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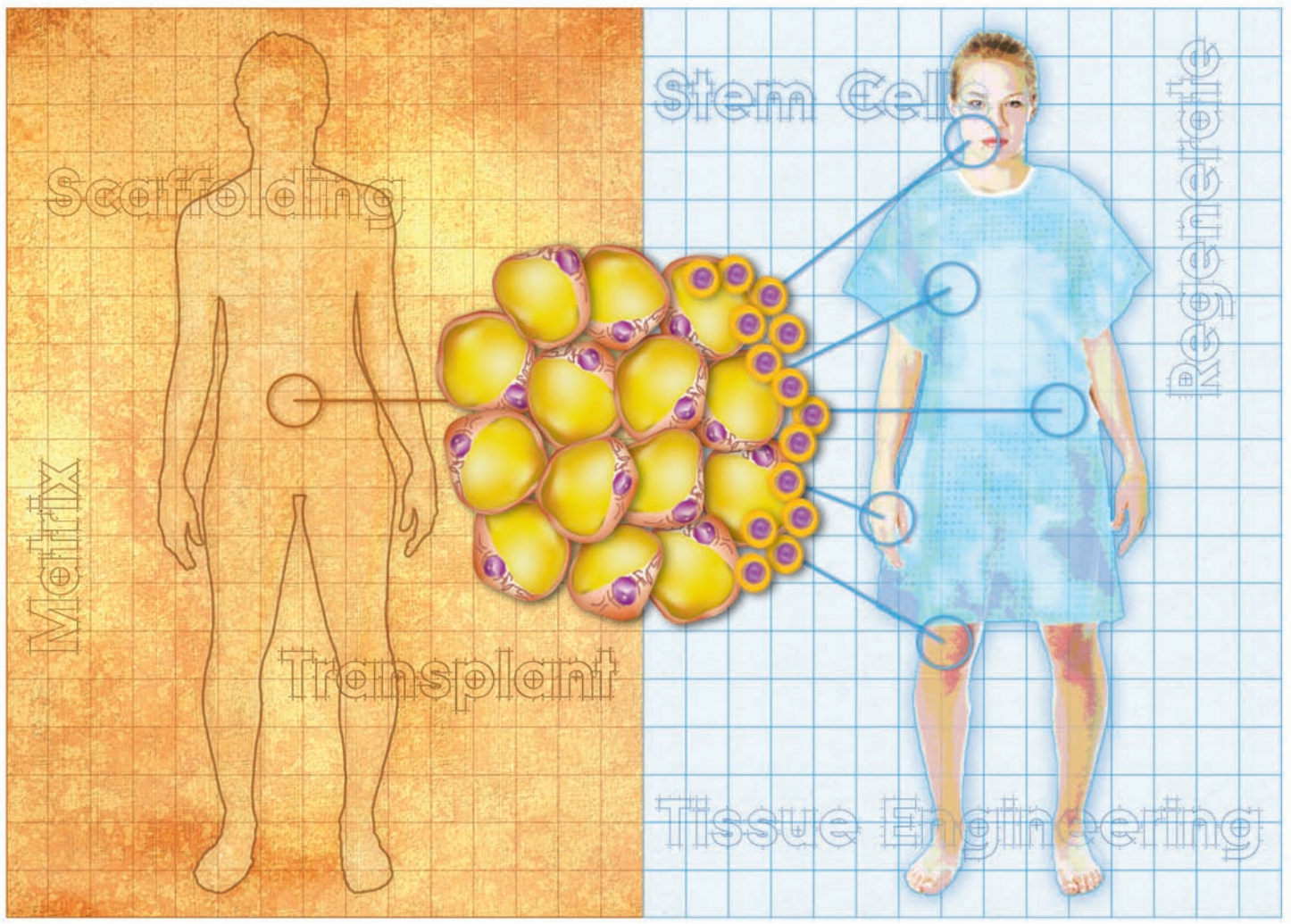

The future of fat

Will plastic surgery-driven stem cell research revolutionize medical care?

BY JIM LEONARDO

Many breast augmentation patients have joked that if they could magically shift fat from one area of their bodies to another, implants wouldn't be necessary. Little do they know that each day, a number of plastic surgeon scientists are inching closer to breakthroughs in fat-derived, adult stem cell therapy that will not only revolutionize plastic surgery, but also carry the potential to reshape medical care in general.

Autologous, fat-derived adult stem cells – "mature" cells re-introduced into the same body, as opposed to embryonic stem cells used as an allograft – are showing tremendous plastic surgery-related promise for such applications as post-mastectomy breast reconstruction, aesthetic breast augmentation and cosmetic hand rejuvenation, as well as the repair of wounds, scars, burns and radiation-damaged skin.

But a real possibility exists that fat-derived stem cells could also be influenced to treat an array of life-threatening conditions involving the heart and cardiovascular system, reversing or treating stroke, cancer and diabetes – and even manipulated to grow into bones and nerves.

Based on their results thus far, plastic surgeons involved in stem cell research could be the scientists who provide the breakthroughs leading to the transformation of medicine as it's understood today.

Body, heal thyself

"It may be possible to direct fat stem cells extracted from a patient to the site of his or her injury – for instance, to treat a central nervous system disorder such as stroke, degenerative disease or myocardial injury – and rely upon those cells to release growth factors and stimulate natural healing processes," according to J. Peter Rubin, MD, University of Pittsburgh Adipose Stem Cell co-director and Division of Plastic and Reconstructive Surgery associate professor, who has been conducting tissue engineering research since 1994.

"It also may be possible to engage in other related tissue engineering applications in which we stimulate these cells to transform into different cell types – such as smooth and cardiac muscle, bone, cartilage, and phenotypes that function as liver cells," he adds. "We have reports from a small number of research groups that have been able to transform fat

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HEALTH REFORM WATCH

Senate finance committee unveils 'Baucus proposal'

On Sept. 16, the Senate Finance Committee unveiled its reform plan – the first move in a long and complicated process involving more than 500 amendments, which is expected to push the mark-up process into October. While the plan provides for a slight increase in physician fees in 2010, ASPS and other surgical societies continue their calls for a full repeal of the sustainable growth rate (SGR). The Finance Committee's so-called "Baucus proposal" includes such elements as health insurance exchanges, mandatory pay-for-performance, formation of a Medicare commission that could set rates (with little recourse for providers), and a structure through which individuals could purchase health insurance.

Meanwhile, in the U.S. House, three committees passed slightly different versions of the same bill – the American Affordable Health Choices Act of 2009 (H.R. 3200). These three need to be codified – and the final version passed by the full House before it can move into a House/Senate conference committee and, ultimately, full passage into law (providing President Barack Obama signs the resulting legislation).

ASPS and 20 other surgical specialties delivered a letter to House and Senate leaders, urging them to include liability reform in all pieces of legislation currently under consideration. The Society also is pleased to note that the Children's Access to Reconstructive Evaluation and Surgery Act has been included in the House bills – and it remains a priority for ASPS. PSN

IN THIS ISSUE

VTE prevention takes center stage at summit

Venous thromboembolism are two words neither patients nor physicians want to hear, because it's one of the most common – and most preventable – causes of in-hospital deaths in the nation. Last year, the U.S. Surgeon General issued a "Call to Action" aimed at eliminating this life-threatening condition, and the American College of Chest Physicians recently published its *Prevention of Venous Thromboembolism* analysis – including prophylaxis recommendations and protocols. **Page 25**

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stem cells into types that could produce insulin and glucagon – so they could actually restore function to reverse diabetes. This is hugely exciting."

"The applications range from ischemic heart and brain injury to systemic inflammatory conditions, to liver and bone repair and beyond," says Adam Katz, MD, University of Virginia (Charlottesville) Plastic Surgery Department associate professor. "Recent clinical work in Finland shows that it may be possible to prompt fat stem cells to make new bone. There are multiple groups around the world working on these types of clinical applications. The practice of reconstructive surgery is on the verge of dramatic change. The future of 'self-cell surgery' is just around the corner."

Kamran Khoobehi, MD, New Orleans, a member of the International Federation of Adipose Therapeutics and Science (IFATS) – a multidisciplinary founded by four ASPS Member Surgeons, including Drs. Katz and Rubin – says the group's meeting last year in Toulouse, France, yielded revelations that point to the unlimited potential of stem cell research.

"What's on the horizon is amazing," says Dr. Khoobehi, clinical associate professor of surgery in the Louisiana State University Division of Plastic and Reconstructive Surgery. "There's a group in Taiwan doing truly revolutionary work, which reinforces the belief that we're just scratching the surface potential.

"Nobody can predict which way it's going to go," he adds. "It's a very exciting area – and plastic surgeons are pioneering it. From this will come tissue engineering, using your own fat to regenerate other parts of the body – and it's going to be something."

Many ASPS members also are involved in research targeting autologous fat transfer without a primary focus on stem cells – although they are an intrinsic part of the equation – and these plastic surgeons report differing levels of uses and results (*see article below*).

Battle wounds and reconstruction

Dr. Katz is ramping-up U.S. Defense Department-funded research that targets wounds and scars, in light of the countless injuries sustained by servicemen and women in Iraq and Afghanistan in particular. "The idea is to learn whether transplanting fat under the scar or wound can affect its ultimate quality or appearance," he says. "Two groups that studied fat grafting for scars found improvement in elasticity, color and appearance, and we're looking to push that forward with a blinded, randomized controlled trial."

Meanwhile, Dr. Rubin also is working with the U.S. Defense Department to determine methods through which stem cells can assist the reconstruction of the soft tissues of the face, and he's received another grant to develop minimally invasive breast reconstruction techniques using fat stem cell technology.

"Addressing these conditions through stem cell engineering is a major goal for my lab and the federal government," Dr. Rubin says. "My laboratory is funded for both of these efforts by the National Institutes of Health's National Cancer Institute, and by the Defense Department's Armed Forces Institute of Regenerative Medicine. The fact that each organization has made funding available demonstrates the high level of interest in tissue engineering."

Stem cells as drug couriers

One significant aspect of stem cell engineering revolves around the possibility that stem cells one day could be treated with a drug and then sent to specific parts of the body to deliver that drug – both treating the condition and acting as a substitute for medication delivered in today's conventional manners, according to Spencer Brown, PhD, Plastic Surgery Research Department director and assistant professor of plastic surgery at the University of Texas-Southwestern, Dallas.

"Some researchers feel it's possible to manipulate stem cells by adding drugs, genes or messenger RNA to them and turning the cells into tiny carriers," Dr. Brown says. "If the stem cell can be fitted with a medication, then delivered to a site and into a host tissue – with the drug becoming incorporated into the host tissue to perform short- to long-term delivery – that's a potentially sensational therapeutic role. This would relieve patients of taking drugs each day, perhaps multiple times per day, or from undergoing countless injections or being submitted to other intrusive drug delivery systems.

"The class of 'reagents,' as they're known, is very likely the next potential breakthrough," Dr. Brown says. "However, we don't know how stable these cells are, so we need to learn that. If you turn on a drug therapy, it would be nice to be able to turn it off."

The big dance

The factors that influence fat stem cells to act as they do upon replantation is one of the questions that researchers must answer before any applications can become widespread.

Dr. Brown compares autologous stem cells to participants in a sophisticated – though very tiny – dance that needs to be understood.

"Each cell has 30,000 little messenger RNAs telling it to make proteins in response to oxygen levels, hydration, temperature, wounding – the list is endless," he says. "They're involved in a dance with one another, and each one knows and dances properly to the music. If you add a stem cell, you've changed the music. What's conducting the orchestra for those 30,000 genes? Will they now know which partner to pick? How much control does the conductor have, and how much independence does each dancer have? What would make one become a 'rogue' dancer that turns cancerous? We need to find out."

"One of the things we know about fat stem cells: They are not just one homogenous population of cells, but a very mixed population," says Dr. Rubin.

Plastic surgeons find novel and effective uses for autologous fat grafts

BY JIM LEONARDO

The use of autologous fat grafts is less questioned and certainly much more employed than its sophisticated cousin, fat-derived stem cell replantation. Because there are fewer constraints and safety concerns, fat grafting – also known as autologous adipocyte transfer – currently is applied in widespread fashion, from adjunct breast reconstruction to the correction and possible reversal of the disabling hand condition known as Dupuytren's contracture.

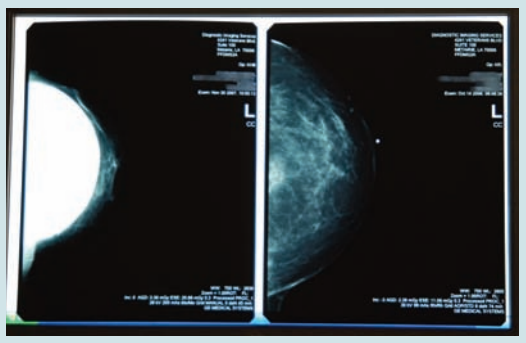
Several ASPS members involved in fat graft research inform *PSN* on the different uses and results, how their processes work and the issues they face in trying to create replicable methods that other plastic surgeons can follow in their wake.

Breast reconstruction

Using autologous fat for breast augmentation would seem the best of both worlds for both patients and plastic surgeons, and to some extent this promise has become reality. But while patients would welcome a "take fat from here and put it there" scenario, there's one major hold-up: fat graft volume restrictions. That is, large amounts of fat grafted in one sitting won't fare well in their new host sites.

"The fat must be introduced in small aliquots, through many injections over several weeks," according to Roger Khouri, MD, Miami. "Big blobs of fat introduced at one time will die. You need to disperse in the recipient site tiny droplets of fat that have a good tissue interface to survive. Because you cannot overstuff the grafts, the recipient size limits the amount of graft possible per session."

Dr. Khouri has created a gradual-expansion device known as the Brava® system, which attaches directly to the breast and through low but continuous pressure over several weeks, prompts the woman's body to enlarge the breast tissue – creating more space into which he can transfer the larger amount of fat required for breast augmentation and reconstruction.



Mammogram images of a patient of Kamran Khoobehi, MD, highlight a breast with an implant and the breast after completion of the fat grafting procedures.

"The system creates a 3-dimensional 'mesh,' or scaffold, you can populate with fat," he says. "You can't introduce 300 ccs of fat into a tight mastectomy scar defect or a very small breast, because the graft/recipient interface requirement would not allow it. But you can in the new, expanded scaffold that also allows for indigenous vascularization – the creation of its own blood flow – which is the key to all fat grafting."

Among the advantages of fat grafting for breast reconstruction, he says, is the satisfaction derived by patients who consider this application similar to regrowing their own breasts. "One of my patients was a 32-year-old cancer victim who said: 'It reminds me of when I was a teenager, watching my breasts grow – and it's my own breast.' We give women back what they lost through mastectomy, not just with an implant or by doing patch work, and they feel their own breasts regenerating," Dr. Khouri says. "The true beauty of this is, we lower the bar for the acceptance of breast reconstruction."

Georgetown University Department of Plastic Surgery Chair Scott Spear, MD, Washington, D.C., uses fat as an adjunct to breast reconstruction, but he's neither strongly for nor against the widespread use of fat grafting. "We see that it works, but we're waiting to see how *well* it works," he says. "Although I use fat grafting as an adjunct procedure, we must look more critically at the negatives of doing it.

"That is, there are certain risks we know are true," Dr. Spear notes. "In some cases, it won't work and the fat will die; or the area will develop lumps; or an infection will result. There's also some very experimental work that's a little concerning due to the conclusions that it might potentiate the growth of cancer cells in the breast – which is an area that's prone to develop cancer. That doesn't mean it's happening, but it would be naive to assume that it's not."

Kamran Khoobehi, MD, New Orleans, has met with success with the technique, and none so notable as the case in which he replaced traditional breast implants with fat grafts.

"The first time I did the procedure, I could not believe the results," says Dr. Khoobehi, clinical associate professor surgery at the Louisiana State University Health Sciences Center and member of the International Federation of Adipose Therapeutics and Science (IFATS).

"If I were to show plastic surgeons the sequential pictures I've taken, they would say: 'This isn't real; this is not believable.' The mammogram *(see photo above)* reveals that implants are gone and there's only fat remaining – and they are actual breasts. If somebody told me 10 years ago that you could take an implant out and through fat grafting could recreate the breast, I would have said 'impossible.' "

Irradiated skin

Among the most difficult reconstruction involves breast tissue that's been irradiated to fight cancer. The skin becomes tight and in many cases brittle. Normally, free flaps are used as a simple – but by no means routine – procedure to replace lost breast tissue.

Sydney Coleman, MD, New York, who has treated patients worldwide with irradiated skin, says the blood supply created by replantation tends to reinvigorate breast tissue – and facial tissue, as well.

"Radiation damage makes surgery much more difficult, as it increases the chance of infection, wound failure and other negative outcomes," he says. "As a result, surgeons are extremely hesitant to operate on these patients. But fat grafting is really promising due to the creation of a new blood supply that allows the skin to repair itself – and this type of repair can apply in many other skin-related cases.

"I also have treated scars through fat grafting, and the results are, in some cases, dramatic, particularly with depressed scars," Dr. Coleman adds. "The potential of fat grafting is very promising – and we're discovering an enormous amount of new information each week."

Gino Rigotti, MD, Verona, Italy, says the positive results he's gained using fat grafts on irradiated skin has altered his belief system. "Before we injected fat, I believed the damage caused by radiation was irreversible – that we would need to excise everything irradiated and replace it with a skin flap," he tells *PSN*. "But after using fat, we've seen a transformation to normal tissue with normal sensation; the burning sensation disappears and the quality of skin returns. This has revolutionized our thinking."

This success has been replicated in head and neck tissues, he adds.

However, Dr. Rigotti acknowledges that his enthusiasm for fat grafting has been based mainly on personal observation – and that more science needs to be employed. "We know with certainty very little regarding the capabilities and possibilities of fat," he says. "We need to conduct additional studies."

Hand treatment

Injecting fat into a hand treated for Dupuytren's contracture with percutaneous needle release has achieved remarkable results, Dr. Khouri says.

"With this condition, ligaments in the palm shorten over time and the hand curls up," he says. "What I've done is to put these

"To a certain degree, we can tell them apart by the surface markers they carry – we can do flow cytometry analysis to help differentiate different cell populations. We can sort these cell populations based on these surface markers, almost like organizing a deck of cards by their suit. In addition, there are cells that are more effective for certain applications, which would compare to aces and kings in the card deck."

Dr. Brown adds that a pair of hypotheses have emerged on stem cell interaction with their environment.

"One is that the stem cell has in its back pocket, or DNA, the ultimate programming plan and enacts that plan wherever it goes," he says. "For instance, they're in a fat tissue, so they follow that plan: 'Okay, I'm a fat tissue, I'm going to become an adipocyte.' "

But others support a competing hypothesis, Dr. Brown adds. "Maybe the stem cell's not so limited by its DNA, but can actually sense the environment, where it is and what's needed. And it will be driven by a number of environmental cues and disregard what it thinks it should become according to its DNA. That has to do with the interplay of sensing what the environment is – the different signals coming through. And there are multiple signals."

Small steps – and patience

Several factors prevent true acceleration in stem cell therapy for healing, two of which are being addressed head-on by these research-based plastic surgeons: the development of a matrix or "scaffold" that would allow transplanted fat to thrive, as well as rigorous, scientific studies that would allow for replication – and acceptance by the medical community in general.

"These cells require some sort of scaffolding or framework with which they feel comfortable enough that, once placed into the wound or into the body site, they have a little 'dance floor' to walk on," Dr. Brown says. "Indeed, many scientists are trying to determine the 'magic scaffold.' Some plastic surgeons use fat itself as a scaffold, in a 'super fat graft,' so to speak, where the matrix is provided by the body itself. Several studies now are focusing on providing the framework to which stem cells can attach and flourish. This is vastly important for the field."

Roger Khouri, MD, Miami, agrees that elusive scaffolding remains a focal point for researchers. "Tissue engineers for a long time have sought implantable, biodegradable and biocompatible scaffold," he says. "The idea is, you place the scaffold in space and seed it with cells – and you create an organ. Solving the matrix problem will throw open the doors of stem cell research."

ASPS member Elisabeth Beahm, MD, professor of surgery at the University of Texas (Houston) MD Anderson Cancer Center, says that although she has seen startlingly good results from stem cell therapy employed to repair skin damaged by radiation treatment, any excitement must be tempered by sound scientific study.

"We must refine this science to reap the greatest benefits," says Dr. Beahm, who has conducted research on fat in breast reconstruction for more than five years. "That means expanding scientific inquiry to fully understand the mechanisms of cell growth and survival – with follow-up for five or 10 years. We know stem cells are present in the fat we transfer for breast reconstruction, but are they these stem cells the *de facto* reason for the overlying skin improvement in the radiated breast? Or are other factors at work, coincidentally or in concert with fat stem cells, such as fibronectin – 'basement membrane'?

"These questions point to the importance of fat survival studies," she says. "If we're going to use tissue engineering for reconstructive purposes – not simply to correct contour deficiencies – then we need to know how to use these manipulated cellular populations are going to behave longitudinally and understand the process better."

Dr. Brown says the factors that drive a stem cell's reaction upon its introduction into an environment need to be addressed. "How does the individual cell know to become the fat tissue or the blood vessel – or how to assist the environment?" he says. "Related, how do we know that the cell won't differentiate into something we may not want, such as a bone cell in the middle of fat tissue – or worse, an oncogenic cell?"

"No one knows the long-term safety or risk profile of these cells," says Dr. Katz. "There are potential downsides that theoretically could happen; these stem cells could form cancers or turn into other tissue we don't want. On the other hand, an abundance of research with these cells in immuno-suppressed animals has not, to my knowledge, yielded evidence of tumor formation. It's also probable that these adult, tissue-derived stem cells won't turn into unwanted tissues – of which there's some precedent. But these issues can only be clarified with confidence through multiple, independent and controlled long-term studies."

Karol Gutowski, MD, Evanston, Ill., served as chair of the ad hoc ASPS Fat Graft Task Force, which published in the journal *PRS* a report (*"Current Applications and Safety of Autologous Fat Grafts: A Report of the ASPS Fat Graft Task Force,"* PRS*, vol. 124, Issue 1, pages 272-280*) in July on the applications and safety of fat grafts. He agrees that while early research shows the promise of fat grafting, more studies are needed.

"There are many relatively small reports of people using fat grafting for many different things, but most of the information wasn't provided by prospective, randomized studies. So it's difficult to say the results will hold up over time," Dr. Gutowski says.

"Studies need to be more formal, where physicians try, for instance, six or eight techniques in an animal and see what works best there – then transfer those to a human and try the top two ways in a lab, and see what works best," he says. "Also, some of the basic science regarding the optimal ways of harvesting, preparing, storing and injecting these tissues still needs to be defined. No one's shown that there's an acceptable standardized way to do it."

"We need codified information on the mechanics of success," Dr. Beahm adds. "It's likely there are several – but armed with the right information, we can improve the results and ensure that we use this material safely."

Dr. Khoobehi, however, believes the field is too broad for standardization. "There's a process for cardiac bypass, for instance, and for breast augmentation," he says. "But there's not one for a facelift, and tissue engineering lies in this milieu. Anything replicable may resemble more of a 'tree trunk' model, but this field won't become standardized. However, rigorous study of any technique should never be given the short shrift – ever." PSN

ligaments under strong tension and use a needle to divide them without making an incision, and then inject the hand with fat. This combination has had a tremendous effect. The fat prevents the released ligament ends from meeting up again and shortening once more over time, and it also restores padding to the hand – and for some reason rejuvenates it.

"The hand more or less returns to normal function without the down time of traditional surgery," Dr. Khouri says. "I like to say that with fat injection, we've turned back the clock for hands with Dupuytren's contracture."

Variables and 'Coleman method'

ASPS member Elisabeth Beahm, MD, professor of surgery at the University of Texas (Houston) MD Anderson Cancer Center, says fat grafting has shown great promise in many areas, but the lack of standardization for many related techniques is troubling.

"Questions abound," she says. "These include: What is the best donor site for harvest; whether the fat is affected by the different medications used in the liposuction infiltration solution; which is most efficacious among high-pressure or manual suction techniques; how should the fat be processed; what is the best method of fat injection; and does injection site location affect outcome? There's some controversy in some of these areas.

"However, I want to be clear that I'm not dismissive of fat grafting," Dr. Beahm adds. "It seems to be a very promising application, with a number of practitioners in the United States, Asia and Europe showing success, albeit empirically. These and other accounts demonstrate that autologous fat grafting can be used as an adjunct to improve contour in reconstruction, and as a stand-alone technique for volume restoration. The results, however, remain highly variable, the techniques are not standardized, and the outcomes have not been objectively quantified. We seem to be at a very exciting crossroads in reconstruction; however, improved understanding of these issues is essential."

Dr. Coleman addresses harvest and injection points as creator of what's widely known as the "Coleman method" – a widely used set of guidelines that produces similar results under similar circumstances when executed by any qualified medical professional.

"I harvest the fat under relatively low pressure, using a 10cc syringe and two-hole cannula that I work by hand," he says. "Once the fat's harvested, the syringe is capped and the plunger removed – and the fat is spun for three minutes with a gravitational force of about 1.98. The G-force is the important factor, not the RPMs; studies originating in Japan have shown this to be the optimal force for separating the oils, fat and blood – which settle in the vial in that order.

"I use a 1cc syringe for face and hand injections and make a lot of passes," Dr. Coleman notes. "No one disagrees with making many passes and introducing small aliquots rather than large volume. The only drawback in that is the swelling that occurs with multiple injections.

"These applications have enormous potential," he adds. "I believe they have begun to revolutionize medicine. Fat grafting will become an amazing addition to medicine."

Dr. Khoobehi says the applications of fat graft therapy will be limited only by imagination. "We often create brain barriers for ourselves, that 'this thing' is the way that it's supposed to be – like the world was once accepted as flat," he says. "We put certain barriers in our brain. Change means you have to accept the new rules and realities; some people can't accept that. The different applications currently employed in fat grafting show that its potential is unlimited."

"It seems as if the trend in medicine right now is to look ahead for prophylactic maneuvers that are minimally invasive and sort of holistic, and that's where fat grafting really comes in," Dr. Coleman says.

"We're discovering that we can treat many problems in a very holistic, using-the-body-to-heal-itself fashion that requires a minimal amount of invasion. In this regard, fat grafting is a very important advance – and fits in very well with modern medicine." PSN