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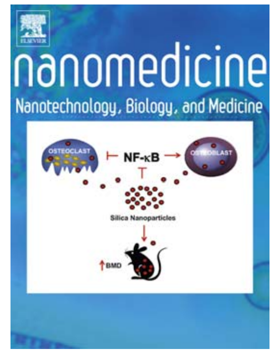

Transparent Nanocrystalline Yttria-Stabilized-Zirconia Calvarium Prosthesis

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Transparent Zirconia Calvarial Prosthesis

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Abstract:

Laser-based diagnostics and therapeutics show promise for many neurological disorders. However, the poor transparency of cranial bone (calvaria) limits the spatial resolution and interaction depth that can be achieved, thus constraining opportunity in this regard. Herein, we report preliminary results from efforts seeking to address this limitation through use of novel transparent cranial implants made from nanocrystalline yttria-stabilized zirconia (nc-YSZ). Using optical coherence tomography (OCT) imaging of underlying brain in an acute murine model, we show that signal strength is improved when imaging through nc-YSZ implants relative to native cranium. As such, this provides initial evidence supporting the feasibility of nc-YSZ as a transparent cranial implant material. Furthermore, it represents a crucial first step towards realization of an innovative new concept we are developing, which seeks to eventually provide a clinically-viable means for optically accessing the brain, on-demand, over large areas, and on a chronically-recurring basis, without need for repeated craniectomies.

Keywords: optical neuroimaging, calvarial prosthesis

Background

Laser-based techniques have shown promise for enhancing the diagnosis and treatment of many neurological disorders, including cerebral edema, stroke, and cancer, among others (1-3). However, the poor transparency of cranial bone to clinically-relevant laser wavelengths (i.e. λ = 550 - 1300 nm) typically necessitates use of invasive craniectomies to provide optical access to the brain. This constrains the ultimate utility of such techniques, particularly for applications where chronically-recurring access over large areas is required.

Recent studies have demonstrated potential for increasing cranial transparency through thinning (4,5). However, since this diminishes protection for the brain, associated safety concerns may preclude opportunity for translation of such techniques to the clinic. Other studies have reported use of transparent glass-based implants, either in place of cranium (6), or as an overlay to increase the rigidity of thinned-skull preparations (7). However, the extremely low fracture toughness of typical glasses (K_{IC} = 0.7 – 0.9 MPa·m$^{1/2}$) increases potential for catastrophic failure by fracture, which will limit opportunity for use of such implants beyond the laboratory. This, therefore, motivates the search for alternate materials that will provide better potential for eventual clinical use.

While a number of synthetic materials have been evaluated for use in calvarial reconstruction, including titanium, alumina, and acrylic (8), none provide the requisite combination of transparency and toughness required for clinically-viable transparent cranial implants. Yttria-stabilized zirconia (YSZ) represents an attractive alternative, due to its relatively high toughness (K_{IC} ~ 8 $MPa{\cdot}m^{1/2}$), as well as its proven biocompatibility in dental and orthopedic applications. However, YSZ is typically opaque, thus precluding its consideration thus far.

Herein, we report the preliminary evaluation of novel transparent nanocrystalline YSZ (nc-YSZ) cranial implants that seek to provide new opportunity in this regard. Using optical coherence tomography (OCT), we demonstrate the initial feasibility of nc-YSZ cranial implants within the context of cortical imaging in an acute murine model. We then discuss the implications of these implants with regard to a broader concept we are developing, which may eventually serve as a critical enabler for the wider use of lasers in the diagnosis and treatment of neurological disorders.

Methods

The transparent nc-YSZ cranial implants were made possible through use of the CAPAD process (9), an emerging technique that enables reduction of internal porosity to nanometric dimensions, and thus, reduction of the optical scattering that renders typical YSZ opaque (10). Densified nc-YSZ blanks were polished, annealed, and machined into rectangular implants with dimensions of 2.1 x 4.2 x 0.2 mm^3. Figure 1A demonstrates the transparency of the finished implants.

As shown in Figs. 1B – 1D, right-sided craniectomies were performed on anesthetized mice, followed by fixation of nc-YSZ implants to the surrounding skull with dental cement. The left-side of the cranium was left unmodified to serve as a control. All animal experiments were conducted under a protocol approved by the University of California, Riverside Institutional Animal Care and Use Committee (#2010-0018), and in conformance with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996).

To evaluate initial nc-YSZ implant feasibility, OCT was used as a representative optical imaging modality. Imaging was performed over a 2 x 2 mm^2 area on the coronal position for both the nc-YSZ implant and the native cranium. Further details regarding nc-YSZ fabrication, implantation, and OCT imaging can be found in the *Supplemental Materials*.

Results

Figure 2 shows cross-sectional OCT images of murine brain through native cranium (left of midline) and nc-YSZ implant (right of midline) in the same animal. Detailed description of the image interpretation is presented in the *Supplemental Materials.* The enhanced transparency of the nc-YSZ implant is evidenced by the opportunity it provides for imaging of sub-cortical white matter (darker band at bottom of image, right of midline), which is nearly imperceptible when imaging through native cranium (left of midline).

Figure 3 shows OCT signal strengths as a function of depth from the cortical surface when imaging through native cranium and nc-YSZ, respectively. As would be expected, intensity decays with depth for both, aside from the increase associated with sub-cortical white matter. However, signal strength at nearly every depth is significantly higher when imaging through the nc-YSZ implant, further demonstrating the enhanced imaging performance.

Discussion

Figures 2 and 3 demonstrate that OCT imaging through nc-YSZ implants is indeed possible and provides greater signal strength than imaging through native cranium. This, therefore, establishes the initial feasibility of nc-YSZ as a transparent cranial implant material for optical diagnostic and therapeutic applications. Moreover, when coupled with the high toughness of nc-YSZ, this suggests unique potential for eventual clinical application.

However, before such potential can be realized, further studies are required to evaluate the long-term biological response to nc-YSZ implants, since: a) the demands imposed upon cranial implants differ from those in dental and orthopedic applications; and b) the need for transparency will require minimization of fibrosis and/or bone regrowth over the implant. Regarding the latter, it may ultimately be more beneficial to thin the cranium significantly and then cover with a nc-YSZ implant, as Shih et al. recently demonstrated for glass-based implants (13).

Although beyond the scope of the current study, it is important to also briefly consider the effect of the scalp on imaging performance, since: a) coverage of the nc-YSZ implant with native scalp will be preferred for applications requiring long-term implantation; and b) repeated scalp removal is unlikely to be desirable when chronically-recurring access over large areas is required. Optical clearing agents (OCAs) represent a compelling possibility in this regard, since they have been shown to provide capability for temporarily rendering skin transparent on demand (14-17). When used in conjunction with nc-YSZ implants, we envision potential for realization of an innovative new concept we have named Windows to the Brain (WttB), which seeks to eventually provide opportunity for optical accessing the brain, on-demand, over large areas, and on a chronically-recurring basis, without need for repeated craniectomies or scalp removal.

While the current study represents only the first step towards realization of the WttB concept, it is instructive to consider the opportunities this may eventually afford. For example, opportunity may arise for chronic monitoring of cerebral edema, which is largely precluded by the invasiveness of current techniques (18). Similarly, it may enable chronic monitoring and more precise targeting of photodynamic therapies for residual gliomas (19), which could prolong survival and improve quality of life for many suffering from brain cancer. Finally, it could provide a platform for development of new optical neuromodulation modalities, with potential applications ranging from fundamental neurophysiology studies to clinical psychiatry (20).

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Figure Captions

Fig. 1 Transparent nc-YSZ cranial implants: A) Photograph of implant placed on printed scale to demonstrate transparency; B) Schematic of craniectomy location on murine cranium; C) Photograph of craniectomy with dura mater left intact; and D) Photograph after implant placement. Note: Implant opacity in (D) is flash-induced image artifact.

Fig. 2 OCT cross-sectional image of murine brain (coronal view) through: (Left) Native cranium; and (Right) nc-YSZ implant.

Fig. 3 OCT signal strength depth profile for imaging through native cranium vs. nc-YSZ implant.

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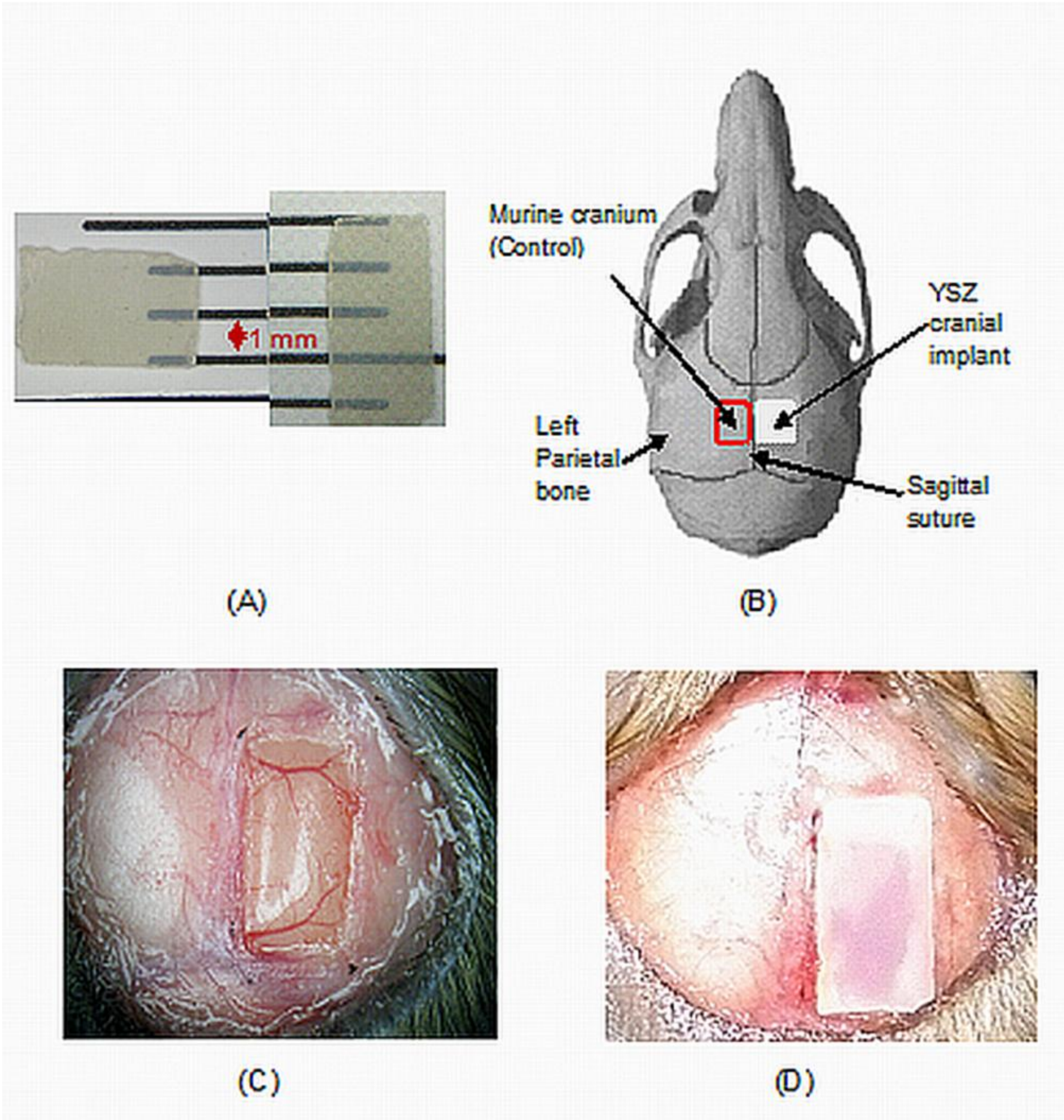
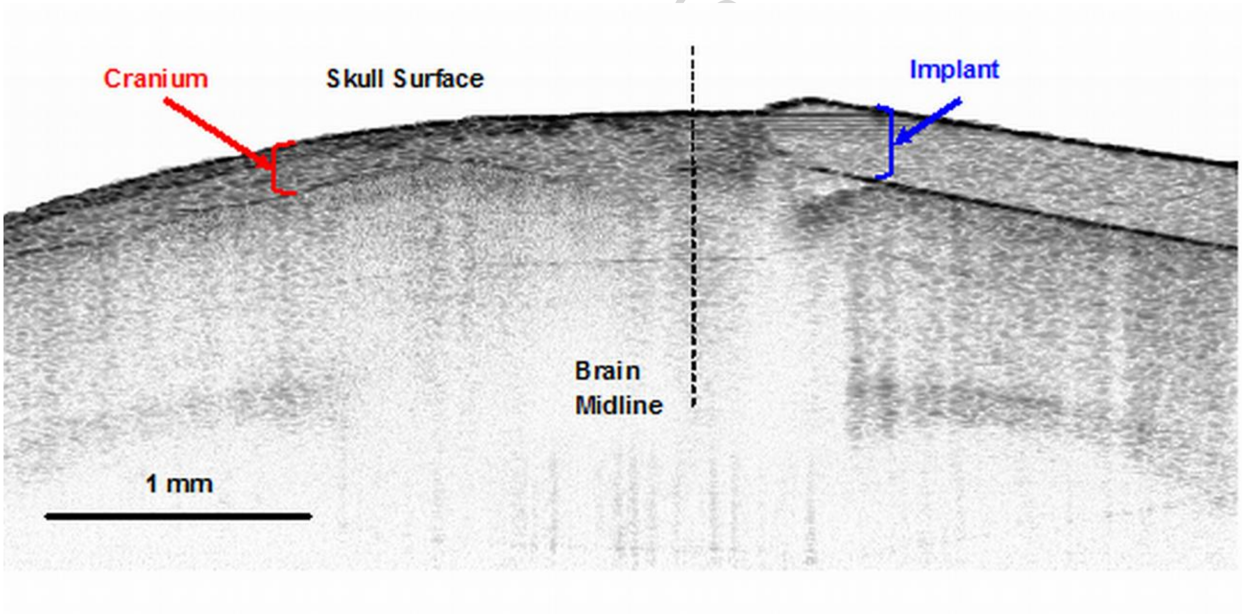
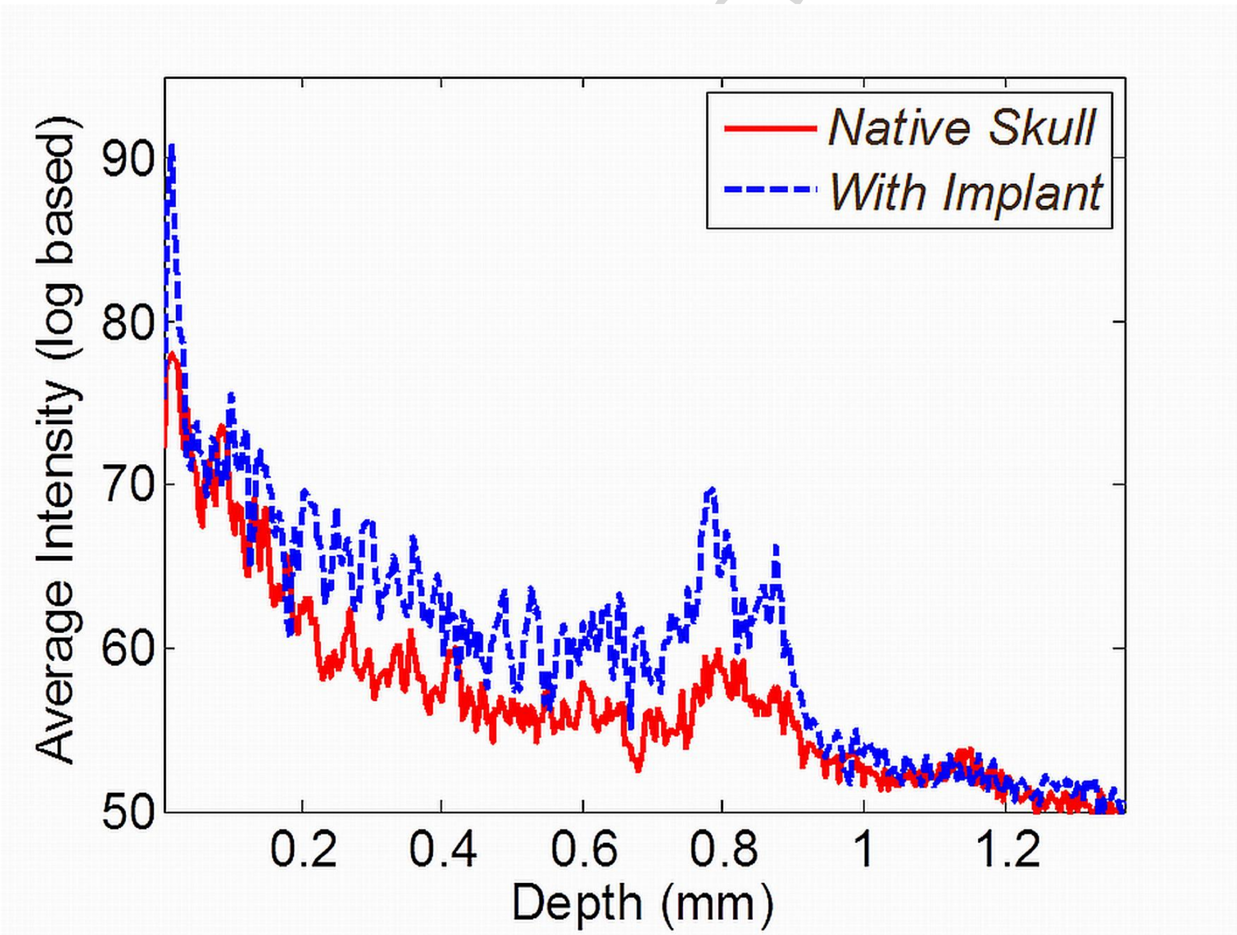
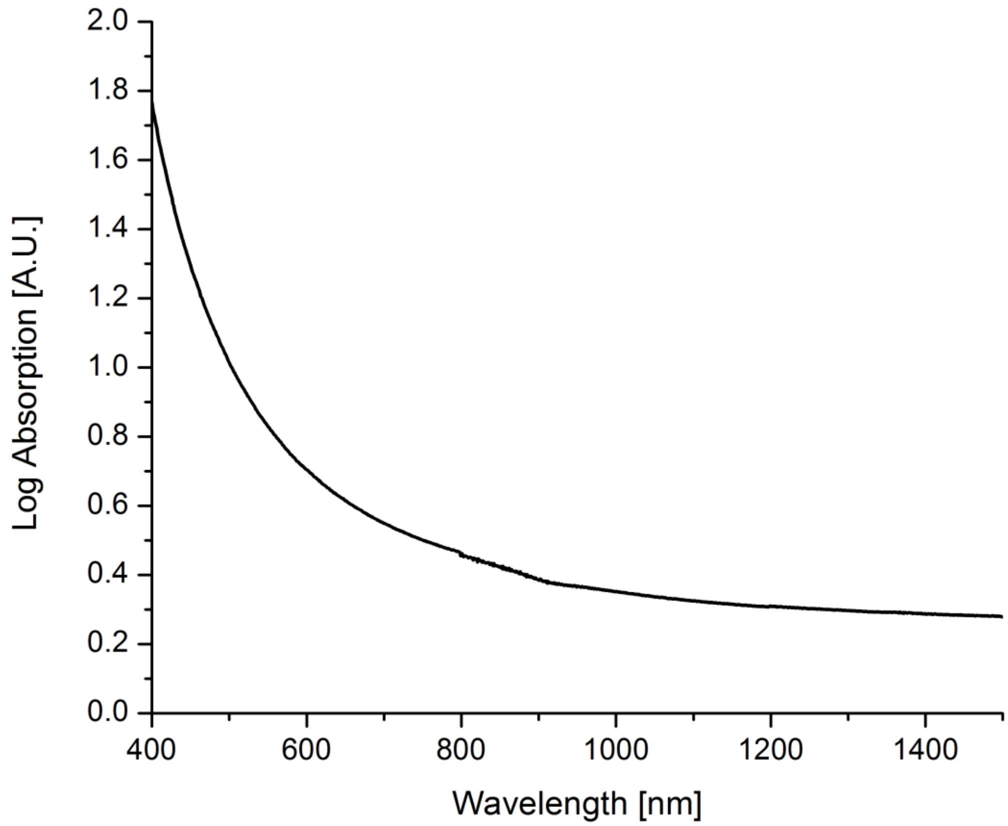
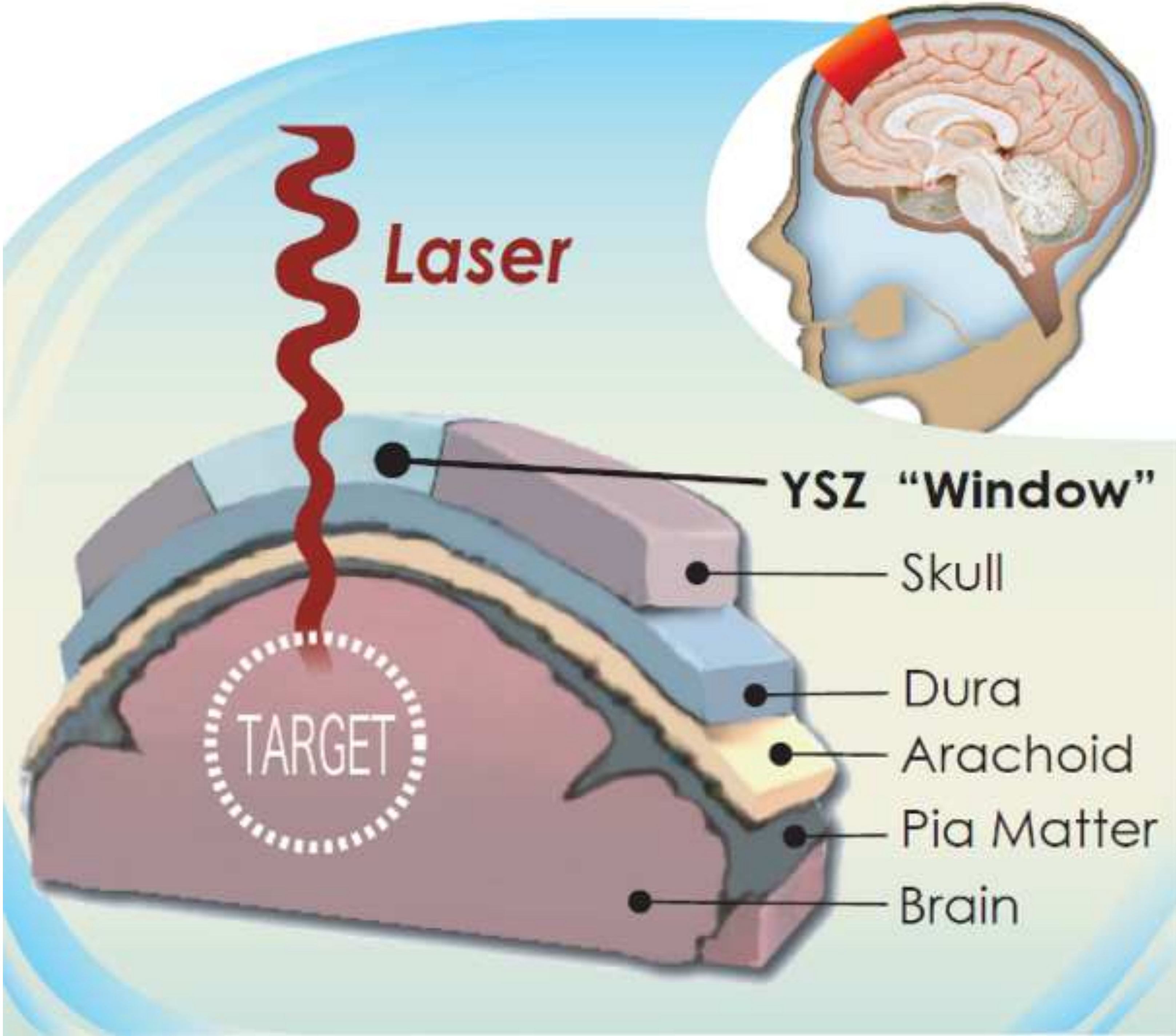

1 mm
Murine cranium
(Control)
YSZ
cranial
implant
Left
Parietal
bone
Sagittal
suture
(A)
(B)
(C)
(D)


Cranium
Skull Surface
Implant
Brain
Midline
1 mm


Native Skull
With Implant
Average Intensity (log based)
Depth (mm)
50
60
70
80
90
0.2
0.4
0.6
0.8
1
1.2


2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Log Absorption [A.U.]
400
600
800
1000
1200
1400
Wavelength [nm]

Transparent cranial implants could serve as a critical enabler for laser-based diagnosis and treatment of many neurological disorders. However, the intrinsic brittleness of transparent implants reported thus far predisposes them to catastrophic fracture-based failure, thus limiting opportunity for clinical translation. Novel nanocrystalline transparent implants are reported herein that seek to address this limitation through use of zirconia, a tough ceramic with well-proven biocompatibility in other chronic implantation applications.


Laser
YSZ "Window"
Skull
Dura
Arachoid
Pia Matter
Brain
TARGET