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Fish Scales and Bullfrog Skin Targeted for Oral Tissue Repair

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NTU Singapore

Researchers at Nanyang Technological University (NTU) Singapore have developed a biomaterial made entirely from discarded bullfrog skin and fish scales that could help in bone repair, including the jawbone, and in other oral tissue regeneration.

The porous biomaterial, which includes the same compounds that are predominant in bones, acts as a scaffold for bone-forming cells to adhere to and multiply, leading to the formation of new bone.

The researchers have found that human bone-forming cells seeded onto the biomaterial scaffold successfully attached themselves and started multiplying, which is a sign of growth. Also, the risk of the biomaterial triggering an inflammatory response is low.

Such a scaffold could be used to help with the regeneration of bone tissue lost to disease or injury, such as jaw defects from trauma or cancer surgery. It also could assist bone growth around surgical implants such as dental implants.

The researchers believe the biomaterial is a promising alternative to the current standard practice of using a patient's own tissues, which requires additional surgery for bone extraction.

At the same time, the production of this biomaterial tackles the problem of aquaculture waste, said assistant professor Dalton Tay of the NTU School of Materials Science and Engineering, who led the multidisciplinary study.

More than 20 million tons of fishery byproducts such as fins, scales, and skins are discarded every year, NTU said. In Singapore, about 100 million kilograms of frog flesh and fish are consumed each year, making bullfrog skin and fish scales two of its largest aquaculture waste side streams.

"We took the waste-to-resource approach in our study and turned discards into a high-value material with biomedical applications, closing the waste loop in the process," Tay said.

"Our lab studied showed that the biomaterial we have engineered could be a promising option that helps with bone repair. The potential for this biomaterial is very broad, ranging from repairing bone defects due to injury or aging to dental applications for aesthetics," Tay said.

"Our research builds on NTU's body of work in the area of sustainability and is in line with Singapore's circular economy approach towards a zero-waste nation," Tay said.

"These waste streams can also be converted into green chemicals and materials for environmental remediation and timely treatment can reduce wastewater contamination," said Matthew Hu Xiao, coauthor and director of the Environmental Chemistry and Materials Centre, Nanyang Environment and Water Research Institute.

"The National Dental Centre Singapore is excited about the use of bullfrog skin as a natural biomaterial for tissue regeneration," said clinical associate professor Goh Bee Tin, director for research at the National Dental Center Singapore, who was not involved in the study.

"We see many potential dental applications ranging from the regeneration of gum tissues in periodontal disease to bone for placement of dental implants to jawbone following tumor surgery," Bee Tin said.

"Obviating the need for additional bone harvesting surgery also translates to time and cost savings and less pain for patients," Bee Tin said.

The researchers have filed patents for the biomaterial's wound healing and bone tissue engineering applications. They now are evaluating its long-term safety and efficacy for dental products under a grant from the China-Singapore International Joint Research Institute and aim to bring the waste-to-resource technological pipeline closer to commercialization.

The researchers collected the fishery waste for their experiments from the Khai Seng Fish Farm and Jurong Frog Farm. They extracted hydroxyapatite (HA) from the scales of snakehead fish, commonly known as the Toman fish.

Also, the researchers extracted Type 1 tropocollagen, many molecules of which form collagen fibers, from the discarded skins of the American bullfrog, locally farmed and imported into Singapore in large numbers for consumption.

HA and collagen are two predominant components found in bones, conferring a structure, composition, and ability to promote cell attachment that are like bone on the biomaterial. These two components also make the biomaterial tough.

The researchers removed all impurities from the bullfrog skin and blended it to form a thick collagenous paste diluted with water. They then extracted collagen from this mix.

"Using this approach, we were able to obtain the highest ever reported yield of collagen of approximately 70% from frog skin, thus making this approach commercially viable," said Tay.

The researchers harvested HA from discarded fish scales through calcination, which is a purification process that requires high heat, to remove the organic matter, and then air-dried.

The biomaterial was synthesized by adding HA powder to the extracted collagen and then case into a mold to produce a 3D porous scaffold. The entire process took less than two weeks, and the researchers believe it can be further shortened and scaled up.

To assess the biological performance of the porous biomaterial scaffold for bone repair, the researchers seeded bone-forming cells onto the scaffold. The researchers found that the number of cells increased significantly.

After a week, the cells were uniformly distributed across the scaffold, indicating that it could promote proper cellular activities and eventually lead to the formation of tissues. The presence of HA in the biomaterial also significantly enhanced bone formation, the researchers said.

The biomaterial also was tested for its tendency to cause an inflammatory response, which is common after a biomaterial is implanted in the body.

Using real-time polymerase chain reaction, the researchers found that the expression level of pro-inflammatory genes in human immune cells exposed to the biomaterial remained relatively modest compared to a control exposed to endotoxins, a compound known to stimulate immune response, said Tay.

For instance, the expression of the gene IL6 in the biomaterial group was negligible and at least 50 times lower than that of the endotoxins-exposed immune cells. This suggests that the risk of the NTU-developed biomaterial to trigger an excessive acute inflammatory response is low.

Taken together, the researchers said, these findings demonstrate the potential of the biomaterial scaffold, synthesized from discarded bullfrog skin and fish scales, as a promising waste-to-resource bone graft substitute material for bone repair and regeneration.

"The aquaculture industry is an important avenue to meet the global growing demand for safe and quality seafood, but a big challenge we face is the huge wastage and downcycling of valuable aquatic resources," said Chelsea Wan, director of the Jurong Frog Farm.

"The integration of multiple seafood waste streams into a single high-value product is a leading example of sustainable innovation for the aquaculture industry," Wan said.

The researchers hope to work with clinical and industrial partners on animal studies to find out how tissues in the body would respond to the biomaterial in the long term and its ability to repair bone defects and dermal wounds, as well as to bring the entire waste-to-resource technological pipeline closer to commercialization.

The study, "Sustainable Aquaculture Side-Streams Derived Hybrid Biocomposite for Bone Tissue Engineering," was published by *Materials Science and Engineering C*.