Stem cell, pluripotent and reprogrammable: the perspective of living robots

[1,2]Marian Proorocu, [1,3]Antonia Odagiu, [1,4,5]I. Valentin Petrescu-Mag, [6]Bogdan Georgescu

[1] Department of Environmental Engineering and Protection, Faculty of Agriculture, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania; [2] Enviromep SRL, Colonia Făget, Cluj, Romania; [3] Balkan Environmental Association, Thessaloniki, Greece; [4] Bioflux SRL, Cluj-Napoca, Romania; [5] University of Oradea, Oradea, Romania; [6] Faculty of Animal Science and Biotechnologies, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Cluj-Napoca, Romania. Corresponding author: I. V. Petrescu-Mag, zoobiomag2004@yahoo.com

Abstract. The present study aims to highlight the achievements of maximum novelty and scientific relevance obtained by a team of researchers at the border between robotics and cell biology: xenobots. Formed from the stem cells of the African clawed frog (*Xenopus laevis*) from which they take their name, the xenobots are less than a millimeter in size. The small entities were first revealed in 2020, after experiments showed that they can move, perform group operations and heal themselves. Embryonic stem cells are known to be non-specialized cells, which can follow different pathways depending on the biochemical, electrical, and hormonal signals received from neighboring cells and an information control center. It is about cellular signaling that aims to specialize the cell according to the needs of the body. The researchers cited in this article show us through their studies that by removing the cell from the influence of these regulatory signals that dictate differentiation, the stem cell becomes reprogrammable. That is, another set of stimuli or signals, different from those in the embryo, can define its destiny in terms of specialization and functioning. The cells thus disconnected from the embryo continue to work like those in the embryo, but because they are disconnected from the embryonic control center, they become susceptible to a new set of tasks and a new path of development.
Key Words: environment, health, living robots, xenobots, *Xenopus laevis*.

Introduction. The present study aims to highlight the achievements of maximum novelty and scientific relevance obtained by a team of researchers at the border between robotics and cell biology: xenobots (Ball 2020; Kravchenko & Morozova 2020; Levin et al 2020; Kriegman et al 2021). Although research on xenobots and related research rises some ethical discussions (Dabrock 2009; Botkin-Kowacki 2020; Coghlan & Leins 2020), their achievement deserves all the attention.

Formed from the stem cells of the African clawed frog (*Xenopus laevis*) from which they take their name, the xenobots are less than a millimeter in size (Ball 2020; Kravchenko & Morozova 2020; Levin et al 2020; Kriegman et al 2021). The small entities were first revealed in 2020, after experiments showed that they can move, perform group operations and self-heal (the-scientist.com; Kriegman et al 2021).

Now, scientists who developed them at the University of Vermont, Tufts University and the Wyss Institute for Biological Engineering at Harvard University have said they have discovered a completely new form of biological reproduction that is different from anything known to any plant or animal (Kriegman et al 2021). Michael Levin, professor of biology and director of the Allen Discovery Center at Tufts University, who was the lead author of the new research, said they were amazed. The researcher explained that, although frogs have their own specific way of reproducing, when you release the cells from the rest of the embryo, they discover a new way to move and find a new way to reproduce (Digi24.ro) (Figure 1).

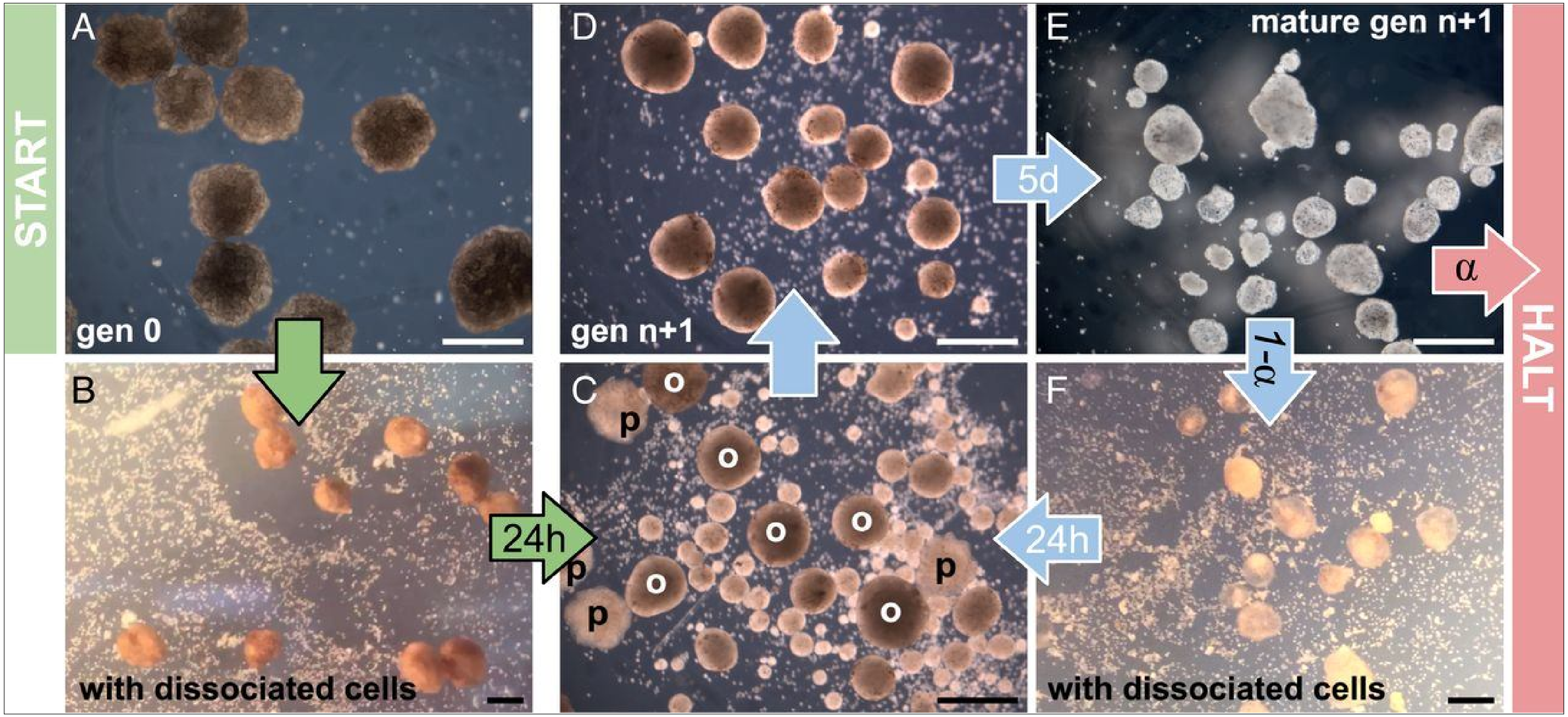

Figure 1. Spontaneous kinematic self-replication of the xenobots according to Kriegman et al (2021). (A) Stem cells are removed from early-stage frog blastula, dissociated, and placed in a saline solution, where they cohere into spheres containing ~3,000 cells. The spheres develop cilia on their outer surfaces after 3 d. When the resulting mature swarm is placed amid ~60,000 dissociated stem cells in a 60-mm-diameter circular dish (B), their collective motion pushes some cells together into piles (C and D), which, if sufficiently large (at least 50 cells), develop into ciliated offspring (E) themselves capable of swimming, and, if provided additional dissociated stem cells (F), build additional offspring. In short, progenitors (p) build offspring (o), which then become progenitors. This process can be disrupted by withholding additional dissociated cells. Under these, the currently best known environmental conditions, the system naturally self-replicates for a maximum of two rounds before halting. The probability of halting (α) or replicating (1−α) depends on a temperature range suitable for frog embryos, the concentration of dissociated cells, the number and stochastic behavior of the mature organisms, the viscosity of the solution, the geometry of the dish's surface, and the possibility of contamination (Scale bars, 500 μm) (source: Kriegman et al 2021).

The claw frog - an excellent model organism for biomedical research. The African claw frog (*X. laevis*, Figure 2) is an exclusively aquatic species that lives in freshwater, lakes, rivers, ponds and swamps in southern Africa, especially south of the Sahara. It is also known as the platanna and presents itself as a rather interesting amphibian, perfectly adapted to life at the bottom of ponds, lakes, etc. (Amaral & Rebelo 2012). The species has become increasingly important in biomedical research, such as studies in toxicology, ecotoxicology, genetics, physiology, anatomy, neurology, metabolism, cell and molecular biology (Borodinsky 2017; Lee-Liu et al 2017; Marin-Barba et al 2018; Petrescu-Mag & Grădinaru 2018; Lasser et al 2019). The species demonstrated an invasive potential (John & Tinsley 1998; Lillo et al 2011; Ihlow et al 2016; Araspin et al 2020).

Figure 2. The African clawed frog (*X. laevis*) (source: Flikr.com).

Robots or completely new life forms? Xenobots fall into both categories: they are at the same time robots and completely new life forms. However, researchers at the University of Vermont say that a more precise classification would consider them as a new class of living, programmable organisms. To produce xenobots, the researchers took living stem cells from frog embryos and let them incubate (Kriegman et al 2021).

Most people believe that robots are made of metal, silicone, and ceramic, but it's not about the materials a robot is made of, it's about what a robot does. Robot is any automatically operated machine that replaces human effort, though it may not resemble human beings in appearance or perform functions in a humanlike manner. Thus, the robot is meant to act in the service and interest of humans, believes Josh Bongard, professor of computer science and robotics, expert at the University of Vermont and lead author of the study of Kriegman et al (2021). He also said that, from this perspective, the xenobot is a robot, but it is also clearly an organism made of non-genetically modified frog cells (Digi24.ro).

Bongard said they noticed that the xenobots, which were originally sphere-shaped and made of about 3,000 cells, could replicate, but this was rare and only in specific circumstances. The researcher also explained that xenobots used kinematic replication (Kriegman et al 2021) - a process that is known to take place at the molecular level, but which has never been observed before on a cell scale or in whole organisms (Digi24.ro).

With the help of Artificial Intelligence, researchers then tested billions of body shapes to make xenobots more efficient at this type of replication (Kriegman et al 2021). The supercomputer used by scientists proposed a "C" shape that resembled Pac-Man, the well-known video game of the 1980s. They discovered that a xenobot had thus managed to find tiny stem cells in a Petri dish, gather hundreds of them in its "mouth" and, a few days later, the assembled bunch of cells turned into a new xenobot (the-scientist.com).

In other words, Artificial Intelligence did not program these machines the way we usually think of writing code, but modeled, sculpted, and created this Pac-Man shape (Kriegman et al 2021). The form is essentially the program. The shape influences the way xenobots behave to amplify this incredibly surprising process (Digi24.ro; Kriegman et al 2021).

Xenobots and their utility. Xenobots are the first "living robots" capable of self-healing. The new biological machinery can be used in a variety of areas: removing radioactive waste, collecting microplastic from the oceans, transporting drugs into the human body, or cleaning arteries from atheroma plaques (Kriegman et al 2021). They can also be used to help researchers obtain more information from cell biology, for studies on human health - birth defects, trauma, degenerative diseases, etc. - and longevity (Kriegman et al 2021). Xenobots are less than a millimeter in size, small enough to travel in the human body. They can move, swim, survive for several weeks without food, and associate in groups to perform the operations for which they were scheduled. These are completely new life forms, say researchers (Digi24.ro).

The stem cells that formed the basis of xenobots were collected from frog embryos, cultured in the laboratory, cut and modeled in certain patterns designed by a supercomputer (Kriegman et al 2021) - shapes that have never been seen in nature, according to the statement issued by the University from Vermont. Later, the cells began to grow independently - epithelial cells joined to form the structure, and living cardiac muscle cells allowed the xenobots to move on their own (Digi24.ro; Kriegman et al 2021).

Early technology that could cause concern. Xenobots are a very new, emerging technology, just like a 1940's computer that had no practical applications yet. However, this combination of molecular biology and Artificial Intelligence could be used in a number of missions in the human body and the environment, according to the researchers. This may include such things as collecting microplastics from the oceans or using them in regenerative medicine (the-scientist.com).

While the prospect of self-replicating biotechnology may be of concern, researchers say that these real living machines are produced and stored only in the laboratory and are easy to neutralize because they are biodegradable and regulated by ethics experts. The research was funded in part by the Defense Advanced Research Projects Agency, a US federal agency that oversees the development of technology for military use (Kriegman et al 2021). Bongard said that there are many things that would be possible if we wanted to take advantage of this type of technology and the ability of cells to solve health, environmental and other problems (Digi24.ro).

Programmable organisms that live a little more than a week. Researchers at the University of Vermont say that they are neither traditional robots nor any known species of animals, but a new class of living, programmable organisms (Digi24.ro). Specifically, xenobots look like small pink moving entities, the shade being deliberately chosen because they can be used as biological machines (the-scientist.com). Some have holes in the middle that can be used as a medicine carrier. Traditional robots degrade over time and affect the environment, while xenobots are environmentally friendly and safer for the human body (Digi24.ro).

Xenobot organisms come with their own food source, consisting of protein or fat stores (Kriegman et al 2021), live a little more than a week and can not reproduce or evolve, say researchers, thus wanting to remove any concerns in this regard (Digi24.ro).

Conclusions. It is known that embryonic stem cells are non-specialized cells, which can follow different pathways depending on the biochemical, electrical and hormonal signals received from neighboring cells and from an information control center. It is about cellular signaling that aims to specialize the cell according to the needs of the body.

Through these studies, researchers show that by removing the cell from the influence of these regulatory signals that dictate differentiation, the cell becomes reprogrammable. That is, another set of stimuli or signals, different from those in the embryo, can define its destiny in terms of specialization and functioning. The cells thus disconnected from the embryo continue to work like those in the embryo, but because they are disconnected from the embryonic control center, they become reprogrammable.

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Authors:
Marian Proorocu, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Agriculture, Calea Mănăştur 3-5, 400372, Cluj-Napoca, Romania, European Union, e-mail: mproorocu@yahoo.com
Antonia Odagiu, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Agriculture, Calea Mănăştur 3-5, 400372, Cluj-Napoca, Romania, European Union, e-mail: antonia.odagiu@usamvcluj.ro
Ioan Valentin Petrescu-Mag, SC Bioflux SRL Cluj-Napoca, 54 Ceahlau Street, 400488 Cluj-Napoca, Romania, e-mail: zoobiomag2004@yahoo.com
Bogdan Georgescu, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Animal Science and Biotechnologies, Calea Mănăştur 3-5, 400372, Cluj-Napoca, Romania, European Union, e-mail: georgescu.bogdan63@yahoo.com

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