Regenerative drug restores bone in preclinical study

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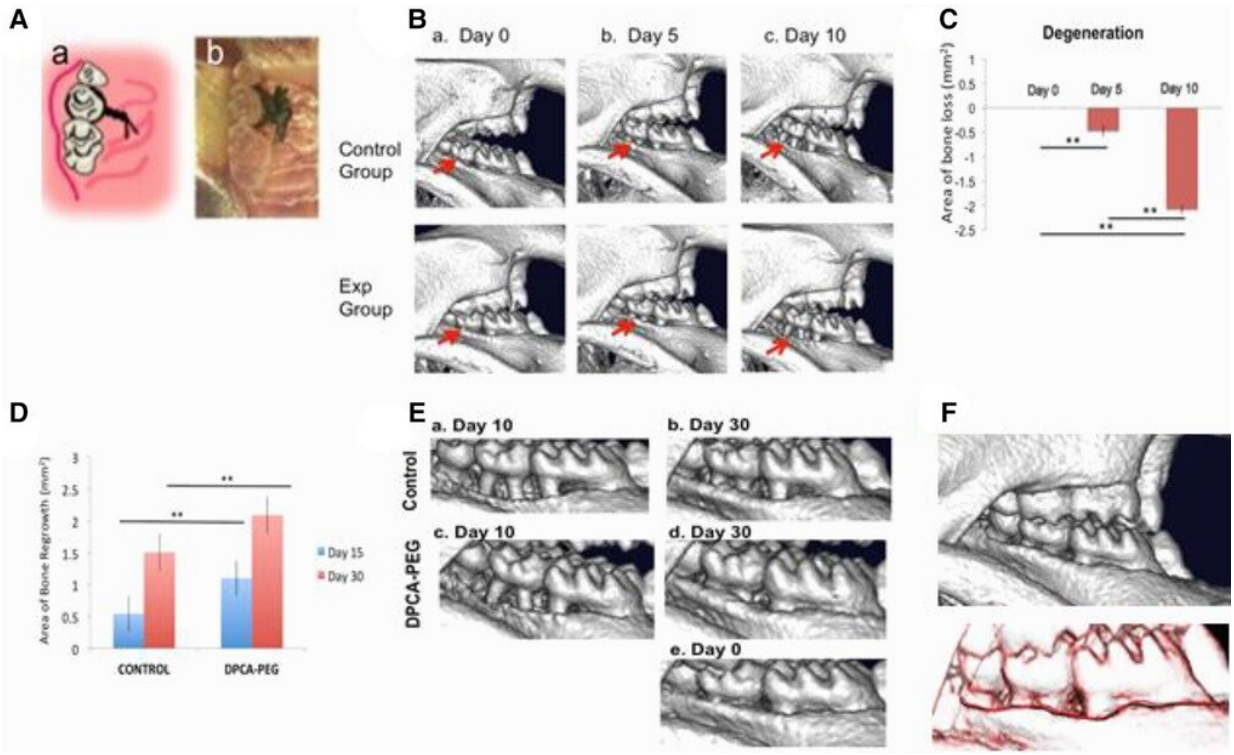

Degeneration of the mouse jawbone in the presence of ligature followed by regeneration of the jawbone post-ligature and post-drug. (Aab) The ligature-induced periodontitis model. 5–0 silk suture was passed through the interdentium between the maxillary first molar, the second molar and third molar using Dumont forceps. Suture was tied firmly using a triple-knot and excess suture was cut using spring scissors as seen in the cartoon (a) and photomicrograph (b). Taken from Ref. (31). (Ba–c) Micro-CT scans of jaws from mice during the 10 day ligature period for days 0, 5, and 10. The control group image is representative of the group (n = 3) that will not receive drug (control, upper row) and the experimental group image is representative of the group (n = 3) that will

receive drug (experimental, lower row). The red arrows show the maxillary left second molars with bone degeneration extending to the adjacent 1st and 3rd molars. For visual clarity, the images are inverted 180 degrees (now: mandible top, maxilla bottom). (C) The area of degeneration was determined for all animals tested and shown for day 5 and day 10 after ligature placement. The y-axis is: Area of bone loss (mm2); (n = 7); error bars represent standard errors; for days 0–5, p = 0.00289; for days 0–10, p = 7.33084 × 10−11; and for days 5–10, p = 3.60818 × 10−7. (**) Represents p less than 0.01. In (D), a graph of area of bone growth is seen for mice post–ligature but not given drug (no drug control) vs. mice given drug (DPCA-PEG). Mice were injected with DPCA-PEG subcutaneously on days 0 and 8 after ligature placement and removal. MicroCT scans were obtained on day 15 of the experiment (day 5 post-ligature) and on day 30 (day 20 post-ligature). Here, a statistical analysis of the area of bone growth (mm2) is seen. Significant differences are found between the no drug control mice (n = 10) and DPCA-PEG-treated mice (p = 0.00253) on day 15 (blue bars) (n = 12). The same is true on day 30, where DPCA-PEG-treated mice showed highly significant differences from non-drug-treated controls (p = 0.00612) (red bars). Area analysis was performed as described in the Materials and Methods. The Y-axis = Area of bone regrowth (mm2); the error bars represent standard errors; and p values are represented as (*) = p less than 0.05; (**) = p less than 0.01. Mouse jaws analyzed were n = 10 for ligature, no drug; n = 12 for ligature/plus drug. In (E) micro-CT data shows a representative mouse maxilla which had ligature removed at day 10, scanned on day 10 and then re-scanned on day 30 (Ea,b) as compared to a representative mouse maxilla receiving ligature and DPCA-PEG drug seen on day 10 and day 30 (Ec,d). The level of regrowth in the drug-treated group shows an almost, if not complete, return to what is seen before the start of the experiment (da0) (Ed,e). In (F), there was no change in bone histology approximately 6 months later. Mice injected with DPCA-PEG drug were kept for additional observation as they aged. Over six months after the da 30 scan, mice were rescanned (upper panel) and then compared to the day 30 scan by overlaying the two scans on da 30 and da 220 (lower panel). The black line is the da 30 scan and the red line is the da 220 scan. Though shown as two lines, they are exactly overlapping. This result is representative of three mice. Credit: *Frontiers in Dental Medicine* (2022). DOI: 10.3389/fdmed.2022.992722

Bone loss is a part of aging that compromises quality of life and movement in many older people, but regenerative treatments to improve their health and well-being have been limited. Now, a study led by Lankenau Institute for Medical Research (LIMR) scientist Ellen Heber-Katz, Ph.D., has demonstrated the ability of an experimental regenerative medicine developed in her lab to restore bone in an animal.

The preclinical study focused on a model of periodontal disease, which causes gum and bone loss that lead to tooth loss. In older individuals, the disease not only causes pain and discomfort but is the most common cause of tooth loss, affecting 30-60% of adults. However, study results showed that time release of the experimental drug, called 1,4-DPCA, fully restored diseased gums and the surrounding jaw bone, completely preventing tooth loss. Findings were published in November by the Heber-Katz team at LIMR, part of Main Line Health, in the journal *Frontiers in Dental Medicine*.

"Development of this experimental drug represents one of the most cutting-edge research directions LIMR has driven in the 21st century," said George Prendergast, President and CEO of the Institute. "In going beyond the uncertainties of stem cell treatments, this study also offers the first preclinical proof of concept for an off-the-shelf drug that could dramatically improve the health span of an individual by regenerating bone. It also for the first time suggests the potential anti-aging uses for this drug treatment as far as broadening how it can be used to instruct perfect healing by the body."

The periodontal disease treatment is one branch of Heber-Katz's research in regenerative medicine, a field that she pioneered in a shocking new direction in the mid-1990s. That's when she discovered a strain of laboratory mice that disproved the scientific assumption that only starfish and amphibians like salamanders were capable of healing wounds in a way that looked as if the injury never occurred.

"The results of this study are as powerful as we could have anticipated," said Heber-Katz, the Daniel B. and Florence E. Green Endowed Chair in Regenerative Medicine Research. "The restoration of significant amounts of lost bone and tissue was complete. I'm optimistic that this drug will move forward and eventually be used to prevent tooth loss in patients suffering from periodontal disease—one of the many ways we think it could be useful."

The drug 1,4-DPCA works by inhibiting a molecule that blocks production of a master molecule called hypoxia-inducible factor-1 (HIF-1a), a key component that is part of the body's healing response. By temporarily elevating HIF-1a, the drug shifts a tissue's metabolic state toward one used in early fetal development, where perfect healing without scarring is possible.

Heber-Katz came to LIMR, an organization with expertise in early drug discovery and development, to advance work on compounds like 1,4-DPCA to activate HIF-1a. The work was based on her earlier biological research on how tissue regeneration can be stimulated during the body's healing response to an injury.

Among Heber-Katz's fellow researchers were LIMR faculty members Azamat Aslanukov, Ph.D., and Kamila Bedelbaeva, MD, Ph.D.. Other collaborating researchers were from the University of Pennsylvania School of Dental Medicine and UC Berkeley.

Heber-Katz has two related patent-pending products that are nearing the stage of human testing:

- Medicines composed of 1,4-DPCA or related compounds that are formulated as topical or injectable hydrogels. These formulations are used to promote skin healing or restore skin integrity, including tissue damaged by natural aging. Chronic

wounds often do not heal for older people
- Sutures infused with 1,4-DPCA to prevent scarring during the healing of surgical wounds

More information: Elan Zebrowitz et al, Prolyl-hydroxylase inhibitor-induced regeneration of alveolar bone and soft tissue in a mouse model of periodontitis through metabolic reprogramming, *Frontiers in Dental Medicine* (2022). DOI: 10.3389/fdmed.2022.992722

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