REGENERATIVE MEDICINE RESEARCH WITH BITE

World-leading research to regenerate lost or damage teeth, bone and cartilage is coming to clinical fruition at OKAYAMA UNIVERSITY

It should come as no surprise that Okayama University has a reputation for excellence in medical research: the university's nearly 150-year-old history can be traced back to the Okayama-Han Medical Training School, founded in 1870. Today, the modern university and its hospital have been designated a Core Center for Clinical Research by the Japanese government.

Notable fields of research excellence at Okayama include regenerative medicine and dental treatment — two fields that come together in the laboratory of Takuo Kuboki at the university's Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. The work on tooth, bone and cartilage regeneration performed in Kuboki's lab — for which Mitsuaki Ono was designated top young researcher at Okayama University in 2016 — spans fundamental research to highly applied projects.

Kuboki and colleagues Ono and Emilio Hara are pioneering the clinical use of a protein called bone morphogenetic protein 2 (BMP-2) that drives new bone formation. One strategic use of BMP-2 is in dentistry. Currently, almost half of dental patients with missing teeth are unable to receive dental implants because they have lost too much of the alveolar bone to attach an implant. Ono's work suggests that BMP-2 therapy could regenerate that missing bone.

However, currently available cell-derived BMP-2 is expensive. To remedy this, the team is working with a Japanese start-up company to develop a low-cost system based on the bacterium *Escherichia coli* to produce BMP-2. "Recent tests in large animals have demonstrated the safety and efficacy of this recombinant BMP-2 for regenerating alveolar bone," Kuboki says. "After almost 15 years of research, we are now close to satisfying the requirements for using *E. coli*-BMP-2 in a clinical trial with human subjects," he adds.

Meanwhile, collaborating with researchers at the National Institutes of Health in the USA, Ono has focused on basic research to better understand and control the activity of BMP-2 to support its clinical application. This research led to the discovery of CCN4/WISP1 as a novel modulator of BMP-2 function to enhance bone regeneration.

But the team does not just work on bone regeneration within the dental research space — Hara has also identified novel compounds that can enhance articular cartilage regeneration, and may hold great promise for osteoarthritis treatment. Moreover, Ono and Masamitsu Oshima have recently demonstrated the possibility of regenerating lost teeth themselves. In a first large-animal study, the team transplanted bioengineered tooth germ cells into the jawbones of dogs. The growing cells formed a bioengineered tooth, which, like a regular tooth, erupted through the gum and could be orthodontically moved with brackets. This suggests whole-tooth regeneration using tooth germ cells derived from a patient's own cells may become feasible. ■

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