

## Ockham's Razor and CD34+

There is something new in the history of bone grafting in the maxillofacial region, where 500,000 bone grafts are done each year in the United States alone. Reconstructive surgeons have just completed a 10-year phase using BMP-2 on bovine collagen as the primary bone grafting material for spinal fusion, orthopedic and maxillofacial defect repair, and treatment of congenital anomalies such as alveolar clefts. After the cloning of BMP-2 by Wozney in 1988, there was always the thought that with autoinduction by signaling protein, bone would soon follow, recruiting matrix along the way, seemingly effortlessly. Like Ockham's razor, which states that the simplest explanation, all things being equal, is generally the best explanation, so with bone grafting: The problem of osseous defect repair should be solved simply and elegantly, one ingredient (BMP-2) being all that is required for almost any skeletal problem. But surgeons eventually discovered that is not how the signaling protein works for large or complex defects, which require the addition of bone mineral matrix and now bone marrow cells for graft replacement to perform optimally, as reported in this issue of the journal.

We now know there are stem cells specified in the body to aid in early bone repair. Reported in this issue by Marx and Harrell is the use of CD34+ stem cells segregated and concentrated from bone marrow aspirates and added to a composite of BMP-2/ACS/allograft to jump-start early bone healing. This is reminiscent of the work Connolly did in the 1980s on the repair of nonunion tibial fractures—often infected, with bone marrow aspirate only. Connolly found that percutaneous injection of 15 to 20 cc of stromal blood led to union in a high proportion of patients treated—in fact, some patients treated previously by surgical intervention with failed free bone grafts. He remarked that “bone marrow injection was as effective as bone grafting.” Once again, Ockham's simpler explanation.

The inventor's paradox in medical science seeks a solution to a specific problem by employing a more general principle. In other words, one needs to look at the big picture. Why nonunion fractures do not heal with local mortising of bone grafts or why segmental mandibular defects do not consistently heal with addition of only a signaling protein are examples of scientists needing to solve a specific problem but doing so by approaching a more general problem.

Marshall Urist, Hari Reddi, and others first established that a protein fraction of bone caused bone formation. They theorized that this substance was what Urist called in 1970 “a morphogenetic property,” or what Reddi termed “the bone factor”—the “living glue” or “bone glue” for piecing fragmented bones together.

Indeed, in 1965 Urist published on the use of bovine bone material to treat elderly hip fractures, the bone glue making “hips as strong as an oak, even stronger than natural hips.” Later he narrowed his search to “bismuth staining proteoglycans with attachment to collagen fibrils—a macromolecular protein complex with morphogenetic activity.” But how did the glue work? Certainly not as glue in a biochemical sense; for a reconstructive surgeon, a bone graft must incorporate into basal bone, ie, become “glued” into place and remain inseparable.

Of interest now is the capability of the CD34+ cell to progress along both MSC and HSC lineages. Such cells have plasticity, with both angiogenic and osteogenic potential. Once again, Ockham's putative perfect combination for relatively avascular bone defect sites.

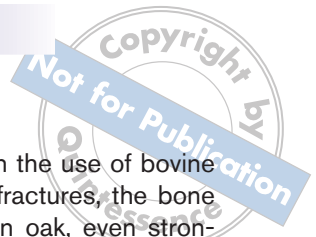
One of the advantages of vascular anastomosis of grafts to the craniofacial skeleton is the almost seamless incorporation a vascularized graft obtains. It appears that vascularity early on is the key to a transfer graft becoming glued, or what Burchardt called “annealed,” into place. This is one of the ways that signaling molecules such as BMP-2 work, a dual pathway of blood vessel/bone matrix elucidation.

However, the practicing clinician, be it neurosurgeon, orthopedist, or maxillofacial surgeon, cannot afford to look for the simplistic, but must instead be *heuristic*, that is to say, make a best guess, work by trial and error, and practice by “rule of thumb.” Francis Crick said, “Ockham's razor is a useful tool in the physical sciences but very dangerous to implement in biology. It is thus very rash to use simplicity or elegance as a guide to biological research.”

In 2003, Dr Reddi wrote a review of Dr Urist's life for the *Journal of Bone and Joint Surgery* describing him as the leader in the field during his lifetime. Dr Reddi continues in that tradition and we are honored that he is now one of our associate editors. He joins other prominent tissue engineers, such as Robert Marx and Minoru Ueda, all of whom focus much of their scientific effort on the tissue engineering of bone. That bone regeneration remains such a complex unfolding mystery with no simple solution in sight is perhaps the heuristic opportunity tissue engineering science needs, as the milieu of regeneration within a functional matrix develops into a future where clinicians re-form and not just “glue” onto that which is lost.



Ole T. Jensen, DDS, MS  
Editor-in-Chief





## A. Hari Reddi Appointed OCTE Associate Editor

Professor A. Hari Reddi received his PhD in 1966 from the University of Delhi, India. He moved to the United States in 1968 for his postdoctoral fellowships at Johns Hopkins University and the University of Chicago. In Chicago he worked on bone induction with Nobel Laureate Dr Charles Huggins. He moved to the National Institute of Dental Research, National Institutes of Health, in 1975 and became the chief of the Bone Cell Biology Section. In 1991 Prof Reddi returned to academia when he was appointed Professor and Percy Endowed Professor of Orthopaedics and Professor of Biological Chemistry at the Johns Hopkins University School of Medicine. In 1997, he was appointed the Lawrence Ellison Endowed Chair at the University of California, Davis, School of Medicine.

Over the last 40 years, Dr Reddi's research group has demonstrated the dynamic reciprocal interactions between the extracellular matrix and the growth factors and morphogens involved in bone morphogenesis. He and his team isolated, purified, and characterized bone morphogenetic proteins (BMPs). The molecular mechanism of bone induction studied by his research group led to the conceptual advance that morphogens such as BMPs bound to an insoluble extracellular matrix scaffolding act in collaboration to stimulate progenitor/stem cells to form cartilage and bone.

Prof Reddi has received several awards during his career:

- 2011 Distinguished Scientist Award for Lifetime Contributions to BMP Research, Tissue Engineering Society, Philadelphia, Pennsylvania, USA
- 2004 JAPSAM Prize, Japanese Association for the Promotion of State of the Art and Science in Medicine, Nagoya, Japan
- 1997 Marshall R. Urist Award for Tissue Regeneration, Orthopaedic Research Society
- 1991 Kappa Delta Award of the American Academy of Orthopaedic Surgeons
- 1990 NIH Director's Award, National Institutes of Health, Bethesda, Maryland, USA

Prof Reddi has published over 350 scholarly articles. He is on the editorial board of several journals and has lectured all over the world as an invited speaker.