Invibio® SPINE White Paper

The Next Generation in Materials for Interbody Fusion: PEEK-OPTIMA® HA Enhanced

Pre-clinical Study Demonstrates Early Bone Apposition

Introduction: PEEK Proven and Accepted in Interbody Fusion

For more than a decade, PEEK-OPTIMA® Natural, the first medical grade unfilled PEEK from Invibio Biomaterial Solutions, has been utilized in spinal fusion surgeries, predominantly in the form of load-bearing cages. Today, PEEK is the most popular biomaterial for interbody fusion devices.[1] Clinical studies continue to suggest that PEEK-OPTIMA performs as well as, or better than, equivalent interbody fusion devices made of metals or allograft, while providing some distinct clinical advantages over competing biomaterials.[2-4]

The properties that make PEEK-OPTIMA one of the leading interbody fusion biomaterials; modulus similar to cortical bone, imaging compatibility, biocompatibility and processing adaptability, make it an ideal platform for tailoring to specific needs. Previous examples of this have included addition of carbon fiber to increase strength, or barium sulfate to increase visibility under X-ray.

Now, despite the clear benefits offered by PEEK-OPTIMA Natural, surgeons are interested in methods to enhance direct bone apposition to interbody fusion devices. In this paper, we introduce a new biomaterial offering, PEEK-OPTIMA® HA Enhanced, which addresses these growing needs.

Desire for Increased Osseointegration

In recent years, one area in which the desire for increased osseointegration has been evident has been in the trend for interbody fusion devices in which titanium surfaces have been incorporated with PEEK cages (Table 1). A potential limitation of some technologies however, especially plasma spray coatings, is the inability to coat all surfaces, including the walls surrounding the graft space; thereby limiting the available area for bone on growth.

Applicant	Device Name	510(k) number	Decision Date
SeaSpine*	SeaSpine Spacer System – Hollywood NM	K102026	May 2011
Aesculap	Aesculap SIBD XP Spinal System	K111122	August 2011
X-Spine	Calix PC Spinal Implant System	K112036	November 2011
Spinal Elements	Lucent/Lucent Magnum	K110632 (Special)	May 2012
Orthofix	Construx Mini PEEK Ti Spacer System	K121649	November 2012
Aesculap	Aesculap CeSpace XP	K123909	April 2013

Table 1. FDA 510(k) clearances of PEEK interbody fusion devices with bone-opposing titanium surfaces.
*Now part of Integra LifeScience

PEEK-OPTIMA HA Enhanced is a new biomaterial introduced by Invibio, bringing together PEEK-OPTIMA and hydroxyapatite (HA) to address the growing surgeon need for increased osseointegration, and the market drive towards materials that play a more active role in the fusion process.

This new material, in which the HA is fully integrated in the PEEK matrix, is a promising solution for medical applications such as spinal interbody fusion, where early bone apposition would be advantageous in achieving early stability. Unlike a conventional coating technology, the even and homogenous dispersion throughout the PEEK matrix, ensures HA is made available on all machined surfaces of a final device for potential bone on-growth (Figures 1 and 2).

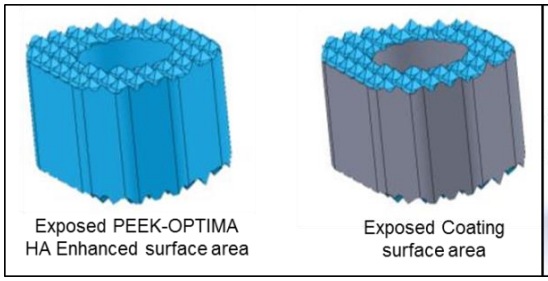

Figure. 1 Representation of available surfaces for bone on-growth (highlighted in blue) with PEEK-OPTIMA HA Enhanced, and Ti-coated PEEK devices.

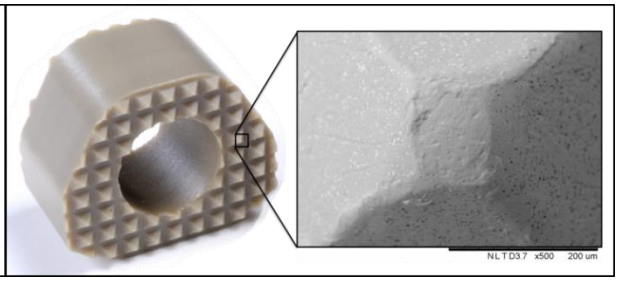

Figure. 2 HA distribution and availability at the surface of a PEEK-OPTIMA HA Enhanced interbody fusion device. The HA is indicated by the speckling on the surface.

HA is the main inorganic constituent of bone. Due to its well-known osteoconductive properties, naturally occurring and synthetic forms of HA have been successfully applied for many years as a bone void filler and as a coating for orthopedic and dental implants to ensure fixation, without obvious material-related bio-incompatibility reactions.[5-9] Indeed, the use of HA in spine applications is not entirely without precedent. A number of pedicle screw systems, including the Dynesys® Dynamic Stabilization system (Zimmer Spine) and the Transition stabilization system (Globus Medical Inc.) made HA-coated titanium screws available for the purpose of improved early screw fixation.

Development of a High Performance Polymer

Ensuring the same high performance as PEEK-OPTIMA Natural was a key aim in the development of PEEK-OPTIMA HA Enhanced and in defining its suitability for use in interbody fusion devices. The incorporation of HA into the PEEK matrix has had minimal impact on mechanical properties (Table 2), whilst maintaining similar imaging characteristics (Figure 3).

Property	Tensile Strength (Yield) (MPa)	Tensile Elongation (Break) (%)	Flexural Strength (MPa)	Flexural Modulus (GPa)	Izod Impact (Notched) (kJ/m^2)
PEEK-OPTIMA Natural	100	40	165	4.1	7.5
PEEK-OPTIMA HA Enhanced	92	18	155	4.9	5.6

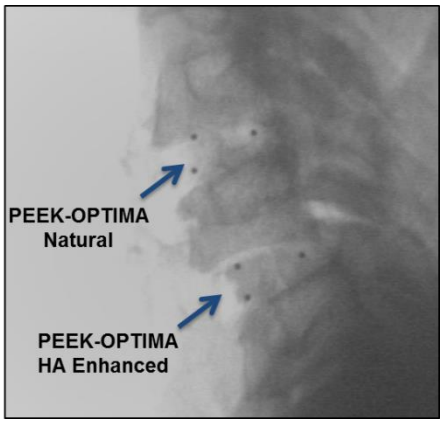

Figure 3. Fluorographic imaging of PEEK-OPTIMA Natural and PEEK-OPTIMA HA Enhanced cervical interbody fusion devices (lateral view).

Table 2. Comparison in mechanical properties of PEEK-OPTIMA Natural and PEEK-OPTIMA HA Enhanced[a].

As can be expected from the introduction of a new biomaterial for long-term implantation, biocompatibility is a pre-requisite, and Invibio have also completed a comprehensive suite of testing, from chemical analyses and cytotoxicity testing to long-term implantation, in accordance with ISO 10993.

Research Results: Early Bone Apposition

Whilst bench testing and *in vitro* studies can provide some information on material performance, ultimately a pre-clinical study is needed to demonstrate efficacy where osseointegration is concerned.

For this reason, Invibio commissioned a study designed to evaluate the *in vivo* response of PEEK-OPTIMA HA Enhanced compared with PEEK-OPTIMA Natural in a large animal model. The study was carried out at the Surgical & Orthopaedic Research Laboratories at the University of New South Wales under the direction of Professor Bill Walsh, following approval of the UNSW Animal Care and Ethics Committee.

The study used implants in the form of simple cylindrical dowels that were implanted in an established ovine model.[10-14] Endpoints for the study included implantation into cortical and cancellous sites in adult sheep followed by radiography, mechanical testing and PMMA histology at 4 and 12 weeks following implantation.

Methods

Surgery was performed in a bilateral fashion using the anteromedial aspect of the tibias and the medial distal femoral condyles for implantation using a previously reported model (Figure 4). For implantation in cancellous bone (distal femur and proximal tibia), implants were inserted in a press fit manner. For the cortical implantations in the tibia, implants were placed in a line-to-line manner.

Fluorochrome labels were administered at intervals during the 4 week and 12 week implantation periods to provide a dynamic view of new bone formation.

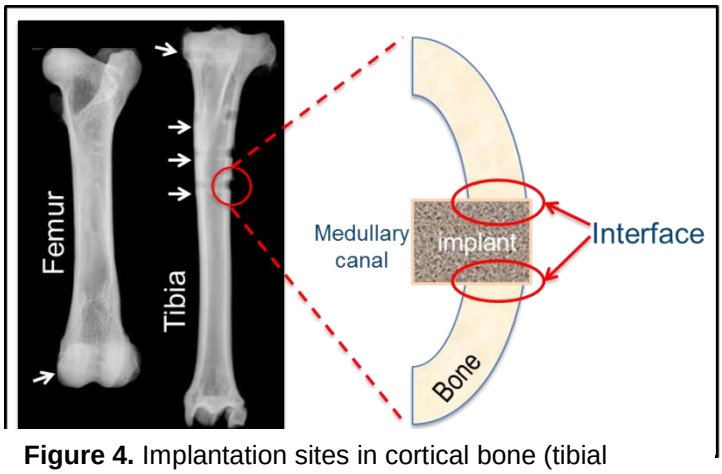

Figure 4. Implantation sites in cortical bone (tibial diaphysis) and cancellous bone (proximal tibia and distal femur).

At harvest, each bicortical implant was cut in half, perpendicular to its long axis, allowing preservation of one half of the implant for histology, whilst the other half was used for mechanical push-out testing. Implantation sites were also radiographed at harvest to acquire

[a] Values stated are for evaluative purposes only and do not constitute product specifications.

anteroposterior and lateral views of the implants *in situ*. Integration of the implants was tested by measuring the implant-bone interface shear strength using a standard push-out test. Briefly, specimens were tested at 0.5mm/min on a calibrated servo-hydraulic testing machine. The thickness of the cortical and cancellous bone samples was measured and the values used to calculate the shear stress.
Following retrieval, samples were fixed and dehydrated prior to embedding in poly(methyl methacrylate) (PMMA). Samples were then sectioned perpendicular to the long axis and stained using methylene blue - basic fuchsin. The histology images from cortical bone sites were examined to determine the percent bone ongrowth based on a semi-quantitative grading scale.

Results
From the radiographs, no adverse reactions were noted in either the PEEK-OPTIMA or PEEK-OPTIMA HA Enhanced group. Similarly, the histological examination revealed no adverse reactions in the adjacent cortical bone, cancellous bone or adjacent marrow.
Histological review and grading did however demonstrate a marked increase in the degree of direct bone contact with PEEK-OPTIMA HA Enhanced compared with PEEK-OPTIMA Natural at both the 4 week and 12 week time points (Figure 5).

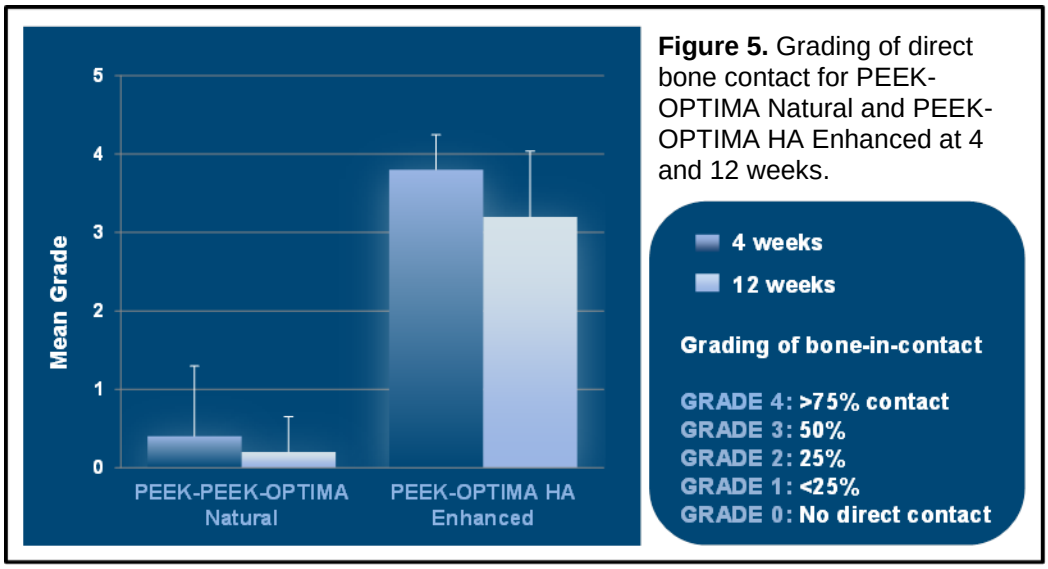

Figure 5. Grading of direct bone contact for PEEK-OPTIMA Natural and PEEK-OPTIMA HA Enhanced at 4 and 12 weeks.

With PEEK-OPTIMA Natural, some areas of direct bone contact were observed, whilst in others there were gaps or small regions of fibrous tissue in the intervening space. For PEEK-OPTIMA HA Enhanced, a more consistent and continuous degree of direct bone contact was observed (Figure 6). The use of fluorochrome labeling

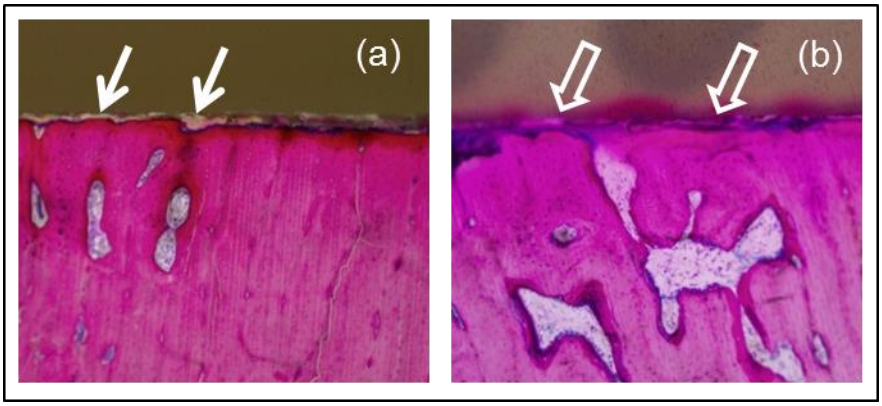

Figure 6. 4 week histology of (a) PEEK-OPTIMA Natural, and (b) PEEK-OPTIMA HA Enhanced. Solid and open arrows show gaps and areas of direct bone contact respectively.

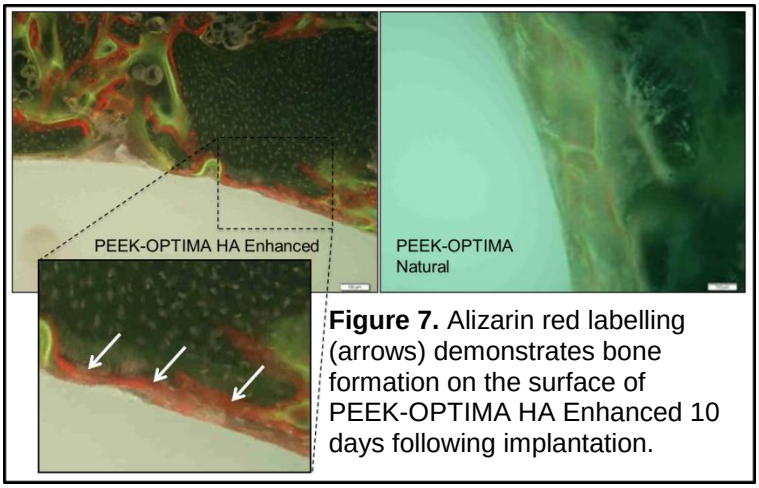

Figure 7. Alizarin red labelling (arrows) demonstrates bone formation on the surface of PEEK-OPTIMA HA Enhanced 10 days following implantation.

supports the notion of early bone apposition. The appearance of alizarin red labeling on the surface of PEEK-OPTIMA HA Enhanced indicates that bone was being deposited as early as 10 days following implantation – the time at which the fluorochrome was administered (Figure 7). In contrast, early bone apposition was not observed with PEEK-OPTIMA Natural.

Finally, push out testing demonstrated increased interfacial shear strength with PEEK-OPTIMA HA Enhanced compared with PEEK-OPTIMA Natural at 4 weeks following implantation (Figure 8), providing further evidence of increased osseointegration. Important to note is the absence of any additional surface geometry used in the implants, which may have influenced both shear stress and percentage bone-in-contact values. Surface roughness was also a consideration in evaluating osseointegration and so all implants, machined from both PEEK-OPTIMA Natural and PEEK-OPTIMA HA Enhanced, were machined to have a similar surface roughness ($R_a \approx 1\mu m$).

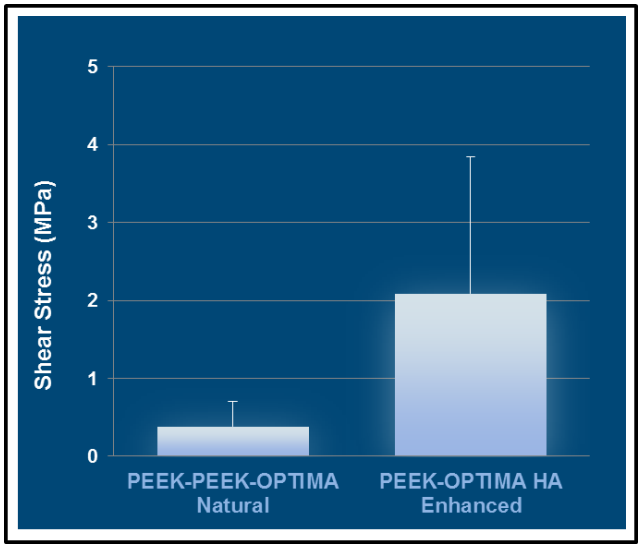

Figure 8. PEEK-OPTIMA HA Enhanced results in increased interfacial shear strength with bone 4 weeks following implantation

Conclusion

Increasing demands are being placed on biomaterials for use in interbody fusion applications. The trend in methods to improve osseointegration of PEEK-based devices, principally through coating technologies, underlines this fact. Despite the long clinical history and performance of PEEK-OPTIMA Natural, Invibio have risen to the challenge in addressing this need from both surgeons and implant manufacturers.

The introduction of PEEK-OPTIMA HA Enhanced, bringing together two well-accepted biomaterials, delivers one unique combination for enhanced bone apposition.

For more information contact:
Dr Mark Brady,
Invibio Product Development Manager for PEEK-OPTIMA® HA Enhanced
mbrady@invibio.com

References

1. 2012 Spinal Surgery Update. Orthopedic Network News, Vol 23, No 4, October 2012. Posted to www.OrthopedicNetworkNews.com at 11:59 am ET on November 1, 2012
2. Chou, Y.C., et al. *Efficacy of anterior cervical fusion: comparison of titanium cages, polyetheretherketone (PEEK) cages and autogenous bone grafts*. J Clin Neurosci, 2008. **15**(11): 1240-5.
3. Lied, B., et al. *Anterior cervical discectomy with fusion in patients with cervical disc degeneration: a prospective outcome study of 258 patients (181 fused with autologous bone graft and 77 fused with a PEEK cage)*. BMC Surg, 2010. **10** (10). Published online 2010 March 21. doi: 10.1186/1471-2482-10-10.
4. Chen, Y., et al. *Comparison of titanium and polyetheretherketone (PEEK) cages in the surgical treatment of multilevel cervical spondylotic myelopathy: a prospective, randomized, control study with over 7-year follow-up*. Eur Spine J, 2013. **22**: 1539-46.
5. Allison, D.C., et al. *A comparison of mineral bone graft substitutes for bone defects*. US Oncol Hematol, 2011. **7**(1): 38-49.
6. Epinette J-A., et al (eds). *Fifteen years of clinical experience with hydroxyapatite coatings in joint arthroplasty*, Springer Verlag France, 2004.
7. Hench, L.L. and Ethridge, E.C. *Biomaterials and Interfacial Approach*. New York, NY: Academic Press; 1982.
8. Nandi, S.K., et al. *Orthopedic applications of bone graft & graft substitutes: a review*. Indian J Med Res, 2010. **132**: 15-30.
9. Zhang, S. (ed). *Hydroxyapatite coatings for biomedical applications*, CRC Press. 2013.
10. Svehla, M.P., et al. *Morphometric and mechanical evaluation of titanium implant integration: comparison of five surface structures*. J Biomed Mater Res, 2000. **51**: 15-22.
11. Svehla, M.P., et al. *The effect of substrate roughness and hydroxyapatite coating thickness on implant shear strength*. J Arthroplasty, 2002. **17**: 304-11.
12. Svehla, M.P., et al. *No effect of a type I collagen gel coating in uncemented implant fixation*. J Biomed Mater Res B, 2005. **74**: 423-8.
13. Bertollo, N., et al. *Effect of surgical fit on integration of cancellous bone and implant cortical bone shear strength for a porous titanium*. J Arthroplasty, 2011. **26**: 1000-7.
14. Chen, D., et al. *Osseointegration of porous titanium implants with and without electrochemically deposited DCPD coating in an ovine model*. J Orthop Surg Res, 2011. **6**: 56.

Europe and Asia Pacific
Invibio Ltd.
Technology Centre, Hillhouse International
Thornton Cleveleys, Lancashire FY5 4QD
United Kingdom
Tel: +44 (0) 1253 898000
FAX: +44 (0) 1253 898001

Americas
Invibio Inc.
300 Conshohocken State Road, Suite 120
West Conshohocken, PA 19428
USA
866-INVIBIO (468-4246)
Tel: +484 342 6004
FAX: +484 342 6005

For further information email us at info@invibio.com or please visit our website at:

- www.invibio.com

S-DP-INV-E-0077-C (10/2013)