A 50-Year Research Journey
—— From Laboratory to Clinic ——

John Ross Jr, MD

Prior important research is not always cited, exemplified by Oswald Avery’s pioneering discovery that DNA is the genetic transforming factor; it was not cited by Watson and Crick 10 years later. My first laboratory research (National Institutes of Health 1950s) resulted in the clinical development of transseptal left heart catheterization. Laboratory studies on cardiac muscle mechanics in normal and failing hearts led to the concept of afterload mismatch with limited preload reserve. At the University of California, San Diego in La Jolla (1968) laboratory experiments on coronary artery reperfusion after sustained coronary occlusion showed salvage of myocardial tissue, a potential treatment for acute myocardial infarction proven in clinical trials of thrombolysis 14 years later. Among 60 trainees who worked with me in La Jolla, one-third were Japanese and some of their important laboratory experiments are briefly recounted, beginning with Sasayama, Tomoike and Shirato in the 1970s. Recently, we developed a method for cardiac gene transfer, and subsequently we showed that gene therapy for the defect in cardiomyopathic hamsters halted the progression of advanced disease. Cardiovascular research and medicine are producing continuing advances in technologies for gene transfer and embryonic stem cell transplantation, targeting of small molecules, and tissue and organ engineering. (Circ J 2009; 73: 3–12)

Key Words:  Cardiac function; Cardiac output; Catheterization

It was a pleasure for me to address the Japanese Circulation Society, at the invitation of Society President, Professor Masunori Matsuzaki, and I am honored to be an International Honorary Member of the Society. During a number of trips to Japan, my wife Lola and I have come to know and love Japanese people, culture and art. I gave my first lecture to your Society at Gifu in 1976, at the invitation of Professor Shoji Hayase. That was the mechanics of cardiac contraction, but my main theme in this lecture will be how prior research in the laboratory often forms the basis for later progress in the clinic or the laboratory, even though the connection often is not stated or even recognized, let alone cited. My first example of this concerns DNA.

During my first year at Cornell University School of Medicine in 1951, I listened to a rather boring lecture on the nucleic acids, but heard nothing of the genetic importance of DNA. Of course, publication of the structure of DNA in 1953 changed all that. However, Watson and Crick would not have known where to look had it not been for Oswald Avery, who nearly 10 years earlier in 1944 published a landmark paper in the Journal of Experimental Medicine! Avery and his colleagues showed that a purified substance isolated from type III Pneumococcus in culture was capable of changing the non-encapsulated type II into the entirely different, encapsulated type III strain. After extensive chemical analyses that fraction, called the “transforming factor”, proved to be deoxyribonucleic acid (DNA) – not a protein as commonly thought! Avery’s brilliant discovery was proved to be deoxyribonucleic acid (DNA) – not a protein as commonly thought! Avery’s brilliant discovery was not cited by Watson and Crick 10 years later. My first laboratory research project was deoxyribonucleic acid (DNA), not a protein as commonly thought! Avery’s brilliant discovery was not cited by Watson and Crick 10 years later. My first laboratory research project was not cited, exemplified by Oswald Avery’s pioneering discovery that DNA is the genetic transforming factor; it was not cited by Watson and Crick 10 years later. My first laboratory research (National Institutes of Health 1950s) resulted in the clinical development of transseptal left heart catheterization. Laboratory studies on cardiac muscle mechanics in normal and failing hearts led to the concept of afterload mismatch with limited preload reserve. At the University of California, San Diego in La Jolla (1968) laboratory experiments on coronary artery reperfusion after sustained coronary occlusion showed salvage of myocardial tissue, a potential treatment for acute myocardial infarction proven in clinical trials of thrombolysis 14 years later. Among 60 trainees who worked with me in La Jolla, one-third were Japanese and some of their important laboratory experiments are briefly recounted, beginning with Sasayama, Tomoike and Shirato in the 1970s. Recently, we developed a method for cardiac gene transfer, and subsequently we showed that gene therapy for the defect in cardiomyopathic hamsters halted the progression of advanced disease. Cardiovascular research and medicine are producing continuing advances in technologies for gene transfer and embryonic stem cell transplantation, targeting of small molecules, and tissue and organ engineering. (Circ J 2009; 73: 3–12)

Key Words:  Cardiac function; Cardiac output; Catheterization

(Received September 30, 2008; accepted October 1, 2008; released online December 2, 2008) Department of Medicine, Division of Cardiology, University of California San Diego School of Medicine, La Jolla, CA, USA Based on a Special Lecture delivered at the 72nd Annual Meeting of the Japanese Circulation Society, March 30, 2008, Fukuoka, Japan. Mailing address: John Ross Jr, MD, UCSD School of Medicine, 9500 Gilman Dr., 0613S, La Jolla, CA 92093, USA. E-mail: jross@ucsd.edu

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
Fig 2. Transseptal left atrial puncture in the first patient. Giant V waves indicate severe mitral regurgitation. When the needle is withdrawn from the left atrium (LA) across the interatrial septum into the right atrium (RA) the pressure becomes normal. Reproduced with permission from Ross et al.

orifice areas in patients with mitral or aortic stenosis, using the indicator dilution method to determine the cardiac output. In 1960, the transseptal method was adapted at the NIH and other institutions to use the Seldinger percutaneous approach. A slightly modified transseptal needle with a 20 or 21 gauge distal tip for use with a large taper-tip catheter was discussed with me by a young clinical associate, Dr. Edwin Brockenbrough shortly before I left the NIH to complete 2 years of residency training in New York City, and the modified approach was later published from the NIH and by others.

In 1962 Eugene Braunwald was appointed Head of the new Cardiology Branch of the NIH at the NIH, and he invited me to become a Section Head in charge of 2 cardiac catheterization laboratories and an experimental laboratory. At that time, Edmund Sonnenblick was at the NIH in another laboratory studying the mechanics of isolated cardiac muscle. I became very interested in this work and decided to apply some of the principles to study of the intact heart, in particular the roles of afterload, preload, and the inotropic state in the normal and failing heart.

The availability of the transseptal technique led to the addition of an early clinical investigation in patients undergoing diagnostic left heart catheterization. We increased the afterload in patients without and with LV dysfunction by graded infusions of the vasopressor angiotensin II. LV pressures were measured, along with determinations of the cardiac output, and function curves of the LV were then constructed plotting LV end-diastolic pressure (LVEDP) vs the stroke work index (SWI), as well as the relations between the LV systolic pressure (LVSP) and the stroke volume index (SVI) (Fig 3). The responses in this mixed set of patients fell into 3 groups, in which the SWI increased substantially (group 1), increased mildly (group 2) or was flat (group 3) (Fig 3, Upper panels). The increases in LVSP to the graded angiotensin infusions were closely similar in the 3 groups; groups 1 and 2 showed increases in the SVI, but in group 3 the SVI fell sharply (Fig 3, Lower panels). In contrast to groups 1 and 2 (which included patients with modest heart disease, such as mild mitral stenosis, pulmonic stenosis, or atrial septal defect), patients in group 3 had cardiomegaly on chest X-ray, a history of heart failure, or cardiomyopathy. I believe this was the first such investigation to demonstrate enhanced sensitivity of the failing human LV to increased afterload.
Fig 3. Changing the afterload in patients without (Groups 1 and 2) and signs of left ventricular (LV) failure (Group 3). The upper 3 panels show the responses of the stroke work index (SWI) to graded increases in the infusion of angiotension II, and the lower 3 panels show the accompanying responses of the stroke volume index (SVI) plotted against the LV systolic pressure. For discussion see text. Reproduced with permission from Ross et al. 8

Fig 4. Responses of the canine left ventricle (LV) to changes in the afterload alone. In the left panel the aortic flow (Ao. Flow) and pressure (Ao. Pr.), LV pressure (Pr.), end diastolic pressure (LVEDPr) and its first derivative (dP/dt) are recorded; at the arrow, the aortic pressure is abruptly reduced using a valve triggered during diastole from the ECG; the valve is connected to a pressure reservoir. The next contraction occurs at a lower LV systolic pressure and results in a higher stroke volume. In the righthand panels, the aortic and LV systolic pressures are progressively increased until an isovolumic LV contraction occurs. The same LVEDP persists throughout the series. Reproduced from Ross et al. 9
Laboratory research in experimental animals was also undertaken to investigate the mechanics of contraction in the intact heart under altered loading conditions and inotropic states. Among those studies was one that demonstrated the effects of changing only the afterload in the normal canine heart (Fig 4). This was accomplished by triggering (from the electrocardiogram) a valve attached to a pressure reservoir in order to suddenly change the aortic pressure during a single diastolic interval. Thus, working with Dr James Covell we were able to change the afterload alone while the preload, heart rate and inotropic state remained unchanged.

Tracings from such an experiment (Fig 4) show an inverse relationship between the systolic aortic pressure and the stroke volume, from which we could calculate the force–velocity relation for the intact ventricle; this inverse relationship was shifted upward by positive inotropic stimulation.

Pressure–volume (PV) loops provide a convenient way of looking at these events. When the preload is held constant as afterload is increased, the stroke volume falls (Fig 5A), showing the inverse relationship. When the preload is allowed to vary, the stroke volume is restored as the LV end-diastolic volume (EDV) increases to compensate for the increased afterload (high wall stress), even at normal arterial pressure (Wst=p.r./Wth).

Later, these clinical and laboratory investigations led to the concept of “afterload mismatch with limited preload reserve” exemplified by the angiotensin study in patients with LV dysfunction. This concept is defined more fully in Table 1. In heart failure, LV wall stress–volume loops are useful for illustrating the responses of the failing heart to modest increases or decreases in the afterload (Fig 5C). The LV responses to mitral or aortic valve replacement also can be understood within this framework; for example, the LV ejection fraction can be markedly reduced in some patients with severe aortic stenosis and mild myocardial dysfunction, but following correction of afterload mismatch by aortic valve replacement the ejection fraction can become nearly normal.

In 1968, Eugene Braunwald became Chairman of the Department of Medicine at the new School of Medicine at
Based primarily on this study, in a 1972 editorial in Circulation, I proposed that the principle of reducing myocardial damage by coronary artery reperfusion should find future application in the early treatment of patients with MI. Later, several small trials of surgical revascularization after acute MI reported some success, and many small clinical trials of thrombolysis using streptokinase for the treatment of acute MI occurred over the years, none of them conclusive. However, 14 years after our study of experimental reperfusion, the landmark GISSI clinical trial in Italy was published, which definitively proved that reperfusion by thrombolysis with streptokinase could be life saving. This remarkable study, the first of the so-called “megatrials” in cardiology, included 12,000 patients randomized to placebo or streptokinase treatment. It showed a 50% reduction in mortality if thrombolysis was begun within the first hour after the onset of symptoms, with more modest reductions in mortality up to 6 h after symptom onset. A later trial, GUSTO, which used tissue plasminogen activator, it took 42,000 patients to demonstrate only a 1% further mortality reduction.

The experimental studies on reperfusion, of which I believe ours was the first to show tissue salvage, together with later studies by others in experimental animals and in patients, established that the concept of reperfusion to reduce myocardial damage was valid. The decision by the investigators in GISSI that a much larger study than used in previous trials would be needed to prove the concept was correct, and led to widespread application of thrombolysis and later of percutaneous transluminal coronary angioplasty (PTCA) for the early treatment of acute MI.

Before concluding with our most recent direction in laboratory research involving cardiac gene transfer, let me consider briefly the scientists from Japan who have worked with me in the Seaweed Canyon Laboratory at UCSD over the years (Table 3). They comprise nearly one-third of the more than 60 such scientists from the United States and many other countries. Several of them also worked with Dr Kirk Peterson. Together, these Japanese scientists were responsible for more than 70 published research papers. Several years ago, a photograph was sent to me by the Japanese scientists who had become Professors and Heads of Divisions of Cardiology or Departments of Medicine in Japan (Fig 7). I would like to mention a few examples of work by some of these now-senior scientists dating from the time they worked with me in La Jolla.

In 1975, Dr Shigetake Sasayama produced chronically instrumented dogs in order to study the development of LV hypertrophy. At that time, there was a consensus that hypertrophy was a pathological condition. Sustained ascending aortic constriction using an implanted inflatable cuff was produced in dogs instrumented with a pressure transducer and ultrasonic dimension gauges on the LV. Significant hypertrophy occurred by 2 weeks in these conscious animals, with large increases in LVSP and wall thickness. Before and after the development of LV hypertrophy, the aortic cuff was first deflated and then a transient acute aortic constriction was produced in order to examine LV end-systolic pressure–diameter (ESPD) relations. In the left panel of Fig 8, the averaged pressure–diameter loops of the LV before and during acute aortic constriction prior to the development of hypertrophy (solid loops).
Fig 7. Scientists from Japan who worked with me in La Jolla who later became Professors and Head of Departments or Divisions in Japan. From left to right, Drs Hitonobu Tomoike, Kunio Shirato, Shigetake Sasayama, Teruhiko Toyo-Oka, and Masanori Matsuoka. To this group should now be added Drs Shunichiro Myazaki and Minoru Hongo.

Table 3 Scientists From Japan at University of California San Diego, La Jolla, CA, USA 1974–2004

<table>
<thead>
<tr>
<th>Scientist</th>
<th>Scientist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hongo, Minoru</td>
<td>Kamada, Toshiaki</td>
</tr>
<tr>
<td>Ikeda, Yasahiro</td>
<td>Lee, Jong Dae</td>
</tr>
<tr>
<td>Iwamoto, Yoshitaka</td>
<td>Matsuzaki, Masanori</td>
</tr>
<tr>
<td>Iwatate, Mitsuhiro</td>
<td>Miura, Toshiro</td>
</tr>
<tr>
<td>Kambayashi, Masashi</td>
<td>Myazaki, Shunichi</td>
</tr>
<tr>
<td></td>
<td>Ono, Shiro</td>
</tr>
<tr>
<td></td>
<td>Osakada, Genta</td>
</tr>
<tr>
<td></td>
<td>Ryoike, Tsutomu</td>
</tr>
<tr>
<td></td>
<td>Sasayama, Shigetake</td>
</tr>
<tr>
<td></td>
<td>Shirato, Kunio</td>
</tr>
<tr>
<td></td>
<td>Tanaka, Nambuki</td>
</tr>
<tr>
<td></td>
<td>Tajimi, Tsukasa</td>
</tr>
<tr>
<td></td>
<td>Tomoike, Hitonobu</td>
</tr>
<tr>
<td></td>
<td>Toyo-oka, Teruhiko</td>
</tr>
</tbody>
</table>

Scientist from Japan who trained in our experimental laboratory at Seaweed Canyon in La Jolla, CA, USA.

Fig 8. Left ventricular (LV) pressure-diameter (Left) and wall stress-diameter loops (Right). LVP, LV pressure; LVWSSt, LV wall stress; LVID, LV internal diameter. The loops and the linear LV end-systolic pressure-diameter and LVWSSt diameter relations are plotted before (solid lines) and after (dashed lines) the development of LV hypertrophy. For discussion see text. Reproduced with permission from Sasayama et al.22

Fig 9. Effects in the canine heart of induced partial coronary artery narrowing maintained for 5 hours (h). Regional systolic wall thickening in the region supplied by the stenosed coronary artery is expressed as a percent of control (100%). The stenosis was maintained for 5h (cross-hatched area) and then released, with reperfusion for 7 days. Reproduced with permission from Matsuzaki et al.25

linear ESPD relation is also shown (solid line). After hypertrophy, there is hemodynamic hyperfunction with a higher systolic pressure (a stronger ventricle) and increased chamber shortening during acute cuff inflation (dashed loops), leading to an upward shift and increased slope of the linear ESPD relation (dashed line), which suggests increased myocardial contractility of the hypertrophied ventricle in the framework of Sagawa and Suga. However, rather than LV pressure, if afterload on the LV or wall stress (WS) is used and WS-D loops are plotted, the pre-and post-hypertrophy ESWS-D relations fall on precisely the same line (Fig 8, Right panel), indicating that myocardial contractility was neither increased nor depressed.22 Those studies established that compensatory hypertrophy can be associated with enhanced hemodynamic function, but with normal myocardial contractility, the LV being stronger simply because there was more muscle, and they also suggested that the ESPD relationship was not reliable as a measure of contractility in chronic heart disease, when the LV has been remodeled.21,22

In 1978, Dr Hitonobu Tomoike performed a study of exercise-induced ischemia in conscious dogs using telemetry. Instrumented animals chased a van before and after partial inflation of a cuff implanted on a coronary artery, in order to produce coronary artery stenosis.23 This study was the first to directly demonstrate that marked regional myocardial dysfunction, reflecting regional ischemia, occurs during exercise in the presence of severe coronary stenosis. Also, several animals died suddenly from ventricular fibrillation, demonstrating the risk of fatal arrhythmia from exercise-induced transient regional ischemia.23
Also in 1978, Dr Kunio Shirato demonstrated that the pericardium is responsible for an apparent shift upward in the LV diastolic pressure-segment length relationship during acute volume overloading. This shift was reversed and the relationship displaced below that in the resting control condition by nitroprusside infusion. These shifts in the LV diastolic pressure–segment length relations were abolished when the same interventions were repeated after pericardectomy, when these relations all fell on a single curve.

Fig 10. Effects of slowing the heart rate (HR) during sustained exercise on a treadmill. Original recordings of left ventricular pressure (LVP), left ventricular (LV) dP/dt, LV anterior wall thickening (ATWT), and the long and short LV axes. The onset of running (run arrow) was recorded at slow paper speed, and at a HR of 230 beats/min atrial pacing was commenced at 240 beats/min (pace). The sinus node was then inhibited with ULFS 49, but no slowing of HR was evident because atrial pacing at 240 beats/min continued; also, no hemodynamic effect of the drug was evident. Then, reductions in the paced rate to 180 and 150 beats/min showed marked reductions in LV dP/dt, with progressive increase in the LV end-diastolic pressure and LV end-diastolic dimensions. Throughout, exercise was continued at the same level. Reproduced from Miura et al. 28

Fig 11. Beta-adrenergic (β-AR) amplification at the force-frequency relation at rest. (A) The control (cont) response of left ventricular (LV) dP/dt to increasing heart rate is shifted upward by low, medium (mid) and high dose infusions of dobutamine. Reproduced by permission from Kambayashi et al. 29 (B) Regulation of myocardial contractility in the intact heart. To the 3 well known determinants of contractility (β-AR stimulation alone, length-dependent activation, and the force-frequency effect) must now be added a 4th determinant, β-AR regulation of the force-frequency effect. Reproduced by permission from Ross J Jr. 30
matic reductions in LV filling pressure that can occur during the treatment of acute heart failure.

In 1983, Dr. Masunori Matsuzaki performed an experiment that is very relevant to what we now call the acute coronary syndrome in patients, which is marked by prolonged ischemia at rest. The experiment was performed in chronically instrumented dogs in which partial coronary stenosis with regional ischemia was maintained for 5 hours. In contrast to Dr. Matsuzaki’s study, the dogs did not seem to be concerned during this experiment. Fig. 9 shows the average percent changes in systolic wall thickening in the ischemic region during the 5-h period. After reperfusion, there was prolonged post-ischemic dysfunction, or stunning, which became normal after 1 week. There was no necrosis across the LV free wall, but the posterior papillary muscle showed some damage on histologic studies, explaining the mild rise in the serum CK level. In that experiment, reperfusion essentially corrected the effects of prolonged ischemia as observed a number of years later in patients after PTCA in a similar setting. In other experiments in instrumented animals with chronic coronary artery stenosis trained to run on a treadmill, Dr. Matsuzaki showed a close correlation between subendocardial blood flow and regional myocardial function measured with an ultrasonic dimension gauge. After β-blockade exercise-induced regional dysfunction was reduced, subendocardial blood flow distribution was improved, and post-exercise myocardial dysfunction was greatly diminished. These and other observations of regional ischemia later led to the concept of “perfusion-contraction matching” in experimental and clinical settings.

In a 1992 experiment, Dr. Toshiro Miura used a method I described earlier in studying the effects of afterload; that is, holding all variables constant except one (in that case the afterload was changed). In Dr. Miura’s experiment only the heart rate was changed. Fig. 10 shows recordings from an instrumented dog running on a treadmill at a high heart rate. At the arrow, while the dog continued to run, an IR channel blocker (called ULFS 49 or zatebradine) was given to slow the sinoatrial node, but no effect of the drug on the heart rate is evident because the atrium was electrically paced at 240 beats/min. Next, the rate was paced down to slower rates, showing a marked negative inotropic effect of reducing the heart rate on myocardial contractility (Fig. 10). I would emphasize that this occurred despite continued running and a high degree of neurohumoral β-adrenergic stimulation to the heart, and it demonstrates a much greater effect of the heart rate on myocardial contractility than the sustained neurohumoral β-adrenergic stimulation under these conditions.

In other experiments, Drs. Masashi Kambayashi and Miura demonstrated a potent effect in resting animals of β-adrenergic stimulation using increasing doses of dobutamine to enhance the force–frequency relation, which was produced by atrial pacing at increasing heart rates. Clearly, the relationship between cardiac frequency and maximum LV dP/dT was shifted upward, or amplified, by increasing doses of dobutamine. So, at rest as well as during heavy exercise, both high frequency and β-adrenergic stimulation are necessary to achieve maximum myocardial contractility. There are 3 well-known major determinants of myocardial contractility, or inotropic state, in the normal heart (Fig. 11B). The discovery of β-adrenergic regulation of the force–frequency effect has added an important 4th determinant to these 3 standard determinants of myocardial contractility (Fig. 11B). Beta-adrenergic regulation of the force–frequency effect is lost in animals and patients with heart failure.

Finally, I would like to discuss briefly a recent research direction in my laboratory. For a number of years we have studied the cardiomyopathic hamster as a model of dilated cardiomyopathy. In 1997 Nigro et al. in Italy and Sakamoto et al. in Japan separately identified the genetic defect in this hamster as a mutation in the delta-sarcoglycan gene. The delta-sarcoglycan protein is a component of the important transmembrane dystrophin–dystroglycan complex in normal heart muscle cells, so we decided to try to correct the defect by cardiac gene transfer. Working with Dr. Yasuhiro Ikeda, we first developed a method of high efficiency gene transfer to the heart via the coronary arter-
ies, a method I will not detail here. We showed that using this method approximately 70% of heart muscle cells can be transfected when a marker protein is attached to an adenoviral vector (Fig 12, Left panels).7 Then, in collaboration with Dr Masahiko Hoshijima, who was then affiliated with Ken Chien’s laboratory in La Jolla, an adenoviral vector was developed containing the missing gene. This particular type of viral vector has only short-term effects, several weeks, but when we delivered it to cardiomyopathic hamster hearts, we obtained good delta-sarcoglycan protein expression 3 weeks later.7 Thus, in the control untreated hearts there was no expression of any of the sarcoglycan proteins (Fig 12, Right panels, C and F), whereas in treated hamster hearts delta-sarcoglycan was clearly present in the myocardial cell membranes, and other sarcoglycans were also upregulated (Fig 12, Right panels, B and E). Also, there was mild improvement of cardiac function.37 Others, including Dr Toyo-Oka, working with Dr Sakamoto in Japan, obtained beneficial effects in cardiomyopathic hamster hearts using a longer lasting adenov-associated viral vector serotype 2 containing the delta sarcoglycan gene, which was directly injected into a region of the LV wall.38 More recently, Dr Wang, working in Dr Xiou’s laboratory, developed a new adenov-associated viral vector serotype 8, which is muscle-specific, long-lasting, and can be injected intravenously. Using this vector, they transfected the delta-sarcoglycan gene into neonatal and 6-week-old cardiomyopathic hamsters, which produced, remarkably, complete recovery.51 By 1 year, the treated hamsters remained alive and well but had a normal appearance. Moreover, by 1 year, LV size and function were normal in both groups. In the control group, both progressive LV dilation and depressed fractional shortening developed, whereas in the treated group LV size and function remained depressed but entirely stable. Moreover, by 1 year, most animals in the control group had died, whereas the treated hamsters remained alive and active. So it appears that the progression of an established genetic dilated cardiomyopathy can be entirely arrested by gene therapy. I believe that these preliminary findings have relevance for the future treatment of hereditary cardiomyopathies in humans.

I have presented a sampling of research studies from my experimental laboratory during the past 50 or so years. But what about the future? With globalization occurring in all arenas from the environment, to industry, to biomedical research, I am very optimistic about the future of both cardiovascular research and cardiovascular medicine. Despite initial clinical difficulties, gene therapy clearly can be effective in animals, and I am now an advisor on a phase 1 clinical trial of gene therapy for heart failure. Certainly, the development of human embryonic stem (ES) cells will have multiple applications, particularly if work in Dr S Yamanaka’s laboratory40 and Dr JA Thomson’s laboratory41 eventually proves applicable; this work began in mice and recently was successful in using 4 genes to reprogram adult human cells into pluripotent cells closely resembling ES cells, without the use of human embryos.42 Other promising avenues include the identification of small peptides, such as specific growth factors and growth factor inhibitors, one of which is currently being used to halt macular degeneration. Also emerging is the development of agents to inhibit specific signaling pathways, such as the kinase inhibitor Gleevec, which prevents the production of an abnormal but required protein within certain cancer cells. A new research area involves micro RNAs, a class of small RNAs that regulate gene expression at the post-translational level by base pairing with messenger RNA targets. It has been shown that a variety of specific micro RNAs are involved in regulating a number of targets, including cardiac hypertrophy, and congenital heart defects, and their potential for manipulation as tools for treatment is promising.43 Also, advances can be expected in tissue engineering, such as the recent generation of a beating rat heart grown from neonatal rat myocardial cells implanted on the fibrous scaffold of the dead rat heart. So, exhilarating times are ahead, and may you all actively participate in them, whether as researchers, clinicians, or both.

References
