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Potential treatment found for debilitating bone disease in wounded soldiers and children

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Promising new research reveals a potentially highly effective treatment for heterotopic ossification (HO), a painful and often debilitating abnormal buildup of bone tissue. HO comes in two main forms—one that appears in children and is congenital, another that strikes wounded military personnel and surgery patients and is triggered by severe injuries and wounds.

An animal study by developmental biologists shows that a drug that interrupts a signaling-nuclear protein pathway can prevent HO. The study appeared online today in *Nature Medicine*.

"There are currently no effective treatments for this disease," said study leaders Masahiro Iwamoto, D.D.S., Ph.D., and Maurizio Pacifici, Ph.D., developmental biologists in the Division of Orthopaedic Surgery at The Children's Hospital of Philadelphia. "Surgeons can remove the abnormal bone masses, but surgery itself may trigger more of those growths."

Calling the work an "elegant study," Frederick Kaplan, M.D., said that it "addresses a vast unmet need in clinical medicine." Kaplan, the Isaac & Rose Nassau Professor of Orthopaedic Molecular Medicine at The University of Pennsylvania School of Medicine, who wrote a commentary on the research in the same issue of *Nature Medicine*, added that the study "provides great hope, insight and direction for the development of effective medications to prevent and treat catastrophic

extraskeletal bone formation."

Iwamoto and Pacifici recently came to Children's Hospital from Thomas Jefferson University, where they performed the study. Pacifici holds the new Bong Lee Endowed Chair in Pediatric Orthopaedics at The Children's Hospital of Philadelphia, where he is director of Orthopaedic Research.

The exact mechanism by which HO occurs is not fully understood, but trauma, surgery or deep burns cause local inflammation, followed by the arrival of skeletal cells that develop into chondrocytes (cartilage cells), and are then replaced by intrusive bone. Thus, 10 to 13 percent of orthopedic patients may develop HO, mostly without major symptoms, after knee replacement or other invasive surgeries. The incidence of HO is far higher in wounded soldiers—nearly 65 percent—because modern weapons cause extreme, wide and deep tissue damage.

Although HO is not life-threatening, the bone growths can press against nerves and blood vessels, resulting in chronic pain, limited motion, problems fitting prosthetic limbs and other complications.

The congenital form of the disorder is called fibrodysplasia ossificans progressiva (FOP) and becomes manifest in children by the age of 5 or 6. While very rare, affecting an estimated 700 U.S. children, it is progressive and often fatal in young adults. Surgery cannot be used in children with FOP because it would trigger explosive HO.

In the current study, Iwamoto and colleagues used retinoid agonists, a class of agents related to vitamin A, in mice that were genetically engineered to model HO. Specifically, they used nuclear retinoic acid receptor-γ (RAR-γ) agonists, which selectively target a regulatory pathway during cartilage formation—an essential step in the development of HO.

The RAR-γ agonists prevented HO from occurring in the mice, with minimal side effects. In contrast, control mice developed HO-like bone masses. Even more encouragingly, the protective effect appeared to be permanent, persisting even after drug treatment ended.

Furthermore, the same agent blocked HO from occurring in mice that had been genetically engineered to express a mutant protein analogous to the one found in children with FOP.

"These agents have the biological properties needed to interfere with the specific events that occur in HO," said Pacifici. "If these animal results are borne out in humans, we may have very potent and effective treatments for both forms of this disease—injury-induced HO and the congenital form."

The authors cautioned that more in-depth preclinical studies must be performed before retinoid agonists are tested in humans with HO. They pointed out, however, that one retinoid agonist is already being used in a current clinical trial for another disease, and it might be possible to gain access to this agent from the manufacturer for clinical trials.

More information: "Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-γ agonists," *Nature Medicine*, published online April 3, 2011. doi:10.1038/nm.2334

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