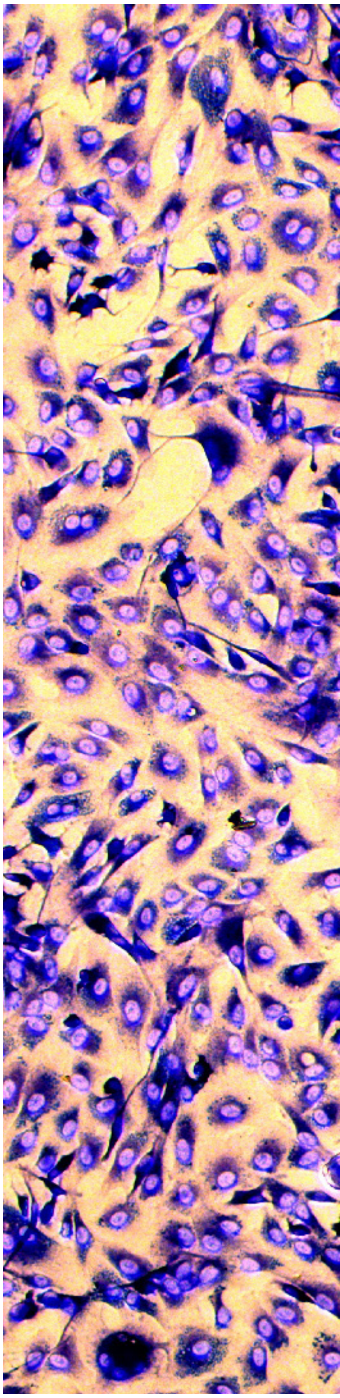

Cellular Scaffolding and pharmacies to repair bone tissue

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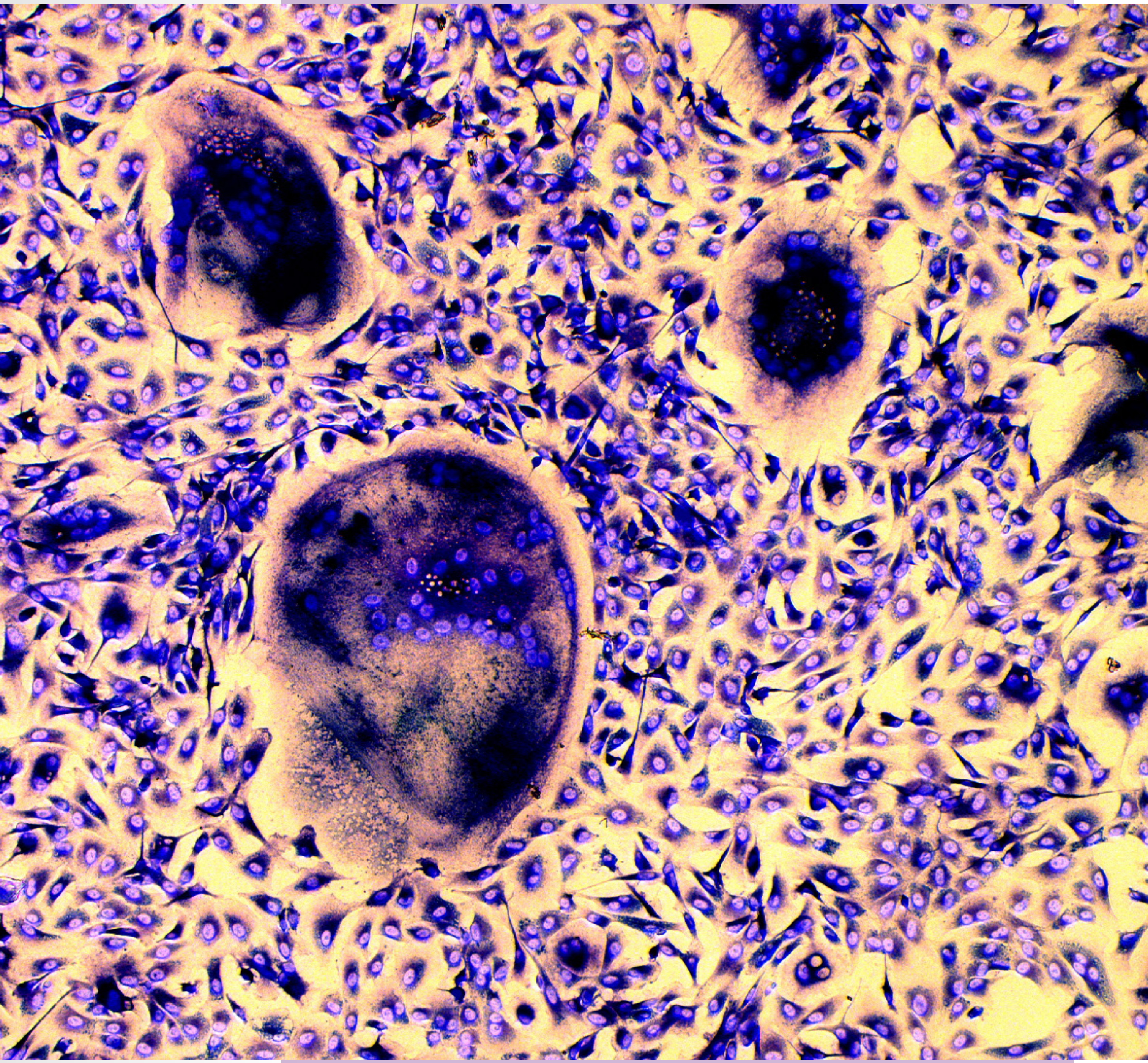


Microphotograph of human bone tissue. Photo: University of Florence - Creative Commons 3.0 Wikimedia Commons license.

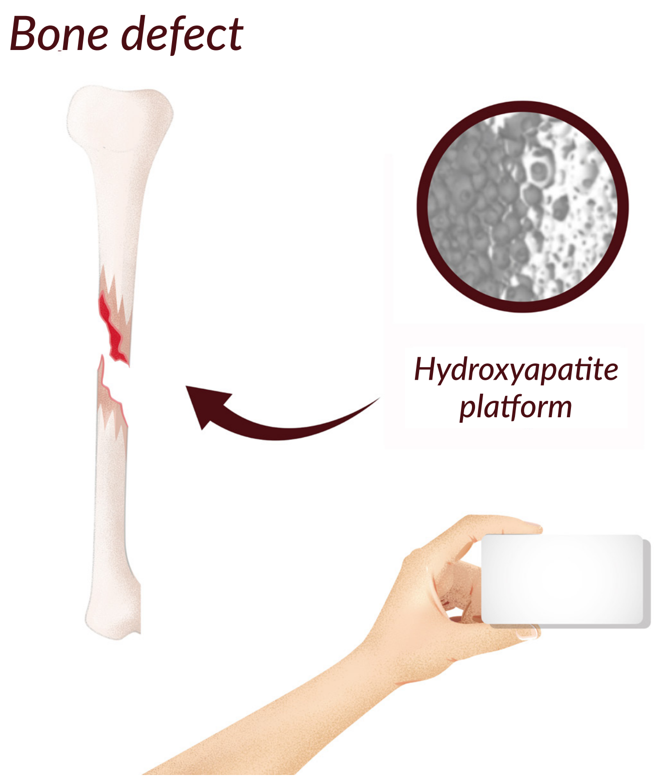
Orthopedic devices, such as bone implants or cell-culture platforms, are important elements in maintaining the quality of life of people whose health has deteriorated due to accidents, illness or age. Today, materials research is enabling these devices not only to fulfill a replacement function but even to release drugs and other substances so that the body better accepts the implant.

Orthopedic devices comprise a wide range of materials that are used to support the functions of the spine, joints, ligaments, muscles and tendons. They are also used to aid recovery from illness or injury to the muscular and skeletal system, which enables us to move. These devices are additionally used to complete or replace a damaged or missing bone or joint.

The demand for these devices is growing due to the increase in the elderly population, which, in turn, brings more related ailments, such as osteoporosis and arthritis. Another reason for the growing demand is the higher number of sports injuries and traffic accidents of our time. All this stimulates research on minimally invasive surgical procedures and recent advances in medical technology. It also reveals the need to develop national products that are more affordable and in tune with the country's economic possibilities.

Today, it is possible to imagine these devices for uses that go far beyond "replacing" tissue or a bone. In fact, materials are being developed so that an implant can also be a medicine cabinet that helps the body accept it better.

For example, in the Pyrometallurgical and Materials (Gipimme) and Ceramic Materials and Coatings (Gimacyr), research groups, from Universidad de Antioquia's Faculty of Engineering, we develop materials that aim to improve the quality of life of patients who must undergo surgical interventions that require the implantation of the so-called cell-culture platforms. These are a type of scaffolding used as a guide and support for cell growth in damaged bones.



The cell-culture platforms that the group created and used in bone regeneration are made of hydroxyapatite.
Image: Hamilton Copete López / Carolina Gomes.

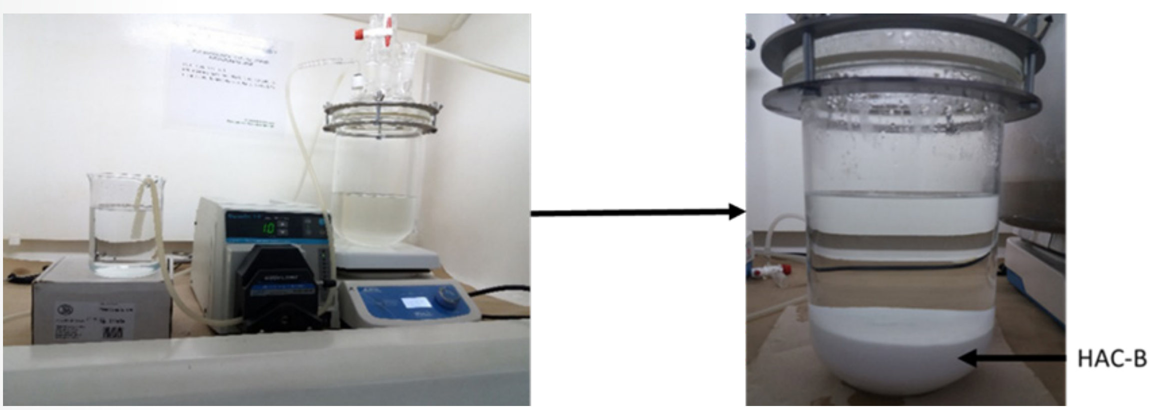
One of the materials used for this purpose is hydroxyapatite (HA). This is the most widely used calcium phosphate in bone regeneration and replacement because its chemical composition is the closest to the mineral part of human bone. This ceramic material has a long history of use as a biomaterial in bone grafting and bone tissue engineering due to its biocompatibility, bioactivity, osteoconductivity, non-toxicity and absence of pyrogenic or inflammatory reactions.

Biocompatibility	Absence of, among others, allergic or immune reactions to the contact between an organism's tissues and some materials.
Bioactivity	A material's ability to interact chemically with an organism's tissues. This ability can be determined by the formation of a calcium- and phosphorus-rich layer on the surface of the material.
Osteoconductivity	A material's ability to act as a structural support in the formation and growth of new bone, for which the implant must be reabsorbed and make room for the new tissue it initially helped to support.
Pyrogen	Any fever-producing agent, i.e., substances that act on the thermoregulatory centers of the hypothalamus and increase the body's temperature.

> Chitosan promotes cell adhesion and is then reabsorbed by the organism through hydrolysis processes. This takes place through the enzymatic action of fluids in the organism, which makes chitosan biodegradable and easily assimilated by the body.

During the synthesis of hydroxyapatite, it is possible to incorporate carbonate ions, for example, and use them to replace other ions, such as hydroxyl or phosphate. Ions are free atoms or molecules with a positive or negative charge that easily bond to other atoms. Depending on the ions present in the material, it is classified as type A and type B. Hydroxyapatite consists of calcium (Ca^{2+}), phosphate (PO_4^{3-}) and hydroxyl (OH^-) ions. During synthesis, these ions can be modified to accelerate their integration into the body. When the carbonate ion (CO_3^{2-}) is used and replaces the hydroxyl ions, it is called type A, and when the removed ion is phosphate, it is called type B (Figure 2).

Type B, also known as biological hydroxyapatite, is the main constituent of human bone. This has made it a material with high po-



Assembly of HAC-B synthesis (right, precipitate obtained during synthesis) tential for biomedical applications, which calls for further research that seeks to synthesize type-B carbonate hydroxyapatites. These have physicochemical properties similar to the biological one, and their implantation process allows the human body to accept such materials better and faster.

The synthesis of this type-B carbonated hydroxyapatite (HAC-B) is carried out in a hermetic reactor under controlled conditions of temperature, atmosphere, addition of precursors, pH and maturation times, as shown in Figure 3.

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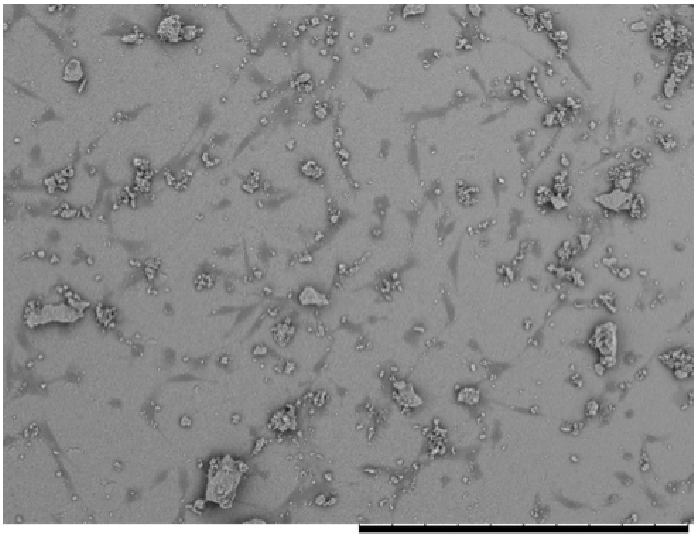

Bone cells on the surface of HAC-B. Osteoblastic cells (dark areas) on the surface of the ceramic material show affinity and spreading over the entire surface. Photo: Hamilton Copete, Carmen Baudín (Instituto de Cerámica y Vidrio, COOPA project 20289, Spain)

Implants with Drugs for Better Acceptance by the Body

Hydroxyapatite is also used in matrices for controlled drug release. Matrices are structures that, while supporting tissue recovery, gradually release drugs. Thus, after the synthesis of the material, our group created porous structures able to transport and control the delivery of antibiotics. This opens new perspectives for improving the human body's response to the presence of synthetic materials and decreases the likelihood that the body will reject them.

This advance also shows a glimpse of the contributions to the treatment and prevention of diseases such as osteomyelitis. This disease is caused mainly by a bacterial infection of *Staphylococcus* au reus, which can be contracted during the orthopedic surgical processes necessary to place an implant inside the organism. If this disease is not treated in time, it can cause the death of bone cells, affect the vascular system and attack the surrounding soft tissue.

One of the main clinical challenges in the treatment of osteomyelitis is the ability of S. aureus to lodge itself inside the cells responsible for generating and maintaining bone: osteoblasts. This ability allows it to protect itself from the body's defenses and antibiotics since these cannot penetrate the cell and attack the bacteria.

It is in the prevention of these complications that we see the importance of developing materials for implants since such materials can generate bone substitutes that release antibiotics in a localized manner. So far, materials that have good affinity with bone cells have been manufactured, as can be seen in Figure 3. These cells settle on the material's surface and take an extended shape that indicates good cell interaction and better cell colonization once the material is implanted.

A Biological Ally: Chitosan

Hydroxyapatite is also used in matrices for controlled drug release. Matrices are structures that, while supporting tissue recovery, gradually release drugs.

The function of harboring and releasing the antibiotic after implantation cannot be performed by the ceramic material alone because of its chemical nature. To support ceramic, a polymer such as chitosan can be used. It is abundant in the exoskeletons — the shells— of animals such as shrimp. With this material, different research has been carried out in fields such as cosmetics, agriculture, water treatment and medicine.

Chitosan promotes cell adhesion and is then reabsorbed by the organism through hydrolysis processes. This takes place through the enzymatic action of fluids in the organism, which makes chitosan biodegradable and easily assimilated by the body. In addition, it stimulates the growth, functionality and cellular activity of osteoblasts, which improves the aforementioned colonization of the implant. All these characteristics make chitosan suitable even for skin grafts, healing material and as a drug delivery vehicle, the subject of this study.

For several years, Universidad de Antioquia has been working on the development of ceramic biomaterials to solve tissue industry problems in the future. With this project, we seek to obtain a ceramic matrix biomaterial with mechanical properties similar to those of natural bone, which will also help in the prevention or treatment of infections contracted during surgical-orthopedic procedures.

We also seek to increase interest in the acquisition of this type of products manufactured in the country, which also reduces postoperative costs thanks to the prevention of infections and the faster and more effective recovery of patients. X

Project
"Development of ceramic matrix composite biomaterials for cell-culture platforms with controlled release of antibiotics for applications such as bone implants."