GEISTLICH BIOMATERIALS

NEWS

VOLUME 14, ISSUE 2, 2019

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Gaining bone height.

Bone block or GBR? Form-stable membrane or customized titanium scaffold? A discussion for treatment options.

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The quest for stability.

Our science comic shows how the L-shape technique was invented by researchers from Zurich and Barcelona.

LEADING REGENERATION.

Editorial

What is needed around implants


Photo: Roger Schuler

Archaeological findings of Celtic, Egyptian and Etruscan dental implants prove just how important a functional set of teeth has always been.

But how does placing an implant affect the surrounding tissues? And which regenerative measures support the long-term success of implants?

As our body works according to an energy saving mode, the alveolar ridge is resorbed when teeth are lost and the formerly supporting bone becomes useless. But this bone loss poses a problem for placing dental implants. To successfully anchor implants and allow them to function, the alveolar ridge, with its bony and connective tissue components, needs to be rebuilt.

Bony regeneration cannot be successful without proper soft tissue regeneration. Bone and soft tissue regeneration must go hand in hand, particularly in the oral cavity, where the risk of infection is high, given the broad bacterial flora.

I am convinced that new scientific discoveries by Geistlich Research and Development and external, collaborative laboratories will yield a better understanding of bone and soft tissue regeneration. In vitro, pre-clinical and clinical research will not only pave the way for a better understanding of oral rehabilitation mechanisms but, more importantly, also fuel the development of new products for our patients.

Dr. Birgit Schäfer
Executive Scientific Manager

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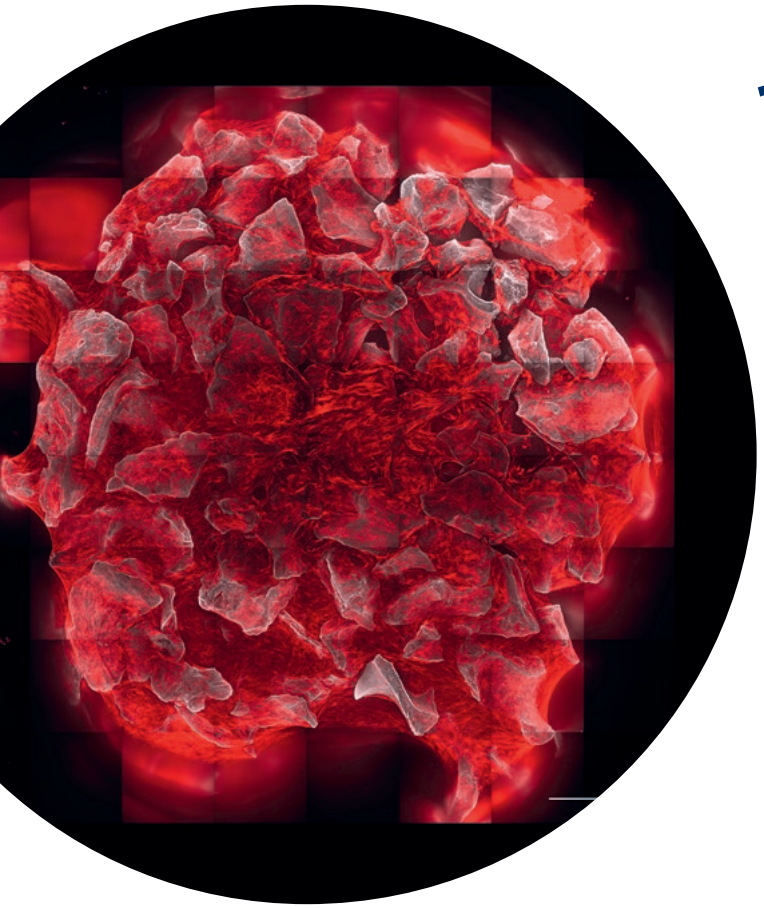

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Geistlich opens new affiliate in Japan

In June 2019 Geistlich Pharma launched its own organization in Japan. “Having our own affiliate in Japan is an outward sign and clear acknowledgement of Asia as a growth region. Japan is set to become another strong pillar in our network,” according to Geistlich CEO Paul Note.
As the market leader in regenerative dentistry, from the outset Geistlich has been committed to the technically competent use of its products and consequently provides training and courses for professionals. An extensive education and training offer is also being planned in Japan.

Lab time @ Geistlich

One highlight of the exhibition at Osteology Barcelona was the "Regeneration Lab." Here, Dr. Lothar Schlösser, Director Material Discovery Research of Geistlich Pharma AG, Switzerland, conducted experiments with our collagen materials and discussed how Geistlich R&D uses our scientific knowledge and can support clinical practice. Instructive, impressive, interactive – and most of the time very crowded! (Ed.)

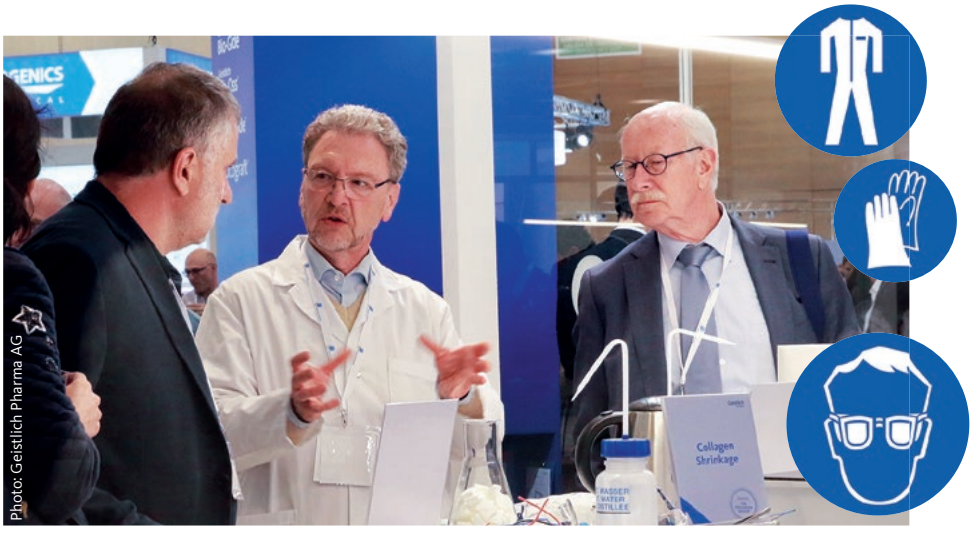

Photo: Geistlich Pharma AG

A hospital ship serving the poorest

If “Mercy Ships” didn’t exist, someone would have to invent them! The eponymous international aid organization gives hope to patients who are unable to access medical services, particularly specialist surgery. Longer-term benefits are assured by projects offering training programs that enable local specialist personnel to help their communities.
Because of the meaningful work carried out onboard, Geistlich Pharma supports the “Mercy Ships” with an annual donation. (Ed.)

Photo: Mercy Ships

Do you have a bright idea?

Are you advocating a new technique, or do you have an idea for a new biomaterial? There is a feedback section on our website that might be of interest! (Ed.)

Photo: Geistlich Pharma AG

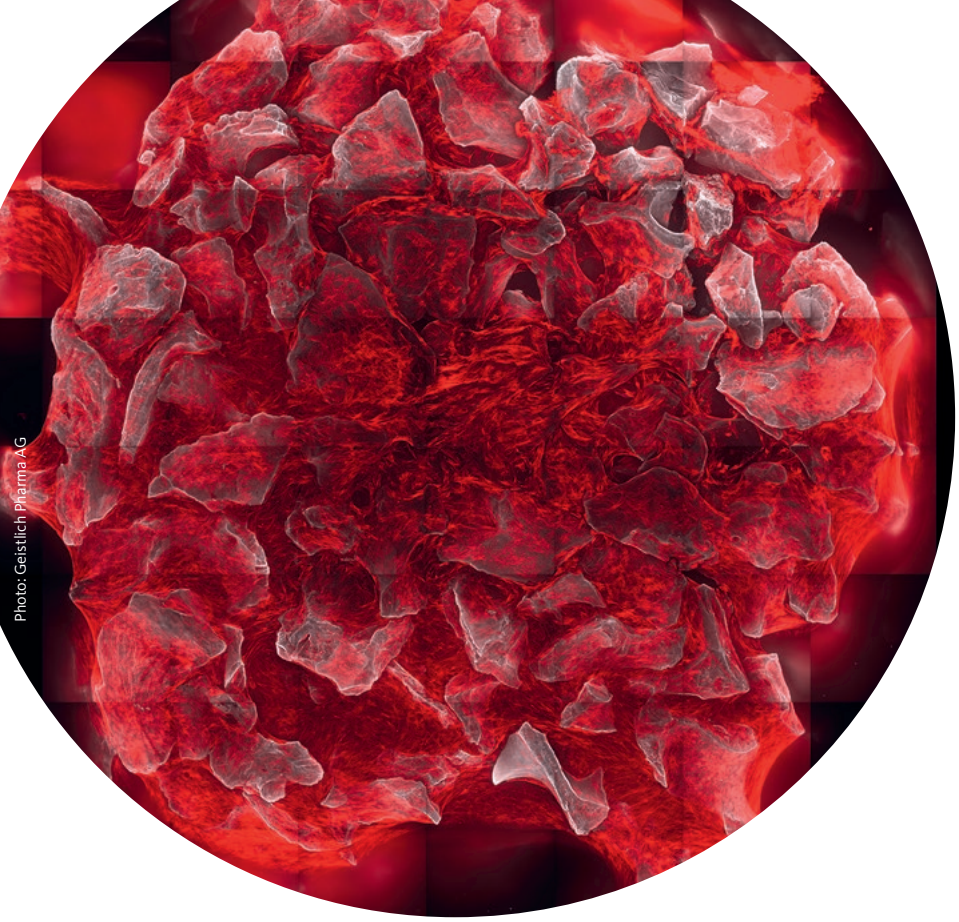

Photo: Geistlich Pharma AG

Living cells and bony scaffold united

After more that 30 years from its market launch, Geistlich is still investing in research for its pioneering product Geistlich Bio-Oss®. In this image from the Geistlich Cell Laboratory in Switzerland, bone precursor cells, whose cytoskeletons have been stained red, grow on Geistlich Bio-Oss® particles. Over time the cells form an extracellular matrix on the scaffold. The extracellular matrix unites the Geistlich Bio-Oss® particles to form a solid clot. (Ed.)

New BioBrief with Yxoss CBR®

A **BioBrief** explains a surgical procedure step-by-step, using a case study - and provides important tips that can be applied to other cases. The BioBrief includes a flyer with all information on the patient and treatment, as well as a webinar that includes a surgical video and a case library.

In the latest BioBrief, Prof. Matteo Chiapasco and Dr. Grazia Tommasato demonstrate the regeneration of a vertical and horizontal bone defect in the posterior mandible – integrating digital planning and the CAD/CAM solution Yxoss CBR®.

A surgery movie is part of the BioBrief, focusing on the question of how to perform the releasing incision – a procedure that is key for soft tissue management. (Ed.)

More information:

The best kept secret

Many people wonder how Geistlich Bio-Oss® is produced. The new film "The best kept secret" reveals part of the secret. Cornel Imhof, Director Material Development and Production Technology at Geistlich Pharma, leads the observer through “black box stations” that the famous bone substitute must pass on its long journey to the dentist. (Ed.)

Photo: Sooli GmbH

Happy “Gappy Game” winners in Barcelona

Geistlich's video game **Gappy - Preserve the Ridge** has been online during 2018. The highest ranking in the two rounds of play was achieved by Dres. Changdong Kang, Korea, Darren Sue, New Zealand, Marc Faura & Elias Casals, both from Spain and Patricia Risso, Uruguay. They won free entry for the International Osteology Symposium 2019 in Barcelona – where they met Dr. Terance Hart, Director of Research for a get-together. (Ed.)

Photo: Geistlich Pharma A

Around implants.

How can surrounding tissues support long-term dental implant success? Our experts discuss regenerative solutions for the daily clinical practice.

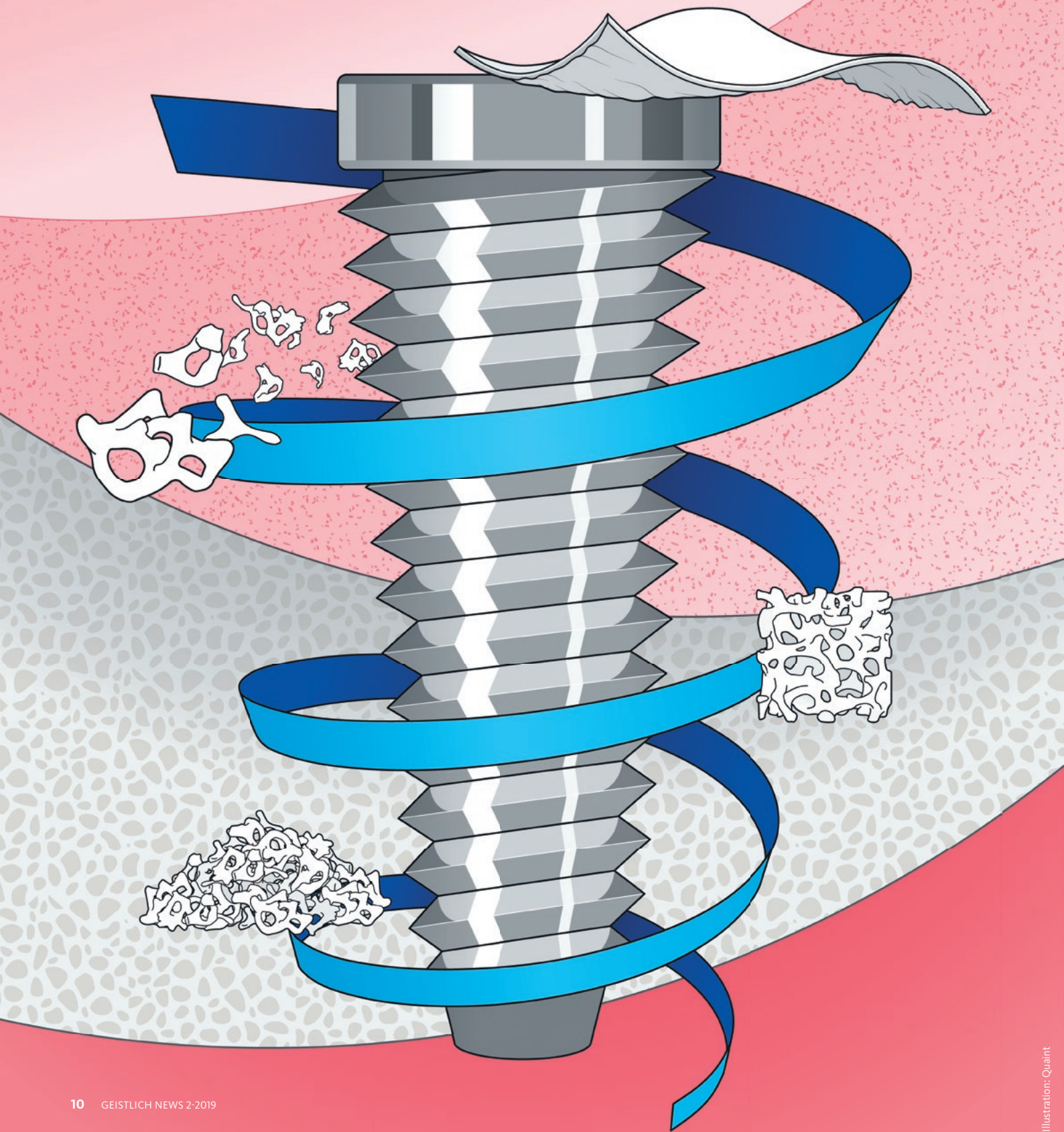

Illustration: Quaint

Essential protection from long-term complications

Prof. Stefan Fickl | Germany
Department for Periodontology
Julius-Maximilian University of Würzburg
Private practice, Fürth

For long time, soft tissue management was seen as purely esthetic. But around implants both keratinized tissue and sufficiently thick soft tissue have protective functions.

In our practice, soft tissue management – in the form of flap advancement, rolled flap, connective tissue or collagen matrix grafting – is part of the treatment in approximately 80 percent of our cases.

What soft tissue conditions are beneficial?

In terms of the quality of the surrounding soft tissue, augmenting an approximately 2 mm band of attached keratinized mucosa should be the goal to establish stable, long-term conditions. One review concluded that a lack of adequate keratinized mucosa is associated with more plaque accumulation, tissue inflammation, mucosal recession and attachment loss.[1]

As to the quantity (thickness and height of the peri-implant soft tissue cover), studies show that thicker peri-implant soft tissue leads to less bone resorption. Thus Linkevicius et al. were able to show that 2 mm thick peri-implant soft tissue induces significantly less crestal bone loss than a soft tissue thickness of less than 2 mm.[2] This phenomenon may be explained by the necessary establishment of an apical biological width with thin marginal mucosa and two-part implants. The group was able to show that peri-implant soft tissue augmented with biomaterials behaves in a similar way to "naturally thick" soft tissue.[2] It was also determined, using the highest level of evidence (Osteology Consensus Conference), that soft tissue augmentations protect against crestal bone resorption.[3] Today it must therefore be concluded that the target for soft tissue thickness should be 2 mm, and the target for attached mucosa also 2 mm **(fig. 1)**.

Techniques for gaining keratinized mucosa

Free mucosal transplants are the gold standard for augmenting attached keratinized mucosa. Free mucosal transplants, however, have various other disadvantages in addition to painful removal and the increased risk of complications. These include scarring and insufficient adaptation to the surrounding soft tissue. According to a retrospective case control study from our working group, covering extraction sockets with gingiva punch products produces considerably more scars, contractions and color deviations than the collagen matrix Geistlich Mucograft® Seal.[4] We consider Geistlich Mucograft® Seal to be preferable as a closure for extraction sockets.

Techniques for volume thickening

Subepithelial connective tissue transplants are the current gold standard for augmenting the volume of soft tissue around implants. However, clinical studies show that a similar tissue volume can be obtained with a volume-stable xenogeneic collagen matrix (Geistlich Fibro-Gide®).[5,6] In this respect this development is interesting for clinicians, as removing subepithelial connective tissue transplants or advancement flap techniques for thickening soft tissue are often very complex and technically sensitive procedures. The introduction of collagenous soft tissue matrices has reduced patients' surgical burden. These modern methods also allow soft tissue augmentations for increasing tissue thickness in the posterior zone. As an approximate value, the use of the collagen matrix can be assumed to increase soft tissue thickness by 1-1.5 mm. In terms of the 2 mm protective soft tissue thickness requirement, this means that sufficiently thick soft tissue can be achieved in a single soft tissue augmentation.

Points in time

The soft tissue can be improved at different times. A Ridge Preservation can be performed **immediately after tooth extraction**. Using a porcine collagen matrix (Geistlich Mucograft® Seal) for covering the extraction socket can achieve a better and faster soft tissue closure with only minor scarring.[4] Soft tissue can also be thickened **at the same time as the implantation**. In this context Geistlich Fibro-Gide® is a tested means for improving peri-implant soft tissue thickness prior to uncovering implants. **Late soft tissue thickening after the implantation** can be more difficult. Scientific data show that secondary soft tissue correction brings little success.[7] Accordingly, I prefer proactive

soft tissue augmentation to subsequent correction and from the outset try to avoid the formation of thin or dehiscent soft tissue around a prosthetically treated implant.

All parameters fulfilled

The clinical case in **Figure 2** shows a patient with a thin and poorly attached mucosa. The aim here was to achieve all the targets required for sufficient peri-implant tissue – 2 mm attached mucosa plus 2 mm soft tissue thickness – by augmenting volume and subsequently managing the soft tissue. Geistlich Fibro-Gide® was placed at the time of the implantation to allow primary healing beneath the mucosa. Visibly, Geistlich Fibro-Gide® thickened the soft tissue significantly. The collagen matrix Geistlich Mucograft® was then used with open healing at the time the implants were exposed in order to obtain an augmented band of attached mucosa.

Why this approach? As already alluded to, soft tissue formation after a complication, e.g., implant dehiscence and/ or poorly at-

"The target for soft tissue thickness should be 2 mm, and the target for attached mucosa also 2 mm."

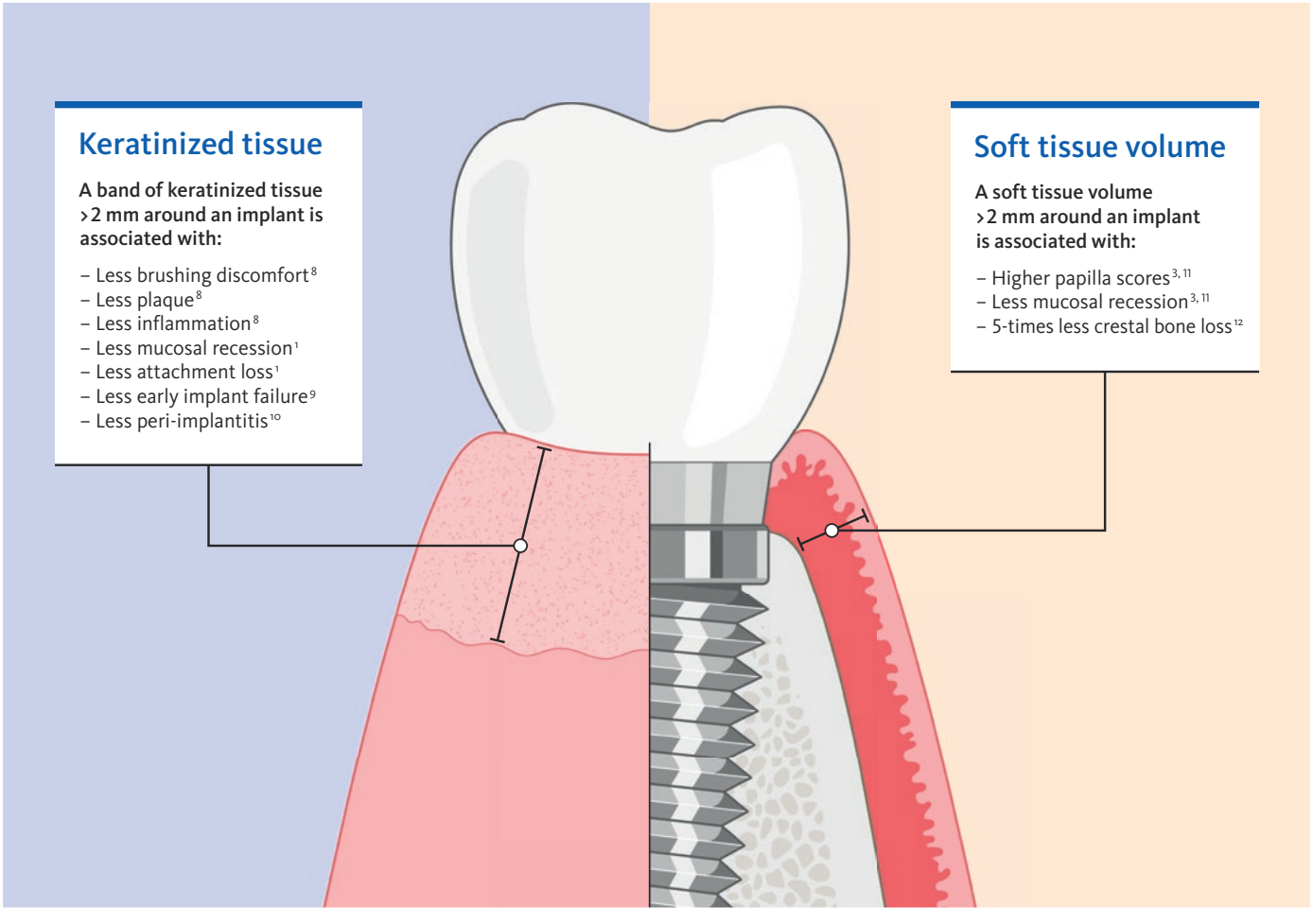

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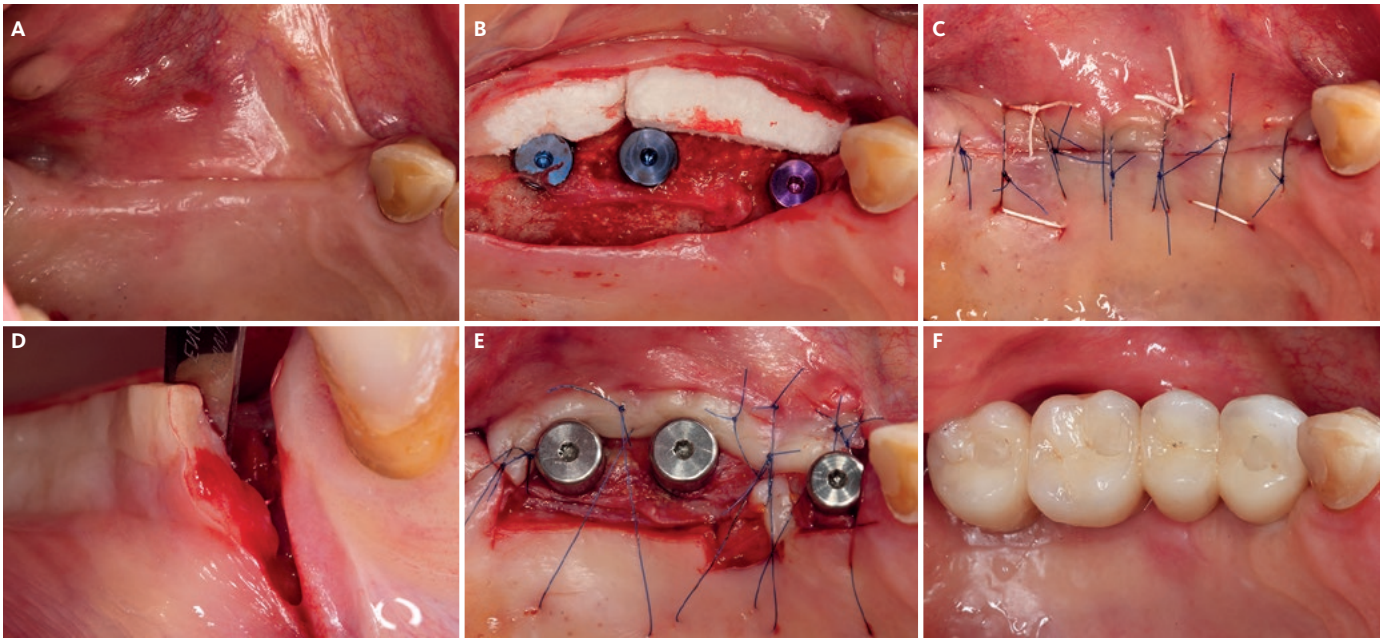
FIG. 1: Illustration showing the target amout for the attached mucosa and for the soft tissue.

FIG. 2: Soft tissue augmentation procedure using Geistlich Fibro-Gide® and Geistlich Mucograft®.



Photos: Stefan Fickl

| **A** Clinical situation with insufficient soft tissue thickness. | **B** Augmentation of soft tissue thickness with Geistlich Fibro-Gide® at the time of implant placement. | **C** Primary wound closure. | **D** Partial thickness flap elevation on the buccal side 4 months after implant placement and soft tissue thickening. Note the established thickness of the buccal soft tissue. | **E** Rolling flap and apically repositioning to position the attached mucosa on the buccal side of the implants. Geistlich Mucograft® to create additional keratinized mucosa in situ. | **F** Final reconstruction.

tached mucosa to a prosthetically treated implant, is a difficult and less predictable process. For this reason the above-mentioned soft tissue augmentations prior to prosthetic restoration are key to avoiding middle- and long-term complications.

Conclusion for clinical practice

Autologous transplantation of soft tissue may still be the standard technique for improving peri-implant health, but the use of collagen matrices extends the indication and the clinical options for improving soft tissue and ensuring patients a long-term and stable soft tissue peri-implant solution.

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“It is indispensable to treat peri-implantitis as a whole unit”

Dr. Hector Sarmiento | USA
Department of Periodontics and Implant Dentistry,
University of Pennsylvania, Philadelphia.
Private Practice, New York
Interview conducted by Dr. Giulia Cerino & Verena Vermeulen

Dr. Hector Sarmiento has broad experience in the treatment of peri-implantitis. He recently published a new classification system and a basic treatment protocol with different surgical alternatives. We asked him to share his findings and opinions.

Dr. Sarmiento, how often do you see peri-implantitis in your daily practice?

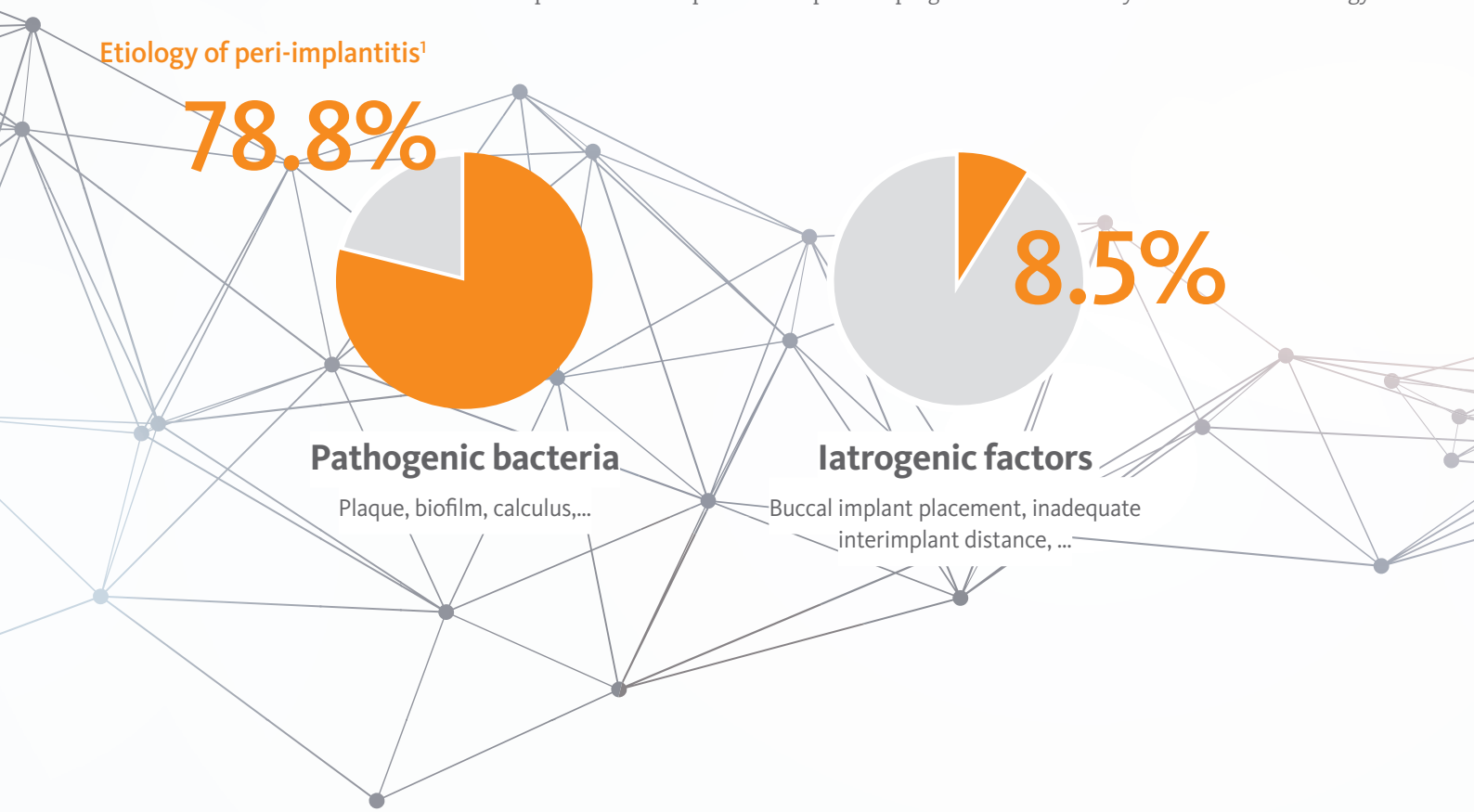
Dr. Sarmiento: A lot of my referring doctors know that I specialize in this area. I would say that around 70 percent of my patients suffer from some sort of biologic complication resulting from an implant in need of repair.

That’s a rather high percentage...

Dr. Sarmiento: It is, but you have to remember that the number of those with peri-implantitis is quite high. About ten percent of all implants end up developing peri-implantitis after eight years. Peri-implantitis bone levels are influenced by not only pathological, but also non-pathological conditions. Our understanding of peri-implantitis has certainly evolved over the past decades. However, its classification is limited to descriptions of disease progression or to classification that involves soft and/ or hard tissues (peri-implant mucositis or peri-implantitis).

Is that why you have published a new classification system?[1]

Dr. Sarmiento: We published the first classification system based on etiology.



We wanted to identify various etiologies for peri-implantitis and to establish a classification system based on the pathogenesis.

What were your principal findings?

Dr. Sarmiento: Most of the bone loss was related to one of the following factors: 1) biofilm, including iatrogenic factors, 2) exogenous irritants, 3) the absence of keratinized tissue and 4) intrinsic pathology. This classification system allows for the clinician to properly diagnose peri-implantitis based on the etiology. (**Fig. 1**)

Does this mean adopting therapy based on etiology?

Dr. Sarmiento: Indeed. When a diagnosis is related to a bacterial component, the clinician can use nonsurgical or surgical therapies, or a combination of both, to prohibit the further progression of the disease. In addition to creating that targeted therapy, the clinician should have a better sense in predicting intervention and prognosis of the implant.
I fully advocate that the determination of the underlying cause of peri-implantitis will strongly aid the clinician in the choice of a successful surgical procedure. For example, if excess cement were to be found on the implant surface, removing the source should lead to the elimination of the causative factor; thus leading to a regenerative approach. If the implant were to break down from the lack of keratinized tissue, soft tissue enhancement in this case should be considered while decontaminating and repairing the implants.

Could you give us an example?

Dr. Sarmiento: If you have an implant with bone loss that is related to an inflammatory response to biofilm, that implant may have a lower efficacy and a diminished long-

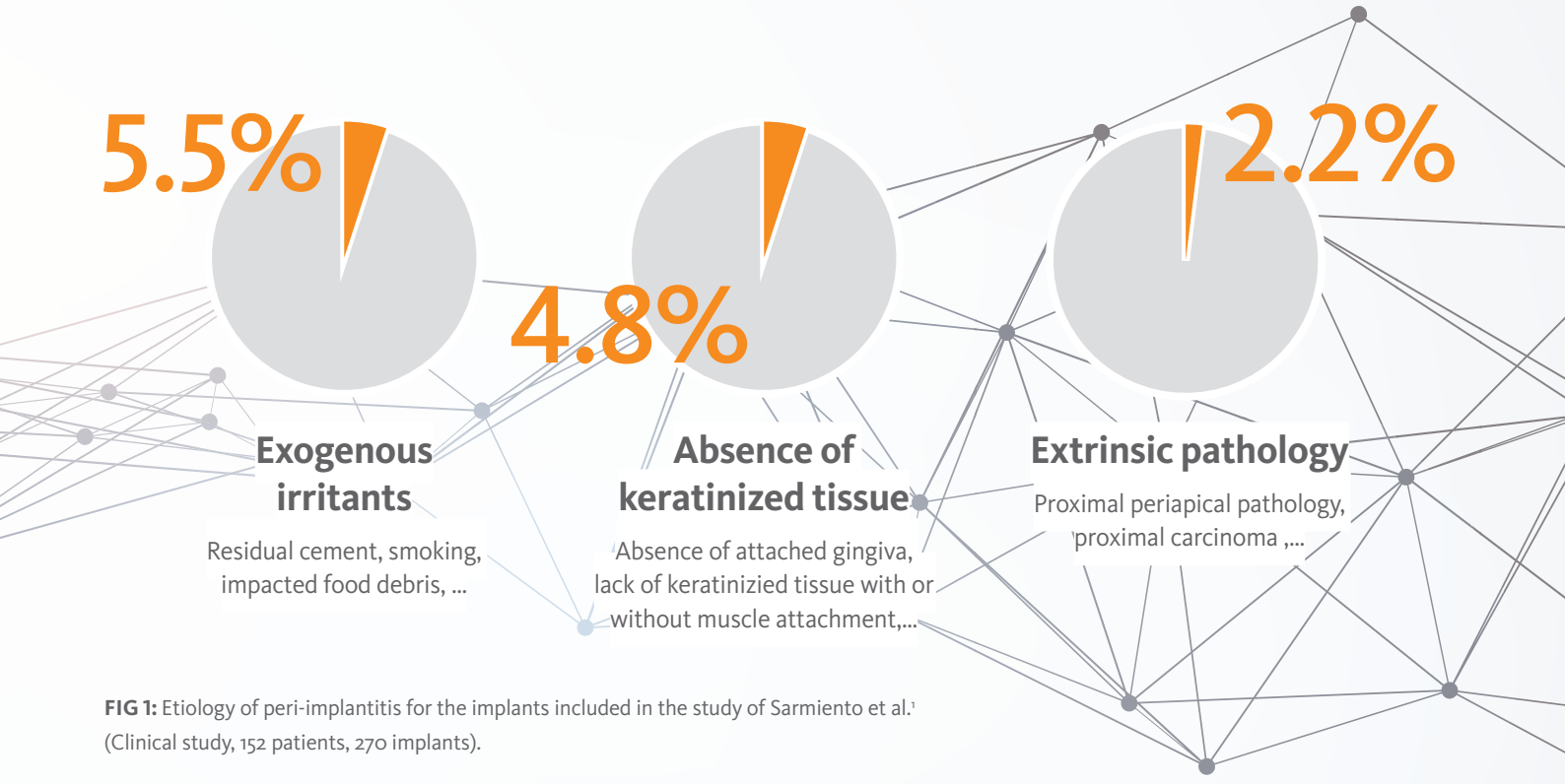


FIG 1: Etiology of peri-implantitis for the implants included in the study of Sarmiento et al.[1] (Clinical study, 152 patients, 270 implants).

term prognosis. On the other hand, if you have an implant that has bone loss related to residual cement, that might be easier to treat, hence leading to a predictable response to treatment and an effective prognosis. Once implants are treated and the surfaces are properly detoxified, the success of a regenerative approach will be dependent upon proper diagnosis but will have a better prognosis.

Are targeted preventions based on etiology also possible?

Dr. Sarmiento: They absolutely are! The main cause usually involves bacteria, which is why patients need to be on strict hygiene regimens.
As noted in our study,[1] 78.8% of the cases involving peri-implantitis were related to biofilm or bacteria induced inflammation with bone loss.

Would a better understanding of microbiology help?

Dr. Sarmiento: As we continue to conduct more research on peri-implantitis, we must focus on the initiation of the disease progression and its impact on its severity.
I believe that understanding the microbiology of peri-implant mucositis has to be the main focus of the prevention of peri-implantitis.

In addition to the classification you have also published a basic treatment protocol followed by different surgical alternatives.[2]

Dr. Sarmiento: We published the treatment option to have a basic protocol for how to treat peri-implantitis in a predictable manner, especially when it comes to the regenerative approach. The levels of debridement and decontamination are key. (**Fig. 2**)
After proper mechanical debridement and surface detoxification using a combination of chemical solutions and lasers, a bone graft should be chosen based on characteristics that the literature have shown us to be superior. When it comes to peri-implantitis, we routinely elect a xenogenic bone substitute. All GBR fundamentals should be taken into consideration, including stabilization of a collagen membrane and tension free repositioning of the soft tissues.

"Understanding the microbiology of peri-implant mucositis has to be the main focus of the prevention of peri-implantitis."

However, none of the surgical approaches proved to be better in terms of probing depth and bleeding on probing...

Dr. Sarmiento: Having gathered all our results, we concluded from our investigation that the three different surgical approaches can all be effective in treating peri-implantitis. Nonetheless, an assessment involving risks and benefits that consider both functional and esthetic outcomes of each approach should be carried out.

Risk/ benefit assessment?

Dr. Sarmiento: This would entail a detailed clinical and radiographic examination of each patient as well as the use of nonsurgical treatment prior to surgery.
After the assessment is done, the elimination of etiology is of extreme importance, followed by the restoration of the health of the implants' surrounding soft and hard tissue. Lastly, to ensure the most effective long-term outcomes, patients undergoing surgical therapies for peri-implantitis should have three-month maintenance recalls.

Using your regenerative approach, how many implants are you able to maintain over a period of about five years?

Dr. Sarmiento: We have been able, and it is proven, to be quite successful in saving many implants. As studies have shown, the success rate is high. We too have had a high degree of success, in the over 500 peri-implantitis cases we treated using a regenerative approach with Geistlich Bio-Oss®.

What conclusions can we draw from the etiologic factors?

Dr. Sarmiento: According to the classification system, it was evident that many breakdowns occurred due to excess cement. We broadly recommend using a screw retained restoration, however, if that is not possible, the clinician must take all and every precaution when cementing crowns. The clinician also should make sure to follow up periodically with patients by having proper maintenance visits so that the absence of gingival inflammation is ensured.
When considering soft tissue, the main priority here is to ensure, not only, that keratinized tissue is present, but attached gingiva is present as well. There are several surgical solutions including new soft tissue graft substitute materials such as 3D collagen matrices that have so far proven to be very successful; providing positive outcomes. Lastly, the clinician can always consider the gold standard in soft tissue augmentation with the utilization of the connective tissue graft and free gingival graft, when appropriate, harvesting the graft from the patient's own palate.

You have used Geistlich Fibro-Gide® as well...

Dr. Sarmiento: Right, I have actually been incorporating soft tissue enhancement into my treatments for the past four years. It has been pretty challenging to get the patients to agree to a second soft tissue graft harvest procedure, considering they have already had an invasive surgical procedure to save their implants.

For a while, I was searching for a biomaterial to replace the harvest grafts. Using Geistlich Fibro-Gide® in the last 13 months has led to significant improvements, facilitating my approach. It has also been a great asset in getting patients to move forward with their treatment plans. In my practice, patients have been more willing to accept the peri-implantitis treatments, once Geistlich Fibro-Gide® was introduced.

Is there a real clinical need for a soft tissue substitute such as Geistlich Fibro-Gide® in the context of peri-implantitis treatment?

Dr. Sarmiento: Of course; I think that because we had been so focused on treating peri-implantitis with just enhancement of hard tissue, we did not realize the deficiencies brought up by soft tissue enhancement. It is absolutely crucial to be treating peri-implantitis as a whole unit involving both soft and hard tissue, which is exactly why we want to move forward with incorporating soft tissue management in treating peri-implantitis.

What are your opinions on the new peri-implantitis classification from the World Workshop?[3]

Dr. Sarmiento: I was delighted to see the American Academy of Periodontology working to build more awareness for peri-implantitis. The breakdown when a clinician doesn't have radiographic history of an implant being treated is so important, and I am glad they highlighted that.

Evidence is still rare in this field. How do you communicate this to your patients?

Dr. Sarmiento: There is an abundance of published surgical techniques. If the etiological factors of the disease are understood, you will be able to know whether a treatment is predictable or not. A patient has to understand that even when grafting a case that is not so predictable, your goal is still to save the implant.

The patient must be informed of every technique being used and the fact that it might not work for ten years. Understanding that placing implants will not necessarily be a long-term solution is an immensely important idea that has to be shared with the general population.

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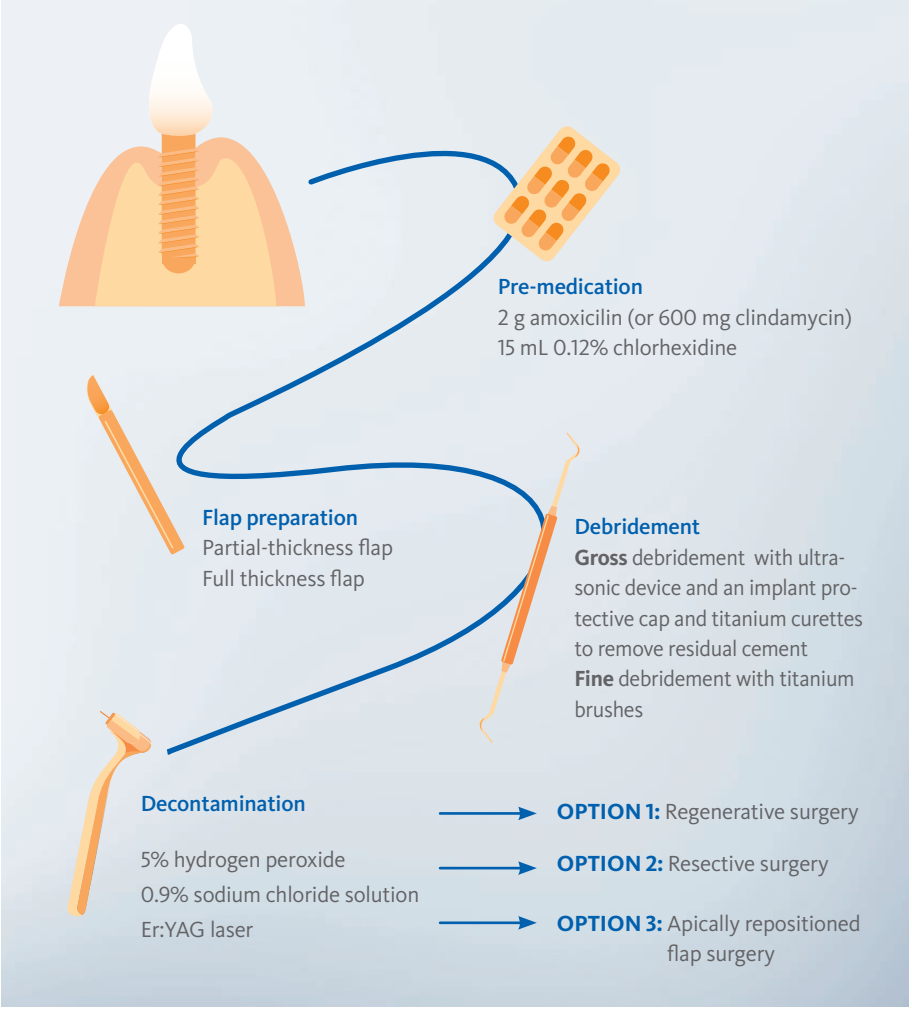
FIG 2: Surgical alternatives for treating peri-implantitis. The basic surgical protocol (pre-medication, flap preparation, debridement, and decontamination) is followed by one of the three options.[2]



Protocols for horizontal and vertical bone defects

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Associate Professor, Loma Linda University
Chairman, gIDE Institute, Los Angeles
Past-President, European Association for Osseointegration (EAO)
Private practice in Implant Therapy and Periodontics, Los Angeles

Dental implant therapy has shown tremendous long-term bone and soft tissue stability when enough bone volume is available at the time of implant insertion. On the other hand, insufficient bone volume around dental implants can be a significant risk factor and negatively affect the long-term prognosis.[1]

Several techniques for augmenting bone defects have been developed. They include protocols both for bone augmentation before implant placement (two-stage approach) and simultaneously with implant placement (one-stage approach), along with adjunctive materials such as bone blocks, particulate bone substitutes, autologous bone chips, form-stable devices, collagen and dense polytetrafluoroethylene membranes (d-PTFE) membranes, fixation screws and pins and bone harvesting devices.

Guided Bone Regeneration: Backed by science

Among the techniques for horizontal and vertical bone augmentation, GBR is one of the most investigated and evidence-based approaches. It produces predictable results and high, long-term implant survival rates.[1,2] Studies show that the survival rates of implants placed into augmented bone do not differ from the survival rate of implants placed into pristine bone.[3] The technique is based on sound biological principles with a step-by-step clinical protocol. The surgical complication rate ranges from low to high, categorizing the procedure at times as technique sensitive. The rate of complication largely depends on proper patient selection and diagnosis, detail-oriented surgical steps, careful patient follow-up and optimal choice of biomaterials.

For smaller bone defects a simultaneous GBR approach delivers the same results as a staged GBR approach. With large horizontal ridge atrophy and vertical defects, a staged protocol seems to be more predictable and produce better results.[4]

GBR can be conducted with a 1:1 mixture of autologous particulate bone and anorganic bovine bone substitute (Geistlich Bio-Oss®) in combination with a native collagen membrane (Geistlich Bio-Gide®) or, for larger horizontal or vertical defects, in combination with a form-stable, titanium-reinforced d-PTFE membrane.

The following sections describe the three main protocols used in our clinical practice and our training programs.

GBR Protocol 1: Implant dehiscence and fenestration defects

In 1992 we published our first study on the GBR protocol around dehisced implant surfaces in 12 patients,[5] and one of the patients who was treated for amelogenesis imperfecta is still in follow-up after 29 years with stable crestal bone and successful implants.
In 2018 we published modifications and the results of 45 consecutive cases (63 implants) treated with our layered bone graft and GBR protocol, and followed the patients for 30 months after loading. No patient dropped out of this study, stable bone and soft tissue was noted and no implant or prosthesis failed (see details in **Box 1**: GBR Protocol 1: Treatment steps).[6]

"Periodontal problems have to be solved before the treatment starts and compliance with recall intervals has to be guaranteed with minimal to no plaque deposits. "

GBR Protocol 1: Treatment steps

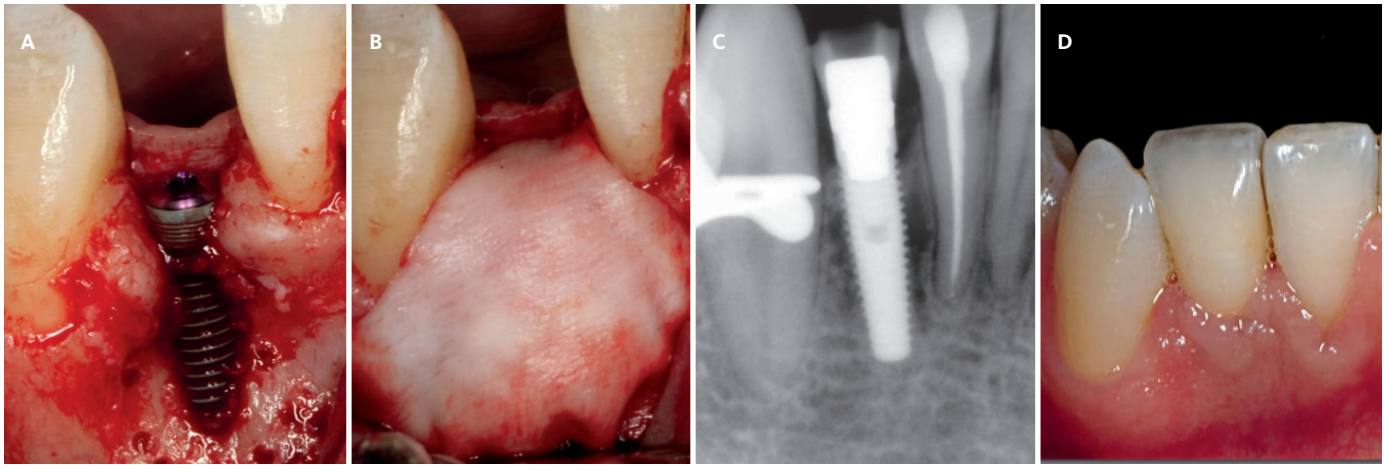
> Periodontal and soft tissue preparation
> Mid-crestal incision into the keratinized tissue
> Elevation of full-thickness flap beyond mucogingival junction and at least 5 mm beyond the bone defect
> Two vertical incisions at least one tooth away from the defect
> Recipient site cleared of soft tissue remnants
> Autologous bone harvested with a minimally invasive cortical bone collector
> Decortication holes (1 mm bur) at recipient site
> Implants inserted and guided by a surgical template
> Exposed threads covered with 2 mm of autologous bone, covered by 2 mm of Geistlich Bio-Oss® and covered by a Geistlich Bio-Gide®
> Membrane stabilized with sutures or fixed with titanium pins both on the vestibular and on the lingual/palatal site
> Periosteal releasing incisions for tension free flap advancement
> Combination of horizontal mattress PTFE suture and single interrupted sutures
> Temporization of surgical site with no tissue contact
> Uncovering six-months after implant placement and GBR ,with mucogingival procedure to increase soft tissue thickness and keratinization
> Preferably simultaneous abutment and CAD/CAM fabricated, screw-retained implant crowns delivered

The key point is to apply this GBR protocol to smaller bone defects, and an accurate CBCT diagnosis is critical for selecting a bone volume between 4 to 6 mm in width. The combination of autologous bone in contact with the implant and anorganic bovine bone on top is the key to success (**Fig. 1**). While the autologous bone has osteoinductive and osteogenic properties, the anorganic bovine bone maintains the volume and contour in the long-term. Collagen membranes are advantageous compared to expanded polytetrafluoroethylene (e-PTFE) membranes in this indication because of the favorable soft tissue healing and because they do not have to be removed. Their lack of form stability can be overcome by the bone mixture and accurate fixation of the membrane that allows immobilization of the graft material.

GBR Protocol 2: Larger horizontal defects

In 1995 we published the use of space-making titanium-reinforced e-PTFE membranes for large horizontal defects and this was later modified to resorbable

FIG. 1: Clinical case pictures of a patient treated in 2007 with a simultaneous resorbable GBR treatment protocol 1 in a thin healed ridge of 4 mm width showing stable crestal bone and soft tissue margin after 12 years of function.[7]



Photos: Sascha Jovanovic

| **A** Esthetic implant placement resulted in labial bone dehiscence. | **B** Simultaneous resorbable GBR procedure with 2-layer bone graft. | **C** Radiograph of implant and abutment after 12 years. | **D** Facial view of restoration on mandibular right lateral incisor following rehydration. Esthetic team work with Dr. Pascal and Michel Magne (Los Angeles, CA).

GBR Protocol 3: Treatment steps

> Full thickness mid-crestal incision into the keratinized gingiva
> Vertical incision at least one tooth away from the surgical site (5 mm away in case of an edentulous area)
> Reflection of a full thickness flap beyond the mucogingival junction and at least 5 mm beyond the bone defect with a periosteal elevator
> Recipient site cleared of soft tissue remnants
> Multiple decortication holes into recipient bed with a 1 mm drill
> Harvesting of autologous bone and placement of 1:1 mixture of autologous bone and anorganic bovine bone particles, and placement of the graft in the defect area
> Covering the immobilized graft with a titanium-reinforced PTFE membrane and fixing it with bone tacks or screws
> Maxillary vertical cases can be combined with a sinus floor elevation to achieve additional apical bone height
> If the edges of the membrane are not well adapted, a bilayer collagen membrane (Geistlich Bio-Gide®) is put over the non-resorbable membrane to close any open space in the grafted area
> Periosteal releasing incision
> Suturing of the flap in two layers (tension-free): horizontal mattress sutures 4 mm from the incision line, single interrupted sutures to close the edges of the flap and leave at least a 4 mm thick connective tissue layer between the membrane and the oral epithelium (to prevent exposure of the membrane)
> Closure of vertical incisions with single interrupted sutures
> Implant placement 9 to 12 months later

membranes in one-wall large horizontal defects.[8] For these larger horizontal defects, a staged GBR procedure is safer and more predictable than a simultaneous GBR and implant approach. The bone graft (now a larger volume mixture of autologous bone and anorganic bovine bone) can be covered with a native collagen membrane (Geistlich Bio-Gide®) or with a titanium-reinforced d-PTFE membrane depending on the severity of the bone deficiency. In general, one-wall large buccal defects with a CBCT bone width of 3 to 4 mm can be grafted and covered with a collagen membrane fixed with pins both lingually/palatally and buccally. In cases with severe two-wall horizontal resorption and with a CBCT bone width of less than 3 mm the autograft/bone substitute mixture is covered with a non-resorbable d-PTFE membrane fixed with screws on the periphery.

Healing periods of six to eight months are used in this GBR protocol, and over 5 mm of new horizontal bone is created, as evidenced in multiple clinical studies.[9,10] This creates enough bone width for predictable implant placement. Soft tissue management before, during and after the GBR technique is essential to ensure healthy, thick soft tissue for tension-free flap closure and to create enough keratinized tissue for implant success.

GBR Protocol 3: Vertical bone defects

Vertical ridge augmentation is the most challenging of the GBR protocols, as it aims to regenerate large amounts of vertical and horizontal bone with little or no bone walls to use as a base for the bone formation. For the blood supply to reach the full distance from native bone into the outer part of the grafted area and for complete mineralization to take effect, a longer healing period of 9 to 12 months is needed. In addition, to protect the bone graft from soft tissue invasion during the healing period, a space making device with long-term cell exclusion and a thick and advanced soft tissue flap is needed to provide a closed healing environment for the GBR-grafted area (**Fig. 2**).

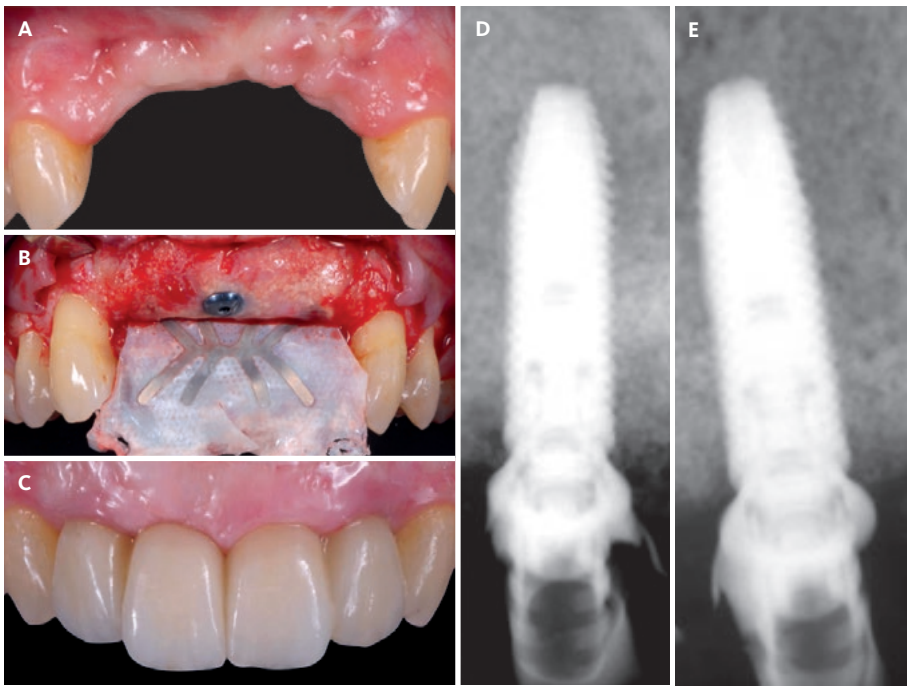
When treating vertical bone defects, a titanium-reinforced e-PTFE membrane was designed, and we tested the first prototype designs in 1993 and published for the first time in 1995 in our animal and human studies.[8-11] The large amount of clinically documented cases has shown that a maximum vertical gain of 12 mm is possible with a mean of more than 5 mm and a horizontal gain of 8 to 10 mm, which is sufficient in most cases to place an implant in the optimal esthetic position. (see details in **Box 2**: GBR Protocol 3: Treatment steps). [12,13]

Key to success

Placing an implant into vertically augmented bone is rather challenging, because the bone is still early in its mineralization nine months after augmentation. Therefore, implant placement in this indication should be done by an experienced surgeon, and implant selection has to be performed carefully.

As in all GBR procedures, it is mandatory to select the right kind of patient for this challenging procedure. Periodontal problems have to be resolved before the treatment starts, and compliance with recall intervals has to be guaranteed with

FIG. 2: Clinical case pictures of a patient treated with a non-resorbable d-PTFE staged GBR protocol 3 treatment for a severely vertical resorbed ridge in the anterior maxilla.



Photos: Sascha Jovanovic

| **A** Buccal view of a vertical defect in the anterior maxilla. | **B** Vertical augmented ridge result after 9 months at d-PTFE removal time and implant placement. | **C** Final esthetic work with stable gingival margins performed by Dr. Mintrone (Sassuolo, Italy). | **D** Radiograph of the regenerated bone, tooth 12. | **E** Radiograph of the regenerated bone, tooth 22.

minimal to no plaque deposits. Regarding bone graft biomaterial, we always stick with the proven combination of autologous bone plus xenogeneic bone substitute – for the combination of osteoinductive properties and long-lasting volume stability – plus collagen or PTFE membranes depending on the defect (horizontal/vertical/combined). The need for and benefit of adding platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) is still to be fully seen but has possible early wound healing benefits that could help with flap closure. (see details in **Box 3**: GBR Key to success).

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GBR Key to Success: gIDE Institute Protocol

1 Establish periodontal health in natural dentition
2 Prepare soft tissues in the GBR/implant site before, during and/or after treatment to increase mucogingival thickness and keratinization
3 Full-thickness flap elevation (remote or papilla preservation)
4 Clean and perforate bone surface
5 Release periosteum to advance flap and achieve tension-free closure
6 Trim membrane - native collagen (horizontal GBR) or d-PTFE (horizontal/vertical GBR)
7 Harvest autologous bone with scraper and place in saline/ blood
8 Prepare anorganic bovine bone substitute with saline/ blood
9 Mix bone graft in a 1:1 ratio of autograft and anorganic bovine bone substitute
10 Apply and fix membrane with suture/tacks/screws
11 Place bone graft mixture
12 Adapt and fix membrane to cover the complete bone graft
13 Advance flap and close using PTFE suture with horizontal mattress and single interrupted suture
14 Temporize site with no tissue contact
15 Allow healing period of 6+ months for horizontal GBR cases and 9+ months for vertical GBR cases

Which measure when?

Time points for bone and soft tissue augmentation

Dr. Andres Orozco | Australia
Periodontist – Periodontics & Dental Implant Centre
Indooroopilly

Dr. Ehsan Mellati | Australia
Periodontist – Precision Periodontics
Chatswood

Dr. Jeremy Vo | Australia
Periodontist – Australian Dental Specialists
Sydney

Many combinations of bone and soft tissue management sequences are possible. Clinicians offer their preferred approaches after tooth extraction, discussing indications and advantages.

RIDGE PRESERVATION & SOFT TISSUE MANAGEMENT > LATE IMPLANT PLACEMENT

Technique

Dr. Orozco: The tooth is removed as atraumatically as possible[1] and the socket cleaned. Ridge Preservation (RP) is done with Geistlich Bio-Oss® granules, and the socket is covered with Geistlich Mucograft® Seal. After a minimum of 6 months, I insert a single-stage dental implant with a narrow healing abutment plus a SCTG on the buccal aspect to thicken the soft tissue before closing the flap. Shaping is done at the osseointegration check, 3 to 4 months post implant placement.

Dr. Mellati: I use Geistlich Bio-Oss® granules for large defects and Geistlich Bio-Oss® Collagen for smaller defects. Geistlich Bio-Gide® is used for damaged or missing buccal wall. In the esthetic zone, I may use SCTG or FGG for soft tissue augmentation. If some part of the implant will end up in native bone at the time of placement, I would wait 4-6 months. If implant is going to be placed in 100% grafted bone, I would wait 6-9 months.

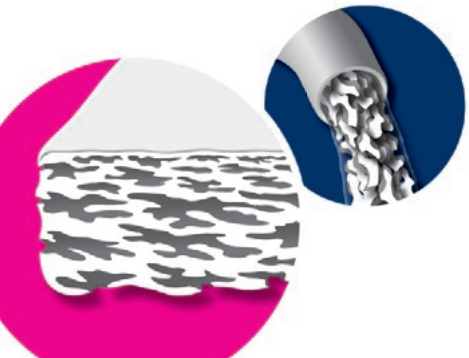
Dr. Vo: In terms of soft tissue management during RP, FGG works a little better, as it is more robust to suture, particularly where access is more difficult. I would use Geistlich Mucograft® Seal for anterior sites. Following RP, waiting 6 months is enough before implant placement; 9 months would be more appropriate for staged augmentation.

When and why?

Dr. Orozco: RP performed at the time of extraction minimizes the need for further bone augmentation. Soft tissue management with Geistlich Mucograft® Seal ensures a good amount of keratinized tissue for later implant placement.

Dr. Mellati: Mainly for anterior sites when early placement cannot be considered, e.g. due to large defects of endodontic origin.

Dr. Vo: I stage the approach in cases of soft tissue deficiency or if the patient intentionally wants to delay implant placement.



RIDGE PRESERVATION > LATE IMPLANT PLACEMENT WITH GBR & SOFT TISSUE MANAGEMENT

Technique

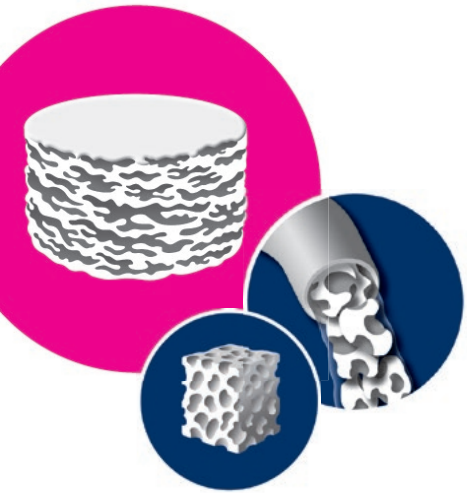
Dr. Orozco: With a significant defect in the buccal bone wall, I perform RP with Geistlich Bio-Oss® granules and Geistlich Bio-Gide®. I prefer Geistlich Bio-Oss® Collagen if I need to enter earlier (6 rather than 9 months). At the late implant insertion, I perform further augmentation in conjunction with the implant placement, using Geistlich Bio-Oss® granules and Geistlich Bio-Gide® for the minor GBR procedure. I shape Geistlich Bio-Gide® with a biopsy punch, and then place it over the abutment, to protect the newly augmented region from soft tissue infiltration. SCTG is used to provide a peri-implant contour and "bulk-up" the tissue.

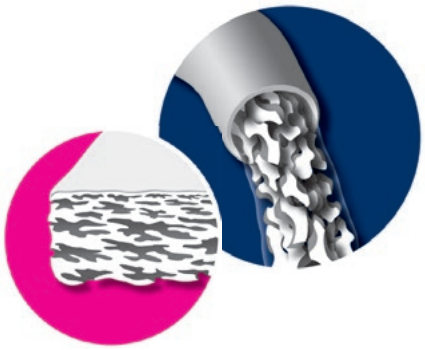
Dr. Mellati: When RP is done at the time of extraction, GBR is rarely needed at the time of implant placement in posterior areas. In anterior areas, sometimes further GBR and soft tissue management is needed – especially in esthetically demanding cases.

When and why?

Dr. Orozco: When socket wall defects are present and/or when traumatic tooth extraction is unavoidable. Although RP does not prevent later GBR, it is still less invasive and allows for sufficient soft tissue volume.

Dr. Mellati: When further GBR is required after RP, it is mostly for contour augmentation to achieve a better soft tissue profile. Simultaneous GBR and soft tissue management using SCTG is surgically challenging,





so I rather separate these two procedures and "create one miracle at a time."

RIDGE PRESERVATION > DELAYED IMPLANT PLACEMENT & SOFT TISSUE MANAGEMENT

Technique

Dr. Mellati: SCTG is sutured to inside of the flap in a way to add volume to the both buccal and crestal dimensions. Once Geistlich Fibro-Gide® is launched, it would make a useful alternative in such situations.

Dr. Vo: With Geistlich Bio-Oss® Collagen and Geistlich Bio-Gide®. I will be happy to try Geistlich Fibro-Gide® when it is available in Australia.

When and why?

Dr. Mellati: Soft tissue management is more commonly needed in anterior sites. In posterior sites, it may be needed where there is very limited keratinized tissue. In such cases, apically repositioned flaps plus Geistlich Mucograft® can be used instead of FGG.

Dr. Vo: To develop the peri-implant profile. Use in anterior sites is indicated, as it will enhance esthetics.

IMMEDIATE IMPLANT PLACEMENT & GBR & SOFT TISSUE MANAGEMENT SIMULTANEOUSLY

Technique

Dr. Orozco: The implant is placed directly after tooth extraction, and I use Geistlich Bio-Oss® granules between the implant and the buccal plate. A SCTG is placed on top of the graft material, then a customized or anatomical healing abutment is delivered to seal the socket. This allows for the retention of the contour and anatomy of the pre-existing soft tissues.[2]

Dr. Mellati: I am not a big fan of IIP. If indicated, I do a flapless approach and use either Geistlich Bio-Oss® or Geistlich Bio-Oss® Collagen for supplementary filling in the jumping gap, and use SCTG for bulking up the soft tissue profile. I follow this with immediate provisionalization.

Dr. Vo: A split-thickness flap is required with a design based on the GBR area and the amount of access needed. A SCTG is used for the soft tissue management component.

When and why?

Dr. Orozco: It is my preferred option. We can use as much of the existing bone as possible, and, in many cases,[3] it does not involve flap elevation. The socket walls must be undamaged, and primary stability must be achievable. Placing bone substitute reduces/compensates resorption of the buccal bone after the immediate implantation in fresh extraction sockets.[4]

Dr. Mellati/ Dr. Vo: If a strict set of criteria is met - intact socket walls, good palatal/lingual bone to achieve primary stability, thick tissue phenotype, and no large infection.

EARLY IMPLANT PLACEMENT & GBR & SOFT TISSUE MANAGEMENT

Technique

Dr. Mellati: Performing GBR and simultaneous soft tissue management is surgically challenging, and I prefer to separate these procedures.

When and why?

Dr. Mellati: Early placement is my preferred method for most anterior sites. If soft tissue augmentation is required in addition to GBR, I tend to leave it for the second stage (implant uncovery).

Dr. Vo: Not regularly, due to the nature of the flap required for each individual procedure. Rather, I prefer to augment the soft tissue at a later stage, often with a rolling flap.

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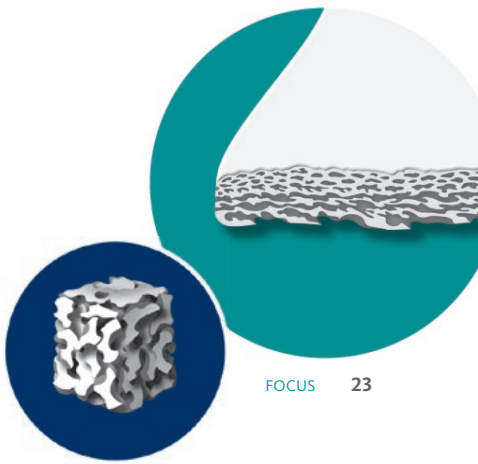

Gaining bone height

“Most patients like the idea of getting a customized solution”

Interview with Dr. Isabella Rocchietta and Prof. Bilal Al-Nawas
conducted by Dr. Marcelo Calderero and Verena Vermeulen

Bone block or GBR? Form-stable membrane or customized titanium scaffold? We discussed vertical ridge augmentation treatment options with two experts: Dr. Isabella Rocchietta, United Kingdom and Prof. Bilal Al-Nawas, Germany.

Photo: Geistlich Pharma AG

FIG. 1: Yxoss CBR® is an innovative customized 3-D printed titanium scaffold for regeneration of complex bone defects. ReOss® (manufacturer) offers the option of integrated prosthesis positioning in the surgical planning.

What was the first technique you learned and practiced for vertical ridge augmentation?

Dr. Rocchietta: I began with GBR, and though I have tested other techniques, I will probably stay with that approach.

Prof. Al-Nawas: Maxillofacial surgeons are always trained first with bone blocks, but later I learned about titanium meshes and the GBR concept.

Two recent reviews compare techniques for vertical ridge augmentation and come to the same conclusion: distraction osteogenesis has the highest bone gain, but also the highest complication rate.[1,2] Is there a trade-off between gain and predictability?

Prof. Al-Nawas: I wouldn't say so. It is difficult to compare techniques, such as distraction osteogenesis and GBR based only on those two parameters. There are other factors. Undergoing distraction osteogenesis is much more intense and time consuming for the patient than undergoing GBR. Although simple numbers might suggest superiority of one technique over the other, such a conclusion would be an oversimplification.

Dr. Rocchietta: I agree. For example, sometimes systematic reviews can be difficult to interpret, because the numbers shown are the average mean. But every, single surgical procedure is related to the surgeons themselves. Which technique works well depends on the indication and on the surgeon's skills, his or her experience and learning curve.

Bone blocks are still very common for vertical ridge augmentation. Looking at the data, is this still justified?

Prof. Al-Nawas: Their resorption pattern and differing quality make blocks unpredictable. We don't know whether they turn into vital bone or not. With the allogeneic bone blocks we have further problems. We don't know which patients they come from, which drugs those patients used, and so on. These factors might have an impact on treatment outcome.

GBR is the more predictable approach?

Dr. Rocchietta: Definitely. The combination of a particulate material – for example, autologous bone chips mixed with anorganic bovine bone particles plus a form-stable element – makes more sense from a biological perspective.

Several form-stable elements are currently available – titanium scaffold, e-PTFE membrane, bone shield, etc. Prof. Al-Nawas, you use the customized titanium scaffold Yxoss CBR® in your daily practice. Do you see an advantage compared to other options?

Prof. Al-Nawas: Advantage may not be the right word, because there is never one technique that is better than others. It's rather a question of what a surgeon is used to and can handle.
But as I treat many patients with complex defects - comprising more than three teeth or a curved area of the alveolar process – I benefit from the fact that Yxoss CBR® is, in those cases, rather straightforward to use.

> **"The preplanning approach allows the patient to be more involved in the decision-making process."**
>
> **Prof. Bilal Al-Nawas**

What feedback do you get from your patients when you use Yxoss CBR®?

Prof. Al-Nawas: There are several aspects that make this approach appealing to them. First, the result of the digital planning I show them to explain the treatment. This is crucial. If patients do not understand the treatment, they do not understand possible complications and cannot help with better healing. Second, most patients like the idea of getting a customized solution created especially for them. And third, 3D printing has a modern, impressive appeal.

As you said, this option involves extensive digital preplanning. Do you see a trend towards more planning and fewer on-site decisions?

Prof. Al-Nawas: Yes. The planning becomes longer, the surgery time shorter. The benefits of this are more precision, fewer complications and more predictability also with regards to cost. Two treatment options, such as placing short implants vs staged augmentation with long implant placement, have different costs, and the decision for one approach or the other should not be made after opening the flap, to be dramatic. The preplanning approach allows the patient to be more involved in the decision-making process.

Dr. Rocchietta: In countries such as the United Kingdom, where I practice, this is also a legal requirement. We must provide proof that we have preplanned a patient's case and have informed him or her accordingly. The preplanning – be it digital or with a plastic model – allows us to better visualize the case and in greater detail than by simply opening a flap and "having a look."

Dr. Rocchietta, you primarily work with titanium-reinforced membranes. What are the advantages?

Dr. Rocchietta: These membranes are very straightforward to use. The preplanning might take less time compared to, for example, Yxoss CBR®, because after choosing the appropriate size, dimension and shape, the membrane can be easily adapted on-site. The surgeon does not have to wait for a material that is customized elsewhere.

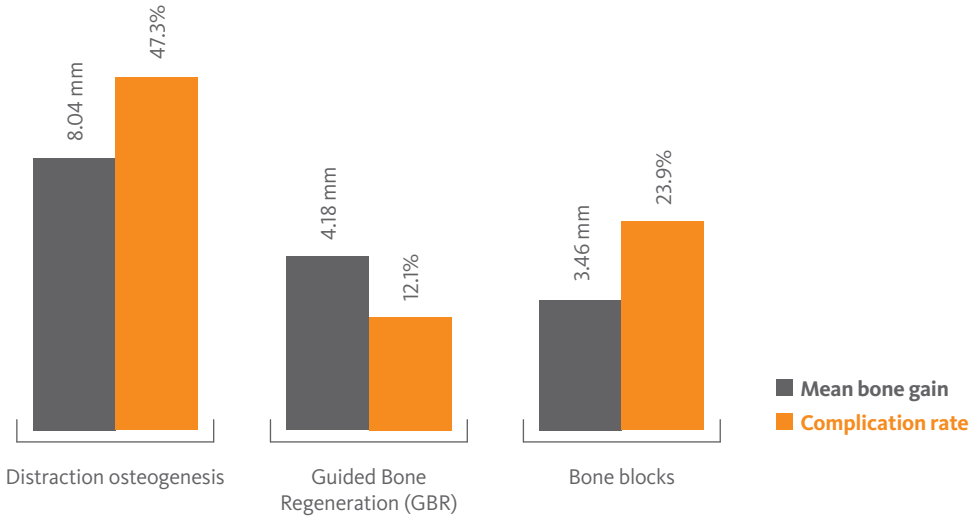

FIG. 2: Mean bone gain and complication rate associated with common procedures for vertical ridge augmentation.[1]

FIG. 3: Bone block or GBR? Dr. Isabella Rocchietta (left) and Prof. Bilal Al-Nawas (right) discuss the topic.

"Several elements are key to vertical ridge augmentation success and they depend on proper training, surgical skills and experience."

Dr. Isabella Rocchietta

From my perspective it's also easy to remove the membrane, easier than removing a titanium grid.

Prof. Al-Nawas: I agree. The PTFE membranes, however, have limitations, for example, for large or complex cases.

Dr. Rocchietta: Very true. When the defect is so large that one membrane is not enough, this concept is no longer straightforward. One needs to combine several membranes, adapt them to one another while avoiding open spaces. In my opinion, here the Yxoss CBR® concept with its prefabricated one-piece titanium scaffold has very clear advantages.

You are both very experienced surgeons. Is it conceivable we might one day have a technique for vertical bone augmentation that makes the treatment predictable for less experienced surgeons?

Dr. Rocchietta: This would be a very difficult and risky statement from my perspective. There are several elements that are key to vertical ridge augmentation success. One very important factor is soft tissue management. These key elements depend on proper training, surgical skills and experience. The form-stable device is only one part of the treatment. Choosing one device over the other will not make it much simpler *per se*. What we can achieve, however, is shorter surgery time, fewer complications and more predictability.

Prof. Al-Nawas: I absolutely agree.

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Five questions for five experts

We asked five renowned clinicians to answer five questions about bone regeneration. Results: 25 professional and personal insights.

Prof. em. Niklaus P. Lang | Switzerland

University of Bern

Bone regeneration: I am expecting that...

We may get advances as our knowledge increases on the molecular level of wound healing. The addition of predictable growth factors and their dosage in a particular procedure needs further study.

Bone biology: I would like to discover...

A factor that determines the speed and quality of bone formation in the wound healing sequence.

And I would like to have discovered...

The first BMP to influence wound healing in bony lesions.

Your opinion about 3D-printing ?

It is in a very experimental stage of development. It needs years to get realistic treatment outcomes.

The happiest moment of my career was when I...

I met Harald Löe, Sigmund Ramfjord and Jan Lindhe. Regarding the clinical activity, it was to witness the first ever bone augmentation in a human jaw under the influence of Prof. Sture Nyman.

Prof. Lisa Heitz-Mayfield | Australia

University of Western Australia

Bone regeneration: I am expecting that...

There will be advances in the fields of bioactive materials and personalized 3D engineered grafts. As part of a push toward personalized medicine, I expect new materials and techniques.

Bone biology: I would like to discover...

The key factors in enhancing angiogenesis to enable predictable bone regeneration in compromised situations such as osteoporosis and diabetes.

And I would like to have discovered...

Osseointegration.

Your opinion about 3D-printing?

An exciting approach to individualizing reconstructive techniques for challenging situations.

The happiest moment of my career was when I...

Shook hands with my PhD opponent Prof. Jan Lindhe following the successful defense of my thesis "Regeneration in periodontal and endosseous implant treatment."

Dr. Tara Aghaloo | USA
UCLA School of Dentistry

Bone regeneration: I am expecting that...
Regenerative solutions will tackle both hard and soft tissue of alveolar ridge defects.

Bone biology: I would like to discover...
The genetic link to alveolar bone atrophy.

And I would like to have discovered...
Runx2, a key transcription factor important in osteoblast differentiation.

Your opinion about 3D-printing ?
I think this is the future of bone augmentation. However, I don't think that we have the materials that can meet our regenerative requirements at this time.

The happiest moment of my career was when I...
Received my first research grant. It was so much work and so much effort, and it really improved my confidence in my research and writing abilities. I knew at that point that I wanted to be both a surgeon and a scientist.

Dr. Bo Chen | China
Beijing University School of Stomatology

Bone regeneration: I am expecting that...
3D printing of bone augmentation procedure will enable more predictable results in critical situation for implant placement.

Bone biology: I would like to discover...
How to achieve predicable vertical bone augmentation in our daily practice.

And I would like to have discovered...
The 3D prefabricated titanium mesh with easy removal for severe vertical bone defects.

Your opinion about 3D-printing ?
It will facilitate bone augmentation for severe bone defect - either by 3D-printing of titanium mesh or of bone block substitute.

The happiest moment of my career was when I...
Achieved a successful bone regeneration in a patient with a severe defect. It enabled ideal implant placement by bone substitute and membrane, avoiding the harvesting of extra oral donor site.

Prof. Reinhard Gruber | Austria
University Clinic of Dentistry Wien

Bone regeneration: I am expecting that...
New therapies will be based on the fundamentals of bone biology and considering the regional anatomic domains.

Bone biology: I would like to discover...
The intrinsic properties of bone that explains the favorable properties of graft consolidation.

And I would like to have discovered...
The role of osteocytes in the control of bone turnover and bone regeneration.

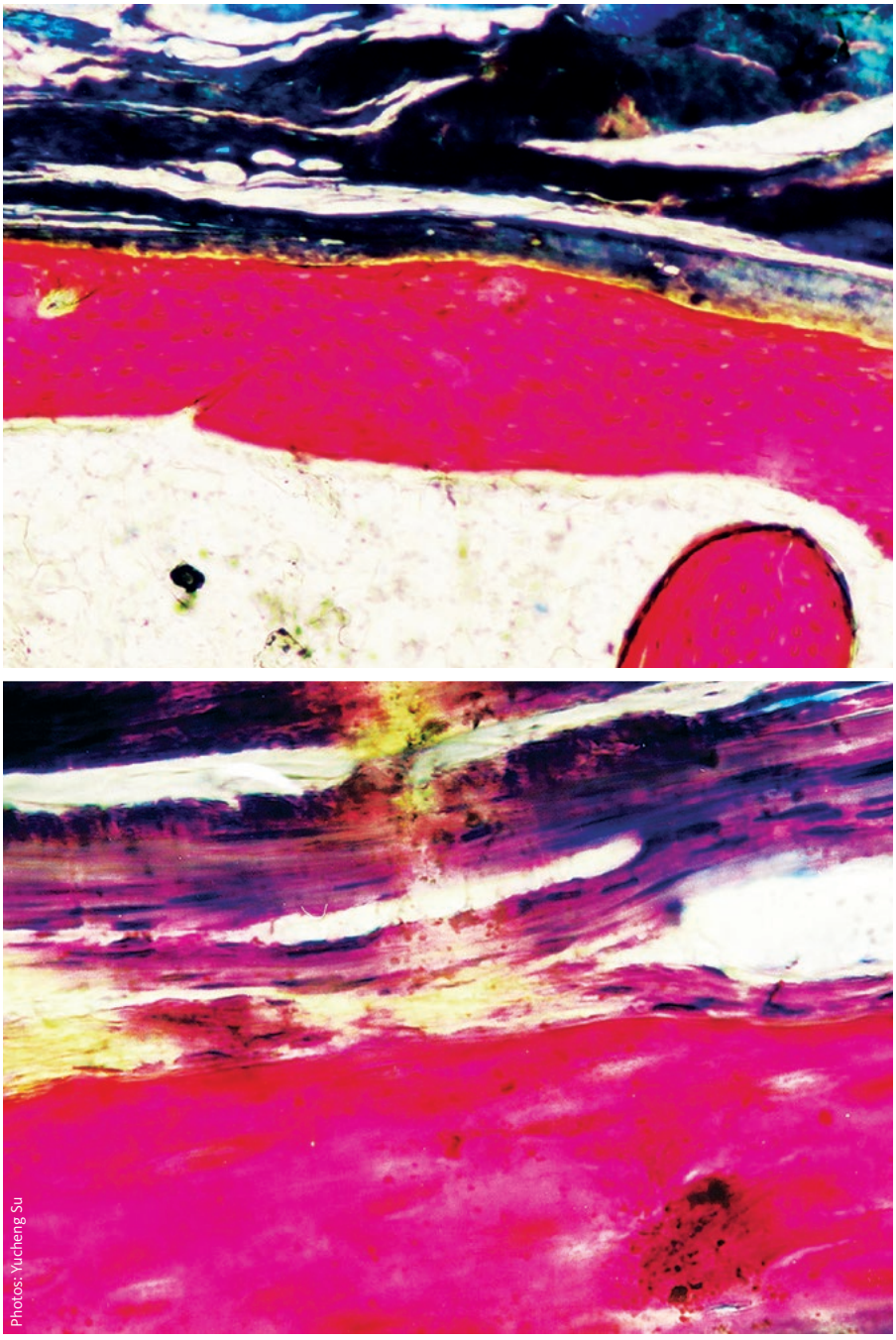
Your opinion about 3D-printing ?
In personalized medicine, there is a growing interest in future clinical application of 3D printed scaffolds. Biology cannot be easily customized.

The happiest moment of my career was when I...
Was formally appointed Professor for Oral Biology, apart from the birth of our three children – Lilly, Theo and George.

Histology

Micro-beauty of regeneration

Prof. Yucheng Su | China
Director of Dental Implant Center, Peking Union Medical College Hospital (PUMCH)



Photos: Yucheng Su

FIGS. 1, 2: Hematoxylin and eosin (H&E) staining after GBR procedure using Geistlich Bio-Gide® in New Zealand rabbit model.[1]

"Micro-beauty of regeneration, paint your palette blue and red. Shadows on the sea, sketch the sun and the cloud. A melody rose from the bottom of my heart."

The resorbable collagen membrane Geistlich Bio-Gide® was applied to cover an intraosseous defect prepared in the area of the rabbit's iliac. After two months, uneventful healing with new bone formation guided by the membrane was noted. Histologic observation revealed that the membrane had covered the newly formed bone in the early stage of healing to provide a protected environment for bone regeneration (**Fig. 1**, HE, x13). The porous structure of the membrane became the scaffold for osteoblast cells to grow and to secrete osteoid (**Fig. 2**, HE, x33).

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A revolutionary genetic tool

In the past few years a new gene splicing method has fundamentally changed the game for genetics: Crispr/Cas9. These “gene scissors” allow DNA genome building blocks to be modified with previously unimaginable precision.

Photo: ©iStock.com/undefined

Dr. Klaus Duffner

At the end of November last year there was an international outcry: Chinese biophysicist Hè Jiànkuí from the University of Shēnzhèn reported the birth of twin girls whose genetic makeup had been genetically modified in the embryonic stage so that they were resistant to HIV. Shēnzhèn University was "profoundly shocked" by this transgression, and countless scientists and politicians were likewise outraged. Shortly afterwards the public authorities arrested Hè, and he is facing punishment. This manipulation of the genome was made possible by a new technique that is considered one of the greatest developments in molecular biology: the "gene scissors" Crispr/Cas9.

In the beginning: Bacteria fight off viruses

As is so often the case with groundbreaking discoveries, Crispr/Cas9 began with an observation: bacteria can effectively defend themselves against hostile viruses. This defense is based on the so-called Crispr/Cas system. When a virus binds to a bacterial cell and injects its genetic material, a short section of it is inserted between the Crispr sequences of the bacterial DNA. These sections are a kind of library of all pathogens the cell has confronted in the past. In the event of a new infection, Crispr/Cas provides a "memory" for the bacteria's defense against infection, enabling it to cut up the virus and render it harmless. This library is preserved for generations, because it is passed on from the bacterium to its descendants. Thus, as with epigenetics an acquired property is inherited – a mechanism that violates Darwin's concept of evolution. Today we know that about one-half of all known bacteria have a Crispr/Cas defense system. Depending on the type, two large Crispr/Cas classes are distinguished. Class-I systems comprise protein complexes consisting of many molecules, whereas class-II systems comprise only one cutting protein each.

Targeted mutations

In 2011 and 2012, Emmanuelle Charpentier and Jennifer Doudna of Berkeley University, California, published the basic research results on bacterias' Crispr/Cas9 defense in the leading professional journals *Nature* and *Science*. One year later, Zhāng Fēng of the Broad Institute of Cambridge published how the method can be applied to higher organisms as well, for Crispr/Cas9 works not only in bacteria but also in cells with nuclei, i.e., in plants, animals and humans.

"Crispr/Cas9 and other methods of 'genome editing' promise a plethora of application possibilities."

The Crispr/Cas system is based on three components: 1) A short RNA molecule serves as a genetic recognition sequence. Such a "probe" can be produced relatively

easily and matches the nucleotide pattern of the respective DNA target sequence. 2) It is linked to the so-called tracrRNA. 3) This RNA complex in turn attaches itself as a "guide" to an enzymatic cutting tool, the Cas9 protein. This completes the molecular "gene scissors" consisting of RNA recognition sequence, tracrRNA and Cas9 scissors. Now the triple complex binds to a specific location on a target DNA and cuts it up with the Cas9 scissors. The American scientists realized the potential of this mechanism. Since the recognition RNA sequence can be varied easily, it is now possible to determine exactly where the molecular gene scissors bind and cut the target DNA. It is true that a cell is able to repair such a cut; however, this repair is usually incomplete, resulting in reading errors. In other words, by cutting up the target DNA, genes can be specifically "switched off." In addition, individual DNA building blocks or larger functional DNA sections can also be inserted into the cut, and thus completely new properties implanted very precisely into the genome.

No chance for chance

Crispr/Cas9 and other methods of so-called "genome editing" promise a plethora of application possibilities. In plant and animal breeding, for example, geneticists are trying to create more productive or disease-resistant varieties and breeds. These include, for example, mildew-resistant wheat, starch-enriched corn or potatoes that can be stored at low temperatures. The basic mechanism – induction of a double-strand break and subsequent cellular repair – is the same mechanism that follows natural mutations. Mutation breeding in plants is likewise based on this process. Previously, however, such breaks were triggered in an uncontrolled manner, often through irradiation or chemicals. So it was a matter of chance at which point in the genome of a plant the new, additional gene might be integrated.

With genome editing and especially with Crispr/Cas9, results are no longer left to chance, because editing occurs at single, pre-determined points. However, even with Crispr/Cas9, unintentional mutations can occur, albeit rarely. Since such so-called "off-target" mutations might have serious consequences, especially in the medical field, scientists have cautiously continued the development of Crispr/Cas9 and other protein scissors to improve accuracy. For example, new Crispr/Cas9 variants cut only a single DNA strand, which significantly reduces the number of missing or additional base pairs (22). If the two single strands are cut at staggered positions, producing "sticky ends," i.e. DNA ends with complementary over-hangs, the accuracy of the genetic modification is significantly improved.

Many things still remain unclear

For years scientists have been trying to address certain diseases by specifically altering the genetic makeup, but mostly unsuccessfully. Since the discovery of the Crispr/Cas9 system, hopes have risen. The first positive results have been reported: a treatment for Duchenne muscular dystrophy (DMD). This condition is based on the mutation of a gene that produces the protein dystrophin – an important component of muscle fibers. After a Crispr/Cas9 treatment, slightly elevated levels of the protein could be detected. In initial clinical studies, the new genome editing methods have also been tested in HIV and cancer patients. However, scientists are still struggling: so far gene repair works in comparatively few human cells, since the repair mechanism is active only in reproducing cells; but most cells in the body do not replicate. In addition there is a question of how to get the gene scissors to their site of action within the body's cells. Both the stomach and the immunocytes in blood destroy such proteins. It is possible that vehicles such as nanoparticles (e.g., liposomes) might be able to transport Crispr/Cas9 molecules directly inside cells. Harmless or artificially inactivated viruses are also being tested as transport vehicles.

Whether defective genes already in the germ line should be repaired – i.e., in egg and sperm cells or in embryos, as seems to have happened to the Chinese twin girls – is highly controversial, for ethical reasons. Most scientists disagree with this approach, since it would pave the way to "designed humans."

FIG. 1: Genetically modified plants.

Photo: ©iStock.com/Pogonici

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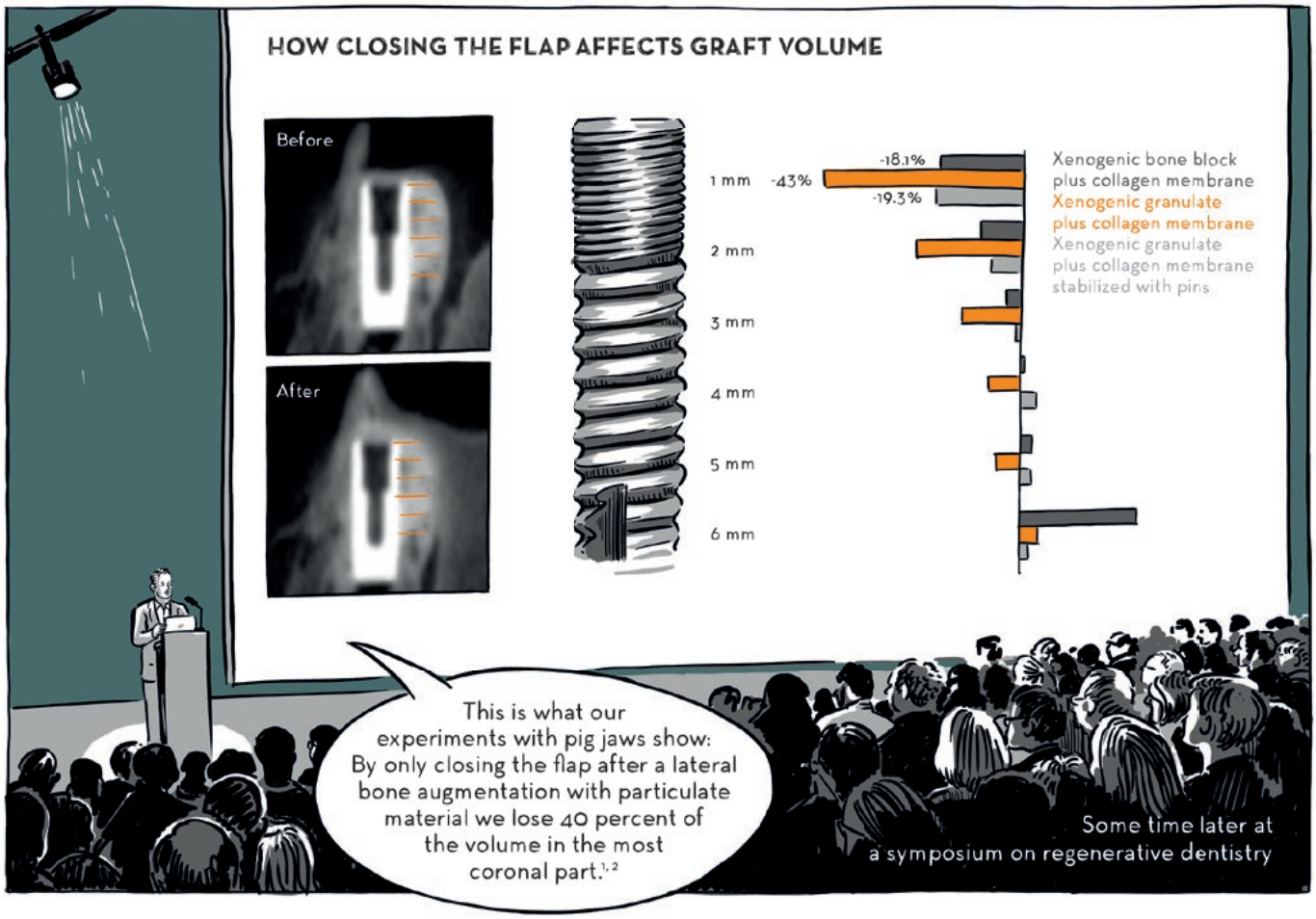
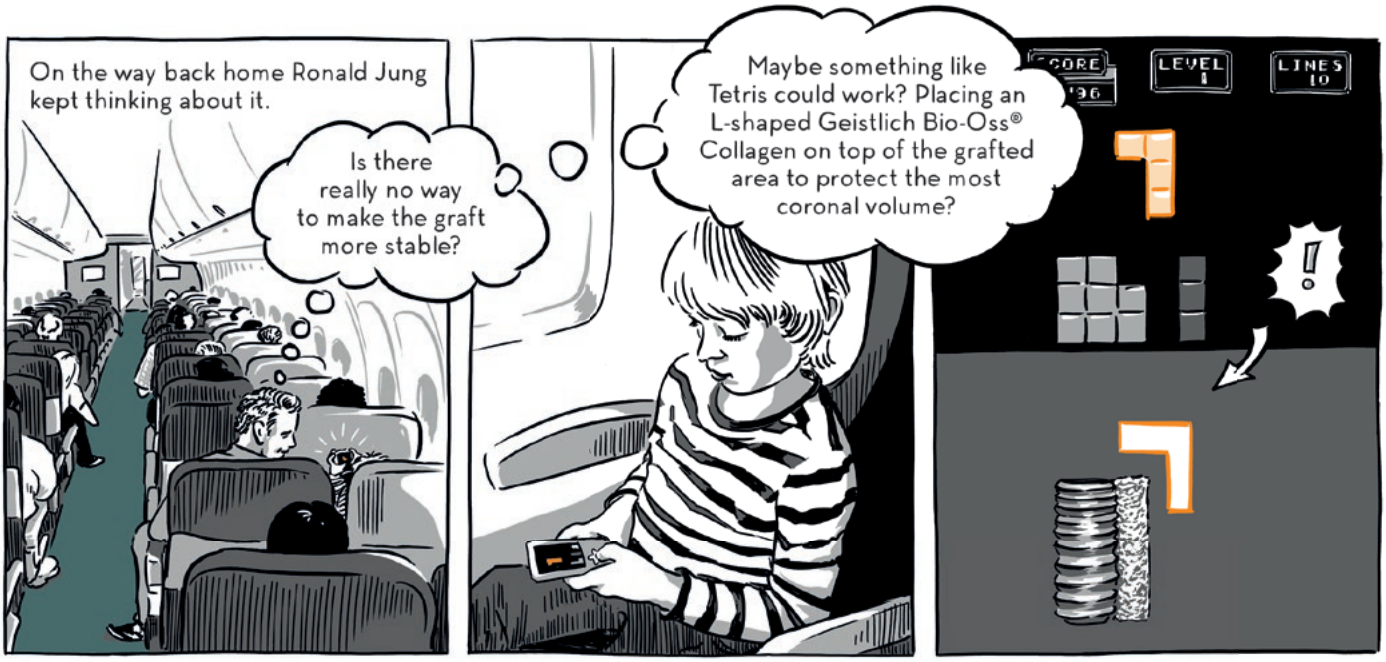
THE QUEST FOR STABILITY

RONALD JUNG, Goran Benic, Javier Mir-Mari and Eduard Valmaseda-Castellon. The two teams from the Universities of Zurich and Barcelona investigate how to improve bone volume stability of the augmented area.





THE L-SHAPE TECHNIQUE

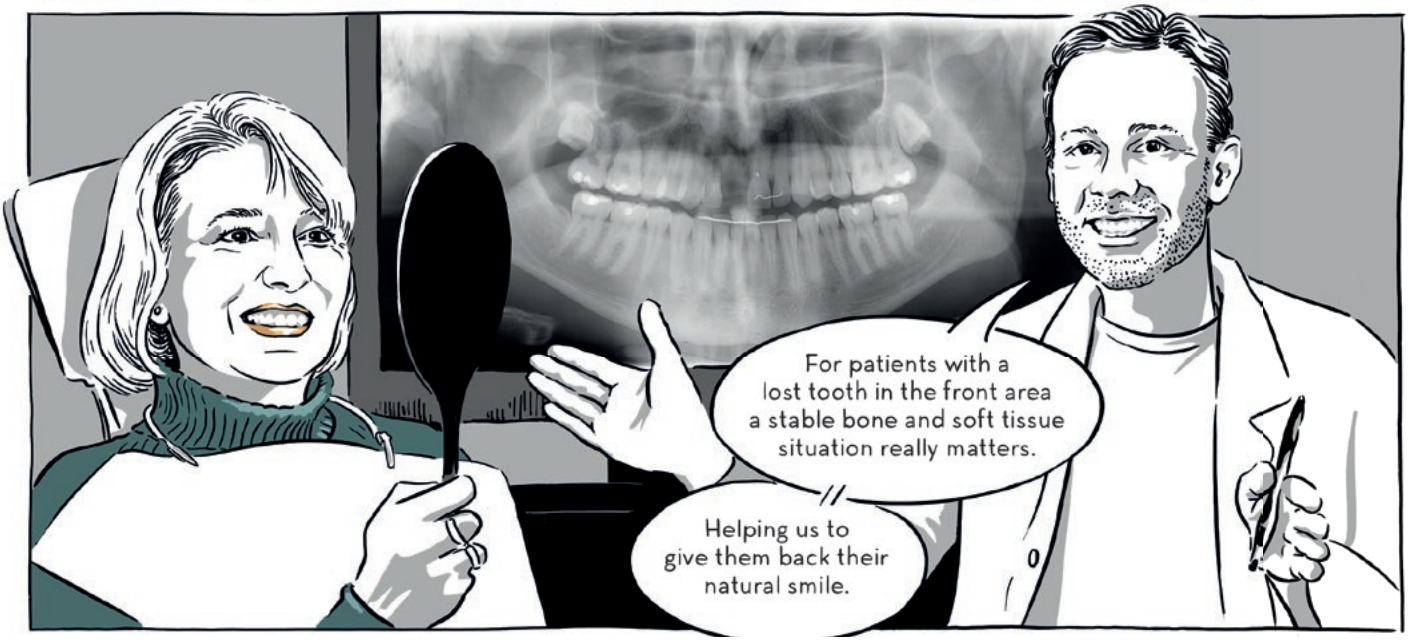
is widely used at the University of Zurich, particularly in the esthetic area.

1. Perform lateral bone augmentation with Geistlich Bio-Oss® and/or autologous bone.

2. Cut Geistlich Bio-Oss® Collagen into an L-shape.

3. Place the L-shaped Geistlich Bio-Oss® Collagen on top.

4. Place a Geistlich Bio-Gide® membrane on top and stabilize it in the apical part with pins before closing the flap.



References: see page 39

Welcome to THE NEXT **RE**GENERATION

Basil Gürber | Osteology Foundation

In April 2019 Barcelona was the place to be for everybody interested in oral regenerative therapies, with the International Osteology Symposium attracting 2,800 scientists and clinicians from more than 70 countries around the world.

The International Osteology Symposium was held for the 6th time between 25–27 April, 2019, in Barcelona. Under the motto "THE NEXT **RE**GENERATION," the congress covered the latest technologies, developments and techniques in the field of Oral Regeneration, and included hands-on workshops, the Research Forum, the first Case Session and the launch of THE BOX app.

The scientific program

Together with the Foundation's Education Committee, the two Chairmen of the symposium, Christoph Hämmerle, Switzerland, and Maurício Araújo, Brazil, put together a program covering all aspects of oral regeneration, including the latest developments in techniques and technologies, while also giving the next generation of experts the opportunity to present.

Linking Science with Practice in Regeneration

Discussing the next generation of technologies, developments and techniques also includes covering the latest results from research. Part of the program was dedicated to science. More than 288 posters were displayed in the exhibition, and on Friday the authors of the six best abstracts in both clinical and basic research presented the content of their posters in the Research Forum. In addition the outcome of the XIII European Workshop of the European Federation of Periodontology in collaboration with the Osteology Foundation, a consensus conference on bone regeneration, was presented and discussed. All with the goal of ensuring that clinicians can orient themselves in the science of regeneration.

For the first time: Case Session and Competition

Prior to Osteology Barcelona, participants were invited to submit a clinical case to THE BOX and participate in the first Case Competition at an International Osteology Symposium. 178 cases in six competitive categories were submitted. The jury assessed the cases based on the outcome and criteria, such as creativity and originality of the treatment and the biological principles behind the technique. The winner in each of the competition categories received a free registration for the congress and presented their case in the Case Session to a targeted audience. When asked about the Case Session, Araújo said, "With this interactive format, participants had the opportunity to get the best out of their cases. They shared their knowledge and expertise, discussed the cases with colleagues from all over the world and got recognition for the excellent work they do."

The congress in beautiful Barcelona drew to a conclusion. The city embodied modernity, culture, freshness and the light of the Mediterranean Sea. All of this, combined with the quality of the scientific program and professional networking of the Osteology Foundation's International Symposia, was a great cocktail for a successful symposium.

2800 participants
70 countries
5 hands-on workshops
178 cases
288 posters

THE BOX app launched at Osteology Barcelona

Basil Gürber | Osteology Foundation

To create an even better interactive experience, the Osteology Foundation launched the app version of THE BOX. Among established features like the symposia and the newsfeed function, an augmented reality interface has been integrated into the app.
It is now available, free of charge, in both app stores for Android and iOS.

Previously only a web-based version of THE BOX was available. To create an even better and simpler user experience, the Osteology Foundation decided to develop the app version. Christian Schmitt, Germany, member of the Osteology Foundation Expert Council and project leader of THE BOX project says: "Enhancing discussions and exchange within the field of oral regeneration is one of the goals of the platform we developed. By making the platform more accessible to those using smartphones, I think we have taken a huge step in this direction." Referring to the symposia function of the app, Schmitt went on to explain: "It is possible to ask the speaker questions, read abstracts, browse through the submitted posters and see the Osteology congress programs. In my opinion this really produces added-value for the participant."

Merging online and offline

Among the established features, an augmented reality interface was also integrated into the app. Augmented reality is the perfect technology for adding extra value to offline content. Multiple scanning points were available at the Osteology booth as well as around the congress center in Barcelona, creating a new experience for the congress participants and bringing the creative activities of the Osteology Foundation even closer to the participants.

What is THE BOX?

THE BOX is an online platform that provides information and tools while connecting scientists and practitioners worldwide. Tools like the Case Box, the Challenges & Complications Forum and the Surgical Checklists support the clinician in his daily life. Tools like the Research Wizard or the Biostatistics Wizard are there to support researchers in setting up a research project or to find the right test for their data. Among these tools, additional information is available on the Global Osteology Community Platform. The user can find the online versions of "Oral Regeneration in a Nutshell" and the "Osteology Research Guidelines." And last but not least, for free users can participate in the Oral Regeneration Topic, which is chosen every six months. It consists of a scientific radar, a conversation with the author of an important study on the subject and an interactive webinar.

THE BOX app is now available in the Google Play store for Android and in the App Store for iOS. Download it now – it's free!

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Interview

A chat with Jia-Hui Fu in Barcelona

Interview conducted by Verena Vermeulen

Dr. Fu, you have lived, studied and practiced both in Singapore and the USA. What did you and your US colleagues learn from each other?
Dr. Fu: I learned from my US colleagues how to communicate better with patients, for example, using positive words to motivate and encourage them. In return I certainly trained my co-residents how to use chop sticks and shared more about my country, Singapore and our unique culture.

You attended the Osteology Research Academy in Hong Kong. How important are education and collaboration?
Dr. Fu: The academy was an eye-opener for me. These courses unite many individuals with a common goal in their professional lives. It allows us to learn from each other, to build a relationship and to catch up after the course. Now we can build a strong scientific community.

Is there a special moment you remember?
Dr. Fu: Professor Lang shared his professional journey with us – the people he had met, the challenges he had faced and how he overcame those difficult times. It was inspiring. As somebody young in this field, you can totally appreciate all the challenges that he described (laughs). You realize that you are not alone with these experiences and someone so successful had faced them as well and obviously overcame them.

We talk more and more about the functional aspects of soft tissue management. Where do you see the biggest benefits?
Dr. Fu: In preventing a disease from happening. The thick soft tissue around teeth or implants acts as a strong physical barrier against trauma and inflammation. So soft tissue thickening before or during regenerative treatments may have a strong impact on esthetics and long-term success.

If you received a huge research grant, on what would you spend it?
Dr. Fu: The gingival phenotype of the Asian population is very thin, and I believe it has an impact on the success of GTR treatment. I would like to investigate whether soft tissue thickening is beneficial in these patients and what materials work best in this indication.

You have won several prizes. Which one was most important for you?
Dr. Fu: Surely the André Schroeder award! This is one of the most prestigious awards in implant dentistry. I received it for a project I did during my Master Program in Michigan, so it was a great testimony to the mentorship and the world class education that you can get there. It was also the first time that University of Michigan won this prize. I am very happy to be able to contribute to my alma mater.

What do you like to do in your free time?
Dr. Fu: I love to spend time with my two kids. They grow up so quickly – suddenly they start going to school. I enjoy taking them on trips to explore different parts of Singapore and overseas to learn more about other countries and cultures.

Photo: Andreas Butz

Ass. Prof. Dr. Jia-Hui Fu studied at the National University of Singapore and finished her master's degree in Periodontics and Implant Dentistry at the University of Michigan. She is a Diplomate of the American Board of Periodontology and an Assistant Professor at the National University of Singapore. The André Schroeder Research Prize 2014 is among the prizes she has won and she is a member of the Osteology Research Council.

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FOCUS

Prevention

› Preventing bone loss after immediate implant placement

› Preventing bone loss after tooth extraction

› Preventing peri-implantitis

› Preventing complications using proper soft tissue management

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