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Integrin αIIbβ3:

From Discovery to Efficacious Therapeutic Target

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Abstract

From the initial description of platelets in 1882, their propensity to aggregate and to contribute to thrombosis was apparent. Indeed, excessive platelet aggregation is associated with myocardial infarction and other thrombotic diseases whereas Glanzmann thrombasthenia, in which platelet aggregation is reduced, is a bleeding syndrome. Over the last half of the 20th century, many investigators have provided insights into the cellular and molecular basis for platelet aggregation. The major membrane protein on platelets, integrin αIIbβ3, mediates this response by rapidly transiting from its resting to an activated state in which it serves as a receptor for ligands that can bridge platelets together. Monoclonal antibodies, natural products, and small peptides were all shown to inhibit αIIbβ3 dependent platelet aggregation, and these inhibitors became the forerunners of antagonists that proceeded through preclinical testing and into large patient trials to treat acute coronary syndromes, particularly in the context of percutaneous coronary interventions. Three such αIIbβ3 antagonists, abciximab, eptifibatide, and tirofiban, received Food and Drug Administration approval. Over the past 15 years, millions of patients have been treated with these αIIbβ3 antagonists and many lives have been saved by their administration. With the side effect of increased bleeding and the development of new antithrombotic drugs, the use of αIIbβ3 antagonists is waning. Nevertheless, they are still widely used for the prevention of periprocedural thrombosis during percutaneous coronary interventions. This review focuses on the biology of αIIbβ3, the development of its antagonists, and some of the triumphs and shortcomings of αIIbβ3 antagonism.

Keywords

acute coronary syndromes; αIIbβ3 antagonists; integrin; percutaneous coronary intervention

Every year, since 1900, cardiovascular disease (CVD) has accounted for more deaths in the United States than any other disease. According to 2012 American Heart Association statistics, CVD claims more lives each year than cancer, chronic lung/respiratory disease, and accidents combined.[1] Despite these grim statistics, dramatic progress has been made in the treatment of CVD, as evidenced by a 30.6% decline in death rates attributable to CVD between 1998 to 2008.[1] Many factors contributed to this reduction, including improved diagnostic and interventional procedures, healthier lifestyles, and the emergence of new

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drugs. With the well-established evidence for the central role of platelet aggregation in thrombus formation, the inhibition of this response has long been recognized an attractive target for drugs to reduce morbidity and mortality arising from acute coronary syndromes (ACSs) and other CVDs. Throughout the late 1970s/early1980s, an understanding of the molecular basis of the platelet aggregation emerged and focused attention on the pivotal role on a single receptor, αIIbβ3, on the platelet surface in orchestrating the aggregation response, and further suggested that this receptor represented a rationale target for antithrombotic therapy. Throughout the late 1980s/1990s, most major bio-pharmaceutical companies and many fledgling biotechnology start-ups had aggressive programs in place to develop αIIbβ3 antagonists. In fact, these programs were successful. Many αIIbβ3 antagonists were identified, and 3 such drugs—abciximab, eptifibatide, and tirofiban—ultimately received Food and Drug Administration (FDA) approval. These drugs have been used extensively; it is estimated that at least 8 000 000 people have been treated with αIIbβ3 antagonists.[2] Importantly, the rational targeting of αIIbβ3 and the clinical efficacy of αIIbβ3 antagonists established the central role of platelets in periprocedural thrombosis in the context of percutaneous coronary interventions (PCI).

Although the use of αIIbβ3 antagonists has waned since their peak years in the mid-2000s, the inhibition of the platelet aggregation response still remains a centerpiece in the treatment of ACS patients, and the development of newer antithrombotic strategies has very much benefited from the knowledge and experience gained in the development of αIIbβ3 antagonists. Furthermore, following the lead that αIIbβ3, an integrin, could be antagonized, researchers now consider at least 4 other integrin family members (α4β1, α4β7, αvβ3, αLβ2) as drug targets.[3–6] Thus, the development of αIIbβ3 antagonists demonstrates how biomedical research can be harnessed for rational drug design and translated into clinical success. Here, we provide a brief summary of the story behind their development.

αIIbβ3: Historical, Functional, and Structural Perspectives

A time line depicting some of the key events in the development of αIIbβ3 agonists is depicted in Figure 1. The discovery of platelets is usually credited to the Italian physician Giulio Bizzozero. In his 1882 article, Bizzozero described platelets as a new element in the blood. Furthermore, he noted that platelets could aggregate, and suggested that this propensity might contribute to thrombosis.[7] Almost 40 years later, the Swiss physician Eduard Glanzmann described a group of patients in whom abnormal platelet aggregation was associated with a bleeding tendency.[8] Over the next half century, great strides were made in characterizing the composition of cell membranes, and these analyses were greatly accelerated by the application of gel electrophoresis technologies to separate the membrane proteins of various cell types. When applied to platelet membranes, a number of protein bands differing in their mobility were discerned.[9,10] After establishing the patterns of the platelet membrane proteins from healthy individuals, Phillips et al[11] showed that 2 glycoprotein bands, glycoprotein IIb (αIIb) and glycoprotein IIIa (β3), were missing from the surface of platelets from patients with Glanzmann thrombasthenia. Subsequent biochemical studies showed that these 2 polypeptides were the noncovalently associated subunits of a single membrane protein, glycoprotein IIb–IIIa (integrin αIIbβ3).[12,13]

When αIIbβ3 is activated, it serves as a receptor for ligands that can bridge to other αIIbβ3 on adjacent platelets.[14,15] Ligands of αIIbβ3 that can mediate this cross-bridging function are fibrinogen and von Willebrand factor,[16,17] whereas other ligands of αIIbβ3, such as fibronectin, vitronectin, thrombospondin, and CD40 ligand, can modulate platelet aggregation.[18–20] As the molecular details establishing the essential role of αIIbβ3 in platelet aggregation emerged, it became clear that inhibition of its ligand binding function would inhibit platelet aggregation and thereby limit thrombus formation. This rationale

became the foundation of the new antithrombotic strategy, αIIbβ3 antagonism. The feasibility of αIIbβ3 antagonism was illustrated with antibodies and peptides that bound to αIIbβ3[21–23]; and these became the forerunners of αIIbβ3 antagonists that were ultimately used to treat patients.

Another aspect of αIIbβ3 biology that is relevant to its antagonism is its familial relationships. As noted above, αIIbβ3 is an integrin, a large family of structurally related and broadly distributed membrane proteins.[24] All integrins are noncovalent heterodimers composed of an α and a β subunit. In mammals, there are 18 α subunits and 8 β subunits, which interact to form the 24 different integrins.[25] Each α and β subunit consists of a large extracellular segment, which is composed of a series of structural domains that are conserved throughout the integrin family (Figure 2A).[26] Each subunit has a single pass transmembrane domain and, with a single exception, a short cytoplasmic tail (see Figure 2A). By virtue of their abilities to bind to ligands of the extracellular matrix on the surface of other cells, via their extracellular regions, and to link to the cytoskeletal matrix within cells via their cytoplasmic tails, integrins serve as a conduit for flow of information between the interior of the cell and its exterior environment. This communication is bidirectional and is used to control a variety of cellular responses ranging from cell adhesion and migration to gene expression and proliferation.[27]

αIIbβ3 is one of the 2 members of the β3 subfamily of integrins. The 2 members, αIIbβ3 and αVβ3,[24,28,29] share the same β3 subunit and their α subunits exhibit 36% amino acid sequence identity. Integrin αIIbβ3 is found on the surface of platelets, megakaryocytes, basophils, mast cells, and some tumor cells.[30] Integrin αVβ3 is expressed on many cell types, where it influences diverse physiological responses, such as cell adhesion, migration, and bone resorption, and pathological responses, such as angiogenesis, restenosis, tumor cell invasion, and atherosclerosis.[29,31,32] These 2 integrins share several macromolecular ligands, including fibrinogen, fibronectin, thrombospondin, von Willebrand factor, and vitronectin.[18,33,34] Common to these ligands is the presence of ≥1 arginine-glycine-aspartic acid sequence (RGD) sequences. RGD containing peptides bind to both β3 integrins, as well as several other integrins, and can inhibit the binding of the aforementioned ligands to αIIbβ3 and platelet aggregation.[35,36] RGD peptides were used as a starting point in the design of several αIIbβ3 antagonists, including the FDA-approved drug, tirofiban.[37] However, sequences other than RGD also bind to αIIbβ3. Particularly notable in this regard is the sequence at the C-terminus of one of the fibrinogen-constituent chains, the -chain, which is integrally involved in fibrinogen binding to αIIbβ3 and platelet aggregation.[23] Glanzmann thrombasthenia can arise from mutations in either the αIIb or β3 genes, and mutations in either gene can lead to deficits in cell surface expression and function of αIIbβ3 and to episodic bleeding arising from a failure of platelets to aggregate.[38,39] Mutations in β3 can also prevent expression of αVβ3. The symptoms of patients with mutations in the β3 subunit do not differ consistently from those of patients with αIIb mutations.[40,41] This information is relevant to αIIbβ3 antagonism because some of the antagonists cross-react with αVβ3, whereas others show specificity exclusively for αIIbβ3. However, the absence of distinguishing symptoms in subjects lacking only αIIbβ3 compared with those lacking both β3 integrins does not imply a lack of biological function for αVβ3, and may just reflect the limited number of patients analyzed for other symptoms. For αIIbβ3 to bind its high–molecular weight ligands, it must undergo activation, a transition from a low- to high-affinity state (Figure 2B). On circulating platelets in blood, αIIbβ3 exists in its resting, low-affinity conformation. Stimulation of platelets with a variety of agonists, including ADP, thrombin, collagen, and epinephrine, triggers the transformation of αIIbβ3 to its higher affinity state.[15,42] This transition is very rapid and depends on a series of intracellular signaling events from the agonist receptors that culminate in the binding of the cytoskeletal proteins, talin, and kindlin-3, to the cytoplasmic tail of the β3

subunit.[15,27] Conformational changes initiated by interaction with these binding partners, are transmitted across the transmembrane domain to change the conformation of the ligand binding site in the extracellular domain. It is now broadly accepted that a central event in the activation process is a shift in the equilibrium from the bent conformation that predominates in the resting state to an extended conformation where ligands can more readily bind to the activated state (Figure 2B).[43–45] Within the headpiece formed as a complex of the amino terminal domains of the α and β subunits, there are movements of helices and loops and a swing out of the hybrid domain in the vicinity of the ligand binding site, which provide greater access of ligands.[30] Ligand binding to αIIbβ3 not only enables platelet–platelet interaction but also transmits an array of signals from the occupied and clustered receptor into the platelet (outside-in signaling), which are important for normal platelet responses, such as the stability and retraction of clots.[46,47] Conflicting results have been reported as to whether αIIbβ3 receptor antagonists can also induce outside-in signaling and whether such signaling would be detrimental.[48–50]

The global structure of αIIbβ3 and the basis of the inside-out and outside-in signaling processes that lead to activation of αIIbβ3 and other integrins have been the subject of extensive investigations and reviews.[14,15,43] Seminal insights were provided by the publication in 2001 of the crystal structure of much of the extracellular domain of αVβ3 by Xiong et al,[51] and this was followed a year later by the structure of αVβ3 with a bound RGD peptide.[52] This latter structure revealed how a ligand peptide nestles into a groove in the headpiece formed between the α and β subunits, with the Asp of the RGD peptide providing a coordination site to a divalent cation bound in the metal ion–dependent adhesion site of the receptor.[52] Since then, several crystal structures of αIIbβ3 with or without various agonists and antagonists bound to the receptor have been reported.[53,54] These crystal structures reveal that small-molecule antagonists bind to a pocket on top of the inte-grin head formed by the β3 A domain and loops from the αIIb β-propeller.[53] The extent to which these antagonists interact with the αIIb β-propeller determines their relative specificity for αIIbβ3 versus αVβ3. With additional structural determinations of the transmembrane[55,56] and cytoplasmic domains,[57–60] a complete picture of the entire αIIbβ3 can be cobbled together. Although these structures became available some time after the design and clinical development of approved αIIbβ3 antagonists, we now have much better insights into their mechanisms of action and have information that can and has been used in the design of new αIIbβ3 antagonists with distinct modes of action.[61] A next key advance in the understanding of the structure and function of αIIbβ3 is likely to come from approaches that allow for high-resolution visualization of the entire molecule as a single, intact entity in resting, active, and ligand-occupied conformers.

Great excitement was raised in 1996 when it was first suggested that a particular single-nucleotide polymorphism in αIIbβ3 was associated with acute myocardial infarction.[62] The single-nucleotide polymorphism, referred to as platelet allo-antigen 1, 2 (PL^{A1}/PL^{A2}), leads to a single amino acid substitution at position 33, Leu in PL^{A1}, or Pro in PL^{A2}.[63] This finding was replicated in several other studies. The PL^{A1}/PL^{A2} polymorphism was reported to influence platelet activation, aggregation, and postoccupancy signaling by αIIbβ3.[63,64] However, functional differences between the polymorphic forms of β3 were not supported in other studies.[65] Furthermore, the first meta-analysis of several separate studies that combined data from 10 638 individuals concluded that the PL^{A2} was not an inherited risk factor for ACS.[66] In 2 subsequent meta-analyses, Burr suggested[67] the PL^{A2} variant was only weakly associated with ACS and restenosis whereas Le et al[68] suggested that the $PL^{A1/A2}$ polymorphism is not a major pathophysiological factor in patients who underwent coronary artery stenting. Indeed, 1 recent study even suggested that it was the PL^{A1} genotype that is disease associated.[69] This polymorphism deserves mention because it was suggested that platelets of 1 genotype may be more sensitive to certain αIIbβ3 antagonists

than the other.[70] In vitro, blockade of aggregation by abciximab was reduced in platelets of the PL^{A2} genotype.[71] Overall, the influence of the $PL^{A1/A2}$ polymorphism on platelet aggregation seems to be modest as is its impact on the response to αIIbβ3 antagonists.

αIIbβ3 Antagonists

At one time >1 dozen αIIbβ3 antagonists were in development, either for intravenous and oral administration, and ultimately 3 received FDA approval for specific indications. These 3, abciximab (ReoPro), tirofiban (Aggrastat), and ep-tifibatide (Integrilin) are quite distinct in design from one another (Table), and all 3 are mechanistically distinct from other platelet inhibitors such as aspirin or P2Y12 inhibitors. Each of the 3 αIIbβ3 antagonists is discussed below. We do not intend to systematically summarize all the numerous clinical trials that supported the development of the 3 αIIbβ3 antagonists as there have been numerous comprehensive reviews of this topic.[72–76] Rather, we touch on some of the key trials and highlights surrounding the development of the αIIbβ3 antagonists.

Abciximab (ReoPro)

In the early 1980s, several monoclonal antibodies directed against αIIbβ3 were developed, and some inhibited binding of fibrinogen to platelets and platelet aggregation.[21,77] One of these, monoclonal antibody 7E3, proceeded into clinical development.[78] This monoclonal antibody was described as inducing a thrombasthenic-like state to platelets,[21,79] which was regarded as a favorable property because bleeding is episodic in Glanzmann's patients and is medically manageable. To limit Fc-mediated platelet clearance and reduce immunogenicity, the antibody was engineered to create a mouse/human chimeric antibody fragment, c7E3 Fab, which was dubbed abcix-imab.[80] The epitope of abciximab in αIIbβ3 was mapped and shown to be dependent on a nonlinear amino acid sequence that resides near the cation binding metal ion–dependent adhesion-site motif in the β3 subunit.[81] After displaying great potency in inhibiting platelet aggregation in ex vivo testing and showing remarkable efficacy in canine[82] and subhuman primate models,[83] the first clinical trial, EPIC, was launched in 1991 in patients at high risk of developing ischemic complications after PCI. Abciximab reduced the risk of the primary end points, death, myocardial infarction, repeat angioplasty, or bypass surgery, at 30 days by 35%: from 12% to 8% in the placebo group to 8% to 3% in patients treated with abciximab. However, bleeding was increased significantly.[84] The EPILOG trial followed and sought to establish more effective administration regimen to maintain efficacy but reduce bleeding complications by weight adjusting the heparin anticoagulant dose. On the basis of these trials, abciximab, under the trade name ReoPro, won FDA approval in 1994 for use in the setting of PCI. Hence, abciximab became the first in class, and the clinical use of αIIbβ3 antagonists became a reality.

The GUSTO IV trial was launched with the anticipation that ReoPro would also be efficacious in high-risk ACS patients under medical management, but the results did not provide evidence of benefit.[85] With abciximab, as well as with the other αIIbβ3 antagonists, optimal dosing was always challenging; the window between the therapeutically efficacious doses to achieve extensive blunting of platelet aggregation and higher doses that can lead to bleeding was narrow.[48] Confounding the problem was the variability in this window among patients and the lack of assays to reliably monitor efficacy. It should be stressed that this problem was not unique to abciximab but confronted development of the entire class of αIIbβ3 antagonists. Recent studies reveal that these agents may have additional effects on platelet aggregates that have already formed, causing them to disengage and disperse, and such effects are more pronounced at doses of the αIIbβ3 antagonists higher than the conventional doses administered intravenously.[86] Hence, the on-label use of ReoPro remains

restricted to the setting of PCI. Nevertheless, millions of patients worldwide have been treated with ReoPro; and, based on the benefits seen in the PCI patients in clinical trials, many lives have been saved by this αIIbβ3 antagonist.

Of particular note is that patients treated with ReoPro showed a long-term and quite remarkable mortality benefit, even >5 years after initial treatment. Follow-ups at 7 years (EPIC), 4.5 years (EPILOG), or 3 years (EPISTENT)[87] have shown that abciximab treatment reduced all-cause mortality by ≈20% during long-term follow-up after PCI. The ADMIRAL trial also reported favorable outcomes for abcix-imab treatment in stented patients from 30 days up to 3 years of follow-up.[88] Not all trials detected the long-term benefit of abciximab; the ISAR-2 trial did not see a sustained clinical benefit at 5 years after the use of abciximab during coronary artery stenting in patients with acute myocardial infarction.[89] One suggested explanation for the often-replicated long-term benefit of abciximab is its cross-reactivity with integ-rins other than αIIbβ3; abciximab also reacts with αVβ3 and αMβ2 (Mac-1, CD11b/CD18), a member of the β2 integrin subfamily of leukocyte integrins.[90] This cross-reactivity contrasts with other αIIbβ3 antagonists, and may responsible for unique anti-inflammatory properties attributed to abciximab.[91] Early data suggested that abciximab may reduce restenosis in patients undergoing PCI,[92] especially in patients with diabetes mellitus, which was attributed to anti-inflammatory effects of the drug.[93] Subsequent studies failed to substantiate the beneficial effect of abciximab in restenosis.[94] Although the cross-reactivity of abciximab with other integrins distinguishes it from the other 2 FDA-approved αIIbβ3 antagonists, there is no clear evidence that such cross-reactivity was either benefi-cial or detrimental. Another unique feature of abciximab is its extended association with platelets. Whereas the free drug is rapidly eliminated from the circulation by the reticulo-endo-thelial system, abciximab circulates, bound to platelets for an extended time, and may dissociate and then reassociate with new target platelets for as long as 21 days after cessation of the drug.[95]

Eptifibatide (Integrilin)

Eptifibatide is a cyclic heptapeptide of <1 kDa. The starting point for its design was barbourin, a 73–amino acid disinteg-rin isolated from snake venom that was shown to have potent antiaggregating activity. Although several such snake venom proteins were isolated and characterized, most contained an RGD sequence, but the antiaggregating activity of barbourin was reliant on a lysine-glycine-aspartic acid sequence.[96] This sequence provided a template for the development of synthetic peptide antagonists that contain a lysine-glycine-aspartic acid sequence.[97] Potency was greatly enhanced by cyclizing the peptide via a disulfide bond (Table). The ultimate product, ep-tifibatide, is a highly potent inhibitor of fibrinogen binding to platelets and was reported to be specific for αIIbβ3[97] although there are some data to the contrary.[98] For a peptide, eptifibatide has a relatively long half-life in plasma; its biological half-life is ≈2.5 hours.[92,95,99] Eptifibatide is eliminated by the kidneys. Trials testing the safety and efficacy of eptifibatide were conducted in the mid-1990s in different clinical settings.[100–103] Together, these trials showed that eptifibatide rapidly inhibited platelet aggregation attaining a maximum effect within 15 minutes after its bolus injection. A bolus injection followed by infusion inhibits platelet aggregation by 75% to 80%. Such potent inhibition is maintained during the infusion period, and platelet function recovers 2 to 4 hours after cessation of drug. Over multiple trials, eptifibatide showed only a slight tendency to prolong bleeding times with normalization within 30 minutes after infusion. Eptifibatide initial clinical trials were directed toward patients with ACS. Efficacy in the initial trial IMPACT II, of 4010 patients, was disappointing[104] but in subsequent trials, PURSUIT (10 948 patients) and ESPRIT (2064 patients), using higher doses of eptifibatide, mortality was reduced by 25% to 35% in the eptifibatide-treated group compared with the placebo groups and only a modest increase in bleeding was

observed.[105–109] FDA approval was gained for eptifibatide in 1998 for treatment of ACS patients, including patients who were being managed medically and those undergoing PCI. Subsequent trials, such as PRIDE continued to optimize the dose of eptifibatide.[110] Eptifibatide still remains the most widely used of the 3 FDA-approved αIIbβ3 antagonists (Table).

Tirofiban (Aggrastat)

Tirofiban is a low–molecular weight (<1 kDa) αIIbβ3 inhibitor. The starting point for its design was an RGD peptide. Peptide bonds were ultimately eliminated from the structure to create a potent and specific nonpeptide αIIbβ3 antagonist (Table). The small-molecule antithrombotic, originally designated MK-0383, was very effective in inhibiting αIIbβ3 function in animal models,[111] and led to the development of tirofiban for clinical usage.[112] Tirofiban has a plasma half-life (1.5–2 hours) and a shorter biological half-life (seconds), which reflect its reversible and relatively low-affinity binding to αIIbβ3. After stopping administration of tirofiban, platelet aggregation recovers to 50% of the baseline value within 4 hours. Tirofiban is removed by both renal and biliary excretion.[113] Patients with renal insufficiency require dose adjustment of tirofiban. Tirofiban does not interact with αVβ3 or αMβ2.[92,95,98]

The clinical trials that led to FDA approval of tirofiban in 1998 for treatment of patients with ACS (unstable angina/ non–Q-wave myocardial infarction) were RESTORE (2139 patients), PRISM (3232 patients), PRISM-PLUS (1915 patients), which differed in their drug regimen. The 30-day reduction in mortality in these trials was 16% relative reduction (P=0.160) in RESTORE and 36% (2.3 versus 3.6%; P=0.02) in PRISM and 27% (8.7 versus 11.9%; P=0.027) in PRISM-PLUS. In the PRISM trial there was no difference in bleeding times between the tirofiban and placebo groups, and bleeding increased only modestly in the PRISM-PLUS (1.4 versus 0.8%; P=0.23) tirofiban+heparin versus heparin-alone groups and in RESTORE (5.3% versus 3.7%; P=0.096) tirofiban versus placebo groups.[114,115] Initial comparative studies showed abciximab and eptifibatide were more effective than the standard dose of tirofiban used in inhibiting platelet aggregation,[116] and abciximab to be more effective than the standard dose of tirofiban in preventing ischemic events in the TARGET trial.[117] However, in a subsequent PCI trial, ADVANCE, tirofiban was given at a higher dose and was not inferior to abciximab[118,119] although the FATA trial failed to show equivalence of higher-dose tirofiban to abciximab as adjunctive therapy during primary PCI for ST-segment elevation myocardial infarction.[120]

Current Usage of αIIbβ3 Antagonists

For more than a decade after FDA approval of the first αIIbβ3 antagonist in 1994, the class of drugs was used broadly in the treatment of ACS patients. According to data in the clinicaltrials.gov 84, large-scale clinical trials involving >90 000 patients and controls were conducted to test the efficacy and safety of the αIIbβ3 antagonists in various settings. In comparison to the widespread use of αIIbβ3 antagonists that characterized their use in the decade after their initial approval, their use has waned in recent years. By current American College of Cardiology/ American Heart Association guidelines, αIIbβ3 antagonists are given a class IIa recommendation; that is, conflicting evidence and a divergent opinion exist as to their usefulness/efficacy, but the weight of evidence/opinion is favorable.[121] An American College of Cardiology/American Heart Association class I recommendation for αIIbβ3 antagonists has been given for their use in unstable angina/non Stelevation myocardial infarction patients undergoing PCI, who cannot tolerate clopi-dogrel (the widely used and inexpensive oral P2Y12 antagonist).[121] According to data in the EvaluatePharma 2013 report (www.evaluatepharma.com), the sales peak of abciximab was in 1999, integrilin

in 2007, and tirofiban in 2000 (Table). Compared with abciximab and eptifibatide, the sales of tirofiban dropped dramatically in the United States between 2003 and 2007, declining to ≈$2 million in the United States in 2007 but remaining considerably stronger, ≈$87 million, in Europe in the same year. Although the overall sales for the class, ≈$365 million worldwide in 2012 (Table) are still impressive, they pale when compared with clopidogrel (Plavix), the P2Y12 antagonist, which had sales of >$9 billion in 2011 and estimated sales of >$5 billion in 2012. This growing preference in part reflects the greater efficacy of clopidogrel compared with αIIbβ3 inhibitors in the PCI-CURE, CREDO, PCI-CLARITY, and ISAR-REACT trials,[122,123] and the cost of the drugs per se; abciximab treatment cost per day is ≈$1000, 3 to 4 times higher than that of eptifibatide and tirofiban, and 200 times higher than that of clopidogrel (≈$5 per day).

At this juncture, use of αIIbβ3 antagonists has become limited primarily to the setting of PCI, particularly in high-risk patients or in patients not adequately pretreated with P2Y12 antagonists. Clopidogrel and the newer P2Y12 inhibitors and anticoagulants all compete in a similar space.[124] However, PCI is not a narrow setting; it is the most commonly performed revascularization procedure worldwide for the treatment of coronary artery disease.[125] Although the benefits of αIIbβ3 antagonists have not always been consistent across all clinical trials, they remain a potent therapeutic adjunct in high-risk and unstable patients undergoing PCI. Bosch et al[126] analyzed the results of 36 randomized control trials of these agents in 30 696 patients undergoing PCI. The rate of death or myo-cardial infarction at 30 days and 6 months was 5.10% versus 7.52% and 7.51% versus 10.45% in the treatment versus the control groups, respectively. In one of the most recent assessments of the effects of αIIbβ3 blockers, Winchester et al[75] analyzed the results of 22 randomized studies with 10 123 patients undergoing PCI with stenting, who were treated routinely with ADP receptor antagonists (thienopyridines). This analysis showed that at 30 days, patients receiving αIIbβ3 antagonists had a significant reduction in myocardial infarction, 5.1% versus 8.3% in the control group without a significant increase in major bleeds, 1.2% versus 0.9%. Minor bleeding was increased 3.0% versus 1.7%. However, overall mortality was not reduced.[75] Ongoing trials using αIIbβ3 inhibitors are focused primarily on reduction of side effects (eg, reduction of bleeding, dosage optimization for patients with renal dysfunction, alternative ways of infusion, treatment of severe sepsis in pneumonia patients).

Side Effects of αIIbβ3 Inhibitors

During the early days of testing in animal models, it was suggested that particular αIIbβ3 antagonists could block platelet aggregation without prolonging bleeding times. In retrospect, such claims seem unrealistic; extensive inhibition of platelet aggregation will be associated with increased risk of bleeding. Indeed, bleeding is the major complication associated with αIIbβ3 antagonism, and is more frequent with αIIbβ3 antagonists than with other platelet inhibitors. In retrospective analyses, in the most severe forms, intracranial bleeds occurred in 2% of patients treated with αIIbβ3 antagonists and gastrointestinal bleeds in 15% of patients.[72] Groin hematoma at sites of catheter insertion accounted for 60% to 80% of the major bleeding events and retroperitoneal bleeds for 5% to 10% of major bleeding events. In the initial clinical trials of αIIbβ3 antagonists, bleeding severity was evaluated based on the need for blood transfusions but was later replaced by physician assessment. The greater experience in dealing with αIIbβ3 antagonists may have tempered such assessments of bleeding.

After bleeding, thrombocytopenia and severe reactions to readministration are the most serious side effects of αIIbβ3 antagonists. Thrombocytopenia may occur after use of all 3 αIIbβ3 antagonists, abciximab, tirofiban, and eptifibatide. On the basis of an analysis of clinical trials (EPIC, EPILOG, CAPTURE, RESTORE, IMPACT II) by Tcheng,[127] mild

thrombocytopenia (<100 000 platelets/mm^3) occurred in 2% to 5% of patients and moderate thrombocytopenia (<50 000 platelets/mm^3) in 2% of patients receiving abciximab and in <1% of patients treated with eptifibatide and tirofiban.[127,128] Severe thrombocytopenia (<20 000 platelets/mm^3) occurred rarely in patients treated with eptifibatide or tirofiban and in 0.7% of patients receiving abciximab. The thrombocytopenia is believed to be antibody mediated.[129] Low levels of antibodies appear among 6% to 7% of patients receiving abciximab. The greatest concentration of such antibodies occurred between 1 week to 1 month after cessation of the αIIbβ3 antagonist and then gradually declined.[127] Readministration of abciximab did not cause an increased risk of anaphylaxis, but 2.4% of patients did develop a severe thrombocytopenia.[128,130] No data are available on the safety of tirofiban readministration, but high antibody titers have been found in some patients who developed thrombocytopenia after tirofiban treatment.[131] It is believed that tirofiban binding induces a conformational change in αIIbβ3, and antibodies arise against the newly exposed epitopes in αIIbβ3.[132,133] Antibodies may also mediate throm-bocytopenia associated with eptifibatide treatment. The rate of naturally occurring eptifibatide-dependent antibodies seems to be lower than seen with abciximab.[131] Readministration of αIIbβ3 antagonists is not recommended after an episode of thrombocytopenia.[128]

Failure of Oral Inhibitors

Orally active αIIbβ3 antagonists were developed with the hope that they would provide long-term suppression of platelet aggregation and thereby secondary prevention of CVD. Four orally active αIIbβ3 antagonists reached the stage of testing in 5 major phase III trials,[134] and several other orally active αIIbβ3 antagonists with encouraging preclinical profiles were in pharmaceutical pipelines. However, to the surprise and disappointment of many, none of the 5 large trials showed a beneficial effect of the oral αIIbβ3 antagonists; and, in fact, 4 of the trials were terminated prematurely because of adverse effects. A combined analysis confirmed this lack of efficacy and revealed a disturbing and highly significant (35% relative, or 0.7% absolute) increase in the risk of death in the combined 45 523 patients within these trials.[135] These disappointing results halted further investigations into the use of these oral agents, and oral αIIbβ3 inhibition is regarded as a failed strategy.

The basis for lack of efficacy and increased mortality of the oral αIIbβ3 antagonists remains a topic of speculation with no definitive answers. It has been suggested that some of the drugs fell out of the therapeutic range between administrations, leaving patients at jeopardy between doses.[134] Another popular hypothesis was that dissociation of drug from αIIbβ3 left the receptor in an activated and therefore prothrombotic state. This proposition was predicated on the long-standing observation that removal of bound RGD ligand from αIIbβ3 led to a brief activation of the receptor.[134–136] Although some data supported this hypothesis,[137] others did not.[138] Some have even challenged the founding assertion that long-term suppression of αIIbβ3 would be beneficial. Although side effects (eg, bleeding and thrombocytopenia) associated with αIIbβ3 antagonists were manageable in the acute setting of PCI, with chronic administration, these effects may have become a life-threatening problem. Thrombocytopenia can increase the risk for bleeding and, in rare instances, may enhance blood clotting. In some studies, oral αIIbβ3 inhibitors facilitated, rather than inhibited thrombus formation; and, paradoxically, such effects were potentiated by concomitant administration of aspirin.[139] Also, with chronic administration, nuisance bleeding may have impacted compliance with the drug regimen, and subjects may become vulnerable if they fell out of the therapeutic window of efficacy. Despite these conjectures, the explanation of the failure of oral αIIbβ3 remains equivocal.

Future Strategies Targeting αIIbβ3

As established by extensive clinical trials and usage, the clinical scenarios in which the current αIIbβ3 antagonists provide efficacy is more limited than originally hoped. Nevertheless, the essential role of αIIbβ3 in platelet aggregation and thrombus formation remains indisputable. Given the premise that targeting αIIbβ3 remains a fundamentally sound strategy, some investigators have sought to identify new αIIbβ3 antagonists, ones that might not induce conformational changes on association or dissociation from αIIbβ3 and might therefore contribute less to the bleeding and thrombocytopenia that occurs in some patients. Two possible approaches have been suggested to achieve this end: finding inhibitors that, like current antagonists, bind to the extracellular domain of the integrin but do so without promoting receptor activation[140] or finding inhibitors that prevent receptor activation by binding to the intracellular domain of αIIbβ3.[141] Both strategies are in early stages of development. Blue et al[142] performed a high-throughput screen of >30 000 compounds and identified a novel low–molecular weight compound, RUC-1. RUC-1 selectively inhibited ligand binding to αIIbβ3 compared with αVβ3.[143,144] A second congener RUC-2, was ≈100-fold more potent than RUC-1[61] and did not seem to induce major conformational changes in the protein β3 subunit or prime the receptor to bind ligand.[140] RUC-2 is currently undergoing additional preclinical studies that will assess its suitability for use in patients with STEMI in the early prehospital setting.[2]

The precedent for intracellular approaches to inhibit αIIbβ3 came from studies in which membrane permeable derivatives of peptides corresponding to portions of the cytoplasmic tails of αIIb and β3 were shown to inhibit activation of the receptor.[145] Koloka et al[141] evaluated the role of the acidic extreme C-terminal region of the αIIb cytoplasmic tail, residues 1000 to 1008, and showed that a palmitoylated form of the peptide inhibited platelet activation. Supporting the notion that targeting αIIbβ3 activation from the inside would be advantageous, Petrich et al[146] showed that a mutation in the cytoplasmic tail of the β3 subunit in mice, which prevented talin binding to the receptor and thereby platelet activation, inhibited thrombus formation with limited bleeding. Although such αIIbβ3 antagonists might have distinct advantages over current αIIbβ3 antagonists, the road to clinical development would be formable with potentially insurmountable obstacles, including the staggering expense of clinical trials with relatively small windows for improved efficacy over currently available antiplatelet agents.

Conclusions

The development and deployment of αIIbβ3 antagonists represent a success story: the estimates of >8 million patients who were treated with αIIbβ3 between 1999 and 2011 clearly point to how many lives have been saved with these drugs.[2] On the basis of the report from the CathPCI registry of the National Cardiovascular Data Registry,[147] integrin αIIbβ3 inhibitors were used overall in 28.7% of PCIs and slightly more frequently, 34.0%, among patients with an ACS. This report includes 1 110 150 patients undergoing only diagnostic cardiac catheterization and 941 248 undergoing PCI from January 1, 2010 until June 30, 2011. Thus, the development and deployment of αIIbβ3 antagonists does represent a success story. Nevertheless, it is also clear that the use of αIIbβ3 antagonists has declined in recent years as alternative antiplatelet and anticoagulant strategies have emerged, and αIIbβ3 antagonists have become confined to quite narrow settings. Nonetheless, newer approaches to antagonize αIIbβ3 may lead to superior drugs in this class. With the increase in radial-access PCI versus femoral-access PCI,[148] or by introducing new atraumatic delivery methodologies bleeding has become less problematic and might allow return to the use of more potent antithrombotic strategies, such as αIIbβ3 antagonists. A recent clinical trial has suggested some benefit to direct intracoronary infusion of abciximab compared

with systemic infusion in patients with a large anterior STEMI.[149] Thus, novel routes of administration may open up particular subsets of patients to treatment with αIIbβ3 antagonists. Despite the dramatic reductions in deaths from coronary artery disease over the past few years, a coronary event still occurs once every 25 seconds, and there is a death from such events every 39 seconds in the United States.[1] Antagonism of αIIbβ3 function on platelets, either directly or indirectly, remains a theoretically sound and practically proven approach to treat CVD in specific settings. Thus, the book on αIIbβ3 antagonism should be viewed as a success story, however, a book with chapters still to be written.

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CVD	cardiovascular disease
FDA	Food and Drug Administration
PCI	percutaneous coronary interventions
PL^{A1}/PL^{A2}	platelet alloantigen 1, 2
RGD	arginine-glycine-aspartic acid sequence

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Translational Success Stories

highlight how basic discoveries have led to clinical advances (such as the use of new drugs or diagnostic modalities in patients). This initiative reflects the renewed emphasis of our journal on translational research. It is hoped that these articles will stimulate efforts to translate basic insights into clinical practice.

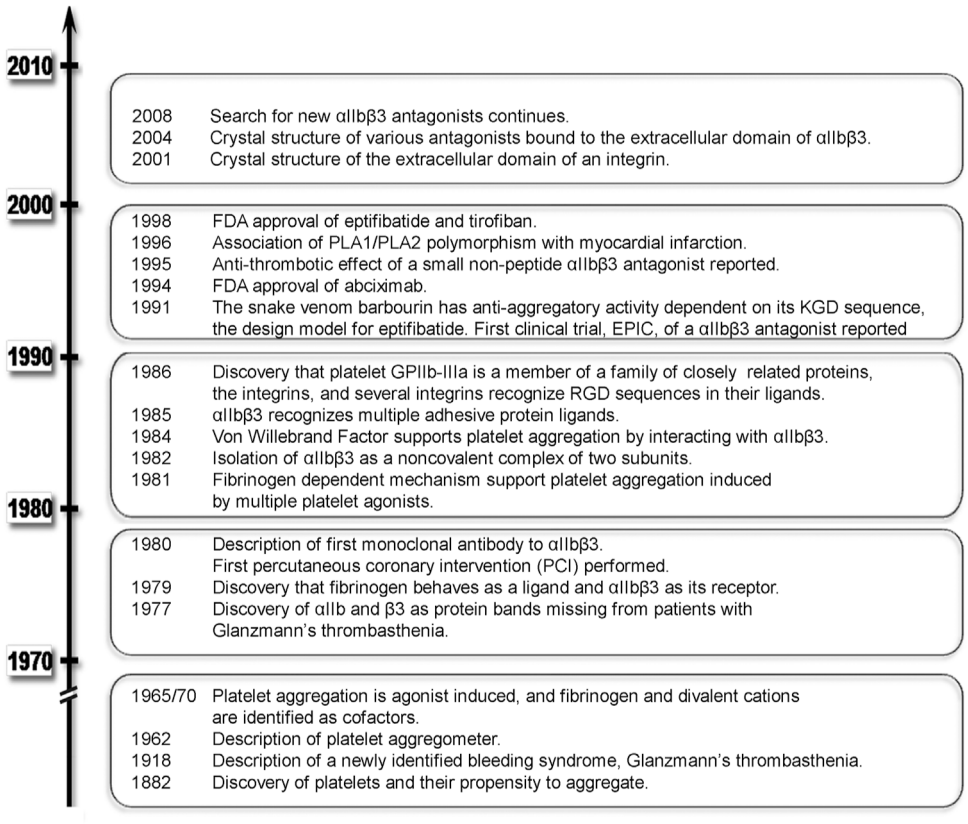


Figure 1. Highlights of the chronology of key discoveries in αIIbβ3 receptor antagonists

FDA indicates Food and Drug Administration; PL^{A1}/PL^{A2}, platelet alloantigen 1, 2; KGD, lysine-glycine-aspartic acid sequence; and RGD, arginine-glycine-aspartic acid sequence.

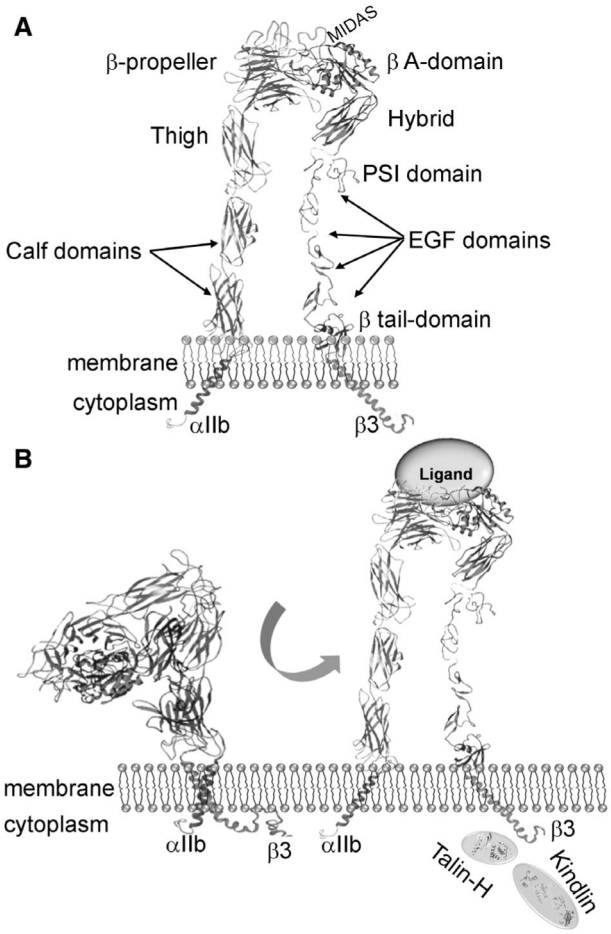
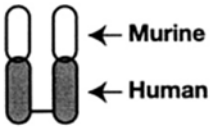
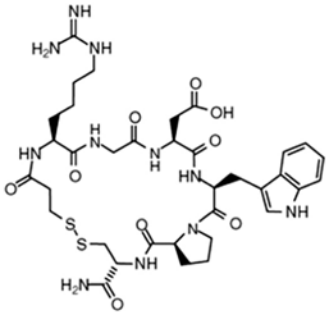
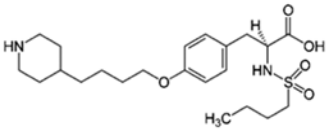


Figure 2.

A, **Depiction of the domain organization of the αIIb and β3 subunits in an extended conformation. B**, Pathway for activation of αIIbβ3. Inside-out signaling can be induced by different agonists, usually binding to a G-protein coupled receptor, which initiate signaling pathways that lead to the cytoplasmic tails of αIIbβ3. Inside-out signaling to activate the receptor begins with unclasping of the membrane proximal complex between the αIIb and β3 cytoplasmic tails. Talin and kindlin cooperate in this activation process. Their separation triggers dissociation of the transmembrane complex of the subunits. These changes then trigger a conformational switch in the integrin extracellular domain, resulting in its conversion from a bent conformation in its resting state to an extended conformation in which it becomes competent to bind soluble ligands. The subsequent outside-in signaling initiated by ligand binding is transmitted back to the cytoplasmic tails to trigger intracellular responses. Portions of this figure are adapted from reference [44]. EGF indicates epidermal growth factor; MIDAS, metal ion–dependent adhesion site; and PSI, plexin-semaphorin-integrin.

Table 1

Table Integrin αIIbβ3 Antagonists

αIIbβ3 Antagonist	Abciximab (REOPRO)	Eptifibatide (INTEGRILIN)	Tirofiban (Aggrastat)
Molecular design	Fab fragment of a chimeric human-murine monoclonal antibody to αIIbβ3.	Cyclic heptapeptide (6 amino acids+1 mercaptopropionyl (des-amino cysteinyl)	Small nonpeptide (N(butylsulfonyl)-
	Monoclonal antibody 7E3 used as starting point for its development	On the basis of the sequence of the snake venom, barbourin	O-[4-(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate) RGD peptide used as template
Structure			
Molecular weight	47 615 Da	832 Da	495 Da
Initial FDA approval	1994	1998	1998
Licensed indication	cardiac ischemia, PCI	ACS	ACS
Specificity/selectivity	αIIbβ3, αvβ3, αMβ2 (Mac-1)	αIIbβ3 (αvβ3)	αIIbβ3
Affinity for αIIbβ3	K_D=5 nmol/L	K_D=120 nmol/L	K_D=15 nmol/L
Platelet-bound half-life	12–24 h	Seconds	Seconds
Plasma half-life	2.5 h	Minutes	2 h
Route of administration	IV (bolus+infusion)	IV (bolus+infusion)	IV (bolus+infusion)
Manufacturer and distributor	Eli Lilly (Centocor)	Merck and Co. (Schering Plough, Millennium Pharmaceuticals Inc COR Therapeutics)	Merck and Co
Clinical trials	52	21	21
2000–2013			
2012 Sales ($millions)			
Worldwide	$147	$213	$5.6
United States	$48	$193	$5.0
Peak sales year	1999	2007	2000
Worldwide	$447	$332	$130
United States	$322	$312	$100

ACS indicates acute coronary syndrome; FDA, Food and Drug Administration; PCI, percutaneous coronary interventions; and RGD, arginine-glycine-aspartic acid sequence.