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# Implant Surface Design: Using Biotechnology to Enhance Osseointegration

The successful osseointegration of dental implants depends on the types of implant-to-bone interactions that occur at the point of contact. Dental implant surfaces play a key role in these interactions. The initial migration of cells, and their adherence, proliferation, and differentiation directly affect how bone forms, as well as the quality of the bone.

The CELLplus (DENTSPLY Friadent; Mannheim, Germany) implant surface possesses a homogenous surface morphology, which positively influences cell attachment and improves bone apposition to implants. BioPoreStructuring (an etching process derived from the semiconductor and pharmaceutical industries) is used to create CELLplus, according to **Peter Gehrke, DDS**, prosthodontist and Global Marketing Director, DENTSPLY Friadent, and **Jörg Neugebauer, D.D.S.**, Dentist, and Implant Specialist at University of Cologne, Department of Craniofacial and Plastic Surgery.

According to Gehrke, "CELLplus represents the further development of the first micro-retentive grit-blasted/acid-etched titanium oxide surface introduced 15 years ago by Friadent." He adds that CELLplus represents the "latest developments in microdesign and production, opening new, innovative technologies,that until now were unavailable" in implant dentistry. According to Neugebauer, "We have done what other dental supply manufacturers have been unable to do with the surfaces of their implants. With the new CELLplus surface, Friadent fulfilled the requirements for dental implants arising from the latest scientific knowledge on surface morphology."

## The CELLplus Surface Design

The Friadent CELLplus surface is created using an automated process called BioPoreStructuring, which includes both semiconductor-microchip thermal etching and highly purified water treatment technology, modeled after that used in the pharmaceutical industry. The CELLplus surface is a textured, micro-retentive titanium surface achieved by grit blasting and specific innovative high-temperature acid etching.

The blasting material provides a defined macrostructure, while small micropores are created by etching with mineral acids.

According to Neugebauer, "We take a previously existing, well documented surface and then modify and enhance it."

Friadent BioPoreStructuring was developed in close cooperation with leading companies in the field of etching technology and computer chip manufacturing. This fully automated, high-temperature etching technique allows for precise setting and maintenance of all process parameters. BioPore-Structuring was enhanced through a series of complex experiments to ensure the homogenous microstructure of the implant surface. Consequently, a precise and consistent surface texture is achieved. All of the process steps are carried out under clean room conditions. Friadent uses highly purified water to rinse the etched surface, the same kind of water that is used in the pharmaceutical industry. Neugebauer points out that Friadent is probably the only implant manufacturer that utilizes a fully automated and monitored process to microstructure its implant surfaces.

## How CELLplus Works

The characteristics of CELLplus are unique. Typically, dental implant systems demonstrate bone growing from bone to the implant surface. With CELLplus, bone grows not only from bone to the implant surface but also, in essence, from implant surface back to bone.

Gehrke explains that any endosseous healing compartment will display distance and contact osteogenesis. Osteogenesis at the implant interface represents the balance of these two distinctly different phenomena by which bone can become juxtaposed with an implant surface. In distance-osteogenesis the osteogenic cells line the old bone surface, and the extracellular matrix establishes the implant surface contact. The blood supply to these cells is between the cells and the implant and bone is laid down on the old bone surface. "The implant surface," Gehrke continues, "will always be partially obscured from bone by intervening cells and the general connective tissue extracellular matrix."

In the case of contact osteogenesis, cells have first been recruited to the implant surface, as shown with the Friadent CELLplus surface. "The blood supply is between the cells and the old bone," Gehrke notes. New bone formation is laid down directly on the implant surface. The developing bone matrix can directly interlock within the surface morphology. Animal studies have shown large numbers of direct contacts of osteogenesis starting from the CELLplus surface with the bone growth not only in soft bone but also in cortical bone.[1-3] "We see a direct growth of bone starting at the surface," Neugebauer states, "and this is proven by these animal studies. Also, the variation of the bone contact is very small, so we see a very homogenous osseointegration of the implant over the whole implant surface."

According to Gehrke and Neugebauer, the enhancement of the implant surface affects the cells and the integration of the implant because during initial bone healing, CELLplus enhances the early cell activity and, therefore, the apposition of new bone, resulting in an excellent secondary stability within a few weeks. The three-dimensional architecture of CELLplus represents the ideal morphology for instant cell attachment, as well as progressed cell migration, proliferation and differentiation, and the after effect of accelerated osseointegration. Very early on, the micropores allow for secure retention of cell extensions (filopodia). Gehrke notes, "This is probably the most important difference to what we have seen on the currently available Friadent DPS surface."[4]

## Advantages and Disadvantages of the CELLplus Surface

The advantages of the CELLplus surface include its superiority to comparable systems, its use in



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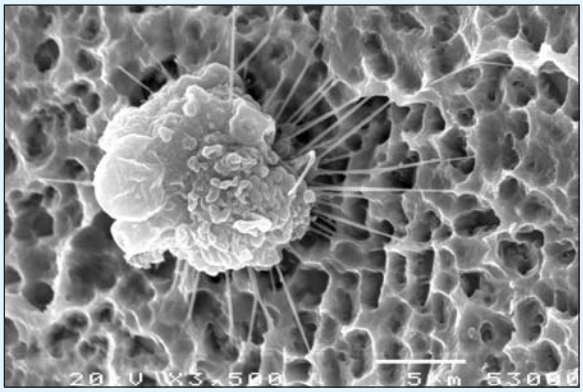

*Figure 1: Initial contact and anchorage of osteoblast via small extensions (filapodia) on CELLplus.*

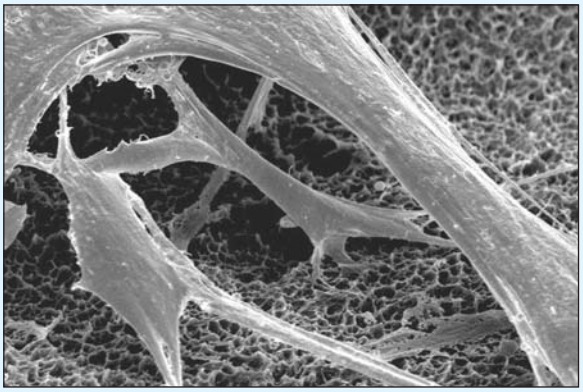

*Figure 2: Cells on CELLplus typically form widespread multifocal contacts, connecting each other, spanning surface pores and cavities over long distances. Cell chains consist of 3-6 cells, each approximately 30 µm long.*

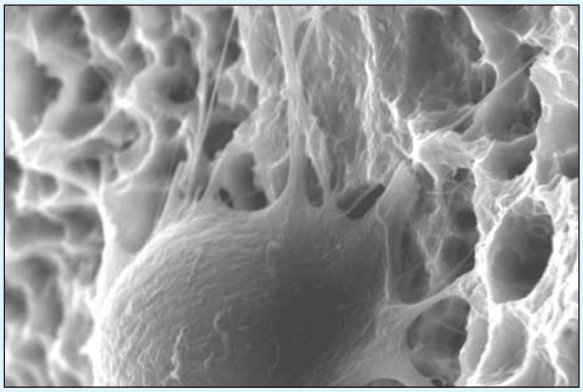

*Figure 3: Cell at stage 2—extension of lamellipodia form close contact with CELLplus.*

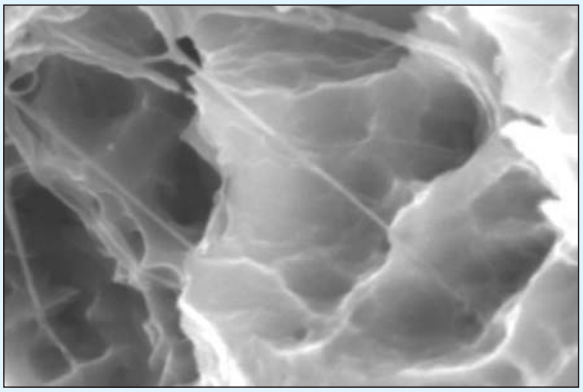

*Figure 4: Cell at stage 2—filapodia span across surface pores, enter them, or wrap around protruding ridges.*

compromised alveolar bone, and its complementary use with other biological enhancements for osseointegration. A disadvantage is the sensitivity of the new surface as it can be visibly manipulated by using gloves, e.g.

*CELLplus vs. Other Implants.* According to Neugebauer, what sets this surface apart from other commercially available surfaces is that the growth-activating microstructure of CELLplus shows ideal wettability qualities, increasing cell attachment within the first minutes of fluid and tissue contact. Proactive cell adhesion enhances the spread and maturation of cells, along with rapid differentiation of osteoblasts and accelerated bone formation. However, before any initial bone formation can take place, the attaching cells must be able to span distances 100 times their size. The properties and surface structure of the CELLplus surface make bridging such gaps possible. The accelerated attraction of the osteoblasts that attach to the CELLplus surface creates extraordinary bone formation in the early stages of osseointegration (~25 days after implant placement).

Several studies have compared the CELLplus surface to other surfaces, determining that this surface provides better and/or faster osseointegration than other surfaces commercially available.[1-3,5,6] Gehrke states, "The most important study is probably the one that we conducted on osteoblast interactions on different micro-structured implant surfaces."[2] This was a comparative study of combined cell attachment, migration, proliferation, and differentiation performed by Dr. Rachel Sammons and coworkers at the University of Birmingham. This in vitro study on the comparison of CELLplus with six different commercially available implant surfaces included two basic methods:

- The suspension method, which compared cell attachment and spreading of osteoblasts to different implant surfaces placed in a suspension of rat cavarial osteoblasts for 30 minutes in four experiments. The cells were classified by SEM into four stages of

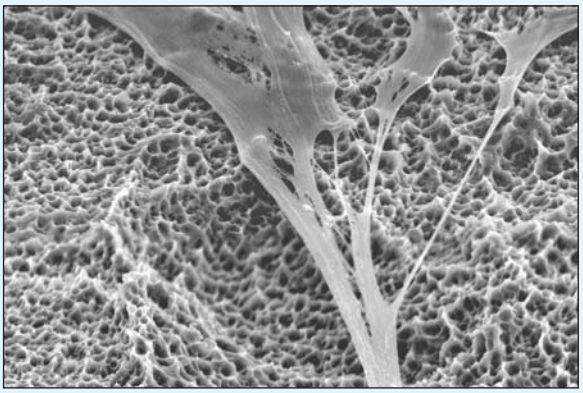

*Figure 5: Composite SEM image showing bridging cells on CELLplus surface. Original magnification 1000x; bar = 10 µm.*

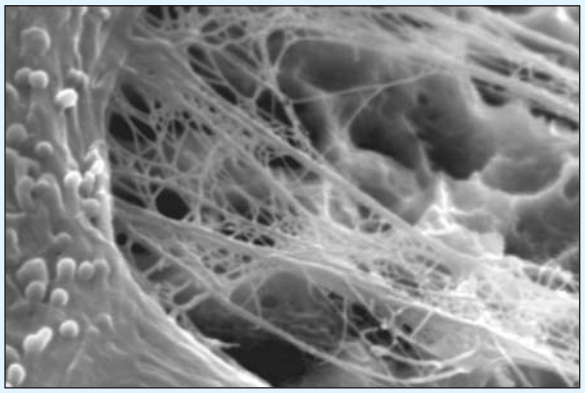

*Figure 6: Three-dimesnional appearance of cell sheet showing cell connection to CELLplus surface after four-week culture (courtesy of R. Sammons).*

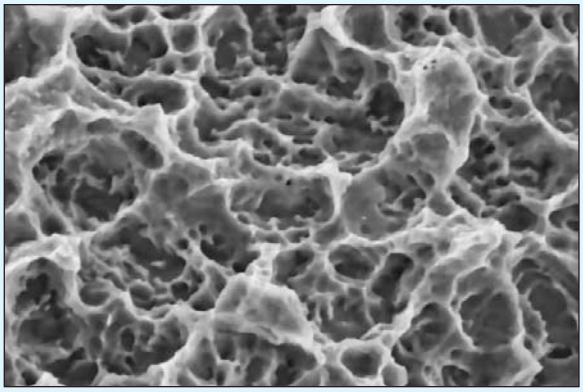

*Figure 7: SEM (3000x) of CELLplus surface structure. Bimodular topography with micropores (0.5 -1 µm) in macropits.*

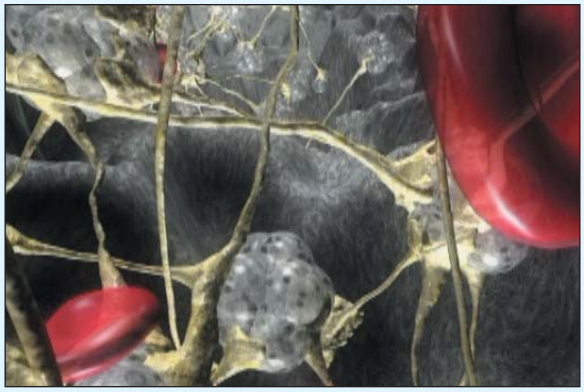

*Figure 8: Osteogenesis stage I—graphic of osteoconduction. In the first stage of bone healing, bone inducing cells (osteoblasts) migrate over temporary fibrin network (yellow) to the implant surface.*

attachment.

- The organ-culture pocket method, which compared cell migration, proliferation, and differentiation in a study model that simulates the sequences of osseointegration.

In this second model, implants were placed in infusion tubings, which had been cut lengthwise (exposed section 2 mm). The different implant surfaces were covered with rat cavarial bone fragments and then placed and sutured in nylon pocket and incubated for two or four weeks. In comparison to the six different surface modalities, CELLplus showed a unique pattern of cell spreading and progressed to later stages of cell spreading more rapidly. A significantly higher percentage of fully spread cells and more extensive cell sheets with firmer attachment to the CELLplus micropores were found. Consequently, CELLplus has proven faster osteoblast differentiation and extracellular matrix formation resulting in enhanced bone formation at the implant interface.

*CELLplus and Compromised Alveolar Bone.* Even in situations involving poor bone quality, superior structure integrity and stronger bone maturation on the implant surface provide clinically higher secondary stability. In vivo examinations of the new surface show improved bone density and intimate bone-to-implant contact.[3] The CELLplus surface demonstrates a significant increase in bone formation and accelerated osseointegration within the key healing period of three days to eight weeks. Thus, Neugebauer notes, the CELLplus surface yields faster rehabilitation of the maxilla and mandible.[5]

He points out, "Using CELLplus for type 4 bone or geriatric patients is ideal since in comparison studies with the DPS surface, we have seen more breakability of the osseointegration process under these different loading circumstances.[4] Animal studies show that the variation of

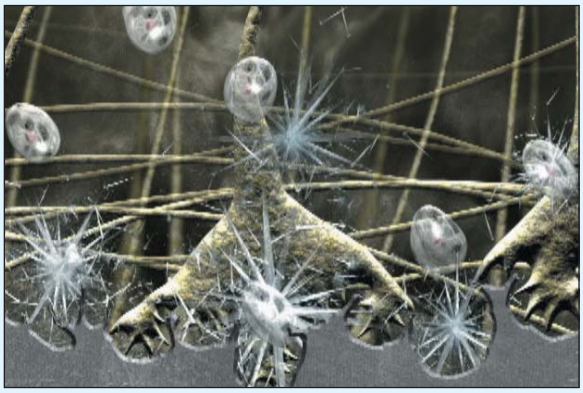

*Figure 9: Osteogenesis stage II—graphic of de novo bone formation. Extra cellular matrix (collagen) attaches itself to implant surface and mineralizes.*

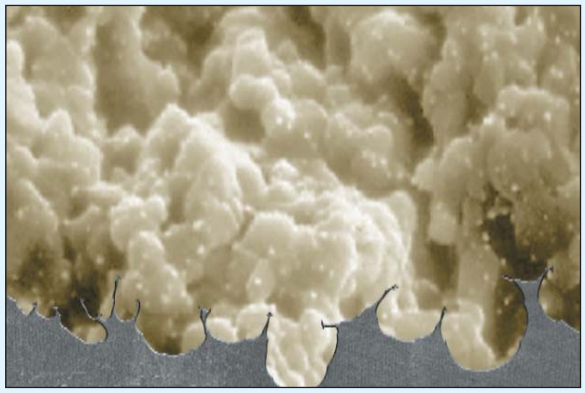

*Figure 10: Osteogenesis stage III—graphic of bone remodeling. Widespread cellular activity at implant-bone interface leads to formation of trabecular structures along collagen fibers and thus the ingrowth of new bone.*

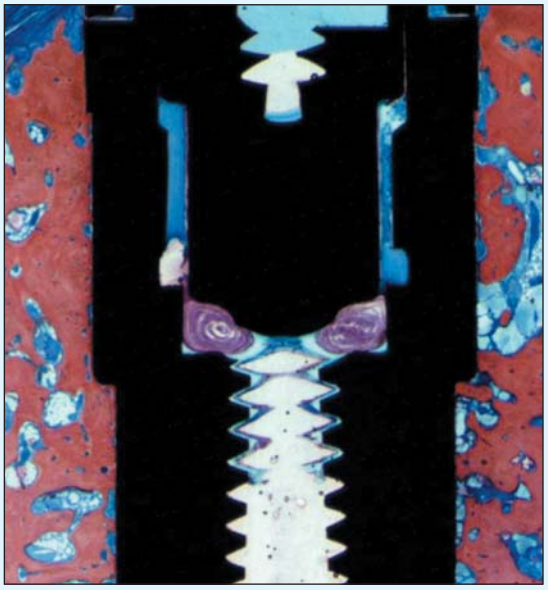

*Figure 11: Histomorphometric picture of bone-to-implant contact of CELLplus surface on Frialit® implant (courtesy of A. Novaes).*

*Figure 12: BioPoreStructuring—a process delivered from the semi-conductor industry. This process, exclusive to Dentsply Friadent, is carried out under clean room conditions with individually adjusted parameters.*

the osseointegration and the bone contact for the CELLplus surface is very small."[1-3] In the comparison study from the University of Vienna, the standard deviation of the torque and of the ISQ values was the smallest for the CELLplus surface."[5]

As CELLplus provides a faster integration as well as improved integration in less dense bone, its use in more technique-sensitive procedures (such as ridge splitting or immediate loading[11]) offers distinct advantages, starting with the critical time in osseointegration between five and 25 days. Neugebauer explains, "There are promising results from Michael Weinländer, University of Vienna, showing better bone quality and better bone formation. This observation is confirmed by studies of Arthur Novaes, University of Sao Paulo; for example, clinically, if there is more bone at the implant interface, it is probably more stable in offering secondary stability.[1] He continues, "Concerning the speed of bone formation, the results from the University of Birmingham are promising because it appears that bone mineralization and bone formation come close to the results of early bone loading." All of these findings will need to be confirmed in the ongoing clinical studies that we are performing right now."[2]

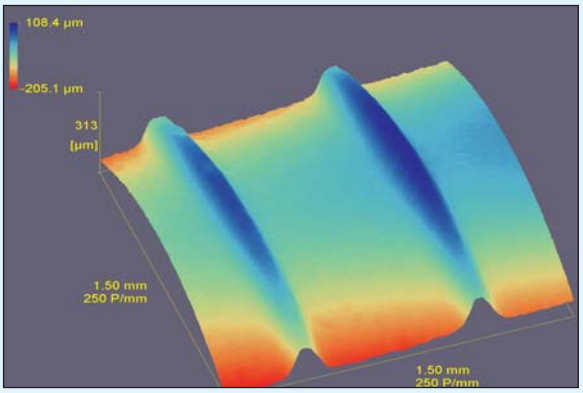


*Figure 13: Filtered three-dimensional laser scan illustrates CELLplus macrostructures (grooves/threads of XiVE implant).*

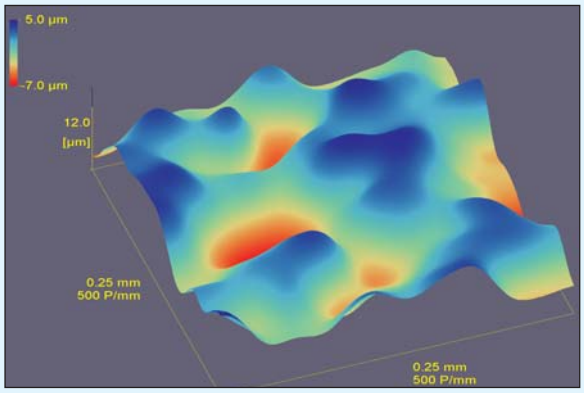


*Figure 14: CELLplus primary microstructure—roughness within range of 20-200 µm, achieved by grit blasting.*

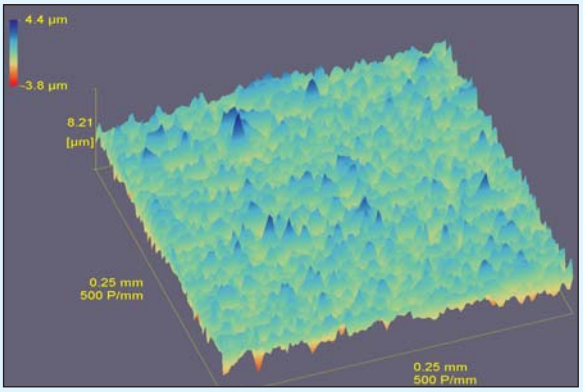


*Figure 15: CELLplus secondary microstructure—roughness within range of 0.5-20 µm, achieved by the thermal acid etching.*

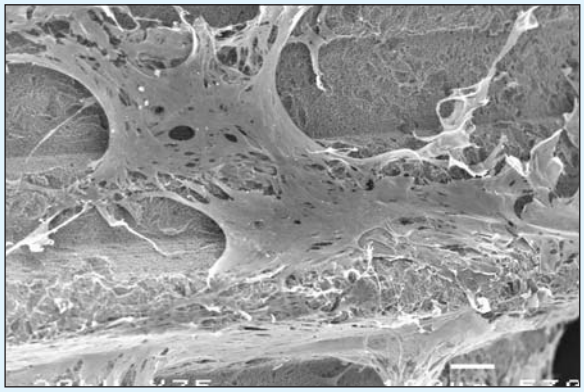

*Figure 16: Cells traversing threads of Dentsply Friadent® implant. Possible span distance of 120-350 µm (courtesy of R. Sammons).*

Neugebauer explains, "We have also conducted one study comparing the implant loading after one month to three, four, and five months and also immediate loading using the current DPS surface and the CELLplus surface.[10,12] In this study, we have seen 40% less failures with the new CELLplus surface in the period of one, two, and three months. We are now performing studies with different indications with reduced healing time or immediate loading."

*CELLplus and PRP.*Friadent CELLplus has ideal wettability qualities that allow for increased cell attachment within the first minutes of fluid and tissue contact.[7,8] Initially, CELLplus is lipophilic, which favors the connection of proteins and the formation of a temporary fibrin network. Bone-inducing cells (osteoblasts) quickly adhere to the implant surface via this fibrin scaffold. Biomolecules, such as lipids and proteins, cause a dynamic change in the surface wettability to hydrophilic. It is at this point that optimal blood supply between local bone and bone cells on the surface of the implant is achieved.

"Hypothesizing along these lines," Gehrke explains, "what we have done is modified the surface to increase the fibrin connection to it. If you were also to increase the fibrin and the fibrin contact in that interface by spraying on Platelet Rich Plasma (PRP) into the socket before placement of that implant, you have now enhanced essentially, the biology and the surface. By doing both, you would expect a greater response than you are getting just with enhancing the surface."

He cautions, however, "This is quite a difficult question to answer because there always seems to be some doubt about how PRP works

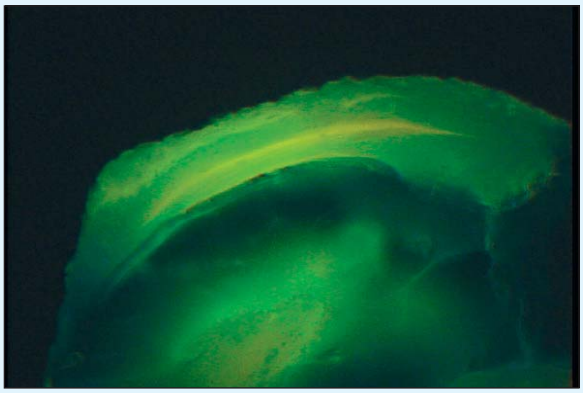

*Figure 17: Contact osteogenesis starting at CELLplus surface in cortical and spongy bone.*

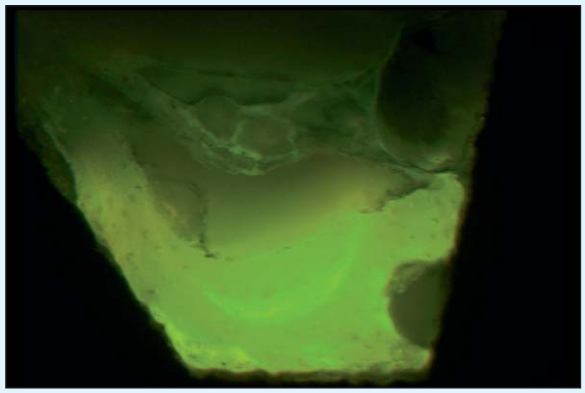

*Figure 18: MRG with good bone contact at microstructured CELLplus surface (courtesy of M. Weinländer).*

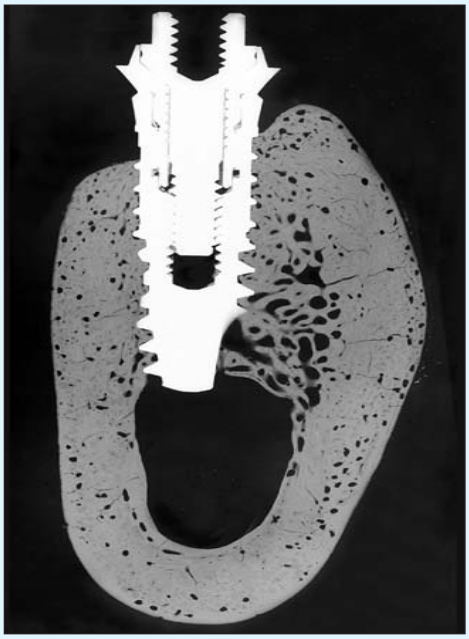

*Figure 19: Woven remodeling of cortical bone with high activity after three months in transitional thread region (courtesy of M. Weinländer).*

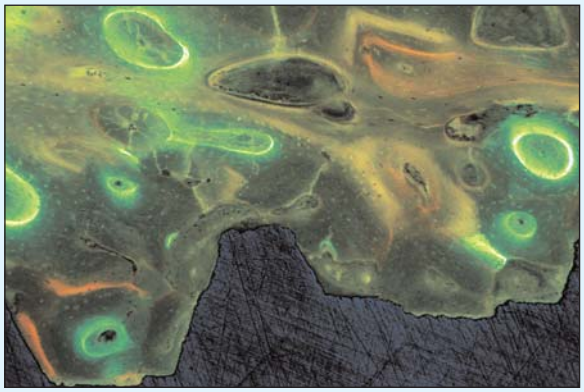

*Figure 20: Osseointegration at high-power magnification.*

in certain circumstances, especially in this limited area of the bone implant surface. I think several studies have been done to support these hypotheses." He adds, "Most of the work with the PRP technique is used for the bone grafting materials where we have to deal with larger spaces. In this case we have seen on the CELLplus surface bone growth of about 1 micron up to 2 microns per day." Gehrke concludes, "I think it is very difficult to enhance this bone formation because it is already at a very high level."

*Potential for Peri-implantitis.* Depending on which implant system is used, the surface roughness will ascend the implant a certain amount, and the implant will have a different size collar depending on which specific system the surface is applied to. However, when surface roughness is taken to the top on a particular system, the roughness may affect the potential for peri-implantitis.

Neugebauer notes, "On the CELLplus surface, it seems that we have a very rough surface up to the

top, but in the transitional area between the osseous and epithelial tissue contact, the implant is only solely etched." Due to the thermal etching, which appears very rough, the surface has a very homogenous roughness. Gehrke explains, "We have also run a study with the University of Hamburg on the orientation of keratinocytes and fibroblasts.[9] The orientation of these cells was not so good on the smooth and etched surface, but it was very favorable on the solely etched surface.

"Considering these principles of biological width, we have designed a double zone at the crestal part of CELLplus implants." At the top crestal section of 0.4 millimeters, the implants are machined, followed by a solely acid-etched zone of 1.1 millimeters respectively 1.6 millimeters. Below this double-crestal zone, CELLplus implants have a grit-blasted and acid-etched endosseous microstructure.

## Cost

Drs. Gehrke and Neugebauer indicated that the costs associated with the manufacturing of this surface, as apposed to prior manufacturing processes, are influenced by the biotechnology used to produce it. The implementation of new technology from the semi-conductor industry provides the opportunity to produce an implant with very high standard of performance. The new procedure is fully computer controlled, and the process employs purified water for treatment.

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