Supplementary Table 1: Characteristics of Fc fusion proteins

Drug	Fusion protein	Mechanism of action	Indication	Molecular Weight (kDa)	Expression System	Post-translational modification	Pharmacokinetic parameters
Approved drugs							
Etanercept	Dimeric fusion protein comprising the extracellular domain of human p75 TNF receptor fused to Fc (hinge, C_H2, and C_H3 domains) of human IgG1 (Enbrel®, 2011, Goldenberg, 1999, Mohler et al., 1993)	Inhibits binding of TNFα and TNFβ to cell surface TNF receptors (Enbrel®, 2011)	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis (Enbrel®, 2011)	150 (Enbrel®, 2011)	CHO cells (Enbrel®, 2011, Mohler et al., 1993)	Glycosylation (Walsh, 2010)	• Mode of administration = SC injection (Enbrel®, 2011) • Mean ± SD $t_{1/2}$*= 4.24 ± 1.25 days (Enbrel®, 2011) • Mean ± SD CL* = 160 ± 80 mL/h (Enbrel®, 2011) • Vd** = 18.5 L; extravascular distribution expected to be very small (Zhou, 2005) • Mean absolute bioavailability* = 58% (Zhou, 2005) • Metabolism and elimination*: Following binding of etanercept to TNF, the complex is thought to be metabolized via peptide and amino acid pathways, with either recycling of amino acids or elimination in bile and urine (Zhou, 2005)
Alefacept	Extracellular CD2-binding portion of human LFA-3 fused to Fc (hinge, C_H2 and C_H3 domains) of human IgG1 (AMEVIVE®, 2011, Miller et al., 1993, Majeau et al., 1994)	Inhibits T lymphocyte activation by binding to the lymphocyte antigen, CD2, and preventing it binding to the LFA-3 ligand on APCs (AMEVIVE®, 2011)	Adult moderate to severe chronic plaque psoriasis (AMEVIVE®, 2011)	91.4 (AMEVIVE®, 2011)	CHO cells (AMEVIVE®, 2011, Miller et al., 1993)	Glycosylation (Walsh, 2010)	• Mode of administration = IM injection (AMEVIVE®, 2011) • Mean $t_{1/2}$*= 11 days (AMEVIVE®, 2011) • Mean Vd* = 94 mL/kg (AMEVIVE®, 2011) • Mean CL* = 0.25 mL/h/kg (AMEVIVE®, 2011) • Bioavailability* = 63% (AMEVIVE®, 2011)
Abatacept	Extracellular domain of CTLA-4 fused to modified Fc (hinge, C_H2, and C_H3 domains) portion of human Ig G1 (Orencia, 2011)	Binds CD80 and CD86 , blocking their interaction with CD28 and, therefore, inhibiting T cell activation (Orencia, 2011)	Adult rheumatoid arthritis, juvenile idiopathic arthritis (Orencia, 2011)	92 (Orencia, 2011)	Mammalian cell expression system (Orencia, 2011)	Glycosylation (Walsh, 2010)	• Mode of administration = IV loading dose followed by SC injections (Orencia, 2011) • Mean (range) $t_{1/2}$ following IV administration**= 13.1 (8-25) days (Orencia, 2011) • Mean (range) CL following IV

Drug	Fusion protein	Mechanism of action	Indication	Molecular Weight (kDa)	Expression System	Post-translational modification	Pharmacokinetic parameters
							administration ** = 0.22 (0.13-0.47) mL/h/kg (Orencia, 2011) • Mean (range) Vd at steady state following IV administration ** = 70 (20-130) mL/kg (Orencia, 2011) • Bioavailability following SC administration = 78.6% (Orencia, 2011)
Rilonacept	Dimeric fusion protein consisting of ligand-binding domains of the extracellular portions of the human IL-1 receptor component (IL-1RI) and IL-1RAcP linked in-line to Fc portion of human IgG1 (Arcalyst, 2010)	Acts as a soluble decoy receptor by binding IL-1β and inhibiting its signalling (Arcalyst, 2010). Also binds IL-1α and IL-1ra with reduced affinity (Arcalyst, 2010)	Cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome in adults and children >12 years (Arcalyst, 2010)	251 (Arcalyst, 2010)	CHO cells (Arcalyst, 2010)	Glycosylation (Walsh, 2010)	• Mode of administration = SC injection (Arcalyst, 2010) • $t_{1/2}$ = 6.3 days in pediatrics and 7.0 days in adults (Gillespie et al., 2010) • Bioavailability* = 50% (Rilonacept_SmPC, 2009) • CL***= 0.808 L/day (Rilonacept_SmPC, 2009)
Belatacept	Modified CTLA-4 (at sites L104E and A29) fused to Fc domain of human IgG1(Larsen et al., 2005, NULOJIX, 2011)	Blocks CD28-mediated costimulation of T cells by binding CD80 and CD86 on APCs (NULOJIX, 2011). *In vitro*, belatacept inhibits T cell proliferation and the production of IL-2, IFN-γ, IL-4 and TNF-α (NULOJIX, 2011)	Kidney transplant rejection (NULOJIX, 2011)	90 (NULOJIX, 2011)	Mammalian cell expression system (NULOJIX, 2011) COS cells (Larsen et al., 2005)	N/A	• Mode of administration = IV injection (NULOJIX, 2011) • Mean (range) $t_{1/2}$**= 9.8 (6.1-15.1) days (NULOJIX, 2011) • Mean (range) CL**= 0.49 (0.23-0.70) mL/h/kg (NULOJIX, 2011) • Mean (range) Vd at steady state**= 0.11 (0.067-0.17) L/kg (NULOJIX, 2011)
Aflibercept	Second Ig domain of human VEGFR1 and third Ig domain of human VEGFR2 fused to Fc domain of human IgG1 (Eylea, 2011, Holash et al., 2002)	Inhibits angiogenesis by acting as a decoy receptor that binds VEGF-A, VEGF-B, PlGF, blocking their interaction with VEGFRs (Eylea, 2011, Papadopoulos et al., 2012)	Neovascular (wet) age-related macular degeneration (Eylea, 2011), in combination with FOLFIRI approved for metastatic colorectal cancer (Ciombor et al.,	97 (Eylea, 2011)	CHO cells (Eylea, 2011, Holash et al., 2002)	Glycosylation (Eylea, 2011)	• Mode of administration = ophthalmic intravitreal injection (Eylea, 2011) and IV injection • $t_{1/2}$ following IV injection = 5-6 days (Eylea, 2011) • Vd following IV injection = 6L (Eylea, 2011) • Elimination: expected to be eliminated through target-

Drug	Fusion protein	Mechanism of action	Indication	Molecular Weight (kDa)	Expression System	Post-translational modification	Pharmacokinetic parameters
			2013)				mediated disposition via binding to free endogenous VEGF, and metabolism via proteolysis (Eylea, 2011)
Romiplostim	Two tandem dimers of thrombopoietin mimetic peptides fused to Fc domain of human IgG1 (Molineux and Newland, 2010)	Stimulates platelet production through binding to the thrombopoietin receptor (Mpl) (Molineux and Newland, 2010, Nplate, 2011, Wang et al., 2004)	Thrombocytopenia in patients with chronic immune thrombocytopenia (Nplate, 2011)	60 (Molineux and Newland, 2010, Wang et al., 2004)	E. coli (Molineux and Newland, 2010)	N/A	• Mode of administration = SC injection (Nplate, 2011) • Median (range) $t_{1/2}$ following SC injections** = 3.5 (1-34) days (Nplate, 2011) • Mean (SD) $t_{1/2}$ following IV injection* = 13.8 (3.9) hours (Wang et al., 2004) • Mean (SD) CL* = 6.69 (1.03) mL/kg/h (Wang et al., 2004) • Mean (SD) central Vd* = 48.2 (7.4) mL/kg (Wang et al., 2004)
Drugs in Development							
rFVIIIFc	Monomeric fusion protein: single rFVIII molecule covalently fused to human IgG1 Fc domain, with no intervening linker sequence (Dumont et al., 2012)	Replacement clotting factor (Dumont et al., 2012, Peters et al., 2013)	In phase 3 development for treatment of hemophilia A (Biogen_Idec, 2012, Mahlangu et al., 2013)	N/A	HEK293 cells (Powell et al., 2012)	N/A	• Mode of administration = IV (Powell et al., 2012) • Mean (95% CI) $t_{1/2}$ * = 18.8 h (14.8, 23.8) for 25 IU/kg dose, and 18.8 h (14.3, 24.5) for 65 IU/kg dose (Powell et al., 2012) • Mean (95% CI) CL* = 1.68 [1.31, 2.15] mL/hour/kg for 25 IU/kg dose, and 2.32 (1.64, 3.29) mL/hour/kg for 65 IU/kg dose (Powell et al., 2012) • Mean (95% CI) Vd at steady state* = 45.4 (39.3, 52.5) mL/kg for 25 IU/kg dose, and 62.8 (55.2, 71.5) mL/kg for 65 IU/kg dose (Powell et al., 2012)
rFIXFc	Monomeric fusion protein: single rFIX molecule covalently fused to human IgG1 Fc domain, no intervening linker sequence (Peters et al., 2010)	Replacement clotting factor (Peters et al., 2010)	In phase 3 development for treatment of hemophilia B (Biogen_Idec, 2012, Powell et al., 2013)	120 (Peters et al., 2010)	HEK293 cells (Shapiro et al., 2012)	Propeptide processing, ɣ-carboxylation, Ser 158 phosphorylation, Tyr 155 sulfation, N-	• Mode of administration = IV injection (Shapiro et al., 2012) • Mean (range) $t_{1/2}$ * = 56.7 (42.4-74.5) h (Shapiro et al., 2012) • Mean (range) CL* = 3.18 (2.05-4.18) mL/hour/kg (Shapiro et al., 2012)

Drug	Fusion protein	Mechanism of action	Indication	Molecular Weight (kDa)	Expression System	Post-translational modification	Pharmacokinetic parameters
						and O-linked glycosylation, β-hydroxylation (Peters et al., 2010)	• Mean (range) Vd at steady state* = 227 (162–296) mL/kg (Shapiro et al., 2012)
Atacicept	Homodimeric fusion protein, which comprises the extracellular domain of TACI, the 3'end of which is fused to the 5' end of human IgG1 (Gatto, 2008)	Soluble decoy receptor that binds BLyS and APRIL and prevents their interaction with membrane-bound receptors (Gatto, 2008)	In phase 2/3 development for SLE [clinicaltrials.gov: NCT00624338]	73.4 (Gatto, 2008)	CHO cells (Gatto, 2008)	One putative N-glycosylation site; most abundant glycans identified were agalacto-biantennary fucosylated glycans (Gatto, 2008)	• Mode of administration = IV injection (Pena-Rossi et al., 2009) • Median (range) $t_{1/2}$* = 27-32 (20-44) days (Pena-Rossi et al., 2009) • Median (range) CL* = 0.282-0.319 (0.201-0.315) L/h (Pena-Rossi et al., 2009)
APG101	Fully human fusion protein comprising the extracellular domain of the CD95 receptor and IgG Fc domain (Apogenix, 2012b)	Binds to CD95 ligand inhibiting binding to its receptor (Apogenix, 2012b)	In phase 2 development for glioblastoma and phase 1 development for myelodysplastic syndromes (Apogenix, 2012a)	N/A	N/A	N/A	• Mode of administration = IV injection (Tuettenberg et al., 2012) • For dose of 0.2 to 20 mg/ml, mean (SD): o $t_{1/2}$* = 3 (1) to 14 (0.5) days (Tuettenberg et al., 2012) o CL* = 0.88 (0.25) to 0.44 (0.014) ml/h•kg (Tuettenberg et al., 2012) o Vd at steady state* = 89 (2.6) to 170 (5.5) ml/kg (Tuettenberg et al., 2012)
AMG 386	Peptibody in which angiopoietin-2 peptides are fused to Fc domain of human IgG1 (Neal and Wakelee, 2010)	Binds to angiopoietin-1 and angiopoietin-2 and blocks Tie-2 receptor signaling (Neal and Wakelee, 2010)	In phase 2 development for multiple cancers, and phase 3 development for ovarian cancer	N/A	E. coli (Neal and Wakelee, 2010)	N/A	• Mode of administration = IV injection (Herbst et al., 2009) • For doses of 0.3 mg/kg: o Mean $t_{1/2}$ ranged from 3.1 to 5.1 days (Herbst et al., 2009)

Drug	Fusion protein	Mechanism of action	Indication	Molecular Weight (kDa)	Expression System	Post-translational modification	Pharmacokinetic parameters
							o Mean CL ranged from 0.7 to 1.27 mL/kg/hour (Herbst et al., 2009) o Mean Vd at steady state ranged from 79.8 to 110 mL/kg (Herbst et al., 2009)
Sotatercept	Chimeric fusion protein comprising the 2 extracellular components of ACVR2A and Fc domain of human IgG1 (Raje and Vallet, 2010)	Sequesters activin and inhibits downstream signaling (Raje and Vallet, 2010), which increases hemoglobin and red blood cell levels (Acceleron, 2012)	In phase 2/3 development for anemia (Acceleron, 2012)	106 (Raje and Vallet, 2010)	HEK293 cells (Raje and Vallet, 2010)	Glycosylation (Raje and Vallet, 2010)	• Mode of administration = IV and SC injection (Ruckle et al., 2009) • Over IV dose range of 0.1–3.0 mg/kg: o Mean CL* = 0.092-0.128 ml/h/kg (Ruckle et al., 2009) o Mean Vd* = 73.7 - 110 ml/kg (Ruckle et al., 2009) o Mean $t_{1/2}$ * = 23.7 to 31.8 days (Ruckle et al., 2009)

*Single-dose PK evaluation; **Multiple-dose PK evaluation; ***Based on PK modeling; ****Published phase 1 and/or beyond; TNF = tumor necrosis factor; CHO = Chinese hamster ovary; SC = subcutaneous; $t_{1/2}$ = half-life; SD = standard deviation; CL = clearance; Vd = volume of distribution; LFA = lymphocyte function-associated antigen; IM = intramuscular; ELISA = enzyme-linked immunosorbent assay; IL = interleukin; IL-1RacP = interleukin-1 receptor accessory protein; IL-1ra = IL-1 receptor antagonist; CTLA = cytotoxic T-lymphocyte antigen; IV = intravenous; APC = antigen presenting cell; IFN = interferon; VEGFR = vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor; PlGF = placental growth factor; rFVIII = recombinant factor VIII; rFIX = recombinant factor IX; TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor; BLyS = B lymphocyte stimulator; APRIL = proliferation inducing ligand; SLE = systemic lupus erythematosus; ACVR2A = activin receptor 2A

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Supplementary Table 2: Mutations in the Fc fragment with enhanced FcRn affinity (modified according to (Presta, 2008)).

IgG variant	Alteration (Fc Domain)	Engineered Antibody	FcRn binding pH 6.0 -fold increase-	Serum $t_{1/2}$ -fold increase-	Ref
Fc Mutations with increased in vivo half-life					
QL	T250Q (CH2) M428L (CH3)	anti-HBV OST577 IgG1	37x (rhesus) 29x (human)	2.5x (rhesus)	(Hinton et al., 2004, Hinton et al., 2006)
		anti-HBV OST577 IgG1	28x (human) 27x (rhesus)	1.9x (rhesus)	(Hinton et al., 2004)
		anti-TNFα IgG1	40x (cynomolgus) 500x (mouse)	unchanged (cynomolgus)	(Datta-Mannan et al., 2007b)
LS	M428L (CH3) N434S (CH3)	anti-VEGF IgG1 (bevacizumab)	11x (human)	3.2x (cynomolgus) 4x (hFcRn Tg mice)	(Zalevsky et al., 2010)
		anti-VEGF IgG1 (cetuximab)		3.1x (cynomolgus) 5x (hFcRn-Tg mice)	
A	N434A (CH3)	anti-HER2 IgG1 (Hu4D5)	3.4x (human)	2.2x (hFcRn Tg mice)	(Petkova et al., 2006, Shields et al., 2001)
AAA	T307A (CH2) E380A (CH3) N434A (CH3)	Anti-HER2 IgG1 (Hu4D5)	11.8x (human)	2.5x (hFcRn Tg mice)	(Petkova et al., 2006, Shields et al., 2001)
YTE	M252Y (CH2) S254T (CH2) T256E (CH2)	Anti-RSV IgG1 (MEDI-524)	10x (cynomolgus) 10x (human)	4x (cynomolgus)	(Dall'Acqua et al., 2006)
NA	N434A (CH3)	Anti-HER2-IgG1 (Hu4D5, trastuzumab)	4x (cynomolgus)	1.6–2.3x (cynomolgus)	(Yeung et al., 2009)
Fc mutations with unaltered or reduced in vivo half-life					
NW	N434W (CH3)	anti-HER2 IgG (Hu4D5, trastuzumab)	80x (cynomolgus)	unchanged (cynomolgus)	(Yeung et al., 2009)
VH	D376V N434H	anti-TNF IgG1	15x (human) 52x (cynomolgus) 17x (mouse)	0.8x (cynomolgus) 0.1x (mouse)	(Datta-Mannan et al., 2007a)
IH	P257I N434H	anti-TNF IgG1	16x (human) 52x (cynomolgus) 197x (mouse)	0.7x (cynomolgus) 0.03x (mouse)	(Datta-Mannan et al., 2007a)

II	P257I Q311I	anti-TNF IgG1	19x (human) 80x (cynomolgus) 25x (mouse)	unchanged (cynomolgus) 0.1x (mouse)	(Datta-Mannan et al., 2007b)

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