

Platelet GPIIb/IIIa antagonists: the first anti-integrin receptor therapeutics.

B S Coller

J Clin Invest. 1997;**99**(7):1467-1471. <https://doi.org/10.1172/JCI119307>.

Perspective

Find the latest version:

<https://jci.me/119307/pdf>



Perspectives Series: Cell Adhesion in Vascular Biology

Platelet GPIIb/IIIa Antagonists: The First Anti-Integrin Receptor Therapeutics

Barry S. Collier

Department of Medicine, Mount Sinai School of Medicine, New York 10029

The platelet glycoprotein GPIIb/IIIa ($\alpha_{IIb}\beta_3$) antagonist c7E3 Fab (the Fab fragment of the mouse/human chimeric monoclonal antibody 7E3; abciximab; ReoProTM) was approved for human use in the United States in December 1994 based on its safety and its efficacy in reducing the risk of ischemic complications after percutaneous coronary intervention (PCI,¹ angioplasty or atherectomy) (1, 2). The success of this agent reflects our emerging ability to identify adhesion molecules as therapeutic targets, and then construct effective inhibitors that meet the stringent safety standards required for a new drug. As the first rationally designed antiplatelet and anti-integrin receptor drug, c7E3 Fab serves as a prototype for other anti-integrin receptor, and more generally, antiadhesion receptor, agents designed to treat and/or prevent human disease.

Ischemic cardiovascular disease

The emergence of ischemic cardiovascular disease as the most common cause of death in the United States is a remarkably recent phenomenon, beginning just in the current century (3). The outlines of the pathophysiology of this disorder are well established: atherosclerosis of blood vessels begins in early adulthood, setting the background on which acute occlusive thrombosis, initiated primarily by platelets in the arterial circulation, occurs on damaged atherosclerotic plaque at some unpredictable time later in life, resulting in irreversible ischemic damage to the heart or brain. The risk of dying from ischemic cardiovascular disease increased, therefore, as a result of the conquest of many infectious diseases, which resulted in longer life spans during which atherosclerosis could develop, and the unfortunate adoption of a variety of practices that accelerate the atherosclerosis process, including high fat diets and cigarette smoking.

However, it is the hemostatic system that is responsible for the final thrombotic event; and paradoxically the hemostatic

system has probably been under strong evolutionary pressure to become highly active. Thus, since the risk of bleeding to death is great from birth on, especially for animals or humans in the wild, humans with more active hemostasis were more likely to survive to sexual maturity and pass on their genes. This led to the considerable redundancy in our hemostatic systems, which is perhaps best attested to by our ability to treat patients with anticoagulants, antiplatelet agents, and even thrombolytic agents with relative safety (4). Ironically, there probably has been very little evolutionary pressure against thrombotic disorders since the vast majority of patients die from these diseases after they have passed the peak of their reproductive years, when for all practical purposes, they are genetically dead.

Thus, our originally adaptive hemostatic systems have become maladaptive for those suffering from atherosclerosis, and so we have found it beneficial to rebalance the hemostatic systems of individuals with atherosclerotic vascular disease, both acutely and chronically. Therefore, it is likely that other therapeutic opportunities lie in identifying where evolutionary pressures have led to homeostatic systems that have become maladaptive as a result of changes in our condition.

Platelet physiology and the rationale for GPIIb/IIIa antagonists

Occlusive thrombus formation in coronary arteries probably begins with the deposition of platelets on a damaged atherosclerotic plaque as a result of the interaction of constitutively active platelet surface receptors [including GPIb/IX, GPIIb/IIIa (restricted in ligand specificity to immobilized fibrinogen), GPIa/IIa ($\alpha_2\beta_1$), GPIc/IIa ($\alpha_5\beta_1$), GPIc/IIa ($\alpha_6\beta_1$), and perhaps $\alpha_v\beta_3$, GPIV, and GPVI] with adhesive proteins in the plaque (5–7). Rheologic forces probably contribute significantly in determining the nature of these interactions (8). The adhesive proteins may be directly exposed by the vascular damage [e.g., collagen or von Willebrand factor (vWf)], deposited from plasma or platelets onto exposed proteins (e.g., the binding of vWf to collagen), or deposited from plasma or platelets onto newly formed fibrin (as for example, vWf) (7). Recent evidence identifying large amounts of tissue factor in the lipid-rich region of atherosclerotic plaques suggests that the generation of thrombin and deposition of small amounts of fibrin may be early events in the process (9).

The initial layer of adherent platelets is unlikely to decrease blood flow by itself. Under certain circumstances, however, the platelet GPIIb/IIIa receptors on the luminal surface of the adherent platelets are activated and undergo a conformational change that results in their binding plasma fibrinogen, vWf, or perhaps other glycoproteins with high affinity. The bivalent structure of fibrinogen and the multivalent struc-

Address correspondence to Barry S. Collier, Department of Medicine Box 1118, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Phone: 212-241-4200; FAX: 212-876-5844; E-mail: bcollier@smtplink.mssm.edu

Received for publication 12 February 1997.

1. Abbreviation used in this paper: PCI, percutaneous coronary intervention.

J. Clin. Invest.

© The American Society for Clinical Investigation, Inc.

0021-9738/97/04/1467/05 \$2.00

Volume 99, Number 7, April 1997, 1467–1471

ture of vWf allow these proteins to bind to GPIIb/IIIa receptors on two different platelets simultaneously. This permits the recruitment of an additional layer of platelets, which in turn can recruit an additional layer of platelets by a similar mechanism, ultimately resulting in vaso-occlusion (7, 10). In addition, nonocclusive platelet aggregates, if friable, can break off and embolize downstream to small blood vessels, causing both ischemic damage and electrical instability of the heart. The platelet thrombus also facilitates thrombin generation and fibrin deposition (11), and through exposure of P-selectin, may facilitate leukocyte adhesion and transmigration (12).

The GPIIb/IIIa receptor is expressed only in megakaryocytes and platelets and so is uniquely adapted to its role in platelet physiology. Presumably reflecting the need for an instantaneous response to hemorrhage, the density of GPIIb/IIIa receptors on the surface of platelets is extraordinary ($\sim 80,000$ copies spaced $< 200 \text{ \AA}$ apart), and there is an additional internal pool of GPIIb/IIIa receptors in α -granules and perhaps elsewhere that can be rapidly mobilized to the surface. If the GPIIb/IIIa receptor were constitutively in its high affinity ligand binding conformation, thrombosis would be ongoing, and so the receptor is under elaborate control mechanisms that limit its activation both geographically and temporally. Thus, agents that are released (e.g., ADP and serotonin), synthesized and released (e.g., thromboxane A_2), or generated as part of the hemostatic cascade (e.g., thrombin) when vessels are damaged are all able to initiate signals that result in the transformation of the GPIIb/IIIa receptor to a high affinity state. Adhesion itself and shear forces are also able to initiate activation signals, as may thrombolytic agents, either directly or through the paradoxical generation of thrombin. Inhibitors of activation, including PGI_2 and NO also contribute to the final result, as may an ecto-ADPase on the surface of endothelial cells and the products of transcellular metabolism (13). The signal transduction mechanisms involved in converting these stimuli into changes in the GPIIb/IIIa receptor are complex and still incompletely understood, but involve as a minimum seven transmembrane protein receptors, G proteins, phospholipases, calcium release, arachidonic acid metabolism, protein kinase C, adenylyl and guanylyl cyclases, and other protein kinases and phosphatases (7). The biochemical and biophysical basis of this conformational change and the signaling events induced by ligand binding will be reviewed in other Perspectives in this series (May 15 and July 1). The currently approved antiplatelet agents, aspirin and ticlopidine, act by inhibiting arachidonic acid metabolism and ADP-induced signal transduction, respectively, but their inhibition of platelet aggregation is incomplete because other pathways can lead to GPIIb/IIIa activation.

The rationale for blockade of GPIIb/IIIa receptors as a strategy for preventing or treating ischemic cardiovascular disease thus rests on data derived from research conducted by many different laboratories: (a) platelet thrombus formation secondary to platelet aggregation is the dominant initiating factor in occlusive vascular disease; (b) the GPIIb/IIIa receptor is a key element in the final common pathway leading to platelet aggregation; (c) the GPIIb/IIIa receptor is platelet specific; and (d) patients who lack GPIIb/IIIa receptor function on a genetic basis (Glanzmann thrombasthenia) have variably severe mucocutaneous bleeding, but rarely suffer from spontaneous central nervous system hemorrhage (14).

Blockade of the GPIIb/IIIa receptor has been accom-

plished with monoclonal antibodies (15) or peptides or peptidomimetics based on the RGD (arginine-glycine-aspartic acid) cell recognition sequence (16); the latter mediates the binding of a number of different ligands to the GPIIb/IIIa receptor and other integrin receptors. Many RGD-based compounds have been synthesized, some of which are orally active, and a number are in human trials (17). Ironically, although fibrinogen contains two RGD sequences in its $A\alpha$ chain, data indicate that fibrinogen binds to GPIIb/IIIa via a dodecapeptide sequence at the extreme carboxy terminus of the γ chain that probably has structural similarity to the RGD sequence (18).

Data from animal models

GPIIb/IIIa antagonists are more effective antithrombotic agents than aspirin in a wide variety of animal models (15). Moreover, when compared with the use of a thrombolytic agent alone, the combination of a GPIIb/IIIa antagonist and a thrombolytic agent produces more rapid and extensive clot lysis, reduces the risk of reocclusion, and diminishes infarct size, even when the dose of the thrombolytic agent is reduced by as much as 75% (19).

Human studies

GPIIb/IIIa antagonist therapy with c7E3 Fab, as well as RGD-based peptides and peptidomimetics, inhibits *ex vivo* platelet function to a much greater extent than does aspirin; c7E3 Fab, and to a more variable extent, the peptides and peptidomimetics inhibit *in vivo* platelet function more than aspirin as judged by prolongation of the bleeding time (17, 20–22).

A 2099 patient phase III study in humans demonstrated that, when used in combination with aspirin and heparin, a bolus + 12-h infusion of c7E3 Fab begun just before PCI significantly reduced the risk of suffering death, myocardial infarction, or need for urgent coronary artery bypass surgery or repeat PCI over 30 d in patients who were judged to be at high risk of suffering such events (1). At 6 mo, the absolute benefit persisted, even when considering elective PCI and bypass procedures (2).

However, treatment of patients with c7E3 Fab in this study resulted in a significant increase in major bleeding, although there was no increase in fatal or central nervous system bleeding. In a later study, however, in which the heparin dose was decreased and weight-adjusted, c7E3 Fab treatment was not associated with an increased risk of major bleeding (23). This same study demonstrated the efficacy of c7E3 Fab treatment in preventing ischemic complications of PCI in patients at low risk of such events as well as those at high risk (24). Studies using a peptide (intrifiban; IntegrilinTM) and a peptidomimetic (tirofiban; AggrastatTM) have also shown favorable trends in preventing ischemic complications of PCI, but the benefits did not reach statistical significance. Other studies using GPIIb/IIIa antagonists suggest that they may be beneficial in treating unstable angina and myocardial infarction even without PCI.

Blood vessel passivation

The long-term benefit of therapy with c7E3 Fab after only a bolus + 12-h infusion provides important insight into the process of blood vessels passivation after injury. Thus, although it is well established that blood vessels come become highly reactive to platelets immediately after vascular injury, it is less well appreciated that blood vessels lose their platelet reactivity (i.e., become passivated) sometime thereafter. Animal studies in-

volving damage to a normal vessel suggested that the process takes up to ~ 8 h (25, 26), but data from one of the phase III studies of c7E3 Fab, based on the time between the initial and the repeat urgent PCI, suggest that passivation occurs within ~ 2 d in most patients, but with some patients requiring up to 8 d. These data support a strategy of trying to achieve high grade GPIIb/IIIa receptor blockade during the period from vascular injury until passivation has occurred, but no longer, thus gaining the antithrombotic benefit but limiting the hemorrhagic risk. The biochemical basis of blood vessel passivation is unknown, and insights into the mechanism(s) may provide new opportunities for improving antithrombotic therapy (27).

Mechanism(s) of action

Although the predominant antithrombotic benefit of GPIIb/IIIa antagonist therapy most likely results from inhibition of platelet aggregation and thus platelet thrombus formation, additional related phenomena may contribute. For example, platelets probably play an important role in thrombin generation because activated platelets provide a highly efficient catalytic surface that facilitates the reactions leading to thrombin formation and platelets release, and probably activate, Factor V (11). Thus, GPIIb/IIIa antagonists can potentially decrease thrombin generation via two different mechanisms: quantitatively by decreasing the number of platelets in a thrombus, and qualitatively by decreasing platelet activation and release of Factor V(a). In fact, evidence from clinical studies of c7E3 Fab (28) and intrifiban (29) and in vitro data using c7E3 Fab (30) support the ability of GPIIb/IIIa antagonists to decrease thrombin generation initiated by either contact activation or tissue factor. Therefore, decreased thrombin production may contribute to the antithrombotic effects of GPIIb/IIIa antagonists, and thus these antiplatelet agents may also function, in essence, as anticoagulants.

The positive effects of GPIIb/IIIa antagonists in facilitating thrombolysis in animal models may reflect the ability of GPIIb/IIIa antagonists to inhibit: (a) clot retraction, which has been implicated in limiting the diffusion of thrombolytic agents; (b) release of the fibrinolytic inhibitors plasminogen activator inhibitor-1 and α_2 -plasmin inhibitor from platelet α -granules; (c) Factor XIIIa binding to platelets and local release of platelet Factor XIII (since Factor XIII cross-links fibrin and cross-links fibrinolytic inhibitors to fibrin); and (d) thrombin production and thus the generation of the thrombin-activatable fibrinolysis inhibitor (TAFI) (31). These mechanisms may contribute to how GPIIb/IIIa antagonists prevent reocclusion after thrombolysis, but they cannot account for the increased rate of thrombolysis achieved when GPIIb/IIIa antagonists are combined with fibrinolytic agents. One hypothesis to explain this finding is that when a fibrinolytic agent is administered alone there is a period of time when the agent's platelet activating effects result in increased platelet deposition into the thrombus, which then delays reperfusion. By preventing this enhanced platelet deposition, GPIIb/IIIa antagonists can allow fibrinolysis to proceed unimpeded, resulting in more rapid lysis.

The $\alpha_v\beta_3$ integrin, which was originally designated the vitronectin receptor, but which also binds fibrinogen, vWf, and other RGD-containing ligands, shares the same β subunit (GPIIIa or β_3) with GPIIb/IIIa. It is widely distributed on different cell types, including endothelial cells, smooth muscle cells, and osteoclasts. It has been implicated in a variety of different functions, including bone resorption, tumor invasion

and metastasis, cell adhesion and spreading, and tumor angiogenesis. Since c7E3 Fab inhibits $\alpha_v\beta_3$ in addition to GPIIb/IIIa, it is possible, but unproved, that some of its effects are related to blockade of $\alpha_v\beta_3$. For example, in vitro data suggest that platelet $\alpha_v\beta_3$ may contribute to its ability to facilitate thrombin generation (11).

Blockade of $\alpha_v\beta_3$ receptors by monoclonal antibodies or peptides decreases the extent of intimal hyperplasia after vascular injury in animal models (32, 33), and intimal hyperplasia may play an important role in restenosis, a complex phenomenon that frequently results in the need for repeat PCI within ~ 6 mo of the initial PCI. However, other factors almost certainly also contribute to restenosis, including elastic recoil, neurohumoral luminal adjustments, mural thrombus formation, and progressive atherosclerosis. Clinical data regarding an antirestenosis effect of c7E3 Fab are inconsistent and anatomic data are not available. Since the time course of restenosis is different from that of acute thrombotic occlusion, however, the optimal doses and durations of therapy may well be different for these two effects, and thus this subject merits further study. c7E3 Fab is alone among the GPIIb/IIIa antagonists in clinical trials in potently inhibiting $\alpha_v\beta_3$, and thus it is especially important to establish whether any of its beneficial effects derive from $\alpha_v\beta_3$ blockade.

It is possible, however, that optimal GPIIb/IIIa antagonist therapy can decrease the ultimate luminal compromise caused by vascular injury by mechanisms other than $\alpha_v\beta_3$ blockade. Thus, it may decrease the release or generation of agents implicated in inducing intimal hyperplasia (PDGF, ADP, serotonin, thrombin) and may limit the size of the mural thrombus that becomes incorporated into the atherosclerotic blood vessel wall.

The future of GPIIb/IIIa antagonists

Trials of a number of GPIIb/IIIa antagonists in myocardial infarction and unstable angina are currently ongoing in different combinations with aspirin, thrombolytic agents, PCI, stents, and anticoagulants. Other conditions in which platelet thrombus formation may contribute to organ damage may also benefit from GPIIb/IIIa antagonist therapy, including stroke, cerebral and peripheral arterial angioplasty, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, heparin-induced thrombosis, microvascular surgery, and cerebral malaria. The risks of excessive hemorrhage are considerable, however, in these disorders, and so it is uncertain whether the overall contribution of GPIIb/IIIa receptor blockade will be beneficial. Few authenticated animal models of these disorders exist, but our preliminary data indicate that 7E3 treatment could ameliorate the renal insufficiency and microangiopathic hemolysis in a primate model containing features of both disseminated intravascular coagulation and thrombotic thrombocytopenia purpura/hemolytic uremic syndrome (34).

Orally active GPIIb/IIIa antagonists have been developed and offer the prospect for chronic therapy, including secondary and even primary prevention of thrombotic disease. It will be a considerable challenge to define an optimal chronic dose for an oral agent. Development of rapid and simple assays to monitor and adjust therapy is likely to improve both the safety and efficacy of these agents.

Conclusion

The success of GPIIb/IIIa antagonist therapy in preventing is-

chemic complications of PCI inaugurates rationally designed antiplatelet therapy and anti-integrin receptor therapy. It is sobering to note that c7E3 Fab was only the twentieth biotechnology agent approved for human therapy, and perhaps more importantly, only the second approved biotechnology therapeutic that was not a naturally occurring human product. Successfully interfering with fundamental biologic processes, such as cell adhesion, that have been honed by evolution over millions of years, is not a trivial task, but it is very likely to be achieved with increasing frequency in the near future.

Acknowledgments

I would like to recognize the contributions of my colleagues who have worked on the basic and preclinical studies of 7E3, in particular, Lesley Scudder, John Folts, and Chip Gold; the physicians, scientists, and staff at Centocor, in particular Harlan Weisman and Robert Jordan; and the leaders of the clinical trials of 7E3, in particular, Drs. Eric Topol, Robert Califf, and Maarten Simoons. I also want to thank Suzanne Rivera and Jennifer Bernucca for outstanding secretarial assistance.

This work was supported by grants 19278 and 54469 from the National Heart, Lung, and Blood Institute.

References

1. The EPIC Investigators. 1994. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N. Engl. J. Med.* 330:956-961.
2. Topol, E.J., R.M. Califf, H.F. Weisman, S.G. Ellis, J.E. Tchong, S. Worley, R. Ivanhoe, B.S. George, D. Fintel, M. Weston, K. Sigmon, K.M. Anderson, K.L. Lee, and J.T. Willerson, on behalf of the EPIC Investigators. 1994. Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet.* 343:881-886.
3. Olshansky, S.J., and A.B. Ault. 1986. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Milbank Mem. Fund Q.* 64:355-391.
4. 4th American College of Chest Physicians Consensus Conference on Antithrombotic Therapy. Tucson, Arizona, April 1995 Proceedings. *Chest.* 108: 225S-522S.
5. Collier, B.S. 1980. Interaction of normal, thrombasthenic, and Bernard-Soulier platelets with immobilized fibrinogen: defective platelet-fibrinogen interaction in thrombasthenia. *Blood.* 55:169-178.
6. Savage, B., E. Saldívar, and Z.M. Ruggeri. 1996. Initiation of platelet adhesion by arrest onto fibrinogen or translocation on von Willebrand factor. *Cell.* 84:289-297.
7. Ware, A.J., and B.S. Collier. 1995. Platelet morphology, biochemistry and function. In Williams Hematology. E. Beutler, M.A. Lichtman, B.S. Collier, and T.J. Kipps, editors. McGraw-Hill, Inc. New York. 1161-1201.
8. Goldsmith, H.L., and V.T. Turitto. 1986. Rheological aspects of thrombosis and haemostasis: basic principles and applications. ICTH Report. Subcommittee on Rheology of the International Committee on Thrombosis and Haemostasis. *Thromb. Haemostas.* 55:415-435.
9. Thiruvikraman, S.V., A. Guha, J. Roboz, M.B. Taubman, Y. Nemerson, and J.T. Fallon. 1996. In situ localization of tissue factor in human atherosclerotic plaques by binding of digoxigenin-labeled factors VIIa and X. *Lab. Invest.* 75:451-461.
10. Collier, B.S. 1990. Platelets and thrombolytic therapy. *N. Engl. J. Med.* 322:33-42.
11. Reverter, J.C., S. Béguin, H. Kessels, R. Kumar, H.C. Hemker, and B.S. Collier. 1996. Inhibition of platelet-mediated, tissue factor-induced thrombin generation by the mouse/human chimeric 7E3 antibody. Potential implications for the effect of c7E3 Fab treatment on acute thrombosis and "clinical restenosis." *J. Clin. Invest.* 98:863-874.
12. Diacovo, T.G., S.J. Roth, J.M. Buccola, D.F. Bainton, and T.A. Springer. 1996. Neutrophil rolling, arrest, and transmigration across activated, surface-adherent platelets via sequential action of P-selectin and the beta 2-integrin CD11b/CD18. *Blood.* 88:146-157.
13. Marcus, A.J., L.B. Safier, M.J. Broekman, N. Islam, J.H. Fliessbach, K.A. Hajjar, W.E. Kaminski, E. Jendraschak, R.L. Silverstein, and C. von Schacky. 1995. Thrombosis and inflammation as multicellular processes: signifi-

cance of cell-cell interactions. *Thromb. Haemostas.* 74:213-217.

14. Collier, B.S., U. Seligsohn, H. Peretz, and P.J. Newman. 1994. Glanzmann thrombasthenia: new insights from an historical perspective. *Semin. Hematol.* 31:301-311.
15. Collier, B.S. 1995. Blockade of platelet GPIIb/IIIa receptors as an anti-thrombotic strategy. *Circulation.* 92:2373-2380.
16. Cook, N.S., G. Kottirsch, and H. Zerwes. 1994. Platelet glycoprotein IIb/IIIa antagonists. *Drugs Future.* 19:135-159.
17. Lefkowitz, J., E.F. Plow, and E.J. Topol. 1995. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N. Engl. J. Med.* 332:1553-1559.
18. Zaidi, T., L.V. McIntire, D.H. Farrell, and P. Thiagarajan. 1996. Adhesion of platelets to surface-bound fibrinogen under flow. *Blood.* 88:2967-2972.
19. Collier, B.S. 1992. Inhibitors of the platelet glycoprotein IIb/IIIa receptor as adjunctive therapy for coronary artery thrombolysis. *Coron. Art. Dis.* 3: 1016-1029.
20. Jordan, R.E., C.L. Wagner, M. Mascelli, G. Treacy, M.A. Nedelman, J.N. Woody, H.F. Weisman, and B.S. Collier. 1996. Preclinical development of c7E3 Fab; a mouse/human chimeric monoclonal antibody fragment that inhibits platelet function by blockade of GPIIb/IIIa receptors with observations on the immunogenicity of c7E3 Fab in humans. In Adhesion Receptors as Therapeutic Targets. M.A. Horton, editor. CRC Press, Inc., Boca Raton. 281-305.
21. Barrett, J.S., G. Murphy, K. Peerlinck, I. De Lepeleire, R.J. Gould, D. Panebianco, E. Hand, H. Deckmyn, J. Vermynen, and J. Arnout. 1994. Pharmacokinetics and pharmacodynamics of MK-383, a selective non-peptide platelet glycoprotein-IIb/IIIa receptor antagonist, in healthy men. *Clin. Pharmacol. Ther.* 56:377-388.
22. Harrington, R.A., N.S. Kleiman, K. Kottke Marchant, A.M. Lincoff, J.E. Tchong, K.N. Sigmon, D. Joseph, G. Rios, K. Trainor, D. Rose, et al. 1995. Immediate and reversible platelet inhibition after intravenous administration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention. *Am. J. Cardiol.* 76:1222-1227.
23. Aguirre, F.A., D.J. Talley, J.J. Ferguson III, J. Tchong, N.S. Kleiman, E.A. Montague, J.E. Booth, and A.M. Lincoff. 1996. Efficacy of abciximab, despite patient weight, using lower heparin dosing during percutaneous coronary intervention. *Circulation.* 94:I-198a. (Abstr.)
24. Ward, S.R., A.M. Lincoff, D.P. Miller, J.E. Booth, E.A. Montague, J. Tchong, and E.J. Topol. 1996. Clinical outcome is improved at 30 days regardless of pre-treatment clinical and angiographic risk in patients receiving abciximab for angioplasty: results from the EPILOG study. *Circulation.* 94:I-198a. (Abstr.)
25. Wilentz, J.R., T.A. Sanborn, C.C. Haudenschild, C.R. Valeri, T.J. Ryan, and D.P. Faxon. 1987. Platelet accumulation in experimental angioplasty: time course and relation to vascular injury. *Circulation.* 75:636-642.
26. Groves, H.M., R.L. Kinlough-Rathbone, and J.F. Mustard. 1986. Development of nonthrombogenicity of injured rabbit aorta despite inhibition of platelet adherence. *Arteriosclerosis.* 6:189-195.
27. Collier, B.S., J.L. Kutok, L.E. Scudder, D.K. Galanakis, S.M. West, G.S. Rudomen, and K.T. Springer. 1993. Studies of activated GPIIb/IIIa receptors on the luminal surface of adherent platelets. Paradoxical loss of luminal receptors when platelets adhere to high density fibrinogen. *J. Clin. Invest.* 92:2796-2806.
28. Moliterno, D.J., R.M. Califf, F.V. Aguirre, K. Anderson, K.N. Sigmon, H.F. Weisman, and E.J. Topol. 1995. Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (the EPIC trial). Evaluation of c7E3 Fab in the Prevention of Ischemic Complications trial. *Am. J. Cardiol.* 75: 559-562.
29. Aguirre, F.V., E.J. Topol, J.J. Ferguson, J.C. Blankenship, L.H. Gardner, E.A. Caracciolo, T.J. Donohue, R.A. Harrington, and J.E. Tchong, for the IMPACT-II investigators. 1996. Effect of platelet glycoprotein IIb/IIIa antagonism with Integrelin on activated clotting times during coronary interventions: results from the IMPACT-II trial. *Circulation.* 94:I-197a. (Abstr.)
30. Ammar, T., L.E. Scudder, and B.S. Collier. 1997. In vitro effects of the platelet GPIIb/IIIa receptor antagonist c7E3 Fab on the activated clotting time. *Circulation.* 95:614-617.
31. Collier, B.S., J.D. Folts, L.E. Scudder, and S.R. Smith. 1986. Antithrombotic effect of a monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor in an experimental animal model. *Blood.* 68:783-786.
32. Matsuno, H., J.M. Stassen, J. Vermynen, and H. Deckmyn. 1994. Inhibition of integrin function by a cyclic RGD-containing peptide prevents neointima formation. *Circulation.* 90:2203-2206.
33. van der Zee, R., J. Passeri, J.J. Barry, D.A. Cheresch, and J.M. Isner. 1996. A neutralizing antibody to the alpha v beta 3 integrin reduces neointimal thickening in a balloon-injured rabbit iliac artery. *Circulation.* 98:I-257a. (Abstr.)
34. Taylor, F.B., B.S. Collier, A.C.K. Chang, G. Peer, R. Jordan, W. Engellener, and C.T. Esmon. 1997. 7E3 F(ab)₂, a monoclonal antibody to the platelet GPIIb/IIIa receptor, protects against microangiopathic hemolytic anemia and microvascular thrombotic renal failure in baboons treated with C4b binding protein and a sublethal infusion of *Escherichia coli*. *Blood.* In press.

“Cell Adhesion In Vascular Biology”

Series Editors, Mark H. Ginsberg, Zaverio M. Ruggeri, and Ajit P. Varki

October 15, 1996	Adhesion and signaling in vascular cell–cell interactions	Guy Zimmerman, Tom McIntyre, and Stephen Prescott
November 1, 1996	Endothelial adherens junctions: implications in the control of vascular permeability and angiogenesis	Elisabetta Dejana
November 15, 1996	Genetic manipulation of vascular adhesion molecules in mice	Richard O. Hynes and Denisa D. Wagner
December 1, 1996	The extracellular matrix as a cell cycle control element in atherosclerosis and restenosis	Richard K. Assoian and Eugene E. Marcantonio
December 15, 1996	Effects of fluid dynamic forces on vascular cell adhesion.....	Konstantinos Konstantopoulos and Larry V. McIntire
January 1, 1997	The biology of PECAM-1	Peter J. Newman
January 15, 1997	Selectin ligands: Will the real ones please stand up?.....	Ajit Varki
February 1, 1997	Cell adhesion and angiogenesis.....	Joyce Bischoff
February 15, 1997	von Willebrand Factor.....	Zaverio Ruggeri
March 1, 1997	Therapeutic inhibition of carbohydrate–protein interactions in vivo.....	John B. Lowe and Peter A. Ward
March 15, 1997	Integrins and vascular matrix assembly.....	Erkki Ruoslahti
April 1, 1997	Platelet GPIIb/IIIa antagonists: The first anti-integrin receptor therapeutics.....	Barry S. Coller
April 15, 1997	Importance of shear stress in endothelial adhesion molecule expression.....	Michael Gimbrone
May 1, 1997	Proteoglycans and proteoglycan-binding proteins in vascular biology	Robert Rosenberg
May 15, 1997	New insights into integrin-ligand interaction	Robert Liddington and Joseph Loftus
June 1, 1997	Adhesive interactions of Sickle erythrocytes with endothelium	Robert Heibel
June 15, 1997	Cell migration in vascular biology	Stephen Schwartz
July 1, 1997	Integrin signaling in vascular biology.....	Sanford Shattil and Mark Ginsberg
July 15, 1997	Multi-step mechanisms of leukocyte homing.....	Eugene Butcher
August 1, 1997	Role of PSGL-1 binding to selectins in leukocyte recruitment.....	Rodger McEver and Richard Cummings