The Ashwell-Morell receptor regulates hepatic thrombopoietin production via JAK2-STAT3 signaling

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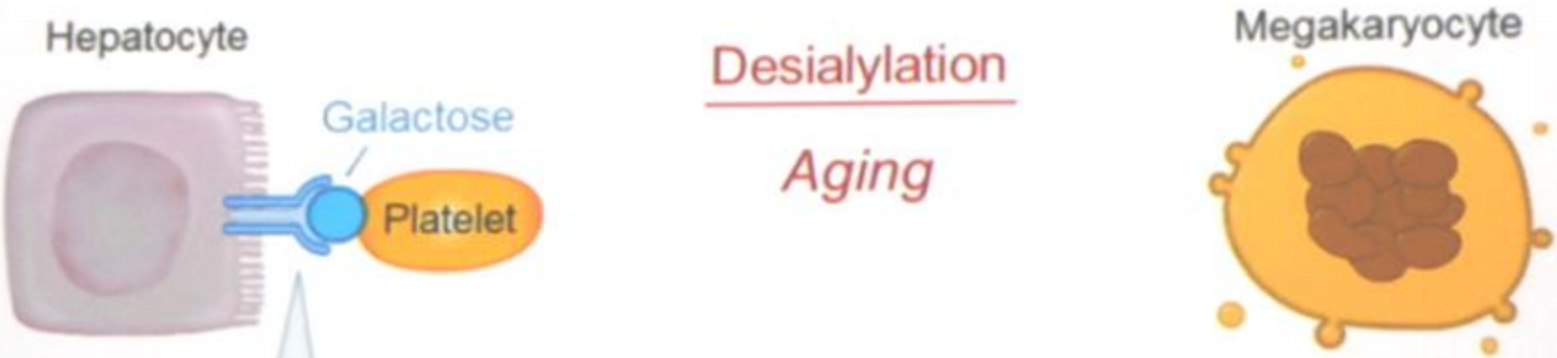
Nature Med 2015

Ashwell-Morell receptor (AMR) clears platelets

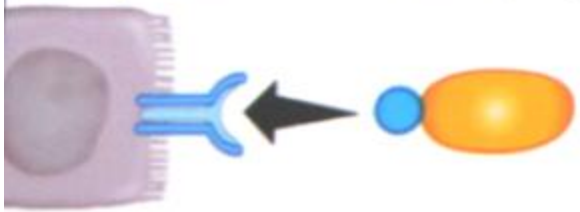


Ashwell-Morell receptor (AMR)

- Galactose receptor exclusively expressed in hepatocytes
- Trimer – Deletion of one subunit leads to receptor inactivation
- Identified in 1974, but its physiological role is not fully understood

Mouse strains of platelet clearance by the Ashwell-Morell receptor

	Platelet survival (t1/2)	Platelet count	Platelet sialic acid content
Control (WT mice)	47 h	1,420 k/µl	100%
AMR deficient (*Asgr2*$^{-/-}$ mice)	64 h	2,150 k/µl	60%
Sialyltransferase null (*St3gal4*$^{-/-}$ mice)	18 h	428 k/µl	15%



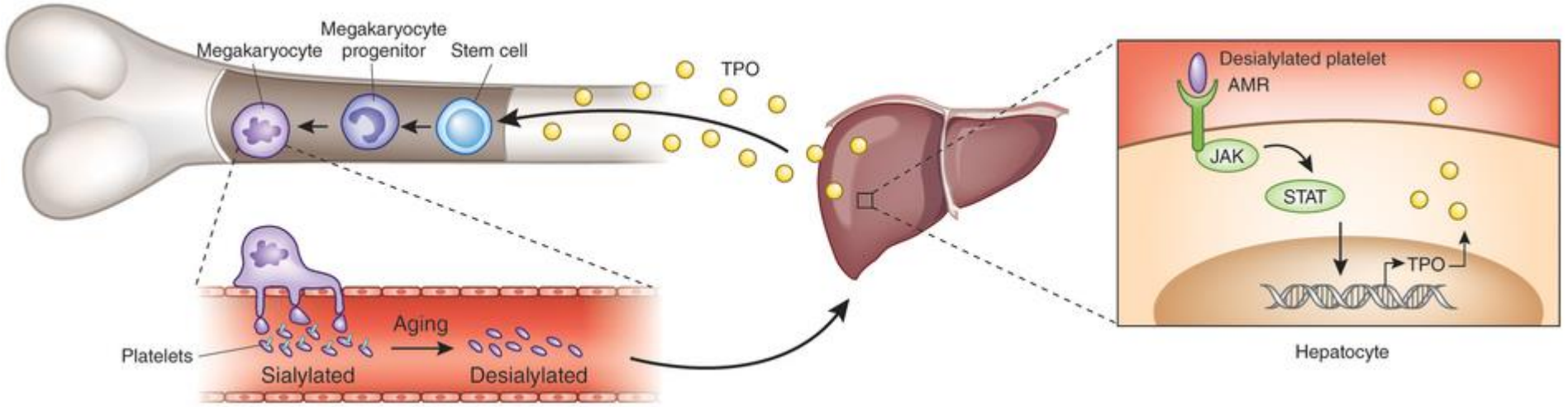
Baseline clearance

No clearance

Maximal clearance

• La clairance des plaquettes desialylées par le récepteur Ashwell Morel stimule la production de TPO par le biais de la voie JAK STAT.

• Explique pourquoi les inhibiteurs de JAK2 donnent souvent des thrombopénies.



Desialylation is a mechanism of Fc-independent platelet clearance and a therapeutic target in immune thrombocytopenia

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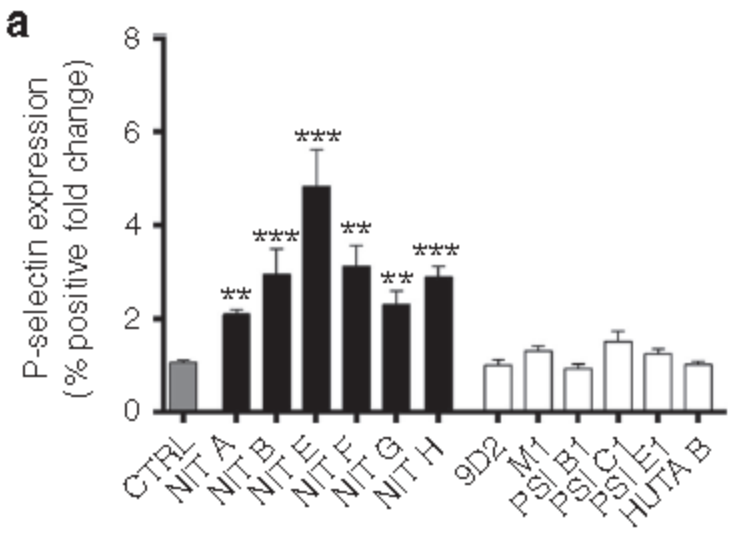
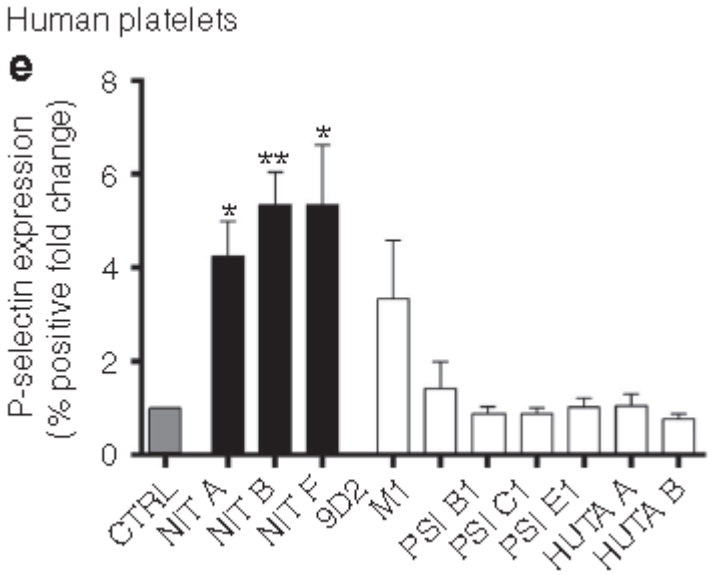


Activation plaquettes souris par Anti-Ibα
Pas d'activation par Gp2b3a



Activation plaquettes humaines par Anti-Ibα
Activation inconstante par Gp2b3 (9D2)

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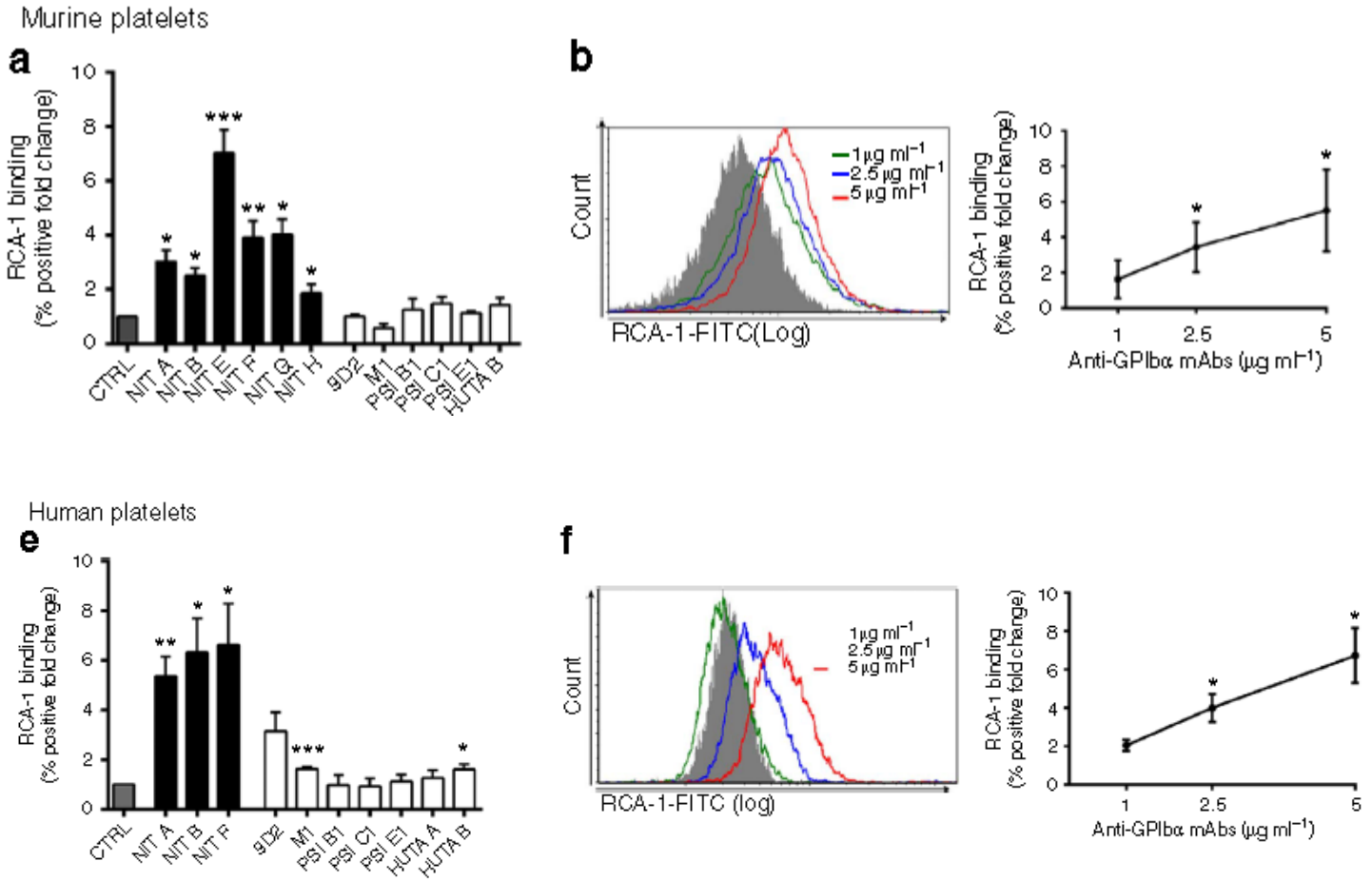
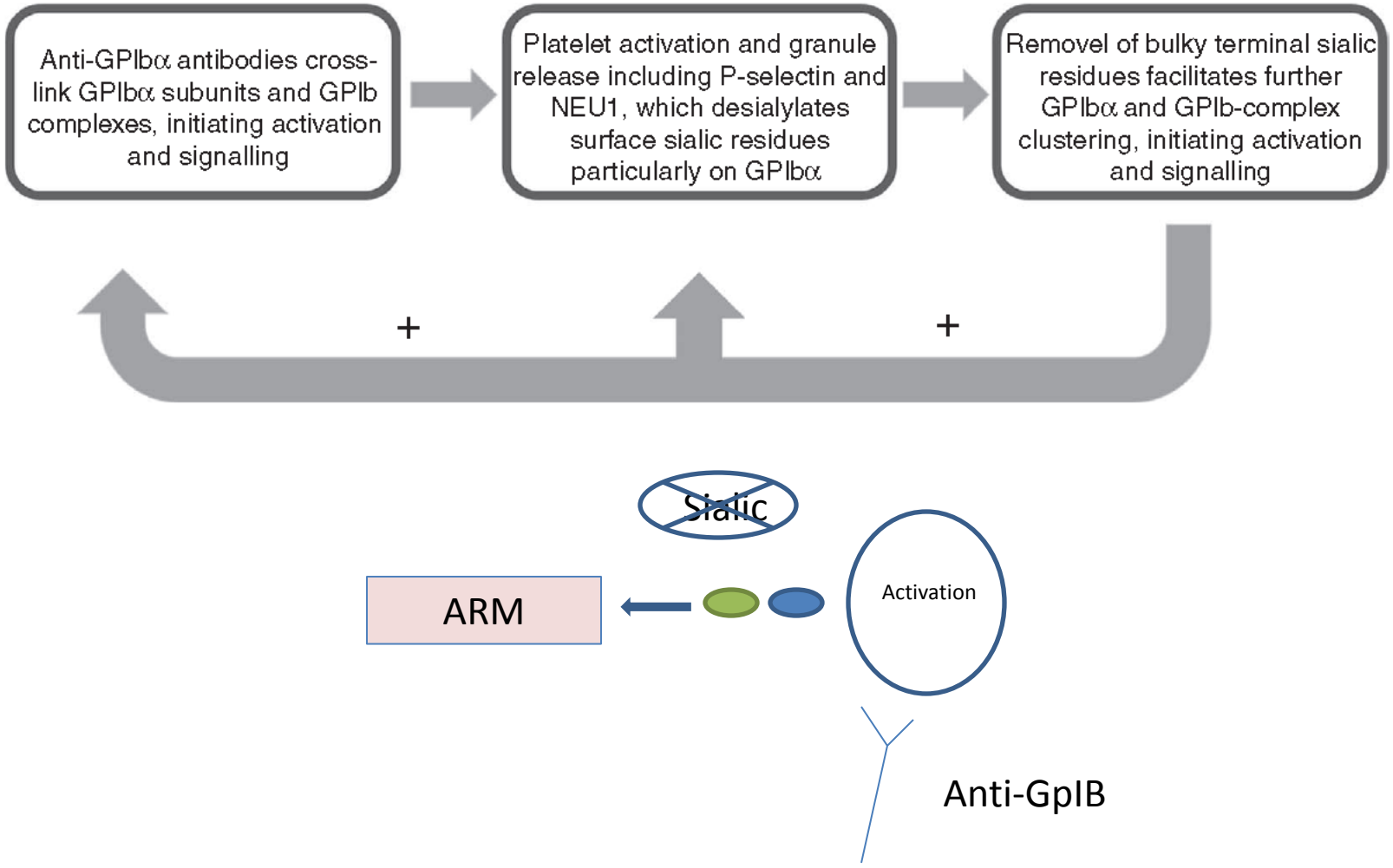
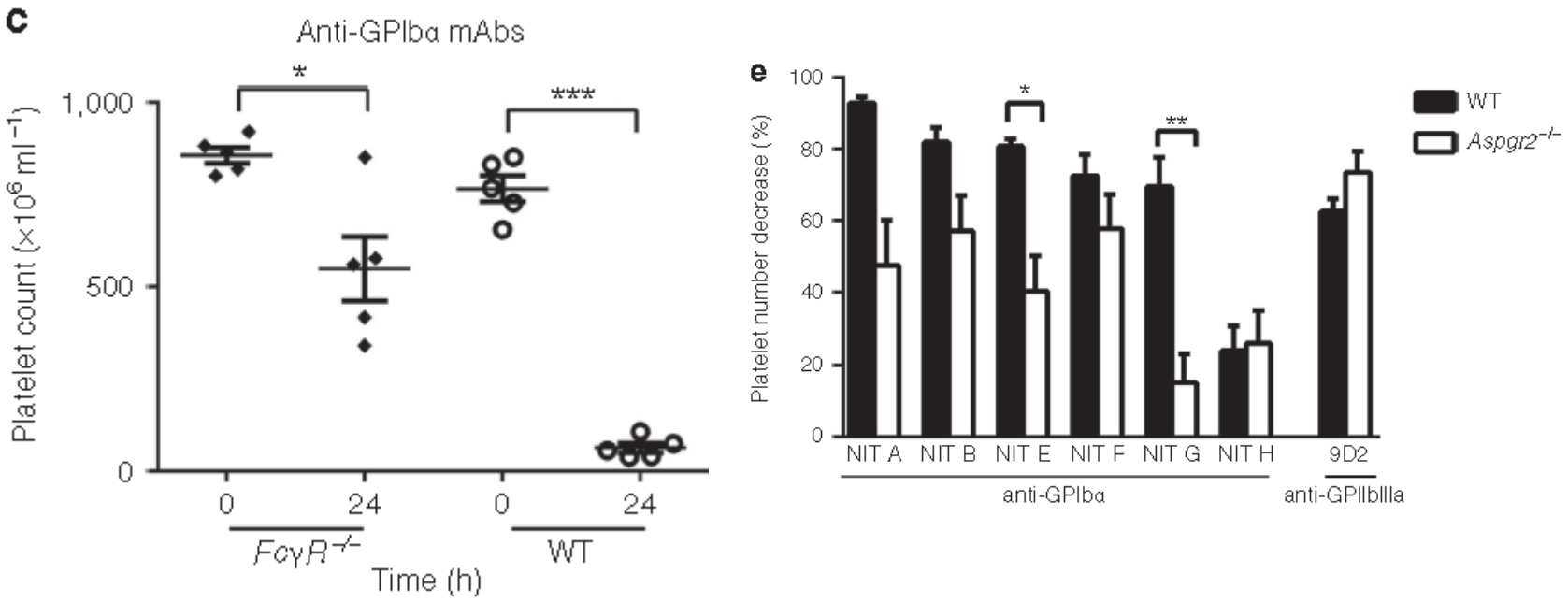
Anti-GPIb augmentent la désialylation




Anti-GPIbα antibodies cross-link GPIbα subunits and GPIb complexes, initiating activation and signalling
Platelet activation and granule release including P-selectin and NEU1, which desialylates surface sialic residues particularly on GPIbα
Removel of bulky terminal sialic residues facilitates further GPIbα and GPIb-complex clustering, initiating activation and signalling
+
+
Sialic
ARM
Activation
Anti-GpIB

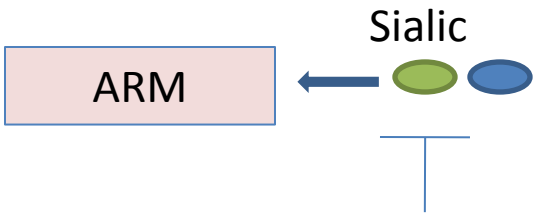
In vivo



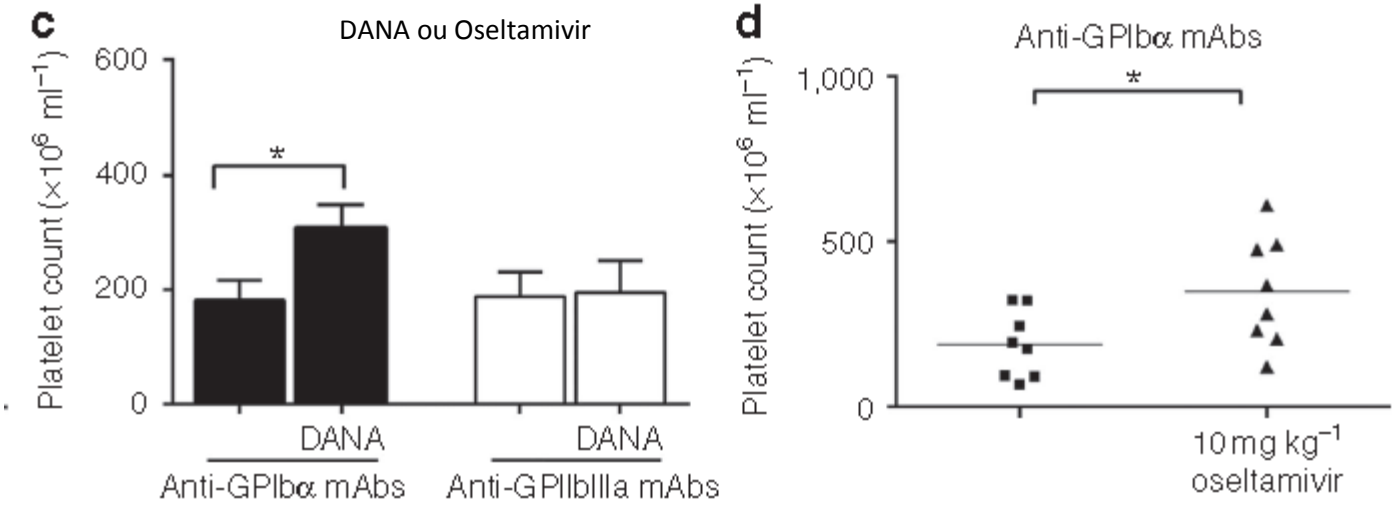
Anti-GpIα peu dépendant du Fc

Diminution de l'activité de l'anticorps sur fond ASH KO

Inhibition de la désyalilation



Augmentation in vivo du chiffre de plaquettes modèle passif anti-GpIb



ITP (Fig. 8d). In conclusion, this is the first study in mice to provide evidence to support utilization of sialidase inhibitors as a viable therapeutic alternative for refractory ITP patients.

Journal of Thrombosis and Haemostasis, **12**: 497–504 DOI: 10.1111/jth.12524

ORIGINAL ARTICLE

Association of autoantibody specificity and response to intravenous immunoglobulin G therapy in immune thrombocytopenia: a multicenter cohort study

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Etude rétrospective de 156 patients traités par IgIV

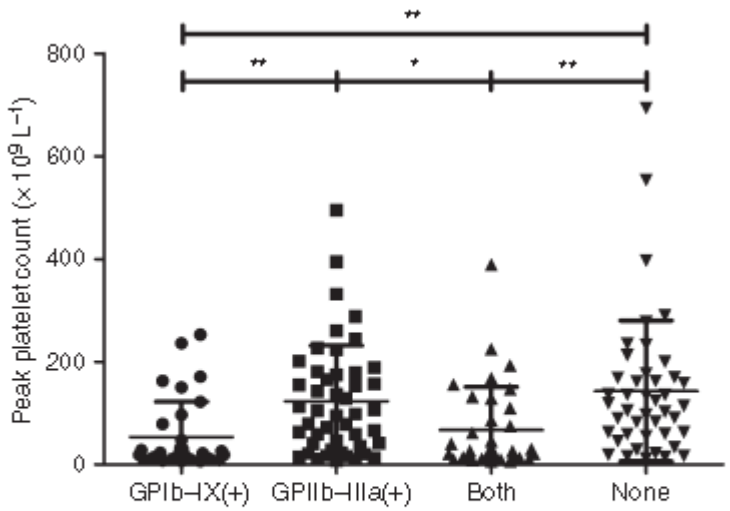

Fig. 2. The peak platelet counts within 8 days of initiation of intravenous immunoglobulin G treatment in all patients with autoantibodies against glycoprotein (GP)IIb IIIa alone, GPIb IX alone, or both GPIIb IIIa and GPIb IX, and those without detectable autoantibodies against either GPIIb IIIa or GPIb IX. Data are presented as mean ± standard deviation. $^{*}P < 0.05$; $^{**}P < 0.01$.

Table 2 Association of platelet autoantibody specificities and response to intravenous immunoglobulin G

GPIIb IIIa	GPIb IX	Response, *n* (%)
		36/43 (83.7)
	+	10/32 (31.3)
+		36/47 (76.6)
+	+	14/34 (41.2)
Total		96/156 (61.5)

GP, glycoprotein.

CASE REPORT

Successful treatment with oseltamivir phosphate in a patient with chronic immune thrombocytopenia positive for anti-GPIb/IX autoantibody

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Abstract

The management of chronic immune thrombocytopenia (ITP) remains to be a challenge. Oseltamivir phosphate is a sialidase inhibitor agent used to treat influenza in the conventional sense. At present, we demonstrate for the first time that an adult chronic ITP patient with anti-GP Ib/IX autoantibody, who was resistant to corticosteroids, IVIG, recombinant human thrombopoietin, rituximab, danazol and vindesine, but was successfully treated with oseltamivir phosphate. Through flow cytometric analysis of β-galactose and β-GlcNAc exposure on platelet surfaces, we showed that oseltamivir phosphate could reduce the desialylation level of platelet glycoproteins in ITP patient. The substantial alleviation of thrombocytopenia in this case, though not leading to conclusions, lays a foundation for a novel approach for the treatment of ITP.