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Perspective

Platelet Glycoprotein IIb-IIIa Antagonists as Prototypical Integrin Blockers: Novel Parenteral and Potential Oral Antithrombotic Agents

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1. Introduction

Adhesive reactions constitute extremely important cellular functions that are required to maintain certain physiological processes such as cell migration, proliferation, differentiation, and cellular activation. Adhesion can be mediated through cell−cell or cell−matrix interactions, and many are mediated by integrin glycoproteins, a major family of cellular adhesion receptors.[1] The integrin superfamily of adhesion receptors is widely distributed and interacts with all of the key extracellular matrix proteins (e.g. collagens, laminin, fibronectin, vitronectin). Each integrin contains a single α- and β-subunit that forms a noncovalent complex, required for adhesive function. Currently known are 17 unique α-chains and 8 β-chains that give rise to greater than 20 characterized integrin complexes. Integrins can bind either unique single ligands or multiple ligands, thus determining a broad range of specificity with adhesive ligands.[1] Beyond adhesive functions, integrins also mediate more traditional cellular signaling activities of a receptor, initiated by engagement through their relevant adhesive ligands.[1] Integrins have been proposed to play significant roles in diseases and have been extensively studied in areas such as thrombosis, inflammation, angiogenesis, and osteoporosis.[1] Of pioneering importance in this respect is the platelet and megakaryocyte-specific integrin, $\alpha_{IIb}\beta_3$ (also commonly know as GPIIb-IIIa), which has received considerable attention as a drug target due to its requisite role in platelet aggregation, a significant mechanism in mediating arterial thrombosis.[2−8]

Although GPIIb-IIIa is found primarily on platelets, it can also be detected on their megakaryocyte precursors. It is now well-established that GPIIb-IIIa is the key receptor which mediates platelet aggregation by adhesive cross-linking of the divalent plasma proteins fibrinogen and von Willebrand factor.[7,8] Occlusive thrombus formation is believed to be initiated when platelets deposit onto damaged endothelium or ruptured atherosclerotic plaque. While it is unlikely that a monolayer of adherent platelets could ever lead to reductions in coronary blood flow, the monolayer serves as a foundation onto which the platelet thrombus can grow and become occlusive.[2,3] A very high density of GPIIb-IIIa is found on the platelet surface. Approximately 50 000−80 000 GPIIb-IIIa molecules are found per platelet with an additional α-granule pool that can be mobilized to the platelet surface when platelets are activated.[4] The high density of receptors may be required by the platelet to rapidly respond to hemorrhage. Individuals who lack GPIIb-IIIa function, either through absence of GPIIb-IIIa or defective GPIIb-IIIa on a genetic basis (Glanzmann's thrombasthenia), have variable hemorraghic disorders. These affected individuals exhibit only mild bleeding tendency, suggesting that GPIIb-IIIa antagonists, while having the potential to be effective antithrombotic agents, may not necessarily display unacceptable hemostatic toxicity.[9] The biological roles of GPIIb-IIIa noted above were established during the 1980s and 1990s thereby setting in motion a variety of strategies to develop GPIIb-IIIa inhibitors as novel antithrombotic agents.

Adhesive protein ligands are recognized and bind to GPIIb-IIIa through the specific amino acid tripeptide sequence Arg-Gly-Asp (RGD) contained within surface

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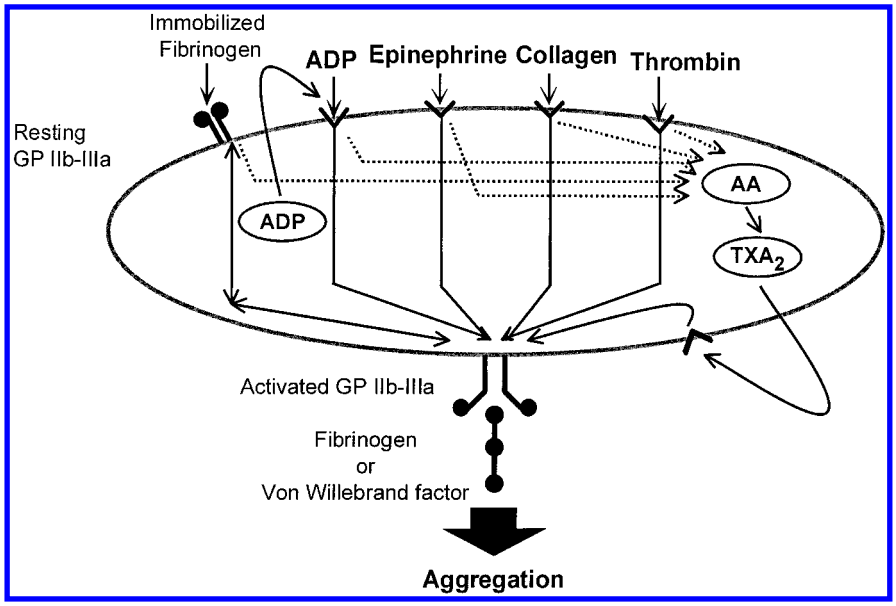


Figure 1. Platelet activation pathways leading to the final common pathway for platelet aggregation through binding of adhesive proteins to the activated form of GPIIb-IIIa. ADP = adenosine diphosphate, AA = arachidonic acid, TXA_2 = thromboxane A_2.

loops of each of these adhesive ligands or a similar adhesive ligand sequence (KQAGDV) found on the carboxyl terminus of the γ-chain of fibrinogen.[7] Other members of the integrin superfamily recognize and bind RGD-containing ligands, and it is known that α_4, α_5, α_8, α_{IIb}, and α_v can form heterodimers with various β-chains giving rise to RGD-dependent interactions.[1] Thus, one of the challenges for developing therapeutically useful integrin antagonists, and to GPIIb-IIIa specifically, is the issue of antagonist specificity. Another major challenge in integrin antagonist development would presumably be the difficult task of identifying small-molecule antagonists capable of disrupting large protein−protein interactions. However, since ligand recognition by GPIIb-IIIa appears to be restricted to rather small linear amino acid sequences such as RGD and KQAGDV, the identification of small molecule antagonists that mimic these short amino acid sequences would turn out to be a solvable problem.

The search for novel antiplatelet therapies beyond the use of aspirin has been stimulated by concentrated efforts to understand the multitude of biochemical mechanisms within platelets that lead to platelet activation and aggregation. These mechanisms include platelet arachidonic acid metabolism, adenosine diphosphate receptors, and thrombin receptors, which are becoming well-characterized platelet agonist targets involved in the activation of platelets. Normally, unactivated circulating platelets will not bind adhesive ligands through GPIIb-IIIa and do not aggregate unless stimulated. However, following platelet activation by agonists (e.g. ADP, thrombin, collagen, thromboxane A_2), platelets undergo a rapid shape change forming protruding pseudopods, which contain a high density of the adhesion receptor GPIIb-IIIa. GPIIb-IIIa appears to undergo a requisite conformational change during the activation process which converts it into a receptor which can now bind adhesive ligands, leading to platelet aggregate formation.[3,7] Importantly, the "final common step" leading to platelet aggregation, irrespective of the agonist which stimulates the aggregation pathway, proceeds through adhesive protein binding to GPIIb-IIIa (Figure 1). Therefore, it was recognized that GPIIb-IIIa antagonists might more effectively inhibit platelet-mediated thrombosis because of their ability to inhibit all agonist-induced platelet activations beyond inhibiting a single agonist pathway, such as aspirin inhibiting the cyclooxygenase pathway or the thienopyridine ADP antagonists.

It might seem "risky" for drug discovery efforts to begin a search for a replacement for aspirin, the inexpensive and widely utilized standard, knowing that large and quite expensive clinical trials with new cardiovascular agents are needed to prove efficacy. However, the limited antiplatelet efficacy of aspirin and the desire to more aggressively treat acute and chronic thrombotic diseases in a large and aging population with increasing cardiovascular risk was the impetus for the search for a "superaspirin".

2. Identification of Potent Parenteral GPIIb-IIIa Antagonists

a. Monoclonal Antibodies. The first attempts to develop specific agents that would block the adhesive functions of platelet GPIIb-IIIa yielded a variety of blocking murine monoclonal antibodies. These reagents were of critical importance in validating the role of GPIIb-IIIa in platelet aggregation both in vitro and in vivo. One such antibody, developed by Coller and associates, called 7E3, has been instrumental in this respect.[2] However, because of concern about the immunogenicity of the murine antibody in treated subjects, hybrid molecules were subsequently constructed which consisted of mouse-derived variable regions linked to human-derived constant regions.[10] This strategy was eventually used to prepare the chimeric monoclonal antibody c7E3-Fab (abciximab) (Figure 2). While monoclonal antibodies are usually extraordinarily specific for the protein of interest, abciximab is not GPIIb-IIIa-specific, since it also can bind to and inhibit the closely related integrin $\alpha_v\beta_3$, also commonly referred to as a vitronectin receptor, as well as the leukocyte integrin, $\alpha_M\beta_2$.[11] Abciximab was the first agent of this class to be

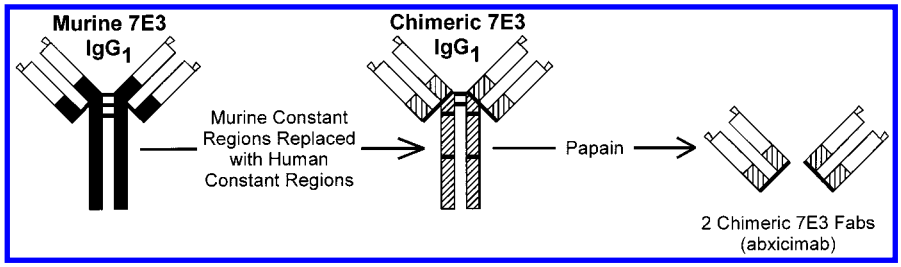


Figure 2. Various forms of the original 7E3 monoclonal antibody of Coller.[10] Conversion of the murine IgG into the chimeric human/murine IgG was accomplished through recombinant DNA techniques. Digestion of the chimeric IgG with papain affords two molecules of the Fab fragment c7E3-Fab (abciximab).

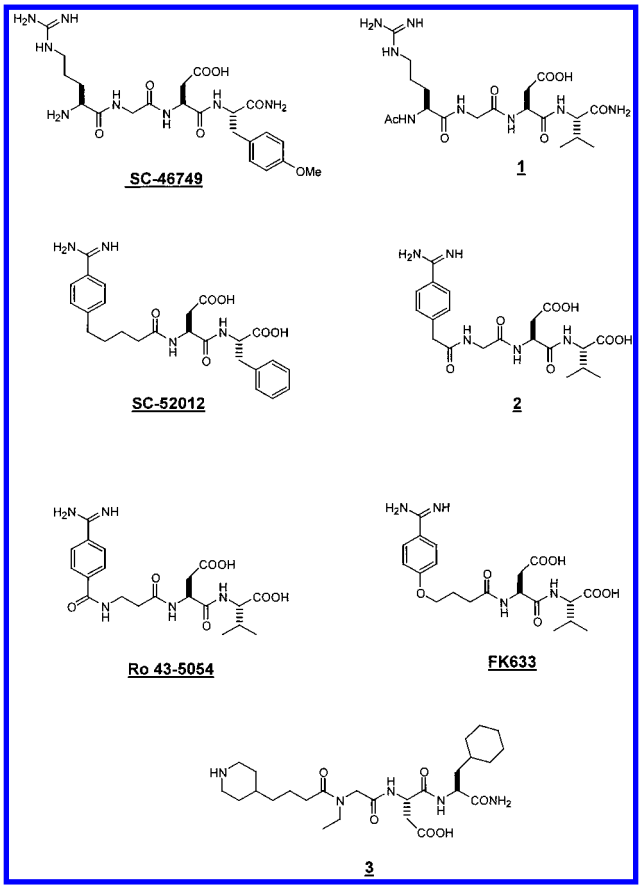
tested clinically and the first to validate the concept that blockade of platelet aggregation through GPIIb-IIIIa antagonism could afford safe and effective reduction of thrombotic clinical events mediated by platelet aggregation.[2,3,10]

b. Snake Venom Peptides. Simultaneous with the development of monoclonal antibodies to GPIIb-IIIa, approaches to the development of novel, nonantibody antagonists were reported. One of the catalysts for this alternate drug discovery strategy was the report of the potent antagonist trigramin, a small protein identified and purified from the venom of the Indian green tree viper.[12] At the time of its discovery, trigramin was the most potent inhibitor of GPIIb-IIIa ($IC_{50} = 130-200$ nM) other than blocking monoclonal antibodies. This polypeptide inhibitor contains 72 amino acids and is highly disulfide-cross-linked. Most importantly, trigramin contains an RGD sequence which is found in one of its small loops and allows this inhibitor to bind to GPIIb-IIIa, thus inhibiting adhesive protein binding.[12]

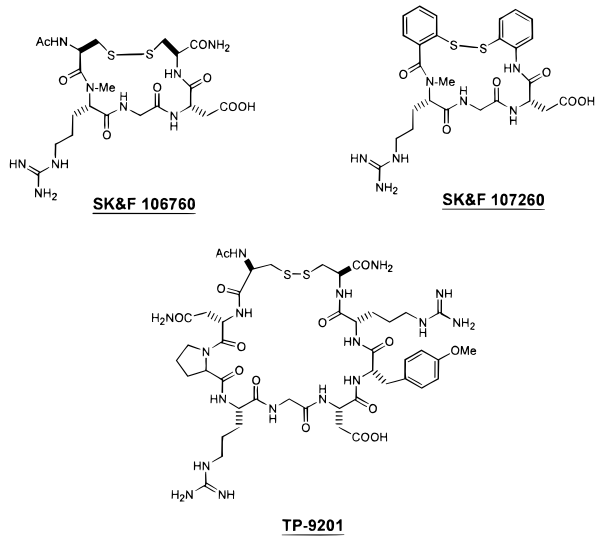
Following the discovery of trigramin, many other peptide inhibitors of GPIIb-IIIa were identified in the venom of other viper and pit viper species. For this reason, these antagonists were collectively given the name disintegrins.[13] In general, disintegrins are nonspecific inhibitors of RGD-dependent integrins including GPIIb-IIIa, $\alpha_v\beta_3$, and the fibronectin receptor $\alpha_5\beta_1$.[14,15] All disintegrins contain the RGD sequence with two notable exceptions. One called barbourin, isolated from the pygmy rattlesnake (*Sistrurus m. barbouri*), contains the KGD inhibitory sequence.[16] More recently, a second KGD-containing inhibitor, called ussuristatin 2, from *Agkistrodon ussruiensis* venom has been described.[17] Barbourin is notable, since it was the first reported disintegrin that is highly specific for GPIIb-IIIa with no reactivity for the closely related vitronectin receptor, $\alpha_v\beta_3$.[16] Ultimately, this specificity information concerning barbourin was an impetus to design cyclic peptide mimics of barbourin.[18] While the disintegrins were useful in studying the interaction of small ligands (i.e. antagonists) with GPIIb-IIIa and evaluating their potential in vivo properties in animal models of thrombosis, they were far from ideal drug candidates.[19] Thus, for a variety of reasons, none of these agents were developed further. However, the discovery and characterization of the disintegrins has allowed for the design of small cyclic peptides and peptidomimetics with more appropriate pharmaceutical properties to proceed.

c. RGD Peptides, Peptidomimetics, and Nonpeptides. Pioneering observations[7] made during the 1980s concerning the ability of peptides containing the RGD recognition sequence to function as antagonists led to the first attempts to mimic this sequence in nonpeptide antagonists.[3-5] The race to develop small-molecule therapeutic agents was thus initiated. Rational approaches to drug design included efforts to understand the structure−activity relationships (SARs) of RGD-containing peptides in more detail. The tripeptide sequence, RGD, is not a potent inhibitor of GPIIb-IIIa ($IC_{50} > 300$ μM in platelet aggregation assays). However, addition of an amino acid residue carboxyl terminal to the aspartate residue significantly enhanced the activity of these peptides. The critical elements of the pharmacophore contained within the tri- and tetrapeptide sequences are the guanidinium functionality of the Arg residue and the β-aspartic acid functionality. Examples of modestly potent peptide antagonist sequences are shown below. SC-46749 was shown by investigators at Searle-Monsanto to be significantly more potent than the RGDS sequence in inhibiting fibrinogen binding to GPIIb-IIIa and in platelet aggregation assays (IC_{50} = 27 and 32 μM, respectively) and to be active in vivo.[20] Similar micromolar inhibitory activity was reported for antagonist **1**, by SmithKline Beecham.[21] Attempts to modify the side chains of these sequences did not enhance inhibitory activity until investigators at Searle and Hoffman-LaRoche reported success with modifications of the Arg residue which yielded the first real improvements. Replacement of the Arg-Gly dipeptide with a 4-benzamidinopentanoyl group yielded SC-52012 with significantly enhanced in vitro activity ($IC_{50} = 72$ nM, canine PRP aggregation).[22] Independently, Roche also found the 4-benzamidine enhancing functionality was useful when introduced into to their antagonists **2** and Ro 43-5054.[23] These novel antagonists displayed IC_{50} values of 300 and 30 nM, respectively, for inhibition of human platelet aggregation. Further modifications of these modified linear RGD mimetics led to some of the first clinical candidates that were tested as both parenteral and oral GPIIb-IIIa antagonists and will be discussed in later sections. Using a similar structural theme FK633 was designed by Fujisawa scientists. Because of its structural similarity to **2** and Ro 43-5054, its in vitro activity (IC_{50} = 103 nM, human PRP aggregation/ADP) is also quite similar.[24] FK633 was studied in early phase I clinical studies, but its clinical development was discontinued. Antagonist **3**, identified by Rhone-Poulenc Rorer, is an extension of work on modifying the RGDS sequence.[25] Piperidine-containing antagonist **3** is potent ($IC_{50} = 97$ nM, inhibition of fixed platelet aggregation; $IC_{50} = 28$ nM, inhibition of fibrinogen binding to activated platelets) and GPIIb-IIIa-specific. Oral administration (5 mg/kg ig) of **3** to dogs

produced robust platelet aggregation ex vivo, which persisted for longer than 12 h.[25]



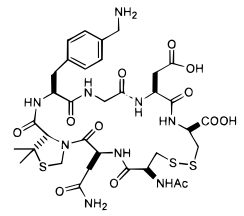
A second approach that relied on the RGD sequence as a starting point involved the identification of potent cyclic peptides containing the RGD, KGD, or other modified sequences. While some groups have suggested that cyclization strategies have been employed to develop highly specific antagonists, in reality, it has been more common to see increased potency of these cyclic peptide antagonists and little modulation of integrin specificity. Attempts to improve integrin specificity have had to rely on other modifications of the adhesion sequence found in these cyclic peptides. For example, SmithKline Beecham disclosed a series of cyclic peptides that utilize a disulfide linkage as the cyclization element. SK&F 106760 is a cyclic pentapeptide from this series (IC_{50} = 230 nM, human platelet aggregation assays; IC_{50} = 0.48 μM, inhibition of fibrinogen binding to purified GPIIb-IIIa).[26] The more constrained analogue, SK&F 107260, is more potent than SK&F 106760 with an IC_{50} value of 90 nM in inhibition of dog platelet aggregation assays and an IC_{50} value of 2.8 nM for inhibition of [^{125}I]fibrinogen binding to purified GPIIb-IIIa.[27] In both series, the introduction of the N-Me-Arg residue appears to have significantly improved the in vitro activity of these peptides. Investigation of the solution conformations of these and similar peptides by NMR suggested that they may adopt a turn−extended−turn conformation with a reversal of chain direction through the RGD sequence.[28] Interestingly, SK&F 106760 and SK&F 107260 do not appear to be integrin-specific, since SK&F 107260 has also been reported to inhibit the vitronectin receptor, $\alpha_v\beta_3$, with a K_i value of 3.5 nM.[29] SK&F 106760 (0.3−3.0 mg/kg iv) was shown to produced complete inhibition of coronary artery thrombosis in conscious dogs. Though stable in plasma, the half-life of SK&F 106760 in the dog was short, approximately 66 ± 12 min.[30]



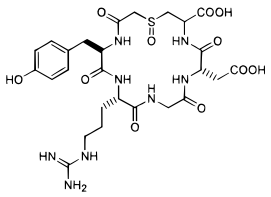
Another cyclic peptide of interest is the nonapeptide TP-9201. This RGD-containing peptide inhibits human platelet aggregation with an IC_{50} value of 220 nM and blocks fibrinogen binding to purified GPIIb-IIIa with an IC_{50} value of 29 nM.[31] The specificity of this peptide is uncertain since its activity against the most closely related integrin, the vitronectin receptor $\alpha_v\beta_3$, has not been reported. Merck has disclosed their efforts to design potent and specific GPIIb-IIIa antagonists which led to MK-0852.[32] MK-0852 has a reported IC_{50} value of 26 nM for inhibition of human gel-filtered platelet aggregation mediated by 10 μM ADP. From an initial series of cyclic RGD-containing peptides, they discovered that replacement of the argininyl residue with a *p*-aminomethylphenylalanine residue (Amf) not only enhanced the inhibitory activity toward GPIIb-IIIa but also dramatically shifted the inhibitory activity away from the other closely related, RGD-dependent integrins. MK-0852 has been shown to be effective in several canine models of thrombosis when administered intravenously as a 100−300 μg/kg bolus followed by a continuous infusion of 1−3 μg/kg/min.[33]

Genentech also developed a series of cyclic peptides displaying the RGD sequence utilizing thioether and sulfoxide linkages. G4120, a sulfoxide-containing cyclic peptide, was chosen from their series based on superior potency in inhibiting platelet aggregation (IC_{50} = 150 nM).[34] Of interest, G4120 is not integrin-selective since it has been reported to inhibit the vitronectin receptor, $\alpha_v\beta_3$.[35] In canine models of thrombosis, G4120 administered intravenously or endobronchially augments tissue plasminogen activator-mediated (t-PA) coronary arterial thrombolysis at doses of 0.3−0.5 mg/kg/h.[36] DuPont-Merck has disclosed a 'template-constrained" cyclic peptide, DMP 728, which is structurally quite similar to G4120. However, DuPont scientists used SK&F 106760 as their starting point to design a linker that would constrain the tripeptide sequence of SK&F 106760 to adopt the same conformation for SK&F

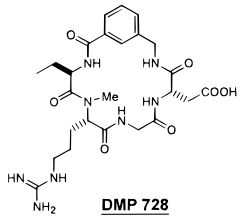
106760 that is found in water as determined by NMR analysis.[37] DMP 728 is a potent inhibitor of human platelet aggregation (IC_{50} = 46 nM) and is quite selective in inhibiting fibrinogen binding to purified GPIIb-IIIa (IC_{50} = 2.3 nM). It displays high affinity for GPIIb-IIIa [dissociation constant K_d = 0.1 nM ([^{3}H]DMP 728)].[38] This cyclic peptide is active both intravenously and when administered orally in several animal models of thrombosis. The reported oral bioavailability of DMP 728 is approximately 8−12% in dogs.[39]



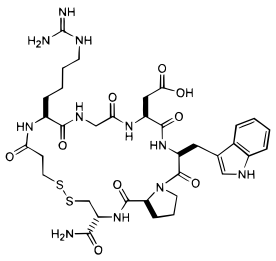
MK-0852



G4120



DMP 728



C68-22 (eptifibatide)

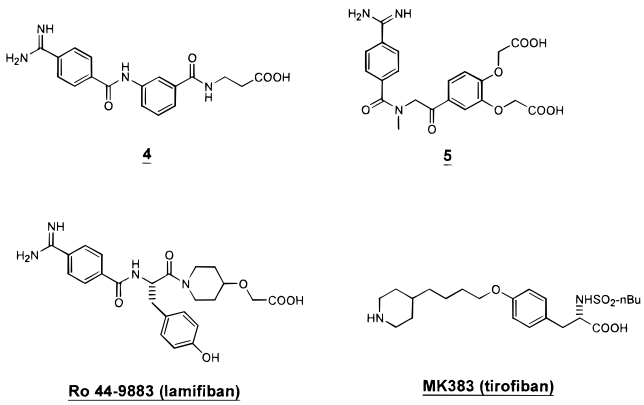
A novel approach to developing potent cyclic peptide antagonists of GPIIb-IIIa was taken by COR Therapeutics. Using the highly GPIIb-IIIa-selective KGD-containing disintegrin, barbourin, as a starting point, mimetics were designed.[16] This KGD-containing disintegrin is highly specific for GPIIb-IIIa, because it contains the alternate basic pharmacophore group $-NH_2$ instead of the guanadinium group of RGD-containing antagonists. Presumably, this change in charge, size, or basicity yields poor interactions with the most closely related integrin $\alpha_v\beta_3$. COR scientists designed a cyclic heptapeptide mimic of barbourin, called eptifibatide (C68-22), which retained both the potency and integrin selectivity of the snake venom-derived disintegrin, barbourin.[18] This modified KGD-containing peptide (containing a homoarginine residue) inhibits human platelet aggregation with an IC_{50} value of 140 nM in human platelet-rich plasma (hPRP) collected with sodium citrate as anticoagulant and an IC_{50} value of 570 nM in hPRP collected using the thrombin inhibitor PPACK as the anticoagulant.[40] The distinct IC_{50} values obtained for eptifibatide using different anticoagulants for blood collection to prepare hPRP samples have emerged as an important detail in the reported activity of antagonists. Unless specifically noted otherwise, the in vitro activities of antagonists reported in this Perspective were determined using citrate as the anticoagulant, since this protocol makes up the bulk of the reported data. However, as in the case of eptifibatide, IC_{50} values obtained with citrate anticoagulation can overestimate the inhibitory activity of many GPIIb-IIIa antagonists in comparison to those obtained under conditions where the ionized calcium level of the sample remains near physiological levels (1 mM).[40]

Eptifibatide is an effective antithrombotic in various animal models of thrombosis, when administered intravenously at doses that range between 2 and 10 μg/kg/min.[41] This peptide is quite stable in plasma yet displays a relatively short half-life in numerous animal species, a property that was deemed desirable in an agent to be used acutely. From the various members of the peptide and cyclic peptide clinical candidates, eptifibatide is the only small peptide to complete clinical testing and progress through FDA approval and commercial launch. The clinical testing of this and other parenteral agents will be discussed in later sections of this Perspective.

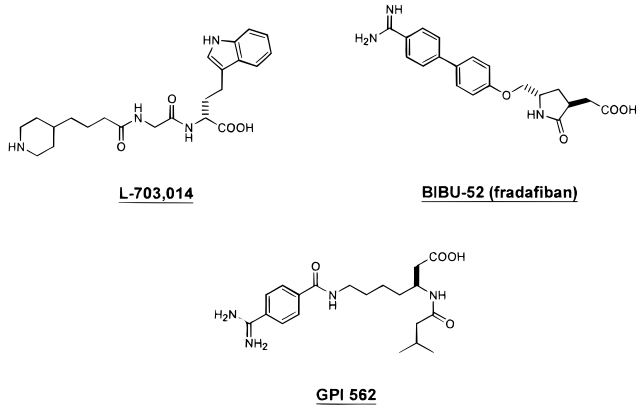
Many additional approaches to preparing peptidomimetics of the RGD sequence have also appeared over the last 10 years. Some of the earliest reports came from the Hoffman-LaRoche laboratories where they described antagonists **4**, **5**, and lamifiban (Ro 44-9883).[23] Each of these compounds was designed from their earlier antagonist **4**. The Roche antagonists each display potent inhibitory activity in platelet aggregation assays (200, 70, and 30 nM, respectively). Each of the distinct series was also shown to be integrin-selective for GPIIb-IIIa versus the vitronectin receptor $\alpha_v\beta_3$. Lamifiban was chosen for further clinical development because of its greater potency and a distinct in vitro property which included the apparent ability to *not* induce certain conformational changes of the receptor that other GPIIb-IIIa antagonists could elicit.[42] The conformational changes to the receptor induced by ligands can be detected with LIBS (**l**igand-**i**nduced **b**inding **s**ites) antibody reagents. It should be noted that after the Roche strategy of choosing a lead compound based on its inability to induce LIBS was disclosed, it has been shown that *all* GPIIb-IIIa antagonists described to date appear to induce one or several LIBS epitopes.[43]

Merck discovered and developed its nonpeptide antagonist tirofiban, L-700,462 (MK383), using the strategy of screening a subset of its compound library containing amine and carboxylic acid functionalities that had a distance separation of 10−20 Å, similar to the RGD sequence. This screening strategy afforded a library hit which was equivalent to the tetrapeptide RGDS but whose chemical structure was more amenable to optimization than the RGD-containing peptides.[44] Optimization of the initial hit led to tirofiban, a tyrosine derivative that displays an IC_{50} value of 35.7 nM for platelet aggregation inhibition mediated by ADP. Although a small molecule, tirofiban is not orally bioavailable and has a relatively short half-life in animals and humans ($t_{1/2}$ = 0.5−3 h), properties that make it suitable as a parenteral antithrombotic agent.[45,46] Currently, tirofiban is the only other FDA-approved parenteral GPIIb-IIIa antagonist besides eptifibatide and abciximab. Tirofiban is also highly integrin-specific. One of the key observations made by Merck during this discovery effort was that the *N*-α-sulfonamide functionality of tirofiban was critical to obtaining its potent activity and that this functional group might be binding to a region of GPIIb-IIIa which is not exploited by the cyclic peptide antagonists. Thus the term "exosite" binding by the sulfonamide functionality was coined. Many other groups have utilized this affinity-enhancing

group to their advantage in the preparation of potent antagonists.[44,46,47]



In their search for orally bioavailable GPIIb-IIIa antagonists, Merck also discovered a series of novel inhibitors structurally similar to tirofiban, as exemplified by L-703,014.[48] While L-703,014 is quite potent (IC_{50} = 94 nM, human PRP aggregation), its poor oral bioavailability (4.9%) in dogs precluded its further development.[48] Dr. Karl Thomae GmbH (Boehringer Ingelheim) identified the biphenylamidine-containing inhibitor fradafiban (BIBU-52) which has an IC_{50} = 80 nM (2.5 μM ADP/hPRP aggregation).[49] This compound was designed using the assumption that RGDX ligands formed either a β- or γ-turn when bound to the receptor and that a γ-lactam could be used as a scaffolding to mimic this turn.[50] This effort was initially envisioned to lead to an orally active GPIIb-IIIa antagonist series, and the corresponding double prodrug form called lefradafiban (BIBU-104) is currently being developed as an oral agent. However, the in vivo properties of this agent suggest that fradafiban might be better utilized as a parenteral agent, and it is currently being studied clinically in this fashion.[50,51] The evaluation of lefradafiban as an oral GPIIb-IIIa antagonist will be discussed further in later sections of this Perspective. A simple amino acid-containing antagonist GPI 562 reported by Novartis came from a weak screening lead that was optimized to GPI 562.[52] This structurally simple antagonist displays an IC_{50} value of 15 nM using washed human platelet aggregation and is orally active in guinea pigs. GPI 562 has progressed to clinical evaluation.[52]



d. Clinical Investigations of Parenteral Antagonists. Several parenteral GPIIb-IIIa inhibitors have been developed clinically thus far (Table 1). The first GPIIb-IIIa inhibitor to be studied and approved for clinical use was the monoclonal antibody, abciximab. Since then, eptifibatide and tirofiban have become commercially available within this therapeutic class. One additional agent, lamifiban, has just completed a second phase III clinical trial without success.[144]

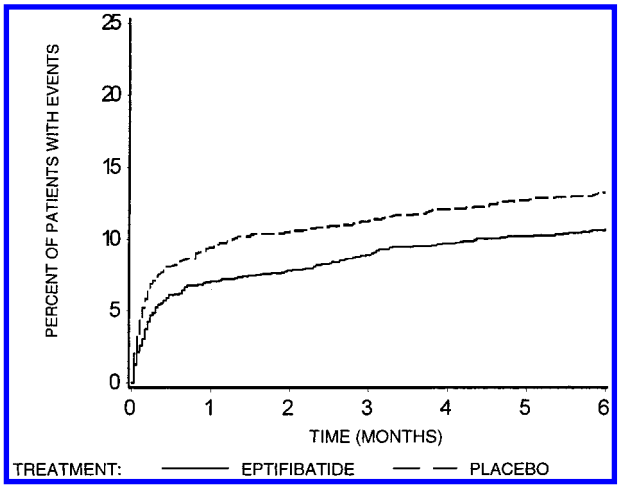


Figure 3. Kaplan−Meier plot of time to death/MI after enrollment for the population enrolled in the United States in the PURSUIT study.[54]

Table 1. Parenteral GPIIb-IIIa Antagonists

compound	phase	sponsor	refs
abciximab (Reopro)	on market	Centocor/Lilly	55, 56, 63, 64
eptifibatide (Integrilin)	on market	COR/Schering-Plough	54, 65
tirofiban (Aggrastat)	on market	Merck	66, 67, 68
lamifiban	III	Roche	23, 69

These agents are typically administered as an intravenous bolus followed by a 12−72-h continuous infusion. Thus, they are best suited for acute situations, notably in the setting of percutaneous coronary interventions (PCI) and/or acute coronary syndromes. The evidence for the efficacy of these agents in these two settings is overwhelming. A meta-analysis of 10 large trials with the four agents listed in Table 1 determined that the odds ratios of death or myocardial infarction at 30 days range from 0.42 to 0.84 in patients undergoing PCI. In acute coronary syndromes, the corresponding odds ratios range from 0.70 to 0.89.[53]

A treatment benefit, consisting of a reduction in hard clinical endpoints (e.g. death or myocardial infarction), usually is observed within hours of the bolus administration, during the time of the infusion. After discontinuation of the infusion, the achieved benefit is typically maintained for as long as patients have been followed. As expected, no additional benefit is achieved after the end of drug administration, and events continue to accrue in both treated and untreated patients. An example of the time course of the treatment benefit for this class is shown in Figure 3 for eptifibatide in the PURSUIT study.[54]

The safety profile of these agents has been quite good, with bleeding being the major consideration. Compared to what was observed in the earlier trials with abciximab,[55] lower heparin doses and better arterial puncture

site management techniques have kept bleeding rates within acceptable levels.[56] Importantly, there has not been any increase in the rate of intracranial hemorrhages with this class of drugs. Reversible thrombocytopenia, which can be profound, has been described in <1% of all patients treated with these drugs.[57]

With the usefulness of GPIIb-IIIa inhibition in the setting of acute coronary syndromes and PCI having been firmly established, increasing attention now has been given to acute ST segment elevation ("Q wave") myocardial infarction (AMI). Specifically, it has been hypothesized that a combination of a GPIIb-IIIa inhibitor plus a thrombolytic agent may improve on the efficacy profile of thrombolysis alone.[58] Moreover, this may allow a reduction in the dose of the thrombolytic agent with the potential for improved safety, specifically, a reduction in the rate of intracranial hemorrhages.

Gold and co-workers were the first to demonstrate the potential usefulness of GPIIb-IIIa inhibitors administered together with a reduced dose of a thrombolytic agent in a dog arterial thrombosis model.[59] The first clinical trial to combine a GPIIb-IIIa inhibitor with a thrombolytic in the setting of AMI was the IMPACT-AMI study.[60] This small trial demonstrated a greater number of patients with normal 90-min coronary blood flow (TIMI grade 3 flow) in the group receiving the thrombolytic, alteplase, plus the highest dose of eptifibatide compared to the group receiving alteplase alone (66% vs 39%). Similar results have been obtained with the combination of lamifiban and alteplase.[61]

A larger study, TIMI 14A, compared a number of treatment regimens in 450 patients.[62] These included abciximab alone and abciximab in combination with either streptokinase or alteplase. While the combination with alteplase showed encouraging 90-min blood flow rates, this was not the case for regimens which included streptokinase. Additionally, the bleeding rates were increased in the streptokinase groups, confirming the findings in previous studies. On the basis of the encouraging data with the combination of a GPIIb-IIIa inhibitor together with one of the newer, more clot-specific thrombolytic agents, which now include alteplase, reteplase, and TNK, several larger scale trials are currently ongoing or in the planning stages.

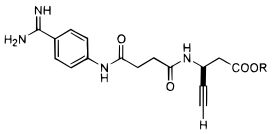
3. Design of Nonpeptide Antagonists for Oral Administration

After initial success in this field that led to the design of potent peptide and peptidomimetic inhibitors of GPIIb-IIIa that have appropriate pharmaceutical properties for use as parenteral agents, attention naturally turned toward the next generation within this class. The identification of inhibitors that would have pharmaceutical properties at the other end of the spectrum (i.e. orally absorbed with prolonged in vivo half-life) turned out to be a difficult challenge. The focus of most groups moved toward identifying nonpeptidic antagonists that would be chemically stable in the gut, be metabolically stable in the circulation, and avoid first-pass metabolism.

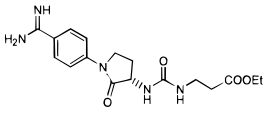
As a starting point in the design of novel nonpeptide antagonists, numerous efforts to deduce a receptor-bound conformation of RGD ligands were conducted. These efforts included NMR and computational methods directed at small linear peptides as well as small and large cyclic peptides containing the RGD sequence.[70] Not surprisingly, a single uniform conformation of the RGD sequence that describes the receptor-bound conformation of the various ligands has not arisen from these investigations. In fact, type II and type II′ β-turns, γ-turns, and variations have all been proposed as receptor-bound conformations of RGD peptides. Fortuitously, the significant differences in proposed conformations of RGD ligands have led to a number of unique and independent nonpeptide approaches to mimicking these conformations. However, the common theme in almost all discovery approaches reported has been the use of a central template to which is appended both an acidic and a basic functionality that serve as the pharmacophore elements. What is quite remarkable is the variety of templates that have been reported which provide good platforms for the identification of potent antagonists. It is apparent from these investigations that in many cases GPIIb-IIIa does not require significant interaction with the central template, whose sole purpose, in most cases, appears to be providing the scaffold for delivering the acidic and basic pharmacophore groups in the correct geometry. This unique ligand recognition aspect of GPIIb-IIIa has allowed for a variety of approaches that have explored many distinct chemical structures in the search for molecules with the desired pharmaceutical properties, which go beyond just potent antagonism of GPIIb-IIIa.

a. Centrally Constrained Monocyclic Antagonists. After its initial success with RGD peptidomimetics, Searle scientists continued their search for potent nonpeptide antagonists and developed a series of aminobenzamidinosuccinyl-based (ABAS) compounds exemplified by xemilofiban (SC-54684A), the ethyl ester prodrug of SC-54701A.[71] This series of antagonists does not contain a centrally constrained monocyclic ring system in the strictest sense. However, the early SAR of this series led to orally active antagonists with promising properties and established some early precedent for the design of antagonists and, in many cases, requisite prodrug strategies. For example, the β-amino acid subunit of SC-54701A was the subject of an extensive SAR effort, where it was determined that the alkyne β-amino acid group, when incorporated into antagonists, afforded both improved oral bioavailability and duration of action. Others have used this and other β-amino acid groups in their search for orally active antagonists.[47] The active antagonist, SC-54701A, is a potent inhibitor of canine platelet aggregation (IC_{50} = 67 nM, collagen), and its ethyl ester prodrug, xemilofiban, is orally available in dogs ($F = 44-53\%$) and in humans and was chosen as the lead compound for clinical development.[71,72] The terminal half-life of SC-54701A in dogs is reported to be 4.4−6.5 h. Although the details of the design of orbofiban (SC-57099B) have not been reported, Searle scientists continued their search for orally available antagonists with improved pharmaceutical properties.[73] This apparently led them to design the pyrrolidinone, orbofiban, which is a backbone-to-backbone conformationally constrained variation of the xemilofiban structure. Orbofiban is a potent and specific aggregation inhibitor (IC_{50} = 80 nM,

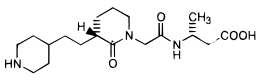
ADP; IC_{50} = 130 nM, collagen). Oral bioavailability of orbofiban is 28% in dogs with a terminal half-life of 18 h. Multidose administration (1.2 mg/kg po b.i.d.) to dogs afforded average platelet aggregation inhibition of 70% at trough levels.[73]



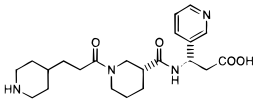
SC-54701A, R =H
SC-54684A (xemilofiban), R=Et



SC-57099B (orbofiban)



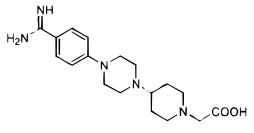
L-734,217



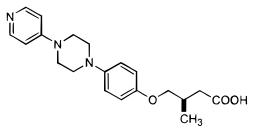
RWJ 53308 (elarofiban)

Merck expanded their efforts with piperidine-containing antagonists such as L-734,217, which is an extension of their previously identified antagonists such as L-703,-014.[74] The backbone-to-backbone cyclization incorporated into L-734,217 employed the Friedinger lactam strategy, previously exploited by Merck to identify conformationally constrained ligands based on linear peptide leads. L-734,217 is a potent inhibitor of platelet aggregation (IC_{50} = 23 nM) and is also a highly specific inhibitor of GPIIb-IIIa.[74] This antagonist also shows preferential affinity for the activated form of GPIIb-IIIa on platelets (K_d = 4.5 nM) versus GPIIb-IIIa on resting platelets (K_d = 650 nM).[75] When administered orally to dogs and chimpanzees at 1−2 mg/kg, significant platelet inhibition effects were noted up to 8 h in the dog and for up to 24 h in the chimpanzee. The reported oral bioavailability of L-734,217 is 8−16% in the dog.[76] Various prodrug forms failed to improve the bioavailability in dogs.[77] This compound reportedly entered clinical trials, but no data from these investigations are available. A compound with very similar structure to L-734,217 emerged from a unique approach employed by investigators at the R. W. Johnson Pharmaceutical Research Institute. They prepared a series of centrally constrained 3-nipecotamide derivatives that were designed based on the solution structure of the carboxyl terminal γ-chain of fibrinogen which is one of the recognition sequences that binds to GPIIb-IIIa.[78] Based on initial success with this template, a solid-phase parallel synthesis paradigm rapidly led to the choice of elarofiban (RWJ 53308) as a clinical candidate.[79,80] Interestingly, while RWJ 53308 has a short half-life in dogs[80] ($t_{1/2}$ = 85 min), the preliminary pharmacokinetics in phase I studies suggest a half-life in humans which ranges from 15 to 32 h and varies with dose.[81]

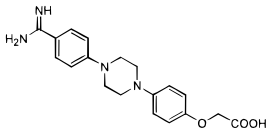
Glaxo discovered the benzamidine-substituted piperazine GR 144053, also based on an early screening lead from their chemical library.[82] This antagonist, which has a linear array of three six-membered rings, is a potent inhibitor of platelet aggregation (IC_{50} = 59 nM) in hPRP and is a highly specific inhibitor of GPIIb-IIIa. When administered to cynomolgus monkeys, it displayed a fairly long duration of action (12 h at 1 mg/kg iv and 8 h at 3 mg/kg po).[82] An additional antagonist, which is structurally similar to GR 144053, is the pyridinylpiperazine ZD 2486, reported by Zeneca, which has a different linear array of three six-membered rings. This antagonist inhibits hPRP aggregation mediated by ADP with an IC_{50} value of 50 nM and is GPIIb-IIIa-specific. The often used benzamidine function has been replaced by the less basic pyridinyl function in ZD 2486 which is apparently responsible for the significantly improved bioavailability of this compound (>50% in rats and dogs) and was accomplished without resorting to prodrug approaches.[83] Another similar antagonist has been described by Solvay Pharmaceuticals based on the phenylpiperazine scaffold such as **6** (IC_{50} = 20 nM).[84] A fourth inhibitor, which utilizes the theme of a linear array of three rings is antagonist UR-12947 reported by Uriach. UR-12947 employs the bipiperidine ring system as the basic functionality, previously employed by SKB in their antagonist lotrafiban (see section b). This antagonist is reported to inhibit ADP (5 μM)-induced platelet aggregation of hPRP with an IC_{50} value of 3.5 nM and to display a long duration of effect in monkeys at a dose of 0.3 mg/kg.[84]



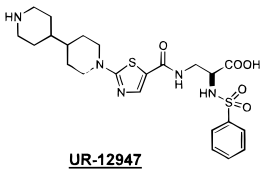
GR 144053



ZD 2486

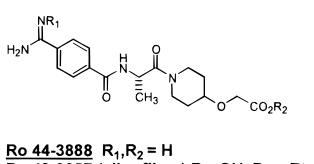


6

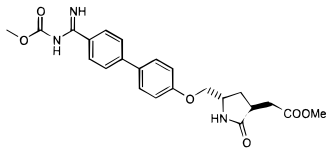


UR-12947

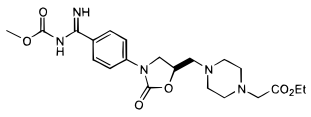
Roche had initially identified a series of piperidine-4-oxyacetic acid derivatives, including the potent and specific parenteral GPIIb-IIIa inhibitor, lamifiban, which proceeded into clinical studies. Continued exploration within this series resulted in replacement of the tyrosyl residue of lamifiban with the smaller residue, alanine. Also, a prodrug masking strategy for the basic and acid pharmacophore groups yielded the potent and orally active double prodrug Ro 48-3657, also known as sibrafiban.[85] The amidoxime prodrug approach, aimed at lowering the pK_a of the basic benzamidine, was novel in this drug class and clearly illustrated the potential for improving the bioavailability significantly within this series. Thus, ubiquitous esterases must cleave the ethyl ester, and liver- and/or gut-mediated reduction of the amidoxime must occur to generate the active metabolite Ro 44-3888. The active metabolite Ro 44-3888 inhibits platelet aggregation of hPRP with an IC_{50} = 38 nM.[85] When Ro 48-3657 is administered orally to rats, dogs, and rhesus monkeys at doses ranging between 1 and 4 mg/kg, the active metabolite Ro 44-3888 is uniformly bioavailable in these species at levels of 26%, 25%, and 33% respectively. The terminal half-life of Ro 44-3888 in dogs and rhesus monkeys is 11.4 and 5.1 h, respectively.[86,87] These properties formed the basis for selection of sibrafiban for human clinical studies.[88]



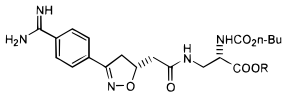
Ro 44-3888 R_1,R_2 = H
Ro 48-3657 (sibrafiban) R_1=OH, R_2 = Et



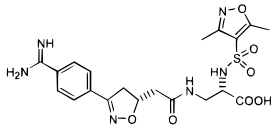
BIBU-104 (lefradafiban)



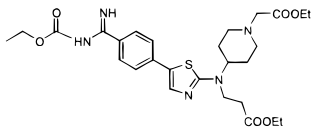
EMD-122347 (gantofiban)



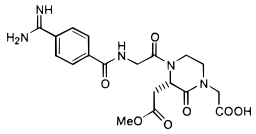
DMP 754 (roxifiban), R=CH_3
XV 459, R=H



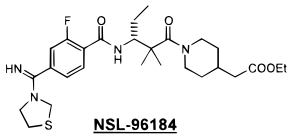
DMP 802



SR121787



TAK-029



NSL-96184

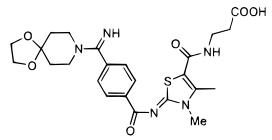
Lefradafiban (BIBU-104), the double prodrug of fradafiban, was the first agent in which a strategy of masking both polarizable pharmacophore groups was employed in order to enhance oral bioavailability.[50] In animals and humans, lefradafiban has modest bioavailability and half-life. It has been administered to subjects in phase II clinical studies 3 times-a-day in order to maintain acceptable levels of platelet aggregation inhibition.[51] Merck KGaA has reported a similar double prodrug, the oxazolidinone gantofiban (EMD-122347), which affords the active metabolite EMD-132338 (IC_{50} = 8 nM, inhibition human platelet aggregation) that is 40% bioavailable in cynomolgus monkeys with a $t_{1/2}$ > 6 h.[89] The benzamidine functionality is masked as the methyl carbamate, as it is with lefradafiban. Gantofiban is under development jointly by Merck KgaA and Yamanouchi Pharmaceuticals and is reported to be in phase II clinical trials.[90]

DuPont-Merck Pharmaceuticals has reported novel isoxazoline-based GPIIb-IIIa antagonists. Their drug design strategy was based on X-ray and NMR analyses of their potent peptide antagonist, DMP 728, which suggested that the glycine residue existed in an extended conformation.[91] Further modeling of structures led to the isoxazoline template to which was appended the requisite acidic and basic functionalities and which eventually led to their most potent series exemplified by roxifiban (DMP 754) and DMP 802.[92,93] Both antagonists contain the activity-enhancing α-carbamate or α-sulfonamide carboxylic acid functionality, originally discovered by Merck scientists. Roxifiban is the ethyl ester prodrug of XV 459, which is a potent inhibitor of human platelet aggregation (IC_{50} = 30−60 nM).[93] The α-sulfonamide-containing inhibitor, DMP 802, is also a potent inhibitor (IC_{50} = 29 nM) and reportedly has a much slower dissociation rate from unactivated human platelets in comparison to XV 459 (dissociation $t_{1/2}$ = 32 min for DMP 802 vs 7 min for XV 459).[93,94] The property of slow dissociation from platelets has been proposed to be the critical element determining the in vivo half-life for these high-affinity drugs.[4] Roxifiban was ultimately chosen for clinical development and is about to enter phase III.

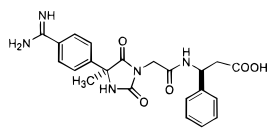
The aminothiazole-containing antagonist, SR121787, described by Sanofi, is another member of the family of potent antagonists that requires a double prodrug form (ethyl ester and benzamidine masked as carbamate) to achieve improved bioavailability.[95] The active metabolite, SR121566, contains two free carboxylic acids, potently inhibits platelet aggregation (IC_{50} = 46 nM, 2.5 μM ADP/platelet aggregation), and is GPIIb-IIIa-specific.[96] In baboon studies, SR121787 gave >90% inhibition of ex vivo platelet aggregation at 12 h when administered orally at 1 mg/kg.[96] TAK-029, is a piperazinone whose structure is reminiscent of that of sibrafiban and lamifiban. TAK-029 is a potent platelet aggregation inhibitor (IC_{50} = 29−38 nM) and specific for GPIIb-IIIa.[97] When administered orally to guinea pigs at 3 mg/kg, a >90% level of platelet aggregation inhibition was achieved at early time points (<1 h) with sustained inhibition of aggregation (40%) at 8 h.[97] A design approach quite different than most others has been described by investigators at Nippon Steel, who discovered that the trisubstituted β-amino acid unit can function as a novel element for restricting conformation, leading to the development of potent GPIIb-IIIa antagonists such as NSL-96184 (IC_{50} = 45 nM, platelet aggregation inhibition).[98] Not only is the β-amino acid unit of NSL-96184 novel, but also the strategy demonstrates that a cyclic scaffold is not required to maintain restricted conformation. Efforts to improve the bioavailability of this series focused on the basicity of the benzamidine function and subsequently identified that *meta*-fluoro substitution in the benzamidine ring as well as *N*,*N*-dialkylation of the benzamidine afforded analogues with good improvements in absorbed drug following oral administration.[98]

Taisho Pharmaceutical Co. described a series of *N*-alkylthiazoline-containing antagonists such as PSA0613, which is a potent antagonist (IC_{50} = 22 nM, ADP/platelet aggregation). When administered to cynomolgus monkeys at 0.5 mg/kg po, ex vivo aggregation inhibition was >80% at 2−8 h.[99] Hoechst AG have described a rational drug design strategy for conformationally constraining the RGDS sequence and substitution of the argininyl side by the benzamidine group to afford a series of antagonists such as the hydantoin-containing antagonist S1197.[100] This antagonist inhibits human gel-filtered platelet aggregation induced by ADP with an IC_{50} = 20 nM. The ethyl ester prodrug of S1197 is 42% bioavailable in dogs with a terminal half-life of 9.9 h. Merck has described the identification of piperazine L-750,034 based on the strategy of obtaining an inhibitor of minimized length spanning the positive and negative charges of the pharmacophore.[101] This highly constrained antagonist is a potent inhibitor of platelet aggregation (IC_{50} = 17 nM) and is orally bioavailable in dogs. DuPont has also disclosed the isoxazole XU 065 that is potent and specific for GPIIb-IIIa (IC_{50} = 50 nM,

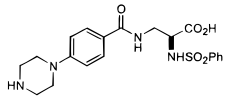
ADP-induced platelet aggregation) and orally bioavailable in dogs at low dose.[102]



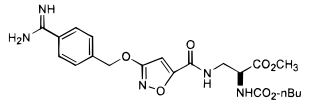
PSA0613



S1197



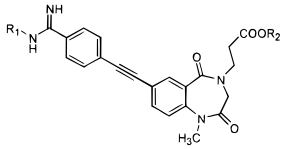
L-750,034



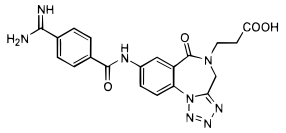
XU 065

b. Centrally Constrained Fused-Bicyclic Antagonists. Employing NMR solution conformation determinations and molecular dynamic methods, Genentech determined a consensus conformation for their rigid cyclic peptide, G4120, that they used as a starting point for designing nonpeptide antagonists. A "cupped" presentation of the RGD sequence was proposed to be required for high potency which they used to design a nonpeptidal scaffold to mimic the contour and backbone of G4120.[103] Their evaluation focused on fused 6,7-frameworks that maintained a cupped shape, and specifically, the benzapines were chosen.[103] Appending the requisite argininyl and aspartate side chains to the benzodiazepinedione nucleus afforded antagonists such as G6788, a double prodrug of the active metabolite G6249, found to be a potent antagonist (IC_{50} = 120 nM, ADP-induced platelet aggregation). The carbamate ethyl ester double prodrug G6788 is orally bioavailable in the rat (F = 6%) and rhesus monkey (F = 21%).[104] An alternate framework utilized a tricyclic nucleus such as in G7453, which is slightly more potent than inhibitors containing the bicyclic nucleus (IC_{50} = 54 nM, ADP-induced platelet aggregation).[105]

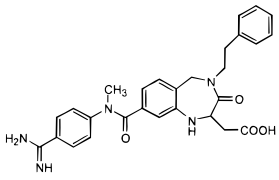
The benzodiazepine scaffold was also independently investigated by SmithKline Beecham scientists who began their search for nonpeptide antagonists through examination of the NMR and X-ray crystal structure of their potent cyclic peptide, SK&F 107260.[106] Major and minor conformers of SK&F 107260 were determined in solution, the minor conformer being the same conformer seen in the crystal structure. The major conformer which contains a turn at the Arg residue, an extended conformation of the Gly, and a C_7 turn at the Asp was chosen for exploration. On the basis of these observations, the 1,4-benzodiazepine nucleus was chosen to mimic the C_7 turn and the extended Gly conformation and resulted in several potent antagonists exemplified by SB-208651 (IC_{50} = 65 nM, hPRP/ADP-induced aggregation).[106] In the course of their synthetic studies they also prepared compounds where the benzamidinecarboxamide is attached to the 7 position of the benzodiazepine nucleus as in antagonist **7**.[107] The potent activity of both **7** (IC_{50} = 160 nM, hPRP/ADP-induced aggregation) and SB-208651 suggested to these investigators that there was indeed an alternate pharmacophore for the receptor where the receptor has an enlarged (or second distinct) cationic binding site.[107] While **7** has been reported to be orally active, the 7-position analogue is not.[108] Attempts to improve the limited oral bioavailability of this series focused on replacing the benzamidine function with a less basic piperidine functionality in analogues such as lotrafiban (SB-214857).[108−110] Lotrafiban also has a methyl group on the benzodiazepine nucleus replacing the phenylethyl side chain of SB-208651 and **7**, a modification found to improve intestinal permeability in rabbits within this series.[111] Lotrafiban also utilizes the *S*-configuration at C-2 of the nucleus. These modifications led to the identification of lotrafiban, which is potent (IC_{50} = 28 nM, hPRP/ADP-induced aggregation; K_d = 1.85 nM, purified GPIIb-IIIa[100]), specific, and orally bioavailable in dogs with good duration of action (>8 h) when intraduodenally administered at a dose of 1 mg/kg.[109] Lotrafiban is currently undergoing phase III evaluation in human subjects.[142]



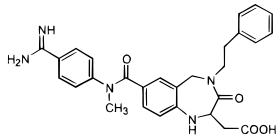
G6788, R1 = EtOCO-, R2 = Et
G6249, R1,R2 = H



G7453



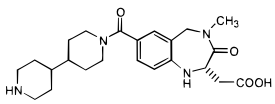
SB-208651



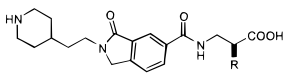
7

Merck began an investigation into centrally constrained antagonists which led to the identification of the isoindolinones such as L-709,780[112] and L-746,-223.[113] The precursors to L-709,780 and L-746,223 were *m*-phthalamide-based inhibitors which were modestly active but suggested that further restriction of the amide linkages would improve potency. Isoindolinone L-709,780, which contains the unsubstituted β-alanine residue, was shown to be potent (IC_{50} = 25 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 13 nM, active form of GPIIb-IIIa; K_D = 550 nM, resting form of GPIIb-IIIa). Oral administration of L-709,780 at 4 mg/kg produced 80−90% inhibition of ex vivo maximal platelet aggregation in conscious dogs which returned to normal values at 8 h after administration.[113] Further improvements in this series were realized with addition of the potency-enhancing, exosite-interacting, α-sulfonamido groups such as in the 3-pyridylsulfonamide-containing antagonist L-746,223. Enhanced activity was observed for L-746,223 (IC_{50} = 15 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 0.38 nM, active form of GPIIb-IIIa; K_D = 2.2 nM, resting form of GPIIb-IIIa), which also gave a similar pharmacodynamic profile to L-709,780 when dosed at the much lower dose of 0.10 mg/kg.[113]

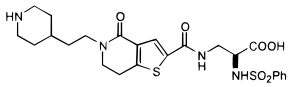
Other centrally constrained templates explored by Merck, such as in the thieno[2,3-*c*]pyridone series as illustrated by analogue **8**, were found to be slightly more potent (IC_{50} = 7 nM, gel-filtered platelets/ADP-induced



SB-214857 (lotrafiban)



L-709,780, R=H
L-746,233, R=NHSO$_2$-3-pyridyl



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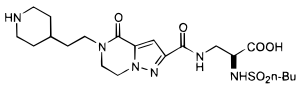
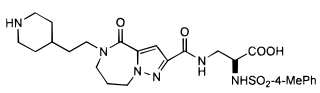
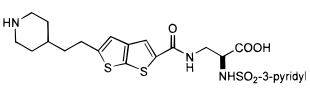


L-734,115

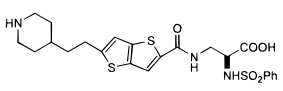
aggregation) but did not display an enhanced pharmacodynamic profile over L-746,223 when orally administered.[114] Further exploration in this series identified the pyrazolopiperazinone L-734,115 (IC_{50} = 9 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 0.12 nM, active form of GPIIb-IIIa; K_D = 1.4 nM, resting form of GPIIb-IIIa) and its homologue pyrazolodiazepinone L-738,167 (IC_{50} = 8 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 0.08 nM, active form of GPIIb-IIIa; K_D = 1.1 nM, resting form of GPIIb-IIIa), which has distinguished itself in vivo.[115,116] When L-738,167 was administered to dogs (1 mg/kg po gavage), platelet aggregation was inhibited by 87% 24 h after administration.[117] The pharmacokinetic properties of L-738,167 and other similar antagonists have been quite useful in understanding the unique pharmacology of GPIIb-IIIa inhibition, a subject that will be discussed in greater detail in section 5.[118] Merck has also reported a number of other central templates using the same theme described above that afforded potent and orally active antagonists such as the [2,3-*b*]thienothiophene L-739,758[119] (IC_{50} = 8 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 0.047 nM, active form of GPIIb-IIIa; K_D = 0.07 nM, resting form of GPIIb-IIIa), the [3,2-*b*]thienothiophene **9**[120] (IC_{50} = 7 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 0.08 nM, active form of GPIIb-IIIa; K_D = 0.15 nM, resting form of GPIIb-IIIa), and the indole L-756,568, (IC_{50} = 13 nM, gel-filtered platelets/ADP-induced aggregation; ED_{50} = 0.099 nM, active form of GPIIb-IIIa).[121] Following oral administration of L-739,758 to dogs, an extended duration of effect (>80% inhibition of platelet aggregation) was noted that could be maintained through 6 days of once-daily dosing at 10 μg/kg.[120] Once-daily dosing of the indole L-756,568 at 0.25 mg/kg over 4 days inhibited platelet aggregation between 82% and 95% at trough plasma concentrations in dogs.[121]



L-738,167



L-739,758



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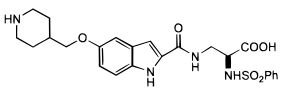
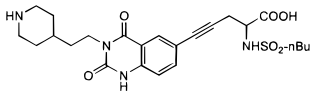


L-756,568

Quinazolinediones and quinazolinones have also been investigated by Merck as central templates and are contained in antagonists **10** (IC_{50} = 37 nM, gel-filtered platelets/ADP-induced aggregation) and **11** (IC_{50} = 43 nM, gel-filtered platelets/ADP-induced aggregation).[122] However, both series of antagonists have short duration of action in dogs following iv infusion. Merck has also developed a series of 3,4-dihydro-1(1*H*)-isoquinolinone-based antagonists that are more rigid versions of their predecessor lactam series of antagonists exemplified by lactam L-734,217. In their attempts to improve on the potency and oral bioavailability, a potent antagonist L-767,679 (IC_{50} = 12 nM, gel-filtered platelets/ADP-induced aggregation) was identified.[123] This compound utilizes the ethynyl β-amino acid subunit first identified by Searle and used in xemilofiban. This antagonist also incorporated the arylpiperazine function, shown to have reduced basicity (pK_a = ~9.0) in comparison to the piperidine function of L-734,217 (pK_a = 11.0), to improve the absorption characteristics within this series. While L-767,679 is orally active in dogs, its ethyl ester prodrug, L-767,685, is superior with oral bioavailability of >17% in dogs and 32% in rhesus monkeys.[123] DuPont-Merck scientists have disclosed benzimidazole/benzoxazole-containing antagonists such as **12** (IC_{50} = 10 nM, hPRP/ADP-induced aggregation) which have been reported to be orally available in dogs.[124]



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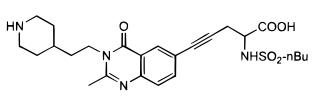

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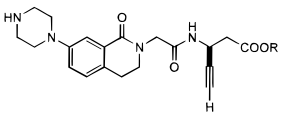
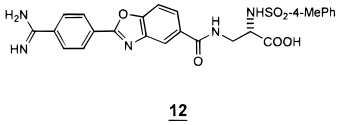


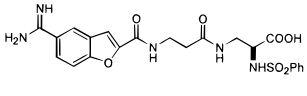
L-767,679, R=H
L-767,685, R=Et



12

Eli Lilly and COR Therapeutics scientists have utilized the strategy of conformational restriction of benzamidine to prepare potent antagonists which employ the *N*-α-sulfonamide exosite interacting group to boost potency.[125,126] One of the more potent antagonists from this series, amidinobenzofuran **13** (IC_{50} = 35 nM, hPRP/ADP-induced aggregation), when administered orally to rats as its ethyl ester prodrug afforded only modest drug levels.[126] Eli Lilly and COR Therapeutics also disclosed a second series of antagonists based on fused bicyclic templates that mimic a Gly-Asp β-turn.[127] Similar to the approaches used by Genentech and SmithKline Beecham, their approach utilized NMR determination of a preferred conformation of a RGD-containing cyclic peptide analogue of eptifibatide. Their analysis revealed a type II′ β-turn in which the Arg and Asp side chains are roughly in the same plane and diagonally disposed across a slightly cupped Gly-Asp β-turn.[127] They chose to mimic this conformation with a linearly fused 6,6-ring system in which one ring was aromatic and the second ring was aliphatic. Initial analogues to explore this hypothesis utilized the 3,4-dihydro-1-oxoisoquinolone ring system. Antagonist **14** (IC_{50} = 90 nM, hPRP/ADP-induced aggregation) was identified as a prototype template that afforded potent activity. Subsequently,

tetralone **15** (IC_{50} = 60 nM, hPRP/ADP-induced aggregation) and benzopyran **16** (IC_{50} = 190 nM, hPRP/ADP-induced aggregation) templates were also described affording antagonists which were orally active when dosed as ethyl ester prodrugs to rats (10 mg/kg, single oral dose AUC's = 11−16 μg·h/mL, C_{max} values of 3.6−5.0 μg/mL).[128] Investigators at Mitsui Pharmaceuticals arrived at similar 6,6-bicyclic templates using computed pharmacophore mapping of the previously described GPIIb-IIIa antagonists: DMP 728, BIBU-52, SC-54701A, GR 144053, and TAK-029.[129] Interestingly, this approach led them to compounds such as the benzopyran MS-180 (IC_{50} = 35 nM, hPRP/ADP-induced aggregation), which is isomeric with benzopyran **16**.[128] This may be a second example of the phenomenon reported by SmithKline Beecham for the isomeric benzodiazepinones SB-208651 and **7** where an alternate pharmacophore or enlarged second cation binding site has been implicated.[107] Mitsui investigators also found that modulation of the benzamidine function by *N*,*N*-dialkylation (i.e. morpholino) could significantly improve the oral profile in this series.[129,130]



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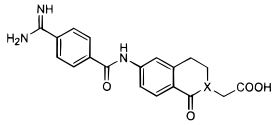
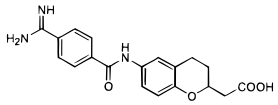


14 X=N
15 X=CH



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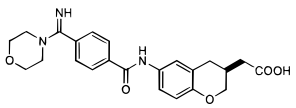
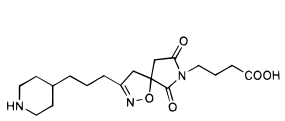


MS-180

c. Centrally Constrained Spirocyclic Antagonists. While the vast majority of investigations into suitable templates for GPIIb-IIIa inhibitors has focused on monocyclic and fused-bicyclic ring systems, spirocyclic templates have received little attention. DuPont-Merck described some initial attempts to utilize the spirocyclic framework as a template and identified the weakly active spiro-isoxazolinylimide **17** (24% inhibition of hPRP/ADP-induced aggregation at 100 μM).[90] They reasoned that the spirocyclic core was restricting the available conformational space of the side chains and that relaxation of the constraints by opening up the imide function would improve the interactions with GPIIb-IIIa. This approach was indeed successful, leading to the isoxazoline class of inhibitors such as roxifiban.[91] However, independent investigations by Eli Lilly and COR Therapeutics identified potent spirocyclic templates such as the spiro-piperidinylhydantoin **18** (IC_{50} = 59 nM, hPRP/ADP-induced aggregation),[131] 3-azaspiro[5.5]undecane **19** (IC_{50} = 44 nM, hPRP/ADP-induced aggregation),[132] and diazaspiro[5.5]undecane **20** (IC_{50} = 21 nM, hPRP/ADP-induced aggregation) nuclei.[133] A new variation on the theme of using the α-sulfonamido-2,3-diaminopropanoic acid unit previously used in many inhibitors (such as UR-12947, DMP 802, L-750,034, XU 065, L-746,223, and L-738,167) was found in the use of an α-sulfonamidoglutaminyl unit, affording potent antagonists such as **18** and **20**.



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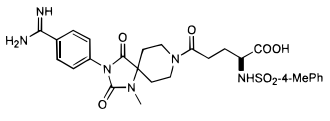

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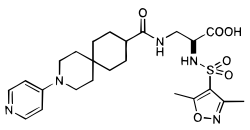

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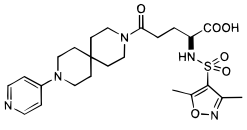

20

4. In Vivo Pharmacology of Oral GPIIb-IIIa Antagonists

With the discovery of potent GPIIb-IIIa antagonists, the relationships among percentage receptor occupancy (defined as the percentage of total surface GPIIb-IIIa blocked by antagonist), platelet aggregation inhibition, and antithrombotic effects could be determined. Many of the GPIIb-IIIa antagonists, which are potent in vitro have also been evaluated in vivo for their pharmacokinetic and pharmacodynamic profiles, and where appropriate, they have also been evaluated for their antithrombotic efficacy to determine what levels of receptor occupancy or platelet aggregation inhibition values are required. This information would be useful in determining appropriate dosing levels in clinical trials with these potent platelet antagonists. Early experiments by Gold and co-workers demonstrated an important principle that antithrombotic efficacy in an acute model of thrombosis could be achieved when >80% receptor occupancy was reached by the monoclonal antibody 7E3.[59] Although these data have been frequently reinterpreted or misinterpreted to be the same or equivalent to >80% platelet aggregation inhibition, the percent receptor occupancy and the degree of platelet aggregation inhibition do not always track to the same percentage. Furthermore, this pharmacodynamic relationship is both platelet agonist- and GPIIb-IIIa antagonist-dependent. Receptor occupancy assays have not been generally developed for the small-molecule GPIIb-IIIa antagonists, due in many cases to the rapid off-rate of these antagonists and the technical difficulties in dealing with this property. Indirect assays measuring LIBS epitope expression induced by antagonist binding and other techniques have been used to measure receptor occupancy ex vivo.

Because of the high receptor density per platelet and large numbers of platelets in the body, there is in fact a considerable concentration of GPIIb-IIIa in the blood compartment (approximately 40−60 nM). For high-affinity antagonists, where the K_d of the antagonist is lower than the concentration of the receptor, at blood concentrations of antagonist below the concentration of receptors, antagonists essentially titrate the receptor and very little unbound drug is found within the blood compartment. For lower-affinity antagonists (K_d > 60 nM), there is a large pool of unbound antagonist at all efficacious concentrations.

One of the more significant recent observations in the field is that GPIIb-IIIa antagonists can be grouped into several distinct classes based on their intrinsic affinity for GPIIb-IIIa that is not readily reflected in platelet

aggregation measurements. For example, L-734,217, while it is relatively potent in platelet aggregation assays (IC_{50} = 32 nM, gel-filtered platelets), it has an equilibrium binding constant (K_D = 600 nM) for the resting form of GPIIb-IIIa or the activated form of the receptor (ED_{50} = 5 nM) which is modest in comparison to an antagonist such as L-738,167 (IC_{50} = 8 nM, gel-filtered platelets/ADP-induced aggregation; K_D = 1.1 nM, resting form of GPIIb-IIIa; ED_{50} = 0.08 nM, active form of GPIIb-IIIa).[75] The in vivo consequences of the relative affinity of compounds are quite dramatic. When administered to dogs as a 30 μg/kg iv bolus, L-734,217 inhibited platelet aggregation >90% within the first 1−15 min but rapidly returned to baseline values by 2 h.[76,116] By contrast, when L-738,167 was administered at a lower dose (10 μg/kg iv), 79% inhibition of platelet aggregation was achieved within 1 min that reached >90% inhibition during the next several hours but *remained* at >90% inhibition at 8 h.[116,117] Similarly, when dosed orally to dogs at 0.20 mg/kg, L-734,217 produced transient inhibition of ex vivo platelet aggregation that returned to normal by 5 h. However, oral administration of L-738,167 at 0.1 mg/kg produced extremely prolonged effects with platelet aggregation inhibited by 87% at 24 h. The measured terminal half-life ($t_{1/2}$) was found to be dose-independent and displayed a mean value of approximately *4 days* in dogs.[118] On the basis of the prolonged pharmacodynamic profile and other pharmacokinetic data, it has been argued that high-affinity antagonists, such as L-738,167, bind tightly to resting unactivated platelets (dissociation $t_{1/2}$ = 28 min),[118] because the rate of elimination is determined by the rate of clearance of the platelet-bound drug. At doses achieving drug levels in the vascular compartment that exceed the platelet binding capacity, excess drug (unbound) is rapidly eliminated. This is reflected in the observation that L-738,167 displays nonlinear pharmacokinetics, with both plasma clearance (*CL*) and volume of distribution at steady-state (V_{ss}) increasing with increased dose.[118] Compounds which appear to share similar prolonged pharmacokinetic and pharmacodynamic properties with L-738,167 are L-734,115, L-739,758, **9**, L-756,568, roxifiban, and DMP 802. On the other hand, the rate of elimination of lower-affinity antagonists with modest affinity for resting platelets such as L-734,217 is determined largely by the rate of clearance of the unbound circulating drug. One of the important clinical implications for the two classes is that compounds of the lower-affinity class intended for oral administration will display larger peak-to-trough ratios unless they are formulated for extended release,[134] whereas with high-affinity antagonists, the peak-to-trough ratio will be significantly less, even with once-a-day oral dosing. The further implications of these pharmaceutical properties of antagonists will be discussed in the following sections.

Any drug that interacts with platelets has the potential ability to induce thrombocytopenia, a side effect that may seriously limit its utility. A platelet-interacting drug could mediate thrombocytopenia either by an immune or a nonimmune mechanism. Antibodies have been elicited by certain GPIIb-IIIa antagonists; in each case the antibodies are directed against GPIIb-IIIa which expresses novel epitopes when antagonists bind to it, such as the reported LIBS antibodies.[42,43] More recently, it has been reported that preexisting drug-dependent antibodies to platelet GPIIb-IIIa can mediate GPIIb-IIIa antagonist-induced thrombocytopenia in chimpanzees and rhesus monkeys. Of interest, when L-738,167 and L-739,758 were used to screen for drug-dependent antibodies in the plasma of 1032 human subjects, the incidence of preexisting antibodies in this relatively large sample size was 0.8% and 1.1%, respectively.[135] Clearly, each antagonist studied in human subjects has the potential to induce thrombocytopenia by this mechanism, and it appears that the incidence is drug-specific. The other potential mechanism that may mediate thrombocytopenia is platelet activation, since it has been recently demonstrated that abciximab, in certain patients where thrombocytopenia occurs, can induce platelet activation in vivo as measured by increases in fibrinogen and PAC-1 binding as well as P-selectin expression.[136] In addition, platelets taken from patients 2 and 4 weeks after the incidence of thrombocytopenia are still sensitive to activation by abciximab, since reinduction of platelet activation in vitro as measured previously when platelets were initially exposed to abciximab was directly correlated in a patient with thrombocytopenia.[136]

Another aspect of the pharmacology of GPIIb-IIIa antagonists is the ability to identify certain antagonists which bind preferentially to activated platelets with considerably lower affinity for resting platelet GPIIb-IIIa. Examples of such antagonists are L-734,217, and MK-852. L-734,217 displays a K_d = 4.5 nM for the activated form of GPIIb-IIIa and a K_d = 650 nM for resting platelet GPIIb-IIIa.[75] In theory, an antagonist such as L-734,217 might have advantages over antagonists with high affinity for resting GPIIb-IIIa. Unfortunately, antagonists with properties similar to L-734,217 and MK-0852 have not proceeded to large-scale clinical trials, and the advantages of antagonists with this property remain speculative.

Table 2. Clinical Status of Oral GPIIb-IIIa Antagonists

compound	phase	sponsor	refs
xemilofiban	discontinued in III	Searle	137, 138, 144
orbofiban	discontinued in III	Searle	138, 145
sibrafiban	discontinued in III	Roche	134, 139, 141
lefradafiban	II	Boehringer Ingelheim	51, 138
roxifiban	II	DuPont	142
lotrafiban	III	SmithKline Beecham	143
ZD-2486	discontinued in II	Zeneca	

5. Clinical Investigations of Oral GPIIb-IIIa Antagonists

Fueled by the clinical success of parenteral GPIIb-IIIa inhibitors, several companies began developing orally bioavailable molecules. Table 2 lists the oral GPIIb-IIIa inhibitors, where their structures and development stage have been disclosed, that have progressed to the clinic.

Searle was the first company to progress oral agents through phase III studies. Phase II studies in angioplasty patients were conducted with their short-acting compound, xemilofiban (ORBIT Trial), where trends in

the reduction of clinical events were not statistically significant.[137] In phase III studies (EXCITE), 7200 patients undergoing PCI received either placebo or 10 or 20 mg of xemilofiban 3 times daily for 2 weeks and 2 times daily for another 2 weeks.[138] Seventy percent of patients received stents, in which case the protocol mandated the use of aspirin and ticlopidine. At 6 months, the primary endpoint, the combined event rate of death, myocardial infarction, and/or urgent revascularization, was similar in all three groups.[138]

In the OPUS/TIMI-16 trial, over 10 000 patients were to receive either placebo or one of two doses of Searle's second oral agent, orbofiban (30 or 50 mg) b.i.d. for the first 30 days, in addition to aspirin. Thereafter, the two drug-treated groups both were to receive 30 mg b.i.d. orbofiban. Enrollment in this trial was stopped prematurely because of a higher 30-day mortality rate in one of the two drug-treated arm. Thirty-day results showed mortality rates of 1.4% in the placebo arm, 2.3% in the low-dose arm, and 1.6% in the high-dose arm. In the long-term followup (median 7 months), both drug-treated groups continued to display a higher mortality rate than the placebo group. Moreover, the rates of major bleeding in patients treated with orbofiban were double that of the placebo group, and the incidence of thrombocytopenia was 0.6% vs 0.1%.[138,145]

A third, large phase III trial of an oral GPIIb-IIIa antagonist, sibrafiban, has been completed recently by Roche (SYMPHONY).[139] In this trial, over 9000 patients were randomized to a high or low dose (3, 4.5, or 6 mg, b.i.d., based on body weight and renal function) of sibrafiban (without aspirin) or to aspirin alone. At 90 days, no statistically significant differences were found in the rate of death, myocardial infarction, and/or severe recurrent ischemia.[138,139] On the basis of the negative findings, a second large sibrafiban trial (second SYMPHONY) was terminated prematurely, after enrolling approximately 6000 patients. The results of the truncated second SYMPHONY trial were also negative.[144]

It is interesting to note that these three large, negative trials studied short-acting GPIIb-IIIa inhibitors with considerable diurnal variation in drug levels and platelet inhibition. Indeed, the pharmacokinetic and pharmacodynamic peak-to-trough ratio may be of utmost importance in this class of drugs, which exhibit a steep dose−response curve and a narrow therapeutic window.[134,141] Exceeding therapeutic concentrations leads to unacceptable bleeding complications, while low levels allow platelet aggregation to go unchecked. A worse scenario is suggested by indications that the latter may potentially lead to platelet activation or a prothrombotic state.[140] To put things in perspective, the longest-acting drug studied thus far, sibrafiban (terminal $t_{1/2} = 11$ h), achieved a drug concentration peak-to-trough ratio of 2.2.[134] The large trials described above offer evidence that intermittent platelet inhibition does not result in a measurable clinical benefit. What has not been tested thus far, however, is the hypothesis that sustained platelet inhibition over prolonged periods of time leads to a reduction in clinical events, as has been conclusively demonstrated acutely with the parenteral agents as well as with other, albeit "weak" antiplatelet agents, aspirin and thienopyridines. Newer, "second-generation" oral compounds, which exhibit higher affinity for the receptor and a longer terminal half-life, should make it possible to obtain long-term, sustained platelet inhibition over prolonged periods of time. Indeed, very encouraging results were recently reported from a 600-patient phase II study (ROCKET) using roxifiban, a molecule with a 20-h terminal half-life and presumably a much lower peak-to-trough ratio. This study demonstrated a robust, dose-dependent reduction in the rate of death, myocardial infarction, and/or recurrent ischemia in patients receiving roxifiban.[142] Upcoming large trials with such "second-generation" compounds will elucidate to what extent achieving continuous and sustained platelet inhibition over the entire 24-h period will translate into a measurable clinical benefit.

6. Future Perspectives

The development of novel GPIIb-IIIa antagonists over the past decade has been an important pioneering milestone in the search for therapeutic agents that target integrin adhesion receptors. The successful development of the parenteral GPIIb-IIIa antagonists has reinforced the central role of platelets in arterial thrombotic disease. These agents are powerful new weapons for reducing ischemic complications when used as an adjunct to PTCA or the management of acute ischemic syndromes and are gaining wide acceptance by the cardiology community.

The ability to identify small-molecule inhibitors of a large protein−protein interaction is a novel aspect of the GPIIb-IIIa antagonist discovery effort but not necessarily a general model for the difficult task of discovering antagonists of large protein−protein interactions. However, lessons learned during this search have been rapidly applied to the discovery of inhibitors of the closely related integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$,[29] vitronectin receptors implicated in cancer,[146] angiogenesis, restenosis,[35] and bone diseases.[147] Many other integrin adhesion receptors such as the leukocyte integrin $\alpha_4\beta_1$, implicated in allergy and inflammation, are also being investigated as therapeutic targets[148] and may afford novel treatment advances soon.

While enormous resources have been applied during the past decade to the discovery of potent parenteral and oral GPIIb-IIIa antagonists, surprisingly, all of these efforts have been conducted in the absence of any insightful structural information. Folding of the N-terminal region of the α-subunit of integrins, which are the ligand-binding domains, into β-propeller structures has been proposed.[149] However, X-ray crystallography will be required to confirm this proposal. Successful antagonist design occurring in this "structure-based" design era without a "structure" may be surprising, but it is simply the consequence of no X-ray crystal structures of GPIIb-IIIa or any integrin protein being solved and reported to date. In the future, the ability to prepare a truncated soluble form of the extracellular domain of GPIIb-IIIa may be achieved allowing for X-ray crystallographic analysis. The assumption that antagonists bind in essentially a similar fashion to GPIIb-IIIa because the pharmacophore elements are retained (acidic and basic functionalities) in all antagonists reported to date may not be valid. Clearly, if crystal structures do become available in the future, a reex-

amination of structurally diverse antagonists may reveal some distinct interactions of certain antagonists that may afford unique pharmacology of clinical interest.

A newer focus of integrin research is the roles these integrins play beyond adhesive protein binding. In particular, integrins have been shown to act as signaling receptors.[1,150] Moreover, it has been demonstrated recently that disruption of GPIIb-IIIa signaling (genetic knock-in) in mice affords a phenotype with unstable hemostatic clot-forming capacity and identifies the integrin cytoplasmic tyrosine motif as a key mediator of integrin signals and a potential new target for novel antithrombotic agents.[151] It may be possible in the future to dissect the discreet components of this signaling and to design antagonists that afford a robust and continuous degree of platelet inhibition that is more amenable to chronic therapy than the oral GPIIb-IIIa antagonist approach. For example, since integrin signaling involves phosphorylation of tyrosines within cytoplasmic domains,[150] the ability to block specific kinases involved in this signaling pathway, using strategies similar to the tyrosine kinase inhibitors being developed for various growth factor receptors, is a logical direction for future antiplatelet agents.[152]

Despite the enormous advances in integrin antagonist development over the past decade, serious challenges remain in the clinical development of oral GPIIb-IIIa antagonists and they are currently at a crossroad. Originally it was hoped that the oral agents would be widely used in unstable angina patients and in patients with post-acute coronary syndromes that are at significant risk for secondary thrombotic events. However, the first-generation oral antagonists have proceeded to phase III clinical trials without success, and there are lingering doubts that any member of this class will be successfully developed. Numerous reasons exist for the failure of these compounds to demonstrate the expected efficacy. For example, all the compounds tested thus far had short half-lives and considerable diurnal variations in drug concentrations (large peak-to-trough concentration ratios). Consequently, the platelet inhibition achieved with these agents was intermittent. In contrast, every antiplatelet agent with proven clinical efficacy affords continuous inhibition of one or more platelet aggregation pathways. This is true for aspirin, the thienopyridines, and the parenteral GPIIb-IIIa inhibitors, the latter being administered by continuous iv infusion. Only since the availability of second-generation GPIIb-IIIa antagonists, with long duration of action, is it possible to test the hypothesis that medium- to long-term continuous inhibition of GPIIb-IIIa is of clinical benefit. Newer antagonists that may be considered second-generation GPIIb-IIIa antagonists are in later stages of clinical testing or clinical studies are just being initiated or are just being planned. The pharmacokinetic properties of several of these agents are sufficiently different ($t_{1/2}$ > 20 h and peak-to-trough ratios < 2.0) from the first generation to generate some optimism that they may show clinical evidence of efficacy.

It must also be noted that the level of GPIIb-IIIa inhibition achieved in past clinical trials with oral agents may have been insufficient. Indeed, the level of receptor occupancy and platelet inhibition is usually targeted to 80% or higher with parenteral inhibitors. The level of inhibition achieved with the short-acting agents tested thus far has been far less. The reason for this is chiefly because of intolerable bleeding events, which have been associated with the peak concentration levels achieved after each dose.[141] Given their low peak-to-trough ratios, long-acting agents are likely to allow higher levels of platelet inhibition over time while minimizing drug level excursions into the toxic range. Last, if a simple point-of-care platelet aggregation monitoring system is found acceptable, individual titration of each patient at the beginning of therapy may allow for even more aggressive platelet inhibition to be achieved safely.[153]

Recently, it has been suggested that GPIIb-IIIa inhibitors may lead to platelet activation and/or lead to the release of inflammatory mediators, at least under certain conditions or at specific drug concentrations, and that certain agents may be implicated more than others.[136,142] As mentioned earlier, the assumption that all compounds bind to GPIIb-IIIa in the same manner may not be correct, and the precise pharmacologic effects may differ among different drugs. The identification of future drug candidates may have to include the determination of a variety of biological markers, including LIBS epitopes, and evidence for proinflammatory and prothrombotic activity.

The efficacy of chronic GPIIb-IIIa inhibition with oral agents may depend on further factors, including the nature or acuteness of the disease, and future studies may also have to take into account the possibility that certain adjunctive therapies, e.g. with aspirin or an antithrombin drug, may be required together with chronic GPIIb-IIIa inhibition. Armed with these considerations, future clinical trials should be able to address these limitations and determine the role, if any, that oral GPIIb-IIIa antagonists will play in the treatment of chronic arterial thrombotic disease.

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