ROMANIAN RED BIOTECHNOLOGY - BLENDING TRADITION WITH STATE OF THE ART IN THE EUROPEAN AND INTERNATIONAL FRAMEWORK

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Abstract

The biotechnology field has grown rapidly in recent years. Much attention is given to the potential of the biotechnology industry, from drugs and medical devices to environmental products which have the potential to generate tremendous opportunities for society, by improving the quality of health care and producing a cleaner environment. Red-biotechnology, or medical biotechnology, is one of the branches of the biotechnology and utilizes the organism to improve health, both in the pharmaceutical and medical sectors, mainly bringing all the biotechnology applications to medicine. Romanian potential was recognized by important biotech companies as an attractive destination for biotechnology research development. Currently running large programs for research, development, and innovation, regulated within a national implementation strategy, and with an attractive higher education offer, Romania is contributing to biotech advances and has great potential for development of biological pharmaceutical products. It also represents a valuable and promising partner for future international collaborations as biotechnology continues to evolve and will remain a major field of innovation and development in many areas of the world.

Key words*: biological drugs, biotechnology industry, biotechnology regulations, national strategies, red biotechnology.*

INTRODUCTION

According to the rainbow code of biotechnology, red-biotechnology, or medical biotechnology, is one of the branches of the modern biotechnology field and utilizes the organism to improve health. Biotechnology is commonly used in the pharmaceutical and medical sectors such as in gene therapies, molecular diagnostic techniques, genetic engineering, drug and vaccine development, cancer research, regenerative therapies, biomedical 3-D-printing, veterinary biochips, cell and tissue research and assessment, stem cell research, protéomics, pharmacogenetics. The medical biotechnology field drives meetings, conferences, and workshops with participants from a variety of science, education, industry, administration, and social work fields. Biotechnology has recently become an essential component of life, in all of its aspects, but most of all in the medical area. The current interest and the magnitude of the employed research forces and economy drive are reflected by the market value in this field. It is currently estimated that the Global Red Biotechnology Market may reach 500 billion US dollars by 2026 (Acumen Research and Consulting, 2019).

EARLY BEGINNING OF RED BIOTECHNOLOGY

Since "the need is the mother of all inventions", the field of biotechnology is not an exception, as its beginning is linked to the domestication of animals, and the production and preservation of food. With the extension of food preservation methods, processed products have emerged and human diet was diversified. Cheese can thus be considered one of the first products of biotechnology, being followed by bread, vinegar, alcohol. On the other hand, in order to benefit more from domestic animals,

the cross-breeding method has been developed, the oldest example being the mule (Verma, 2011). This period, before the XIXth century is known as *"Ancient biotechnology"*.

After 1800, the next phase of biotechnology evolution, known as the *"Classical biotechnology"*, was a period of scientific blossom, starting with the heart of the biotechnology discovery, the transfer of genetic information, detailed by Mendel's "Inheritance Laws". Molecular biology started with the discovery of the nucleus, by R. Brown and nuclein, by F. Miescher. For over a century, the medical and pharmaceutical industry has been driven by technological innovation. T.H. Morgan gave us the chromosomes and the gene knowledge, while in the early XXth century, Johannsen defined the genotype and phenotype concepts. Soon after, Flemming discovered the antibiotics.

The field of biotechnology has gained a lot of momentum during the so-called *"Modern Biotechnology"* stage, with Francis Crick and James Watson's discovery in 1953 of the DNA structure, soon following the development and implementation of genetics in other fields. Further deep understanding of the gene structure was brought by Jacob and Monod, who introduced the new operon concept, while Kohler and Milestein revolutionized diagnostic techniques when they discovered monoclonal antibodies. Later on, the DNA was artificially synthesized, amplified and the first animal clone was successfully produced (Verma, 2011). Relatively recently, in 2003, The Human Genome Project was accomplished.

THE "GOLDEN AGE" OF MEDICAL BIOTECHNOLOGY

The latest progress and significant advances in Red biotechnology triggered even more research, in a circle which drove enormous financial investments, so scientists have considered this field to be the top global economic growth opportunity (Gartland, 2013). Biotechnology scope has grown to previously unimagined magnitude, and two of the most prestigious scientific journals - *Current Research in Biotechnology* and *Current Opinion in Biotechnology* - reveal the fields which are currently addressed by this multidisciplinary science as analytical, environmental, energy, chemical, plant and animal, medical, pharmaceutical, and food biotechnology, genetic and molecular engineering, and nanobiotechnology. More than anything else, biotechnology is a versatile research field, with broad and expanding range of topics.

STATE OF THE ART IN GLOBAL RED BIOTECHNOLOGY

Current scientific interests and trends. As technological innovations come from scientific breakthroughs, the heartbeat of biotechnology also lies in the research conducted at a global level. In order to identify the most prominent research themes and the major contributors on a global scale, Yeung AWK et al. (2019) managed to identify 12351 publications that were published after 2017, from more than 8500 research organizations all over the world. The authors revealed that between 2017 and 2019, the top 5 most productive countries were the United States of America, China, Germany, Brazil and India. These countries were leaders among over 140 countries/regions which were identified to have contributed to biotechnology research literature (Yeung, 2019).

Another recent study (Streltsova, 2018), reviewing the strategies and dynamics in biotechnology patenting in Brazil, Russia, India and South Africa, grouped under the acronym BRICS and commonly referred to as the "BRICS countries", is pointing out that these countries account for 25% of global biotechnology patents. The authors of this study are stressing out the fact that the capacity and the input of these significant contributors might significantly shape the current trends and the future of the biotechnology field.

Graciano et al. (2019) retrieved data from some of the most relevant Patents Databases, such as INPI, USPTO, Esp@cenet, and WIPO, and revealed that the latest Red Biotechnology Patent Applications are mainly related with cancer research, diagnosis kits, vaccines, stem cells and therapeutic antibodies. Analyzed data indicated the USA being the world leader in terms of patent application number (Graciano, 2019). In terms of scientific publications, Yeung et al. (2019) indicate that *Journal of*

Bioscience and Bioengineering was the leading journal in terms of publications metrics, followed by *Biotechnology and Bioengineering*, *Applied Microbiology and Biotechnology, Biotechnology Progress* and *Scientific Reports*. According to Yeung et al. (2019), the most prevalent biotechnology research theme was Metabolic engineering, followed by biotechnology studies involving *E. coli* and *Saccharomyces cerevisiae* about the biosynthesis of various biomolecules, such as myo-inositol (vitamin B8), monoterpenes, adipic acid, astaxanthin, and ethanol (Yeung, 2019). "Nanoparticles and nanotechnology" was highlighted as a greatly significant emerging biotechnology research field. To reveal the most prevailing biotechnology research themes of 2019, the authors analyzed the most prevalent key words in the scientific articles and revealed the top five key words as "protein engineering", "thermostability", "biofuels", "innovative biotechnologies", and "drug delivery".

Expert opinion on biotechnology risks versus socio-political factors. Scientific discoveries and biotechnology innovations have always been subjected to initial public reluctances. Although regulatory authorities, policy makers, the industry, and the general public, all have an impact on the acceptance of new trends, the scientists advocate that too little emphasis is put on the scientific principles which reflect and govern the risks and benefits behind new biotechnologies. In a very recent paper, Lassoued et al. (2019) draws attention to the fact that wide-ranging discoveries and innovation have some degree of uncertainty, which must be addressed and managed by both regulators and the industry, by responsible risk assessment. The study focuses on the contemporary and controversial subject of genome editing and discusses the probabilistic risks, hypothetical risks, and speculative risks which affect product safety and consumer perception. Lassoued et al. (2019) reveal that various countries worldwide have different approaches to risk consideration in regulating new technologies, following either a precautionary approach, or substantial evidence approach. The substantial evidence approach or scientific rationality is dictated by scientific risk assessment, while the precautionary approach is governed by other factors in the final judgement. A relevant example involved the contrasting difference between the EU and the USA in consideration and regulation of new technologies based on contrasting risk approach. While the EU is using the precautionary approach, waiting for evidence of no risks before approval, the USA approves for new technologies in the absence of verifiable scientifically assessed risk. Roberts (2018) has recently stated that the sensible approach is the science-based one, which is currently supported by scientific researchers worldwide and best reflected by the 129 Nobel Scientists campaign aiming to explain and to bring their arguments in favour of the controversial biotechnology technique of genome editing. An important alarm signal is triggered by Lassoued et al. (2019), by raising the concern that valuable advances in genome editing technology in particular and biotechnology in general, are unfortunately, currently limited by socio-political factors, which defy scientific principles.

Hurdles in global red biotechnology advances. Most surveys and reports, which point out limitations in red biotechnology development, indicate that the main hurdle is the lack of financial support for research activities and application of pilot projects. Scientific literature provides various examples, such as the National System of Innovation in Biotechnology in Brazil, which is considered only partially developed, due to deficiencies in technological advances, despite being supported by a sound and powerful scientific scope (Gabardo, 2015).

EUROPEAN STATE OF THE ART IN RED BIOTECHNOLOGY

The beginning of the modern European biotechnology era links back to 1975, three senior scientific officers of the Research Directorate General of the European Commission (Dreux de Nettancourt, Andre´ Goffeau and Fernand van Hoeck) forwarded a historical report on potentials of modern biology. Currently, as key representatives of biotechnology industry are seeking new scientific ideas, knowledge, and results, governments need to provide the right

standard of regulation. The EU is now running projects like *Horizon 2020* and the *Bioeconomy Strategy and Action Plan for Europe,* with important budgets, aiming to help create and maintain an appropriate climate for scientists and industry to establish collaboration through innovative projects and entrepreneurship. According to a report on biotechnology in Europe, "The Tax, Finance and Regulatory Framework and Global Policy Comparison", a joint report by EY and EuropaBio (Report on Biotechnology in Europe), the recent period has brought significant increase in global health care biotechnology sales and the job market.

The legislative framework remains the most significant area which must be improved in order to allow the red biotechnology market to grow. The best example would be the former Directive 2001/20/ EC on Clinical Trials of the EU, which led to difficult, expensive, and time-consuming processes for clinical trial sponsors (Directive 2001/20/EC). It took 11 years for the EU to acknowledge and attempt to improve the legislation framework. Finally in 2012, the European Commission proposed a revision of the clinical trial legislation in order to strengthen the EU's competitiveness in this important field of red biotechnology. The current Regulation (EU) No 536/2014 of the EUROPEAN PARLIAMENT and of the Council of 16 April 2014 on clinical intervention trials on medicinal products for human use, repealing Directive 2001/20/EC, contributes to the desired harmonization and brings improved efficiency in the regulatory framework for clinical trials, without affecting the high safety standards of patients and the robustness of clinical data (Reg. No 536/2014).

Placing new pharmaceutical products on the EU or EEA (European Economic Area) market requires granting an authorization (Decision No 51/2006/EC) that includes an application submission by the pharmaceutical new product developer to the European Medicines Agency (EMA), which is the European Authority responsible for the scientific evaluation of the safety, efficacy, and quality of the new products. The scientific assessment is conducted by the EMA Committee for Medicinal Products for Human Use (CHMP). The active time for scientific evaluation of the marketing authorization application by the European authorities may take up to 210 days. In the case of Specialized EMA Committees, such as the Committee for Orphan Medicinal Products (COMP) or the Committee for Advanced Therapies (CAT), an additional draft opinion on each specific product's application falling under EMA Committees expertise, is required before the CHMP reaches a final opinion on the granting of the marketing authorization.

Special categories of health care biotechnology are the Orphan medicinal products (OMPs) and the Advanced therapy medicinal products (ATMPs):

- Orphan medicinal products (OMPs) are pharmaceutical products intended for the diagnosis, prevention, or treatment of rare life-threatening or seriously debilitating conditions. The R&D processes which lead to their manufacturing are based on advanced scientific research for sensitive clinical cases and needs additional specific legislation, such as the EU Regulation on OMPs, Regulation (EC) No 141/2000. Through this specific legislative framework, the EU managed to create appropriate environment for the development and authorization of new OMP treatments across the EU, which make a significant difference for rare and very rare diseases (Reg (EC) No 141/2000).
- Advanced therapy medicinal products (ATMPs) are special pharmaceutical products which target gene therapy, cell therapy, or use engineered tissue. Their development requires a long and complex process, which was addressed by the EU with specific regulation on advanced therapies, such as Regulation (EC) 1394/2007. Unfortunately, for ATMPs, the European regulatory framework has not been efficient so far, and there still are significant hurdles in ATMPs European uptake, which must be managed in the future.

In addition to the new pharmacological products authorization process, the EU has created a post-authorization legislative framework, through Regulation (EU) No 1235/2010, to support the pharmacovigilance requirements that improve the data collection after a product approval for marketing (30). For

certain products that require additional monitoring, the EU pharmacovigilance legislation provided a separate EMA Committee - the Pharmacovigilance Risk Assessment Committee (PRAC). PRAC provides feedback to CHMP on pharmacovigilance activities and on risk management systems, according to Directive 2010/84/EU (Directive 2010/84/EU). However, without minimizing the patient safety and the need to provide accurate information to the public, these additional systems must be efficiently managed and supervised, especially by assessing the financial burden and administrative hurdles for the companies.

According to the report on biotechnology in Europe: "The Tax, Finance and Regulatory Framework and Global Policy Comparison", which is a joint report by EY and EuropaBio (Report on Biotechnology in Europe), unless appropriate legislative framework is created that would ease the journey from innovation to manufactured products, the European biotechnology research hub may be at danger of losing the associated innovative products, processes, jobs, and economic growth.

ROMANIAN RESEARCH IN RED BIOTECHNOLOGY - FOLLOWING THE CURRENT TREND OF SCIENTIFIC ADVANCES

Considering the impact of traditions over the wellbeing of a population in a certain geographical area and social acceptance of innovations that are linked to traditional technologies, more and more scientists are considering introducing mature knowledge into innovation development process. Based on the evidence brought by recent publications (Capaldo, 2017), scientist are currently embracing the usefulness of adoption of moderately mature knowledge to sustain the value of moderately mature knowledge-based innovative applications that preserve scientific value and demonstrate sustainable feasibility.

Romanian mature knowledge is now increasingly being adopted from academia following the global trend, although it could not find feasible application in the past and was not able to attract adequate financing along with new scientific results, which need pilot projects to be effectively implemented in new applications. Romanian biotechnology companies are growing collaborations with academia through public-private partnerships and contract research activities by using mature knowledge advancements.

As the academia is always a strategic component of the research and development, the education offer is also an important aspect for the development in biotechnology. The higher education offer in Romania has become increasingly attractive in the recent years, not only for the Romanian students, but also for international students. English and French programs of the most important national universities in the country have been bringing increasing numbers of international students from all over the Europe that mostly attend bachelor's degree programs. The biotechnology educational field is represented by over 20 Romanian universities, providing bachelor's degree, master's degree, PhD and Postdoctoral programs in engineering, biology, agriculture, environment and chemistry (Stanciu, 2010).

Past and present hurdles in Romanian biotechnology development. The biotechnology industry in Romania is still in need for further development. This may be due to the lack of interest of past governments in prioritizing this field, so that very few research programs were granted funding. The main fields of Romanian biotechnology companies are contract-research and manufacturing, veterinarian, medical, environmental, analysis, and diagnostic (Stanciu, 2010). Academic research in Romania is still restricted by difficult access to funding and the limited transfer of knowledge from academia to companies. Moreover, EU funding is not efficiently accessed, despite the fact that absorption of structural funds has been a priority for recent governments, leading to a poor project accessing of the EU funds. Some of the most significant reasons include the weak representation of national companies in European projects, poor information systems and lack of start-up capital for co-financing (Stanciu, 2010).

Another draw-back in biotechnology development in Romania was the so-called "asset-less hyper-competence or competence-less lay-off nearby high-tech assets" (Stanciu, 2010; Vidulescu, 2003). In addition to this, most of the young, passionate researchers are

searching for better paid jobs in a more efficient working environment, in EU, USA, Canada, or UK.

Romanian potential for biotechnology research development. Romanian potential as an attractive destination for biotechnology research development has been advocated by producers of innovative drugs. Companies have grown interest in performing R&D activities in Romania, based on the valuable scientific human resource and on the significant project results despite the lack of financing. Companies such as Amgen Romania is seeking for development of an effective strategy for allocating capital into production facilities for innovative products and are confident that Romania is starting to attract significant investments in the red biotechnology field (Business-review, 2019). This is an important forecast for our country, as Amgen is considered the worldwide research specialized leader in biotechnology and personalized therapies for patients with severe illnesses, focusing on R & D in production of medicines in more than 75 countries worldwide.

Romanian programs for research, development and innovation. Romania has a legislative framework for the Strategy of National Research, Development and Innovation 2014-2020, which was approved by Government Decision no. 929. The main instrument for the implementation of this strategy is the *National Research, Development and Innovation for 2015-2020 (PNCDI III),* approved by Government Decision no. 583/ 22.07.2015. UEFISCDI (Executive Unit for Financing Education Higher Research Development and Innovation) PNCDI III is currently coordinating the following programs (UEFISCDI, CNFIS, 2019):

- Program 1: Developing national R & D system - which aims to help the development of human resource, to increase resource efficiency in public organizations, by developing mechanisms for monitoring and evaluating the quality and relevance of R & D activities; increase the attractiveness of research organizations and their partnerships with scientific international community (UEFISCDI, CNFIS, 2019):
  - Subprogram 1.1. Human Resources;
  - Subprogram 1.3. R & D infrastructure;
  - Subprogram 1.4. Support.
- Program 2: Improving the competitiveness of Romanian economy through research, development and innovation - aims to drive progress on enterprise value chains and partnerships with public universities, by maximizing the added value of innovative goods production (technologies, products, services) based on scientific research (own or outsourced); aims to increase the capacity of companies to absorb the latest technology and to adapt these it to the needs of target markets; creates and enables environment for private sector initiative through entrepreneurship training tools, support for R & D product marketing and establishes partnerships between firms, research organizations and possibly local authorities (UEFISCDI, CNFIS, 2019).
  - Subprogram 2.1. Competitiveness through research, development and innovation.
- Program 3: European and international cooperation - has as main objectives: increasing the international competitiveness of Romanian research in attracting external funding for research; strengthening of national research, development and innovation systems through enhanced international scientific cooperation; supporting Romania's participation in the Framework Program for Research and Innovation EU - Horizon 2020 initiatives Commune Programming (JPI), the European Innovation Partnerships (EIP) on other initiatives, programs, organizations and European and international conventions; providing support for Romania's representation in organizations and pan-European programs and international research; providing Romanian increased visibility in research, development and innovation (UEFISCDI, CNFIS, 2019).
  - Subprogram 3.1. Bilateral/multilateral (excluding the bilateral program with AUF);
  - Subprogram 3.2. 2020;
  - Subprogram 3.5. European and international initiatives and programs;
  - Subprogram 3.6. Support.
- Program 4: Fundamental research and border.

Romanian research in 3D printing technology advances. 3D printing provides the opportunity

to create personalized precision medication to treat patients according to their individual characteristics (genetic background, external factors, history of conditions), as recommended by the FDA: "Providing the right patient treatment, at the right dose, at the right time" (FDA, 2013). 3D printing technologies are close to successful use for the production of pharmaceutical forms with different models and dose levels, in a short time in medical facilities, at affordable prices (Park, 2018; Rahman, 2018). These are considered promising techniques for the precise combination of substances with complex release profiles and providing flexibility in dosing and treatment (Konta, 2017). The 3D printing potential is used in the clinical production and applications of medical implants, organs, and tissues. Biocompatible compounds, cells, and substances are assembled together in complex 3D structures such as tissues and living organs. A model with no faults, similar to the anatomical model, is produced using a high-quality 3D image obtained from the patient to produce the data required for the creation of rapid prototypes of the desired structure (Ozbolat, 2013; Preis, 2017).

Bio-printer 3D works with special ink substances, which must be biocompatible, printable, biodegradable, allowing vascular and nervous regeneration and cell differentiation. In addition, bio-printer inks must be affordable and available in unlimited amounts. Intensive research is thus carried out in the area of biopolymers in Romania, due to their specific properties (Lupuleasa, 2011). Biodegradable polymers have special properties, as they will not induce an inflammatory response, their mechanical properties are designed and pre-established and are cleaved to soluble degradation products, via hydrolytic or enzymatic path, being safely cleared from the body. Currently, scientists believe that 3D printing technologies are capable of overcoming present hurdles in drugs and medical devices manufacturing (Lupuleasa, 2011).

Antibody therapy new product development blooming and Romanian research support.

The recent increasing pace in antibodies - new product development, as reflected by numerous studies (Kaplon, 2018) and revealed by an increasing number of antibody therapeutics grant approval (for phase III and IV of clinical trials), both in the USA and in the EU, has driven a similar trend in the number studies being published in relation to efficiency in various patient categories. The research performed in this red biotechnology application field is also supported by Romanian scientists. For example, in an observational study conducted in Romania concerning the rheumatoid factor (RF) and anti-CPA antibodies, known as negative prognostic factors in the rheumatoid arthritis (RA) treatment, Codreanu et al. (2018) pointed out that the therapeutic significance of the antinuclear antibodies (ANA) in the RA is unclear and aimed the assessment of the possibility of using ANA as a prognostic factor for the therapeutic response to biological RA PR. They included 740 patients with PR and found that patients with positive ANA had significantly higher disease activity score before the biological initiation compared to patients without ANA. They concluded that positivity of the ANA in patients with RA prior to the initiation of biological therapy could be a negative prognostic factor for the effectiveness and persistence of treatment (Codreanu, 2018).

Biological pharmaceutical products in Romania.

Over time, Romanian biotechnology has produced medicines such as insulin, coagulant VIII factor for Haemophilic patients, monoclonal antibodies for targeted therapies as well as for cancer immune therapy, orphan pharmaceutical drugs for rare diseases, vaccines, CAR-T cellular therapies or complex therapies for repairing organs, skin, bone and cartilage lesions.

Despite these advances, there is still a poor market for medical biotechnologies in Romania compared to other countries, hence a lower overall level of information about the implications and the specificity of these therapies. The most common information about bio-based medicines is about comparing original biobased drugs with biosimilar ones, but very little information is found on the specificity of bio-based medicines, patient safety issues and ensuring their traceability.

Due to insufficient analysis of the extent of knowledge of biological medicines or general perceptions of such medicines in Romania,

pharmaceutical companies initiated a research study based on the views of authorities representatives and stakeholders, which has shown that there is a need for more extensive and detailed information (for those who use or regulate them) on the specificity of bio-medicines (Grabowski, 2014; Giezen, 2009).
Therefore, considering the conclusions of consultations held with stakeholders, it would be appropriate to increase the awareness of Romanian decision-makers and stakeholders about biological treatment and their specificity, with a view to increase patients' access to such treatments and safer treatment application (Giezen, 2009).

CONCLUSIONS

Red biotechnology and bio-based medicines have changed and continue to fundamentally change the fate of patients with serious diseases such as cancer, diabetes, haemophilia, rheumatoid arthritis, myocardial infarction, and intestinal inflammatory diseases. At the moment, several hundred bio-based drugs are being developed worldwide, with most of them being cancer medicines. Many medicines are expected to reach the market in the near future, with major challenges for medical practice, for patients, and also for the health system as a whole. The top 5 most productive countries in terms of red biotechnology scientific research were the United States of America, China, Germany, Brazil, and India, while the USA is the world leader in terms of patent application number. On a global perspective, the main hurdle in red biotechnology is lack of financial support for research activities and application of pilot projects.
As European legislation is currently changing rapidly and the needs are increasing accordingly, additional ways to improve communication between scientists, industry, and the society should be found for the desired outcomes of public goods. Financial tools to ensure appropriate climate for research, development, and innovation of biotechnology goods also need to be created. However, the main drawback at the European level remains the legislative framework. Unless appropriate regulations that would ease the journey from innovation to manufactured products are passed, the European biotechnology research hub may be at danger of losing the associated innovative products, processes, jobs, and economic growth.
Even though the biotechnology industry in Romania is still in need for further development due to numerous past and present drawbacks, Romanian potential for biotechnology research development was recognized by important biotech companies as an attractive destination. Currently running large programs for research, development, and innovation, regulated within a national implementation strategy, and with an attractive higher education offer, Romania is contributing to biotech advances, new product development, and has a great potential for production of biological pharmaceutical products, therefore representing a valuable and promising partner for future international collaborations.

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TECHNOLOGIES OF ANIMAL HUSBANDRY