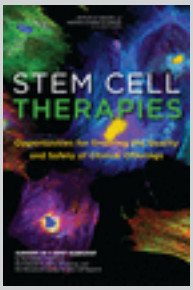

Stem Cell Therapies: Opportunities for Ensuring the Quality and Safety of Clinical Offerings: Summary of a Joint Workshop

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Adam C. Berger, Sarah H. Beachy, and Steve Olson, Rapporteurs; Board on Health Sciences Policy; Board on Life Sciences; Division on Earth and Life Sciences; Institute of Medicine; National Academy of Sciences

STEM CELL THERAPIES

Opportunities for Ensuring the Quality and Safety of Clinical Offerings

SUMMARY OF A JOINT WORKSHOP
by the Institute of Medicine,
the National Academy of Sciences, and
the International Society for Stem Cell Research

Adam C. Berger, Sarah H. Beachy, and Steve Olson, *Rapporteurs*

Board on Health Sciences Policy
Institute of Medicine

Board on Life Sciences
Division on Earth and Life Studies

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COVER: Fluorescence microscopy of pluripotent mouse stem cells undergoing differentiation into a variety of cell lineages. Photo credit: Pablo Perez-Pinera, Jonathan Brunger, Farshid Guilak, and Charles Gersbach, Duke University.

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

I. Glenn Cohen, Harvard Law School
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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **Caswell Evans,** University of Illinois at Chicago, and **Harold J. Fallon,** University of Alabama at Birmingham School of Medicine. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments

were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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Abbreviations and Acronyms

AIDS	acquired immunodeficiency syndrome
ASRM	American Society for Reproductive Medicine
CAS	Chinese Academy of Sciences
CEO	chief executive officer
CIRM	California Institute for Regenerative Medicine
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios (Mexico)
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FTC	Federal Trade Commission
GMP	good manufacturing process
IOM	Institute of Medicine
IRB	institutional review board
ISCT	International Society for Cellular Therapy
ISSCR	International Society for Stem Cell Research
MHLW	Ministry of Health, Labor, and Welfare (Japan)
MS	multiple sclerosis
NAS	National Academy of Sciences
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)

SART	Society for Assisted Reproductive Technologies
U.S.	United States

1

Introduction and Themes of the Workshop[1]

Stem cells offer tremendous promise for advancing health and medicine. Whether being used to replace damaged cells and organs or else by supporting the body's intrinsic repair mechanisms, stem cells hold the potential to treat such debilitating conditions as Parkinson's disease, diabetes, and spinal cord injury (Scadden and Srivastava, 2012). Clinical trials of stem cell treatments are under way in countries around the world, but the evidence base to support the medical use of stem cells remains limited (Bianco, 2013; Daley, 2012) (see Box 1-1).

Despite this paucity of clinical evidence, consumer demand for treatments using stem cells has risen, driven in part by a lack of available treatment options for debilitating diseases as well as direct-to-consumer advertising and public portrayals of stem cell–based treatments. Clinics that offer stem cell therapies for a wide range of diseases and conditions have been established throughout the world, both in newly industrialized countries such as China, India, and Mexico and in developed countries such as the United States and various European nations (Lau et al., 2008). Though these therapies are often promoted as being established and effective, they generally have not received stringent regulatory oversight and have not been tested with rigorous trials designed to determine

[1]The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, are not necessarily endorsed or verified by the Institute of Medicine or the National Academy of Sciences, and should not be construed as reflecting any group consensus.

BOX 1-1
Stem Cell Potential

When a stem cell divides it gives rise to two daughter cells, one of which is at the same stage of development as the original cell, explained Irving Weissman, Virginia and D. K. Ludwig Professor for Clinical Investigation in Cancer Research at the Stanford University School of Medicine. This property of one daughter cell being at the same stage of development as the parent cell is called self-renewal, and it is unique to stem cells. In the body's blood-forming systems–whether bone marrow, mobilized peripheral blood, or umbilical cord blood–only about 1 in 20,000 cells is appropriately called a stem cell.

Beginning in 1988, Weissman and his colleagues learned how to isolate blood-forming stem cells. These cells have been observed to regenerate only blood and no other tissue, despite strenuous efforts to demonstrate otherwise, Weissman said. Only pluripotent stem cells can form cells of different tissues.

To treat people using regenerative medicine, it is essential to have robust, rapid, and sustained regeneration, Weissman said. Any such regenerative-medicine treatment must have gone through four steps:

- A discovery that has been independently replicated,
- Preclinical and published proof of principle,
- Application to a national or other body for successive trials to demonstrate safety and efficacy, and
- Approval from that body that the trial was safe and efficacious.

Today, almost no purified cell products in the clinic have met these four criteria, according to Weissman.

their safety and likely benefits (Daley, 2012). In the absence of substantiated claims, the potential for harm to patients—as well as to the field of stem cell research in general—may outweigh the potential benefits (Barclay, 2009; Bianco, 2013).

To explore these issues, the Institute of Medicine (IOM), the National Academy of Sciences (NAS), and the International Society for Stem Cell Research (ISSCR) held a workshop in Washington, DC, on November 18, 2013, titled Stem Cell Therapies: Opportunities for Ensuring the Quality and Safety of Unregulated Clinical Offerings. The workshop brought together researchers, clinicians, patients, policy makers, and others from North America, Europe, and Asia to examine the global pattern of treatments and products being offered, the range of patient experiences, and options to maximize the well-being of patients, either by protecting them from treatments that are dangerous or ineffective or by steering

them toward treatments that are effective. The workshop was not intended to be a fully comprehensive analysis of the practice of offering stem cell therapies and thus it does not represent activities in all countries where clinics exist. Box 1-2 lists the objectives of the workshop.[2]

BACKGROUND

Many different kinds of stem cell treatments are being offered around the world, said Alta Charo, Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin–Madison and chair of the workshop planning committee. Some are available as procedures offered by clinics, while others, such as skin care products, are available for direct purchase through online marketplaces. These treatments are described as using stem cells from other humans, from animals, or from plants; feature the use of autologous stem cells, in which cells are extracted from an individual, manipulated in a laboratory, and reinfused or reimplanted into that same person; or advertise the use of tissue-specific stem cells.

BOX 1-2
Objectives of the Workshop
Developed by the Planning Committee

- Discuss the current environment in which patients are receiving unregulated stem cell offerings.
- Examine the stem cell treatments that are being offered.
- Assess the potential benefits and risks to individual health.
- Consider the evidence base needed to substantiate the clinical application of stem cell technologies.
- Evaluate legal hurdles for establishing standards and criteria to govern stem cell trials and treatments.
- Discuss potential solutions for assuring the quality of stem cell offerings.

[2]The workshop agenda, speaker biographical sketches, the full statement of task, a list of registered attendees, and a glossary of terms can be found in Appendixes A–E.

Charo said that the status of stem cell therapies is complicated by the legislative and regulatory environment in which medical therapies exist in the United States and other countries. Medicine can be regulated through formal regulatory oversight bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), professional licensure and disciplinary actions, accepted professional practices, professional society certifications, and medical malpractice law. There are a myriad of possible methods to regulate medical treatments, Charo said, "but we are finding ourselves in a situation where it is not clear that [stem cell therapies] are yet being regulated."

The FDA in particular has stated that it "is concerned that the hope that patients have for cures not yet available may leave them vulnerable to unscrupulous providers of stem cell treatments that are illegal and potentially harmful [and that] FDA will pursue perpetrators who expose the American public to the dangers of unapproved stem cells" (FDA, 2012). However, global enforcement can be difficult. While the majority of clinical trials involving stem cells are thought to take place in the United States, there are a large number being conducted elsewhere, particularly in Europe and East Asia; when examining clinical trials involving only mesenchymal stem cells (Dominici et al., 2006), East Asia is thought to be conducting the majority of studies (see Table 1-1). However, the official numbers of trials using stem cells of any kind may be skewed by underreporting of clinical trials to registries. While some trials are required to be entered into public databases, such as trials of drugs, biologics, or devices that are subject to FDA regulation, others are only voluntarily submitted and requirements vary by country.[3]

Another issue, Charo said, is that the marketing of treatments and products is problematic. The information that is available to the average consumer makes it difficult to discern whether a stem cell product that is being marketed has been approved by a regulatory oversight body or even if it has ever been studied. One common practice, Charo said, is to describe products as being less than minimally manipulated[4] in order to

[3]Entering clinical trial information into a registry does not imply endorsement by the regulatory authority of the region in which the trial is taking place. In the United States, registration requirements are described in Section 801 of the Food and Drug Administration Amendments Act.

[4]*Minimally manipulated* is defined as being produced by "processing that does not alter the relevant biological characteristics of cells or tissues" (see 21 CFR 1271.3, revised as of April 1, 2013).

avoid being under the direct jurisdiction of the FDA. Clinics and companies will also claim that journal articles and studies substantiate their claims, while listing elsewhere on their sites that they do not promise that the treatments work.

"It is a very narrow line that we are trying to walk here," Charo said. Patients are potentially being exposed to treatments that are not proven, not approved, not regulated, and possibly dangerous. Yet people also need to be informed that stem cell therapies have great potential, that clinical trials are under way, and that regenerative medicine bears tremendous promise for the future.

TABLE 1-1 Number of Clinical Trials Under Way Using Stem Cells

Country/Region	Clinical Trials Using Stem Cells	Clinical Trials Using Mesenchymal Stem Cells
United States	2,532	73
Europe	993	98
East Asia (including China)	375	122
Canada	194	6
Middle East	172	33
Pacifica	90	8
India	62	16
South America	55	10
Southeast Asia	42	11
Russia	30	7
Central America	28	3
Japan	26	4
Mexico	24	0
Africa	19	8

SOURCE: Data drawn from a search of ClinicalTrials.gov using the terms "stem cells" or "mesenchymal stem cells" (as of March 11, 2014).

THEMES OF THE WORKSHOP

Over the course of the day, several broad topics emerged that were the focus of discussions. Although these points of emphasis should not be seen as consensus conclusions of the workshop, according to several participants, they may warrant further consideration as the fields of stem cell research and regenerative medicine move forward. These points of emphasis include:

Regulatory uncertainty: The best ways to regulate stem cell therapies remain unclear. Stem cells have characteristics that distinguish them from drugs, biologics, or medical devices. Researchers have not yet accumulated the considerable body of science that will be needed to establish regulations that will enable the development and delivery of safe and effective stem cell treatments.

Differing regulatory mechanisms: Countries have taken different approaches to the regulation of stem cell research and therapies, and enforcement of existing regulations also differs. As a result, patients who are willing and able to travel from one country to another can access treatments that are not available in their home countries.

Advertising strategies: In an effort to attract patients, clinics offering stem cell therapies have engaged in advertising on the Internet and elsewhere which is often misleading. This advertising can lead patients to spend large amounts of money on treatments that may not be effective and may even be harmful.

Honoring the needs and autonomy of patients: Patients are frustrated at not being able to access potentially effective stem cell treatments, some of which are being studied in clinical trials and some of which are not. While governments have an obligation to protect patients from ineffective therapies and fraudulent advertising, public policies could also reflect the needs of patients and their autonomy in making medical decisions.

Generating needed information: Governments, professional associations, patient groups, and other organizations all can help generate the information needed to develop effective regulations and allow patients to make informed choices. Self-regulation by the providers of stem cell therapies also could help protect patients and the legitimacy of stem cell research and therapies.

ORGANIZATION OF THE REPORT

Chapter 2 of this summary of the workshop provides an overview of what is known and what is unknown about stem cell therapies, with a particular focus on the kinds of promises being made to patients. Chapter 3 looks specifically at the experiences of patients who have opted for stem cell therapies and their reasons for making the choices they did. Chapter 4 examines the regulatory processes used in five different countries to examine the commonalities and differences among the approaches that national governments are taking to stem cell research and treatments. Chapter 5 discusses the roles of professional societies in educating physicians and patients. Finally, Chapter 6 discusses important challenges, evidence gaps, and possible paths forward to make safe and effective stem cell treatments available as quickly as possible.

2

Stem Cell Therapies—Knowns and Unknowns

A variety of stem cell–based products are being proffered to patients for the treatment of a wide spectrum of disease, though many of these therapies have not undergone extensive testing of their effectiveness and safety (for a summary of highlighted points, see Box 2-1). Individual speakers at the workshop provided broad overviews of the process for developing stem cell–based therapies and the current state of clinical offerings. Much of the excitement surrounding the field is being driven by hype, some participants said. Yet important research is also being conducted that could lead to highly beneficial medical advances.

BOX 2-1
Considerations from Individual Speakers for Assessing Treatment Effectiveness and Communicating with Patients

- Objective outcome measures would be useful for assessing the effectiveness of stem cell therapies. (Wagner)
- Marketing claims by clinics offering stem cell therapies are not necessarily supported by clinical evidence in the scientific literature and may be misleading to patients. (Caulfield)
- Unproven stem cell treatments can harm patients by leading to complications such as tumors, meningitis, or even death; however, patients who have no other treatment options may be willing to take these risks if there is a slight chance of success. (Caulfield)
- Improved communication of clear information about treatment benefits and risks as well as about the value of safety regulations would be useful for patients. (Caulfield)

STEM CELLS AS REGULATED THERAPEUTICS

There are a variety of diseases for which conventional medicine offers no available treatment options, said John Wagner, professor of pediatrics and director of the Division of Hematology–Oncology and Blood and Marrow Transplantation at the University of Minnesota. When patients are desperate, they may turn to experimental or unproven treatments because the therapies afford them hope.

Wagner described his experiences treating patients with epidermolysis bullosa as an example of the process and challenges for developing a stem cell therapy. Epidermolysis bullosa is a mutilating disease of the skin and mucosa that results in shortened survival, a life filled with pain, the inability to perform normal daily tasks, and death due to infection or cancer (Fine et al., 2008; Tolar and Wagner, 2012). As Wagner stated, these patients "would do anything at all for any price. It does not matter. [Any treatment could be made up] and they would be there tomorrow." When Wagner and his colleagues were organizing initial clinical trials to test a potential treatment for the disease, he even had patients offering $1 million to be included because they were so desperate.

Developing a stem cell therapy that can be offered to the public usually begins with an idea that has typically been conceived in a laboratory. For Wagner and his colleagues, they hypothesized that stem cells might be used to repair skin in a mouse model of epidermolysis bullosa. They evaluated the effect of treating these mice with different stem cell populations and found a population of bone marrow cells that resulted in various improvements, such as longer survival times, the absence of blisters, and the appearance of anchoring fibrils, which are missing in disease-affected individuals because of a genetic mutation (Tolar et al., 2009). Even though only three of the treated mice survived, the FDA approved moving forward to clinical trials in humans because of the severity of the disease and the lack of alternative treatment options.

Wagner established the clinical trial under the auspices of an oversight committee which performed data safety and monitoring and reviewed each patient's eligibility. Seven patients received stem cells in the first trial, and, according to Wagner, the treatment produced an "extraordinary" improvement.

Still, the medical community was skeptical of the results. Wagner and his colleagues therefore enrolled more patients, extended the monitoring period, and developed more objective measures for outcomes. Electron microscopy was used to demonstrate that anchoring fibrils were

present post-treatment. In patients whose hands had never formed fingers, it was demonstrated that fingers began to grow after the stem cell transplantation. In addition, Wagner and his colleagues built a device to conduct a blister test that measured the response of a patient's skin to an external stimulus. This device in particular made the reports of improvement more objective and increased overall acceptance in the medical community.

Each step forward in moving a treatment toward approval requires regulatory review and additional expense, Wagner observed. Progressing from basic research to clinical research and then to Phase I, II, and III trials "is a laborious, long, expensive process." The numbers of patients involved in each successive trial gets larger, as does the expense.

The strategic priorities of the FDA's Center for Biologics Evaluation and Research are to enhance the nation's public health preparedness, improve public health globally, improve the quality and safety of biological products, enhance the translation of innovative science and technology into products for patients, advance regulatory science, and strengthen human resources and performance (CBER, 2011). Ensuring safety, however, requires more than just monitoring clinical trials. The FDA must also oversee the manufacturing of products, which includes equipment monitoring, materials management, inventory management, document control, label control, facility control, quality assurance, and other activities. For example, stem cells have to be certified to be free of endotoxin, bacteria, and fungal elements and have certain surface markers before they can be released. These behind-the-scenes activities can be "a big deal," Wagner said, "particularly if you are a small university laboratory."

Therapies Under Development

At the time of the workshop, very few stem cell therapies had received approval from a regulatory oversight body, Wagner said. In North America, the FDA had approved Hemacord®, an umbilical cord blood product developed by the New York Blood Center, while Prochymal, which was developed by Osiris Therapeutics to treat acute graft-versus-host disease in children, had received market authorization from HealthCanada.[1]

[1]In addition to Hemacord®, four other hematopoietic progenitor cell products have been approved by the FDA. For a full list of approved cell therapy products see http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/Approved.Products/default.htm (accessed April 4, 2014).

The majority of stem cell therapies, Wagner said, have been approved outside the United States, with a disproportionate number occurring in South Korea. However, many of these are not really stem cell therapies, Wagner said. Instead, they use allogeneic amniotic membrane, autologous cultured epidermal cells and chondrocytes, or allogeneic bone. Clinical trial numbers indicate that a much broader developmental effort may be under way. A search of the website ClinicalTrials.gov for the term "stem cells" at the time of the workshop found 4,831 studies, though Wagner noted that not all of these were really using stem cells.

CLINICAL OFFERINGS USING STEM CELLS

The issue that the stem cell community is most concerned about is the marketing and sale of stem cell–based therapies that have not been shown to be effective or safe (Caulfield et al., 2012), said Timothy Caulfield, Canada Research Chair in Health Law and Policy and professor in the Faculty of Law and the School of Public Health at the University of Alberta. Desperate patients are searching the Internet and being directed to clinics that look legitimate and offer treatments for virtually everything—Alzheimer's disease, autism, aging, immune deficiencies, liver disease, cancer, diabetes, hair loss, multiple sclerosis (MS), spinal cord injury, and stroke. "This is a marker of quackery, when you have a therapy that allegedly can cure anything," said Caulfield.

A 2008 study found that the claims being made by stem cell purveyors were not supported by published clinical evidence (Lau et al., 2008), and a follow-up study found that marketing practices remained unchanged over the intervening time even though the issue of potentially fraudulent treatments had received increasing attention (Ogbogu et al., 2013). In some respects, Caulfield said, the claims had actually gotten worse, with Internet advertisements saying that the treatments were efficacious, routine, and low risk.

Many of these websites use what Wagner characterized as "debate tactics." For example, they question the motives of an opponent by claiming that the FDA and the pharmaceutical industry are colluding. They cite irrelevant facts or logics, such as claiming that cord blood can cure spinal cord injury because of its effectiveness against leukemia, Caulfield said, or draw on the opinions of unqualified individuals. They play on long-held fantasies and fears, such as implying that a good parent would do anything possible for their child, and they imply that people

who do not pursue a miraculous cure have given up or succumbed to hopelessness.

However, press accounts of stem cell therapies and the clinics in which they are delivered are, with a few notable exceptions, overwhelming positive (see Figure 2-1). Headlines such as "Stem cell miracle gives gift of sight to toddler"[2] make stem cells seem cutting edge, exciting, and legitimate, said Caulfield. Feature stories in magazines, the promise of miracle cures, and promotions by athletes and other celebrities have fed the enthusiasm and hype for this field.

Currently, the words "stem cell" and "regeneration" are being used as marketing tools to play on the excitement that surrounds the field. They are terms that have cultural traction and can influence how people think about an offered cure, Caulfield said. "I call it 'scienceploitation.'

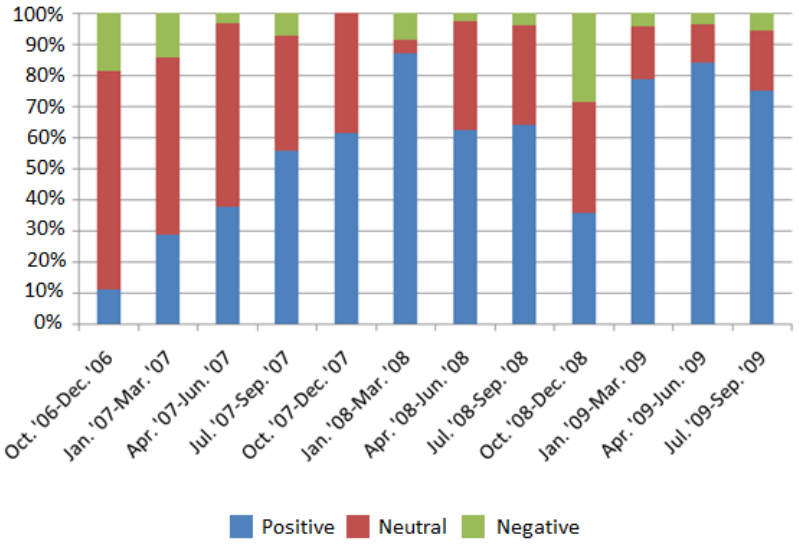

FIGURE 2-1 The tone of news media reports that covered stem cell therapies has been largely positive.
SOURCE: Timothy Caulfield, IOM, NAS, and ISSCR workshop presentation on November 18, 2013. Adapted by permission from Macmillan Publishers Ltd: *Nature Biotechnology* (Zarzeczny et al., 2010), copyright 2010.

[2]See http://www.mirror.co.uk/news/uk-news/stem-cell-miracle-gives-gift-380706 (accessed March 6, 2014).

It happened with electricity. It happened with magnetism. It happened with radioactivity. . . . Any time there is a scientific development that is exciting and sexy, people use it to profit." One way to deal with this would be to pick some clear examples where therapies do not work and make definitive statements in those areas, Caulfield said.

The Number of Patients Seeking Stem Cell Treatments and the Effects on Those Patients

It is very difficult to determine the number of patients who are receiving stem cell treatments, either in absolute terms or compared to other forms of treatments that patients may be seeking in overseas clinics, Caulfield said. There are currently no registries in which this information is recorded, noted Alan Petersen, professor of sociology in the School of Political and Social Inquiry at Monash University in Melbourne, Australia. The field thus relies on indirect information, which makes it difficult to obtain quantifiable data. For example, Caulfield said, one clinic in China has claimed to have seen more than 5,000 patients between 2005 and 2009, but determining the veracity of this claim is difficult. Moreover, patients often do not want their doctors or their patient communities to know that they have sought out these treatments. However, Caulfield said, "if you believe [the claims], the numbers are big."

The home countries of patients are difficult to ascertain, but some evidence suggests that the majority of patients are traveling from developed countries to developing countries, Petersen said. Stem cell clinics are a global phenomenon, Caulfield said, with clinics spread around the world (Regenberg et al., 2009). A survey of 224 patients, most of whom were from the United States, Canada, and the United Kingdom, found that about 60 percent were male and about 44 percent were minors (Zarzeczny et al., 2010). Forty-five percent of these patients traveled to clinics in China, with Mexico, Germany, the Dominican Republic, and India the next most common destinations. The most common conditions being treated were optical disorders and blindness, paralysis, multiple sclerosis, cerebral palsy, and brain injuries or damage, Caulfield said. A separate analysis of the websites advertising stem cell treatments and the blogs of patients who receive treatments at these clinics also concluded that the clinics are primarily located in Asian countries, particularly China and India, but also found Central America and Caribbean countries to be major destinations, Petersen said (Levine and Wolf, 2012). China has been a hotbed for stem cell tourism, added I. Glenn Cohen, assistant pro-

fessor at Harvard Law School. More than 200 institutions in China are offering treatments. Russia also has hundreds of unlicensed clinics that are offering stem cell treatments, and many of these clinics employ practitioners without medical qualifications, he said.

In addition, some stem cell providers are offering treatments in developed countries by exploiting regulatory loopholes, Petersen said. For example, some patients in his study were discovering through the Internet that trials were being conducted in the United States, and when they talked with the scientists they were told that they could be treated outside the trial.

Receiving stem cell treatments has resulted in harm to patients, both Caulfield and Petersen reported. Complications have included tumor growth, meningitis, and even death (Amariglio et al., 2009; Bohgaki et al., 2007; Mendpara et al., 2002; Thirabanjasak et al., 2010). One woman had bone fragments growing in her eye after a cosmetic procedure (Jabr, 2012). There is financial harm as well, with an individual treatment costing between $20,000 and $50,000, not including travel, time away from work and family, and potential long-term physical harms. More broadly, harms to patients have eroded public trust and the legitimacy of the field and have created great challenges for the clinical trial and regulatory process, Caulfield said.

Caulfield's colleagues and others have done an analysis of online blogging by patients which has revealed some of the reasons people pursue such therapies (Ryan et al., 2010). (Chapter 3 examines these reasons in more detail.) Though the evidence is anecdotal, and some of the blogs may be originating from the clinics themselves, many of the themes heard among patients quickly surface in the blog posts (Rachul, 2011):

- "While China is not our first choice, it is our only choice for now. We will go anywhere and do anything to give our children a chance at life."
- "I may die anyway, but at least I died fighting. This is an experiment. What did I have to lose?"
- "We need therapies in our own cities and towns. It is deplorable and inhumane that we must put ourselves in harm's way, pushing our already weakened bodies to the point of exhaustion, to seek stem cell therapy halfway around the world."

People are going to these clinics because they feel that they have no other choice, said Caulfield, and that they cannot afford to wait for stem cell therapies to be approved through traditional regulatory processes.

Overseas clinicians are offering hope, Wagner said, despite their obvious financial conflicts of interest. They seek to create connections with patients who feel victimized by the current system. They offer patients control over their lives so they can choose the therapies they want. Patients go directly to the therapy and bypass their physicians, no matter what scientists or clinicians say.

Caulfield and his colleagues recently finished an analysis of more than 175 websites from scientific societies, stem cell research groups, and patient disease societies examining how they try to educate their communities about stem cell tourism (Master et al., 2013). Many of these sites are trying to do a good job, he said. But very few define stem cell tourism, talk about the evidence and the risk, or discuss what the patients should be seeking. They also do not explain why the regulatory process exists and why it is valuable, which is something that needs to be communicated, Caulfield said. As a participant noted, a vehicle is needed to provide patients with access to better information so that they can educate themselves. However, cautioned Ralph Cicerone, president of the NAS, it has been noted that "simply providing information to patients does not overcome their desperate need for some intervention."

This issue is going to become even more challenging as stem cell therapies become more widespread, Caulfield said. Regulators will have more difficulty saying that treatments are ineffective or that action should wait until the results of clinical trials are available, especially when the therapy is being offered elsewhere in the world. Bolder statements need to be made about what the science says about a potential treatment. The problematic aspects of the field need to be addressed because clinical applications are proliferating, Caulfield said. "We have to get this right now in order to deal with the issue in the future."

3

Patients' Experiences

Individual speakers at the workshop focused specifically on the experiences of patients who seek out stem cell therapies. Many of these patients suffer from life-threatening conditions and cannot wait for therapies to be developed in clinical trials. Yet some are spending their life savings on treatments that are very unlikely to be effective. Patients who engage in what has become known as stem cell tourism consult with their own physicians before going to a stem cell clinic in their home countries or abroad. Yet some also feel abandoned by the medical system, especially when they cannot gain access to clinical trials or to the therapies being tested in those trials (for a summary of highlighted points, see Box 3-1).

BOX 3-1
Summary from Individual Speakers About Discussions on Regulation and Patients' Expectations

- Patients can be motivated to seek treatments outside of their home countries for reasons such as cost, quality, and circumventing domestic laws or regulations. (Cohen)
- Regulation could encourage the responsible development of stem cell therapies while allowing greater access to experimental treatment. (Cohen)
- Government encouragement of accreditation and experimentation would generate a more positive response from patients than simply prohibiting access to clinics. (Cohen)
- Providing more accurate information about treatments to patients does not necessarily mean that the information will affect their decision to take risks on unproven therapies because other factors, such as hope, can play powerful roles in medical decision making. (Charo, Petersen)

MEDICAL TOURISM: PATIENTS SEEKING STEM CELL TREATMENTS

The medical tourism industry can be subdivided in three different ways, Cohen said. The first is by the legal status of the treatment. Some treatments are legal both in the patient's own country and in the destination country, such as hip replacements, cardiac bypass, and cosmetic surgery, while others are illegal both in the patient's home and in the destination country, such as the sale of organs for transplantation. Finally, some are illegal in a patient's home country but legal in the destination country—a situation that Cohen termed *circumvention tourism*. Examples of treatments that attract circumvention tourism include abortion, assisted suicide, and stem cell therapies. In the case of stem cell tourism, a treatment may not be illegal in a patient's home country, but rather it simply may not be approved.

The second division is based on who is paying for the treatment, Cohen said. In some cases, patients pay out of pocket; in other cases, insurers are willing to pay. For example, some large insurers in the United States now offer incentives to private employers to send their patients abroad. In places that have universal health care coverage, the government may pay for individuals to be treated in other countries.

The final division is according to where patients are traveling to receive treatment. Patients may go from a developed country to another developed country; they may travel from less developed countries to more developed countries; or they may go from a developed country to a less developed country, which is common with stem cell tourism, Cohen said.

Motivations for Stem Cell Tourism

Patients have a variety of motivations for pursuing treatments abroad, Cohen said. These include cost, quality, circumventing domestic prohibition, inability to participate in clinical trials, and lack of access to unapproved treatments. For example, in the United States the FDA regulates such items as drugs, medical devices, and blood and biological products. Though the FDA does not regulate surgical interventions, legal barriers for patients getting experimental surgeries also exist. Insurers in the United States typically do not reimburse for experimental or investigational surgeries unless clinical effectiveness has been proven. Medical malpractice liability may also limit a surgeon's willingness to provide

therapies. Finally, innovative surgery that is considered research is governed by the Common Rule,[1] which ensures proper protection of human subjects in research and essentially imposes an ethical and regulatory review restriction similar to that of clinical trials.

Medical tourism to countries with more permissive drug approval or access regimes can be an enticing alternative for patients who want the drug or treatment in question, Cohen said. By traveling abroad, patients can engage in a form of "regulatory arbitrage" in order to get experimental therapy. While stem cell therapy and liberation therapy for MS are prominent current examples, medical tourism for experimental therapies has occurred for decades. Many U.S. patients used to travel to Mexico and elsewhere for treatment with laetrile and other experimental cancer therapies. However, laetrile was later shown to be ineffective and unsafe (Moertel et al., 1982). "One of the big questions is whether stem cell therapy is the laetrile of our generation," Cohen said.

Potential for Regulatory Involvement

From a regulatory perspective, prohibiting stem cell tourism is difficult, Cohen said. Stem cell therapies do not fit well into the current FDA model. Stem cells are living biological products susceptible to genetic instability and do not have the predictability of the small molecules that are used in pills. While some stem cell–based interventions may prove amenable to multistage clinical trial approaches, a surgical or transplantation approach may be more appropriate for others (Hyun, 2010). With those interventions, clinical trials are the exceptions rather than the norm because they are so hard to do properly. Cohen suggested that stem cell treatments may be better suited to the same regulatory constraints as transplantation and surgery instead of drugs, small molecules, or biologics.

ISSCR—discussed in greater detail in Chapter 5—posed two questions on its website for clinicians or patients considering stem cell therapies. The first asked about the protocol of a clinical trial and the head of the institutional review board (IRB) overseeing that trial, which was designed to indicate whether the trial was independent. The second asked which regulatory body had shown a treatment to be safe and efficacious. The website was viewed by a large number of people, but it also generated a letter from a lawyer asking on whose authority these questions were

[1] 45 CFR part 46.

being asked. In response, ISSCR shut down the website to avoid legal proceedings, Weissman said.

The government needs to encourage accreditation and experimentation that falls into the category of research rather than charlatanism, Cohen said. He suggested that a consortium of private and public actors, including the FDA and the EMA, could produce a quasi-governmental version of the ISSCR's approach. By calling attention to such factors as IRB approval, whether data from treatments are being published, and the intention to pursue treatments in more widespread clinical trials, such an approach could provide a seal of approval. Eventually, accreditation may be the best option, with standards increasing over time.

Cohen pointed to concerns about the lack of information about both safety and efficacy from treatments that are being performed in these clinics because they are not required to report this information. Treatments done outside the United States raise difficult issues in such areas as fraud, monitoring pediatric patients, and incentives to institute best practices. In particular, Cohen pointed to the involvement of children in stem cell therapies. "It is a very difficult situation for everybody involved," he said. Physicians may try to educate parents about the risks or dissuade them from a particular decision. One question, Cohen said, is whether physicians also have an obligation to report cases to authorities in situations where treatment is considered not only ineffective but actually dangerous. In such cases, it may be appropriate for the states to step in and exert medical guardianship, he suggested.

PATIENTS SEEKING UNPROVEN OR UNREGULATED TREATMENTS

Many factors drive patients to seek out unproven or unregulated stem cell therapies, said Petersen, who has been leading a sociological investigation into the phenomenon since 2009 (Seear et al., 2010). The reasons are underpinned by hope and the desire to exhaust all available options, particularly with parents who are seeking treatment for children, but also with adult patients. Many patients are disillusioned with the available medical care and see limited treatment options. They could be called desperate, but the language of desperation often simplifies the situation because it implies a lack of understanding and a lack of due consideration of all the risks.

Internationally, many clinical trials involving stem cells are currently

recruiting subjects. However, the majority of these trials are in early stages and are only enrolling small numbers of patients (Trounson et al., 2011). As a result, patients are turning to overseas clinics as a way of receiving treatments that they cannot access in their home countries, Petersen said.

Patients often learn about these clinics through word of mouth, such as from work colleagues or patient groups. Newspaper coverage spurs online investigations, especially with stories that frame stem cell research in a positive light, Petersen said (Petersen and Seear, 2011). Support from families, patient groups, and communities is often quite strong. Many of these groups even participate in fundraising efforts that make the trip possible.

Patients generally do not receive strong attempts at dissuasion from clinicians or others when discussing these treatments, which is taken almost as an endorsement, Caulfield said. The clinicians tend to believe that the therapies do not work and that a lot of the treatments are dangerous, but they also want to keep their patient's hopes alive, Petersen said. "They are, in a sense, managing patients' hopes." As Charo noted, there is an argument that patients should be able to seek out and receive treatments even if they are unproven or unregulated, especially when dealing with degenerative or terminal diseases. Ultimately, patients are more willing to tolerate uncertainty, and they have different conceptions of risk. An impression gained through early contact with a provider may be enough for a patient to decide that a treatment is worth the risk, Petersen said. Cohen added that countervailing testimony on clinic websites and in patient blogs can also be convincing enough to outweigh warnings about the potential health risks from the treatments.

Individual decisions to seek stem cell treatments also occur in a larger political and economic context, Petersen noted. Stem cell treatments are just a subset of a range of different treatments that people can seek wherever they are available and must be seen within the context of the entire health and medical tourism industry (Connell, 2011; Kangas, 2010). For example, the World Health Organization has published reports on health and medical tourism and sees it as a potential contributor to the economies of developing countries (NaRanong and NaRanong, 2011). In Australia, in a case similar to the U.S. situation that Cohen described earlier, the insurer NIB Health Fund announced a plan to sell medical tourism packages to Australians who are looking for lower cost options in Asian clinics but with safety and quality guaranteed (Parnell, 2013).

Patient Experiences

In a study focused specifically on patients who sought treatment in China (Chen and Gottweis, 2013), patient testimonies were found to generally include three themes, Cohen said. The first was suspicion about the motives of home country physicians who do not offer these treatments. The second was the fact that some consultation did take place with home country physicians about using Chinese stem cell treatments. The third was the idea that parents need to try everything for their children. As one study participant noted, "It is good to know you have done everything and you have tried everything for your child even if that means going offshore and trying something experimental." Most of the parents did not get exactly what they want from these treatments, but they remained hopeful. They were often offered booster therapies as an incentive to return for more treatments, Cohen noted.

Experiences during treatment were positive for many of the interviewees in Petersen's project (Petersen et al., 2013). Respondents generally had little knowledge about the source, storage, or handling of the stem cells used, but *all* respondents reported benefits from an initial treatment, such as stabilization of a patient's condition or a minor improvement in physical function. Sometimes they reported more substantial improvements. For example, one commented that while he was in India he began to breathe independently of his ventilator for the first time in many years. After the initial treatment, though, some people said they did not have any further benefit. But the initial positive experience led some patients to take multiple trips.

None of the patients expected a "miraculous" recovery after receiving their stem cell treatment, Petersen said. Rather they looked for small improvements and used subjective forms of assessment, such as being able to wiggle their toes. The improvements were not things that, in clinical terms, would be seen as restoration of function, and some Australians did not experience the improvements they sought. Improvements could not be clinically verified and could not be linked to the stem cell treatment, as these patients are often exploring complementary and alternative treatments in addition. In most cases, however, patients were pleased that they had at least tried it. The organizations offering these therapies are marketing hope, Petersen said.

How Patients Use Information

More needs to be done than simply providing information to patients who are considering stem cell therapies, Petersen concluded. The idea of providing a package of information is based on assumptions about how patients understand information. It assumes that if people are given the requisite information they will act in a certain predefined way. But this is a limited way of thinking about how people make decisions. It does not take account of all of the other factors that shape decisions, such as expectations developed by various constituencies or hope. For example, patients and clinicians each have their own set of hopes which often do not correspond. A full understanding of the issue will require a multifaceted approach rather than just thinking about more information as the answer.

ONE PATIENT'S EXPERIENCES

Michael Phelan co-founded a successful software company and served as its chief executive officer (CEO) until he recently had to step down due to health issues related to MS. He has gone to top neurologists in the United States and has been on standard FDA-approved treatments for more than 6 years, but the treatments have not been effective for him.

Not being satisfied with his existing options, he began to research promising clinical trials and found the results with autologous stem cell treatments impressive. But the only way to get this type of treatment in the United States is to be in an approved trial. Phelan tried to qualify for two separate trials that he identified, even paying $10,000 out of pocket for the testing involved for one trial, but he was told that he did not meet the requirements for either. He corresponded with physicians and researchers at the Stem Cell Institute in Panama, and after noting that they had published some of their research, he pursued therapy there, receiving an autologous stem cell treatment using cells that were derived from his adipose tissue. After his treatment in May 2012, the double vision problems he had been having for the previous year resolved, and he was able to continue driving. His mental and physical energy also improved dramatically, as did other problems such as incontinence. "I was very pleased with the outcome," he said. "I do not know the science behind it. I do not know if the trophic factors or the immunomodulation helped, but the bot-

tom line was it helped." Some people may think of stem cell therapy as a disservice, Phelan said, but "it helped me, so I consider it a service."

Extracting a patient's cells and preparing them for reinjection carries risk, but so does banking blood or freezing cells for later use. Of more than 2,000 patients in 66 different completed trials that Phelan identified as using expanded mesenchymal stem cells, not a single adverse condition had been reported. "To me that was easy to demonstrate safety. In fact, [this is] probably safer than some of the approved treatments."

Transplants and in vitro fertilization are regulated as medical procedures, but the FDA wants to regulate cells taken from a person's body that are manipulated and injected back into that person's body as a drug. "From my viewpoint, it looks like the FDA is more interested in protecting markets over patients," Phelan said. If these types of treatments were available in the United States, they could be regulated in such a way that data could be collected on safety and efficacy.

Phelan suggested that there may also be financial motives involved with trying to limit access to treatments. Many of those voicing safety concerns hold patents on potential stem cell therapies. While patents and financial incentives are not a bad thing, he said, it could indicate a conflict of interest.

If research on embryonic stem cells or induced pluripotent stem cells results in new, cell-based, mass-produced products, those products will require regulatory attention, Phelan noted. But autologous stem cell treatment is not something new. The use of one's own cells for treatment is a one-on-one decision, Phelan said, and should be treated as the practice of medicine for which multiple layers of regulation already exist. Accreditation could ensure that laboratories follow proper procedures, which is difficult to determine as an outsider and a nonprofessional (Trounson et al., 2012). More regulation will not stop charlatans or incompetent physicians from committing malpractice or malfeasance. That is why the civil tort system exists. But, he said, "if the safety has been proven, I do not understand why this has not become a standard treatment in this country."

Patients have to wait for legal decisions and clinical trial results. Unfortunately, disease does not wait, Phelan said. "I consider this a crime against patients. For me, it is robbery. It robs my time and my money. But I am fortunate to have the resources to travel overseas for treatment. Not everyone does. This crime could cost them much more."

4

Comparative Regulatory and Legal Frameworks

Stem cell therapies are regulated differently in various countries around the world, with some countries offering stem cell therapies that are not available elsewhere. In some cases, offering a particular stem cell therapy can have a positive economic impact for the country in which it is offered because patients are willing to travel in hopes of finding effective therapeutic options. However, a lack of regulations concerning stem cell treatments or a lack of enforcement of such regulations could cause patients harm and damage the industry. For a summary of issues related to these concerns, see Box 4-1.

BOX 4-1
Summary Points from Individual Speakers About Regulatory and Legal Issues Related to Stem Cell Therapies

- In the United States, stem cell therapies are regulated as biologics and are subject to premarket approval under the risk-based approach to approving cellular and tissue-based products. Treatments that are "minimally manipulated" are exceptions to this regulation, but this phrase could use further clarification. (Riley)
- European Union law states that cells or tissues that are "substantially manipulated" are subject to regulation; however, an exemption is given to member states in the non-routine case of custom-made treatments for individual patients. (Bianco)
- The Japanese government has made innovation, including innovation in stem cell research, a national priority, and new laws regarding regenerative medicine products are expected to provide a more efficient path to the translation of these therapies to the clinic. (Miyata)

- Mexico has benefited economically from offering stem cell therapies that are not available in other countries; however, regulations for treating patients with cells and tissues that are based on evidence could help to address challenges relating to therapy, safety, and efficacy. (Arellano)
- While stem cell therapies offered in China must be registered, there are not yet approved quality control guidelines available. (Zhou)

REGULATORY AND LEGAL FRAMEWORKS IN THE UNITED STATES

If regulations for stem cell therapies were only just now being developed in the United States, they would look much different than the ones that exist today, said Margaret Foster Riley, professor of law at the University of Virginia School of Law. The FDA uses regulations to ensure the safety and effectiveness of drugs, biological products, and medical devices under the Biologics Control Act of 1902 and the Food, Drug, and Cosmetic Act of 1938. These statutes have been amended and modernized over time, but they are still a "remarkably ill fit" for stem cell technology, Riley said.

In 1997, the FDA issued a risk-based, tiered approach to regulating cellular and tissue-based products (FDA, 1997). As a result, human cells, with the exception of those deemed minimally manipulated and used for autologous treatments, would be subject to FDA premarket approval as biologics. These products are and the stem cell clinics that offer them, are subject to registration and good practice requirements, Riley said. Thus far, the FDA has not recognized many products as falling into the minimally manipulated category, despite earlier expectations that more and more products would do so over time.

A tissue reference group at the FDA is used to determine the applicability of premarket approval requirements, Riley said. The tissue reference group provides "a single reference point for product specific questions received by FDA concerning jurisdiction and applicable regulation of human cells, tissues and cellular and tissue-based products" (FDA, 2013). However, because of confidential information and other considerations that limit access to the full data, it can be difficult to fully understand the reasoning behind the tissue reference group's recommendations, Riley said.

Experimental Treatments

The expansion of access to and expedited approval of investigational treatments being evaluated in clinical trials in the United States resulted largely from the acquired immunodeficiency syndrome (AIDS) activism movement, Riley explained (Young, 1988). To receive such access, patients need to have a serious or immediately life-threatening disease or condition, with no comparable or satisfactory alternative therapy available. The potential benefit to the patient must outweigh the risks, and providing the investigational drug for the requested use must not interfere with the initiation, conduct, or completion of clinical investigations, Riley said.

Regulating stem cell therapies is a challenge. The FDA has sent warning letters to several clinics that claim to offer treatments, prevention, or even cures using stem cell therapies that are not approved. For example, the FDA took action against Regenerative Sciences, LLC, which manufactured a product called Regenexx™, which consisted of autologous mesenchymal stem cells that were manipulated outside of the body and injected back into patients with orthopedic injuries (FDA, 2009).[1]

The Federal Trade Commission

A core task of the Bureau of Consumer Protection of the Federal Trade Commission (FTC) is to protect U.S. consumers from false, misleading, or deceptive advertising, said David Vladeck, a former director of the bureau. The agency focuses on advertising that promotes inaccurate health claims, including dietary supplements and food products that are said to provide health benefits, as well as various kinds of cures for diseases and conditions such as cancer, diabetes, alcoholism, and obesity. The FTC works closely with the FDA in pursuing this mission. Under the Food, Drug, and Cosmetic Act, advertising for treatments based on stem cells that are not approved by the FDA is a serious infraction of the law. The FDA has the option of proceeding against an entity touting stem

[1]In February 2014 the U.S. Circuit Court of Appeals for the District of Columbia ruled that the cell mixture used for this procedure contained both a drug and biologic, that it was more than minimally manipulated, and that it qualified as interstate commerce and thus, it was subject to the regulation and approval of the FDA. See *United States v. Regenerative Sciences, LLC*, No. 12-5254 F.3d (D.C. Cir. 2014).

cell usage for unapproved uses either through civil or criminal law enforcement. Depending on the circumstances, civil actions can begin with warning letters. If the warnings are not heeded, actions can escalate to lawsuits, seizures, and other orders directly regulating the conduct of those involved.

In cases that the FDA judges to pose more of a threat to human health, the agency also may proceed criminally, and it has done that with respect to unproven uses of stem cells, Vladeck said. In September 2012 two individuals who ran several businesses advertising and promoting the use of stem cells, dietary supplements, and vaccines to treat amyotrophic lateral sclerosis, MS, and Parkinson's disease pled guilty to their charges.[2] "The point of this prosecution for the FDA was to send a warning [to] those who would follow in their footsteps and make it clear that recurrences of this would be met by further criminal enforcement actions by the FDA," Vladeck said. In 2013 the FDA obtained a guilty plea from an assistant professor of pathology and laboratory medicine at the Medical University of South Carolina for "causing the introduction of stem cells into interstate commerce without the approval of the FDA."[3] The laboratory for which the defendant worked was authorized to conduct research on kidney cancer, but it was not permitted to use, harvest, or process stem cells for other purposes, and the defendant sold stem cells to unauthorized recipients, Vladeck said.

Generally, but not always, the FTC has principal responsibility with respect to advertising, Vladeck said, while both the FTC and the FDA have authority over Internet marketing. With emergent scientific issues like stem cell therapies, the FTC will look to the FDA for guidance on scientific issues. However, the FTC enforces its own statute, not the Food, Drug, and Cosmetic Act. With respect to health claims, the FTC can act only if it can show that a claim is false or deceptive; the issue is thus whether there is adequate scientific substantiation to support the claim.

For the FDA, the issue of advertising comes down to a yes-or-no question, Vladeck explained: Has the FDA approved the therapy? If not,

[2]FDA, September 7, 2012: Convictions entered in two separate Texas cases involving stem cells. See http://www.fda.gov/ICECI/CriminalInvestigations/ucm319377.htm (accessed March 9, 2014).

[3]FDA, July 31, 2013: South Carolina man enters plea to introducing stem cells into interstate commerce. See http://www.fda.gov/ICECI/CriminalInvestigations/ucm363400.htm (accessed March 9, 2014).

it is an unapproved use, and the advertised sale of the product is illegal. By contrast, for the FTC the issue is whether a claim is scientifically valid. If it is, then the FTC cannot act, but if it is not, then the FTC has a role to play. These can be difficult cases for the FTC, Vladeck admitted. The FTC will be less inclined to pursue situations in which there are respectable arguments to be made on both sides of the issue. But if the science is inadequate, risks are high, and little evidence suggests benefits, the FTC would be more interested in intervening.

Enforcement

To date, the FTC has not brought up charges in an enforcement case regarding the advertising of unapproved or unsubstantiated stem cell therapies. The issue has not become prominent at the agency, Vladeck said, adding that the FTC received "no or virtually no complaints" about stem cell advertising during his tenure at the agency. It may be that only a limited number of U.S. patients are using clinics offering these therapies in other countries, that patients may be unaware of the complaint mechanisms that are available or think that complaining would be futile, or that U.S. patients may not believe they had been misled or harmed, Vladeck said.

A typical website has a litany of disclaimers tailored to escape U.S. regulation, Vladeck said. Examples of disclaimers include

- "The statements, treatments, and other information on this website have not been evaluated by the U.S. FDA,"
- "The stem cell protocols we offer are not approved in the United States as treatments, therapies, drugs, new drugs, or investigational drugs,"
- "We do not claim that our treatment protocols are approved by the U.S. FDA or proven to be effective in the United States for any condition that appears on this site or for any other condition,"
- "There could be significant and unknown risks associated with adult stem cell treatment as long-term studies have not yet been performed," and
- "Very few randomized controlled trials of adult stem cells have been performed; therefore, no guarantee of safety or effectiveness is made or implied."

None of these disclaimers would necessarily defeat an FTC claim, Vladeck said, because the sites claim that these therapies have some scientific grounding and hold out some promise of effectiveness. "But these are certainly sophisticated operators who understand the dynamics of U.S. law," he added.

Whether a company is physically in the United States does not matter to the FTC, Vladeck said. If a company is selling a product in the United States, the FTC can pursue it. But offshore activities can raise problems for the FTC. If activities are illegal in both the United States and in the host state, it is easier for the FTC to pursue a company because it has counterpart agencies in most countries with which it can work. Where it is legal in the host country, the FTC cannot depend on the cooperation of the host country. That does not mean, however, that the FTC is powerless; it can still bring charges against advertising in the United States even if the advertising takes place over the Internet. The media outlets that convey such information can be put on notice that the FTC believes the information is false or misleading, and a media outlet that disseminates false and misleading information may have liability under U.S. laws.

The FTC bases enforcement actions on several sources of information. It receives about two million original complaints from consumers each year, gets referrals from other agencies, including the FDA, and receives complaints from trusted sources such as academics and experts in the field. However, stem cells have not been the source of widespread complaints.

There should be a balance between paternalism and individual choice, Vladeck said. "At the FTC, our job is not to prevent people from making bad choices. It is to ensure that people do not make bad choices on the basis of bad information." Government needs to play a greater role in making sure that understandable information flows to patients who can make their own decisions. Websites are being constructed by "very skilled marketers who are selling hope," Vladeck said. "We have all seen the mythology and the lure of miracle cures." One year acai berries or green tea may be heralded as promising treatments. Currently it is stem cells that are getting such attention.

REGULATORY AND LEGAL FRAMEWORKS IN ITALY

Most of the regulatory framework that dictates how to use stem cells in Italy derives from a set of European regulations, based largely on the

FDA guiding principles, that have the force of law, said Paolo Bianco, professor and director of anatomic pathology and chief of the Stem Cell Laboratory in the Department of Molecular Medicine at the Sapienza University of Rome and the Umberto I University Hospital. A 2007 regulation, called 1394/2007, covers advanced therapy medicinal products (EMA, 2007). It states that cells that are either cultured or differentiated in culture or used in a location and for a function that is not the same as the same cells in the donor's body and these cells are referred to as advanced therapy medicinal products. This regulation sets the use of stem cells apart from the use of any other kind of directly transplanted cells or tissues.

Cells that are engineered are defined in the 1394/2007 regulation as cells that have been "substantially manipulated" or modified in such a way that "biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved." The use of extensive culture, the use of chemicals to induce any kind of differentiation, or the direction to a tissue organ other than the one from which they were derived is considered by European regulators as making cells "substantially manipulated" and thus subject to regulation, Bianco said. The regulation also clearly states what is not considered substantial manipulation, including actions such as centrifugation, the addition of antibiotics or antimicrobials, and irradiation (EMA, 2007).

The regulation also includes a hospital exemption which allows the use of stem cell treatments under certain conditions, Bianco said. The regulation states,

> Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined. (EMA, 2007)

In April 2013 the Senate in Italy voted to reclassify the infusion of mesenchymal stem cells as a transplants procedure, which abrogated the

need for good manufacturing process (GMP) procedures, Bianco said. This took cell therapies out of the jurisdiction of the Italian Medicines Agency made it easier for patients with a variety of unrelated diseases to be treated, without the requirement of conducting clinical trials or pursuing approval of medicines.

Several factors, such as the hospital exemption and unclear regulation wording that contributes to misunderstandings, have led to gaps in regulation. These gaps have been used in some countries by unauthorized stem cells clinics, Bianco said. For example, the private Stamina Foundation in Italy gained substantial support from the public for stem cell therapies they promoted to treat a wide range of medical conditions (Abbott, 2013). The Foundation advertised cures for diseases ranging from autism and psoriasis to urinary incontinence, but with a specific focus on severe lethal neurodegenerative diseases, Bianco said. The therapeutic procedure involved the intravenous or intrathecal injection of mesenchymal stem cells that were said to have been differentiated into nerve cells, though how these were isolated and cultured was largely unknown until 2013 when the methodology was released to an expert review committee (Abbott, 2014).

In May 2013, after support from the national and international scientific community, the Italian lower house countered the April 2013 vote of the Senate, Bianco said, and GMP procedures and vigilance by the Italian Medicines Agency were restored as mandatory. Nearly $4 million was allocated for a government-supervised clinical trial to evaluate the Stamina Foundation stem cell therapy. However, following the review of the procedures by an expert committee, in October 2013 the health minister halted the trial (Abbott, 2014). It was reported that the expert committee had concerns over pathogen screening, the method for generating mesenchymal stem cells, and the use of inappropriate assays to identify the cells, among other things (Abbott, 2014).

Remaining Concerns

The problems with stem cell regulation have not been eradicated, Bianco said. Other interests were exerting pressure on the Italian government at the same time. For example, during the Stamina controversy, the minister received a report claiming that the marketing of mesenchymal stem cells should be allowed with no trial of efficacy but only after a small Phase I trial indicating, but not demonstrating, safety had been performed.

Of 361 clinical trials using intravenous infusion of mesenchymal stem cells for autism and urinary incontinence, only two have been completed and reported on ClinicalTrials.gov as Phase III trials, Bianco said, and both of these had negative results. Indeed, the only product based on mesenchymal cells that has ever been approved is one for which two Phase III trials were completed with negative results. Additionally, many clinical trials are not reported to ClinicalTrials.gov or other registries, making it difficult to determine the incidence of adverse events in all trials, Bianco said.

The problem is not simply a scientific or medical problem, Bianco said. The translation of science to the marketplace needs to be considered, not just the translation of science to medicine.

REGULATORY AND LEGAL FRAMEWORKS IN JAPAN

Japan has a very similar regulatory framework to that of the United States and the European Union, said Toshio Miyata, executive director of the Health and Global Policy Institute in Japan. Prime Minister Shinzo Abe has been eager to push forward the development of Japanese innovation, including stem cell research, especially since the Nobel Prize–winning work of Shinya Yamanaka (Nobel Media, 2013; Takahashi et al., 2007). The prime minister has submitted a bill to establish a new independent administrative agency that would ensure integrated management of research, Miyata said.

As of December 2012, Japan had approved only two regenerative medicine products, compared with 20 in Europe, 14 in South Korea, 9 in the United States, and 6 in other regions, including Southeast Asia and Australia, Miyata said. Sixty-five products were undergoing clinical research under guidelines established by the Ministry of Health, Labor, and Welfare (MHLW). Under the Pharmaceutical Affairs Law, which provides regulation for drugs and devices in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) conducts conformity audits and scientific reviews and reports to the MHLW, which issues approvals. Essentially, the PMDA acts as the technical arm of the MHLW, which has the ultimate responsibility for policies and administrative measures.

In 2012 the PMDA established the Office of Cellular and Tissue-Based Products under the Center for Product Evaluation, Miyata said. Under a new 5-year clinical trial activation plan, the number of pharmaceutical trials has been increasing in Japan. Clinical trials in Japan go

through a series of phases that are similar to those in the United States and the European Union.

As part of its Life Innovation Project for Health Care, Japan has been developing a strategy for drugs and medical devices aimed at achieving practical application of projects originating in Japan, Miyata said. The country also is creating early phase clinical trial centers for innovative drugs and medical devices. In addition, it is developing guidance based on regulatory science to streamline review for innovative drugs, medical devices, and biologics. Among these innovative products are platelets and retinal cells derived from induced pluripotent stem cells (Kamao et al., 2014; Nakamura et al., 2014).

The Japanese government has been considering the unique characteristics of regenerative medicine products in establishing regulations. For example, it has labeled therapies that use stem cells as "regenerative medicine products" and has introduced a new definition of regenerative and cellular therapeutic products that sets them apart from pharmaceuticals and medical devices. It also has developed an approval system for earlier commercialization of regenerative medicine products, with the introduction of a tentative approval after which safety and efficacy are further confirmed. Pharmaceutical regulation is a high hurdle for academia, Miyata said, and the reform of the regulations will create a unique category for regenerative medicines.[4]

The new approval system for the commercialization of cellular therapy products would move approval from the end of clinical trials to a stage intermediate between the confirmation of probable benefit and safety and marketing with further confirmation of efficacy and safety to follow (see Figure 4-1). The post-market phase would include informed consent and safety measures such as period reports and record retention, Miyata said.

Japan has experienced various controversies surrounding stem cell treatments. In 2010 a Korean patient traveled to Japan to receive a stem cell therapy not offered in Korea and then died of a pulmonary embolism (Cyranoski, 2010). In response, a bill for ensuring the safety of the

[4]In November 2013 the National Diet (Japan's legislative branch) passed legislation to revise the Pharmaceutical Affairs Law and approve the new Regenerative Medicine Law with the goal of bringing safe stem cell therapies to patients more quickly. See Japan's bold initiative in regenerative medicine and who the big winners might be, http://www.marketwatch.com/story/japans-bold-initiative-in-regenerative-medicine-and-who-the-big-winners-might-be-2014-03-03 (accessed March 9, 2014).

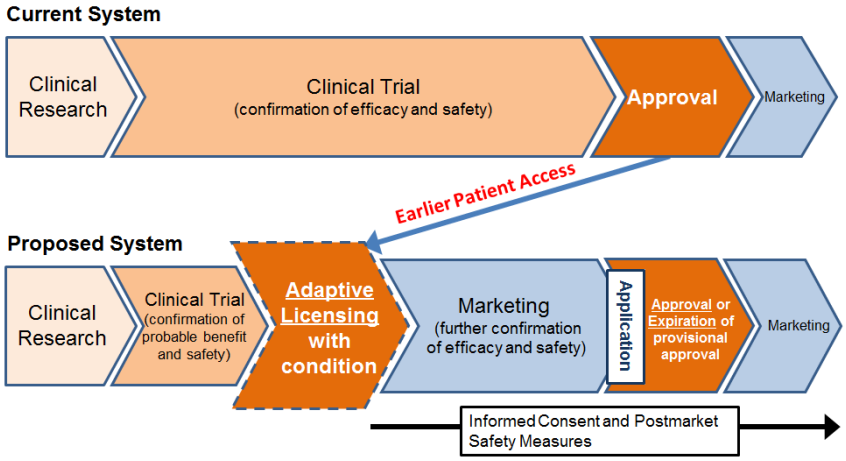

FIGURE 4-1 A new approval system under consideration in Japan would create earlier patient access to cellular therapy products.
NOTE: Probable benefit—Confirmation of efficacy with a small patient population; Safety—Earlier detection and evaluation of adverse events.
SOURCE: Toshio Miyata, IOM, NAS, and ISSCR workshop presentation on November 18, 2013.

procedures has been proposed. It outlines a number of safety measures including prior notification to authorities to ensure the safety of the treatment, establishing a permitting and notification system for cell-processing facilities, and obtaining informed consent, and it also calls for the protection of personal information and the reporting of adverse events to authorities, Miyata said.

REGULATORY AND LEGAL FRAMEWORKS IN MEXICO

The medical tourism industry is an important business in Mexico, which has been a popular destination for foreign patients who are seeking stem cell treatments, said María de Jesús Medina Arellano, an attorney from Universidad Autonoma de Nayarit who has studied health law and human rights in Mexico. The main consumers of services have been Americans and Canadians who travel to Mexico to obtain treatments that are either unavailable in or are less expensive than in their home countries.

Many private companies in Mexico offer stem cell treatments. However, with just three exceptions, none of the treatments offered in Mexico have been evaluated in Federal Commission for the Protection Against Sanitary Risk (in Spanish, Comisión Federal para la Protección contra Riesgos Sanitarios, or COFEPRIS) registered clinical trials. Yet, many of these treatments are offered as proven and effective therapies. COFEPRIS is an independent government authority of the Ministry of Health that has the exclusive statutory authority to oversee the inspection, approval, and authorization of activities concerning the use, storage, and transplantation of umbilical cord blood or derived human stem cells. However, COFEPRIS does not have standards or guidelines to implement and enforce when evaluating, authorizing, and monitoring research and therapeutic activities involving human tissues and cells, Arellano said (Arellano, 2012).

Mexico has a constitutional right to access to health care, Arellano noted. Based on that right, the General Health Law governs biomedical research and, arguably, is applicable to the clinical use of experimental stem cell treatments. In addition, the Biomedical Research Regulation gives the conditions required to perform clinical trials on human subjects, including research involving the use of human organs, tissues, and derivatives. However, none of these regulations specifically applies to stem cell therapies. The General Health Law prohibits false advertising of treatments or clinical interventions that are not supported by scientific evidence and at least five official Mexican standards prohibit and regulate the advertising of medical products and services, Arellano said. However, the regulations have little effective oversight, and COFEPRIS reportedly lacks financial as well as well-trained human resources.

Changes in the Laws

In December 2012 the law governing stem cell therapies changed, following lobbying from private medical enterprises in Mexico, Arellano said. Previously the law had prohibited any kind of commercialization of organs, tissues, and cells. The law now states that the procurement, extraction, analysis, derivation, preservation, transportation, and supply of organs, tissues, and stem cells are not considered acts of commerce.

This change in the law has created problems in Mexico, Arellano reported. An article in the June 2012 issue of *Medical Tourism Magazine* states that "Mexico offers an alternative treatment destination" for stem cell therapies that have not been approved in a prospective recipients

home country (George, 2012). But without proof of safety and efficacy, Arellano said, it will be difficult to protect patients undertaking what is essentially experimental medicine.

Regulations should be flexible, Arellano acknowledged, but there should also be evidence that treatments are going to work. To date, clinics have not been asked or required to share information about their offerings. Doing so would provide an opportunity for the government to effectively oversee stem cell science applications while fostering innovation in the area, Arellano said. Both the government and the medical sector need greater transparency in order to build confidence among patients. International regulation or harmonization in the area of stem cells, despite skepticism about international regulations, could help address many of the challenges Mexico faces.

REGULATORY AND LEGAL FRAMEWORKS IN CHINA

The Ministry of Science and Technology, the Chinese Academy of Sciences (CAS), and the National Science Foundation of China all support stem cell research in China, with funding that totaled a little less than $500 million over a 5-year period, said Qi Zhou, director of the State Key Laboratory of Reproductive Biology and vice director of the Institute of Zoology at CAS. For example, the Innovation 2020 Stem Cell Research Project of CAS involves about 3,000 scientists, including staff scientists and postdoctoral fellows, working on stem cell research at almost 30 different institutions. Altogether, said Zhou, about 200 hospitals and many institutions are working on stem cell research and cell therapy, and China now publishes the second largest number of stem cell publications, behind researchers in the United States.

New regulations have recently been put into place in China, Zhou said, with the Ministry of Science and Technology and the Ministry of Health publishing ethical guidelines and regulations for human embryonic stem cell research. This has been in response to the increasing use of unapproved stem cell treatments in clinics and skepticism over their therapeutic efficacy (Cyranoski, 2009, 2012; Dobkin et al., 2006). These new guidelines and standards have been disseminated in Chinese and described in several published papers.

In October 2011, a National Stem Cell Research Supervision and Coordination Committee was formed to coordinate all stem cell research and technology. The director of the committee is the Minister of Science

and Technology, and the National Science Foundation, the Ministry of Health, the Ministry of Education, and other ministries are represented on the committee. A committee also exists for industrial applications of stem cells and regenerative medicine.

Oversight of Stem Cell Treatments

Since June 2012, all organizations conducting stem cell therapy have had to register their treatments, Zhou said. Guidelines on quality control and preclinical research on stem cell preparations have been published but have not yet been approved by the government. Organizations involved in these guidelines include the National Health and Family Planning Commission of China, the China Food and Drug Administration, the National Leading Group of Clinical Stem Cells Study, and the National Stem Cell Experts Committee. The guidelines cover the isolation, purification, culture, amplification, modification, differentiation, cryopreservation and resuscitation, and in vivo implantation of stem cells, including embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, hematopoietic stem cells, and other progenitor cells or precursor cells. Security evaluations include the detection of bacteria and fungi mycoplasma, the detection of endogenous and exogenous viral agents, and reagent detection, while validity evaluations include cell identification tests, examining the pluripotency of stem cells, the detection of stem cell–specific markers, cell activity assays, and animal models.

Clinical trials can be halted at each level, Zhou said. The Chinese government has been proactive in this regard, notifying and halting illegal stem cell therapies, as they are identified. This occurred, for instance, with illegal stem cell therapies that were being provided by a hospital in Jilin province. However, physicians in China generally have more freedom to pursue treatments than do physicians in the United States, Zhou said, because there are fewer enforcement mechanisms in China.

"China would like to cooperate with the world to promote stem cell applications," Zhou concluded.

SUGGESTED IMPROVEMENTS FOR REGULATION

The questions being addressed by regulatory science will be important to the future development of stem cell therapies. This idea has been criticized because of the perception that regulation will thwart in-

novation, but regulatory science can develop pathways that allow innovation in the best safety framework, Riley said.

Patient safety is key. More transparency is needed for understanding clinical trials so that patients understand the treatments and the experimental design, Arellano said. The most important goal for stem cell therapy, Bianco said, is to make sure that unproven therapies are not marketed to patients. The FTC's role is to avert harm, and a way must be found to get clear information to consumers, Vladeck said.

If unproven therapies are being offered to consumers in the United States, federal regulatory agencies need to know about it, Vladeck emphasized. The FTC needs to understand the magnitude of the problem, including the risks to patients in both physical and financial terms. The FTC would respond well to comments or overtures by scientific groups, professional bodies, or patients that are pointing to a serious problem, he said, but the FTC needs information about patient experiences. For example, how many patients are traveling outside of the United States for these therapies, and what are the treatment outcomes? Are patients satisfied with the results?

Regulators need to work more closely with scientists, even if they are involved in commercial enterprises, Bianco said. Regulatory agencies need to work more rapidly and efficiently on the processing and approval of everything they regulate. Interactive discussions with the FDA convened by organizations the like California Institute for Regenerative Medicine (CIRM) are important ways for bringing academia and industry together to discuss stem cell therapy regulations, said Ellen G. Feigal of CIRM. A good next step, Arellano said, would be to invite policy makers to these kinds of discussions in order to get them involved in the science and regulation of new therapies along with more people from developing countries who are working on these treatments.

International harmonization for stem cell therapies can be difficult in a domain characterized by complexity and powerful commercial interests, Riley said, but harmonization could be pursued through international societies working together with government agencies. Multi-site international clinical trials would be one avenue toward greater harmonization, she said. Miyata supported the simultaneous global development of Phase I trials in Japan, the United States, the European Union, and other countries, along with the promotion of global clinical trials.

Accelerating regulatory science initiatives, with early communication and coordination among regulatory bodies in different countries, harmonizing guidelines and regulations, and the adoption of simultane-

ous approval in different countries would also be helpful, Miyata said. Perhaps working through groups like the United Nations Educational Scientific and Cultural Organization is also a possibility, Arellano suggested. Trying to harmonize on the basis of ethical issues from a global perspective will be difficult, Bianco said, but there is a role for the NAS and similar institutions around the world.

5

The Roles of Professional Societies

Other means besides government regulation, such as the work of professional societies, are available to monitor and control the provision of stem cell therapies. These organizations require professional standards of their members, and they participate in educating health care consumers. All speakers emphasized that while the societies' efforts are most effective if coordinated with FDA, they nevertheless can have an important independent influence (see Box 5-1).

BOX 5-1
Potential Contributions of Professional Societies and Other Organizations as Suggested by Individual Speakers

- Self-regulation through accreditation and certification can be used to attain a professional commitment to meeting high standards of clinical, laboratory, research, and marketing practices. (Schattman)
- ISSCR has developed professional guidelines for preserving medical innovation while ensuring the responsible practice of stem cell research. (Daley)
- Collaborations among scientific societies, medical associations, industry groups, patient and disease advocacy groups, ethics organizations, and heath economic groups could be beneficial for ensuring effective communication with patients. (Sipp)

THE SOCIETY FOR ASSISTED REPRODUCTIVE TECHNOLOGY

Glenn Schattman, associate professor of reproductive medicine at the New York Presbyterian Hospital, Weill Cornell Medical College, and former president of the Society for Assisted Reproductive Technology (SART), described activities in a closely related field as a possible model for the self-regulation of stem cell technologies. Though some have claimed that assisted reproductive technology is largely unregulated, the reality is otherwise, he said. At the federal level, the Centers for Disease Control and Prevention collects and publishes outcomes data on reproductive success rates and performs annual audits of about 10 percent of programs. Additionally, while not regulating the medical practice of in vitro fertilization, the FDA regulates the medical devices that are used to test and screen gamete donors, with the quality of laboratory testing is overseen by the Centers for Medicare & Medicaid Services.

The field of assisted reproductive technology regulates itself strongly, Schattman said. Practicing physicians are required to have specialized training in reproductive medicine, pass both written and oral examinations, and be licensed by their state medical boards. Specialists have to be certified by the American Board of Obstetrics and Gynecology or the American Board of Urology. Annual re-certification, periodic re-examination, and continuing medical education are required. In addition, the American Society for Reproductive Medicine (ASRM), in collaboration with the College of American Pathologists, accredits programs for reproductive laboratories. "This is a highly regulated field," Schattman said.

SART was founded in 1985 and is an affiliate society of ASRM. Its mission is to set and help maintain the standards for assisted reproductive technologies in an effort to better serve its members and patients. About 85 percent of all clinics in the United States are SART members, and more than 90 percent of the more than 150,000 in vitro fertilization cycles in the United States are performed by SART member clinics. About 1 percent of all births in the United States are from nearly 400 assisted reproductive technology clinics, Schattman noted. SART members include physicians from around the world, laboratory technologists and biologists, practice managers, researchers, scientists, nurses, lawyers, and mental health professionals. To become and remain a member of SART, members must follow practice and laboratory guidelines, committee opinions, and advertising and ethics guidelines. SART monitors member

clinics for adherence to the various guidelines and opinions, including the requirements for data submission to SART's Clinic Outcome Reporting System and the qualifications for staff. Members also must meet the currently published ASRM minimum standards for in vitro fertilization and perform at least 20 in vitro fertilization cycles a year.

A quality assurance committee monitors member programs for adherence to guidelines. The first time that a program is out of line, it gets a warning letter requesting a response and action plan. With a second offense, a program is put on probation, and a mandatory evaluation is conducted to develop an action plan. After a third offense, the executive council reviews the program to consider expulsion from the society. One indication of the program's effectiveness, Schattman said, is that through voluntary compliance with SART's guidelines regarding the number of embryos to transfer, the triplet pregnancy rate has been reduced from 15 percent to less than 1.5 percent.

Financial assistance and consultations are provided for poorly performing clinics in order to bring them up to standards of care. SART helps clinics remain compliant with government regulations, provides a donor-screening test and questionnaire, and has developed a standardized informed consent form describing the risks of assisted reproductive technology which also provides choices for the disposition of excess embryos in the event of death, divorce, or some other situation, Schattman said.

An advertising committee monitors member websites and advertising. If a website is outside of the guidelines, the program receives a letter saying that it must change its advertising within 30 days or else membership in the society will be revoked. Websites are reviewed on an annual basis, and any complaints are investigated. "So far, every single request for a change in advertising has been complied with because the stick of removing membership has been quite strong," Schattman said.

ASRM also has generated various documents, including one on the definition of experimental procedures. Under the definition, procedures are considered experimental until there is sufficient published evidence regarding risk, safety, and efficacy to establish the procedure as standard medical practice. Evidence can only be derived from peer-reviewed, published studies that are reproducible by independent investigators (ASRM, 2013). SART's guidelines dictate that experimental procedures should not be represented or marketed as established or routine medical practice, Schattman said.

Self-regulation is critical, but it only works if membership means something, Schattman said. Practice guidelines have to be effective, and bidirectional interaction with federal agencies is also important.

THE INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ISSCR, which is the largest professional organization of stem cell scientists, encourages responsible clinical translation through the education of scientists and medical practitioners on professional standards, said George Daley, Samuel E. Lux IV Professor of Hematology/Oncology and director of the Pediatric Stem Cell Transplant Program at Children's Hospital, who was ISSCR president in 2007 and 2008.

Many different types of treatments are currently being offered on the market as stem cell therapies. While some purveyors are practicing "quackery and charlatanism," Daley said, there are also well-intentioned scientific and medical personnel who are prematurely disseminating their work.

Comparable situations have occurred in the past, Daley observed. For example, some favorable data in the 1980s on the use of high-dose chemotherapy for women with metastatic breast cancer in the setting of autologous, marrow, or stem cell transplant rescue led to an expansion of the procedure to women with less aggressive disease. Tens of thousands of women were receiving transplants before randomized data demonstrated that this treatment did not enhance efficacy and, in fact, hinted at worse toxicity (Rowlings et al., 1999; Vij et al., 2000). "Even in the best of circumstances, in a highly regulated community of well-intentioned physicians here in the United States, we had this imposition of commercialization and entrepreneurship in a fledgling area of stem cell therapy," he said. "I think it is a cautionary tale."

Guidance for Stem Cell Researchers

In 2007, ISSCR impaneled a broad international taskforce with 30 members from 14 countries to develop a set of professional guidelines for responsible translational stem cell research (Hyun et al., 2008). Bedrock principles were conceived, including high standards of pre-clinical evidence, peer review, scrupulous review of clinical protocol by IRBs, rigorous informed consent, and publication of results whether positive or negative.

The panel also developed principles for preserving medical innovation. Innovation occurs when it is focused on a small number of ill patients, not when it is being marketed widely, Daley said. In the case of stem cells, there should be a written plan and a compelling rationale. There should be scrupulous quality control and characterization of cells that are produced under rigorous standards of manufacturing practice, he said. Voluntary informed consent, costs, adverse events, and institutional accountability all need to be considered as well. Work should be peer reviewed and quickly followed by a formal clinical trial process so that these innovations can benefit everyone in the community. "It is part of our professional imperative as physicians to create generalizable knowledge," he said.

Patient Guidance

ISSCR also has developed guidance and educational materials for patients and their families on stem cell treatments with the goal of helping these individuals make informed decisions (Taylor et al., 2010). As part of this guidance, ISSCR constructed a very effective website that received an enormous amount of attention (as described in Chapter 3). It attempted to codify websites as either lacking professional documentation or as meeting ISSCR's professional standards. However, the threat of a lawsuit shut down the effort, and, at present, the website exists only as an informational platform, Daley said.

Despite ISCCR's experience, social media and the Internet create enormous new opportunities for education and communication, Daley emphasized. In addition, patient organizations can be enormously influential in getting valid information to patients.

Quantitative information is not yet available to define many aspects of the problem, Daley said. Without that information, deciding on an intervention—whether regulatory or educational—is difficult. But patients can help define the problem, perhaps with support from professional societies.

THE INTERNATIONAL SOCIETY FOR CELLULAR THERAPY

Today's marketing claims, whether for stem cells, progenitor cells, immune cells, or xenogeneic fetal cells, tend to be unsupported by the kind of scientific evidence needed to gain authorization from a regulatory

body, said Douglas Sipp, head of the Science Policy and Ethics Studies unit at the RIKEN Center for Developmental Biology in Kobe, Japan. In addition to the medical and cosmetic claims described earlier, there are stem cell nutraceutical claims that certain substances can boost or enhance stem cell activity in the body when ingested. There is also a whole separate industry of veterinary treatments for which claims are being made about the use of stem cells, usually for horses and dogs. The general scientific consensus is that most stem cell therapies are not ready for marketing or commercialization, Sipp said. But the industries that are providing these treatments are increasingly sophisticated and organized and are challenging established regulatory frameworks. In particular, industry and industry-funded think tanks have formed alliances in many countries to advocate for the deregulation of the stem cell industry. This trend risks sacrificing scientific quality and patient protections to the interest of building stem cell businesses, Sipp said.

The International Society for Cellular Therapy (ISCT) has an interest in the promotion of stem cell research and development, but it also is interested in a broader range of cell-based interventions such as immune cell interventions, reproductive medicine, and gene therapy, Sipp said. It has set up a presidential taskforce on the use of unproven cellular therapies, with a particular focus on stem cells, though it also is looking at other kinds of cellular therapies that have gained interest because of the excitement generated by stem cells. The taskforce, which was first convened in the summer of 2013, has 20 members representing 10 countries. It is led by ISCT president Kurt Gunter and president-elect Massimo Dominic and has representatives from academic science, medicine, industry, policy, law, and ethics. The taskforce's goals are to review the major scientific and ethical issues involved in cellular therapeutics, to review the state of the science regarding types of cells being used and their marketed indications, to develop effective communications strategies, to develop tools for patient decision making, and to serve as public advocates for the field.

The ISCT taskforce has working groups on definitions, scientific evidence and biological rationale, laboratory cell processing, clinical practice, regulation, commercial implications, communications, and policy, Sipp said. The working group on definitions has moved away from using the term "stem cell tourism" because many of the treatments offer something other than stem cells and because "tourism" focuses on patient behavior while the taskforce is looking at the behavior of providers. Meanwhile, the policy working group is looking at whether ISCT should develop policies

to take action against members who engage in these activities or whether they should be embraced as individuals who have a differing perspective on the issue.

Once the working groups have drafted initial responses to their charges, other communities such as the regulatory community, the bioethics community, and patient or disease advocacy groups will be consulted to widen representation and participation in this activity, Sipp said.

Key goals are to develop an appropriate terminology, define the levels of scientific evidence needed to justify routine use or commercialization of a cellular therapy, address questions of "experimental" and "innovative" use, and understand the global regulatory landscape in order to identify gaps and contradictions, Sipp said. The taskforce will be looking at the ethics of unregulated direct-to-consumer marketing of therapies as well as the implications for industry. For example, if competitors are able to directly market products without having to invest in the research and development requirements of a three-phase clinical trial, the current incentive structure for developing therapies could be undermined.

ISCT is also working to establish and reinforce collaborations to address significant issues more effectively. Building on a 2010 white paper on stem cell tourism (Gunter et al., 2010), ISCT will be reaching out to other organizations and partners, including scientific societies, medical associations, industry groups, patient and disease advocacy groups, ethics organizations, and heath economic groups, to develop an effective communications strategy. Messages should carry the weight of a broad sector of the scientific and medical communities, Sipp said, as well as incorporating the voices of patients who are interested in safe and efficacious treatments.

Sipp also said that scientific societies need to communicate with regulators to address the concerns that they have about inappropriate business activities. The United States has a well-developed and well-established regulatory structure of which many companies are clearly in overt violation. Groups involved with ensuring the quality of stem cells therapies need to communicate their sense of concern and even alarm to regulators, he said.

6

Moving Forward

Five major concepts seemed to have emerged from the workshop discussions, said Harvey Fineberg, president of the IOM: solving issues related to deceptive advertising; strengthening the scientific process to develop evidence of efficacy and safety; refining, reforming, or harmonizing regulation for stem cell therapies; respecting patient autonomy; and speeding the development and delivery of safe and effective treatments to patients. Fineberg asked speakers to consider these concepts or others while identifying what they see as the most important problems to address, what information they see as being needed to take action, and what actions are most important for moving stem cell therapies forward (see Box 6-1 for proposed ideas from individual workshop speakers).

BOX 6-1
Proposed Solutions to Challenges Encountered with Unproven Stem Cell Therapies as Suggested by Individual Speakers

Ensuring Patient Safety and Providing Factual Information

- Patients need to be protected from fraudulent therapies, but that can be done while also promoting safe and effective treatments based on rigorous science. (Arellano, Rick, Vladeck)
- Balanced information about the positive and negative outcomes for patients who receive stem cell therapies is needed; otherwise, patients may view groups such as regulators and scientists as part of the problem instead of as part of the solution. (Phelan)
- An honest, trustworthy broker who can present clear and accurate information in the appropriate context to patients about therapies and clinical trials is needed. (Arellano, Charo, Feigal)

- Patients need guidance for understanding clinical trials and studies that have demonstrated treatment efficacy. (Phelan)
- Advocacy groups are a valuable resource for communicating important information to patients who need it. (Daley, Rick)
- Researchers and clinicians can play a valuable role in providing clear messaging to patients about the effectiveness of stem cell therapies and offering clarity on advertising for these treatments. (Caulfield)

Evidence Generation

- Research efforts need to focus on generating evidence on the effectiveness of stem cell therapies for treating disease. (Caulfield, Schattman)

Regulatory Mechanisms

- Scientists from academia and industry need to work more closely with regulators on the challenges that arise in regulating new therapies. (Bianco, Van Bokkelen)
- Professional societies could play an important role for setting guidelines for stem cell treatments. (Feigal)
- The United States should adopt a national strategy for regulating stem cell therapies. (Van Bokklelen)
- A mechanism is needed to ensure that unproven therapies are not marketed to patients. (Bianco)
- A better way to regulate stem cell therapies may be to treat them similarly to transplantation and surgery, rather than drugs or biologics. (Cohen)
- Federal regulatory agencies such as the FTC need to know how many patients are seeking treatment as well as whether the patients are satisfied with the results of these therapies. (Vladeck)
- A greater understanding of the financial and health costs for patients who pursue stem cell treatments is needed because they are currently not reported and, therefore, not known. (Arellano, Van Bokkelen)

Global Approaches

- International societies working with government agencies could offer a useful global strategy for regulating stem cell therapies, perhaps through multi-site international clinical trials. (Miyata, Riley)
- Harmonized global regulatory standards should be considered with caution as they could have the opposite of the intended effect and restrict the development of effective stem cell therapies. (Vladeck)
- An individual country approach to solving the regulatory challenges is not likely to be effective because of the international nature under which stem cell therapies are being offered. (Weissman)

- To encourage the development of a government accreditation process for stem cell research, a public-private consortium, including the FDA and the EMA, may be an effective option. (Cohen)

WHAT IS THE MOST IMPORTANT PROBLEM?

Glenn Schattman of Weill Medical College noted that, as a clinician, his major concern is patient safety. "The first thing that I want to make sure is [that] something is safe before it is then brought to clinical trials to see if it is efficacious." María de Jesús Medina Arellano from Universidad Autonoma de Nayarit also emphasized patient safety, but she mentioned in addition the need to maintain best practices within stem cell science. David Vladeck of the Georgetown University School of Law warned, however, against moving toward harmonizing global regulatory standards, arguing that this may constrain rather than spur the development of new products.

Timothy Caulfield of the University of Alberta agreed that safety is critical but also pointed to efficacy. Evidence is currently lacking that stem cell therapies are effective against the kinds of diseases being referred to on websites. Strong statements are needed regarding the current lack of evidence for effectiveness, he said. Gil Van Bokkelen, CEO of Athersys, Inc., agreed that compelling evidence of therapeutic effectiveness has generally not been delivered by the field, and he said that this is one reason why large pharmaceutical companies have held back from significant investment.

A better relationship with regulators is also needed, Van Bokkelen said. Companies are trying to develop therapies for serious unmet medical needs, and constructive engagement with the FDA and other regulators is needed in order to accelerate the pace of development of novel therapies. There is much ground for optimism, Van Bokkelen stated. The FDA has endorsed and is helping to create new regulatory frameworks and streamlined approaches to enable the rapid development of effective therapies. Addressing these needs could have enormous consequences, both economically and medically, for national health care systems.

Michael Phelan said that he would like to see more balance in the information that is being presented to patients, rather than just the possibility of bad outcomes. "What is the truth [about the] positive things that are happening in this market and how can you help patients interpret that?" Clinics that have good laboratory practices, that are helping patients, and are publishing their results could be identified and certified.

However, if governments, regulators, and scientists are simply trying to shut every clinic down, patients will view them as part of the problem rather than part of the solution.

WHAT NEEDS TO BE KNOWN?

Van Bokkelen raised the issue of the size of the stem cell clinic industry and its potential impacts. Rough calculations would suggest that hundreds of millions of dollars are being spent annually on stem cell treatments, he said. The impact of those expenditures on both health and personal finances is unknown, in part because institutions are not obligated to report on and are not voluntarily monitoring the impact of the treatments they are delivering. Arellano agreed that clinics and other enterprises should voluntarily give information to regulators that they gather from patients.

A family with a desperately sick child may be tempted to take college education savings and spend that money on an unproven stem cell therapy instead, Van Bokkelen continued. The therapy may not pose a clinical risk, but it does impose an economic harm on that family, he said. However, the needs of patients and their families cannot be ignored. R. Alta Charo of the University of Wisconsin–Madison added that physicians and the scientific community do not fully appreciate the needs and desires of patients. "Some people want to keep trying things until they are proven to be a bad idea as opposed to waiting until it is proven to be a good idea."

Charo called attention to the need for good information and honest brokers to convey information to patients and physicians. In particular, patients lack the context and explanation they need to understand the outcomes of many of these clinical trials. The professional community needs to speak in lay terms so that patients can engage with the information they provide, said Ellen G. Feigal of the CIRM. Also, as has been seen with warnings about the hazards of tobacco, information about the harms of an activity does not necessarily lead individuals to decide to avoid or stop that activity. Communication is part of the solution, but only part.

Charo also emphasized the need for trust among the groups involved in the stem cell field. A lack of trust regarding the intentions, motivations, and honesty of the different groups involved can be an obstacle to progress. Bringing groups together would help to overcome that obstacle.

WHAT COULD BE DONE?

Phelan advocated focusing on what is working instead of instances of malfeasance. An organization should be collecting positive information and helping patients. "The most productive thing that could be done is to help patients sort through the clinical trials that have shown efficacy."

Certifying clinics would be another way to help patients make decisions on receiving stem cell treatments, Phelan said. Schattman agreed that certification or accreditation of clinics would be very helpful. In addition, requiring clinics and other organizations to submit outcomes data to a central organization would help produce the information that patients and regulators need.

Feigal pointed out that international professional societies could set guidelines for the field. The mission of regulatory bodies is to advance innovation in addition to protecting patients, and guidelines could help achieve a better balance. Efforts by governments to investigate the efficacy of complementary or alternative medicines also could be directed toward the study of stem cell therapies, she said.

Amy Rick, CEO of Parkinson's Action Network, pointed to the value of patient organizations as a source of information for patients. Patients trust these organizations and often turn to them for assistance. But these organizations need support from professionals to work on issues of common interest.

Caulfield pointed to the need for a source of information on the state of the science for patients that is truly independent. However, information about the nature of clinical trials would also need to be included, particularly given that trials have a high failure rate and results are difficult to replicate.

Truth in advertising is also important so that patients are not misled, Caulfield said. Vladeck noted that consumers are getting a mixed message from the scientific community. On one hand, stem cells are touted as the next breakthrough therapy. On the other hand, patients are told that current therapies do not work, which is "a hard message for most consumers to digest." Clinicians can play an important role in helping to inform patients when they come in asking about these clinics, Caulfield said (Levine and Wolf, 2012).

Irving L. Weissman of the Stanford University School of Medicine pointed out that no single country can solve this problem because the entities can move across national borders. The solution also has to in-

volve not only trials overseen by IRBs and FDA-like regulations but medical licensure and regulation of false advertising.

If issues are occurring, complaints can be filed not only by patients but also by their home physicians, Vladeck said. "Where are the people who were involved in the care and treatment of patients before desperation set in and they were forced to go elsewhere?"

Van Bokkelen argued that the United States is "long overdue for the development of a coherent national strategy and a national [or international] initiative" on stem cell therapies. It could marshal expertise and pool resources to drive the development of the field, he said.

A CONTINUED DIALOGUE

In his closing remarks, Fineberg emphasized the opportunity for a higher order of collaboration across the scientific, clinical, and patient communities. Continued dialogue and a clearer definition of needs could hasten the arrival of demonstrably effective stem cell therapies, he said. "The onus is on us in the scientific and health communities to enlist the patients, to enlist the clinicians, to persuade the funders, and to get on with the business of accomplishing what the promise of stem cell research has held from the very beginning—successful treatment."

Ralph Cicerone, president of the NAS, pointed to the value of dialogue. Every stakeholder represented at the workshop has valid and well-intentioned concerns, he said, yet each stakeholder represents just part of the picture. "As people try to figure out where to go next, guidance from the discussion today and the dialogues that have started are really going to be valuable."

References

Abbott, A. 2013. Stem-cell ruling riles researchers. *Nature* 495(7442):418–419.

Abbott, A. 2014. Leaked files slam stem-cell therapy. *Nature* 505(7482):139–140.

Amariglio, N., A. Hirshberg, B. W. Scheithauer, Y. Cohen, R. Loewenthal, L. Trakhtenbrot, N. Paz, M. Koren-Michowitz, D. Waldman, L. Leider-Trejo, A. Toren, S. Constantini, and G. Rechavi. 2009. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Medicine* 6(2):e1000029.

Arellano, M. 2012. The rise of stem cell therapies in Mexico: Inadequate regulation or unsuccessful oversight? *Revista Redbioética/UNESCO* 3(2):63–78.

ASRM (American Society for Reproductive Medicine). 2013. Definition of experimental procedures: A committee opinion. *Fertility and Sterility* 99(5):1197–1198.

Barclay, E. 2009. Stem-cell experts raise concerns about medical tourism. *Lancet* 373(9667):883–884.

Bianco, P. 2013. Don't market stem-cell products ahead of proof. *Nature* 499(7458):255.

Bohgaki, T., T. Atsumi, and T. Koike. 2007. Multiple autoimmune diseases after autologous stem-cell transplantation. *New England Journal of Medicine* 357(26):2734–2736.

Caulfield, T., C. Rachul, and A. Zarzeczny. 2012. The evolution of policy issues in stem cell research: An international survey. *Stem Cell Reviews* 8(4):1037–1042.

CBER (Center for Biologics Evaluation and Research). 2011. Center for Biologics Evaluation and Research strategic plan, FY 2012–2016. http://www.fda.gov/downloads/aboutfda/centersoffices/cber/ucm266867.pdf (accessed March 25, 2014).

Chen, H., and H. Gottweis. 2013. Stem cell treatments in China: Rethinking the patient role in the global bio-economy. *Bioethics* 27(4):194–207.

Connell, J. 2011. A new inequality?: Privatisation, urban bias, migration and medical tourism. *Asia Pacific Viewpoint* 52(3):260–271.

Cyranoski, D. 2009. Stem-cell therapy faces more scrutiny in China. *Nature* 459(7244):146–147.

Cyranoski, D. 2010. Korean deaths spark inquiry. *Nature* 468(7323):485.

Cyranoski, D. 2012. China's stem-cell rules go unheeded. *Nature 484(7393):* 149–150.

Daley, G. Q. 2012. The promise and perils of stem cell therapeutics. *Cell Stem Cell* 10(6):740–749.

Dobkin, B. H., A. Curt, and J. Guest. 2006. Cellular transplants in China: Observational study from the largest human experiment in chronic spinal cord injury. *Neurorehabilitation and Neural Repair* 20(1):5–13.

Dominici, M., K. Le Blanc, I. Mueller, I. Slaper-Cortenbach, F. Marini, D. Krause, R. Deans, A. Keating, D. Prockop, and E. Horwitz. 2006. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 8(4):315–317.

EMA (European Medicines Agency). 2007. *Regulation (EC) No. 1394/2007 of the European Parliament and of the Council*. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf (accessed March 7, 2014).

FDA (U.S. Food and Drug Administration). 1997. Proposed approach to regulation of cellular and tissue-based products. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf (accessed March 11, 2014).

FDA. 2009. Regenerative Services, Inc. http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/complianceactivities/enforcement/untitledletters/ucm091991.htm (accessed March 6, 2014).

FDA. 2012. FDA warns about stem cell claims. http://www.fda.gov/forconsumers/consumerupdates/ucm286155.htm (accessed March 10, 2014).

FDA. 2013. Tissue reference group. http://www.fda.gov/biologicsbloodvaccines/tissuetissueproducts/regulationoftissues/ucm152857.htm (accessed March 6, 2014).

Fine, J. D., R. A. Eady, E. A. Bauer, J. W. Bauer, L. Bruckner–Tuderman, A. Heagerty, H. Hintner, A. Hovnanian, M. F. Jonkman, I. Leigh, J. A. McGrath, J. E. Mellerio, D. F. Murrell, H. Shimizu, J. Uitto, A. Vahlquist, D. Woodley, and G. Zambruno. 2008. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *Journal of the American Academy of Dermatology* 58(6):931–950.

George, D. 2012. Mexico: A new legislation for stem cell therapies. *Medical Tourism Magazine*. http://www.medicaltourismmag.com/mexico-a-new-legislation-for-stem-cell-therapies (accessed April 24, 2014).

Gunter, K. C., A. L. Caplan, C. Mason, R. Salzman, W. E. Janssen, K. Nichols, L. F. Bouzas, F. Lanza, B. L. Levine, J. E. Rasko, A. Shimosaka, and E. Horwitz. 2010. Cell therapy medical tourism: Time for action. *Cytotherapy* 12(8):965–968.

Hyun, I. 2010. Allowing innovative stem cell-based therapies outside of clinical trials: Ethical and policy challenges. *Journal of Law, Medicine & Ethics* 38(2):277–285.

Hyun, I., O. Lindvall, L. Ahrlund-Richter, E. Cattaneo, M. Cavazzana-Calvo, G. Cossu, M. De Luca, I. J. Fox, C. Gerstle, R. A. Goldstein, G. Hermeren, K. A. High, H. O. Kim, H. P. Lee, E. Levy-Lahad, L. Li, B. Lo, D. R. Marshak, A. McNab, M. Munsie, H. Nakauchi, M. Rao, H. M. Rooke, C. S. Valles, A. Srivastava, J. Sugarman, P. L. Taylor, A. Veiga, A. L. Wong, L. Zoloth, and G. Q. Daley. 2008. New ISSCR guidelines underscore major principles for responsible translational stem cell research. *Cell Stem Cell* 3(6):607–609.

Jabr, F. 2012. In the flesh: The embedded dangers of untested stem cell cosmetics. *Scientific American*, December 17. http://www.scientific.americancom/article/stem-cell-cosmetics (accessed March 10, 2014).

Kamao, H., M. Mandai, S. Okamoto, N. Sakai, A. Suga, S. Sugita, J. Kiryu, and M. Takahashi. 2014. Characterization of human induced pluripotent stem cell-derived retinal pigment epithelium cell sheets aiming for clinical application. *Stem Cell Reports* 2(2):205–218.

Kangas, B. 2010. Traveling for medical care in a global world. *Medical Anthropology* 29(4):344–362.

Lau, D., U. Ogbogu, B. Taylor, T. Stafinski, D. Menon, and T. Caulfield. 2008. Stem cell clinics online: The direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell* 3(6):591–594.

Levine, A. D., and L. E. Wolf. 2012. The roles and responsibilities of physicians in patients' decisions about unproven stem cell therapies. *Journal of Law, Medicine & Ethics* 40(1):122–134.

Master, Z., A. Zarzeczny, C. Rachul, and T. Caulfield. 2013. What's missing?: Discussing stem cell translational research in educational information on stem cell "tourism." *Journal of Law, Medicine & Ethics* 41(1):254–268.

Mendpara, S. D., C. Ustun, A. M. Kallab, F. M. Mazzella, P. A. Bilodeau, and A. P. Jillella. 2002. Cryptococcal meningitis following autologous stem cell transplantation in a patient with multiple myeloma. *Bone Marrow Transplantation* 30(4):259–260.

Moertel, C. G., T. R. Fleming, J. Rubin, L. K. Kvols, G. Sarna, R. Koch, V. E. Currie, C. W. Young, S. E. Jones, and J. P. Davignon. 1982. A clinical trial of amygdalin (laetrile) in the treatment of human cancer. *New England Journal of Medicine* 306(4):201–206.

Nakamura, S., N. Takayama, S. Hirata, H. Seo, H. Endo, K. Ochi, K. Fujita, T. Koike, K. Harimoto, T. Dohda, A. Watanabe, K. Okita, N. Takahashi, A. Sawaguchi, S. Yamanaka, H. Nakauchi, S. Nishimura, and K. Eto. 2014. Expandable megakaryocyte cell lines enable clinically applicable generation of platelets from human induced pluripotent stem cells. *Cell Stem Cell* 14(4):535–548.

NaRanong, A., and V. NaRanong. 2011. The effects of medical tourism: Thailand's experience. *Bulletin of the World Health Organization* 89(5):336–344.

Nobel Media. 2013. Shinya Yamanaka—Facts. http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/yamanaka-facts.html (accessed March 7, 2014).

Ogbogu, U., C. Rachul, and T. Caulfield. 2013. Reassessing direct-to-consumer portrayals of unproven stem cell therapies: Is it getting better? *Regenerative Medicine* 8(3):361–369.

Parnell, S. 2013. NIB health fund to offer medical tourism. *The Australian*, October 26. http://www.theaustralian.com.au/news/health-science/nib-health-fund-to-offer offer-medical-tourism/story-e6frg8y6-1226747206131# (accessed March 10, 2014).

Petersen, A., and K. Seear. 2011. Technologies of hope: Techniques of the online advertising of stem cell treatments. *New Genetics and Society* 30(4):329–346.

Petersen, A., K. Seear, and M. Munsie. 2013. Therapeutic journeys: The hopeful travails of stem cell tourists. *Sociology of Health & Illness.* doi:10.1111/1467-9566.12092.

Rachul, C. 2011. "What have I got to lose?": An analysis of stem cell therapy patients' blogs. *Health Law Review* 20(1):5–12.

Regenberg, A. C., L. A. Hutchinson, B. Schanker, and D. J. Mathews. 2009. Medicine on the fringe: Stem cell–based interventions in advance of evidence. *Stem Cells* 27(9):2312–2319.

Rowlings, P. A., S. F. Williams, K. H. Antman, K. K. Fields, J. W. Fay, E. Reed, C. J. Pelz, J. P. Klein, K. A. Sobocinski, M. J. Kennedy, C. O. Freytes, P. L. McCarthy, Jr., R. H. Herzig, E. A. Stadtmauer, H. M. Lazarus, A. L. Pecora, J. D. Bitran, S. N. Wolff, R. P. Gale, J. O. Armitage, W. P. Vaughan, G. Spitzer, and M. M. Horowitz. 1999. Factors correlated with progression-free survival after high-dose chemotherapy and hematopoietic stem cell transplantation for metastatic breast cancer. *Journal of the American Medical Association* 282(14):1335–1343.

Ryan, K. A., A. N. Sanders, D. D. Wang, and A. D. Levine. 2010. Tracking the rise of stem cell tourism. *Regenerative Medicine* 5(1):27–33.

Scadden, D., and A. Srivastava. 2012. Advancing stem cell biology toward stem cell therapeutics. *Cell Stem Cell* 10(2):149–150.

Seear, K., A. Petersen, M. Munsie, and R. Skinner. 2010. *Hopeful journeys: Experiences of stem cell treatments offered outside Australia.* Melbourne, Australia: School of Political and Social Inquiry, Monash University.

Takahashi, K., K. Tanabe, M. Ohnuki, M. Narita, T. Ichisaka, K. Tomoda, and S. Yamanaka. 2007. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 131(5):861–872.

Taylor, P. L., R. A. Barker, K. G. Blume, E. Cattaneo, A. Colman, H. Deng, H. Edgar, I. J. Fox, C. Gerstle, L. S. Goldstein, K. A. High, A. Lyall, R. Parkman, F. J. Pitossi, E. D. Prentice, H. M. Rooke, D. A. Sipp, A. Srivastava, S. Stayn, G. K. Steinberg, A. J. Wagers, and I. L. Weissman. 2010. Patients beware: Commercialized stem cell treatments on the web. *Cell Stem Cell* 7(1):43–49.

Thirabanjasak, D., K. Tantiwongse, and P. S. Thorner. 2010. Angiomyelopro liferativeAngiomyeloproliferative lesions following autologous stem cell therapy. *Journal of the American Society of Nephrology* 21(7):1218–1222.

Tolar, J., and J. E. Wagner. 2012. Management of severe epidermolysis bullosa by haematopoietic transplant: Principles, perspectives and pitfalls. *Experimental Dermatology* 21(12):896–900.

Tolar, J., A. Ishida-Yamamoto, M. Riddle, R. T. McElmurry, M. Osborn, L. Xia, T. Lund, C. Slattery, J. Uitto, A. M. Christiano, J. E. Wagner, and B. R. Blazar. 2009. Amelioration of epidermolysis bullosa by transfer of wild-type bone marrow cells. *Blood* 113(5):1167–1174.

Trounson, A., R. G. Thakar, G. Lomax, and D. Gibbons. 2011. Clinical trials for stem cell therapies. *BMC Medicine* 9(52).

Trounson, A., N. D. DeWitt, and E. G. Feigal. 2012. The alpha stem cell clinic: A model for evaluating and delivering stem cell-based therapies. *Stem Cells Translational Medicine* 1(1):9–14.

Vij, R., J. DiPersio, R. Brown, K. Trinkaus, C. Abboud, K. R. Meehan, G. Frenette, C. Freytes, L. T. Goodnough, H. Khoury, J. Ponnuri, and D. Adkins. 2000. Outcomes of high-dose chemotherapy and autologous stem cell transplant in isolated locally recurrent breast cancer: A multicenter evaluation. *Bone Marrow Transplantation* 26(9):947–953.

Young, F. E. 1988. The role of the FDA in the effort against AIDS. *Public Health Reports* 103(3):242–245.

Zarzeczny, A., C. Rachul, M. Nisbet, and T. Caulfield. 2010. Stem cell clinics in the news. *Nature Biotechnology* 28(12):1243–1246.

A

Workshop Agenda

STEM CELL THERAPIES:
OPPORTUNITIES FOR ENSURING THE QUALITY AND SAFETY OF UNREGULATED CLINICAL OFFERINGS

A WORKSHOP

November 18, 2013

National Academy of Sciences Building, Room 125
2101 Constitution Avenue, NW, Washington, DC

Workshop Objectives:

- Discuss the current environment in which patients are receiving unregulated stem cell offerings.
- Examine the stem cell treatments that are being offered.
- Assess the potential benefits and risks to individual health.
- Consider the evidence base needed to substantiate the clinical application of stem cell technologies.
- Evaluate legal hurdles for establishing standards and criteria to govern stem cell trials and treatments.
- Discuss potential solutions for assuring the quality of stem cell offerings.

8:30 – 8:45 A.M.	**Welcome, Introduction of Moderators, Meeting Goals, and Charge to Participants** Alta Charo, *Workshop Chair* University of Wisconsin–Madison
8:45 – 10:20	**STEM CELL THERAPIES: KNOWNS AND UNKNOWNS** **Session Moderator:** Ralph J. Cicerone National Academy of Sciences
8:45 – 9:10	**Stem Cells as Regulated Therapeutics** John Wagner University of Minnesota
9:10 – 9:25	**Clinical Offerings That Use Stem Cells** Timothy Caulfield University of Alberta
9:25 – 9:40	**Patients Seeking Unproven or Unregulated Treatments: Why and How** Alan Petersen Monash University
9:40 – 10:20	**Moderated Panel Discussion** Panelists: John Wagner, Timothy Caulfield, Alan Petersen
10:20 – 10:35	**BREAK**
10:35 A.M. – 12:30 P.M.	**QUALITY ASSURANCE—PART I** **Session Moderator** Ellen Feigal California Institute for Regenerative Medicine
10:35 – 10:50	**Regulatory and Legal Frameworks for Offering Stem Cell Therapies in the United States** Margaret Foster Riley University of Virginia School of Law

10:50 – 11:05	**Regulatory and Legal Frameworks for Offering Stem Cell Therapies in Italy** Paolo Bianco Sapienza Universita di Roma
11:05 – 11:20	**Regulatory and Legal Frameworks for Offering Stem Cell Therapies in Japan** Toshio Miyata Health and Global Policy Institute
11:20 – 11:35	**Regulatory and Legal Frameworks for Offering Stem Cell Therapies in Mexico** María de Jesús Medina Arellano Universidad Autonoma de Nayarit
11:35 – 11:50	**Regulatory and Legal Frameworks for Offering Stem Cell Therapies in China** Qi Zhou Institute of Zoology Chinese Academy of Sciences
11:50 A.M. – 12:30 P.M.	**Moderated Panel Discussion** Panelists: Margaret Foster Riley, Paolo Bianco, Toshio Miyata, María de Jesús Medina Arellano, Qi Zhou
12:30 – 2:15 P.M.	**LUNCH SEMINAR**
12:30 – 12:50	**BREAK**
12:50 – 1:00	**Introductory Comments** Irving Weissman Stanford University School of Medicine
1:00 – 1:15	**A Patient's Story** Michael Phelan
1:15 – 1:45	**Medical Tourism: Patients Seeking Stem Cell Treatments** I. Glenn Cohen Harvard University Law School

1:45 – 2:00	**Discussion**
2:00 – 2:15	**BREAK**
2:15 – 3:55	**QUALITY ASSURANCE—PART II**
	Session Moderator Amy Comstock Rick Parkinson's Action Network
2:15 – 2:30	**Quality of Information: Advertising** David Vladeck Georgetown University
2:30 – 2:45	**Quality of Information: ISSCR Statements and Guidelines** George Daley Harvard University
2:45 – 3:15	**Quality of Professional Services: Medical and Society-Based Accreditation**
	Professional Society Efforts Calling for Evidence-Based Medicine and Appropriate Independent Oversight Douglas Sipp International Society for Cellular Therapy
	Professional Society Efforts in Parallel with Government Regulation Glenn L. Schattman Society for Assisted Reproductive Technology
3:15 – 3:55	**Moderated Panel Discussion** Panelists: David Vladeck, George Daley, Douglas Sipp, and Glenn L. Schattman
3:55 – 4:10	**BREAK**

4:10 – 5:10 **MOVING FORWARD**

Session Moderator
Harvey V. Fineberg
Institute of Medicine

4:10 – 5:10 **Moderated Panel Discussion**
Panelists: Glenn L. Schattman, David Vladeck, María de Jesús Medina Arellano, Timothy Caulfield, Michael Phelan, Gil Van Bokkelen

5:10 – 5:25 **FINAL REMARKS**

5:10 – 5:25 **Summary of Salient Points and Final Words**
Alta Charo
University of Wisconsin–Madison

Harvey V. Fineberg
Institute of Medicine

Ralph J. Cicerone
National Academy of Sciences

5:25 **ADJOURN**

B

Speaker Biographical Sketches

María de Jesús Medina Arellano, Ph.D., LL.M., is a qualified lawyer who graduated from the University of Nayarit, Mexico, in 2004. After finishing her degree she decided to move to Mexico City to continue her studies in the philosophy of law. In January 2008 she graduated with the equivalent of an M.Phil. (with honors) from the Postgraduate Law Division at the National Autonomous University of Mexico. During her postgraduate degree work she focused on the new paradigm of health law and human rights in Mexico. In December 2008 she was recognized with the Young Academic Talent of the Year award granted by the Nayarit Government in Mexico. She obtained her Ph.D. in bioethics and medical jurisprudence (with honors) in July 2012, from the School of Law/Institute for Science, Ethics and Innovation in the University of Manchester. She is currently studying the regulation of stem cell research in developing countries (Mexico as a case study) under the supervision of Dr. John Harris, Dr. David Gurnham, and Dr. Sarah Devaney.

Paolo Bianco, M.D., is a professor and director of anatomic pathology and chief of the Stem Cell Lab in the Department of Molecular Medicine, Sapienza University of Rome and Umberto I University Hospital, Rome. His specific areas of expertise are skeletal diseases and the biology and clinical use of skeletal stem cells (also known as mesenchymal stem cells). He has contributed extensively in these fields.

Timothy Caulfield, LL.M., is a Canada research chair in health law and policy and a professor in the Faculty of Law and the School of Public Health at the University of Alberta. He was the research director of the Health Law Institute at the University of Alberta from 1993 to 2011 and

is now leading the Faculty of Law's Health Law and Science Policy Group. Over the past several years he has been involved in a variety of interdisciplinary research endeavors that have led to his publishing more than 250 articles and book chapters. He is a health senior scholar with the Alberta Heritage Foundation for Medical Research and the principal investigator for a number of large interdisciplinary projects that explore the ethical, legal, and health policy issues associated with a range of topics, including stem cell research, genetics, patient safety, the prevention of chronic disease, obesity policy, the commercialization of research, complementary and alternative medicine, and access to health care. Professor Caulfield is and has been involved with a number of national and international policy and research ethics committees, including the Canadian Biotechnology Advisory Committee, Genome Canada's Science Advisory Committee, the Ethics and Public Policy Committee for International Society for Stem Cell Research (ISSCR), and the Federal Panel on Research Ethics. He is a fellow of the Royal Society of Canada and the Canadian Academy of Health Sciences. He writes frequently for the popular press on a range of health and science policy issues and is the author of *The Cure for Everything: Untangling the Twisted Messages About Health, Fitness and Happiness* (Penguin, 2012).

R. Alta Charo, J.D., is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin at Madison, where she is on the faculty of the Law School and the Medical School's Department of Medical History and Bioethics. She also serves on the faculty of the University of Wisconsin's Master of Biotechnology Studies program and lectures in the Master of Public Health program of the Department of Population Health Sciences. Professor Charo served as a member of the Obama-Biden Transition Project, where she was a member of the Department of Health and Human Services review team, focusing her attention particularly on transition issues related to the National Institutes of Health (NIH), Food and Drug Administration (FDA), bioethics, stem cell policy, and women's reproductive health. She was on leave for the 2009-2010 academic year to serve as a senior advisor in the Office of the Commissioner at FDA. Professor Charo serves on several expert advisory boards of organizations with an interest in stem cell research, including CuresNow, the Juvenile Diabetes Research Foundation, ISSCR, and WiCell, as well as on the advisory board to the Wisconsin Stem Cell Research Program. In 2005, she was appointed to the ethics standards working group of the California Institute for Regenerative Medicine (CIRM).

Also in 2005, she helped to draft the National Academies' Guidelines for Embryonic Stem Cell Research, and in 2006 she was appointed to co-chair the National Academies' Human Embryonic Stem Cell Research Advisory Committee. In 1994, Professor Charo served on the NIH Human Embryo Research Panel, and from 1996-2001, she was a member of President Clinton's National Bioethics Advisory Commission where she participated in drafting its reports on "Cloning Human Beings" (1997); "Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity" (1998); "Research Involving Human Biological Materials: Ethical Issues and Policy Guidance" (1999); "Ethical Issues in Human Stem Cell Research" (1999); "Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries" (2001); and "Ethical and Policy Issues in Research Involving Human Participants" (2001).

Ralph J. Cicerone, Ph.D., is the president of the National Academy of Sciences and Chair of the National Research Council. His research in atmospheric chemistry, climate change and energy has involved him in shaping science and environmental policy at the highest levels nationally and internationally. Dr. Cicerone has received a number of honorary degrees and many awards for his scientific work. Among the latter, the Franklin Institute recognized his fundamental contributions to the understanding of greenhouse gases and ozone depletion by selecting Dr. Cicerone as the 1999 laureate for the Bower Award and Prize for Achievement in Science. One of the most prestigious American awards in science, the Bower Award also recognized his public policy leadership in protecting the global environment. In 2001, he led a National Academy of Sciences study of the current state of climate change and its impact on the environment and human health, requested by President Bush. The American Geophysical Union awarded Dr. Cicerone its James B. Macelwane Award in 1979 for outstanding contributions to geophysics by a young scientist and its 2002 Roger Revelle Medal for outstanding research contributions to the understanding of Earth's atmospheric processes, biogeochemical cycles, and other key elements of the climate system. In 2004, the World Cultural Council honored him with the Albert Einstein World Award in Science. In addition to the National Academy of Sciences, Dr. Cicerone is a member of the American Academy of Arts and Sciences, the American Philosophical Society, the Accademia Nazionale dei Lincei, the Russian Academy of Sciences, and the Korean Academy of Science and Technology. He has served as president of the

American Geophysical Union, the world's largest society of earth scientists. Dr. Cicerone was educated at the Massachusetts Institute of Technology (B.S. in electrical engineering) and the University of Illinois at Champaign-Urbana (M.S., Ph.D. in electrical engineering, with a minor in physics). In his early career, he was a research scientist and held faculty positions in electrical and computer engineering at the University of Michigan. The Ralph J. Cicerone Distinguished University Professorship of Atmospheric Science was established there in his honor in 2007. In 1978, he joined the Scripps Institution of Oceanography at the University of California, San Diego as a research chemist. From 1980 to 1989, he was a senior scientist and director of the Atmospheric Chemistry Division at the National Center for Atmospheric Research in Boulder, Colorado. In 1989, he joined the University of California, Irvine, where he was founding chair of the Department of Earth System Science and was appointed the Daniel G. Aldrich Professor of Earth System Science. As Dean of the School of Physical Sciences from 1994 to 1998, he recruited outstanding faculty and strengthened the school's curriculum and outreach programs. Immediately prior to his election as National Academy of Sciences president, Dr. Cicerone served as Chancellor of the University of California, Irvine from 1998 to 2005, a period marked by a rapid rise in the academic capabilities of the campus. His research has focused on atmospheric chemistry, the radiative forcing of climate change due to trace gases, and the sources of atmospheric methane, nitrous oxide and methyl halide gases.

I. Glenn Cohen, J.D., is one of the world's leading experts on the intersection of bioethics (sometimes also called "medical ethics") and the law, as well as health law. He also teaches civil procedure. From Seoul to Krakow to Vancouver, Professor Cohen has spoken at legal, medical, and industry conferences around the world and his work has been covered on PBS, National Public Radio, ABC, Mother Jones, *The New York Times*, *The Boston Globe*, and several other media venues. Professor Cohen's current projects relate to reproduction/reproductive technology, research ethics, rationing in law and medicine, health policy, and to medical tourism—the travel of patients who are residents of one country, the "home country," to another country, the "destination country," for medical treatment. His past work has included projects on end-of-life decision-making, FDA regulation and commodification. He is the author of more than 50 articles and chapters, and his award-winning work has appeared in leading legal (including the Stanford, Cornell, and Southern California

law reviews), medical (including the *New England Journal of Medicine*, *Journal of the American Medical Association*), bioethics (including the *American Journal of Bioethics*, the *Hastings Center Report*) and public health (the *American Journal of Public Health*) journals, as well as Op-Eds in *The New York Times* and *The Washington Post*. Cohen is the editor of *The Globalization of Health Care: Legal and Ethical Issues* (Oxford University Press, 2013), and is currently writing *Patients with Passports: Medical Tourism, Law, and Ethics* (under contract, Oxford University Press) as well as working on three other books. Prior to becoming a professor he served as a law clerk to Judge Michael Boudin of the U.S. Court of Appeals for the First Circuit and as a lawyer for U.S. Department of Justice, Civil Division, Appellate Staff, where he handled litigation in the Courts of Appeals and (in conjunction with the Solicitor General's Office) in the U.S. Supreme Court. In his spare time, he still litigates, most recently having authored an amicus brief that was submitted to the U.S. Supreme Court for leading gene scientist Eric Lander in Association of Molecular Pathology v. Myriad, concerning whether human genes are patent eligible subject matter, a brief that was extensively discussed by the Justices at oral argument. Cohen was selected as a Radcliffe Institute Fellow for the 2012-2013 year and by the Greenwall Foundation to receive a Faculty Scholar Award in Bioethics. He is currently one of the key co-investigators on a $100 million award over 10 years from the National Football League Players Association (NFLPA), known as the Harvard Integrated Program to Protect and Improve the Health of NFLPA Members.

George Daley, M.D., Ph.D., is the Samuel E. Lux IV Professor of Hematology/Oncology and director of the Stem Cell Transplantation Program at Children's Hospital Boston. He is also professor of biological chemistry and molecular pharmacology and pediatrics at Harvard Medical School, an investigator of the Howard Hughes Medical Institute, associate director of the Children's Stem Cell Program, founding member of the executive committee of the Harvard Stem Cell Institute, and past-president and current clerk of ISSCR. Dr. Daley seeks to translate insights in stem cell biology into improved therapies for genetic and malignant diseases. Important research contributions from his laboratory include the creation of customized stem cells to treat genetic immune deficiency in a mouse model (together with Rudolf Jaenisch), the differentiation of germ cells from embryonic stem cells (cited as a Top Ten Breakthrough by *Science* magazine in 2003), and the generation of dis-

ease-specific pluripotent stem cells by direct reprogramming of human fibroblasts (cited as Breakthrough of the Year in *Science* magazine in 2008). As a graduate student working with Nobel Prize winner David Baltimore, Dr. Daley demonstrated that the *BCR/ABL* oncogene induces chronic myeloid leukemia (CML) in a mouse model, which validated BCR/ABL as a target for drug blockade and encouraged the development of imatinib (Gleevec™; Novartis), a revolutionary magic-bullet chemotherapy that induces remissions in virtually every CML patient. Dr. Daley's recent studies have clarified mechanisms of Gleevec resistance and informed novel combination chemotherapeutic regimens. Dr. Daley received his bachelor's degree magna cum laude from Harvard University (1982), a Ph.D. in biology from the Massachusetts Institute of Technology (1989), and his M.D. from Harvard Medical School, where he was only the 12th individual in the school's history to be awarded the degree summa cum laude (1991). He served as chief resident in internal medicine at the Massachusetts General Hospital (1994–1995) and is currently a staff physician in hematology/oncology at the Children's Hospital and the Dana Farber Cancer Institute. He has been elected to the Institute of Medicine (IOM) of the National Academies, the American Society for Clinical Investigation, the American Association of Physicians, and the American Pediatric Societies, and he is a fellow of the American Academy of Arts and Sciences and the American Association for the Advancement of Science. Dr. Daley was an inaugural winner of the NIH Director's Pioneer Award for highly innovative research and has received the Judson Daland Prize from the American Philosophical Society for achievement in patient-oriented research, the E. Mead Johnson Award from the American Pediatric Society for contributions to stem cell research, and the E. Donnall Thomas Prize of the American Society for Hematology for advances in human induced pluripotent stem cells.

Ellen Feigal, M.D., is senior vice president of research and development at CIRM. Prior to CIRM, Dr. Feigal was the executive medical director of global development at Amgen, an adjunct professor at the University of California, San Francisco (UCSF), and the founding director of the American Course on Drug Development and Regulatory Sciences, a collaborative effort with FDA, UCSF, and the European Center of Pharmaceutical Medicine, University of Basel, from 2008-2011. She was chief medical officer of Insys Therapeutics, director of medical devices and imaging at the Critical Path Institute, and vice president of clinical sciences/deputy scientific director of the Translational Genomics Research

Institute from 2004-2008. From 1992-2004, she held senior positions at the National Cancer Institute's (NCI) Division of Cancer Treatment and Diagnosis, most recently directing the Division from 2001 to 2004. Dr. Feigal earned a B.S. in biology and an M.S. in molecular biology/biochemistry from the University of California, Irvine; an M.D. from the University of California, Davis; completed her residency in internal medicine at Stanford University; and did a fellowship in hematology/oncology at UCSF. She was on faculty at UCSF and the University of California, San Diego before joining the NCI.

Harvey V. Fineberg, M.D., Ph.D., is president of the IOM. He served as Provost of Harvard University from 1997 to 2001, following thirteen years as Dean of the Harvard School of Public Health. He has devoted most of his academic career to the fields of health policy and medical decision making. His past research has focused on the process of policy development and implementation, assessment of medical technology, evaluation and use of vaccines, and dissemination of medical innovations. Dr. Fineberg helped found and served as president of the Society for Medical Decision Making and has been a consultant to the World Health Organization. At the IOM, he has chaired and served on a number of panels dealing with health policy issues, ranging from AIDS to new medical technology. He also served as a member of the Public Health Council of Massachusetts (1976-1979), as chairman of the Health Care Technology Study Section of the National Center for Health Services Research (1982-1985), and as president of the Association of Schools of Public Health (1995-1996). Dr. Fineberg is co-author of the books *Clinical Decision Analysis*, *Innovators in Physician Education*, and *The Epidemic that Never Was*, an analysis of the controversial federal immunization program against swine flu in 1976. He has co-edited several books on such diverse topics as AIDS prevention, vaccine safety, and understanding risk in society. He has also authored numerous articles published in professional journals. Dr. Fineberg is the recipient of several honorary degrees and the Stephen Smith Medal for Distinguished Contributions in Public Health from the New York Academy of Medicine. He earned his bachelor's and doctoral degrees from Harvard University.

Toshio Miyata, M.D., is currently the executive director of the Health and Global Policy Institute. In 2010–2011, he was engaged in the early phase clinical trials activation program, when he was deputy director of the research and development division, health policy bureau in the Japa-

nese Ministry of Health, Labor, and Welfare. In 2012–2013, he worked on the reform of the pharmaceutical affairs law, when he was the deputy director of the evaluation and licensing division, pharmaceutical and food safety bureau in the ministry. In March 2011, he was involved with the restoration of Fukushima prefecture. Dr. Miyata served as the assistant professor of cardiac surgery in Osaka University Medical School. He completed a surgical internship at Osaka Koseinenkin Hospital and a residency in thoracic surgery at Osaka City General Hospital. He is a graduate of Osaka University Medical School. He received a B.A. degree in mechanical engineering from Waseda University.

Alan Petersen, Ph.D., is a professor of sociology at the School of Political and Social Inquiry, Monash University in Melbourne, Australia. His research interests span the sociology of health and medicine, science and technology studies, and gender studies. He has authored or edited 18 books and numerous articles in these fields, most recently on stem cell tourism, the sociology of bioethics, and the discourse of childhood obesity. His most recent books are *The Politics of Bioethics* (Routledge, 2011) and *Aging Men, Masculinities and Modern Medicine* (Routledge, 2013) (edited with Antje Kampf and Barbara Marshall).

Mike Phelan, B.S., is a serial entrepreneur who was the chief executive officer (CEO) and co-founder of SevOne, one of the fastest growing software companies in the world. He recently stepped down because he has MS. Mr. Phelan has advocated for patients' rights to use their own stem cells for potential life-saving therapies.

Amy Comstock Rick, J.D., is CEO of Parkinson's Action Network (PAN), a Washington, D.C.-based national Parkinson's disease nonprofit advocating for better treatments and a cure. In this capacity, Ms. Rick works in partnership with other Parkinson's organizations and PAN's powerful grassroots network to educate the public and government leaders on better policies for research and an improved quality of life for people living with Parkinson's. PAN serves as the voice of Parkinson's on numerous public policy issues affecting the Parkinson's community. In addition to continuing its work on NIH funding and research, the Parkinson's community is now a powerful voice on many crucial issues including Parkinson's specific programs at the Departments of Defense and Veteran's Affairs and the Department of Health and Human Services, FDA drug approval issues, and the continuing

struggle to achieve research freedom for stem cell research. As CEO of PAN, Ms. Rick currently serves as an officer or board member with several national coalitions and councils. She is president of the Coalition for the Advancement of Medical Research (CAMR), the nation's leading bipartisan pro-cures coalition. Comprising 100 nationally recognized patient organizations, universities, scientific societies, and foundations, CAMR's advocacy and education outreach focuses on research toward developing better treatments and cures for individuals with life-threatening illnesses and disorders. She served as president of CAMR from 2008-2010 and has been a board member since 2004. She serves as Treasurer for the American Brain Coalition (ABC), a national non-profit organization comprising some of the United States' leading professional neurological, psychological, and psychiatric associations and patient organizations. Together, they seek to advance the understanding of the functions of the brain and to reduce the burden of brain disorders through public advocacy. She has served on ABC's Board of Directors since 2008. Ms. Rick also sits on the Board of Directors for the National Health Council (NHC), a national non-profit that brings together all segments of the health community to provide a united voice for the more than 133 million people with chronic diseases and disabilities and their family caregivers. Ms. Rick is called upon frequently by the media and other organizations to speak about biomedical research and the importance of strong federal funding and policy support. She has testified before several congressional committees and subcommittees and in 2011 was honored as an Innovator by the Genetic Alliance for her work on the complex federal embryonic stem cell research policy. Prior to joining PAN, she served as the Senate-confirmed director of the U.S. Office of Government Ethics from 2000-2003 and served as associate counsel to the president in the White House Counsel's Office from 1998-2000. Ms. Rick began her federal service as an attorney at the U.S. Department of Education in 1988, ending her tenure there in 1998 as Assistant General Counsel for Ethics. Ms. Rick began her professional career at the law firm of Beveridge & Diamond. She received a B.A. from Bard College and a J.D. from the University of Michigan.

Margaret Foster Riley, J.D., is a professor of law at the University of Virginia School of Law where she teaches in the areas of bioethics, food and drug law, health law, animal law, and public health law. She also has secondary appointments in the Department of Public Health Sciences at the University of Virginia School of Medicine and in the Batten School

of Leadership and Public Policy. She is a graduate of Duke University and Columbia University Law School. Her areas of interest include health institutions and reform, biomedical ethics and research, food and drug law, genomics, reproductive technologies, stem cell research, biotechnology, health disparities, and chronic disease.

Glenn L. Schattman, M.D., is a specialist in infertility and reproductive surgery. He is board certified in obstetrics and gynecology as well as in reproductive endocrinology and infertility. He currently holds the position of associate professor of reproductive medicine at the New York Presbyterian Hospital, Weill Cornell Medical College. He was the chair of the Practice Committee of the Society for Assisted Reproductive Technology, and he served as the society's president in 2012.

Doug Sipp, B.A., is head of the Science Policy and Ethics Studies unit at the RIKEN Center for Developmental Biology in Kobe, Japan. His work focuses primarily on issues in the clinical application and commercialization of stem cell therapeutics, and the analysis of approaches to stem cell research and development in the Asia-Pacific region. His research and commentaries have been published in numerous high-profile journals including *Science*, *Nature*, *Cell Stem Cell*, *Neuron*, and *Regenerative Medicine*. He serves on the International Society for Cellular Therapy Presidential Task Force on the Use of Unproven Cellular Therapies, and was a member of the ISSCR Task Force on Unproven Stem Cell Treatments. He has also served on the ISSCR international, government affairs, website, and membership committees. He graduated from Rutgers University in 1991.

Gil Van Bokkelen, Ph.D., has served as CEO and chairman of Athersys, Inc., since August 2000. Dr. Van Bokkelen co-founded Athersys in October 1995 and served as CEO and director from Athersys's founding to August 2000. Prior to May 2006, he also served as Athersys's president. Dr. Van Bokkelen is chairman (*ex officio*) of the Alliance for Regenerative Medicine, a Washington, DC–based consortium of companies, patient advocacy groups, disease foundations, and clinical and research institutions that are committed to the advancement of the field of regenerative medicine. He is also the chairman of the board of governors for the National Center for Regenerative Medicine and serves on a number of other boards, including the Biotechnology Industry Organization's ECS board of directors, the McGowan Institute for Regenerative Medi-

cine, and the Regenerative Medicine Foundation. He received his Ph.D. in genetics from Stanford University School of Medicine; his B.A. in economics from the University of California, Berkeley, and his B.A. in molecular biology from the University of California, Berkeley.

David Vladeck, J.D., LL.M., was a professor at the Georgetown University Law Center for 7 years before his appointment to head the Bureau of Consumer Protection. While at Georgetown, he served as the co-director of the Institute for Public Representation, leading the institute's work in civil rights. He taught courses in federal courts, civil procedure, and government processes, and he co-directed the Institute for Public Representation, a legal clinic. Before joining the faculty of the Georgetown University Law Center, Vladeck spent nearly 30 years as a lawyer at the Public Citizen Litigation Group, the litigation arm of Public Citizen, an advocacy organization founded by Ralph Nader. He served as the group's director for 10 years. While at the Public Citizen Litigation Group, Vladeck argued a number of cases in front of the U.S. Supreme Court, including cases about the First Amendment, civil rights, and labor law. He also argued more than 60 cases in front of federal courts of appeal and state courts of last resort. Vladeck received his B.A. from New York University in 1972 and graduated with a J.D. from Columbia Law School in 1976. He received an LL.M. degree from Georgetown in 1977.

John Wagner, M.D., is a professor of pediatrics, director of the Division of Hematology–Oncology and Blood and Marrow Transplantation and co-director of the Center for Translational Medicine at the University of Minnesota. He currently holds two endowed chairs: Hageboeck/Children's Cancer Research Fund Chair in Pediatric Cancer Research and the University of Minnesota McKnight Presidential Chair in Hematology and Oncology. Dr. Wagner is internationally recognized as an expert in the field of stem cells and umbilical cord blood transplantation. He received his M.D. degree at Jefferson Medical College in 1981, completed his internship and residency in pediatrics at Duke University School of Medicine in 1984, and did a postdoctoral fellowship in hematology–oncology at the Johns Hopkins School of Medicine in 1987, where he remained until joining the faculty at the University of Minnesota in 1991. He is board certified in pediatrics and pediatric hematology/oncology.

Irving L. Weissman, M.D., is a professor of pathology and developmental biology at Stanford University, where he is the director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine. Dr. Weissman was raised in Great Falls, Montana, and started his scientific career at the McLaughlin Research Institute there. He obtained his M.D. from Stanford University in 1965 after earning a B.S. from Montana State University in 1961. His research has since focused on hematopoietic stem cell biology. His awards include election to the National Academy of Sciences in 1989 and being named California Scientist of the Year in 2002. He has also received the 2008 Robert Koch Prize and the 2009 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science. He developed methods to identify stem cells and has extensively researched stem cells and progenitor cells. His research focus is the phylogeny and developmental biology of the cells that make up the blood-forming and immune systems. Dr. Weissman is widely recognized as the "father of hematopoiesis," being the first to purify blood-forming stem cells in both mouse and humans. His work has contributed greatly to the understanding of how a single hematopoietic stem cell can give rise to different specialized blood cells. Dr. Weissman is also a leading expert in the field of cancer stem cells, where much of his work has shed light on the pathogenesis of multiple human malignancies. He is known also for transgenic research in which human brain cells were grown in mouse brains.

Qi Zhou, Ph.D., received a Ph.D. in physiology and embryology from Northeast Agriculture University, China, in 1996 with a dissertation titled "Nuclear Transfer and Serial Nuclear Transfer Research in Rabbit." In 1997–1999, he held a postdoctoral and associate professor position in the Institute of Developmental Biology at CAS, and in 1999–2002 he was a postdoc and project leader within the group of J. P. Renard (developmental biology and reproduction, INRA, Jouy-en-Josas, France). In 2001, he was offered a 100-Talent Program position at the Institute of Zoology, CAS, where he is currently the director of State Key Laboratory of Reproductive Biology and vice director of Institute of Zoology, CAS. Professor Zhou studies the mechanisms of reprogramming, differentiation, and de-differentiation as well as cellular plasticity and totipotency of stem cells and somatic cells, with the goal of understanding the mechanisms of mammalian cloning and improving cloning efficiency as well as promoting the application of stem cells in regenerative medicine.

C

Statement of Task

An ad hoc planning committee will plan and conduct a public workshop to examine and discuss stem cell tourism. The goal of the workshop will be to examine the extent of unsubstantiated stem cell therapy offerings, the potential risks involved, the evidentiary basis for claims of efficacy, and to discuss whether there is a need for coordinated efforts to regulate stem cell clinic offerings globally. One issue that will be considered at the workshop is whether the information available to the public is adequate to sort out options. The workshop will advance discussions among a broad array of stakeholders, which may include government officials, industry representatives, professional societies, academic researchers, regulators, providers, and patients. The planning committee will develop the workshop agenda, select and invite speakers and discussants, and moderate the discussions. An individually authored summary of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures. This workshop will be held jointly with the International Society for Stem Cell Research.

D

Registered Attendees

Lida Anestidou
Institute for Laboratory Animal Research
The National Academies

María de Jesús Medina Arellano
Autonomous University of Nayarit, Mexico

Andrew H. Baker
University of Glasgow, Scotland

Paolo Bianco
Department of Molecular Medicine
Sapienza University of Rome

Alessandro Blasimme
Institut National de la Santé et de la Recherche Médicale, France

Laura Bocanera
Akron Clinical

Michael Boo
National Marrow Donor Program

Joel Brill
Predictive Health, LLC

Maria Cabreira
Texas Heart Institute

Tim Caulfield
University of Alberta, Canada

Sheila Chari
Cell Press—*Cell Stem Cell*

R. Alta Charo
University of Wisconsin–Madison

George Daley
Harvard University

Reed Davis
International Cellular Medicine Society

Ellen G. Feigal
California Institute for Regenerative Medicine

Fred H. Gage
Salk Institute for Biological Studies

Nara Gavini
National Heart, Lung, and Blood Institute
National Institutes of Health

Larry Goldstein
University of California, San Diego, School of Medicine

Nady Golestaneh
Georgetown University School of Medicine

Barbara Graves
Howard Hughes Medical Institute

Rebecca Jorgenson
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Jacquelyn Liberto
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Vivian Lopez-Blanco
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Michael May
Center for Commercialization of Regenerative Medicine

Roger Medel
MEDNAX
National Medical Group

Maria Millan
California Institute for Regenerative Medicine

Toshio Miyata
Health and Global Policy Institute

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Alan Petersen
Monash University, Australia

Michael Phelan
Osage Partners

Amy Comstock Rick
Parkinson's Action Network

Margaret Riley
University of Virginia School of Law

Pamela Robey
National Insitute of Dental and Craniofacial Research
National Insitutes of Health

Heather Rooke
International Society for Stem Cell Research

Beth Roxland
New York University School of Law

Glenn L. Schattman
Weill Medical College

Christopher Scott
Stanford University

Aditi Sengupta
Department of Continuing Medical Education
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Douglas Sipp
RIKEN Center for Developmental Biology

Susan Soloman
New York Stem Cell Foundation

Alan Spitzer
MEDNAX
National Medical Group

Sally Temple
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Kemi Tomobi
Student National Medical Association

Gil Van Bokkelen
Athersys, Inc.

Luciano Vidal
Hospital Lanari

David C. Vladeck
Georgetown University School of Law

John Wagner
University of Minnesota

Irving L. Weissman
Stanford University School of Medicine

Michael Werner
Alliance for Regenerative Medicine

Frank Williams
Hawaii Institute of Molecular Education

Nancy Witty
International Society for Stem Cell Research

Jiwen Zhang
GE Healthcare

Qi Zhou
Institute of Zoology
Chinese Academy of Sciences

E

Glossary

Allogeneic: refers to cells or tissues from different individuals of the same species, but that are genetically different from each other.

Autologous: refers to cells or tissues derived from the same individual and are therefore genetically identical.

Clinical trial: any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.[1]

Efficacy (or therapeutic efficacy): the measure of the performance of a treatment for a given indication.

In vitro fertilization: combining eggs and sperm outside of the body with the goal of the sperm fertilizing (entering) the egg. The fertilized eggs (embryos) are then transferred to the uterus for implantation.

[1]International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance Guideline for Good Clinical Practice. See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf (accessed April 8, 2014).

Institutional review board (IRB): a committee that reviews, approves, and monitors biomedical research involving human subjects for the purpose of protecting the rights and welfare of participants.[2]

Medical tourism: the act of traveling across borders to seek medical treatment.

Mesenchymal stem cells: multipotent cells that can differentiate into bone (osteocytes), cartilage (chondrocytes), fat (adipocytes), and possibly other cells.[3]

Minimally manipulated: the processing of cells in a way that does not alter their relevant biological characteristics.[4]

Nutraceutical: an ingestible foodstuff that is purported to impart health or medicinal benefit.

Pluripotency: the cellular characteristic of being able to differentiate into all specialized cell types.

Regenerative medicine: an area of biomedical research focused on developing treatments for the repair, replacement, or regeneration of damaged cells, tissues, or organs.

Regulatory science: the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy, and quality.[5]

Stem cell: a general term for cells that have the ability to self-renew and differentiate into a variety of mature specialized cell types.

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[2]FDA Regulatory Information. See http://www.fda.gov/regulatoryinformation/guidances/ucm126420.htm (accessed April 8, 2014).

[3]Also known as multipotent stromal cells, there is controversy over whether these are actually stem cells, including whether they can perpetually self-renew and differentiate.

[4]FDA CFR—Code of Federal Regulations Title 21 revised 2013. See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=1271.3 (accessed April 7, 2014).

[5]FDA News and Events. See http://www.fda/gov/NewsEvents/Newsroom/PressAnnouncements/ucm201706.htm (accessed April 8, 2014).

Stem cell tourism: a type of medical tourism whereby a patient travels across borders to seek stem cell therapies to treat or cure disease.