

'Bone in a dish' opens new window on cancer initiation, metastasis, bone healing

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Luiz Bertassoni D.D.S., Ph.D., and Avathamsa Athirasala, M.Sc.Eng., inspect the 3D mineral structure populated with living cells, providing a unique model to study bone function, diseases, regeneration. Credit: OHSU/Joe Rojas-Burke

Researchers in Oregon have engineered a material that replicates human

bone tissue with an unprecedented level of precision, from its microscopic crystal structure to its biological activity. They are using it to explore fundamental disease processes, such as the origin of metastatic tumors in bone, and as a treatment for large bone injuries.

"Essentially it is a miniaturized bone in a dish that we can produce in a matter of 72 hours or less," says biomedical engineer Luiz Bertassoni, D.D.S., Ph.D., an assistant professor in the OHSU School of Dentistry and a member of CEDAR, the Cancer Early Detection Advanced Research Center in the OHSU Knight Cancer Institute.

Like real bone, the material has a 3-D mineral structure populated with bone cells, nerve cells and [endothelial cells](#) that self-organize into functioning [blood vessels](#).

"What is remarkable is that researchers in our field have become used to cultivating cells within a protein mixture to approximate how cells live in the body. But this is the first time anyone has been able to embed cells in minerals, which is what characterizes the bone tissue," Bertassoni says.

And that's what makes the new material promising as a model to study bone function, diseases, and bone regeneration. "With this [model system](#), you can start asking questions about how bone cells attract different types of cancers, how cancer cells move into bone, how bone takes part in the regulation of marrow function," says Bertassoni.

"It can even be relevant to dissect the mechanisms that are leading to diseases such as leukemia." Bertassoni published the results in the journal *Nature Communications* with postdoctoral researcher Greeshma Nair, Ph.D., doctoral student Avathamsa Athirasala, M.Sc.Eng., and other co-authors.

"Being able to engineer truly bone-like tissues in the lab can also be

transformative for regenerative medicine," Bertassoni says, "since the current treatment for large bone fractures requires the removal of the patient's own healthy bone so that it can be implanted at the site of injury."

The recipe starts with the mixing of human stem cells into a solution loaded with collagen, a protein abundant in the matrix of [bone tissue](#). The collagen proteins link together, forming a gel embedded with the stem cells. The researchers then flood the gel with a mixture of dissolved calcium and phosphate, the minerals of bone. They add another key ingredient, the protein osteopontin derived from cow milk, to keep the minerals from forming crystals too quickly. This additive, which clings to calcium and phosphate, also minimizes the minerals' toxicity to cells.

The mixture diffuses through a network of channels about the width of a strand of DNA in the spongy collagen, and the dissolved minerals precipitate into orderly layers of crystals.

"We can reproduce the architecture of bone down to a nanometer scale," says Bertassoni. "Our model goes through the same biophysical process of formation that bone does."

In this calcified environment, stem cells develop into functioning bone cells, osteoblasts and osteocytes without the addition of any other molecules, as if they knew they were being embedded in an actual bone matrix. Within days, the growing cells squeeze slender protrusions through spaces in their mineralized surroundings to connect and communicate with neighboring cells. The bone-like engineered structure creates a microenvironment that is sufficient to cue [stem cells](#) that it's time to mature into [bone cells](#).

"It's nature doing its job, and it's beautiful," Bertassoni says. "So, we went farther and decided to try it with the bone vasculature and

innervation as well."

Nerve cells added to the mixture formed interconnected networks that persisted after mineralization. Endothelial cells, likewise, formed networks of tubes that remained opened after mineralization.

To test the usefulness of the material as a disease model, the researchers implanted their engineered bone beneath the skin of laboratory mice. After a few days, the lab-made blood vessels had connected with the vasculature in the mouse bodies. When the researchers injected prostate [cancer cells](#) nearby, they found that tumor growth was three times higher in the mice given mineralized bone constructs than in those with the non-mineralized controls.

The team now is engineering versions with marrow [cells](#) growing within a surrounding of artificial bone for use as a model to study the initiation and development of blood cancers including the various forms of leukemia. Also, they have tested the engineered bone-like material as a replacement for injured [bone](#) in animal models—with positive results that they expect to report in the near future.

More information: *Nature Communications* (2019). [DOI: 10.1038/s41467-019-11455-8](#)

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