Translational Biotechnolgy: hemopressin and other intracellular peptides

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Introduction

THE TERM *biotechnology* was first used in 1919 by Hungarian engineer Karl Ereky, but its official definition was established in 1992 at the Convention on Biological Diversity. This definition was subsequently ratified by 168 countries and accepted by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products and processes for specific use." With this definition in mind, we conclude that biotechnology is one of the oldest practices of humanity, since its use in beer brewing and bread making started in ancient Egypt, between 4000-2000 BC; and the fun continues with the use of biotechnology for the production of cheese and wine.[1] The expression used here, *translational biotechnology*, is paraphrased from that used in medicine, i.e., "from bench to bedside", and aims to emphasize the use of biotechnology as a science linked to innovation, whose results are applicable to improve the living conditions of the population as well.

In daily academic life, biotechnology is a science deeply guided by the scientific method. Ideally, the results generated by biotechnology should be ultimately converted into commercial products, thus establishing a strong correlation between this science and the concept of innovation; in the case of general industry, innovation means making a product available for consumption. Biotechnology applies both to radical innovation, which involves original discoveries, and to incremental innovation, which can involve mere improvements to existing processes. For example, the development of a new molecule containing an active principle and that can serve as a basis for a new drug to be patented can ultimately become a radical innovation. So, the development of biotechnology projects is expected to yield results for the purpose of commercial ownership, thus contributing to improve the quality of life of individuals.[2]

The discovery of the DNA structure by Watson & Crick (1953) in March 1953 demonstrated the mechanism for copying the genetic material responsible for the perpetuation of the species. This discovery enabled quickly advancing

the so-called "recombinant DNA techniques", popularizing genetic manipulation and making biotechnology a major agent for integrating various areas of knowledge such as genetics, microbiology, biochemistry, physiology, cell biology, pharmacology, and chemistry among others. An important fact in the popularization of biotechnology was the development by Kary B. Mullis, in 1983, of the polymerase chain reaction (PCR) technique (Saiki et al. 1985). The PCR technique enables, in a very simple way, amplifying the genetic material in test tubes and has been applied to various fields of biotechnology.

In healthcare, biotechnology has been applied to the development of vaccines, gene and cell therapy, development and use of embryonic stem cells, as well as in the newly created synthetic cell, designed and developed in Craig C. Venter's laboratory (Gibson et al., 2010). Furthermore, an important application of biotechnology is the development of biopharmaceuticals, which may be understood as recombinant proteins intended for therapeutic use. The biopharmaceuticals market already accounts for approximately 10 percent of the annual turnover of the pharmaceutical industry, which is around 800 billion dollars, with an expected annual growth of 3-6 percent. According to forecasts by IMS Health, Brazil should contribute to this market between 5 and 15 billion dollars in annual sales of pharmaceutical products in 2013, with estimated revenue, for the Brazilian biopharmaceuticals market of 0.5-1.5 billion dollars.[3]

The use of biotechnology allowed the development by the company Genentech, in 1978, of the first biopharmaceutical produced using bacteria, namely recombinant human insulin. in 1982, Genentech, in partnership with the Eli Lilly Company, produced recombinant human insulin in an optimal way and received approval for human use from the Food and Drug Administration (FDA).[4] The production of insulin for human use manufactured from genetic engineering techniques has led to a significant reduction in problems associated with the impurity of the substance, which was originally purified from the pancreas of farm animals. The technique used in recombinant human insulin production is based on the insertion of human DNA into a host cell (*E. coli*, for example). The cells grow and reproduce normally, and thanks to the DNA code inserted into the host, produce their own insulin for human therapy. It should be noted that biotechnology is a pragmatic science, which today benefits more than 250 million patients who use biopharmaceuticals for the treatment of heart attacks, multiple sclerosis, breast cancer, cystic fibrosis, leukemia and diseases of genetic origin. Biotechnology has had a positive impact on the production of safe and effective vaccines for infectious diseases.

Currently, more than 350 drugs produced using biotechnology are in the process of being approved for the treatment of over 150 diseases, among which are cancer, infectious diseases and autoimmune disorders.[5] The most important biopharmaceuticals at present are:

- Factors such as blood Factor VIII and IX, used as clotting factor for hemophilia A and B.
- Thromboembolic activators for tissue plasminogen: used for conditions associated with thrombosis and embolism.
- Hormones, such as insulin (used for diabetes), growth hormones and gonadotropins.
- Hematopoietic growth factors such as erythropoietin, which are factors related to the production of red blood cells used in the treatment of anemia caused by chronic renal failure or chemotherapy for cancer.
- Interferons-α,-β,-γ, which are natural proteins produced by immune cells in response to threat agents such as viruses, bacteria, parasites and tumors. Used to treat conditions such as multiple sclerosis, systemic cancer, hepatitis C, and leukemia.
- Interleukin-based products, which are used to treat Crohn's disease and ulcerative colitis.
- Vaccines: for the prevention of various diseases.
- Monoclonal antibodies, which are antibodies produced by a specific type of immune cells, all from a single mother cell (monoclonal). Used to treat a wide variety of diseases.
- Other products, such as therapeutic enzymes and tumor necrosis factor are used for autoimmune diseases such as rheumatoid arthritis, Crohn's disease and many others.

Thus, we see that biotechnology is present in everyday life and provides options for the recombinant production of blood- or tissue-derived proteins, ensuring the safe and effective production of drugs, with no negative consequences for the environment. Most of the biopharmaceuticals described above and commercialized worldwide currently have a biogeneric substitute under development, because their patents are in the process of expiring. As a result, the development and production of generic biopharmaceuticals is currently an excellent opportunity both for academic laboratories with expertise in the production of recombinant protein wishing to enter the field of innovation, and national biotechnology companies intending to expand their line of products and services.

Development of biotechnology

The following is a chronological description of the development of biotechnology:

- *4000-2000 BC:* "Biotechnology" was first used in Egypt for the production of bread and beer, using the technique of fermentation by yeasts.
- *1322:* Horses of a superior breed were artificially inseminated by an Arab leader.
- *1761:* Plants of different species were crossed by German naturalist Joseph Gottlieb Koelreuter.

- *1859:* The distinguished British scientist Charles Darwin published his theory of evolution by natural selection. The concept of selecting and destroying the weaker offspring had great influence among livestock breeders in the mid-nineteenth century, although genetics was not yet a recognized science.
- *1865:* Genetics emerged under the mentorship of Austrian scientist Gregor Mendel. Through his experiments with peas, Mendel found that characteristics are hereditary, passed from father to son; he also discovered the patterns of heredity.
- *1870:* Using Darwin's theory, plant breeders began to cross different cotton species and ultimately succeeded in developing a superior variety of the plant.
- *1876:* Louis Pasteur proved that fermentation was caused by the action of tiny living beings, i.e., microorganisms, thus disproving the then existing theory that fermentation would be a purely chemical process.
- *1879:* Scientist Alexander Fleming discovered chromatin, a structure resembling a wand inside the nucleus of cells, which was later called "chromosome."
- *1897:* Eduard Buchner proved possible to convert sugar into alcohol, using macerated yeast cells, i.e., in the absence of living organisms.
- *1900:* Fruit flies, *Drosophila melanogaster,* were used in early studies of genes.
- *1906:* The term "genetics" was coined.
- *1919:* The word biotechnology was used by Hungarian engineer Karl Ereky.
- *1941:* The term genetic engineering was used for the first time.
- *1942:* Penicillin began to be produced as a drug and used as an antibiotic in humans.
- *1944:* DNA was found to be the structure responsible for the transmission of genetic information.
- *1953:* Scientists James Watson and Francis Crick resolved the structure of DNA. Their article was published in the journal Nature and marked the era of contemporary genetics.
- *1956:* The fermentation process was optimized; Arthur Kornberg discovered the DNA polymerase I enzyme that catalyzes DNA synthesis in bacteria, leading to the understanding of how DNA is replicated.
- *1958:* DNA was first produced in a test tube.
- *1969:* An enzyme was synthesized in vitro for the first time ever.
- *1970:* Restriction enzymes (specific nucleases) were identified, paving the way for molecular cloning of genes.
- *1972:* The composition of human DNA was found to be 99 percent similar to that of chimpanzees and gorillas.
- *1975:* The first monoclonal antibodies were produced.
- *1982:* FDA approved the first human insulin produced by genetically modified bacteria.
- *1983:* Kary B. Mullis developed the polymerase chain reaction (PCR) technique.
- *1984:* The first cloning and sequencing of the entire HIV virus was announced.

- *1986:* The first recombinant vaccine against hepatitis B for humans was produced; the first anticancer drug was produced through biotechnology.
- *1990:* The Human Genome Project was launched. In the United States, a four-year old girl suffering from immune system disorder became the first human recipient of gene therapy .
- *1994:* The first breast cancer gene was discovered.
- *1995:* Gene therapy joins the fight against cancer. The first sequenced genome of a living organism other than viruses is completed for the *Haemophilus influenzae* bacterium.
- *1996:* Scottish scientists cloned identical copies of a sheep from embryos.
- *1997:* Dolly the sheep, the first animal cloned from an adult cell, was born.
- *1998:* Human embryonic stem cells were discovered. The first complete genome of an animal, nematode *C. elegans*, was sequenced.
- *1999:* The concept of interactome and the idea that proteins rarely perform their functions individually emerged.
- *2003:* Dolly the sheep was submitted to euthanasia after developing lung cancer; China approved the first regulation for a gene therapy product.
- *2004:* The first pet was cloned*:* a cat. The genome of mice used in laboratory research was sequenced.
- *2005:* The FDA approved the first drug for a specific ethnic group*:* a drug for heart problem unique to people of African descent. The dog genome was published.
- *2010:* Craig C. Venter published an article in the Science journal describing for the first time the development of a synthetic cell whose initial DNA was totally synthesized in laboratory under human control.

Source: Adapted from http://www.shire.com.br/tecnologia/biotecnologia.

The use of biotechnology in the academic discovery of novel bioactive molecules

The study of small proteins called peptides that act on the nervous system has its origin in the 1940s-1950s, with the discovery of the peptide *bradykinin*, published in 1949 by Professor Mauricio Rocha e Silva et al. (1949), at the School of Medicine of Ribeirão Preto, and backed by more than eighteen thousand internationally recognized manuscripts. Bioactive peptides found in mammals which, like bradykinin play the most diverse physiological functions, currently total more than a hundred. What the peptides have in common is a protein structure encoded from a specific nucleotide sequence stored in the DNA. This peptide protein structure is initially produced as a protein, which needs to be hydrolyzed into very specific amino acids by enzymes called proteases. After the release of their protein precursor, peptides gain biological activity and signal, usually in conjunction with other small non-protein molecules, cells and tissues that perform many different functions. Therefore, we now know that peptides play crucial functions in animal cells and organs, whether unicellular or

multicellular. It is common for the same cell or tissue to produce several peptides simultaneously and use them to properly perform its functions. Like their protein precursors, peptides also need to be constantly degraded and recycled into amino acids, thus enabling a constant process of cell renewal. The enzymes that perform this peptide hydrolyzing function are termed peptidases, due to their ability to hydrolyze peptide bonds.

Peptidases, along with proteases, are proteins conserved throughout the evolution of species, accounting for approximately 2 percent of the genes encoded by the human genome, reiterating the biological importance of peptides and peptidases. A class of peptidases conserved throughout evolution and expressed ubiquitously in cells and tissues of mammals, including humans, are oligopeptidases. These oligopeptidases, which were also discovered at the School of Medicine of Ribeirão Preto by Professor Antonio Carlos Martins de Camargo et al. (1969) are scientifically interesting enzymes for many reasons, among them their unique structural conformation that allows entry of only small peptides in their hydrolytic site. Molecular cloning - i.e., the identification of the encoding DNA sequence - of the first mammalian oligopeptidase - was made in the early 1990s by the group of professors James L. Roberts and Marc J. Glucksman, from the Mount Sinai School of Medicine (New York), and spurred the development of knowledge in this area. Particularly, molecular cloning has enabled using bacterial expression systems for the production of an enzyme called thimet oligopeptidase (TOP or EP24.15) in previously unthinkable quantities and purity (cf. Rioli et al. 1998). The advantages of using biotechnology to produce in microorganisms proteins that are normally found in vital organs of mammalians, such as the brain, the kidneys and the heart, include the quantity and purity of the material obtained. For example, at the end of the process and months of work, micrograms of purified material were obtained by the chromatographic method originally used to obtain this enzyme from kilograms of biological material (usually rabbit, rat or bovine brain). Biotechnology currently enables obtaining grams of this protein in just five days' work, using a system of expression of recombinant proteins in bacteria. This has enabled determining the crystallographic structure of EP24.15, which is a determining factor for understanding its restriction to hydrolyzing small peptides.

Thus, mastering the process of producing recombinant oligopeptidase such as EP24.15 has enabled using it for the structural characterization of its biochemical specificities, as well as for the production of highly specific antibodies. In addition to these important aspects, protein expression in biotechnology enables performing rational structural changes in the amino acid sequence of the expressed protein. This manipulation of the genetic code (genetic engineering) can be used for several purposes, among them to rationally manipulate enzyme activity. It is therefore possible to produce enzymes, for example, that are stable at high temperature or catalytically inactive.

Given these biotechnological possibilities, the use of a catalytically inactive form of oligopeptidase EP24.15 has allowed using it for the discovery of a novel family of molecules, i.e., intracellular peptides. In her doctoral thesis, defended in 2003 at the Federal University of São Paulo in the area of Molecular Biology Concentration, biologist Vanessa Rioli first described the use of inactive oligopeptidases for the isolation of new peptide sequences (Rioli et al. 2003). Among the original peptides identified was a fragment of the alpha chain of the nine amino acid hemoglobin which, due to its hypotensive activity was named hemopressin. It is important to point out that the identification of hemopressin, and subsequently of a hundred several other intracellular peptides, was only made possible by the use of mass spectrometry, drawing attention to the multidisciplinary nature of biotechnology which, combined with other contemporary sciences enables significant advances in scientific knowledge. With the discovery of a new bioactive peptide sequence like hemopressin, it was possible to carry out further investigations involving its pharmacological function and molecular mechanism of action. With additional pharmacological tests, a group of researchers led by physicians Camila S. Dale (Syrian-Lebanese Hospital), Andrea S. Heimann (Proteimax Biotechnology Ltd.) And Lakshmi A. Devi (Mount Sinai School of Medicine) found that, in addition to hypotensive action, hemopressin also has an analgesic activity that involves the antagonism of cannabinoid receptors (Heimann, 2007). The discovery that the molecular mechanism of action of hemopressin involves the antagonism of cannabinoid receptors had worldwide repercussions. More recently, the demonstration that hemopressin acting as an inverse agonist of cannabinoid receptors inhibits food intake in laboratory animals - an effect opposite to that of cannabinoid agonists present in plants such as *Cannabis sativa* - has further increased the interest of both the scientific community and society in this peptide.

The extent to which hemopressin - a peptide discovered using biotechnology in the course of a thesis guided by a hypothesis and popularized by scientific publications demonstrating its potential therapeutic relevance - will become an innovation remains a question to be answered. Both individuals and companies have endeavored in this regard, considering what has been learned from the experiences of previous research groups.

The use of biotechnology in changing scientific paradigms

The use of biotechnology for the production of inactive oligopeptidases allowed the development of a method, patented by the University of São Paulo and the Research Support Foundation of the State of São Paulo (FAPESP), which led to the discovery of new peptides (Cunha, 2008). As a result, what was observed was the presence of large numbers of peptides derived from proteins present, particularly, in the cytoplasm, nuclei and mitochondria. Intracellular protein-derived peptides had hitherto been described only separately and spo-

radically, and in general were seen only as inactive intermediates in the production of amino acids for the synthesis of new proteins, as well as an integral part of the autoimmune recognition system. However, signals for post-translational modifications, especially phosphorylation, which are often found in proteins that participate in the regulation of intracellular signaling cascades, particularly during transduction of the signal mediated by plasma membrane receptors, were found in the peptides identified with the use of inactive oligopeptidases. The doctoral thesis of pharmacist Fernanda Marques da Cunha, defended at the Federal University of São Paulo, and of biomedical scientist Denise Aparecida Berti, defended at the University of São Paulo, investigated the possible existence and physiopharmacological relevance of what had been envisioned as a new family of intracellular signaling molecules. Thus, it was demonstrated for the first time ever that peptides naturally found intracellularly are capable of interfering in cell signaling mediated by two important pharmacological agonists, namely angiotensin II and isoproterenol. Furthermore, it was demonstrated that manipulation of the intracellular activity of oligopeptidase EP24.15, which alters per se the intracellular peptide composition was sufficient to alter the gene transcription resulting from the cell signaling initiated by the aforementioned pharmacological agonists (cf. Cunha, 2008; Berti et al. 2009).

A specific physiological role of intracellular peptides seems to be that of regulating glucose uptake by adipose tissue. As a result of a hypercaloric diet (cafeteria diet), the composition of specific intracellular peptides changed in adipose tissue of mice that developed obesity and insulin resistance. Important to reaffirm the initial concept of translational biotechnology, the reintroduction of these intracellular peptides into fat cells was able to improve glucose uptake in insulin resistant cells. These recent studies, although still in progress, suggest an additional physiological role for intracellular peptides in insulin signaling in adipose tissue (Berti, n.d.).

Subsequent studies led by Professor Lloyd D. Fricker, from the Albert Einstein College of Medicine (New York) resulted in the systematic identification of a large number of intracellular peptides in tissues such as brain, blood vessels and heart (see Gelman & Fricker, 2010). Additionally, studies conducted by biomedical scientist Leandro Mantovani Castro, from the University of São Paulo, demonstrated that intracellular peptides described in mammalian tissues are not part of the autoimmune recognition system (Castro et al., 2010). These systematic studies demonstrated definitively the existence of a family of intracellular peptides that can be found in many animals and their respective tissues. The existence of a similar composition of intracellular peptides in various cell types has also been demonstrated. Recent studies also show significant changes in the composition of specific intracellular peptides, in animal models, of neurodegenerative diseases, as well as after the induction of cerebral ischemia. Therefore, it is possible to suggest that intracellular peptides play different physiopathological

functions in mammals. Thus, these studies developed within the process of academic science based on hypothesis and using biotechnology among other sciences, change the paradigm that peptides formed during intracellular proteolysis are rapidly converted into amino acids for protein synthesis. Additional studies may be conducted to investigate the possible occurrence of changes in the intracellular content of peptides in human diseases (cf. Fricker & Sweedler, 2010).

The new proposal of intracellular peptides acting in health and disease

An event organized in 2009 by Rao Rapaka, director of the National Institute of Drug Abuse (NIDA) / National Institute of Health (NIH) discussed the prospects and future actions to discover the "hidden peptidome" (Fishing for the Hidden Peptidome in Health and Disease; USA, 2009). Proteome and peptidome are defined respectively as the set of proteins and peptides present in a tissue or biological sample. The suggested mechanism for the action of peptides intracellularly involves an internal operation in the cellular environment (Ferro et al., 2004), and another in the extracellular environment (Gomes, 2010), where they can be secreted. Intracellularly, it is suggested that peptides are modulators of protein interaction networks, which are physiologically responsible for maintaining various cellular processes. These protein interaction networks are also correlated with disease and may be used as prognostic methods, as they are altered, for example, in cancer. The first experimental evidence in investigating the role of intracellular peptides in protein interaction comes from the study of biologist Lilian Cristina Russo Vieira. Using surface plasmon resonance, Dr. Lilian demonstrated that the interaction of specific proteins with those present in the cytosol of neuronal tissue is altered by the addition of specific intracellular peptides. Some of these peptides are able to increase - while others reduce - protein-protein interactions. To act in the extracellular environment, it is suggested that these peptides are secreted from cytosol by an unconventional secretory pathway. Examples of known peptides derived from cytosolic proteins and that are secreted include hemorphins, which are peptide fragments derived from the beta chain of hemoglobin that act as opioid receptor agonists. However, to date there are no studies on the possible secretion of hemopressin or its precursors, such as RVD- and Vd-hemopressin or on other intracellular peptides resulting from the studies discussed herein. However, it is important to mention that recent studies have shown, in a very elegant way, hemoglobin expression in neuronal cells. In neurons it is suggested that hemoglobin functions as an antioxidant protein. Thus, both the protein precursor (hemoglobin alpha chain) and the hemopressin receptor (CB1 cannabinoid receptor) can be found in neurons of the central nervous system. As a result, we observe that our understanding of cell biology is far from being sufficient, and that constant research in the most different areas of knowledge, such as biotechnology, mass spectrometry, cell biology, pharmacology, physiology, and pathology, among others, is essential for anyone planning to improve the quality of life of the population.

Final considerations

In this paper we have sought to report the use of the knowledge acquired in the academic setting to establish correlations between a pragmatic science like biotechnology and hypothesis-oriented academic science. Note that are not necessarily disadvantages when these two sciences intertwine; instead, the primary result is the advancement of knowledge. The advances made over as little as eleven years, and that led to the identification of intracellular peptides as a new family of biologically active molecules, were only possible with the use of biotechnology and recombinant DNA techniques in conjunction with the introduction of mass spectrometry and classical concepts of pharmacology, physiology, biochemistry and cell biology. With the incorporation of new sciences such as mass spectrometry applied to macromolecules and surface plasmon resonance, the time period required for fundamental discoveries has been significantly reduced. The ongoing work of researchers, generation after generation, is invaluable and contributes to the development of research lines that incorporate new findings and are improved as knowledge advances. The recent history of the discovery of hemopressin and intracellular peptides is an example in this regard.

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Notes

1 See <http://www.roche.com.br/fmfiles/re7193008/pdf/medicamentosbiologicos1. pdf>; Fardelone & Branchi (2006); Vieira & Ohayon (s. d.); Global... (2008); Como estimular a inovação tecnológica (2010).

2 See <http://www.roche.com.br/fmfiles/re7193008/pdf/medicamentosbiologicos1. pdf>; Fardelone & Branchi (2006); Vieira & Ohayon (s. d.); Global... (2008); Como estimular a inovação tecnológica (2010).

3 See. <http://www.roche.com.br/fmfiles/re7193008/pdf/medicamentosbiologicos1. pdf>; Fardelone & Branchi (2006); Vieira & Ohayon (s. d.); Global... (2008); Como estimular a inovação tecnológica (2010).

4 See <http://www.shire.com.br/tecnologia/biotecnologia>.

5 See <http://www.roche.com.br/fmfiles/re7193008/pdf/medicamentosbiologicos1. pdf>; Fardelone & Branchi (2006); Vieira & Ohayon (s. d.); Global... (2008); Como estimular a inovação tecnológica (2010).

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Abstract – Biotechnology has been used since ancient Egypt for the production of bread and beer. In the modern world, biotechnology has been used in several ways, including for the treatment of diseases. In academia, biotechnology has allowed a rapid advance of knowledge. In this article, we provide a brief summary of what biotechnology is and its relation to the process of innovation and production of biopharmaceuticals. In academia, biotechnology has contributed decisively to the discovery of new bioactive molecules, such as in hemopressin and several other intracellular peptides.

Keywords: Translational medicine, Interactome, Molecular biology, Cell signaling, Mass spectrometry.

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