

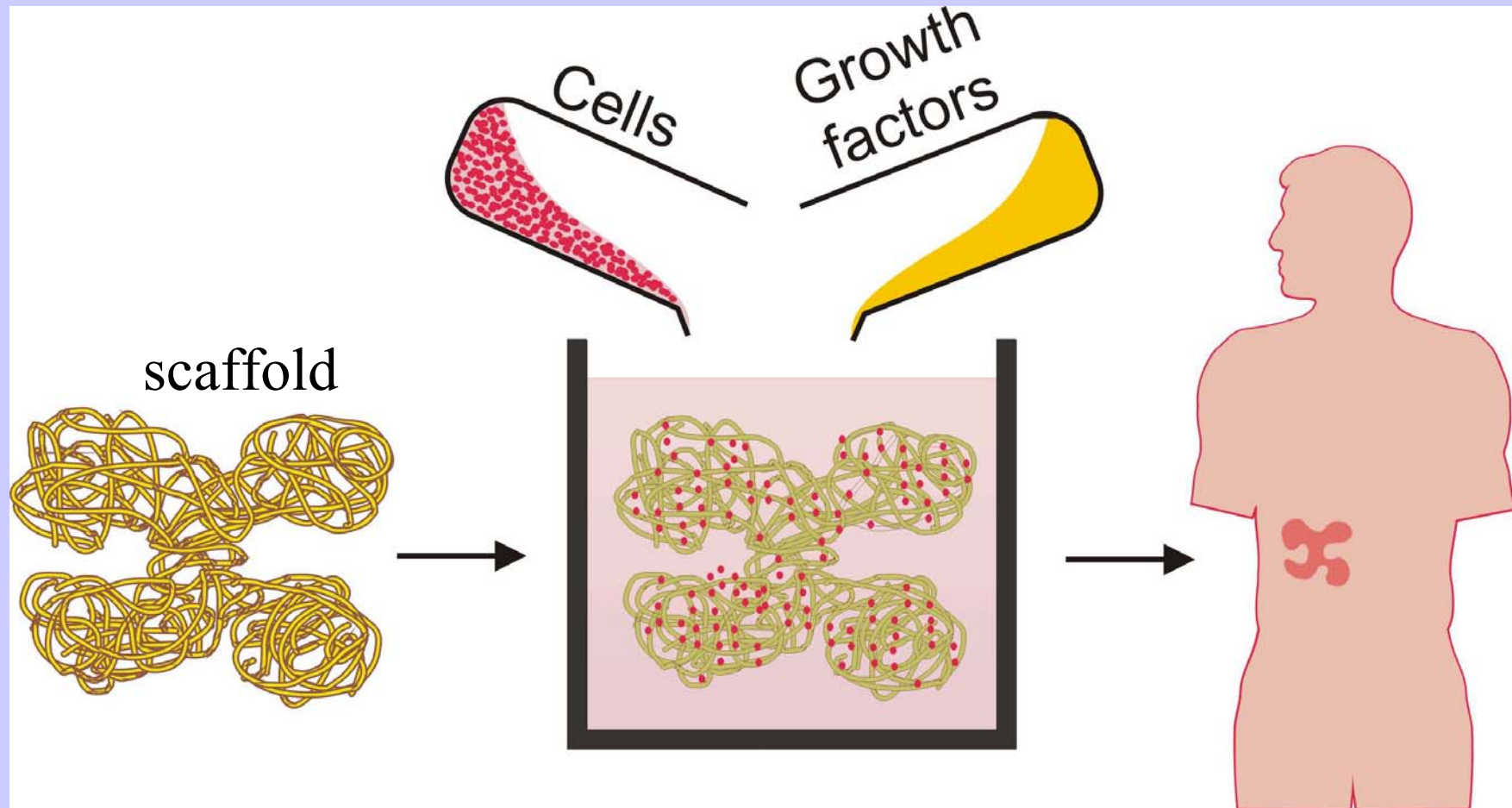
Harvard-MIT Division of Health Sciences and Technology
HST.535: Principles and Practice of Tissue Engineering
Instructor: Fu-Zhai Cui

Biomimetic Design of Scaffold

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In Tissue Engineering, growth factors and Cells are definite, but scaffold may be various depending on design.



What is the best design?

- We believe that nature is the best designer for organ development. What should we do is just to follow Nature's design---Mimetic.
- In a specific tissue (bone, brain or liver) repair by tissue engineering, the Natural ECM of this tissue with hierarchical structure and mechanical behavior should be ideal scaffold.

- Thus, our object is to manufacture the scaffold with similarity to the special natural ECM, in composition and hierarchical structure, as well as in physiology.
- However, this object is not easy. In one hand, the exact structure and fabrication process are still obscure for many ECMs, from the opinion of Materials Engineering. In another hand, the available technology has not be able to fabricating the known hierarchical structure of ECM.
- We had made our effort in biomimetic fabrication of scaffold in bone, liver and brain. Here, is the example of bone scaffold.

Scaffold in Bone Tissue Engineering

We learnt from five representative stages of bone callus evolution during bone self-healing after bone fracture

Structure model of natural bone on molecule level

Image removed for copyright reasons.

See:-

Landis, W. J., et. al. *J. Structural Biology* 110, no. 39 (2003).

- The formation of a two-dimensional array of molecules as detailed by Hodge and Petruska
- A three-dimensional array leading to the creation of extensive channels or gaps throughout the assemblage.
- A number of cylindrically shaped molecules 300 nm in length and 1.23 nm in width aggregated in parallel.
- Our aim is to make it in lab.

Biomimetic Fabrication of Artificial Bone

◆ The nano-HAp/collagen (nHAC) composite has been developed for the first time by mineralizing the type I collagen in the solution of calcium phosphate.

HA crystals and collagen molecules self-assembled into a hierarchical structure through chemical interaction, which resembles the natural process of mineralization of collagen fibers

Du chang et al, JBMR 1999

zhang wei et al, Chem Mater 2003

Image removed for copyright reasons.

See:-

Zhang, W., S. S. Liao, and F. Z. Cui.

“Hierarchical Self-assembly of Nano-fibrils in Mineralized Collagen.” □

Chemistry of Materials 15, no. 16 (Aug 12, 2003): 3221-3226.

HRTEM of
mineralized
collagen fibers.

Image removed for copyright reasons.

See:-

Liao, S. S., F. Z. Cui, W. Zhang, et. al.

"Hierarchically Biomimetic Bone

Scaffold Materials: Nano-

HA/collagen/PLA Composite."

Journal of Biomedical Materials

Research Part B: Applied Biomaterials

69B, no. 2 (May 15, 2004): 158-165.

SEM morphology of the
porous composite
nHAC/PLA.

Image removed for copyright reasons.

See:-

Liao, S. S., F. Z. Cui, W. Zhang, et. al.

"Hierarchically Biomimetic Bone Scaffold

Materials: Nano-HA/collagen/PLA Composite."

Journal of Biomedical Materials Research Part B:

Applied Biomaterials 69B, no. 2 (May 15, 2004):

158-165.

TEM micrographs of nHAC/PLA material; insert is selected area of the electron pattern of the central part of the image.

- Firstly, the collagen molecules and nano-hydroxyapatite assembled into mineralized fibril bundle.
- Secondly, the mineralized collagen fibril parallel arranged. The fibril array patterns also show the same pattern in bone. The cluster of the mineralized collagen fibrils uniformly distributes in the PLA matrix.
- The pore size of scaffold is above 100-300 μ m. The high porosity (85-90%) of the scaffold make interconnected pore in three-dimension directions. This porous scaffold is similar to the spongy bone in which is the high hierarchical level of the bone.

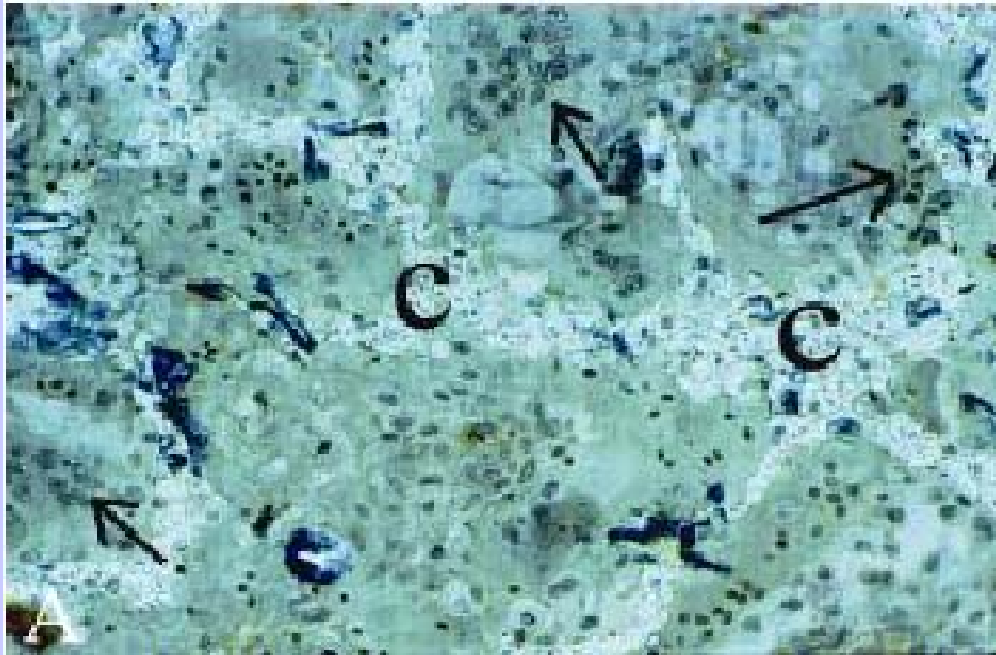
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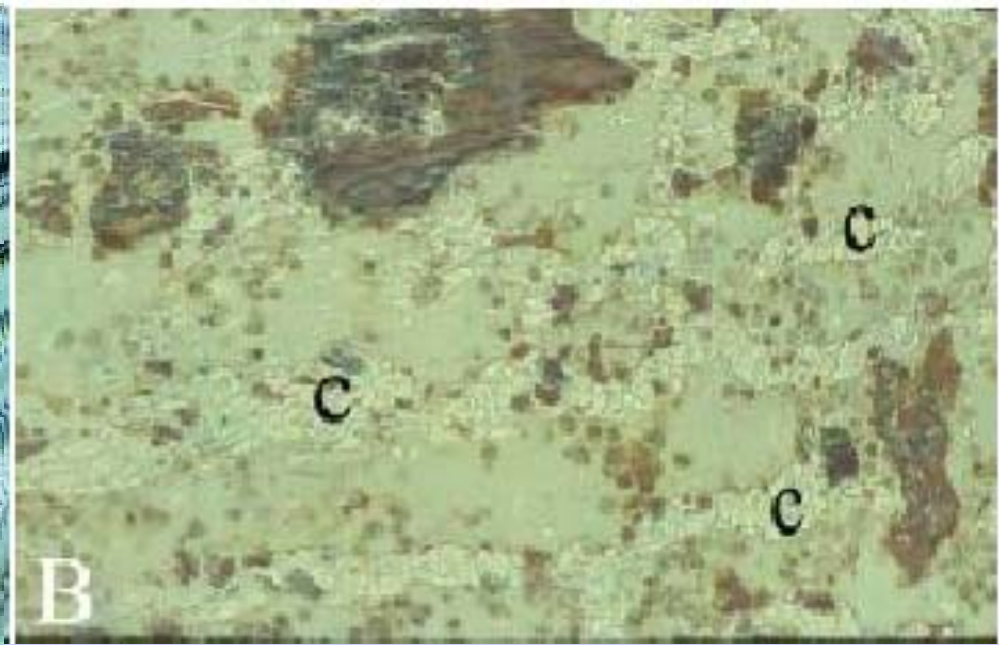
Liao, S. S., F. Z. Cui, and Y. Zhu. "Osteoblasts Adherence and Migration through Three-dimensional Porous Mineralized Collagen based Composite: nHAC/PLA." *Journal of Bioactive and Compatible Polymers* 19, no. 2 (March 2004): 117-130.

(c) Cells grow into inner pores about 400um to the surface

Histologic results of the spinal fusion on rabbit model

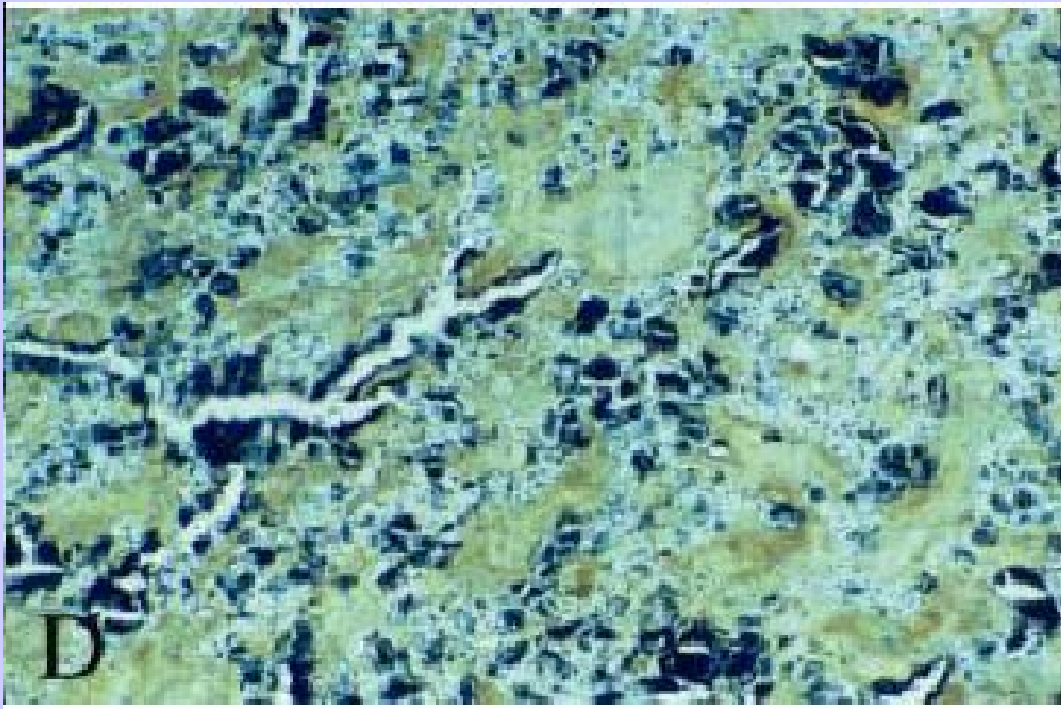
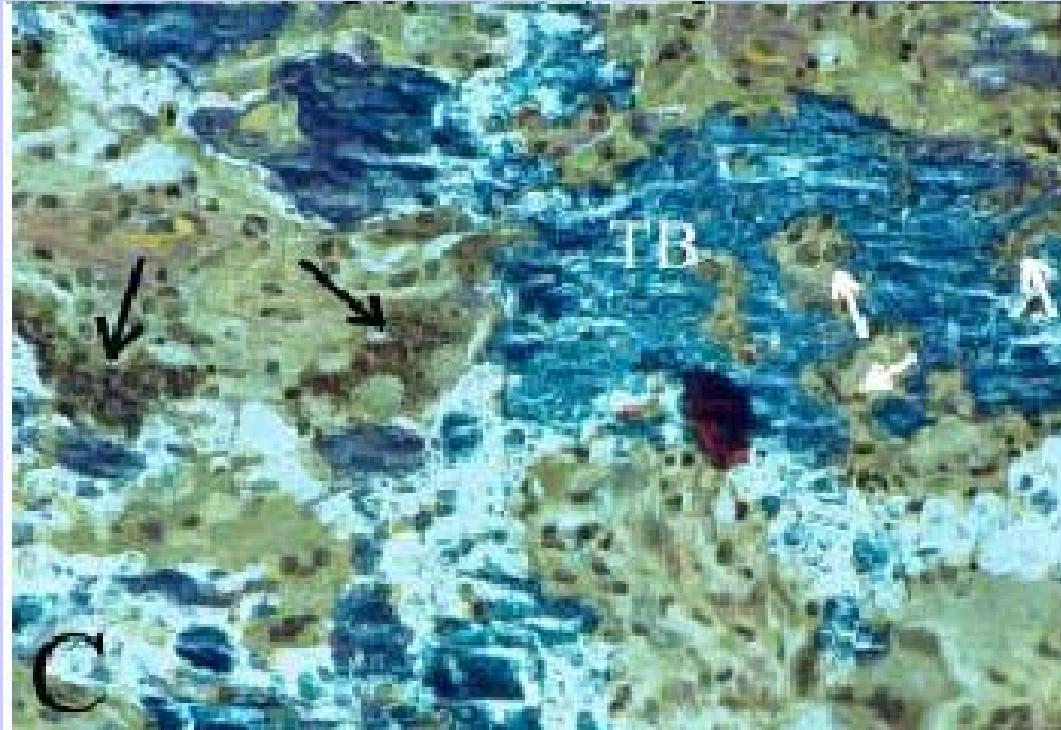


(A) Group nHAC/PLA 4 weeks, 200×;



(B) Group nHAC/PLA+rhBMP-2 2 weeks, 200×;

C means the scaffold of composite nHAC/PLA, the black arrow means the gather of multi-nucleus cells.



(C) (D)

Group nHAC/PLA+rhBMP-2 4 weeks,

the new trabecular bone (TB) distribute in the whole fusion mass area, the mature bone matrix were shown as particle to block, $200\times$ and $100\times$. The white arrows refer to the osteoblast and osteocyte around the new trabecular bone.

Biomechanical Testing

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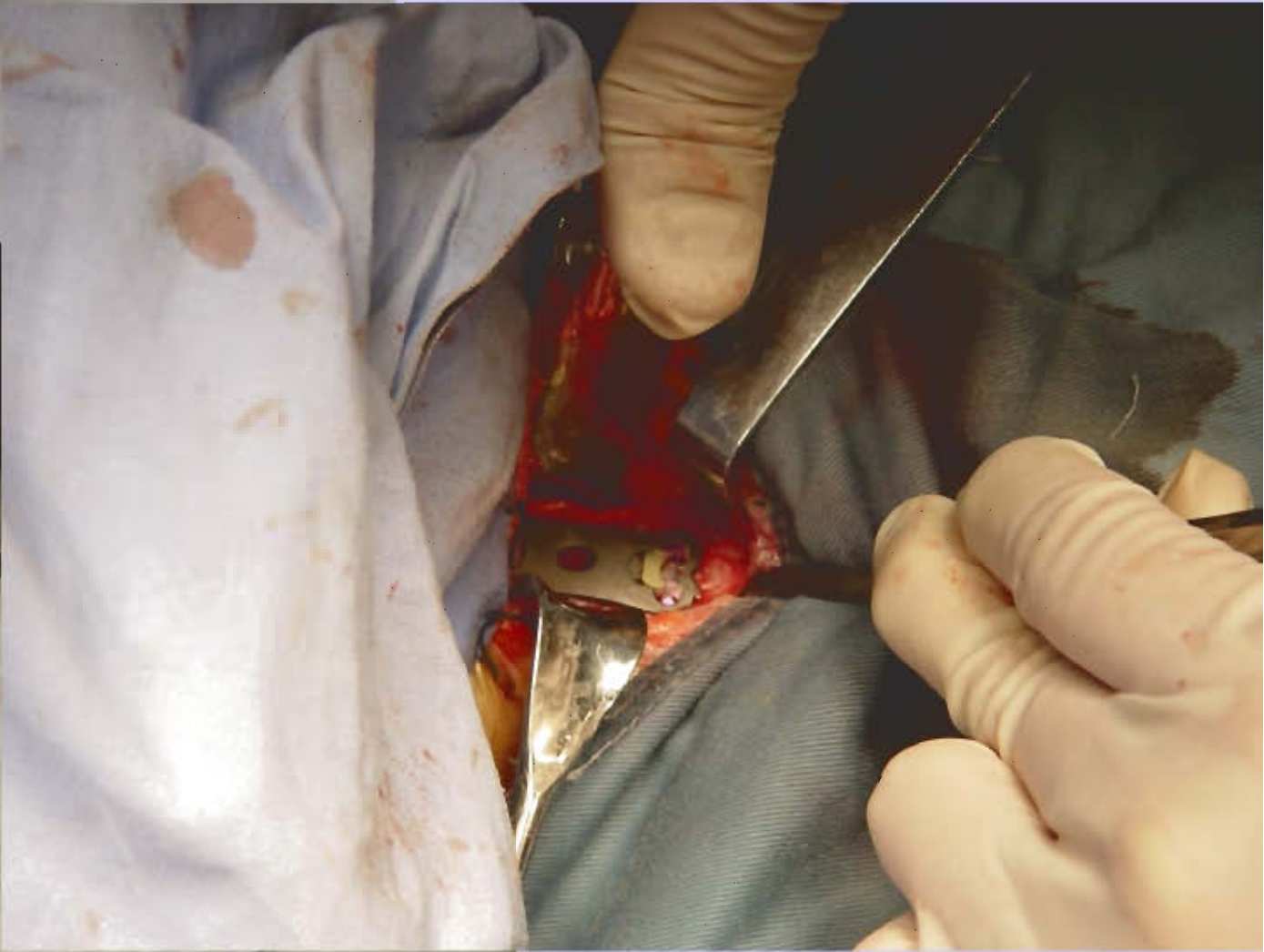
Diagram of rabbit vertebrae and graph.

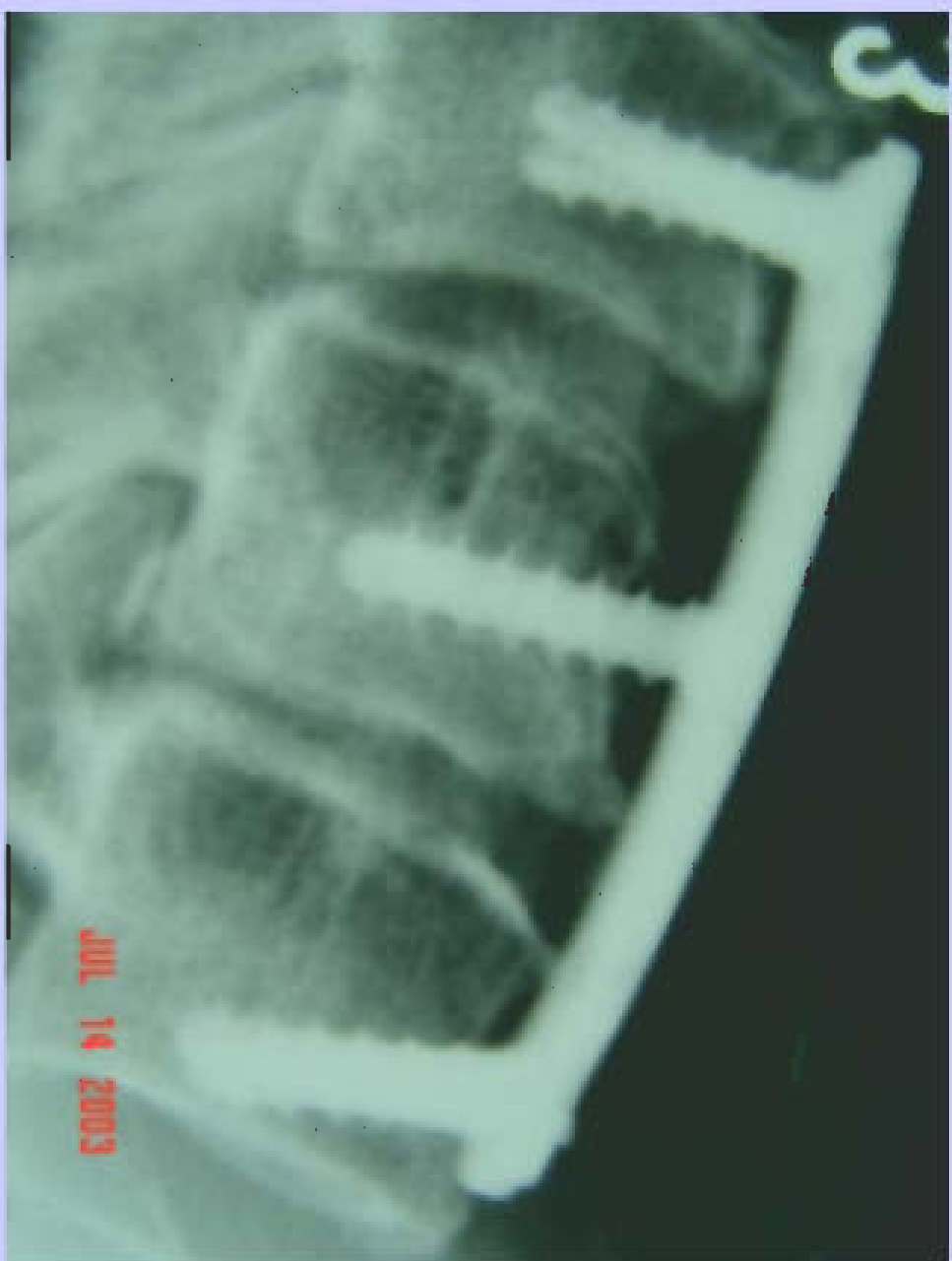
See:-

Liao, S. S., K. Guan, F. Z. Cui., et. al. "Lumbar Spinal Fusion with a Mineralized Collagen Matrix and rhBMP-2 in a Rabbit Model." *Spine* 28, no. 17 (Sept. 1, 2003): 1954-1960.

Six week, 6周 最大拉伸应力







Clinical trials

More than 500 patients of bone defect were healed by using the NHAC/PLA scaffold.

SFDA approved the product in April,
2004

- **From this study, we recognized that good design for scaffold materials of tissue engineering should be as close as to the extracellular matrix of the tissue both in composition and in structure.**