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# Platelet Interactions with Viruses and Parasites

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Ana Lopez Alonso and Dermot Cox

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## 1. Introduction

Over the last few years our understanding of the role of platelets has evolved. While originally considered to be solely involved in thrombus formation recent studies suggest that they play an important role in the innate immune system. As the most numerous particles in the blood platelets are the first responders to any breaches in the vasculature where they bind to the damaged vessel and aggregate to seal the leak. They also become activated and secrete the contents of their granules, which contain anti-microbial peptides, which acts to sterilise the wound and to recruit other immune cells. As a result thrombocytopenia is a common response to infection by many different organisms [1, 2].

As part of the innate immune system platelets express many different pathogen recognition molecules that are involved in immune function rather than thrombosis. Thus platelets express Toll-Like Receptors (TLRs), which are pathogen recognition receptors [3] and in particular platelet TLR2 [4], TLR4 [5] and TLR7 [6] have been shown to be functional. Another important immune receptor is FcγRIIa, a receptor for the Fc-portion of IgG, which is typically expressed on phagocytic cells [7]. While platelets express functional FcγRIIa there is evidence of limited phagocytic ability for platelets [8-11]. DC-SIGN is another important pattern recognition molecule [12] that has been identified on platelets and found to be functional [13]. While both immune-mediated and haemostasis-mediated platelet activation result in activated platelets the platelet response is quite different in both cases [14].

The best-studied example of a role of platelets in infection is that with bacterial infection. While most effort has focused on Gram-positive bacteria many bacteria have been shown to activate platelets and these studies show a number of common features. The interaction of bacteria with platelets typically occurs due to direct binding to platelets, binding of a platelet-binding plasma protein to the bacteria or the secretion of a substance that activates platelets [1, 15, 16]. Typically streptococcal species such as *S. sanguinis* and *S. gordonii* bind directly to platelet GPIb.

In contrast *Staphylococcus aureus* binds fibrinogen, which in turn binds to GPIIb/IIIa on the platelet surface. *S. aureus* also produces toxins that activate platelets [17]. For the majority of bacteria that activate platelets, binding of IgG is required. This binds to FcγRIIa on the platelet surface triggering platelet activation [18]

## 2. Platelets in viral infection

While thrombocytopenia and in severe cases disseminated intravascular coagulation (DIC) are associated with bacterial infection this is also true for viral infection. Viral Haemorrhagic Fever (VHF) is similar to sepsis and both can be considered as forms of Systemic Inflammatory Response Syndrome (SIRS) [19, 20]. Equally thrombocytopenia is a common response to viral infections. However, it is worth noting that in some case the use of anti-viral agents may mediate the thrombocytopenia such as where neuraminidase inhibitors are associated with an immune thrombocytopenia [21] and abacavir enhances platelet activity by inhibiting guanylate cyclase [22].

### 2.1. Viral Haemorrhagic fever

Unlike with bacteria where virtually any species can lead to sepsis the viral equivalent (VHF) only occurs with members of 4 families of viruses known collectively as VHF viruses [20, 23].

**Flaviviruses.** These include Dengue virus (DENV) [24] and Yellow fever virus, which are transmitted by mosquitos and Omsk hemorrhagic fever virus [25] and Kyasanur Forest virus [26], which are transmitted by ticks. DENV is the most studied flavivirus due primarily to the 100 million infections per year with case fatality rates between 1-15% [27, 28]. Of these around 500,000 will progress to develop Dengue haemorrhagic fever (DHF) [27-30].

Dengue haemorrhagic fever is unusual as it typically occurs in response to a secondary infection with the primary infection producing relatively minor 'flu-like symptoms. In fact there are 4 serotypes of DENV and it is infection with a second serotype that leads to dengue haemorrhagic fever. This suggests that the presence of anti-DENV antibodies is necessary for DHF to occur and this process is known as antibody-dependent enhancement (ADE) [31, 32]. These antibodies have been shown to enhance virus uptake and replication through an interaction with Fc receptors [32-35]. However, just as antibody binding to bacteria can trigger platelet activation it is likely that antibody binding to DENV will also activate platelets in an FcγRIIa-dependent manner. This platelet activation has been shown to lead to enhanced permeability [36]. Bone marrow infection occurs in animal models of Dengue [37], which could lead to thrombocytopenia due to impaired platelet production.

**Filoviruses.** Filoviruses are primarily represented by Ebola and Marburg viruses both of which cause a very severe VHF. The Ebola virus is transmitted by fruit bats. Very little is known about the pathogenesis of filovirus-induced VHF although, not surprisingly there is evidence of platelet activation [38, 39]. Sudan virus (SUDV) has been shown to be associated with an increase in von Willebrand factor (vWf) levels, which is associated with poor outcome as well as haemorrhagic presentation [40].

**Bunyaviruses.** This family includes the Phleboviruses (Rift Valley fever virus), Nairoviruses (Crimean-Congo Haemorrhagic fever, CCHF) and Hantaviruses (Hantaan virus). Thrombocytopenia and an increase in mean platelet volume are associated with CCHF [41]. Thrombocytopenia is a common feature of Severe fever with thrombocytopenia syndrome (a Phlebovirus infection) and is a predictor of fatal outcome [42] and direct binding to platelets was demonstrated [43]. Thrombocytopenia in Hantaan virus infection is also associated with poor outcome [44]. The use of steroids and IVIg was found to be successful in the treatment of CCHF in twelve patients [45] and as IVIg has been shown to act as an inhibitor of FcγRIIa [46] it suggests a potential role for FcγRIIa in CCHF.

**Arenaviruses.** These include the Old World Lassa fever virus and lymphocytic choriomeningitis virus (LCMV) and the New World Junin, Guanarito, Machupo and Sabia viruses [47]. Little is known about the pathogenesis on Arenavirus VHF although there is evidence that partial platelet depletion increases disease severity in LCMV infection [48-50].

## 2.2. Other viral infections

Although there is a paucity of data on the mechanisms involved thrombocytopenia is a common response to many viral infection and not just VHF. However, in general, viral-induced thrombocytopenia is either due to platelet activation leading to consumption or infection of the megakaryocytes leading to impaired platelet production.

**Viral-induced platelet activation.** Coxsackieviruses B infection is associated with thrombocytopenia and has been shown to directly infect platelets. This appears to be beneficial as thrombocytopenic mice had higher mortality rates than normal mice. Thus, platelets appear to act as a sponge mopping up virus particles [51]. Platelets have been shown to express Toll-like receptors that play a role in the response to infection. Recently TLR-7 has been shown to be functional in platelets and to trigger platelet activation in response to encephalomyocarditis virus in a mouse model [6]. Cytomegalovirus binds to platelet TLR-2 leading to platelet activation [52]. On the other hand platelet activation leads to secretion of CXCL4, which prevents HIV-1 infection of neighbouring T-cells [53] as well as secretion of other pro-inflammatory factors such as CD40L [54]. FcγRIIa also plays an important role in platelet activation by viruses just as happens with bacteria. Influenza A H<sub>1</sub>N<sub>1</sub> forms immune complexes that can trigger platelet activation in a FcγRIIa-dependent manner [55]. DC-SIGN is present on the platelet surface and is implicated in the binding of HIV-1 [56] and Dengue virus [13]. In the case of HIV-1 it acts in conjunction with CLEC-2 [57]. Adenovirus Type 3 enhanced ADP-induced platelet activation [58]. Enhanced platelet activation and sequestration was found with Hepatitis B infection [59]. Co-infection of influenza H1N1 and *Staphylococcus aureus* greatly increased the chances of developing DIC [60]. SIV infection in macaques leads to thrombocytopenia [61]. The occurrence of thrombocytopenia in influenza H1N1 infection is associated with mortality [62].

**Platelet interaction with other cells.** HIV-1 infection increases platelet-monocyte interactions, which is associated with neuroinflammation [63]. Influenza infection of endothelial cells leads to activation and recruitment of platelets, which can further increase permeability and reduce platelet count [64]. HIV-1 infection leads to increased levels of platelet-derived CD40L and

platelet-monocyte aggregates. This results in monocyte activation and enhanced levels of extravasation especially in the brain microvasculature. It is proposed that this may play a role in the cognitive decline seen in AIDS [63-66]. The enhanced platelet activity seen in HIV patients can be reduced by treatment with aspirin [67]. The enhanced inflammation and endothelial cell activation seen in HIV [68] has been shown to persist even being present 12-years after anti-retroviral therapy [69]. Anti-retroviral therapy was found to reduce the thrombocytopenia that was found to re-occur if treatment was stopped. Re-starting treatment resolved the thrombocytopenia [70]. HIV-1-derived Tat has been shown to directly bind to platelets and activate them in a process dependent on CCR3 and  $\beta_3$ -integrins [71]. SIV infection in macaques leads to increased platelet-monocyte interactions [61]. Platelets interact with neutrophil extracellular traps (NETs) and facilitate their ability to neutralise poxvirus [72]. In hepatitis there is evidence that platelets are being sequestered to the liver which may play a significant role in hepatitis-associated thrombocytopenia [73].

**Effect of viruses on platelet production.** In SIV, TGF $\beta$ -mediated down-regulation of thrombopoietin leads to reduced production of platelets [74]. Reduced platelet production has also been seen in Dengue-infected mice [75] and megakaryocytes have been shown to be infected by Dengue virus [76]. Platelets are involved in hepatocellular carcinoma in mice infected with hepatitis B [77] and aspirin and clopidogrel therapy reduced the incidence in infected patients [78]. Respiratory syncytial virus (RSV) is associated with a decrease in mean platelet volume (MPV) [79] as is rotavirus [80] while HIV infection is associated with an increase in MPV [81]. Infection of mice with  $\gamma$ -herpes virus has also been shown to induce the formation of anti-platelet antibodies, which leads to an immune thrombocytopenia [82].

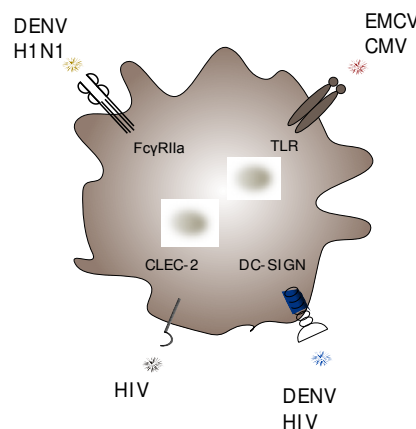
**Pathogen inactivation.** A major problem with blood transfusions is the potential for passing on both bacterial and viral infections. This was a major cause of transmission with both HIV and Hepatitis C. As a result strategies for pathogen inactivation have been developed. One of the challenges in this area is that it is necessary to develop strategies that will be effective against known pathogens such as HIV and hepatitis C as well as pathogens that we are not aware of yet. There are two specific products that need to be treated requiring different strategies. In the case of plasma solvent-detergent treatment can be effective however, this cannot be used for cell-based products such as red blood cells or platelets [83-86].

**Conclusion.** The platelet response to viral infection has many of the similarities of the response to bacterial infection. The primary purpose of this is host-defence and in this context there is evidence that platelets act as sponges to absorb the viruses and subsequently being cleared from the circulation. However, thrombocytopenia can also arise from infection of the endothelium, which binds platelets and removes them from the circulation. The other cause of viral-induced thrombocytopenia is impaired platelet production in response to megakaryocyte infection. There is evidence to support all of these mechanisms with different viruses having different effects. In fact even with a single virus multiple effects on platelets can be seen just as different bacteria have different mechanisms for activating platelets [1, 16] and even individual bacteria have multiple mechanism that depend on the shear stress of the local environment [87].

While the strategy of an anti-viral sponge is effective it is not without its problems. Excessive platelet activation can lead to disseminated intravascular coagulation such as occurs in an



extreme form in VHF. Correcting this DIC is critical for survival of the patient. Equally the prolonged hyper-activity of platelets in HIV-positive patients is a risk factor for cardiovascular disease in these patients. There is some evidence that anti-platelet agents can play a role here but as they inhibit platelet activity they may not be the ideal solution especially in DIC. A better strategy is to identify the mechanisms involved in the thrombocytopenia and to develop an inhibitor of the virus-platelet interaction without compromising platelet function (Figure 1). Interestingly FcγRIIa has been found to be an important drug target in bacteria-platelet interactions [1, 16] and there is evidence that with some viruses it may also be an important drug target as well [55].



**Figure 1.** Virus can interact with platelets through multiple different receptors. Dengue (DENV) and Influenza H1N1 bind to FcγRIIa; HIV binds to CLEC-2; DENV and HIV can bind to DC-SIGN and Cytomegalovirus virus (CMV) and encephalomyocarditis (EMCV) bind to Toll-like receptors (TLR).

### 3. Parasites

As platelets are part of the innate immune system and interact with bacteria and viruses they also interact with parasites. In this context they bind to parasites and in some cases will kill them. As a result there can be a thrombocytopenia as well as evidence of micro-thrombi formation. The most studied parasites that interacts with platelets are the malaria parasites [88] although there has been some work on other parasites as well.

#### 3.1. Malaria

Malaria is a mosquito borne parasite infection (*Plasmodium*), which is transmitted to humans through the *Anopheles* mosquito. Malaria is a major cause of morbidity and mortality in the developing world with 207 million cases of malaria in 2012 and an estimated 627 000 deaths, mostly children under five and pregnant women who live in Sub-Saharan Africa (WHO 2013). Malaria is caused by infection with *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi*. Most of the deaths are due to infection by *P. falciparum* as it is the most severe infection as well as the dominant infection. *P. bergeri* and *P. chabaudi* infect mice and are frequently used

for animal studies. Most cases of malaria present as uncomplicated malaria with characteristic symptoms of fever, nausea and aches, however, some can present with severe malaria that involves impaired function of various organs. The most serious form of severe malaria is cerebral malaria, which is estimated to occur in 10% of hospitalised cases and is associated with 80% of deaths. Cerebral malaria occurs when infected red blood cells (RBCs) occlude cerebral blood vessels [89].

**Thrombocytopenia in malaria.** Thrombocytopenia is a common feature in malaria [90, 91]. In fact it is considered to be diagnostic in suspect febrile patients [92, 93]. The extent of the thrombocytopenia is also a predictor of outcome [94-96]. There are a few studies suggesting that malarial thrombocytopenia is driven by platelet activation in patients with malaria [97, 98], and infected mice [99, 100]. A possible explanation for platelet activation in malaria is complement formation. The formation of C3d, indicating complement activation, was associated with thrombocytopenia in malaria-infected patients [101]. Nevertheless activation of platelets in malaria could also be related to direct interaction with the parasites [102, 103]. There is also evidence of immune-mediated clearance with two studies identifying an increased level of platelet-associated antibodies in thrombocytopenic malaria patients [104, 105]. This was further supported by a study that showed an association between polymorphisms in Fc $\gamma$ RIIa, the platelet IgG receptor and disease severity [106]. IgE levels have also been associated with severity of malaria [107].

Platelets have been shown to be involved in clumping of parasitized red cells [108] and they have been found to accumulate in the brains of patients with cerebral malaria [108, 109].

**Plasmodium and platelet interaction.** GPIV (CD36) is a glycosylated protein [110] present in platelets - other cells such as macrophages, dendritic cells, adipocytes, muscle and some types of endothelial cells. While CD36 is a cell receptor for *P. falciparum*-infected erythrocytes [111, 112] there is evidence for other interactions, as antibodies to CD36 did not inhibit interactions with all isolates [95, 113]. The complement receptor gC1qR/HABP1/p32 on both endothelial cells and platelets has been shown to support an interaction with infected RBC's and supports platelet mediated clumping of infected RBC's although the parasite ligand is not known [113]. PECAM-1 was also shown to be an endothelial receptor for infected RBC's [114] and as this is also expressed on the platelet surface it is likely to mediate an interaction with platelets as well.

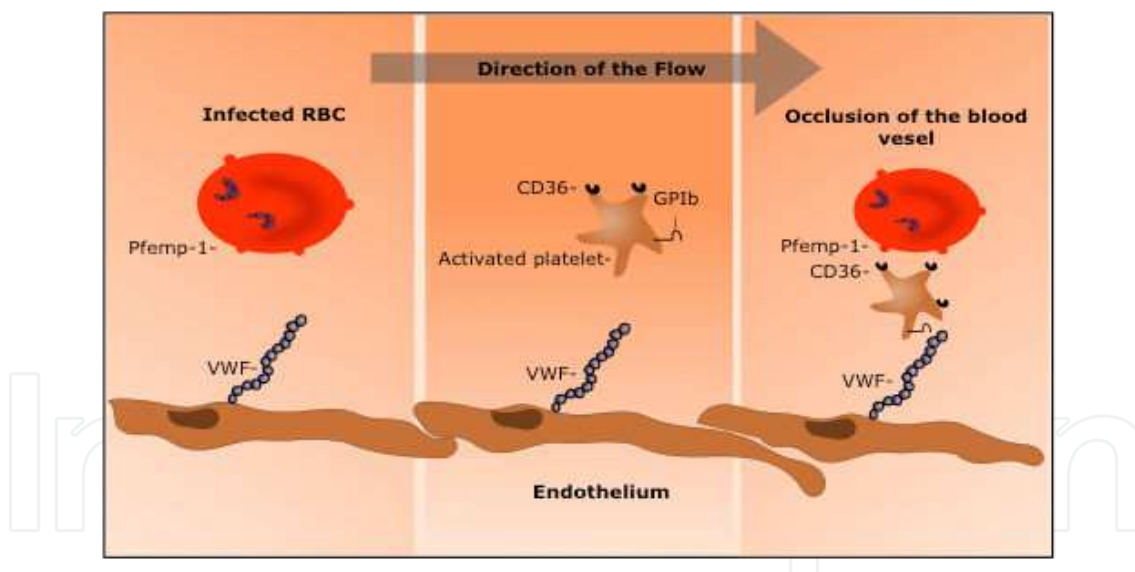
**Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1).** Some strains of falciparum malaria parasites induce the formation of small membrane protrusions known as knobs on erythrocytes. These knobs have been identified as the site of contact with endothelial cells and high molecular weight malarial proteins expressed on these knobs mediate this interaction [115-117]. PfEMP1 was subsequently identified as the knob protein that binds to CD36 [118] but also to ICAM-1 and VCAM-1 and it contains a number of different binding domains. PfEMP1 contains two different modules, the Duffy binding-like domain (DBL) of which there are six and the cysteine-rich inter-domain regions (CIDR) of which there are three [119]. The CD36 binding domain has been localized to one of the CIDR's, CIDR $\alpha$ . A C-terminal 166 amino acid sequence appears to be responsible for the interaction with CD36 and that amino acids 106-166 appear to be especially important [120]. The region of CD36 that binds to PfEMP1 has been located to the region between amino acids 139-184 [121]. While PfEMP1 can directly bind

to CD36 and a number of CD36 ligands can induce platelet aggregation there is no evidence that PfEMP1 triggers platelet activation. However, *P. falciparum* does trigger clumping of infected erythrocytes that is mediated by platelets in a CD36-dependent manner [95] and thus it is possible that this may be due to PfEMP1-CD36 mediated platelet activation.

### 3.2. Role of the endothelium

The endothelium plays an important role in the pathogenesis of malaria. The clumped RBC's bind to the endothelium and can ultimately occlude smaller blood vessels, especially in the brain. Activated endothelium is a key component of cerebral malaria and has been shown to occur in children [122]. Overproduction of cytokines plays a major role in the activation of the endothelium [123, 124]. One of the key cytokines involved is TNF, which is produced by macrophages in response to malaria antigens [125], possibly acting on TNFR2 [126]. Platelets play a significant role in the destruction of TNF-activated endothelial cells [127-129] while TGF $\beta_1$  released from activated platelets can kill TNF-activated endothelial cells [130].

A recent model has been proposed that draws together many of these observations in malaria (Figure 2). Activated endothelial cells secrete high molecular weight vWf, which form strings under high shear. Platelets bind to these strings, which also bind to the activated endothelial cells. Infected RBCs can then in turn bind to the immobilised platelets ultimately occluding the blood vessel which if in the cerebral micro-circulation leads to cerebral malaria [131].



**Figure 2.** Platelets mediate plasmodium-infected red blood cells binding to the endothelium by GPIb binding to von Willebrand factor (vWf) strings on the endothelium and CD36 binding to *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) on the red blood cell.

**Platelets as a double-edged sword.** The role of platelets in malaria is complex. On one hand platelet activation is critical in mediating the binding of infected RBCs to the endothelium and subsequent aggregate formation that is cause of cerebral malaria and animal studies suggest that blocking platelet function in mice is beneficial [124, 132, 133]. On the other hand platelets as part of the innate immune system play an important role in mediating the initial immune



response to infection. Studies suggest that platelets play a beneficial role in malaria [134, 135] and mice rendered thrombocytopenic prior to infection had a much higher mortality rate compared with normal mice and thrombocytopenia only occurred in normal rats and not in splenectomised although mortality was much higher in splenectomised rats [134, 136]. Platelets also have been shown to be cytotoxic to plasmodium [137] and that platelet factor 4 (CXCL4) plays a key role in mediating this cytotoxicity [138, 139].

### 3.3. Other parasites

Schistosomes are trematodes and a major pathogen that causes over 200 million cases of schistosomiasis per year. Thrombocytopenia is a common symptom of infection with *Schistosoma mansoni* primarily due to platelets gathering in the spleen. There is also an increase in vWf and an increase in MPV [140]. Induction of thrombocytopenia prior to infection has been shown to significantly increase *S. mansoni* growth and platelets have been shown to bind to and kill the schistosomes [141, 142]. It appears that the cytotoxicity of platelets is enhanced significantly by factors secreted from immune cells such as interferon, tumour necrosis factor and IL-6 [143].

Trypanosomatids are unicellular parasites with a single flagellum and there are two clinically relevant genera. Genus *Trypanosoma* has two major pathogenic species: *T. brucei* which is transmitted by the Tsetse fly and causes African sleeping sickness (a neurological disorder) [144] and *T. cruzi* which is transmitted by triatomine bugs and causes Chagas disease (a cardiac disease) [145]. Genus *Leshmania* contains a large number of species that cause leshmaniasis in humans and are transmitted by sandflies. *T. cruzi* infection of mice causes thrombocytopenia [146]. Chagas disease is associated with thromboembolism leading to stroke [145] and interestingly pentamidine which is often used to treat Chagas disease is also an anti-platelet agent (GPIIb/IIIa antagonist) [147] and *T. cruzi* binds fibronectin which could facilitate an interaction with platelets [148]. Trans-sialidase secreted from the trypanosome has been implicated in Chagas-associated thrombocytopenia as it cleaves sialic acid residues from platelets, which are then cleared from the circulation by Kupffer cells [149]. Kala Azar, a form of leshmaniasis is associated with thrombocytopenia and DIC [150]. In dogs with leshmaniasis there is evidence of an immune mediated thrombocytopenia [151].

## 4. Conclusions

It is clear that platelets are a key component of the innate immune system where they are the initial responders to infection. They appear to respond to the full range of pathogens including bacteria, parasites and viruses. Thus, thrombocytopenia is a characteristic symptom of infection by any organism. The response to bacteria infection is the best studied and a key role of the platelets is the secretion of anti-microbial peptides that as their name implies kill bacteria. While there is evidence that this also occurs with parasites it may not be true of viruses as they are not cells. There are what appear to be conflicting data on the role of platelets in infection. On one hand severe thrombocytopenia is associated with poor outcome suggesting that platelet activation is important in pathogenesis. On the other hand thrombocytopenic animals are more likely to have a poor outcome suggesting that platelets prevent the disease.

These conflicting data can be resolved in a model where platelets have a dual role. Upon initial exposure to a pathogen there is a decline in platelet number due to the initial immune response. Platelets are activated and bind the pathogen. This then results in pathogen killing or at least clearance of the platelet-pathogen complex from the circulation. If that works then it is the end of the story. The pathogen is ultimately cleared and the disease resolves. However, sometimes platelets fail to clear the pathogen or pathogen replication exceeds the clearance. As a result there is excessive platelet activation that can progress to disseminated intravascular coagulation. Thus, in the early stage of infection platelets are good as they help clear the pathogen, however, in the later stages of infection platelets are bad as they are contributing to the problem.

This then leads to the question of whether platelets are a good target for treating infection. It has been proposed that anti-platelet agents may not be wise in patients with malaria since they are protective [152]. However, it is important to appreciate the stage of the disease. During the early stages of an infection an anti-platelet agent would be undesirable, as it would inhibit the immune functions of the platelets. However, as the disease progresses towards DIC an anti-platelet agent would be desirable as at this point platelets are now part of the problem and their excessive activation must be contained. While conventional anti-platelet agents may be useful in a patient with VHF or DIC this may not be advisable. The result may be that platelet number is preserved but the price paid would be platelet function, which in VHF would exacerbate the bleeding problems. Thus, a better approach may be targeting the platelet receptors that mediate the interactions with the pathogen. This would prevent platelet activation while maintaining platelet function. While some of these targets are likely to be pathogen specific a good target may be FcγRIIa. It has been shown to be critical in bacteria-induced platelet activation but also appears to play a role in some viral infections.

## Author details

Ana Lopez Alonso and Dermot Cox\*

\*Address all correspondence to: [dcox@rcsi.ie](mailto:dcox@rcsi.ie)

Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland

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