The deliberate search for drugs to inhibit the αIIbβ3 (GPIIb/IIla) receptor ushered in the era of rationally designed antiplatelet therapy and thus represents an important milestone in the evolution of antiplatelet drug development. The selection of the αIIbβ3 receptor as a therapeutic target rested on a broad base of basic and clinical research conducted by many investigators in the 1960s and 1970s working in the fields of platelet physiology, the rare bleeding disorder Glanzmann thrombasthenia, platelet membrane glycoproteins, integrin receptors, coronary artery pathology, and experimental thrombosis. Thus, αIIbβ3 was found to mediate platelet aggregation by virtually all of the physiology agonists (e.g., ADP, epinephrine, and thrombin) through a mechanism in which platelet activation by these agents results in a change in the conformation of the receptor. This is followed by increased affinity of the receptor for the multivalent ligands fibrinogen and von Willebrand factor, both of which are capable of binding to receptors on two platelets simultaneously, producing platelet crosslinking and aggregation. At about the same time, experimental studies demonstrated platelet thrombus formation at sites of vascular injury, and biochemical studies in humans demonstrated evidence of platelet activation during acute ischemic cardiovascular events.

Our own studies initially focused on platelet-fibrinogen interactions using an assay in which normal platelets agglutinated fibrinogen-coated beads. The agglutination was enhanced with platelet activators. Platelets from patients with Glanzmann thrombasthenia, who lack the αIIbβ3 receptor, did not agglutinate the beads. We adapted this assay to a microtiter plate system to identify monoclonal antibodies that inhibited platelet-fibrinogen interactions and then demonstrated that these antibodies bound to αIIbβ3. They were also more potent inhibitors of platelet aggregation than any known antiplatelet agent and produced a pattern of aggregation that was virtually identical to that found using platelets from patients with Glanzmann thrombasthenia.

I recognized the theoretical potential of using an antibody to inhibit platelets in vivo but also recognized the challenges and limitations. Since experimental models of thrombosis had been developed in the dog, and since the antibody we initially worked with did not react with dog platelets, we had to go back to our original samples to identify an antibody (7E3) that reacted with dog platelets in addition to human platelets. We adapted this assay to a microtiter plate system to identify monoclonal antibodies that inhibited platelet-fibrinogen interactions and then demonstrated that these antibodies bound to αIIbβ3. They were also more potent inhibitors of platelet aggregation than any known antiplatelet agent and produced a pattern of aggregation that was virtually identical to that found using platelets from patients with Glanzmann thrombasthenia.

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endotoxin. With the small amount of 7E3-F(ab')2 we initially prepared, we were able to show dose response inhibition of platelet aggregation in three dogs, achieving greater inhibition than with aspirin or ticlopidine, the only antiplatelet agents approved for human use at that time. We also devised an assay using radiolabeled 7E3 to quantify the percentage of platelet αIIbβ3 receptors that were blocked when a specific dose of 7E3-F(ab')2 was administered in vivo. This allowed us to directly measure the effect of the agent on its target receptor on its target cell.

I considered two criteria most important in selecting the initial animal models in which to test the efficacy and safety of administering 7E3-F(ab')2: 1) the model had to convincingly simulate a human vascular disease, and 2) aspirin had to have failed to produce complete protection from thrombosis. The latter criterion was particularly important because I planned to stop this line of research if the 7E3-F(ab')2 was not more efficacious than aspirin.

Ultimately, we collaborated with Dr. John Folts of the University of Wisconsin, who had developed a dog model of unstable angina by attaching a short cylindrical ring to partially occlude a coronary artery and using a hemostat to induce vascular injury. Pretreatment of the animal with 7E3-F(ab')2 was more effective than aspirin or any other compound Dr. Folts had previously tested in preventing platelet thrombus formation, as judged by its effects on the characteristic repetitive cycles of platelet deposition and embolization. Electron microscopy of the vessels confirmed the reduction in platelet thrombi by 7E3-F(ab')2, with only a monolayer of platelets typically deposited.

Dr. Chip Gold and his colleagues at Massachusetts General Hospital had developed a dog model to assess the effects of tissue plasminogen activator (t-PA) on experimental thrombi induced in the dog coronary artery. Although t-PA was effective in lysing the thrombi, the blood vessels rapidly reoccluded with new thrombi that were rich in platelets. Aspirin could not prevent reocclusion, whereas 7E3-F(ab')2 not only prevented reocclusion, but also increased the speed of reperfusion by t-PA.

The next steps in drug development could not be performed in my laboratory because they required resources far in excess of those in my grant from the National Heart, Lung, and Blood Institute to study basic platelet physiology. As a result, in 1986 the Research Foundation of the State University of New York licensed the 7E3 antibody to Centocor, Inc., a new biotechnology company specializing in the diagnostic and therapeutic application of monoclonal antibodies.

The subsequent development of 7E3 as a therapeutic agent required extensive collaboration among myself, a large number of outstanding scientists at Centocor, and many leading academic cardiologists. Many decisions and hurdles remained for us, including the decision to develop a mouse/human chimeric 7E3 Fab (c7E3 Fab); the design and execution of the toxicology studies; the assessment of the potential toxicity of 7E3 crossreactivity with αVβ3; the development of sensitive and specific assays to assess immune responses to c7E3 Fab; the design, execution, and analysis of the Phase I, II, and III studies; and the preparation, submission, and presentation of the Product Licensing
Application to the Food and Drug Administration, and comparable documents to European and Scandinavian agencies.

Based on the results of the 2,099 patient EPIC trial, in which conjunctive treatment with a bolus plus infusion of c7E3 Fab significantly reduced the risk of developing an ischemic complication (death, myocardial infarction, or need for urgent intervention) after coronary artery angioplasty or atherectomy in patients at high risk of such complications, the Food and Drug Administration approved the conjunctive use of c7E3 Fab (generic name, abciximab) in high-risk angioplasty and atherectomy on December 22, 1994. Since then it has been administered to more than 2.5 million patients in the U.S., Europe, Scandinavia, and Asia. Its optimal role in treating cardiovascular disease continues to evolve in response to the introduction of new anticoagulants, antiplatelet agents, stents, and procedures.

We have also been able to apply the monoclonal antibodies we prepared to $\alpha$IIb$\beta$3 to the prenatal detection of Glanzmann thrombasthenia, and have used the antibodies as probes for characterizing both the biogenesis of the receptor and the conformational changes that the receptor undergoes with activation. We have been able to precisely map the 7E3 epitope on $\beta$3, providing additional insights into the mechanism by which it prevents ligand binding. We have also exploited the ability of another antibody to $\alpha$IIb$\beta$3 to stabilize the receptor complex in order to facilitate production of crystals of the $\alpha$IIb$\beta$3 headpiece; the x-ray diffraction properties of these crystals were studied in collaboration with Dr. Timothy Springer's group at Harvard and provide the first structural information on the receptor.

In landmark studies in the 1980s, Pierschbacher and Ruoslahti demonstrated the importance of the arginine-aspartic acid (RGD) sequence in the interaction of the integrin $\alpha$5$\beta$1 with fibronectin, and they went on to show that peptides with the RGD sequence could inhibit this interaction. Subsequent studies by many groups demonstrated that these peptides could also inhibit the interaction of platelet $\alpha$IIb$\beta$3 with fibrinogen and von Willebrand factor. Dr. David Phillip and Dr. Robert Scarbrough led the team at Cor Therapeutics that made a cyclic pentapeptide with high selectivity for $\alpha$IIb$\beta$3 over $\alpha$V$\beta$3 by patterning their compound on the KGD sequence in the snake venom barbourin. The resulting antiplatelet agent, eptifibatide, received FDA approval in May 1998. At Merck, Dr. Robert Gould led the team that developed the nonpeptide RGD-mimetic tirofiban, which also is selective for $\alpha$IIb$\beta$3 compared to $\alpha$V$\beta$3. It also received FDA approval in May 1998. Our recent x-ray crystallographic studies in collaboration with Dr. Springer’s group provided structural information on the mechanisms and sites of binding of these drugs with $\alpha$IIb$\beta$3.

Many important elements and an enormous amount of good fortune were needed for the translation of the basic science information about platelet aggregation into the drug abciximab, including, but not limited to: 1) the support of basic studies of platelet physiology by the National Institutes of Health in my laboratory and many other laboratories, 2) the creation and ongoing funding of a core facility available to all faculty members to prepare monoclonal antibodies at the State University of New York at Stony Brook under the direction of Dr. Arnold
Levine, 3) the 1988 Bayh-Dole Act and its subsequent amendments, and the expertise of the Technology Transfer Office at Stony Brook in licensing 7E3 to Centocor, which then provided the capital and additional expertise required for its development, and 4) the expert and enthusiastic collaboration by two large and disciplined cooperative groups of interventional cardiologists (TAMI, EPIC) under the dynamic leadership of Drs. Eric Topol and Rob Califf, that were eager to test the safety and efficacy of the 7E3 derivatives. Although the translation of each new scientific discovery into improved health via novel preventive, diagnostic, or therapeutic strategies requires the blazing of a unique path, optimizing these elements and similar ones may allow the path to be shorter and/or to be traversed more easily, at a lower cost, or in a shorter period of time.