



2012 Association of American Physicians George M. Kober Lecture

Translating from the rivers of Babylon to the coronary bloodstream

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I was attracted to medicine because it affords the opportunity to integrate science and humanism in service to others. And I became attracted to a career in research when I realized that the application of the scientific method to alleviate suffering from disease is one of our species' proudest achievements. I feel privileged to be able to participate in this process and recognize that it carries with it enormous responsibilities (1).

The evidence of the power of the scientific method to improve human health is compelling. In fact, since approximately 1840, people in the scientifically most advanced countries have enjoyed an amazing linear increase in life expectancy at birth, with the life expectancy at birth for women increasing nearly 40 years, from approximately 45 to 85 years (Figure 1A and ref. 2). During the first approximately 100 years, from 1840 to 1940, increases in life expectancy were primarily due to improvements in sanitation, access to clean water, early attempts at vaccination, and the introduction of medical microbiology, epitomized by the research of Dr. George M. Kober, who improved the safety of the milk supply in Washington, DC, as a model for the country. During this period, children were the major beneficiaries of these scientific advances, since they were especially vul-

nerable to contagious illnesses. During the last 70 years, fueled in large part by the growth in funding by the NIH in the US and on a smaller scale by similar governmental agencies in other countries as well as the investments by pharmaceutical and, later, biotechnology companies, the increase in life expectancy has reflected medical innovations – new drugs, vaccines, devices, diagnostic and imaging technologies, surgical procedures and nonsurgical interventions, and disease prevention strategies that build on a solid base of evidence (3–5). Increasingly, the benefits have been enjoyed by the elderly, with the majority of benefit now going to those over 65 years of age and with the fastest growth in benefit going to those over 80 years of age (2).

As dramatic as these statistics are in their own right, they take on much more profound import when considered against humans' estimated 200,000 years on earth (6). Assuming a life expectancy at birth of 25 years at the very beginning of the prescientific era, it took approximately 200,000 years to gain approximately 20 years of life expectancy at birth or approximately 10,000 years to gain a single year of life expectancy. In contrast, throughout the 170 years of the scientific era, it has required less than five years to gain a year of life expectancy at birth (Figure 1B). If the current trend continues, approximately half of the children born in the United States in the year 2000 will live to 100 years of age. The challenges before us are, therefore, clear: to sustain the improvements in life expectancy, reduce the burden of disability, and ensure that people the world over share equally in the benefits of better health.

Research is *the* mission of academic medical centers

As I started my medical career, I was told that medical schools had a tripartite mission, graphically depicted as a 3-legged stool – patient care, education, and research (Figure 2A and refs. 7, 8). Over

the years, however, I came to the conclusion that, while this construct was well intentioned, it was ill conceived because it implied that research was something separate from patient care and education or, worse yet, something one did if there were leftover resources on the margin. Since the scientific method has the potential to improve virtually all processes, I would propose an updated image in which research is the cushion that covers a four-legged stool – patient care, education, community service, and global health (Figure 2B). Thus, research isn't one of the missions of the modern academic medical center – it is *the* mission.

Academic medical centers need to apply the scientific method, embodied in rigorous research, to each of the legs of the stool. And they need to educate the public that conducting research is an integral component of their commitments to the expert and compassionate care of individual patients and to the health of the communities they serve. Moreover, since medicine knows no geographical or political boundaries, it is important to highlight for young, idealistic people the power of science to advance the cause of social justice both locally and globally (9). Good health is an essential component of human dignity (10), and thus, by affording one the opportunity to develop new methods to prevent, diagnose, and treat disease, a career in biomedical science provides rewarding opportunities to achieve social justice. There are also social benefits in eradicating endemic disease and improving health, as they can dramatically improve economic productivity and living standards and even result in the recapture of abandoned land (11, 12).

Translational research and the application of the scientific method to address a health need

The introduction of the Clinical and Translational Science Award (CTSA) program by the NIH in 2006 galvanized interest in translational research – and

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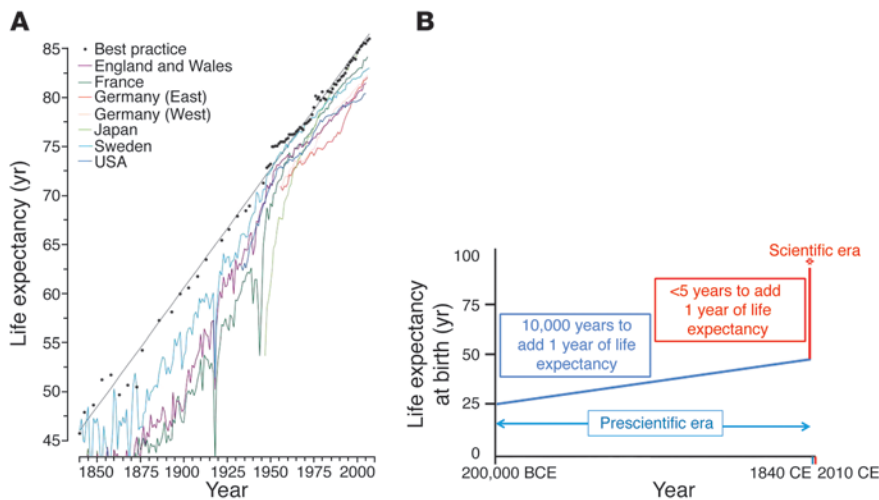


Figure 1

Life expectancy. **(A)** Best-practice life expectancy (that is, the best life expectancy reported by any country) and life expectancy for women in selected countries, 1840–2007. Reproduced with permission from the *Lancet* (2). **(B)** Life expectancy at birth for *Homo sapiens* from 200,000 BCE to the present, separated into prescientific (200,000 BCE until 1840) and scientific (1840 until the present) eras.

incidentally opened up a verbal free-for-all to define the term. Dr. Elias Zerhouni, the originator of the program, identified two critical components: the process of applying discoveries generated during laboratory research and in preclinical studies to the development of trials and studies in humans and enhancing the adoption of best practices in the community (13). Harkening back to the principle that has motivated my own career, I define translational research as the application of the scientific method to address a health need (14). Translational research differs from basic science in that the goal of the former is to improve human health, whereas the goal of the latter is to increase human knowledge. Basic science advances as individuals

test the predictions inherent in a field's dominant scientific paradigms. If the studies are conducted carefully, they will inevitably result in the generation of new knowledge regardless of whether the data are consistent with, or at odds with, the current paradigm. Translational research, in contrast, is intrinsically riskier, since there are almost always major gaps in the knowledge one needs to translate data from experimental models into successful interventions in humans – and many uncontrollable and unforeseeable events can derail a translational project up until the very end. Strategically, therefore, it is desirable to try to build basic science hypotheses into translational projects (along with the collection of sufficient data to test the hypotheses) so that if an

intervention fails, there will be sufficient mechanistic information to understand why it failed.

To achieve success, I believe a translational investigator or investigative team needs three cardinal skills: (a) the ability to define a health need with the same precision as a basic science hypothesis; (b) the ability to design an assay that is reductionist enough to interrogate one aspect of the system and that yet incorporates sufficient medical and biologic reality as to make it likely that if an intervention has a positive impact in the assay that the results will be able to be extrapolated to intact animals and humans; and (c) the ability to conceptualize a path to either regulatory approval or widespread adoption by the medical community (14, 15). Physician-

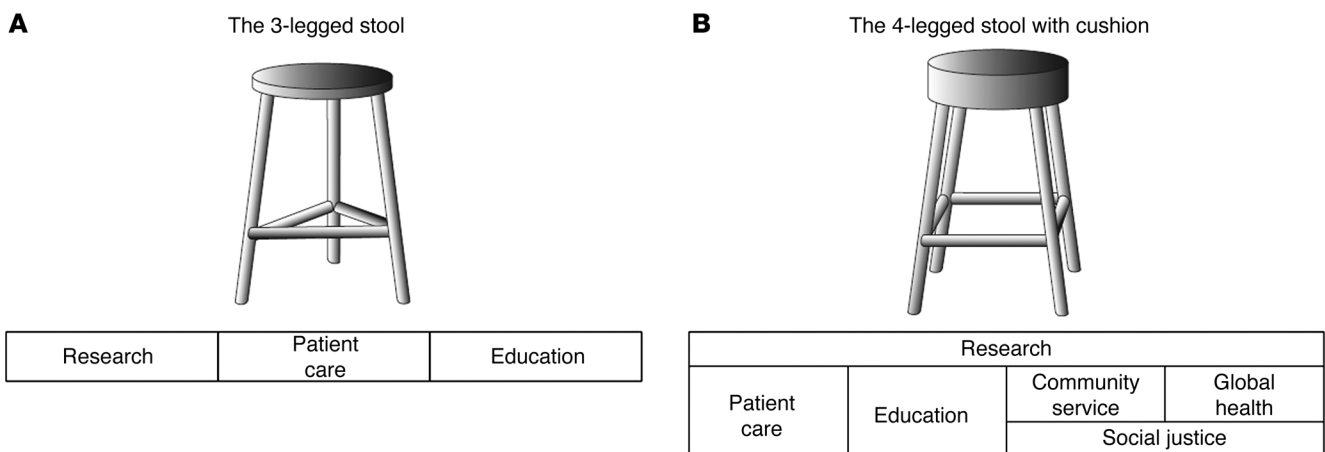


Figure 2

The missions of the academic health center. The old three-legged stool model **(A)**, composed of research, education, and patient care, needs to be updated **(B)** to emphasize the importance of using the scientific method to improve all of the institution's missions. In addition, community service and global health are important recent additions that provide opportunities for connecting the institution's medical mission to the attainment of social justice. Reproduced with permission from Cornell University Press (15).



scientists play outsized roles in the translational research process precisely because they have the ideal background to acquire and hone these skills. In fact, acquiring these skills is at the core of many of the CTSA educational programs, and it is the centerpiece of our programs at Rockefeller University. My own career in platelet research provides one example of how these skills build on each other in pursuit of translational goals.

Blood platelet: the health needs

As a fourth-year medical student at New York University School of Medicine in 1970, I developed a sense of the medical importance of blood platelets by my interactions with a patient with an artificial heart valve who suffered a disabling thrombotic stroke and with another patient who had the rare platelet disorder termed Glanzmann thrombasthenia (GT) (16). There was mounting evidence at that time that platelets played a role in thrombotic disease, but there were no specific therapies to inhibit platelets, and so their contribution remained unclear. On the other hand, the clinical impact of having platelets that could not clump together (aggregate) was clear, since patients with GT, which is inherited as an autosomal recessive trait, were known to suffer from a variably severe lifelong mucocutaneous hemorrhage (17). I went on to study patients with this disorder as a student with Dr. Marjorie Zucker and later at the NIH, the State University of New York at Stony Brook, Mount Sinai School of Medicine, and now at Rockefeller University. Pioneering studies by several laboratories in the 1970s identified the loss of 2 different proteins in the platelets of GT patients, initially termed GPIIb and GPIIIa (based on their mobility in sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and later given the integrin receptor designations α IIB and β 3, respectively (18, 19). It was also known that the platelets of patients with GT are partially deficient in the soluble plasma protein fibrinogen. From these clues, several groups put the pieces of the puzzle together and showed that α IIB and β 3 form a heterodimeric complex that serves as a receptor for fibrinogen (as well as von Willebrand factor). Moreover, since fibrinogen and von Willebrand are both macromolecular proteins and contain more than one α IIB β 3-binding site, they can mediate platelet aggregation by bind-

ing simultaneously to α IIB β 3 receptors on two different platelets, creating a bridge between the platelets.

Blood platelets: developing and applying an assay

In 1980, we were able to support this model of platelet aggregation by developing a miniaturized assay to assess the ability of platelets to agglutinate fibrinogen-coated beads and showing that platelets from patients with GT failed to aggregate the beads (20). We further tested the model by screening for mAbs that could inhibit the agglutination of fibrinogen-coated beads by platelets. In fact, all of the antibodies that inhibited the agglutination reacted with the α IIB β 3 receptor (21). We went on to use these antibodies in translational studies in collaboration with Drs. Deborah French, Peter Newman, and Uri Seligsohn on the diagnosis of GT, including prenatal diagnosis (18, 22–31). In particular, we studied a large number of patients from the Iraqi-Jewish population living in Israel. This group has had a high rate of intragroup marriage because it existed in relative isolation in Babylonia, modern Iraq, from the time of its captivity in 586 BCE until its return to modern-day Israel in 1950–1951. They are the subjects of Psalm 137: “Beside the rivers of Babylon, we sat and wept as we thought of Jerusalem.” Thus, the relatively high rate of consanguinity within the group made it more likely that autosomal-recessive disorders like GT would become manifest.

We also used the antibodies in basic biochemical studies and, ultimately, in collaboration with Dr. Timothy Springer and his colleagues, x-ray crystallographic analysis of the molecular mechanism of ligand binding to α IIB β 3 and the conformational changes in the receptor that accompany ligand binding (32).

We subsequently modified the fibrinogen bead assay for use in whole blood (33) and then worked with Dr. Robert Hillman and the scientists at Accumetrics to convert it into an automated cartridge-based system (34). By activating platelets with different agonists, we were able to establish assays to monitor the antiplatelet effects of aspirin, clopidogrel, and α IIB β 3 antagonists (reviewed in ref. 35). Recent meta-analyses indicate that there is an association between a poor antiplatelet response to clopidogrel, as measured by this assay, and the risk of subsequent vascular events (36, 37).

Blood platelets: application of insights from patients with GT to patients with thrombotic cardiovascular disease and development of a path to regulatory approval of a new class of antiplatelet agents

While GT is a rare disorder, affecting approximately one person in a million, we wondered whether the insight we obtained from studying these patients might bear on the most common cause of death in the United States, ischemic cardiovascular disease due to thrombosis (38). Data obtained by many investigators during the 1970s and 1980s implicated platelets in this process, although their precise role remained uncertain. Clinical studies of aspirin, which had been previously shown to partially inhibit platelet aggregation, were initially equivocal, but a major meta-analysis in 1988 (39) suggested an important role in reducing thrombotic vascular events (reviewed in ref. 40). However, since aspirin has many other effects, it was not possible to unequivocally ascribe its impact to its antiplatelet effects. In 1991, ticlopidine, a more potent antiplatelet agent that emerged from random screening of organic compounds (41) and showed antithrombotic activity in animal models and clinical efficacy in a variety of thrombotic disorders (42), was approved for human use. Ticlopidine’s mechanism of action, namely inhibition of the platelet P2Y₁₂ ADP receptor, was unknown at the time and would only be discovered in 2001 (43).

During this same period, studies by many groups established the central paradigm of platelet physiology in which, under normal conditions, platelets circulate in an unactivated state and do not interact with the blood vessel wall because the endothelium produces two potent soluble inhibitors of platelet activation, prostacyclin (PGI₂) and nitric oxide (NO), and contains an enzyme (CD39) that can degrade adenosine diphosphate (ADP), a potent platelet agonist that is released from activated platelets (NO, PGI₂, CD39) (44). Vascular injury, which may pose a threat of hemorrhage, results in the exposure of proteins that are either in the subendothelial space and/or deposited from plasma, including von Willebrand factor and collagen, for which platelets have constitutively active receptors, including the GPIIb/IX complex for the former and both GPVI and α 2 β 1 for the latter (45–47). This results in platelet



adhesion, which is then followed by platelet activation, augmented by the synthesis and/or release from platelets themselves of potent agonists, including thromboxane A_2 and ADP, and the conversion of the α IIB β 3 receptor into a conformation with high ligand-binding affinity (19). This in turn results in the binding of plasma fibrinogen and/or von Willebrand factor and the recruitment of additional platelets to the growing platelet thrombus (that is, platelet aggregation) via the α IIB β 3 receptor-mediated bridging mechanism. The platelets then serve to initiate both coagulation and inflammation by helping to catalyze the generation of thrombin (itself a potent platelet activator) (48) and the recruitment of leukocytes through exposure of P selectin (49), respectively.

As viewed against this background, the enormous increase in death from cardiovascular disease in the US between 1900 and 1960 can be seen as the result of a number of factors, including the increase in longevity due to the reduction in deaths due to infectious diseases (thus allowing conditions that predispose individuals to atherosclerosis, such as hypertension and diabetes, to operate over a longer period of time), the increase in cigarette smoking, and the adoption of both a proatherosclerotic diet and a more sedentary life style. The connection between underlying atherosclerosis, which rarely leads to vasoocclusion by itself, and platelet-mediated acute thrombosis leading to vasoocclusion and ischemic infarction lies in the exposure of platelet-reactive proteins when the atherosclerotic plaque erodes or ruptures (50–52). These processes lead to a major biologic misunderstanding, namely the platelet misinterpreting the exposure of the proteins, which are similar or identical to those exposed with vascular injury, as posing a risk of hemorrhage and thus responding with platelet adhesion and aggregation, leading to vasoocclusion. From an evolutionary standpoint, it is likely that the risk of death from hemorrhage from birth on, and especially in the hemostatically challenging postpartum period, favored the survival of individuals with more active hemostatic symptoms. This natural selection process was highly adaptive for our ancestors, but became maladaptive in our modern age for individuals who develop atherosclerosis as they age. In fact, many of the advances in the therapy of cardiovascular disease introduced in the second half of the 20th century were based on inter-

fering with the native hemostatic system with anticoagulants, antiplatelet agents, and thrombolytic agents. Collectively, these agents better balance the hemostatic system to minimize thrombotic events in those at higher risk, but at the cost of increasing the risk of hemorrhage.

The platelet α IIB β 3 emerged from studies of platelet function as a potential therapeutic target, and we and others demonstrated that mAbs and small molecule inhibitors based on the Arg-Gly-Asp all-recognition sequence in adhesive glycoproteins (53) could prevent platelet thrombus formation in a number of animal models, including those in which aspirin, which is a less potent platelet inhibitor, failed to prevent thrombosis and vasoocclusion (54–59). We then worked with the scientists at Centocor to develop one of our mAbs, 7E3, into a therapeutic agent (60, 61). Based on data from initial studies, 7E3 was redesigned as a recombinant chimeric Fab fragment comprised of the murine variable regions and human IgG1 constant regions (c7E3 Fab; abciximab) (62). Clinical studies led by Drs. Robert Califf and Eric Topol established the efficacy of abciximab therapy in patients undergoing percutaneous coronary interventions (PCI) who were at high risk of developing ischemic complications (63), leading to its approval as adjunctive therapy in this population by the US FDA in December 1994. This marked the first time an antiplatelet agent was produced, developed, and approved based on an understanding of platelet physiology and the molecular target. Subsequent studies demonstrated its efficacy in patients undergoing stent placement and reduced the risk of hemorrhage associated with its use by decreasing the dose of heparin used in conjunction with abciximab (64). Two small molecule inhibitors of α IIB β 3 were approved by the FDA in 1998: eptifibatid, which was developed by Drs. David Phillips and Robert Scarborough (65), and tirofiban, which was developed by Dr. Robert Gould and his colleagues (66). With the dramatic increase in the use of PCI and stent placement, collectively, these agents have probably been used to treat at least 8,000,000 people worldwide. A 2009 Cochrane review of 36 randomized controlled clinical trials of these agents in 30,696 PCI patients found them to reduce the 30-day odds ratio for death by 24% ($P = 0.01$) and for death and myocardial infarction by 35% ($P < 0.000001$) (67).

There have been many advances in PCI therapy since abciximab's approval, including the development of more potent thienopyridine compounds than ticlopidine (clopidogrel, prasugrel, ticagrelor) (68) that target the platelet P2Y $_{12}$ ADP receptor, the direct antithrombin bivalirudin (68, 69), and drug-eluting stents (70). Since the α IIB β 3 antagonists have been associated with an increased risk of hemorrhage (67), and hemorrhage is associated with poor clinical outcomes (71), the indications for α IIB β 3 antagonists have narrowed to conditions in which the thrombotic risk is very high. The majority of hemorrhagic complications associated with α IIB β 3 antagonist therapy occur at the catheter access site. Fortunately, the risk of access site bleeding can be dramatically reduced by using the radial artery rather than the femoral artery, and the radial approach is now becoming more common in the US (72).

α IIB β 3 antagonists are currently under investigation for several indications, including (a) intracoronary therapy of ST segment elevation myocardial infarction (STEMI) (73, 74); (b) immediate recanalization of the culprit artery in STEMI with high thrombus burden, but delaying stent placement until the antiplatelet therapy has diminished the thrombotic potential (75, 76); (c) reducing the risk of thrombotic complications of PCI in patients who do not have a good response to clopidogrel (77, 78); (d) bridging therapy for patients with recently placed coronary artery stents who need to undergo surgery during the interval between when they stop thienopyridine medication and shortly before surgery (79); (e) treating acute thrombotic complications of detachable coil embolization of cerebral aneurysms (80); and (f) very early treatment of STEMI, prior to hospitalization, to arrest the thrombotic process and thus prevent progression to myocardial necrosis and infarction (aborted myocardial infarction) (81).

The last experimental use is of particular interest because, in contrast to the dramatic decrease in in-hospital mortality caused by STEMI over the past 40 years, there has been much less success in reducing prehospital mortality (82). In fact, more than one-half of the deaths from coronary heart disease in the US occur in the prehospital phase (82). Prehospital cardiovascular deaths, many of which are due to myocardial infarction, account for more than 350,000 deaths each year in the US (83). By comparison, death due to can-



cer of the lung, breast, and colon together accounted for approximately 257,000 deaths in the US in 2004. Very early administration of α IIB β 3 antagonists has been shown to increase coronary artery blood flow (84) and decrease both infarct size and mortality in high-risk groups (85, 86). Speed of administration is of the essence, since the benefit decreases rapidly if the α IIB β 3 antagonist is administered more than one hour after the onset of symptoms (81). Thus, the variability in reported benefits of early administration of these agents is paralleled by the length of time between the onset of symptoms and drug administration (86, 87).

Since the three approved α IIB β 3 antagonists must be administered intravenously, it would be desirable to develop α IIB β 3 antagonists that could be more easily administered in the prehospital setting. Previous attempts to develop orally active α IIB β 3 antagonists based on the Arg-Gly-Asp motif for secondary prevention of vascular events were all unsuccessful because the agents either lacked efficacy or were paradoxically associated with increased mortality (88, 89). Moreover, the agents were also associated with the development of thrombocytopenia in a small percentage of patients (90). It has been hypothesized that both the increased mortality and thrombocytopenia result from the agents inducing the receptor to adopt a high-affinity ligand-binding conformation(s) (88, 89). This could lead to paradoxical platelet aggregation and thrombosis when the plasma level of the drug declines and the drug leaves the binding site. Similarly, the mechanism of the thrombocytopenia may be related to the conformational change(s) induced by the agent exposing epitopes on the receptor for which some individuals have preformed antibodies (90, 91).

In an attempt to address the need for an α IIB β 3 antagonist that does not induce the active state of the receptor and that does not require intravenous administration, we performed a high-throughput screen of more than 30,000 compounds using an assay based on inhibition of platelet adhesion to immobilized fibrinogen (92). We identified a single compound (RUC-1) that inhibited platelet binding and went on to show that RUC-1 specifically inhibits ligand binding to human α IIB β 3, but not the closely related α V β 3 receptor, by selectively interacting with the α IIB subunit (93, 94). RUC-1's binding mechanism differs from

that of eptifibatide and tirofiban in that it does not interact with a Mg^{2+} ion in the β 3 metal ion-dependent adhesion site (MIDAS). In collaboration with Dr. Mortimer Poncz's group, we demonstrated that RUC-1 is effective in inhibiting thrombus formation in both large blood vessels and in the small blood vessels of the microvasculature (93). We then made a number of congeners of RUC-1 in collaboration with Dr. Craig Thomas' group and found that one of these, RUC-2, was approximately 100-fold more potent than RUC-1 (95). X-ray crystallographic studies conducted in collaboration with Dr. Timothy Springer's group demonstrated that RUC-2's greater potency was due, in part, to its additional interaction with an amino acid (β 3 Glu220) that ordinarily coordinates the Mg^{2+} ion in the MIDAS, resulting in the loss of the Mg^{2+} (95). Since fibrinogen binding to α IIB β 3 requires the interaction of the ligand with this MIDAS Mg^{2+} , the receptor cannot bind ligand in the presence of RUC-2. Moreover, since ligand interaction with the MIDAS Mg^{2+} is associated with inducing the receptor to adopt an activated conformation with high ligand-binding affinity, the inability of RUC-1 and RUC-2 to interact with the MIDAS Mg^{2+} may provide a therapeutic advantage (32, 96, 97). In fact, RUC-1 and RUC-2 produce much less extensive conformational changes in α IIB β 3 than eptifibatide and/or tirofiban, as judged by a number of different techniques, including direct visualization by electron microscopy of the ability of the agents to induce extension of the receptor (92, 95). Similarly, RUC-1 and RUC-2 are much less able to "prime" α IIB β 3 to spontaneously bind fibrinogen when the agent is removed by washing (95, 97, 98). RUC-2 is currently undergoing additional preclinical studies to assess its suitability for use in patients with STEMI in the early prehospital setting.

Reflections

As I reflect on the evolution of our studies on α IIB β 3, I realize just how fortunate I have been to be able to benefit from the advances in basic science that have provided remarkably powerful tools, including mAbs, synthetic peptides, molecular cloning and gene sequencing, recombinant proteins and site-directed mutagenesis, molecular dynamics simulations, libraries of organic compounds, 3-dimensional reconstructions of electron density maps, and x-ray crystallography. These have

unleashed translational opportunities for academic investigators that were unthinkable when I began my career.

I also recognize how fortunate I have been to be able to sustain a career as a physician-scientist. The synergism that comes from integrating basic science with clinical medicine is extremely powerful, making it possible to use the lever of the scientific method to improve the health of people throughout the world. At the same time, I recognize the cognitive dissonance that can come from trying to "live" in two different cultures simultaneously. For example, clinicians are used to acting rapidly to address their patients' immediate needs, whereas basic scientists wait to weigh evidence very carefully and avoid rushing to judgment; clinicians are encouraged to conform to practice guidelines and standards of care, whereas basic scientists are encouraged to be bold in constructing hypotheses that overturn current paradigm; clinicians try to avoid error at all cost, since the patient's life may be at stake, whereas basic scientists view error as an inevitable element of scientific experimentation and learn that some of the greatest discoveries grew out of apparent "errors"; clinicians have a high degree of respect for medical authority, whereas basic scientists are skeptical of authority and challenge it repeatedly; clinicians tend to focus on the unusual feature of an illness, whereas basic scientists hunt for principles that are generalizable even if it means excluding "outlier" values; clinicians are bound by the self-imposed obligations of the physician's oath, whereas basic scientists prefer the unfettered pursuit of scientific truth; clinicians recognize that they are unable to control the many variables that may confound their ability to establish cause and effect, whereas basic scientists constantly strive to improve their ability to control all of the variables in an experiment except the one under study. Finally, our species' tribal origins place physician-scientists in the unenviable position of having to choose which tribe they will align with on any given day by virtue of their binary choice to wear either clothes appropriate for caring for patients or jeans and a T-shirt! There are, however, also great benefits in living in two cultures, since it provides greater objectivity to assess the strengths and limitations of each culture and, most importantly, the chance to feel the energy, excitement, and satisfaction that comes from standing at the interface of two noble traditions.



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