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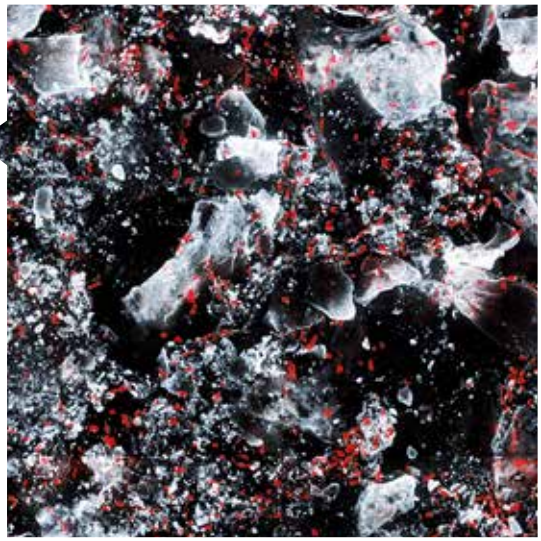
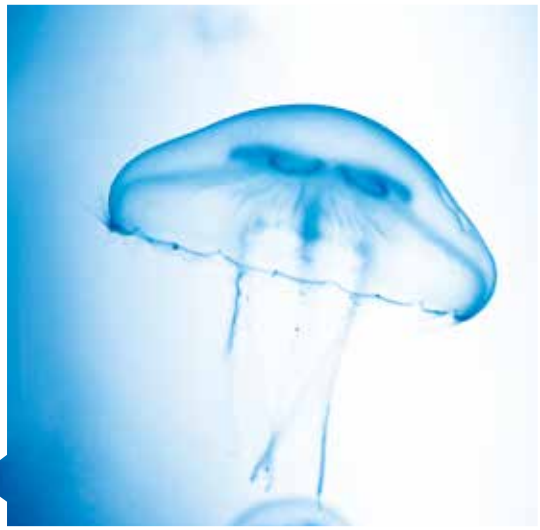
LEADING REGENERATION

Issue 1|2016





“Thousand and One Study!”

Dear readers,
In 1985 I went on a trip to study with Prof. Myron Spector at Emory University in Atlanta. We applied freshly isolated cells from chicken bones to different bone replacement biomaterials, including Geistlich Bio-Oss®. We then analysed the samples under an electron microscope and characterised what took place. It is indeed possible that this 1985 study is not listed among the 1000 studies which have been conducted with our products since then and which we want to celebrate with this issue of Geistlich News. In any case, for me it was my first impression of the fascinating world of regeneration.

“I hope you have a good jubilee year with Geistlich.”

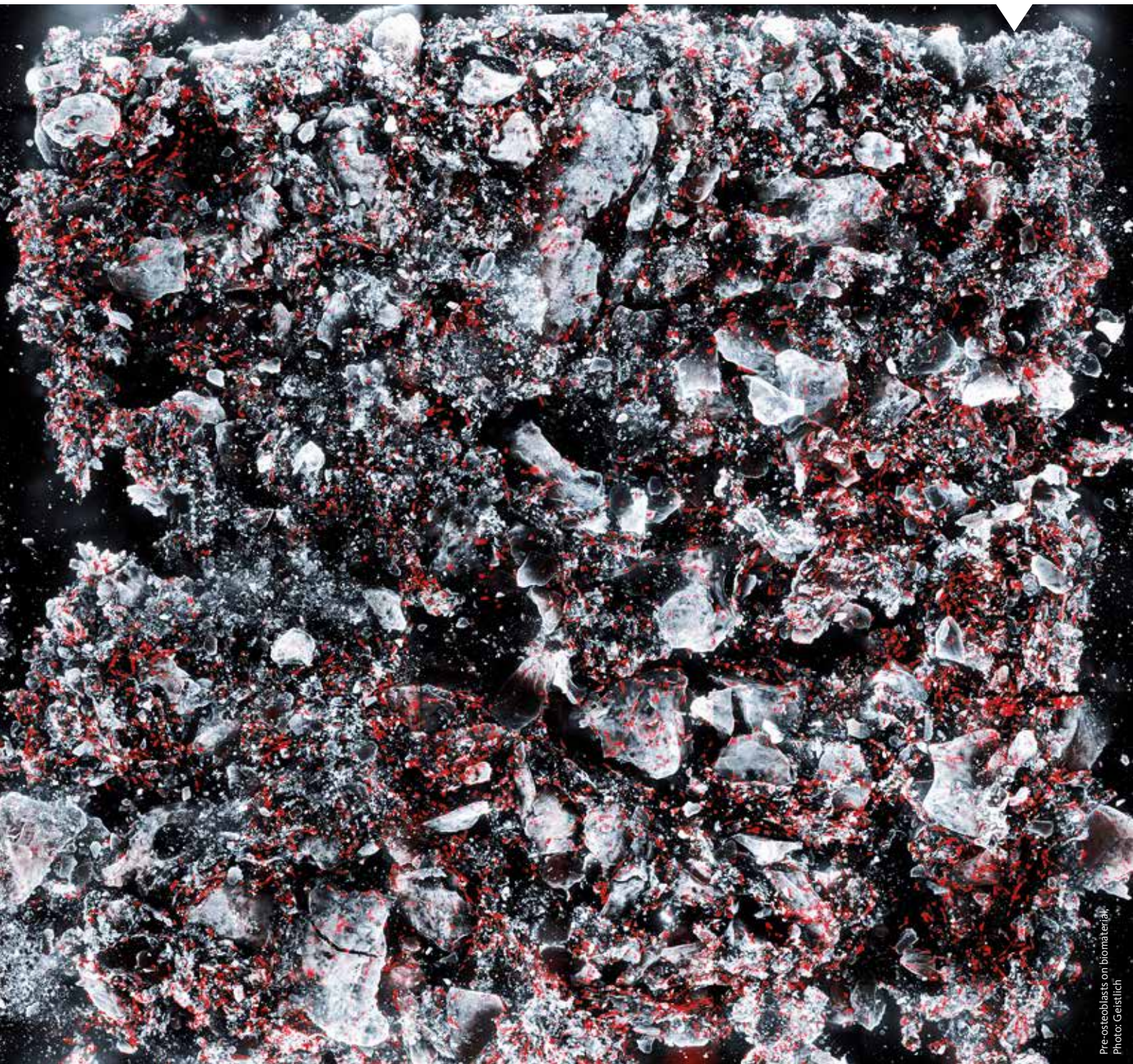
Geistlich Bio-Oss® and Geistlich Bio-Gide® have gone on to become clinically reliable regeneration biomaterials and the gold standard in dentistry. No other products have been able to achieve a wider acceptance in oral regenerative applications. Nevertheless, Geistlich Bio-Oss® and Geistlich Bio-Gide® continue to be studied. To this very day they are still inspiring clinicians to try new techniques and scientists to find explanations for why they work so well. This marriage of science and practice spurs us on, and it is also what makes us unique and successful.

Our proven products are always finding uses in new applications, like the “sausage technique” of Prof. Urban or the “pinhole technique” of Dr. Chao, which are just two examples.

Yours sincerely, Dr. Andreas Geistlich
Chairman of the Board of Directors

BONE AUGMENTATION.

What is the current state of knowledge regarding bone regeneration? What are the ideal combinations of biomaterials and autologous bone? And what will the future hold?



Pre-osteoblasts on biomaterial.
Photo: Geistlich

Blood vessels are crucial for bone regeneration

Prof. Reinhard Gruber | Austria
Professor for Oral Biology
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Angiogenesis and osteogenesis are coupled. Recent studies shed light on some of the main actors in this process, for example, special endothelial cells, osteoblast progenitors, macrophages and osteocytes.

Guided Bone Regeneration (GBR) depends critically on angiogenesis and osteogenesis. Augmentation biomaterials including Geistlich Bio-Oss® and autologous bone chips form a loose bulk allowing new blood vessels and, later, bone to fill void spaces **(Figure 1)**. Membranes serve as barriers towards the soft tissue and provide mechanical stability to the augmented area. Underneath the membrane, angiogenesis and osteogenesis originate from the pristine bone, while soft tissue cells are excluded **(Figure 2)**.
Graft consolidation is almost complete when a conglomerate of Geistlich Bio-Oss® and autologous bone chips with newly formed woven bone and bone marrow spaces has formed. Autologous bone chips and immature woven bone then remodel into mature lamellar bone, capable of responding to biomechanical loading and replacing fatigue damage. Lamellar bone has an innate regenerative capacity, which is the prerequisite for dental implant osseointegration.

Angiocrine signals crucial for bone formation

Geistlich Bio-Oss®, like autologous bone chips, visibly allows angiogenesis and osteogenesis to occur. Angiogenesis is initiated by the sprouting of new endothelial capillaries from existing vessels, which then undergo maturation by attracting mural cells, mainly vascular smooth muscle cells and pericytes.
Sprouting blood capillaries are guided through the blood clot that fills the void space by angiogenic stimuli. Thus, augmentation biomaterials have to provide an interconnected network and mechanical stability as prerequisites for angiogenesis followed by osteogenesis.
If we take the "osteon" as an evolutionary standard, the void space between the particles should be around 200–300 µm in diameter. Geistlich Bio-Oss® particles fulfil these criteria[1]. They also provide a surface on which new bone is deposited, a feature called "osteoconductivity". Later, bone remodelling follows its conserved pattern, while Geistlich Bio-Oss® particles are maintained and thereby define the anatomical margins[2]. When not embedded in bone, Geistlich Bio-Oss® can be resorbed[3]. Dissecting this differential process remains a challenge.

The role of barrier membranes

The functional coupling of angiogenesis and osteogenesis and the possible role of barrier membranes during Guided Bone Regeneration are beginning to be understood. One likely explanation for why bone formation occurs without scar tissue comes from a new understanding of blood vessels in bone biology.
Bone vasculature holds a specialized population of endothelial cells that release angiocrine signals supporting bone formation and maturation[4]. Angiocrine signals liberated by so-called type H endothelial cells control the sequential process of bone formation, at least in sophisticated mouse models[4]. Moreover, the formation of this subtype of blood vessels is supported by platelet-derived growth

Angiogenesis and bone regeneration
Angiogenesis, the growth of new blood vessels from the existing vasculature, is fundamental for Guided Bone Regeneration for the following reasons:

1	Blood vessels hold a population of endothelial cells that release signals supporting bone formation.
2	Blood vessels are a source of progenitors that give rise to bone-forming osteoblasts and the bone-resorbing osteoclasts.
3	Blood vessels transport macrophages, originally "pro-inflammatory" and later turning into "wound-healing macrophages" supporting bone regeneration.
4	Blood vessels maintain the viability and control the activity ofwosteocytes, which are major players in bone remodelling.

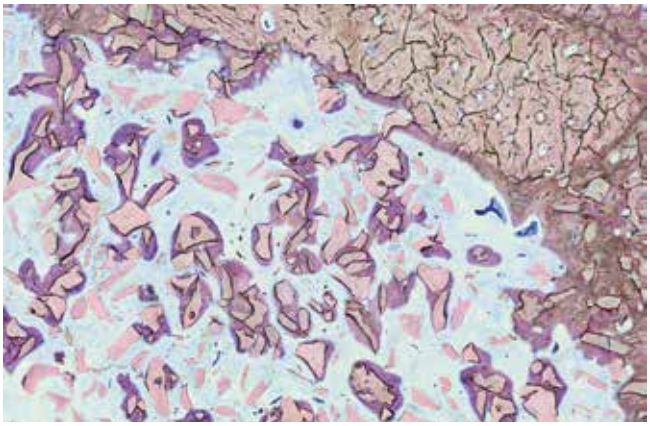
factor-BB (PDGF-BB) secreted by preosteoclasts[5], linking angiogenesis and osteogenesis. These observations provide a new perspective on the importance of angiogenesis during graft consolidation, and they further support the concept of Guided Bone Regeneration, namely that the membrane might protect the augmented site from the immigration of endothelial cells that do not support bone formation.

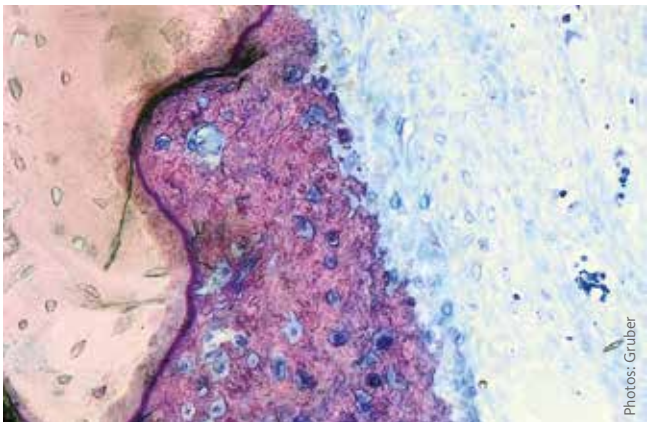
Osteoblast progenitors from blood vessels

Blood vessels are also a source of progenitors that give rise to bone-forming osteoblasts and the bone-resorbing osteoclasts. Osteoclasts originate from hematopoietic cells of the monocyte lineage that are transported via the blood stream[6]. Earlier attempts to isolate osteogenic cells from blood have not been widely reproduced[7], and the recently discovered skeletal stem cells cannot be transported via the blood stream[8,9].
Nevertheless, some "pericyte-like" cells have long been suspected of holding a pool of osteogenic progenitors[10], now being localized in the vicinity of sinusoidal vessels[11]. Thus, not only the periosteum and the bone marrow, but also blood vessels are a source of osteoblast progenitors[4].
Interestingly, blood vessels containing type H endothelial cells represent one source of osteoblast progenitors, besides the angiocrine signals that drive their differentiation into mature osteoblast progenitors[4]. These recent observations provide a scientific basis for re-evaluating the role of angiogenesis and osteogenesis in Guided Bone Regeneration.

Transient inflammation is important

Blood vessels also transport macrophages, the professional phagocytic cells. Macrophages release growth factors and cytokines that are originally "pro-inflammatory," for instance, which is essential for fracture healing[12]. Also, cyclooxygenase-2 (COX-2), the key enzyme for prostaglandin synthesis, is necessary for bone regeneration[13]. Together, both of the studies supporting this healing mechanism underscore





Photos: Gruber

1 Ground specimen of minipig maxillary sinus augmented with Geistlich Bio-Oss® and stained with Levai–Laczko [1,26]. At 6 weeks new bone tissue is depicted in purple; old pristine bone and Geistlich Bio-Oss® appear pink. Erythrocytes indicating the presence of blood vessels are dark blue.

2 Detailed view of new woven bone (purple) growing on the surface of Geistlich Bio-Oss® particles (pink). Erythrocytes in blood vessels are visible as dark blue discs.

the relevance of a transient inflammatory microenvironment for fracture healing.

Macrophages later turn into "wound-healing macrophages" supporting angiogenesis and the formation of a new extracellular matrix[14]. Evidence suggests that macrophages are required for wound healing[15] and also bone regeneration[16]. Macrophages are not restricted to bone regeneration, they also control bone modelling during growth and development[17], and their relationship to biomaterials has also been evaluated[18].

Whether macrophages control bone remodelling remains a matter of debate[19]. However, for graft consolidation it appears to be important that macrophages can immigrate into the space between the particles of the augmentation biomaterial.

Dying osteocytes provoke bone resorption

Blood vessels are also crucial for maintaining the viability and controlling the activity of osteocytes, former osteoblasts embedded in bone. Osteocytes have recently been called "amazing" as they are major players in controlling bone remodelling and modeling[20]. This hypothesis is based on observations of dying osteocytes provoking massive bone resorption[21]. This observation makes sense in the context of bone remodelling, where necrotic areas have to be replaced by new bone.

Osteocyte necrosis can, however, have many causes, including aging, cortisone intake, etc. – all associated with bone loss[22]. Moreover, osteocytes are master regulators of effector cells. For example, osteocytes almost exclusively produce sclerostin, a potent suppressor of osteoblastogenesis and consequently bone formation[23]. Osteocytes also produce receptor activator of nuclear factor kappa-B ligand (RANKL)[24,25], which is the central regulator of osteoclastogenesis and subsequent bone resorption. Thus, blood vessels in an augmented area control osteocyte activity and bone homeostasis.

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Let's shape the future of Guided Bone Regeneration!

Prof. Christer Dahlin | Sweden
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A better understanding of the processes underlying Guided Bone Regeneration might lead to a new generation of products – such as bioactive membranes or "doped" bone substitutes. A look into the crystal ball.

Guided Bone Regeneration (GBR) was developed and introduced as a biological concept and treatment modality to repair bone deficiency of the alveolar bone in order to allow placement of oral implants[1,2]. The concept has been in clinical use since the early 90's and is still an established technique that has spread and is now used globally. Looking in the rear view mirror, non-resorbable membranes were considered the standard for GBR. ePTFE was considered a stable device, because it provoked only a minimal immunologic reaction[3]. Later a titanium reinforcement was added to prevent membrane collapse and improve stability and space maintenance, which was considered essential for a successful regenerative outcome. The need for a second surgical intervention for membrane removal in combination with difficulties in handling complications led to the development of natural resorbable membranes based on collagen. Due to their lack of rigidity, collagen membranes are in general used in conjunction with grafting materials that maintain the defect space.

The biological principle of GBR revisited

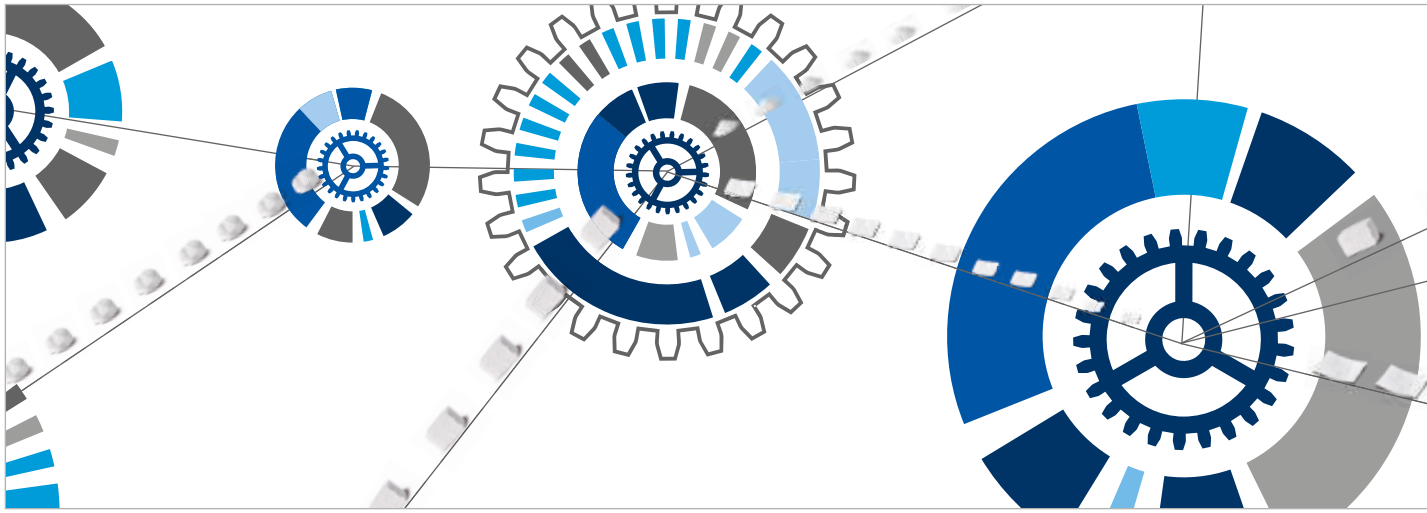
As mentioned before, GBR membranes are used in combination with various bone substitute materials. The original hypothesis implies that the membranes would isolate the bone defect site from non-osteogenic soft tissue, and the bone substitute would act as a "ladder" or scaffold for the newly formed bone, thereby promoting osteogenic cells and *de novo* bone formation. However, although more than 25-years old and quite successful in the clinical setting, this hypothesis remains to a certain extent speculative, since the mechanism of GBR in conjunction with membranes and bone substitutes is not completely understood.

In order to design future regenerative products, for both membranes and bone substitutes and also for more complex situations, i.e., medically compromised patients and more advanced cases, it is imperative to gain a more in-depth knowledge regarding the mechanisms of regeneration. This would open up possibilities for tailoring materials with specific properties for various clinical indications.

Bioactive membranes

Native (not chemically manipulated) membranes, based on collagen, have received considerable attention over recent years. This is not only due to their configuration and user-friendly status in the clinical setting, but also because of positive biological factors such as low immunogenicity, stimulatory actions by means of the collagen itself[4] and potential presence of growth factors and other signals within the native extracellular matrix, such as fibroblast growth factor 2 (FGF-2), which, for example, stimulates angiogenesis[5,6,7].

There is a belief that the classic role of the membrane acting as a passive barrier and graft container might shift into a situation where the membrane takes a more active role by guiding and directing the healing events during regeneration. With this new view of the GBR principle, tailor making bioactive barrier membranes seems to be a logical development for the future, where structural and functional



mimicry of the native extracellular matrix using novel tissue engineering techniques is the ultimate goal.
Examples of these techniques are specialized extraction techniques that preserve native extracellular components, including angiogenic and regenerative signals, electro spinning technology and 3D printing to produce biocompatible and degradable membranes that mimic the native extracellular matrix. Furthermore, multilayered barrier membranes with altered composition and structural behaviour have been explored[6,7,8].
Interestingly, protocols such as the double-layer technique utilizing resorbable collagen membranes indicate an improvement in regenerative outcome[9]. However, at present a development of currently used collagen membranes is also imperative. Many types of collagen membranes are commercially available for GBR. They usually originate from different bovine and porcine sites, for example, small intestine, tendon and dermis[5].
By moving away from the classical barrier function only, and also demonstrating an active involvement in the wound healing, issues such as degradation rate and membrane dimensions might be of more importance in the future.

New bone substitutes

Deproteinized bovine bone, which is widely used as grafting material for oral applications, contains only the mineral phase of bone after removal of organic components and purification[10]. Deproteinized bovine bone is classified amongst the calcium phosphate group of materials with a chemical composition mimicking that of human skeletal bone. Numerous reports have shown that deproteinized bovine bone facilitates bone healing and subsequent implant integration.
Many efforts have been made to develop synthetic grafting materials as options for bone substitution. This is not only due to concern regarding the origin of autogenous and xenogenic graft material, but also because novel techniques within tissue engineering allow controlled and standardized modifications of the chemistry and structure of synthetic materials. Bone mineral is a carbonate containing hydroxyapatite and, hence, various amounts of different ions are present in the tissue, such as sodium, fluoride, magnesium, strontium and others. In order to mimic original human bone, extensive efforts have been made to introduce these components into synthetically manufactured materials. From a biological perspective, this is quite an interesting development, since several of the previously mentioned ions are considered bioactive, and this “doping” of a calcium phosphate structure can alter its biological performance[11]. One example of such an ion is strontium, which has received attention for stimulating bone formation and inhibiting bone resorption[12,13].
An interesting observation regarding deproteinized bovine bone is that this material also demonstrates an active release of silicon ions, which are considered stimulatory for osteoblast activity. Furthermore, an active uptake of calcium ions on the surface of deproteinized bovine bone particles further confirms that this material most probably is quite actively involved in the early bone formation stage.[14]

Future perspectives

Based on current trends and knowledge, I foresee future scientific developments that will focus on the effect of specific membrane properties, for example, porosity, thickness and cell affinity. Furthermore, research will focus on how the differences in the

structure of the membrane will alter the regulation of cellular and molecular events inside the membrane as well as within the protected defect areas. A continuous development and a renewed interest in non-resorbable membranes, in particular for more advanced reconstructions, can be anticipated, combined with novel material knowledge in this field.

In parallel I also see similar evaluations of different bone substitutes or scaffolds that are "doped" in order to trigger specific cellular and molecular events during bone healing.

A third area of great potential interest is to explore whether it is advantageous to prime both bone substitutes as well as membranes with, for example, mesenchymal cells in order to optimize healing.

In summary, I expect research within the fields of GBR will not develop with isolated projects on membranes and bone substitutes, respectively. Current findings strongly suggest that membranes and bone substitutes are tightly linked to one another during healing and should be evaluated as a "family" of regenerative biomaterials.

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Ideal combinations of autogenous bone grafts and biomaterials

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Autogenous bone grafts stimulate new bone formation but are prone to resorption. Biomaterials are merely osteoconductive but maintain the volume. So, how about combinations of the two materials?

The loss or absence of teeth because of periodontal disease, trauma, congenital malformations and, unfortunately, malpractice, is always followed by a volume reduction of the alveolar ridge. This may render the use of osseointegrated implants to restore the missing dentition impossible or inadequate from a functional and aesthetic point of view. Nowadays, whenever possible, the re-creation of an adequate bone and soft tissue volume to allow implant placement in an ideal, prosthetically driven position has become routine and almost a necessity. To reach this goal, Guided Bone Regeneration (GBR) with biomaterials and/or autogenous bone has been shown to be a reliable procedure with strong research support.[1,2]

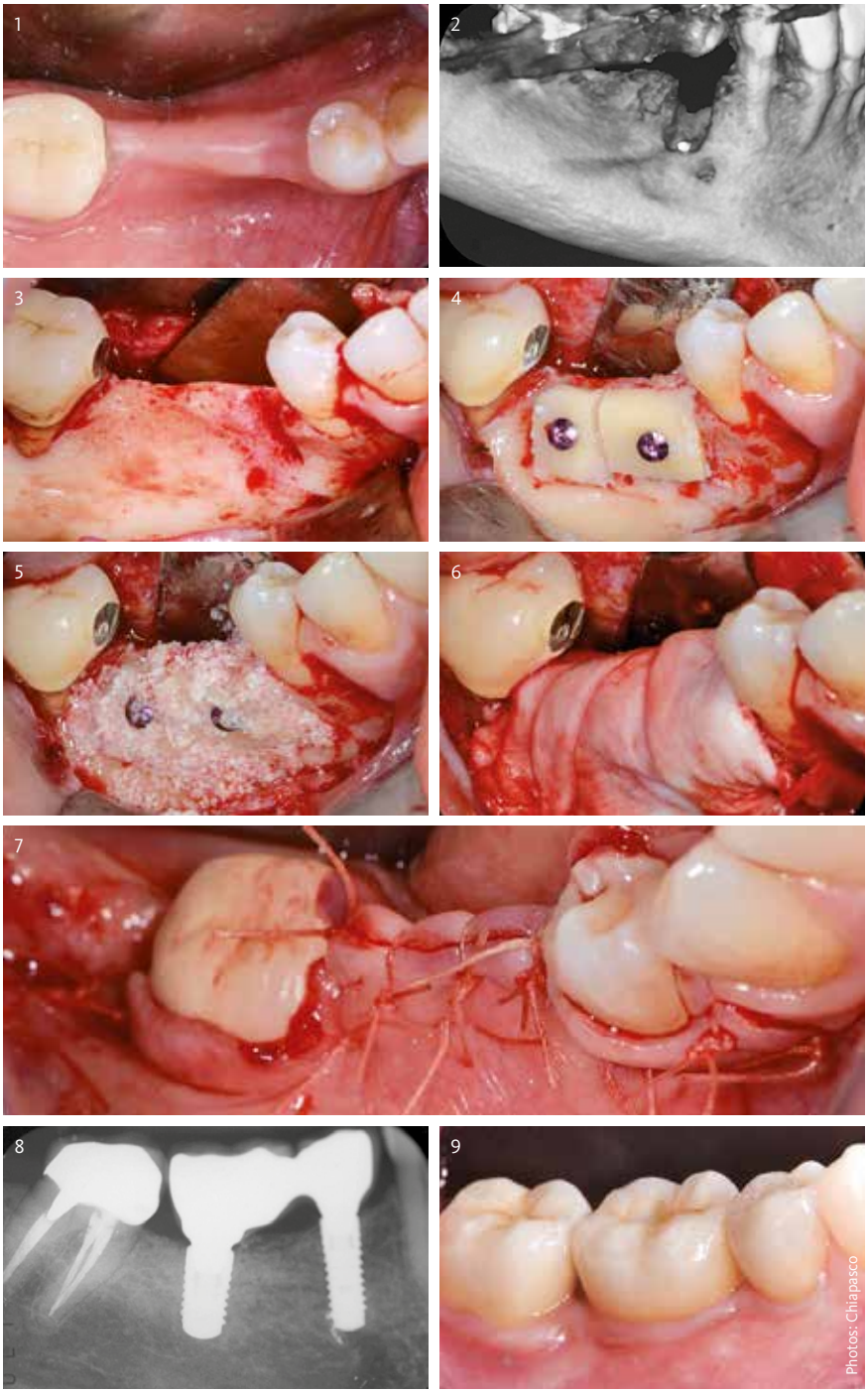
> The main advantage of biomaterials is that they will maintain volume if they are characterized by a very slow resorption rate.

Bovine bone mineral: the volume stabilizer

Biomaterials, typically xenografts such as bovine bone mineral, are generally used in the form of porous granules. On average each particle has a diameter ranging from 500 to 2000 microns. The biomaterial has osteoconductive capabilities. It acts as a scaffold, where – thanks to the arrival of blood that contains bone progenitor cells – newly formed bone grows inside and outside the particles.
The main advantage is that these biomaterials, if characterized by a very slow resorption rate, will maintain volume. New bone will incorporate the biomaterial granules, thereby creating a new compound that is ideal for osseointegration of implants and maintenance of volume. The drawback is that osteoconductive materials are not capable of inducing bone formation themselves. In large reconstructions, and particularly in vertical defects, their efficacy is limited unless combined with autogenous bone.

Autogenous bone: the bone formation promotor

Autogenous bone, on the contrary, both in blocks or particulated in "chips," has osteoconductive, osteogenic and osteoinductive capabilities. This means that autogenous bone can act as a scaffold while at the same time promoting new bone formation by itself. The reason is that autogenous bone contains bone morphogenetic proteins, and sometimes live cells, which can activate new bone formation[3–5].
Autogenous bone is still considered the "gold standard" to which all biomaterials should be compared. Also, it can be used successfully for cases requiring large vertical reconstructions. The main drawback, however, is postoperative morbidity due to the necessity for bone harvest from intra-oral



1 Loss of teeth 45 and 46 with horizontal atrophy of the residual ridge.

2 CBCT picture of the region shows reduced bone volume.

3 The bone defect after flap exposure.

4 Correction of the bone defect with two autogenous bone blocks harvested from the mandibular ramus.

5 Filling of every void between the grafts and the recipient bed with autogenous bone chips mixed in a 1:1 ratio with bovine bone mineral.

6 Coverage of the graft with a resorbable collagen membrane.

7 Water-tight closure of the flaps to guarantee primary healing of the surgical wound.

8 The radiographic picture shows that an adequate bone volume has been obtained.

9 Final prosthetic results after the insertion of two endosseous implants in the reconstructed area.

or extra-oral sites (extraoral sites, such as the iliac crest or the calvarium, are used only when large amounts of bone are needed). In addition, autogenous bone volume can be lost due to resorption and remodelling in the long-term.

Ideal combinations

Clinicians can minimize the disadvantages and maximize the advantages of both materials by combining autogenous bone particles or blocks with their osteoinductive and osteogenic capabilities, and biomaterials with their osteoconductive capabilities, along with their capacity for maintaining volume over time, thus minimizing the loss of initial bone gains.

Biomaterials, in the form of porous granules, can be effectively used with-

Tab 1: Regenerative therapies: When using bone, when using bone replacement material?

Technique	Bone / Bone replacement material	Membrane/Matrix
Treatment of peri-implant dehiscence	Particulate bone replacement material	Resorbable membrane
Treatment of peri-implant fenestration	Particulate bone replacement material	Resorbable membrane
Sinus floor elevation	Particulate bone replacement material	Resorbable membrane
Ridge Preservation	Particulate bone replacement material	Resorbable collagen matrix
Horizontal GBR	Autologous bone block + particulate bone replacement material **or** Autologous bone chips + particulate bone replacement material 1:1 mixture	Resorbable membrane
Vertical GBR	Autologous bone block + articulate bone replacement material **or** Autologous bone chips + particulate bone replacement material 1:1 mixture	Possibly rigid membrane

out autogenous bone in the following cases: **(Tab. 1):**

- Correction of "small" defects, such as peri-implant dehiscences or fenestrations, in association with resorbable membranes such as collagen membranes;
- Grafting of the maxillary sinus via a lateral or crestal approach;
- Ridge Preservation after tooth extraction (generally a compound of bovine bone mineral particles and collagen is used in this case) in combination with a thick collagen matrix that covers the open socket, encouraging soft tissue healing and preventing dispersion of the biomaterial.[1,6]

Autogenous bone blocks can be used in any inlay and, in particular, onlay grafting procedure for the correction of both horizontal or vertical defects, from single tooth gaps to fully edentulous, deficient alveolar ridges[2]. In such cases, bone blocks can be covered with a layer of slowly resorbing biomaterials and a collagen membrane to reduce the risk of graft resorption over time[7].

Finally, particulated autogenous bone and biomaterials in a 1:1 ratio, approximately, can be safely used in the following indications:

- Horizontal GBR;
- Vertical GBR;
- In association with autogenous bone blocks to cover or fill any voids between the recipient site and the blocks.

Membranes stabilize the graft

It is well known that any voids between the graft and the recipient site can be penetrated and colonized by connective tissue, which grows at a faster rate than autogenous bone. The interposition of connective tissue may be deleterious, as it may compromise the integration of the graft with the native bone bed and eventually cause graft loss or significant resorption.

In cases of horizontal GBR, resorbable collagen membranes, preferably stabilized with tacks or pins, are essential to guarantee stability of the grafted material and allow safe integration.

In cases of vertical GBR, the efficacy of resorbable membranes is still being debated. Some authors have demonstrated they can create the desired vertical increase with more flexible membranes, while others wish for stiffer membranes to guarantee an efficient "space-maintenance" capability. In such cases, the mixture of autogenous bone and biomaterial can be used together with a non-resorbable membrane reinforced with titanium reinforcing struts or titanium mesh. However, it must be emphasized that these membranes present a higher risk for soft tissue dehiscenses and, subsequently, exposure to the oral environment.[1,2,7,8]

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“Before Geistlich came, bone was just the hard wall between the roots”

Prof. Jan Lindhe | Sweden
Faculty of Odontology
University of Gothenburg

Interview conducted by Verena Vermeulen

Jan Lindhe shaped periodontology and implant dentistry research like few others. Here he looks back to the early days of oral tissue regeneration and compares 1985 to 2015.

Can you visualize the Jan Lindhe of the early 1980s?

Prof. Lindhe: Yes, that was the time when I was still young enough to be offered different new positions around the world. So it was sort of a “temptation time.” But we also did very interesting research in Gothenburg. We conducted longitudinal studies on periodontal treatments where we tried to find out the best technique to eliminate or at least reduce dental pockets to 4–5 mm. In addition, Klaus Lang and I were preparing our international textbook on clinical periodontology and implant dentistry.

What was your regenerative focus at that time?

Prof. Lindhe: Together with Stüre Nyman and Thorkild Karring we were trying to find out which cells produced new root cementum, for example: gingival connective tissue cells or bone cells. Then Nyman and Karring were the first to place a membrane between the tooth and the soft tissues in order to give the periodontal ligament and the root cementum space and time to regenerate and form new attachment. This was the basis for the later Gore-Tex® membrane. The predictability of this technique was not so good though, due to the frequent soft tissue dehiscenses. We never used bone substitutes at that time in Gothenburg.

And then you met Dr. Peter Geistlich who changed your mind?

Prof. Lindhe: No, first two other people visited us in Gothenburg. I think it was the former Managing Director Michael Peetz and the American researcher Prof. Myron Spector. We were very, very sceptical about the new bovine bone material they showed us.

Why?

Prof. Lindhe: We thought it was just another hydroxylapatite, and we knew that this material didn’t have any regenerative potential. We were also not enthusiastic about the allografts that were used in America. Our concentration on membranes – pure Guided Tissue Regeneration – was very strict at that time.

Then what happened?

Prof. Lindhe: One thing was that we in Gothenburg started to place implants, and we were thinking about the bony defects that arise after extracting a tooth. That was, I think, in the end of the 80s or the early 90s. So our focus shifted from only periodontal regeneration to also bony defect regeneration. And then the Geistlich people came back together with Dr. Peter Geistlich, who was a very nice gentleman. We agreed to conduct an animal study where we placed implants into native bone and into Geistlich Bio-Oss® augmented bone[1].

Is this the study that was awarded a prize last year for being the most cited study with Geistlich biomaterials?

Prof. Lindhe: Yes it is. The funny thing is that we mainly conducted it to investigate the soft tissues. Our focus was: is there any difference regarding epithelium cells, connective tissue cells, etc., between the soft tissues above bone and the soft tissues above a bone substitute material? The composition of the soft tissue around implants was what concerned us.
But the reason this study is cited so often is, of course, that we could also show that the osseointegration in the Geistlich Bio-Oss® augmented area was just as good as in the native

Trend in the numbers of implantations from 1986 to 2016 (forecast) with the USA as an example.

Sources: iData Research Inc.,US Dental Bone Graft Substitutes and other Biomaterials Market / Medical Data International Report 1999.

1986

Implants: 120,000
First clinical use of Geistlich Bio-Oss®

2006

Implants 1,526,225
Bone replacement procedures 983,860

2016

Implants 2,579,559
Bone replacement procedures 1,999,309

bone. This much more important finding was, at the time, just a side observation.

So your first study with Geistlich biomaterials was about osseointegration of implants? Did you go back to periodontal indications later on?

Prof. Lindhe: Yes, we investigated a new collagen membrane later on called Geistlich Bio-Gide®. It was designed as an alternative to the Gore-Tex® membrane for the regeneration of periodontal ligament. First, it seemed disadvantageous that the membrane was not as form-stable as Gore-Tex®. But we used it together with Geistlich Bio-Oss® that supported the membrane, preventing it from sinking into the angular defect. Additionally, Dani Buser advised us to use the membrane in a double-layer technique, which was a very simple, but nonetheless important advance for Geistlich Bio-Gide®.

Could you describe the two following scenarios: A patients comes to the dentist with a hopeless tooth in 1985 vs. 2015. How is he treated? Which concepts are predominant in 1985 vs. 2015?

Prof. Lindhe: I think the main change is that in the 80's patients mainly received a three- or four-unit bridge, while nowadays teeth are replaced with an implant. But besides that, what is a hopeless tooth? For you and me, running 100 meters in 11 seconds would be a hopeless exercise. But for others, it's not. It's the same with so-called hopeless teeth – some call them hopeless, others know how to manage them. But of course, the more implants you want to place, the more "hopeless" the teeth appear.

Is this still true? Others say that the pendulum has swung back from replacing teeth to saving teeth.

Prof. Lindhe: The pendulum has started to swing back, that's true. In the 90's and the first decade of the new millennium, lots of teeth were replaced with implants. But the new generation of dentists is much less impressed by the features of dental implants than we were when Brånemark and Schroeder introduced the concept to us. At least in Scandi-

navia, younger dentists are becoming more and more interested in tooth retention.

If you compare the early days of regenerative dentistry with today, where do you see the biggest changes or advantages?

Prof. Lindhe: The biggest advantage is the predictability. Regenerative procedures are highly predictable today, if you follow the protocols. This is because we have done a lot to prepare a sound scientific basis, for example, with systematic reviews, consensus meetings and so on.

On the other hand, the people involved in clinical studies are mainly excellent surgeons, who sometimes make a technique seem more predictable than it is.

Is regenerative dentistry still very skill dependent?

Prof. Lindhe: No, for example Ridge Preservation following tooth extraction is nowadays a common procedure all over the world. I think most dentists can manage this straightforward technique and thereby simplify the treatment. Therefore, I have claimed many times: following tooth extraction, care for the ridge! But when it comes to using autologous grafts or combining patient tissue and biomaterial, when it comes to larger augmentations or more difficult soft tissue management, the individual clinician skills are still very important.

What is the biggest breakthrough you hope for in the near future of regenerative dentistry?

Prof. Lindhe: The identification of a growth factor locally stimulating cementoblasts to produce new root cementum, because in order to create new tooth attachment, you first have to produce a docking site at the root surface for the fibres of the periodontal ligament. Without this, the fibres cannot invest and, subsequently, the newly formed periodontal ligament cannot support the tooth. This growth factor product will come sooner or later.

So, with this you think that within the next 20 or 30 years we will be able to turn teeth severely compromised with periodontitis into an aesthetically acceptable state without extracting them?

Prof. Lindhe: Yes, I do. But again, what is aesthetically acceptable? The photos we see at the congresses with lifted lips – this is not how the patient appears in daily life. Patients are frequently much happier with the aesthetic appearance of their teeth than a dental professional, who cares about every portion of a millimetre. Frequently those who are specialists in a field have completely different demands than the rest of the world.

> "The new generation of dentists is much less impressed by the features of dental implants then we were."

Do you think that the research on Geistlich biomaterials has contributed to a better understanding of human bone and bone regeneration?

Prof. Lindhe: Absolutely. For Periodontists, what matters are the tooth and the tooth-retaining structures – periodontal ligament and root cementum. So, before Geistlich came, bone was just the hard wall between the roots. Then, suddenly, one asked how new bone was formed around Geistlich Bio-Oss® and how the particles were being resorbed. Not only Geistlich but also the Osteology Foundation has played a very important role in this. Their research funding, their national and international symposia and, nowadays, their research training seminars have all contributed and continue to contribute to worldwide interest and knowledge. So we are very proud of what we have achieved in this field.

You were one of the founding members when the Osteology Foundation was established in 2003.

Prof. Lindhe: Yes, I was. The Osteology Foundation was a generous gift made by Dr. Peter Geistlich, and he managed to set up this foundation as an independent institution. This was a very courageous move for him. But he was very proud of his products, and he was strongly convinced of their features. So, he said, let's test them, and let's compare them to other products under the most scientific terms.

Thank you very much, Prof. Lindhe!

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Taking the patient's view into account

Dr. Michael McGuire | USA
PerioHealth Professionals, Houston
Chairman, The McGuire Institute
(a not for profit, practice-based
clinical research network)

Interview conducted by Verena Vermeulen

Objective treatment outcomes are measurable and comparable. However, it is also worth taking the patient's subjective measures into account. This is the goal of "patient-reported outcomes."

Can you remember the last time you were unhappy as a patient?

Dr. McGuire (laughs): A few years ago I was having a stress test, and after extensive preparations, it turned out the doctor was not going to be there because he had an emergency surgery. And they didn't even cover the cost of my parking ticket! But, well, my unhappiness was obviously not related to a miserable treatment itself.

When did you become interested in patient satisfaction from a professional point of view?

Dr. McGuire: When you are in private practice, your patients' satisfaction is "job one." Therefore, I have always been interested. Nonetheless, about five or six years ago, I became concerned with the more formal aspects of measuring patient reported outcomes (PRO's).

Why?

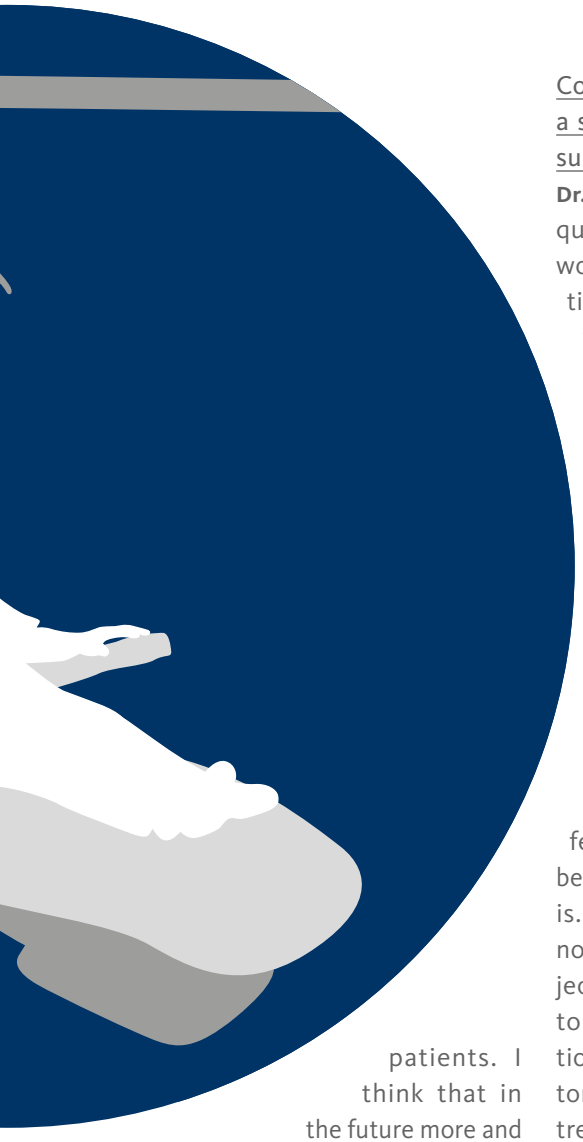
Dr. McGuire: Take, for example, a surgery that requires a remote tissue donor site – so a second surgery associated with additional morbidity. It is very easy to say intuitively that this additional surgery is something a patient would rather not have; however, it is hard to find measured reports in the literature – to provide scientific evidence for something that our patients really experience is very challenging.

But is the patient's own view on his or her treatment really important?

Dr. McGuire: Yes, because we must strive to meet the real need. What a clinician thinks a patient wants is not necessarily what the patient really wants. Let's have a look again at the surgery with the donor site. We did some studies on recession coverage with autologous soft tissue versus biomaterials. When we measured the aesthetic satisfaction, it was exactly the same for both groups, even if the autologous graft was statistically slightly superior. But the difference was so small that the patients didn't realize it. So, sometimes we, as professionals, beat ourselves up about a 10th of a millimetre, while our patients really don't care.

What is it that the patient does care about?

Dr. McGuire: Patients largely care about comfort, cosmetics and convenience – the three C's. If we can provide these, most of the time we satisfy our



patients. I think that in the future more and more treatment alternatives will likely be chosen over "gold standard" therapies based off of PROs rather than traditional clinical measurements.

Could this mean that a therapy with a slightly poorer outcome becomes superior?

Dr. McGuire: I was struggling with this question for a very long time. Why would you want to provide your patient something that is not the very, very best of what you can do? It has taken me a while to understand that you have to look at all parts of a procedure, not just at how much root is covered; but rather, how much time did the treatment take, how much discomfort was involved, and what was the aesthetic outcome?

And do all patients value the same things, such as shorter treatment time or less pain?

Dr. McGuire: No, everybody is different. A football player might not be tough at all, while a fragile old lady is. The key in working with PROs is not just to collect the patients' subjective assessments afterwards, but to take their wishes, their expectations, maybe also their personal histories into account, when planning a treatment.

What is it that matters most to the patient when it comes to regenerative treatments such as GBR or soft tissue regeneration?

Dr. McGuire: Again, it's not the same for all patients. Some are very keen on aesthetics; others care more about root sensitivity; still others put a focus on their general health status. But in general, although "selling" may not be the right word, it is very easy to "sell" regeneration to the patient, because regeneration turns back the clock and gives back to the patient something they used to have and value.

Would you say that biomaterials are positive for the patient in that they help achieve positive outcomes?

Dr. McGuire: Yes, I think so. It is surely most important to achieve our treatment goals, for example, to cover a recession defect or fill an osseous defect. Nowadays we can achieve these goals with different options. This is a situation where PROs are really worth considering. They allow us to decide which procedure is not only going to provide the clinical outcome we would like to achieve but also what other aspects should be taken into account, such as treatment time, pain, patient goals and expectations. But we must beware: no single procedure is going to be best for all patients, and the incorporation of PRO's will allow us to tailor our treatment to each patient.

Thank you very much, Dr. McGuire!

Implant placement with GBR in the mandible: case study

Prof. Daniel Buser | Switzerland
Department of Oral Surgery and Stomatology
School of Dental Medicine, University of Berne

Circumferential bone anchorage in the alveolar ridge is key to the long-term success of an implant. Therefore, bone defects at the implant site have to be corrected by means of GBR.

The same surgical technique with simultaneous GBR therapy presented in this case report has been used at our clinic since the turn of the century. In addition, the long-term result after 11.5 years is presented.

GBR with bone, biomaterial and membrane

The patient was referred after the extraction of two molars (36 and 37). The result was a local bone defect in region 36. The implant surgery took place about four months later. This involved a 10 mm long tissue level implant (Straumann AG, Basel) inserted in the correct prosthetic position with good primary stability. There was a medium-sized buccal bone defect with a favourable 2-wall defect morphology. This defect was filled initially with locally harvested, autologous bone chips and then covered with Geistlich Bio-Oss® granules. The graft was covered with a Geistlich Bio-Gide® membrane applied in a double layer. After the periosteal incision, the tension-free primary wound closure concluded the procedure. Five months later the implant was uncovered and prosthetic restoration was performed by the referring colleague.
The clinical examination after 11.5 years revealed a peri-implant mucosa that was free of inflammation, and the radiograph showed stable bone crest levels. A Cone Beam CT confirmed the existence of an intact buccal bone wall.

What makes the method work so well?

Two long-term studies with CBCT imaging showed excellent results with regeneration of a buccal bone wall. These results can be attributed primarily to the applied biomaterials that complement one another optimally. The locally harvested autologous bone chips stimulate new bone formation across the defect area in the early phase of healing. This stimulation is caused by growth factors in the bone matrix that are passed into the surrounding blood clot. The Geistlich Bio-Oss® granules applied have the critical function of preserving the regenerated bone volume long-term.
Various histological studies have indicated that Geistlich Bio-Oss® has a very low substitution rate. Geistlich Bio-Gide® membrane made from non-cross-linked collagen is simple to apply, has few complications, fulfils the vital barrier function for four to eight weeks and stabilizes the applied bone filler. And it does not have to be removed, because it is slowly absorbed by tissue.

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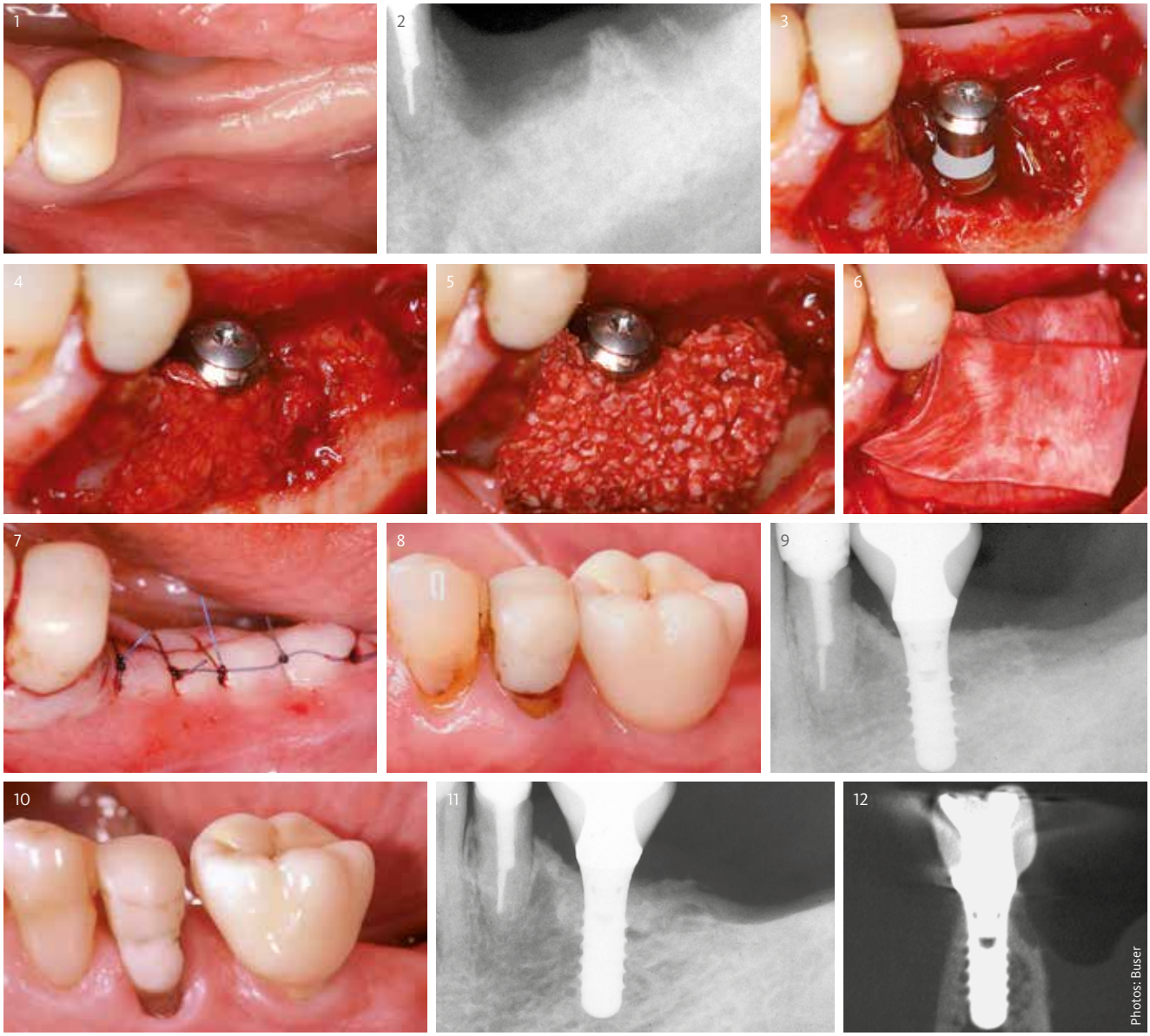
CASE



1 Situation after the extraction of tooth 36 and 37.

2 Local bone defect in region 36.

3 Buccal bone defect with dual-walled morphology.

4 Situation after implantation and filling the defect with autologous bone chips.

5 Geistlich Bio-Oss® Granulate is applied to the bone.

6 A double layer of Geistlich Bio-Gide® covers the graft.

7 Primary wound closure after periosteal incision.

8 Prosthetic restoration 1-year after implantation.

9 Radiograph findings 1-year after implantation.

10 Stable clinical situation after 11.5 years.

11 The radiograph shows a stable bone situation after 11.5 years.

12 The CBCT image shows an intact buccal bone wall after 11.5 years.

KEY STUDIES SELECTED.

Prof. Gustavo Avila-Ortiz | USA
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THE ROLE OF MEMBRANES IN GBR

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INTRODUCTION

How important are membranes for GBR treatments? Do they lead to superior bone fill? Are form-stable or resorbable membranes the better choice?

The core theoretical principles of GTR were formulated in 1976 by Dr. Anthony Melcher in his classic article entitled "On the Repair Potential of Periodontal Tissues." On the basis of these principles, Nyman and collaborators published the first histologic proof of periodontal regeneration in humans via GTR using a porous, non-resorbable cellulose membrane (sterile GS Millipore®) around a mandibular incisor, which initiated a paradigm shift in the treatment of periodontal defects.
As the early preclinical and clinical GTR studies were developed and the potential of using barrier membranes to promote osteogenesis in severe periodontal defects was proven, the concept of GBR for the reconstruction of alveolar ridge defects to facilitate implant placement emerged.

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First evidence

A preclinical study published in 1988, **Dahlin et al.** showed for the first time histologic evidence supporting the efficacy of a GBR technique, consisting of the application of an expanded polytetrafluoroethylene (ePTFE) membrane to treat standardized mandibular defects (30 rats for a total of 60 bilateral defects, left side was untreated, specimens sacrificed at 3, 6, 9, 13 and 22 weeks). Although certain variability in the regenerative outcomes was observed, which was mainly attributed to difficulties in standardizing the surgical procedure, it was concluded that the barrier clearly hindered connective tissue proliferation into the bone compartment in the early stages of healing (up to 3 weeks) and led to more robust bone healing as compared to the control sites.

- **Dahlin C, et al.: Plast Reconstr Surg 1988; 81: 672–76.**

First detailed human case series

In 1990 **Buser et al.** published the first human case series that described the GBR technique in detail and reported the clinical outcomes after treating patients in need of horizontal ridge augmentation for delayed implant placement. In 12 subjects an ePTFE membrane was used to cover alveolar ridge defects. Tenting screws to maintain the space underneath the membrane and collagen sponge fragments to stabilize the blood clot were utilized in 3 cases. The procedure failed in 3 subjects due to an early acute infection. In 2 additional patients the membrane had to be removed early due to premature exposure, but in these cases the sites continued to heal uneventfully. Following a variable 6 to 10 month healing period, sites were re-entered and implant placement was attempted in the remaining 9 patients. Implant placement was possible in all the cases. A variable bone gain of 1.5 to 5.5 mm from baseline and increased radiographic bone density in all sites were reported.

- **Buser D, et al.: Clin Oral Implants Res 1990; 1: 22–32.**

Resorbable or non-resorbable?

Whether non-resorbable membranes are more effective than resorbable membranes to obtain superior outcomes is a recurrent topic of discussion. **Zitzmann et al.** conducted a split-mouth clinical trial involving a total of 25 patients (from an original population of 72 individuals) which was aimed at evaluating the efficacy of a resorbable porcine collagen membrane for the treatment of a variety of peri-implant defects, created at the time of implant placement, as compared with an ePTFE membrane. All study sites (n=84) were treated in combination with a particulated anorganic bovine bone replacement material. No statistically significant differences in terms of defect area coverage were observed, although the net results were superior in the sites treated with the collagen membrane (92 % vs. 78 %). Furthermore, a higher incidence of complications occurred in the ePTFE group. A recently published long-term (12–14 years) follow-up study by **Jung et al.**, including 58 of the original 72 patients, reported that implant survival rate was comparable between the groups that underwent GBR procedures (Resorbable: 91.9 % / Non-resorbable: 92.6 %).

- **Zitzmann NU, et al.: Int J Oral Maxillofac Implants 1997;12: 844–52.**
- **Jung RE, et al.: Clin Oral Implants Res 2013; 24: 1065–73.**

Complications with ePTFE membranes?

In another clinical trial conducted by **Simion et al.**, a total of 18 implant fenestration or dehiscence defects in 9 patients were treated using autologous bone particles in combination with either a resorbable PLA/PGA membrane (test) or a non-resorbable ePTFE barrier (control). Sites were re-entered at 6 to 7 months. Although no statistically significant differences were observed between groups, interestingly, the results of this study contrast with those of Zitzmann et al., since bone fill was higher in the ePTFE (98 %) as compared to the resorbable membrane (88 %) sites, and no complications were reported. It is important to remark that the type of resorbable membrane was different in each study.

- **Simion M, et al.: Int J Oral Maxillofac Implants 1997; 12: 159–67.**

Membranes for sinus lift

Wallace et al. 2005 conducted a clinical trial including **51 patients** in need of maxillary sinus augmentation via lateral approach for a total of 64 sites. All sinuses were grafted using anorganic bovine bone particles. The lateral window was covered with a resorbable porcine collagen membrane in 37 sites and with an ePTFE barrier in 21 sites, while 6 sites received no membrane. No significant differences in terms of vital bone formation and implant survival were observed among groups. However, the proportion of bone formation in the sites that received no barrier was lower (12.1 %) as compared to the collagen (17.6 %) and the ePTFE membrane (16.9 %) sites.
Similarly, **Barone et al.** 2013 reported in a study involving 18 patients that the amount of vital bone formation in maxillary sinuses treated with a combination of autologous bone and a porcine xenograft was slightly lower if no barrier membrane was applied (28.1 % vs. 30.7 %).

- **Wallace SS, et al.: Int J Periodontics Restorative Dent 2005; 25: 551–59.**
- **Barone A, et al.: Clin Oral Implants Res 2013; 24: 1–6.**

Treatments compared

In a preclinical study, **Nociti Jr. et al.** evaluated the effect of different GBR protocols in the treatment of ligature-induced peri-implantitis defects in terms of vertical bone fill. A total of 30 sites in 5 mongrel dogs were randomly assigned to one of the following therapies (n=5): 1. Debridement alone; 2. Debridement plus GBR with a non-resorbable PTFE membrane and bovine xenograft particles;

3. Debridement plus GBR with a resorbable porcine collagen membrane and bovine xenograft particles; 4. Debridement plus GBR with non-resorbable PTFE membrane (without bone graft); 5. debridement plus GBR with resorbable membrane (without bone); 6. debridement plus bovine xenograft particles (without membrane).
The following average bone filling values were measured at 5 months: group 1: 14.03 %, group 2: 19.57 %, group 3: 27.77 %, group 4: 18.86 %, group 5: 21.78 %, group 6: 21.26 %. Although the treatment 3 (debridement plus GBR with resorbable porcine collagen membrane and bovine xenograft particles) outperformed the other treatments, no statistically significant differences were detected among groups.

Nociti FH, Jr., et al.: Clin Oral Implants Res 2001; 12: 115–20.

The vertically deficient alveolar ridge

It is well known that the process of osteogenesis progresses from the margins of the defect. Hence, in large non-contained osseous defects, bone formation and maturation is likely to be impaired in zones distant to the bony walls, if the clinical management is not adequate. A paradigmatic example of a challenging clinical scenario is the vertically deficient alveolar ridge.
In an important clinical study including **35 patients**, **Urban et al.** 2009 demonstrated that a GBR technique consisting of the use of autologous bone chips and ePTFE membranes is a safe and predictable approach to correct vertical bone defects regardless of the location and extension. Surgical re-entry and implant placement were done at 6 to 9 months. Implant follow-up after delivery of the final prosthesis ranged from 1 to 6 years. The mean marginal bone loss for the 81 implants placed was 1.01 mm, and the survival rate was 100 %, although 3 implants exhibited bone loss slightly over 2 mm and were not considered successful.

Urban IA, et al.: Int J Oral Maxillofac Implants 2009; 24: 502–10.

ePTFE membranes vs. microplates

In 2014, **Merli et al.** published the results of a 6-year randomized controlled trial involving a total of 22 patients who underwent vertical bone augmentation in mandibular edentulous segments and subsequent implant-supported prostheses. Eleven sites were treated using a combination of autologous bone particles and a titanium-reinforced ePTFE membrane (control), while the other 11 defects were reconstructed using osteosynthesis microplates and a porcine collagen membrane, also in conjunction with autologous bone chips (test). The mean vertical bone level gain at baseline was 2.16 mm in the test group and 2.48 mm in the control group. At the 6-year follow-up the average marginal bone loss in both groups was minimal and comparable (Test: 0.58 mm / Control: 0.49 mm). No implant failures or complications occurred after functional loading during the study period.

Merli M, et al.: Int J Oral Maxillofac Implants 2014; 29: 905–13.

VIRTUALLY IMMORTAL!

The regenerative capacity of some sea creatures can be considered “superhuman”

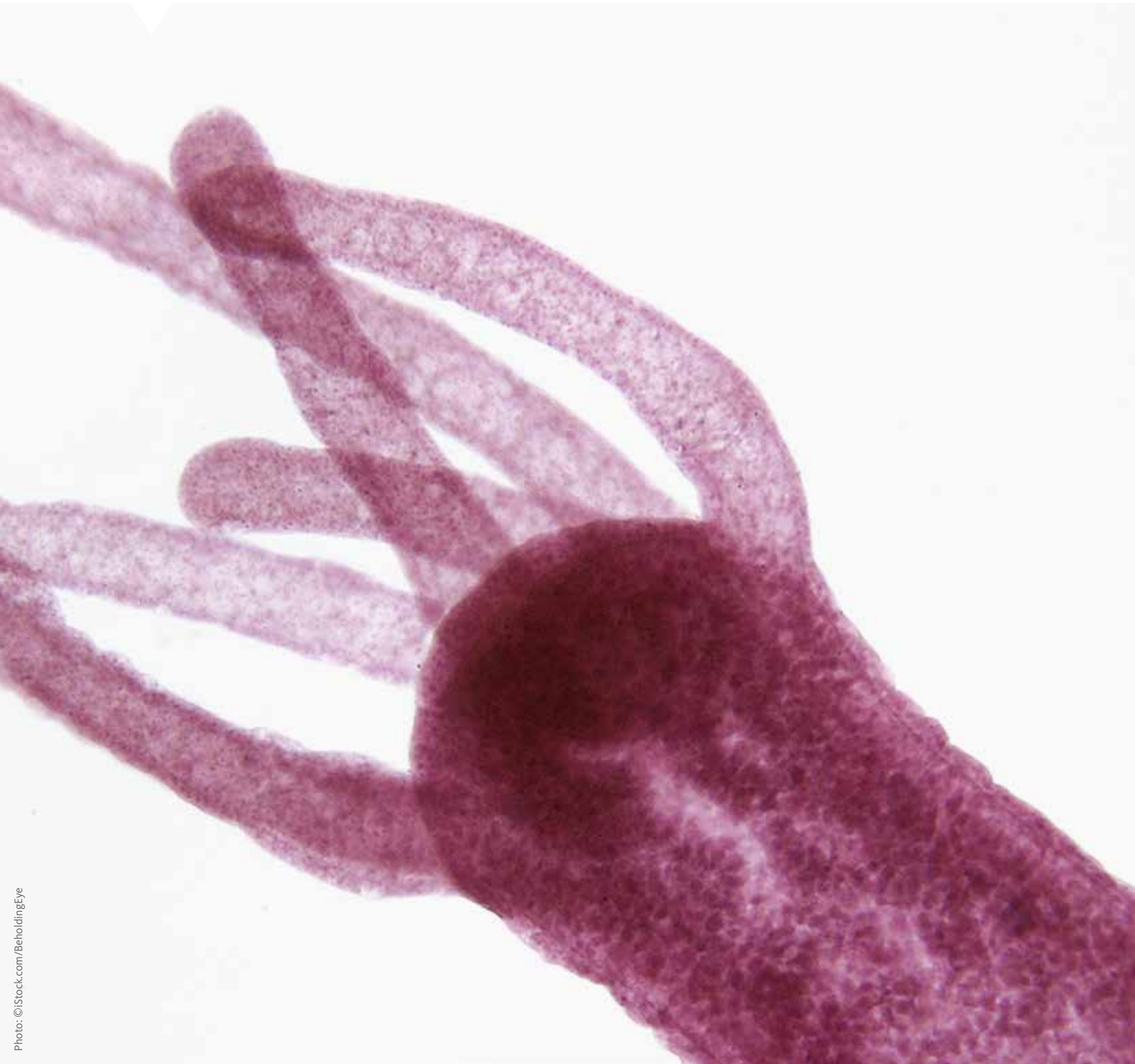

Photo: ©iStock.com/BeholdingEye

Dr. Klaus Duffner

What is the secret of longevity? With its incredible regenerative capacity, the fresh water polyp hydra possesses virtual immortality. Particular genes are crucial. They are the key to stem cells constantly renewing themselves.

When the Greek mythological hero Heracles set out to hunt down the quasi-serpentine Hydra, because she was always preying on herds of cattle, he had a problem. Whenever he lopped off one of Hydra's nine heads, she grew two more.
The Genevan scholar Abraham Trembley must have had this legend in mind when he set about describing the native fresh water polyp in the 18th century. His experiments and observations on the barely one centimetre long, tentacled animal were seminal. He cut up the polyps, but they still clung to life. What is more, the severed body parts were fully able to regenerate, thus giving rise to several completely new polyps from one animal. Trembley could not resist naming this strange organism "hydra."

Tremendous abilty to regenerate

Experiments have shown that one hydra cut into tiny sections can bring forth up to 100 complete polyps, if there are at least 300 to 500 cells in the individual parts. So-called interstitial cells (I-cells) are the key to this amazing regenerative capacity. These undifferentiated stem cells continue to be able to divide throughout their lives and are continuously forming new nerve cells, gland cells, muscle cells, germ cells and – typical for the cnidaria phylum – cnidoblasts. Hydra reproduce either asexually by bulging to produce and constrict lateral buds or sexually as hermaphrodites by discharging sperm and egg cells into the water. In turn, the new larvae are also able to form new polyps by budding. This tremendous capacity for regeneration has stimulated the imagination of many scientists. Are hydra immortal?

No aging, but death?

To probe this question, researchers at the Rostock Max-Planck institute offered the "little critters" a completely carefree life for almost ten years: constantly uniform water temperature, regular food and no predators. The findings of their recently published study? Although individuals do succumb to a natural death, the mortality rate is identical at any age. No matter whether an individual is one or ten years old, the mortality risk remains the same – unlike humans whose mortality rate increases with age. In other words, a hydra does not age, and every cell is continuously renewed. Although polyps were long considered to be immortal, experiments indicate there seems to be a natural end for them too. The life expectancy for these tiny animals is, nevertheless, extremely high, because only one out of 220 individuals dies each year.

Genes for immortality

Why are their cells so durable? In March 2010 international scientists announced that they had succeeded in completely unravelling the genome of fresh water polyps. The genetic material of primitive polyps is unexpectedly voluminous and, at approximately 20,000 genes, is just as complex as that of vertebrates. The core gene for longevity is the so-called "FoxO." It is not only found in fresh water polyps but in all animals, and it controls stem cell formation. If the FoxO gene is ex-

perimentally "switched off" in hydra, stem cell activity slows down drastically. The animal's immune system also weakens. We humans also lose more stem cells as we age, and the remaining cells become less active. This is why aging tissues are so difficult to regenerate. Conversely, postcentenarians have been found to have particularly high levels of active FoxO, which gives rise to the name "Methuselah gene." Aging processes are no issue for hydra. A polyp can replace its full complement of body cells in only five days. For this reason the researchers are certain that a hydra's FoxO genes are the key to understanding (an infinitely) long life

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Return to the roots

The first known case of a sexually mature, multicellular organism regressesing to an immature lifeform is the cnidarian *Turritopsis dohrnii*, which inhabits numerous oceans (including the Mediterranean).

Whereas most jellyfish die after depositing sperm and eggs in water, the jellyfish *Turritopsis*, which is only half a centimetre long, sinks down to the seabed after reproduction and regresses to a gelatinous mass. But this amorphous mass soon develops into a new, genetically identical polyp, which then goes on to discharge new jellyfish.

The *Turritopsis* thus undergoes rejuvenation along with regressive aging. As this process can theoretically repeat itself indefinitely, it is regarded as as a key to "immortality."

Ferdinando Boero, one of the authors who published a detailed paper in 1996 on the lifecycle of *Turritopsis dohrnii* ("The reversal of the lifecycle"), compared this regression to a butterfly, which, instead of dying, can regress to a caterpillar. This transformation can occur when environmental conditions worsen or when the animals are harmed. As they regress, they benefit from an unusual ability called "cellular transdifferentiation," wherein mature cells are able to transform into totally different cell types, e.g., from a gland cell into a neuron.

Although laboratory studies indicate that 100 percent of the *Turritopsis* can undergo the recovery process, the transformation has not yet been observed in a natural sea habitat. This, say the biologists, is related to the rapid unfolding of the process, making the likelihood of observing such a phenomenon in naure extremely low.

Although one might think studying the mechanism that leads to "eternal life" ought to be a field of research with much potential, amazingly few scientists in the world are involved with these animals. One of them is Shin Kubota from Shirahama, Japan, a small coastal town south of Kyoto. The zoologist is convinced that both oncology and gerentology could benefit from the findings that are slumbering in jellyfish. Kubota is one of the few experts worldwide who has managed extended culture of the delicate animals in the laboratory.

Although cnidarians are one of the most primitive organisms, their genome shares an amazing number of similarities with higher animals and, thus, also humans. They provide us an exciting opportunity to explore "eternal life."

Photo: ©iStock.com/Alejandro Barrio Martínez

BACKGROUND.

Geistlich Pharma & Osteology Foundation

Visiting a cell laboratory

Interview conducted by Verena Vermeulen

How do human cells respond to biomaterials? And how can the interaction be further improved? Geistlich traces these questions in its cell laboratory.

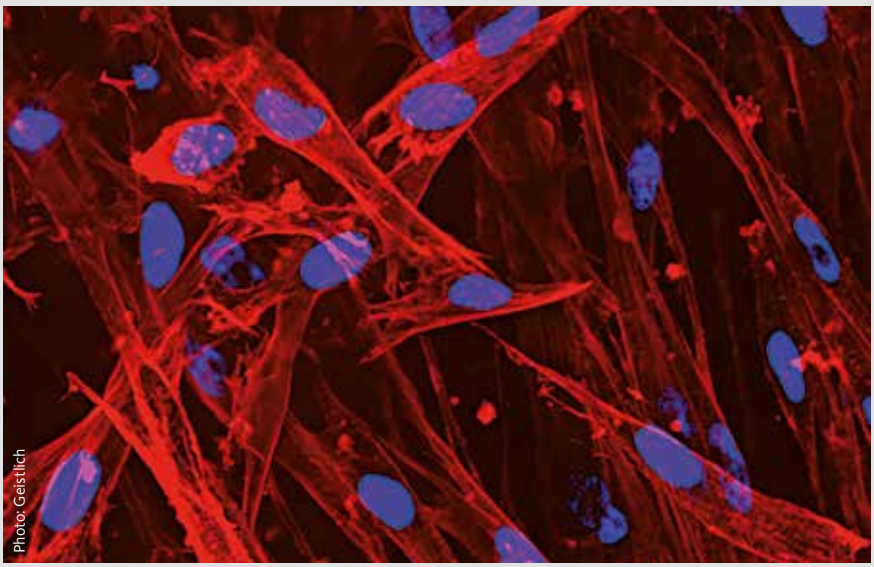
The human body, taken at a cellular level, has long ceased being the closed village community that it was once considered to be. In 1890 Themistocles Gluck fitted the first artificial knee joint in Berlin. Since then, foreign matter within the body has become almost a matter of routine. There are now 950,000 artificial hip and knee joints implanted each year, just in Europe. To this can be added 6 million dental implants, 2 million of which are accompanied by bone replacement augmentation.

An entire arm of research is now concerned with perfectly integrating biomaterials into human tissue. How do cells respond to the impostor? How can integration be made better, faster and with fewer complications?

At Geistlich Pharma's research site in Wolhusen, a research team is dedicated to these questions. Seven biologists are currently working on investigating the precise interactions between somatic cells and Geistlich biomaterials. Research group leader Dr. Paul Buxton explains to us why this cell research is important.

Dr. Paul Buxton in the interview with Geistlich News.

Photo: Alfons Gut



For approximately five years Geistlich Pharma has conducted cell research at an advanced level. The researchers investigate, for example, which RNA and which proteins are being expressed in different cell types – depending on their surroundings and the biomaterials with which they interact. The cells are grown in incubators that imitate the conditions of the human body.

Gingival fibroblasts on Geistlich Bio-Gide®.

Geistlich has its own laboratory for testing how cells react to our products. For what exactly are you looking?

Dr. Buxton: We test, for example, different variants of a new bone replacement biomaterial, or we vary specific parameters in the production of Geistlich Bio-Oss®. The key question then is: how does the new product affect the bone-forming cells? What variant best promotes osteogenesis?

So, before testing the products on animals or humans?

Dr. Buxton: Precisely. Cell tests make it possible for us to compare biomaterials at a very early stage of development. Still, findings about cell behaviour in a test tube alone are insufficient. Cell tests have to be so well controlled that they really allow conclusions about the situation in a patient. In a certain way this, in turn, is more chaotic, as many different cell types are involved.

Is it at all possible to make such reliable statements with cells such as, for example, with a mechanical tear-resistance test?

Dr. Buxton: To some extent yes. Let's take, for instance, collagen structures. For the cells these fibres are their home, and they detect the tiniest differences.
Certain structures have a function for these cells, others do not, although this is nearly impossible to see "from the outside." Neither can we calculate it from the chemical, physical and mechanical description of a product, although there are rules. For example, soft materials tend to give rise to neural cell types during cell differentiation, while stiff materials tend to give rise to bone cells, but these hypotheses always require individual tests.

You also analyse expression patterns. To what end?

Dr. Buxton: To compare which genes are transcribed in mesenchymal stem cells in various situations or on various biomaterials. This, in turn, allows conclusions about how these stem cells further differentiate, and whether they multiply.
Such tests permit "objective" statements on whether a product, for instance, promotes the production of bone-forming cells.

Does your research confirm the general wisdom: the more natural the better?

Dr. Buxton: Nature is certainly a good starting point because cells accept natural biomaterials best. Therefore, Geistlich focuses on preparing its biomaterials as "gently" as possible.
On the other hand it is nonsensical to only imitate nature without first understanding it. We remained unsuccessful as long as we continued to design, for example, a flying machine just like a bird. Only when we let go of the natural template did "artificial birds" actually take to the sky.

What does this signify for the development of new products?

Dr. Buxton: Our cell research also puts us in a position to fully understand what happens during regeneration and why our materials work so well.
We have made some very interesting discoveries in this area, mainly regarding the differentiation of mesenchymal stem cells into osteoblasts. Now we

Photos: Alfons Gut

would like to use the discovered mechanisms further... so not just creating new products by "trial & error," but by thoroughly understanding interactions at a cellular level.

Is there such intensive cell research at other companies, too?

Dr. Buxton: Biological tests on biomaterials are normal. However, it is no doubt very rare within a company focussing on dental applications to conduct, for example, cell research with prototypes as systematically as we do. Geistlich has set a very high scientific standard.

What can ideally be achieved through such research?

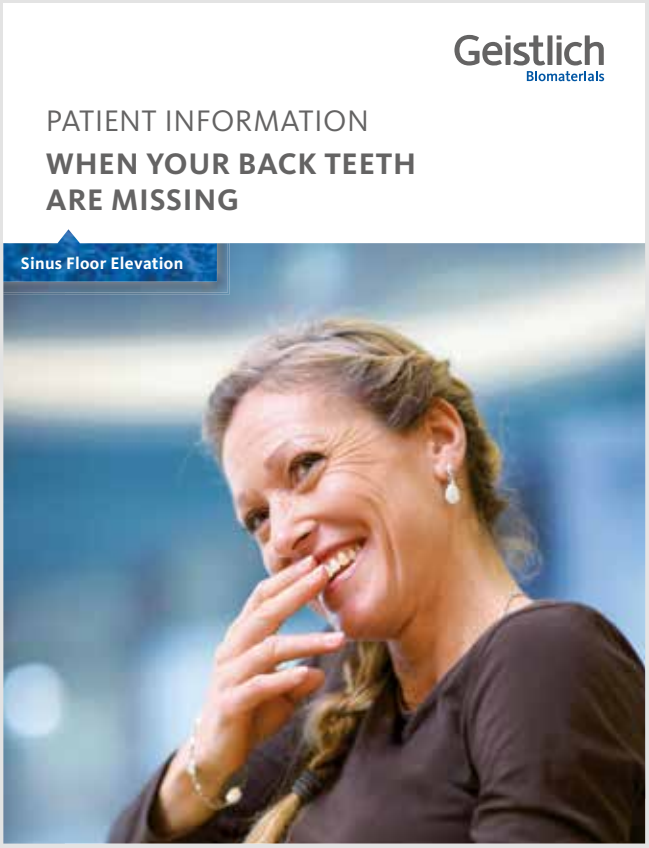
Dr. Buxton: If a good biomaterial contributes to lowering the complication rate by one percent, for a million patients that at least means 10,000 better treatment results.

Well-informed patients have fewer worries

Susanne Schick

The internet, news reports, television or a neighbour's advice? Nowadays interested patients often inform themselves independently about medicine and medical technology before they consult a doctor.

To help you easily inform your patients about upcoming treatments, Geistlich Pharma provides a specially prepared patient information package.



Tailored information

Brochures with details about individual indications, as well as individually organised notepads and a personal biomaterial pass for patients, form the core of the new Geistlich patient information package. The brochures are divided into typical indications: extraction socket management, minor bone augmentations, major bone augmentations, periodontitis, sinus floor elevation and soft tissue regeneration, when there is insufficient keratinised tissue or gingival recession.

As a dentist you can use the indication-specific notepads for support: notepads with ready-made diagrams help you outline the treatment for your patients and provide them with a reminder of and reference for their therapy.
After surgery has taken place patients can view the Geistlich biomaterials that have been used in their personal biomaterial pass. An additional benefit: traceability is supported in the event of a follow-up or a new procedure.

Would you like to help inform your patients with a Geistlich patient information package? Contact your Geistlich partner for further details.

Better informed...

The patient information tools from Geistlich Pharma provide fundamental information about:

- Existing disease or pathology and its course of therapy,
- Advantages of treatment,
- Advice for better success (patient compliance),
- Biomaterials from Geistlich Pharma used in the procedure.

The "Presenter's kit": Version 2016

Dr. Varvara Mitropoulos

The USB stick with helpful material for presentations is available once again. Request yours now.

Geistlich Pharma is offering its collected knowledge and collected expertise in dental regeneration to speakers in the "Presenter's kit." The "Presenter's kit" USB stick contains over 170 images and videos – from product pictures to application illustrations, rare scanning electron microscope images and collagen expert information. The kit is supplemented with study summaries, product information and much more. The kit materials can be integrated into lecture presentations, courses or workshops.

Are you interested in a "Presenter's kit", or do you want to provide us with feedback? If so, email us at: presenterskit@geistlich.ch

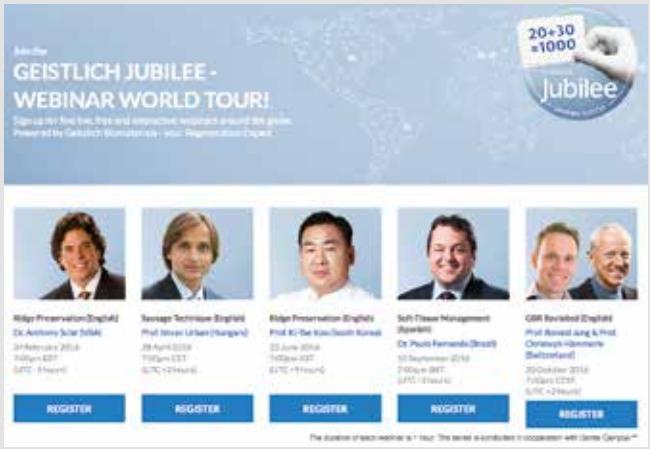
20 + 30 = 1000 – the formula for "Leading Regeneration"

Evelyn Meiforth

How does a scientific company arrive at the equation "20+30=1000"? The answer is easy: 20 years of Geistlich Bio-Gide® and 30 years of Geistlich Bio-Oss® equate to 1000 studies of Geistlich biomaterials.

Every anniversary in itself is exceptional. Celebrating all three anniversaries in 2016 is a milestone in regenerative dentistry.
For Geistlich Pharma it is not enough to reflect on our pioneering achievements of the past. We also hope to mould the future of regenerative dentistry and share regenerative knowledge. So Geistlich is launching two global projects in its anniversary year: The anniversary page, **www.geistlich-jubilee.com**, where clinical cases, publications and statements can be shared, and the global **Geistlich Jubilee – Webinar World Tour –** a series of five webinars in different time zones – all live, free, interactive and with world class experts. For further information, go to: www.dental-campus.com/geistlich_webinar.

Clinicians can participate with cases, statements and publications at www.geistlich-jubilee.com



Register now for the webinars that Geistlich is organising in 2016.

A strong combination – expanded!

Turgut Gülay

Geistlich Bio-Oss® now comes in a new pack size: 1.0 g.

With Geistlich Bio-Oss® 1.0 g, Geistlich Pharma is extending its regenerative dentistry product range. The new size offers more flexibility with GBR treatments like ridge and sinus augmentation, where excellent long-term results with predictable implant survival rates of 91.9 % have been reported after 12–14 years[1].
In the new flyer, Prof. Matteo Chiapasco, Italy, shares a successful case study using Geistlich Bio-Oss® 1.0 g.

Link to the product flyer:

References

1 Jung RE, et al.: Clin Oral Implants Res 2013; 24(10): 1065–73.

Welcome to **“THE BOX”!**

Dr. Heike Fania

The Osteology Foundation networks scientists and practitioners in a global context. In **THE BOX** a new global online platform has been created that not only enables discussions between users worldwide, but also provides innovative content and tools for everyday research and practice.

Since its creation in 2003 the Osteology Foundation has been committed to training scientists and practitioners and promoting research in oral tissue regeneration. True to its motto “Linking Science & Practice in Oral Regeneration,” the focus is on promoting dialogue between practitioners and scientists.

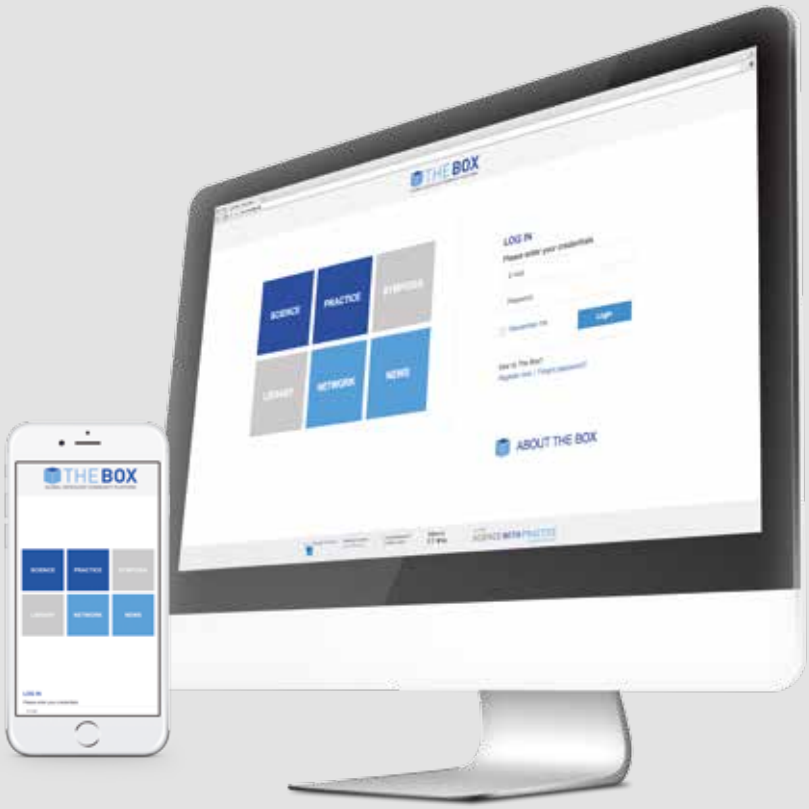
In a constantly growing global environment this networking across frontiers and continents is becoming increasingly important. A major challenge for the Osteology Foundation now is to not only educate but also to spread knowledge to as many people as possible – to network experts, scientists and practitioners and students worldwide. Ultimately, only by disseminating new knowledge more efficiently in the future can it be made available to doctors effectively in everyday practice.

Taking this challenge as a starting point, the Osteology Foundation has decided to develop the global Osteology Community Platform **THE BOX**. This is where scientists and practitioners can find information and tools for their research and everyday practice and can contact, network and enter into dialogue with specialists worldwide. Furthermore, all of the Osteology Foundation’s pre-existing activities and courses are also digitally supplemented and supported.

Photo: ©iStock.com/poba

Join the Osteology community!

THE BOX is still in its infancy, exciting content and functions already exist. Nearly 2,000 users have already registered and use the online platform, which was officially premiered at the International Osteology Symposium in April 2016 in Monaco.



SCIENCE

In the **Science** section, scientists can plan projects using the **Osteology Research Wizard**, which guides users step-by-step through the process, reminds them of relevant points and keeps additional information and links ready. In the online version of the **Osteology Research Guidelines**, researchers can find details about different scientific protocols as well as required background science.

PRACTICE

The **Practice** section makes the **Osteology CASE BOX** available to all practitioners, to document clinical cases from the field of oral regeneration in a user friendly and flexible way, to analyse and, if required, to publish – or just to share and discuss the cases with colleagues. In the public case collection, users can click through other users' cases and compare them with their own results.

Learn – Interact – Discuss!

And **THE BOX** offers yet more. **Network** – network with colleagues and find new contacts, look up information and documents in the **Library** and browse the abstracts and posters from scientific **Symposia**. And, of course, there is always the latest News about the Osteology Foundation in **THE BOX**.

My BOX – My individual cockpit

To simplify navigation and have everything immediately at hand, there is **My BOX**. Here a user can find everything that he or she has stored in **THE BOX** or what he has been contributed. In **My BOX** you can view, edit and administer your own grant and scholarship requests, poster abstracts, cases and research projects. In addition, you can find your personal course documents and certificates, bookmarks, a summary of your own contacts and groups and what's new.

Find out for yourself what **THE BOX** has for you, and join the global Osteology Community. You can register once and access **THE BOX** at no cost.

Register now,
it's free!
www.box.osteology.org

A chat with Pam McClain

Interview conducted by Reto Falk

Aurora, Colorado, your home town, is located at an average altitude of about 1700 meters (5500 feet). How do you feel down here in Orlando?

Dr. McClain (laughs): I can breathe much easier. The air is not as thin. But I love where I live, so...

You just became a member of the Education Committee of the Osteology Foundation. What is your personal goal for this new position?

Dr. McClain: As a Periodontist, I want to make sure that we really talk about what we can do to preserve the natural dentition, especially with regenerative approaches.

Do you see big improvements in this field?

Dr. McClain: Yes, both diagnostically as well as from a treatment standpoint, there have been significant advances in the field of periodontal regeneration.
It's exciting to see the pendulum swinging from extracting teeth and placing implants to saving teeth using regenerative approaches.

Your father is a renowned Periodontist too. Now you are practicing together with your father, your sister and your niece. Is periodontology THE topic at family gatherings?

Dr. McClain (laughs): We are a very large family, so actually, no. My husband is not a dentist, neither are my four brothers. But when the four of us from the dental practice are together, the conversations easily shift to teeth!

Does the new generation challenge the old generation, or vice versa?

Dr. McClain: My dad has been an incredible mentor and continues to educate and encourage us to strive for excellence. Having my niece Dr. Rachel Schallhorn join the practice has definitely expanded our use of technology and brings a fresh perspective. Being in the middle of these two generations is a huge advantage, as I glean incredible information from both.

When you are not working, what is your favorite hobby?

Dr. McClain: I grew up in Colorado, so I love hiking and biking, skiing and swimming. Golf is a newer hobby for me, and it continues to be a challenge, but it's something my husband and I can enjoy together wherever we go.

Photo : Ben Lenz

Dr. Pamela McClain has maintained a full-time private practice in periodontics incorporating clinical research since 1987 and is an Associate Clinical Professor in the Department of Surgical Dentistry at the School of Dental Medicine, University of Colorado. She is a past-president of the American Academy of Periodontology (2012) and joined the Osteology Foundation Board in 2015. We met her at the AAP Congress in Orlando.

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Will be published in October 2016.

FOCUS

Diagnosis and case planning

How to thoroughly plan regenerative procedures

JOURNAL CLUB

Sinus lift

When to use which technique and with what biomaterials?

BACKGROUND

Jubilee

Geistlich is celebrating 20 years of Geistlich Bio-Gide® and 30 years of Geistlich Bio-Oss®

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www.geistlich-pharma.com

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