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REALIVE (2016): FROM CELLULAR TO HUMAN CRYOPRESERVATION. MYTH AND REALITY FOR TEACHER TRAINING IN THE AREA OF HEALTH SCIENCES

Proyecto Lázaro (2016): de la criopreservación celular a humana. Mito y realidad para la formación docente en el área de ciencias de la salud

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Abstract

There is a growing thought of delaying the progression of a terminal illness by cryopreservation of the bodies of patients. Faced with the fear of dying from diseases, they are confident that in the future they will be able to be revived and treated with novel therapies that will lead to the cure and elimination of the pathology. Although it seems science fiction, the reality is that it is already being carried out with cellular organisms for the conservation of species and against diseases that alter reproduction. However, when it comes to embryos, the ethical committees do not yet have a defined strategy. For this reason, this work tries to focus on an interrelation between teachers and students for the discussion and reflection of the cryopreservation of patients, showing the latest advances and reports on this aspect.

Keywords: cryopreservation; cryogenics; cryonics; revival.

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Resumen

Existe un creciente pensamiento de postergar el avance de una enfermedad terminal mediante la criopreservación de los cuerpos de los pacientes. Ante el miedo a morir de enfermedades se confían que en el futuro podrán ser reanimados y tratados con novedosas terapias que le supondrán la cura y eliminación de la patología. Aunque parezca ciencia ficción la realidad es que ya se está realizando con organismos celulares para la conservación de especies y ante enfermedades que alteran la reproducción. Sin embargo, cuando se trata de embriones los comités éticos no tienen todavía una estrategia definida. Por esa razón, este trabajo intenta enfocar una interrelación entre profesorado y alumnado para la discusión y reflexión de la criopreservación de pacientes, mostrando los últimos avances e informes sobre este aspecto.

Palabras clave: criopreservación; criogenia; criónica; reanimación.

Technical details

Original title: *Proyecto Lázaro*.

Country: España.

Year: 2016.

Director: Mateo Gil.

Music: Lucas Vidal.

Photography: Pau Esteve Birba.

Film editor: Guillermo de la Cal.

Screenwriter: Mateo Gil.

Cast: Tom Hughes, Charlotte Le Bon, Oona Chaplin, Barry Ward, Julio Perillán, Rafael Cebrián, Bruno Sevilla, Daniel Horvath, Alex Hafner, Godeliv Van den Brandt, Efrain Anglès, Sebastian R. Bugge, Tony Corvillo, Jordi Cots, Oscar Dorta, Mark Schardan.

Colour: Colour.

Runtime: 112 min.

Genre: Science fiction, drama.

Original language: English.

Production Company: Arcadia Motion Pictures, Canal+ España, Noodles Production.

Synopsis: At 32 years old, Marc Jarvis (Tom Hughes) is terminally ill. He has one year left to live. Right now that he and Naomi (Oona

Chaplin) have started building a life together. Therefore, unable to accept the end of him, Marc decides to cryogenize his body with the hope of the future. More than sixty years later, in 2084, he becomes the first resurrected man in history, but his resurrection will not occur in the idyllic way that Marc had imagined before dying (FILMAFFINITY).

Awards: 2016, Sitges Festival (Feature films official section); 2017, Fantasporto (International Fantasy Film Award); 2018, Gaudí Awards (Nominee to Best Visual Effects: Días de Cine Award (Nominee to Best Spanish Film); 2018, Golden Trailer Awards (Best Drama Poster Award).

Availability: Realive (Blu-Ray). Condor Entertainment.

Links:

<https://www.filmaffinity.com/es/film612775.html>

https://www.imdb.com/title/tt4074928/?ref_=ttawd_awd_tt

Original trailer versions:

https://www.imdb.com/title/tt4074928/videogallery/?ref_=tt_vi_sm

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English version poster: *Realive* (2016)

Introduction

The term cryogenics was coined in 1899 and is defined as the scientific study of materials and their behaviour at extremely low temperatures¹. Cryogenics is a technique allowed in the United States (USA) and is in an emerging expansion in other countries, being considered within the funeral law as a precondition for a future resuscitation that allows to cure diseases that are currently incurable. However, despite the great debate on European laws, not all countries accept them due to the great ethical, moral and legal issues². A main problem lies in the lack of previous studies that guarantee the return to life and, in addition, without manifesting negative side effects.

Not far from fiction, the French bioethics law published in 2004 did not authorize the transfer of embryos subjected to a research program, not even from gametes affected by experimentation. At that time, the oocyte vitrification process was still considered an experimental technique, without the possibility of vitrifying oocytes or embryos. Different international studies allowed the legislation to be changed in July 2011, authorizing the use of oocyte vitrification for oocyte donors without children³. In today's society, it is evident that many women are delaying the ideal age for pregnancy, allowing the freezing of eggs for non-medical reasons, being legal in many countries with the generation of new debates and discussions⁴.

Cryonics or cryopreservation is a technique based on the process of preserving cells, tissues, organs or any biological material at -196 °C in liquid nitrogen to maintain their viability. Keeping cells at such a low temperature stops all biological activities, including biochemical reactions that lead to cell death and DNA degradation¹. Through cryopreservation, cells can be preserved for centuries and later revived by thawing¹.

The cryogenics of whole bodies (or only functional parts) achieves anapirexia at extremely low

temperatures, but also maintaining vital signs under the use of cryoprotectants, also called cryopreservatives, which are water-soluble substances with low toxicity in order to reduce the point eutectic of a given solution and prevent freezing of all body structures. Anapirexia is defined as the regulated drop in core temperature, this being beneficial for animals and humans when oxygen supply under different conditions (such as hypoxia and ischemia) is limited, as a strategy to reduce oxygen consumption. In addition to hypoxia, anapirexia can be induced by various exogenous and endogenous substances capable of producing hypothermia, called cryogens^{5,6}. Knowledge for the overexpression of these endogenous cryogenic proteins could be considered very useful in different human activities such as space stasis and in brain hypothermia therapies.

Realive (2016) by Mateo Gil is an interesting proposal for reflection for the healthcare professional and researcher, raising medical questions in the pharmacological, genetic, anatomical and physiological areas during the treatment and reconstruction of an individual during stasis. In addition, it raises an interesting moral and ethical dilemma about: a) patients and human experimentation, together with the lack of transparency in experimental procedures, avoiding all bioethical committees; and b) addresses approaches to philosophical consciousness, to differentiate it from the soul and consciousness, which is the eternal challenge of neurobiological science.

Results and Discussion

Realive (2016) runs through five chapters describing pre- and post-freeze situations.

Chapter 1: Lazarus Project

Marc Jarvis, the main protagonist, manifests oropharyngeal cancer and is predicted one year of life. The protagonist meditates on his suicide

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assisted under a cryonics contract that allows, just after his death, to be quickly cryonized and avoid cell damage during the process of veiling the corpse. The idea of cryonization arises from the reading of scientific articles that extract cells from the heart matrix and their injection into the heart of a dead rat allows the genesis of a new heart rhythm (Photo 1). Marc Jarvis explains the fundamentals of cryonics as a technique that allows low-temperature preservation of people who can no longer be sustained by contemporary medicine, in the hope that the medicine of the future will allow them to be revived and restore their health. The small chances of success may be enough to think that the option for cryonics is a rational choice⁷.

This is the premise that the protagonist sets as the objective of replacing his pharynx with a new one and satisfying the medical need as a patient. The protagonist justifies that have revived insects and small animals that have been in cryogenics for long periods of time, as well as the fertilization of eggs and sperm after being frozen for so long. Animal sperm can survive storage at freezing temperatures. Current literature collects the term cryopreservation as long-term preservation for the storage of sperm at very low temperatures for an indefinite period. Since 1939 work began on protocols for the collection, evaluation and preservation of semen from domestic animals (including mammals)^{1,8}. However, there was an inverse relationship between preservation and recovery of these cells, that is,

it was decided not to report successful cryopreservation attempts for many cells due to poor results obtained when resuscitating viable cells¹. This detail of information concealment and lack of transparency is also shown in *Realive* (2016), with the drawback of using frozen patients as experimental subjects associated with a chain of disastrous results with very severe damage in resuscitation. In reality, slow cooling and the discovery of cryoprotectants allowed an enormous advance in modern cryobiology for the optimization of the cryopreservation technique and the recovery of the specimen. Cryoprotectants are added for protection and stored in a cryogen that can produce a very low temperature due to its existing varied state (eg liquid nitrogen at -196 °C). Cryopreservation therefore involves cooling a cell and storing it at a temperature where all metabolic processes stop. An example of them was the introduction of glycerol as the first cryoprotectant that allowed the recovery of sperm and its functional capacity to fertilize an ovum with normal development^{1,9}.

In *Realive* (2016) it is explained that it is necessary to cryogenize immediately after declaring the patient dead to avoid cellular deterioration, since otherwise during the legal declaration of the death of a person a process of between 24 - 48 hours and the damage from autolysis would be quite large. Suicide is also considered before waiting a year of death due to illness since deterioration from cancer and drug treatment would cause less curable or treatable anatomical and

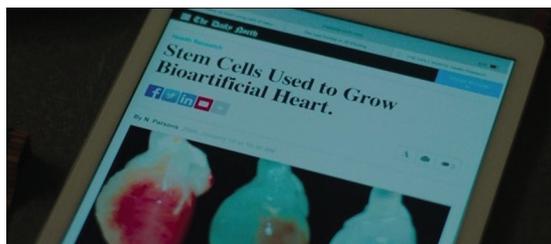


Photo 1. Source of information used by Marc Jarvis to meditate on cryogenics

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physiological damage. Marc Jarvis devises a plan so that they can collect their body between death and cryonization, helped by another person to continue pumping blood at the exact moment of their death and reduce further damage.

Doctors propose the complete reconstruction of the human body (Photo 2), with the exception of vital organs such as the nervous system, while patients hibernate in cryogenics deposits (Photo 3). It is explained that to fulfil the dream of a resurrection and not reduce the cost to avoid a thaw, the patient must deposit a bond (40,000 - 50,000 \$). At present, although the protocols for freezing people with antifreeze are correct and successful, there is no record of knowing yet whether that person is really still alive. Even if it were true

that they survive, this would lead to a great social and business dilemma. There is a debate about disconnecting and letting a person die in the face of patient defaults, insufficient structural resources or the very ruin of the cryogenics company.

Cryopreservation is possible in some countries, but not in Spain, establishing cryonic self-help groups whose mission is to cryopreserve human bodies or brains after a legal death and send them to cryonic organizations. In Spain there is still no knowledge of cryopreservation being regulated, implying that it is not allowed to avoid possible fraud situations. This technique still has a high component of experimental practice and, at the moment, it has not yet been scientifically validated in bodies. When a person

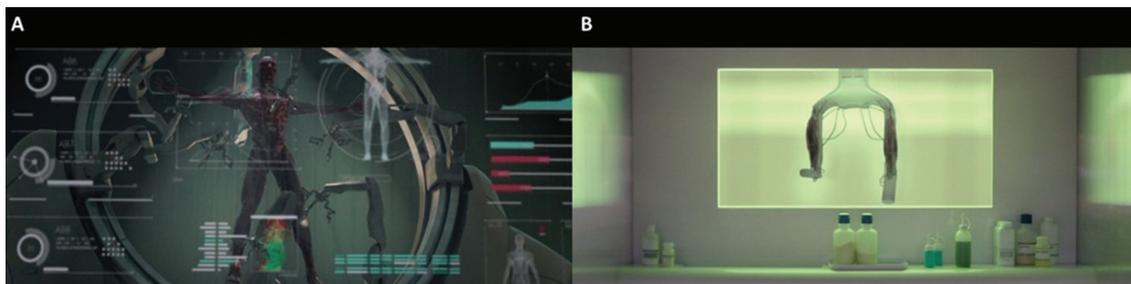


Photo 2. (A) *Lazarus Project* consisting of the complete reconstruction of Marc Jarvis. (B) Each of the muscles with their tendon sections are reconstructed as separate units in a personalized way for the patient, subjecting them to exercises for muscle toning within organ baths

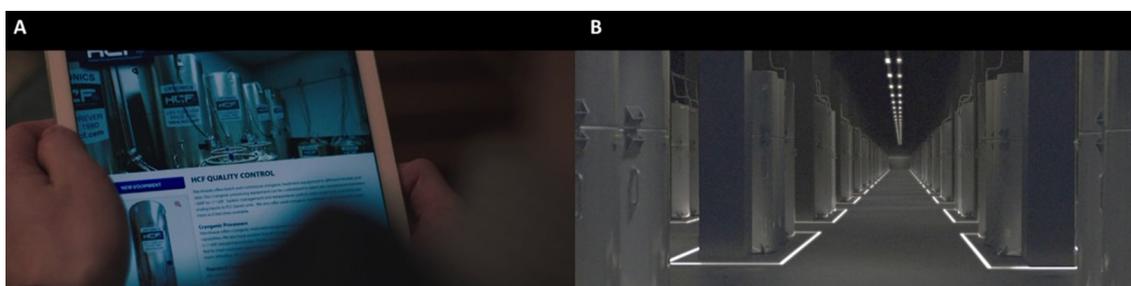


Photo 3. (A) Business announcement for the acquisition of clients in cryogenics companies before the death of Marc Jarvis. (B) Current preservation chambers of frozen patients once the protagonist is revived

dies in Spain, the Law only allows burial or cremation. In case of wanting to save in another way, body and organs become public property. To be cryopreserved in Spain you must have the services of a cryonics center and good legal support that disputes the rights of the patient's will. Currently the procedure for cryonics begins within minutes of death, when they are legally dead¹. To prevent ice formation during cryopreservation they use cryoprotectants¹⁰, but the low probability that a corpse has to be resuscitated after undergoing vitrification, as a direct consequence of damage to the brain and its neural networks, is still debated¹. However, a new study contradicts that possibility of brain damage. So far there is a first report that shows the correlation of human cryoprotection procedures with the results of complementary experiments in rats¹¹. In this case, the head of a legally dead person was subjected to intracarotid perfusion with cold physiological saline solution containing the cryoprotectants dimethylsulfoxide (13%) and glycerol (13%). The brain was harvested, temporarily frozen at -80 °C, and sent to a cryostasis facility in the US in parallel, they were compared to the brains of rats (control and cryopreserved), revealing that cryopreservation does not affect the synaptic network in the hippocampus, they keep the mature neurons of the cerebral cortex intact but there are changes in the immature neurons¹¹.

Chapter 2: The Resurrection of the Flesh

During the beginning of the story, it is explained that while the patient is cryonized, a deep study of all their anatomy and physiology is carried out to know which parts of the body can be revived and which other parts must be replaced by bionic implants and new organs. This still sounds like fiction, however the gap between the real world and the fantasy world is getting closer. There is currently a computational theory

of man and living beings that identifies cyborgs with the man of the new age¹². Understand this nexus between biological systems and intelligent biomaterials with the ability to work together to replace or improve lost functions and contribute to the well-being of the patient. This futuristic concept is creating a paradigm shift in disease management and the healthcare sector as a whole^{13,14}.

When Marc Jarvis is successfully resuscitated he immediately manifests symptoms such as pain and numbness throughout his body, but he has the ability to remember his entire past life by keeping the synaptic connections intact. This data coincides with the results obtained in the first real report that shows the preservation of memory circuits¹¹. In turn, the character manifests anxiety and fear when dying upon awakening.

Marc Jarvis is considered the first resurrected in the future, with 20% of vital organs and tissues recovered from the old body (brain and rest of the central nervous system); 65% of cloned organs (bones, muscles, skin, nerve endings and other organs); 10% of bionic implants to reinforce the locomotor system (musculoskeletal system), and the sensory organs; 5% internal technology designed to regulate and control the proper functioning of the body. In addition, an external connection system must be added (an umbilical cord that connects from the umbilical or mesogastric region with a computerized life support), resulting in a fragile organism on the verge of collapse after resuscitation with insufferable solutions despite the desire to living again, along with memory loss as a result of cerebral apoplexy and deterioration of cells while maintaining neural circuits (Photo 4).

In the cryonics process, it has already been commented that the original goal is to cryopreserve animals and humans so that they can be revived in the future. Although no frozen corpse has yet been revived, the case of Dr. James Bedford is known, who is the first corpse to be

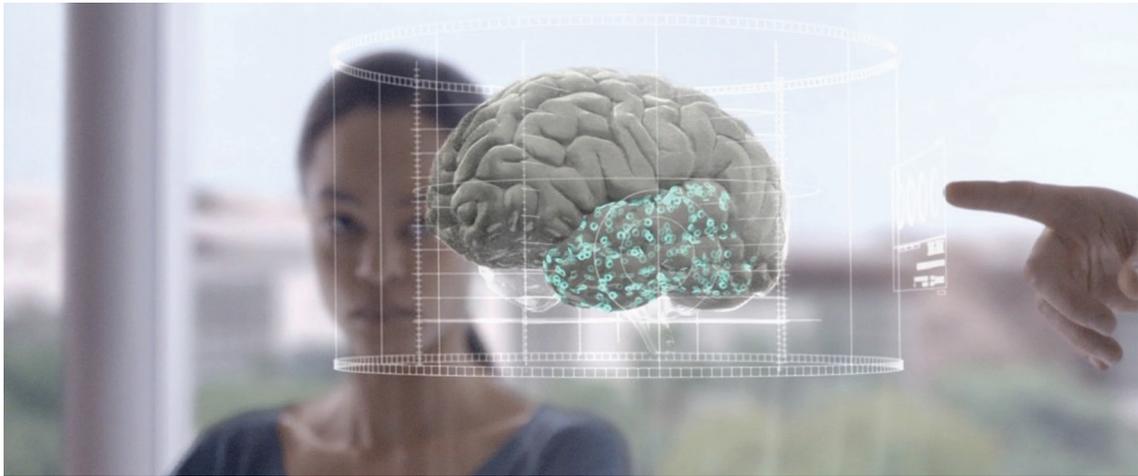


Photo 4. Augmented Reality (AR) indication of the brain areas where cerebral apoplexy and memory loss are located

cryonized in 1967¹⁵. Reports note that approximately 250 bodies were cryopreserved in the U.S. in 2014, and 1,500 people had arranged for cryopreservation after their legal death⁷.

Chapter 3: The Momentless Lovers

Marc Jarvis begins to question his existence without his partner, family and friends in a world that is not his. The moral dilemma of being born in a different time than yours appears and not fitting in or conforming to the new era, loving different people, seeking harmony in life outside of your time. It is considered that subjecting a dying person to cryopreservation is an act that may become incompatible with the human dignity of the patient.

Chapter 4: We Will Last

Immortality is only a matter of time, but Marc Jarvis questions having sacrificed a love for an insurmountable dream and not having lived until the final stage of his life with the disease surrounded by his loved ones. Being the first person to be resurrected in history is the result of a chain

of failures with patients prior to the protagonist, showing the concealment of evidence and the lack of transparency in the investigations to sell resuscitation as a commercial product of direct success. Therefore, the reflection of whether there is a lack of morality in the face of the pain produced is raised. Different current studies also call for the need for greater depth and diversity in the analysis of ethical considerations related to this technology in different tissues, such as those where genetic disorders or prepubertal cancer therapy cause risks of infertility¹⁶⁻¹⁹.

Chapter 5: No Gifts

Marc Jarvis decides not to revive his fiancée in a body that cannot be his, in the face of such a great deterioration of her body during the cryogenization process, refusing a possible experimentation with her. Marc, considering that he will be alone in a time that is not his, makes a series of questions and reflections:

- Could I live in the past, going back over and over again in the mind, completing it, polishing it, until it reaches perfection? I don't

know, now there is only one thing that I see clearly.

- Life is nothing more than a state of matter, like gas or liquid, a form of molecular organization without greater transcendence or divine purpose. Its only goal is to perpetuate itself through movement, change, adaptation. Life does not care about species, much less individuals, we are only the pieces of mud that it uses as a vehicle. It is life that is scary, not death, which is always on the brink of extinction. That it exists where it shouldn't. And the soul? You ask yourself, what happens to the soul? The soul may be what the steak loses when it is frozen and defrosted again.

Here a new concept is already introduced, the soul for religion, consciousness for neuroscience. It is thought that once a body is frozen after death, the body separates from the soul, and there may be a problem of great depth and theologically unresolved at the time the patient is resuscitated. Without going any further, scientific ethics treats the mind as a matter-energy process, very different from the soul, the eggs and embryos of any species as full individuals of that species, with a defined genome that gives them autonomy²⁰. The unresolved debate about frozen embryos remains unclear what to do with them: 1) leave them frozen indefinitely; 2) thaw and discard and 3) use for research. Whether embryos or frozen patients, the foundation is the same, the individuality of a being as a person, both metaphysically and morally, that is why the recognition of this factual fact would allow the defenders of all religious and ideological beliefs to defend their principles and realign their positions in an environment within the limits of current scientific knowledge^{21,22}.

Faced with the questions raised by the protagonist, he reconsiders suicide as the only way to avoid the agony and pain of the memory of the past and be alone in peace. Cryopreservation only supposes the protagonist a false

hope and control over life, where he ends up accepting death as one more process of the biological cycle.

Conclusions

In the past, the interest of soldiers was triggered on the possibility of preserving cells of germ origin before a warlike conflict¹. Now the circumstances are different, it has become a reality and people recognize its importance within a population of greater longevity where death occurs due to the appearance of diseases. Cryopreservation of germ cells for conception is a milestone passed, but preserving more complex organism as a patient carries a greater challenge. Despite these, the new studies of cryoprotectors and the conservation of brain synaptic structures encourage a safe conservation of bodies, closer to reality than fiction, but unfortunately, even achieving a perfect recovery of the patient, it is unknown if is viable and under what conditions or what side effects would occur during resuscitation.

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	<p>Isaac Narbona-Sánchez. Doctor in the Biomolecules doctoral program at University of Cádiz. Official Master in the Biomolecules program at University of Cádiz. Degree in Chemical Sciences at the National University of Distance Education. Postdoctoral fellow at the Institute for Research and Innovation in Biomedical Sciences (INiBICA). His line of research focuses on the activation and transduction of signals in T lymphocytes through the LAT adapter, and on the appearance and evolution of autoimmune diseases, including Rheumatoid Arthritis.</p>
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