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Review article

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The therapeutic age of the neonatal Fc receptor

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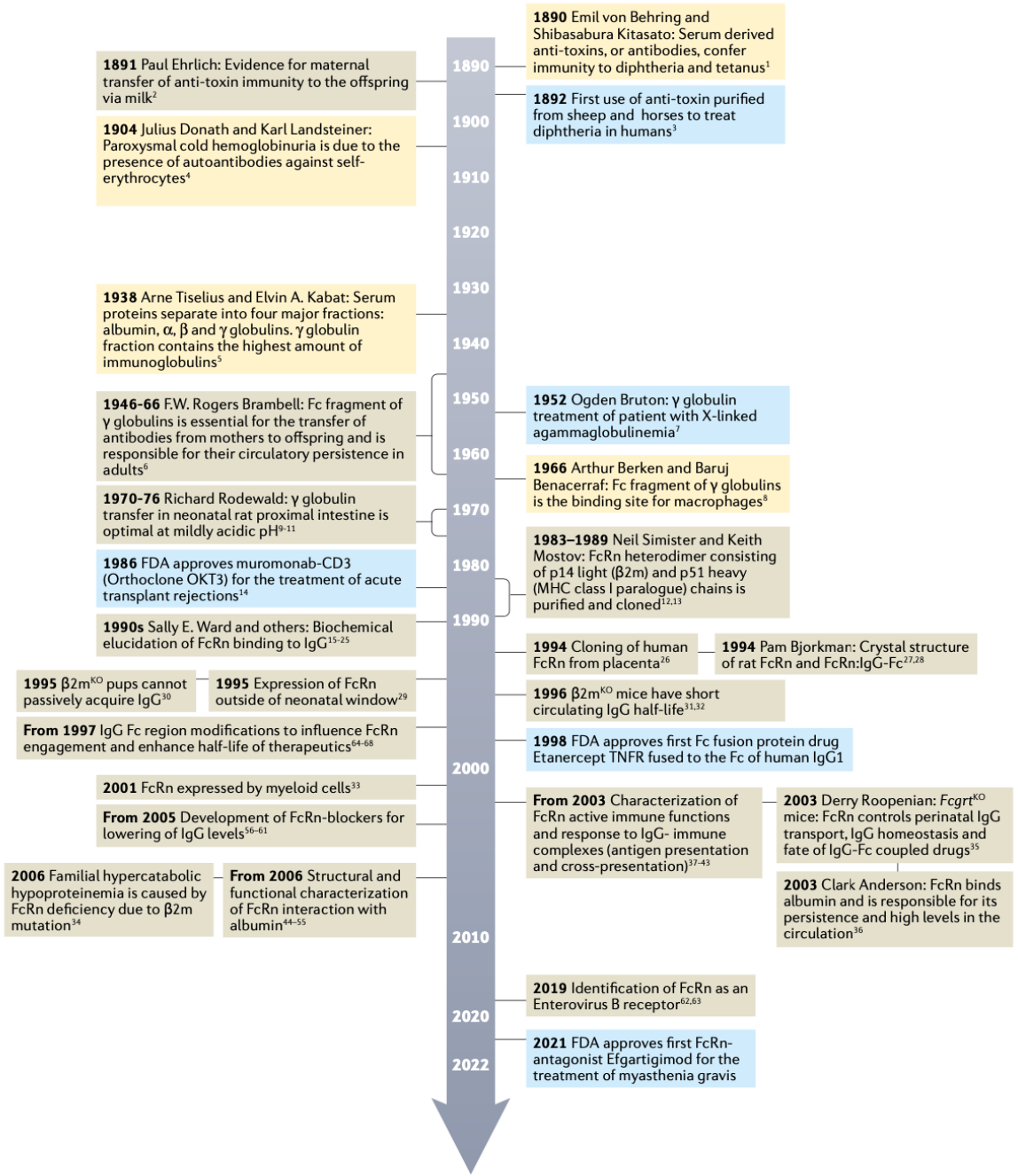
Supplementary Figure 1 | The history of scientific progress in the field of FcRn in the context of selected events in antibody discovery

Major events in the history of antibodies (yellow) and FcRn (beige), with major clinical milestones (blue) listed. The early studies on FcRn-mediated biology are contemporaneous to the original identification of antibodies, since only a year later, in 1891, the observation that ricin or abrin exposed mothers transferred protection from lethal administration of these toxins to their offspring via milk were published. The veritable advance in the FcRn-field was made by F.W.R. Brambell, who not only continued to investigate materno-fetal immunity, but also illustrated the extended persistence of γ globulins in the circulation, and showed that these two phenomena required the Fc portion of the Ab. During the next 30 years FcRn was specifically identified, cloned, and structurally described, which allowed in the 1990s and onwards to characterize the pH-dependent FcRn-IgG interactions both on a molecular, cellular, and functional level in animal models and in humans. Later it was discovered that FcRn can also engage albumin, and more recently was identified as Echovirus-B uncoating receptor. FcRn = neonatal Fc receptor, IgG = immunoglobulin G, beta-2 microglobulin = β2m, KO = knockout, Fc = fragment crystallizable, MHC = major histocompatibility complex, FDA = Food and Drug Administration (USA).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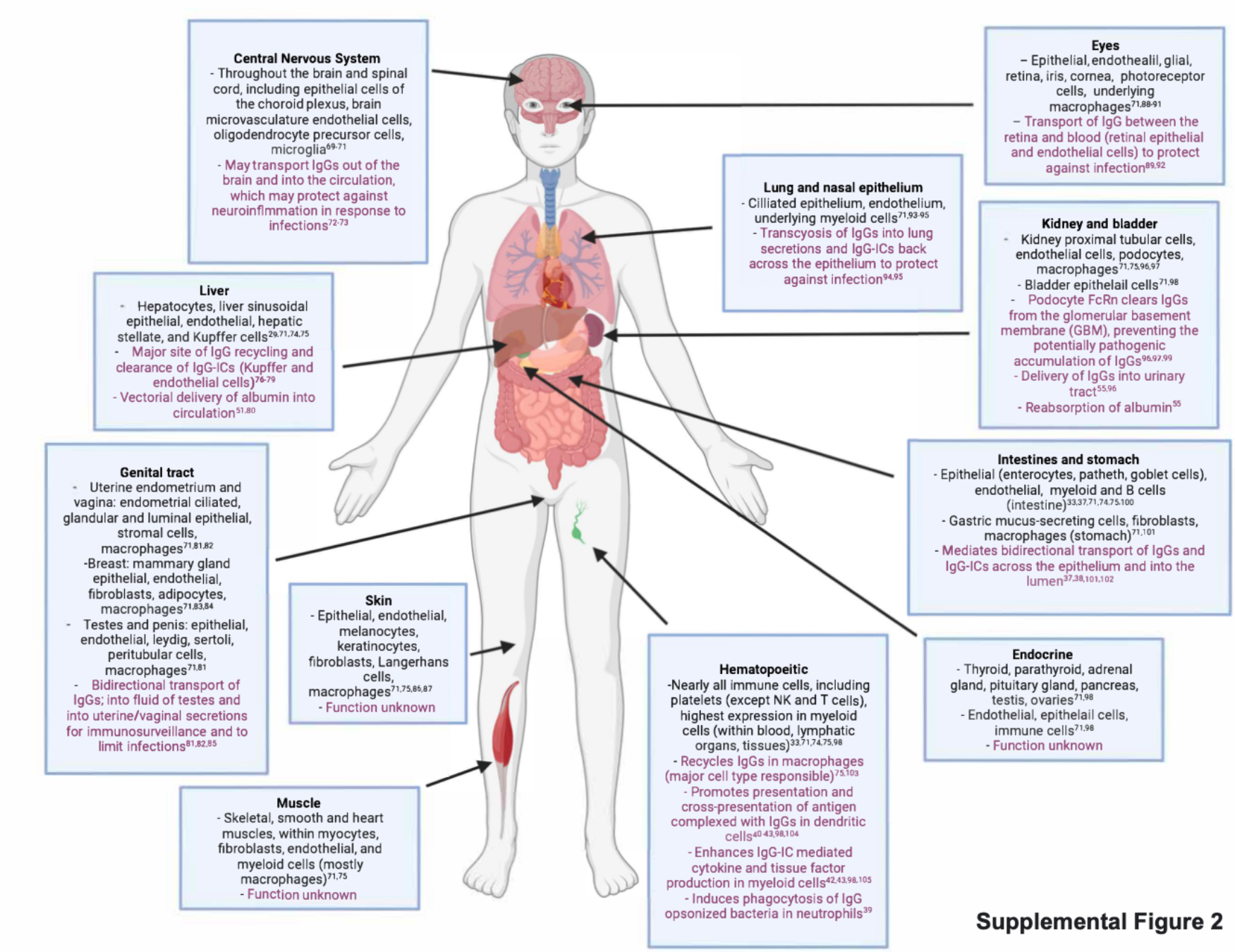
1890 Emil von Behring and Shibasabura Kitasato: Serum derived anti-toxins, or antibodies, confer immunity to diphtheria and tetanus[1]
1891 Paul Ehrlich: Evidence for maternal transfer of anti-toxin immunity to the offspring via milk[2]
1892 First use of anti-toxin purified from sheep and horses to treat diphtheria in humans[3]
1904 Julius Donath and Karl Landsteiner: Paroxysmal cold hemoglobinuria is due to the presence of autoantibodies against self-erythrocytes[4]
1938 Arne Tiselius and Elvin A. Kabat: Serum proteins separate into four major fractions: albumin, α, β and γ globulins. γ globulin fraction contains the highest amount of immunoglobulins[5]
1946-66 F.W. Rogers Brambell: Fc fragment of γ globulins is essential for the transfer of antibodies from mothers to offspring and is responsible for their circulatory persistence in adults[6]
1952 Ogden Bruton: γ globulin treatment of patient with X-linked agammaglobulinemia[7]
1966 Arthur Berken and Baruj Benacerraf: Fc fragment of γ globulins is the binding site for macrophages[8]
1970-76 Richard Rodewald: γ globulin transfer in neonatal rat proximal intestine is optimal at mildly acidic pH[9-11]
1983–1989 Neil Simister and Keith Mostov: FcRn heterodimer consisting of p14 light (β2m) and p51 heavy (MHC class I paralogue) chains is purified and cloned[12,13]
1986 FDA approves muromonab-CD3 (Orthoclone OKT3) for the treatment of acute transplant rejections[14]
1990s Sally E. Ward and others: Biochemical elucidation of FcRn binding to IgG[15-25]
1994 Cloning of human FcRn from placenta[26]
1994 Pam Bjorkman: Crystal structure of rat FcRn and FcRn:IgG-Fc[27,28]
1995 β2m^{KO} pups cannot passively acquire IgG[30]
1995 Expression of FcRn outside of neonatal window[29]
1996 β2m^{KO} mice have short circulating IgG half-life[31,32]
From 1997 IgG Fc region modifications to influence FcRn engagement and enhance half-life of therapeutics[64-68]
1998 FDA approves first Fc fusion protein drug Etanercept TNFR fused to the Fc of human IgG1
2001 FcRn expressed by myeloid cells[33]
From 2003 Characterization of FcRn active immune functions and response to IgG- immune complexes (antigen presentation and cross-presentation)[37-43]
2003 Derry Roopenian: *Fcgrt*^{KO} mice: FcRn controls perinatal IgG transport, IgG homeostasis and fate of IgG-Fc coupled drugs[35]
From 2005 Development of FcRn-blockers for lowering of IgG levels[56-61]
2003 Clark Anderson: FcRn binds albumin and is responsible for its persistence and high levels in the circulation[36]
2006 Familial hypercatabolic hypoproteinemia is caused by FcRn deficiency due to β2m mutation[34]
From 2006 Structural and functional characterization of FcRn interaction with albumin[44-55]
2019 Identification of FcRn as an Enterovirus B receptor[62,63]
2021 FDA approves first FcRn-antagonist Efgartigimod for the treatment of myasthenia gravis

Supplementary Figure 2 | Tissue expression and physiologic function of FcRn

FcRn expression has been observed, using various types of methods to detect mRNA or protein expression, within most organs of the body (black font), however its precise in situ functions (dark purple font) are not necessarily evident. In general, organ-specific epithelial, endothelial, and immune cells, such as macrophages, express FcRn within these tissues. The recognized tissue-specific FcRn roles within each organ are mentioned, including the central nervous system, eyes, lungs and nasal epithelium, kidney and bladder, liver, intestines and stomach, endocrine organs, genital tract, skin, hematopoietic compartments and muscles. FcRn = neonatal Fc receptor, IgG-IC = immunoglobulin G immune complex.



Supplemental Figure 2

Supplementary Table 1 | First in human studies with FcRn antagonists

Compound (Brand name)	Aliases	Type	K_D (nM)	Clinical trial identifier	Regimen	Route	Dose mg/kg (Subjects enrolled)	Max % IgG_{Total} reduced	Nadir (days post injection)	C_{max} (µg/ml)	$AUC_{(0-t)}$ or $AUC_{(0-inf)}$* (hour*µg/ml)	$t_{1/2}$ (hours)	TEAE (Most common)
Rozanolixizumab	UCB7665 DX-2507	IgG_4 S228P	pH 7.4 = ~0.034 pH 6 = ~0.023[1]	NCT02220153	SAD	*i.v.*	0 (7)						Mild-moderate (Headache)
							1 (6)	14.5	~7- 10	11.11	55.21		
							4 (6)	33.4		89.33	2213		
							7 (6)	47.6		154.5	5753		
						s.c.	0 (6)						
							1 (6)	16.8	~7- 10	NA	NA		
							4 (6)	25.9		NA	NA		
							7 (6)	43.4		12.41	643.3		
Efgartigimod alpha[$] (Vyvgart)	Abdeg	IgG_1 Fc M252Y S254T T256E H433K N434F	pH 7.4 = 320.5 pH 6 = 14.2	NCT03457649	SAD	*i.v.*	0 (10)	9.77 IgG1					Mild-moderate (Headache, differential WBC count)
							0.2 (4)	7.4 IgG1	~6-21	1.81	NC	140	
							2 (4)	21.8 IgG1		34.8	998	104	
							10 (4)	49.1 IgG1		209	6818	85.1	
							25 (4)	54.3 IgG1		436	12826	89.7	
							50 (4)	58.3 IgG1		1175	23435	91.3	
					MAD		0^{4d} (2)	8.32 IgG1	After last dose				Mild-moderate (Headache)
							10^{4d} (5)	78.5 IgG1		161-229	4206-5298		
							0^{7d} (4)	8.32 IgG1					
							10^{7d} (6)	73.0 IgG1		195-237	5392-6024		
							25^{7d} (6)	77.7 IgG1		393-535	10061-12458		
Orilanolinumab[#]	SYNT001, ALXN-1830	IgG_4 S241P	pH 7.4 = 1.19 pH 6 = 0.87	NCT03643627	SAD	*i.v.*	0 (8)		5-10				Mild-moderate (Headache)
							1 (6)	19.2		18.084083	29.296491	0.636	
							3 (6)	14.8		73.41655	392.122944	1.407	
							10 (6)	24.8		299.330	3283.820283	5.297	
							30 (5)	47.3		912.819	15752.080833	7.794	
Nipocalimab	M281	IgG_1 N297A	pH 7.6 = 0.0435 pH 6 = 0.0287	NCT02828046	SAD	*i.v.*	0 (10)						
							0.3 (3)	NA	~7-14	0.446	NA	NA	Mild-Moderate (Headache)
							3 (3)	25		53.8	945*	7.82	
							10 (6)	55		206	9757*	24.4	
							30 (6)	74		600	39213*	30.7	
							60 (6)	80		1320	115288*	33.7	
					MAD[xx]		0^{7d} (4)						
							15^{7d} (6)	~85	~5-7				
							30^{7d} (6)	~85					
Batoclimab	HL161, HBM9161, RVT-1401, IMVT-1401	IgG_1 L234A, L235A	pH 7.4 = ~0.0247 pH 6 = ~0.018[2]	NCT03971916	SAD	*s.c.*	0 (6)	5.54					
							340 (6)	21	~11	2.980	171	37.9	Mild (Influenza like illness)
							510 (6)	39.8		21.1	1940	16.9	
							680 (6)	41.2		30.3	3300	14.8	

[1,] WO2014019727A1; [2,] WO2015167293A1 for HL161A; SAD = single ascending dose; MAD = multiple ascending doses; 4d = dosed every 4 days on 6 occasions; 7d = dosed every 7 days on 4 occasions; WBC = white blood cells; xx = not all subjects received the 4 doses; TEAE = treatment-emergent adverse events; AUC = area under curve; *i.v.* = intravenous; *s.c.* = subcutaneous; # = discontinued. $ = approved by FDA and PMDA for the treatment of generalized MG. Antidrug antibodies were low and of transient nature or absent across these studies.

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