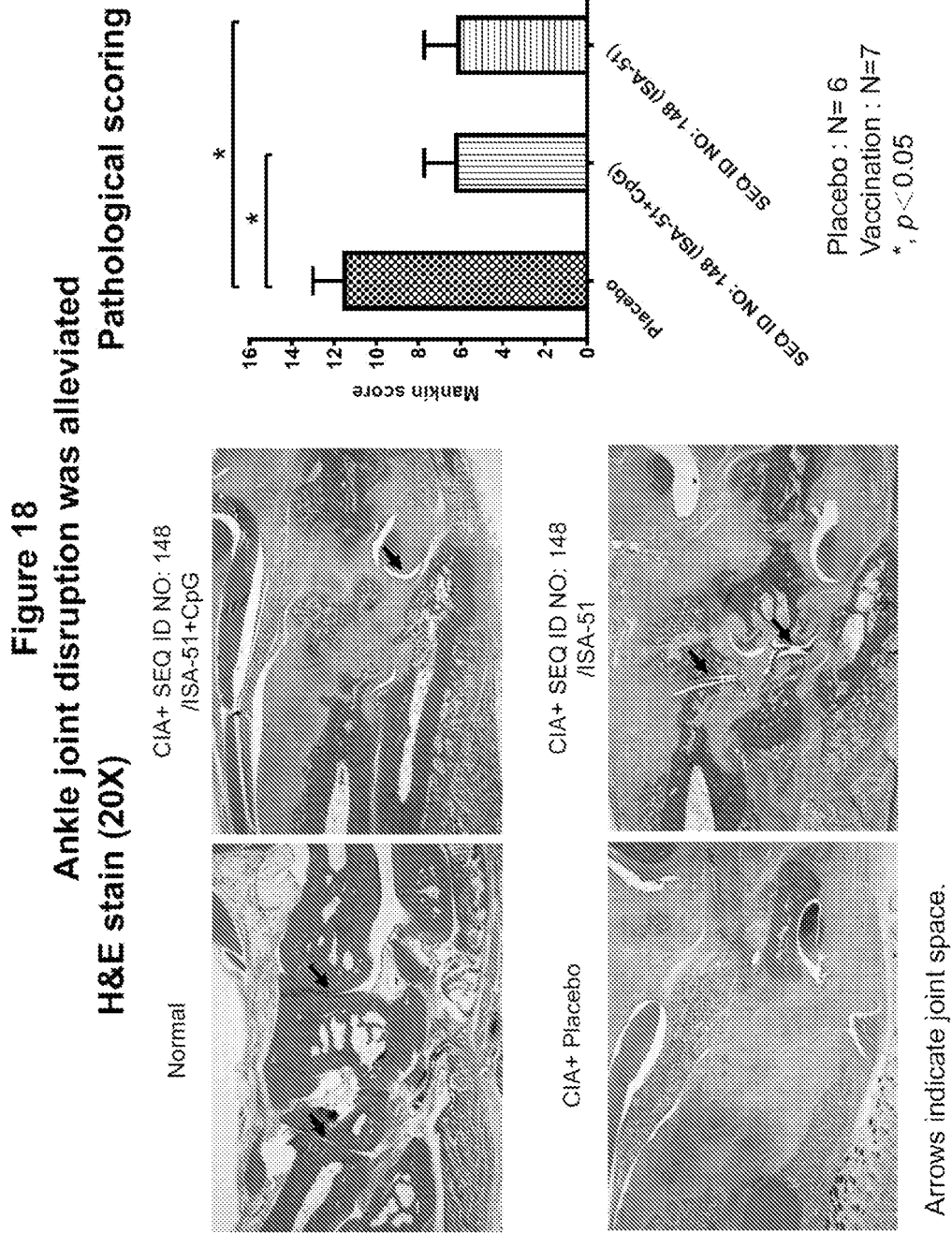


Figure 19
Production of tissue TNF- α , IL-17 and MCP-1 was significantly suppressed

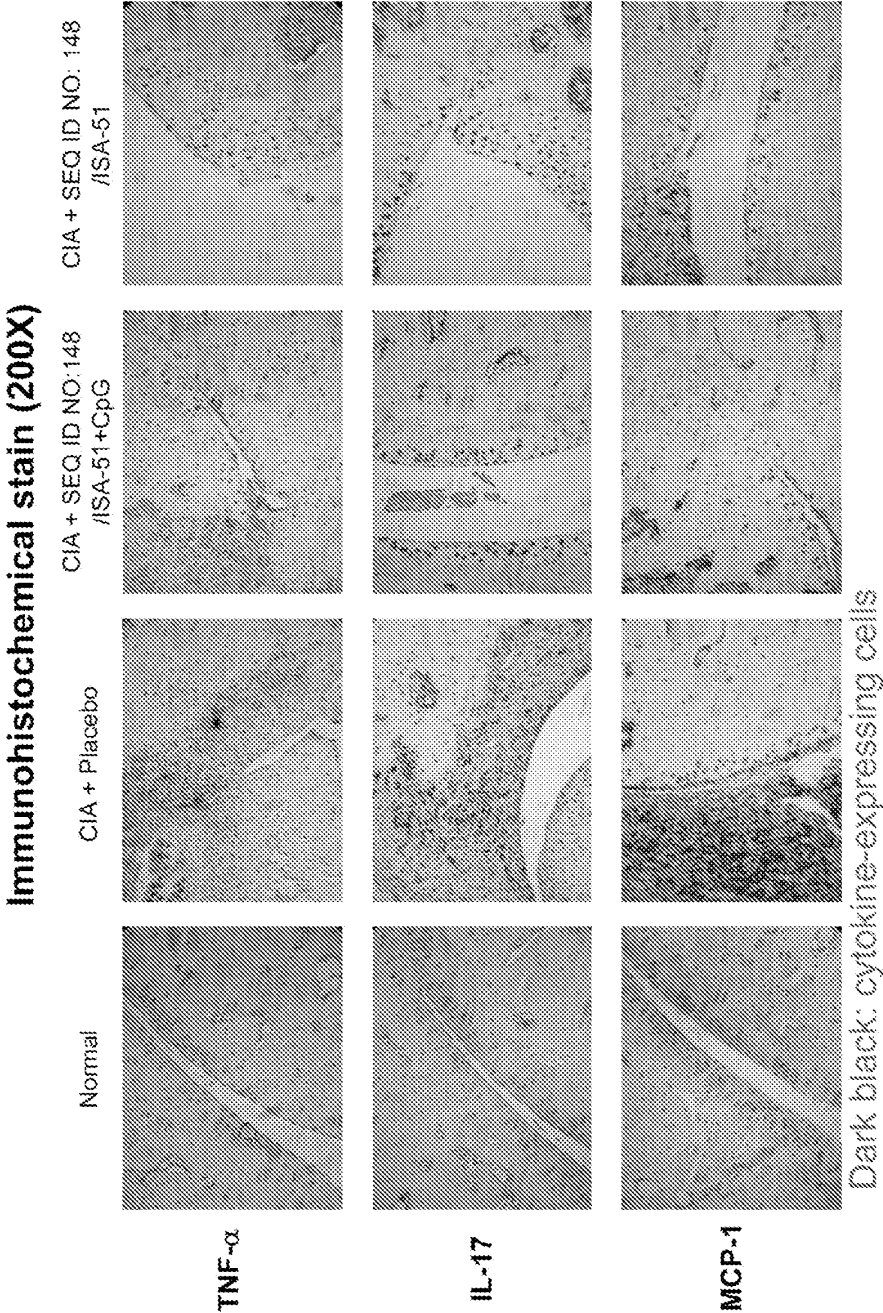


Figure 20

MONTANIDE ISA 51 elicited greater anti-IL-6 IgG titer than ADJU-PHOS

Antibody titers (Log_{10}) to recombinant rat IL-6

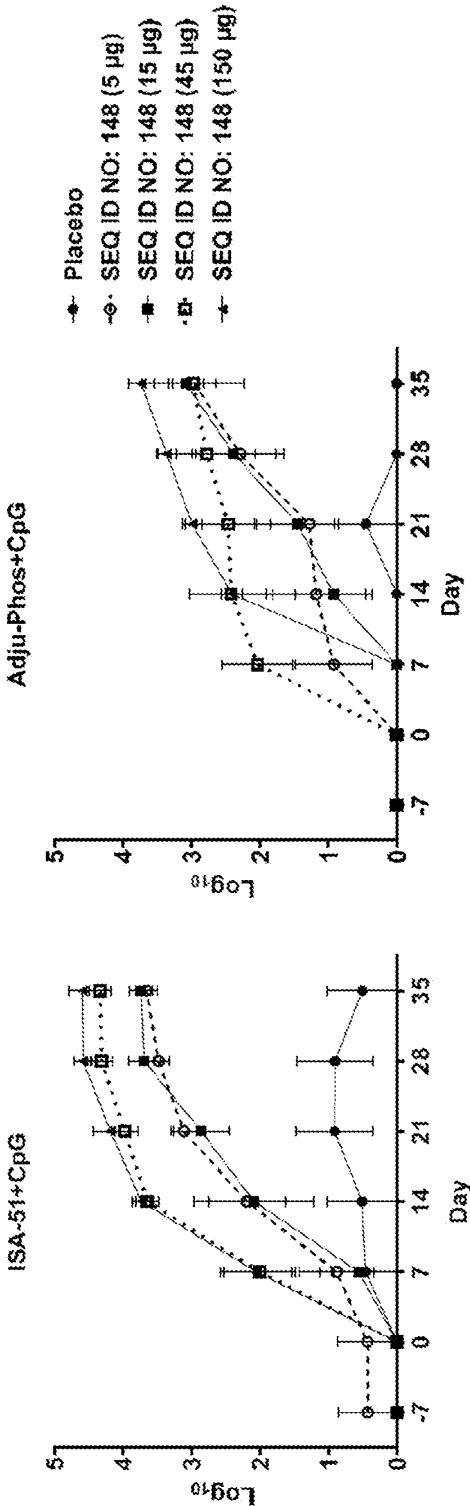


Figure 21
IL-6 vaccination at the dose of 150 µg/dose partially reversed body weight loss

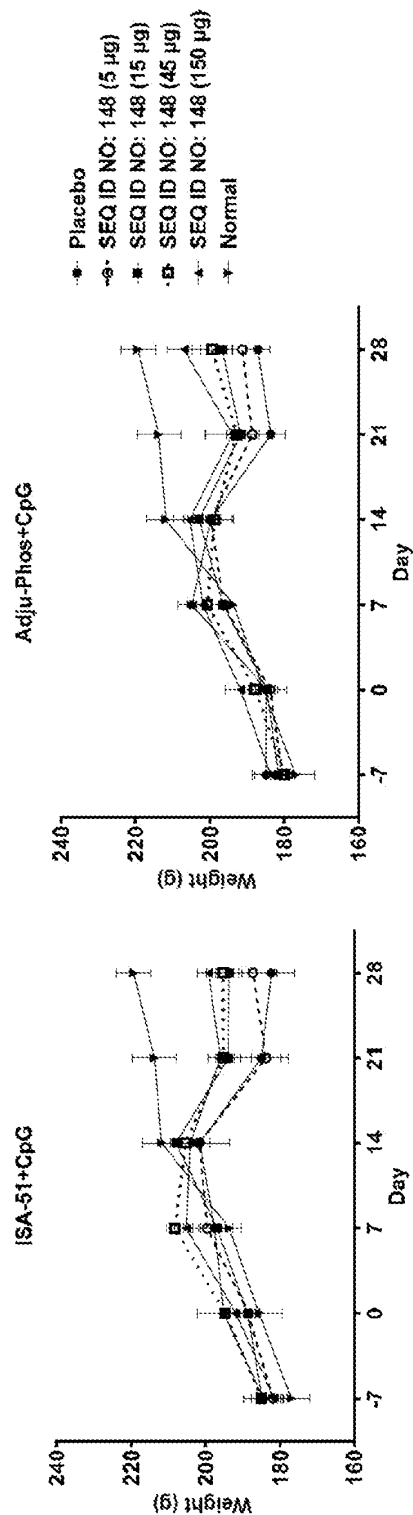


Figure 22
IL-6 vaccination at the doses of 45 and 150 µg/dose significantly
reduce hind paw swelling

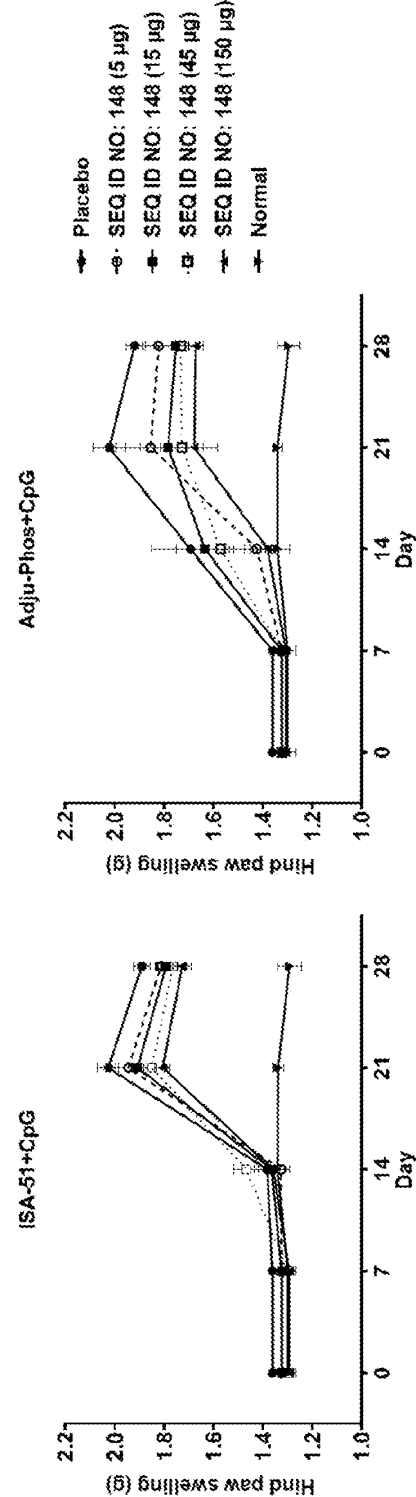


Figure 23
The macroscopic observation of hind paw on day 24
Adju-Phos+CpG
ISA-51+CpG

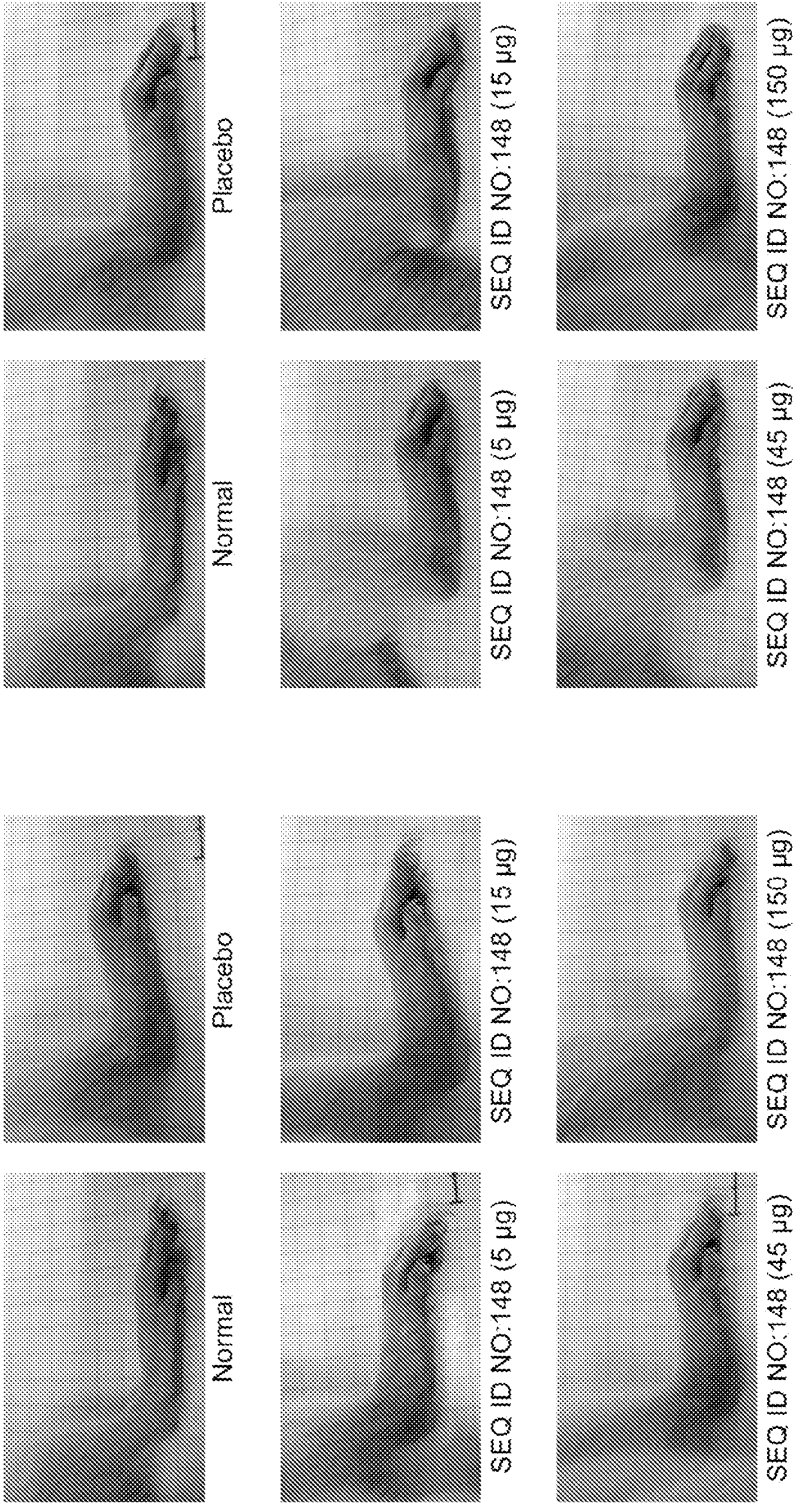


Figure 24
IL-6 vaccination at the doses of 45 and 150 µg/dose significantly
reduce arthritis symptoms

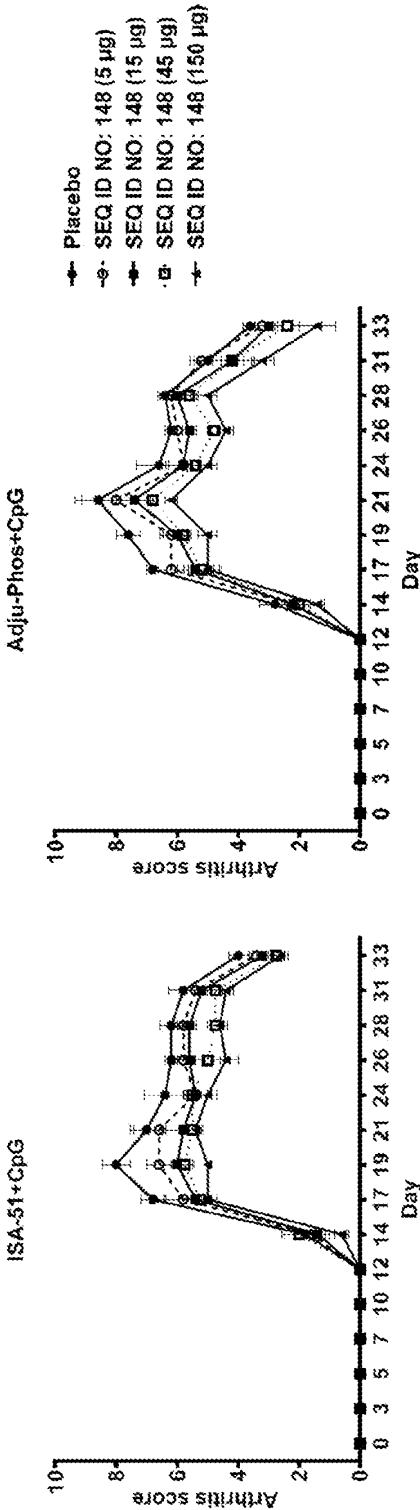


Figure 25
IL-6 vaccination at the doses of 45 and 150 µg/shot significantly
attenuated neutrophilia

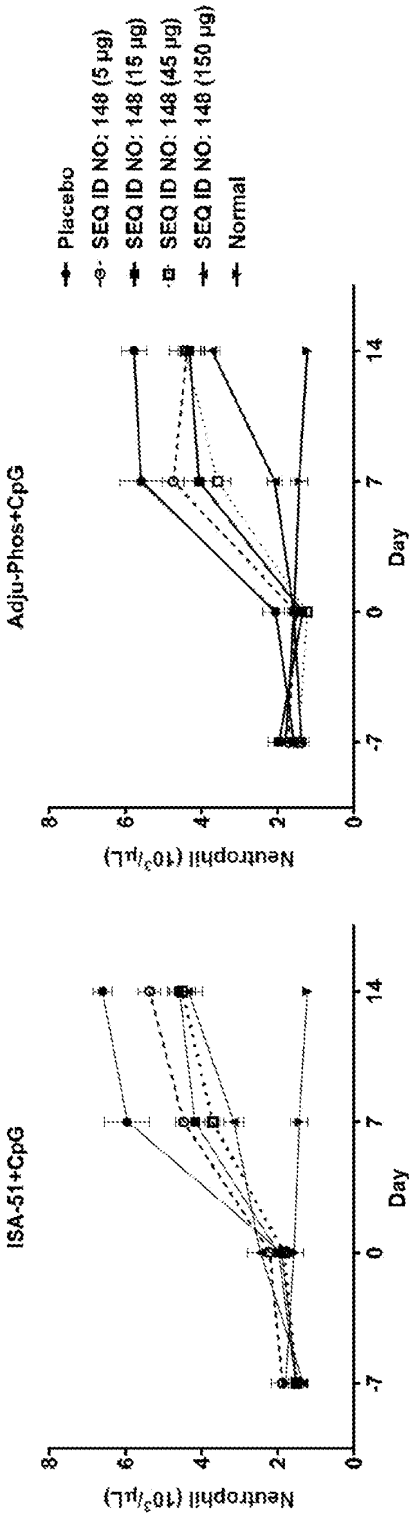


Figure 26
IL-6 vaccination at the doses of 45 and 150 µg/shot significantly
attenuated platelet release

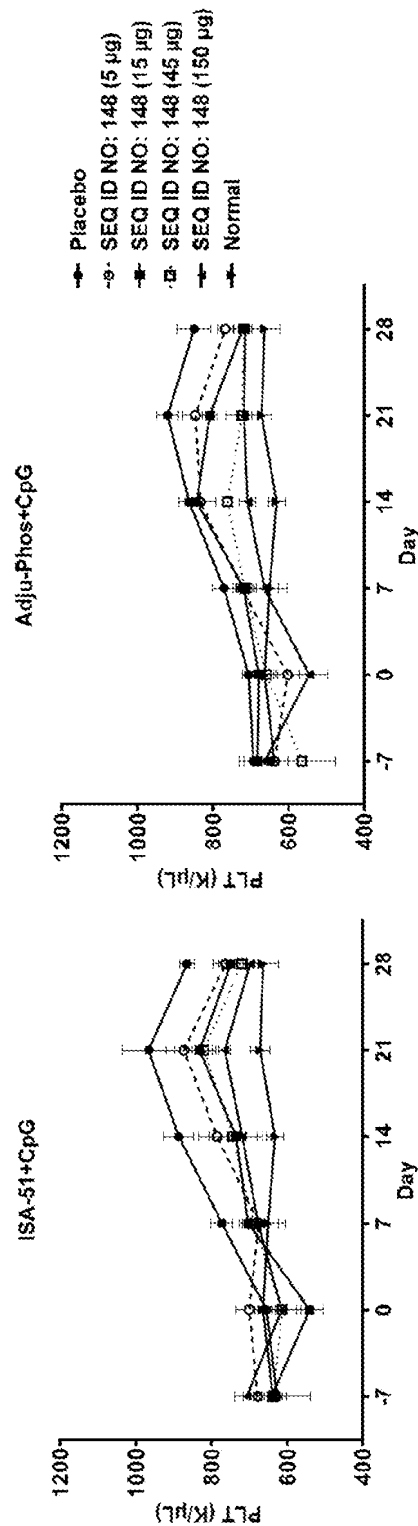


Figure 27
AST (liver function) in rat CIA model

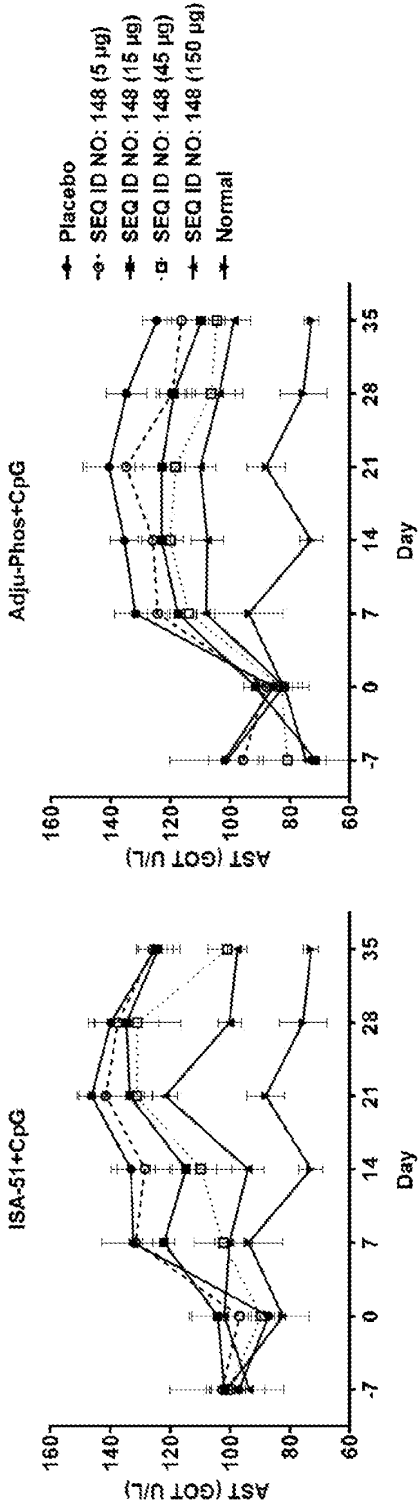


Figure 28
Effects of UB1Th®, peptide linker and adjuvant on immunogenicity

Anti-serum titration (LogEC₅₀) to human IL-6 protein

