foresight

The long-term development of Russian biotech sector

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Introduction

Biotechnologies are one of the fastest growing "horizontal" technological directions that form the basis for future economic transformations. New achievements in promising areas of biotech are in high demand because they can help to guarantee food supplies, sustain the supply of resources, increase lifespans and improve health. The crisis of traditional technologies (including environmental and energy-related ones) provides new opportunities for this area's development. According to OECD estimates, in 2030 biotechnologies may be used for 35% of chemical industry production, 50% of agricultural production, 80% of pharmaceuticals [1]. The development pathways in this area should be determined by achievements in the field of systemic, structural and synthetic biology, genomics, proteomics and cellular technologies.

In Russia, more than 80% of biotechnological products are imported, which is why the development of the bioeconomy is an essential factor for the modernization of the economy in the country. In addition, Russia has a significant potential for introducing biotechnology into industry. For example, in 2010 the world market for bioenzymes amounted to $2,8B, at the same time in Russia in 2013 it was only $0,18B.

New institutional and organizational changes taking place abroad lead to an accelerated development of this area (for example, permission for gene editing of human embryo or widespread distribution of GMOs) [for example 2,3]. In the event that the effective state policy in the field of biotechnology is not implemented, a lag from the advanced countries may become unattainable. Without effective state support Russia can forever fall behind the leading countries. In this regard, it is so important to select key biotech areas taking into account the available potential. At present even the most developed countries cannot conduct R&D over the whole range of scientific and technological fields. Therefore, the priority areas where Russia can take competitive positions should be identified. The process of priority setting should include an understanding of the key areas of biotechnology development and the grand challenges that will form the future shape of this sector and an analysis of available resources including R&D capacity for particular thematic areas.

In order to define strategic directions for Russia's social, economic, scientific and technological development in 2011-2013, a large-scale foresight study (Russia 2030: Science and Technology Foresight) was undertaken [4]. This article delves into its results in the area of biotechnology as one of the seven priority areas of science and technology development.

Methodology

This study represents the results of the third cycle of the national foresight project. The first cycle was conducted in 2007-2008 and based on results of a large-scale Delphi survey. Over time the procedure of prognosis projects in Russia has become more complicated and involved more advanced methods.

The third national foresight cycle integrated two approaches: technology push (new knowledge and technologies drive the launch of new products) and market pull (needs of society prompt S&T development).

According to these principles, on the one hand, grand challenges that have the potential to dramatically transform the future face of the economy, science and S&T sphere were identified. These grand challenges were specified for particular priority areas including biotechnology. In its turn, thematic trends determine the demand for innovative products in the future. According to these results, a list of promising markets, products and services was created.

On the other hand, the future technological supply was analyzed. Hereby for every priority area a list drawn up of thematic fields, promising research areas and R&D topics was formed. In addition, the selected areas were assessed according to the Russian R&D level in comparison with the world. Also centers of excellence in Russia and abroad were identified.

The methodology of the project combines both qualitative and quantitative methods: expert panels, horizon scanning, bibliometric and patent analysis, weak signals and wild cards, SWOT analysis, stakeholders mapping. More than 2,000 experts from science, government and business were involved in the work including foreign specialists. They took part in different types of expert activities: discussions, surveys, interviews, etc. The objective foundation of the study was formed on the basis of bibliometric and patent analysis and a review of more than 200 sources.

Further, the received results were used in the strategic decision-making process. For example, a list of advanced R&D areas formed the basis for the state program "R&D development" [5] and other strategic documents.

Global trends in the development of biotechnologies

Until now, most of the biotechnological developments have been carried out for biomedical and biopharmaceutical products (drugs, biocompatible materials, biochips, diagnostic agents et al.) and to a lesser extent for the food and agricultural sectors. Therefore, until now medicine and pharmaceuticals have been the main drivers in this area. However,

new technologies in this area can have a multiplicative effect and be successfully used in other industrial sectors.

A number of socioeconomic, scientific and technological trends determine the structure and operational principles of the national biotechnological industry [6]. For several sectors, modernization is possible only in the case of a transition to biotechnological methods and products (e.g., the agro-food sector, the forestry sector, and the biomedical sector).

According to the methodology of the project based on literature analysis, expert studies, there were selected trends that form the future of biotech sector within or outside Russia. These trends were evaluated according to their impact on Russia (strong/low and positive/negative) and expected period of maximum effect (fig. 1).

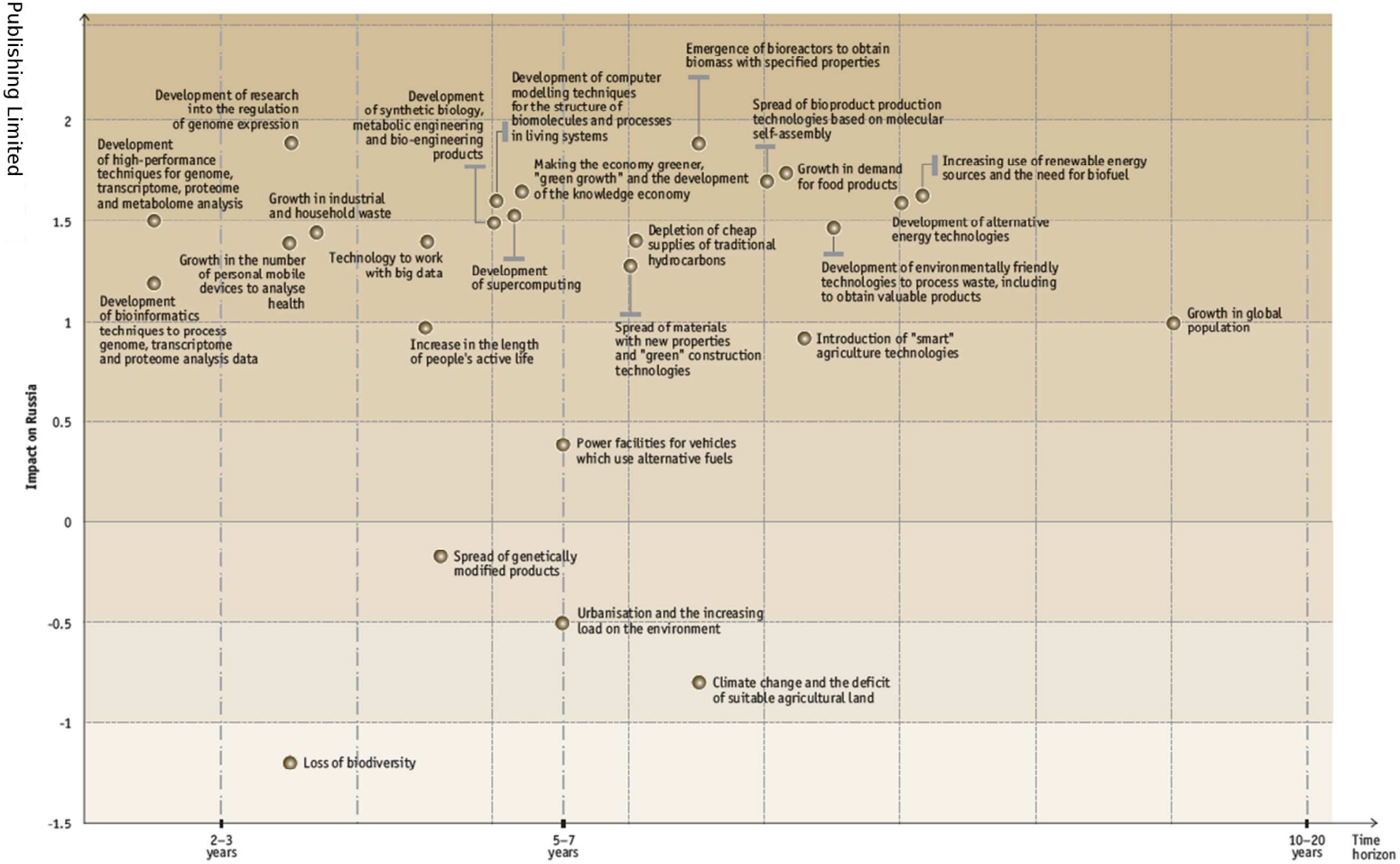

Fig. 1. Global trends for biotechnological sector development

New biotechnological products with advanced and new properties will help to respond to the main global socioeconomic challenges that mankind will face in the long and short term: population growth, aging, food shortages, environmental degradation, climate change, the depletion of hydrocarbon natural resources, and others. The technological drivers are not limited to progress in biology but also include developments in nanotechnology and information and communication technology.

Population growth causes increased demand for food, pressure on the agricultural sector and growing rates of fertile soil contamination and erosion. All these problems can be addressed using biotechnological solutions. Along with that, high-income consumers will request organic and functional food. New bioproducts will help address the challenge of hidden hunger (deficiency of vitamins and minerals), which includes an unbalanced diet, a lack of essential vitamins and minerals.

In the short and long term, pervasive changes in the energy sector are expected. The depletion of cheap supplies of hydrocarbons, the tightening of ecological requirements will give an impetus to the development of renewable power generation. Moreover biogeotechnological methods to increase oil recovery and to remove unwanted admixtures from extracted minerals will be in demand [7].

One of the most important global challenges is the environmental degradation in many regions of the world. The increasing human-induced burden on natural ecosystems is associated with the emission of greenhouse and other harmful gases into the atmosphere, land and water pollution, the depletion of sources of drinking water and stocks of raw materials. The development of biotechnologies will help to solve this problem according to conception of a circular economy, which involves the restoration of natural resources [8].

A strong impetus for progress in biotechnology will provide for the development of other scientific and technological areas. New technologies to store, process and transfer big data and supercomputing can be useful for genome, transcriptome and proteome analysis, in metabolic engineering and bio-engineering.

The convergence of ICT, bio- and nanotechnologies will have a significant impact on the agricultural sector [9] and will lead to development of “smart” agriculture (diagnostic agents, biosensors to gauge growth, optimizing biodevices, biorobots, etc.). The adoption of new technologies will raise the efficiency of use of agricultural land, prevent erosion, the leaching of nutrients, maintain soil structure, and as a whole - reduce the negative impact on the environment.

Thus, biotechnological development can help to find answers for the following major global challenges:

- population growth and food shortages;
- crisis in traditional sectors: substitution of chemical processes with biotechnological ones;
- dependence on fossil fuels: development of renewable bioenergy will contribute to the diversification of the energy sector and reduce dependence on hydrocarbons;
- depletion of non-renewable resources;
- destruction of natural ecosystems as a result of human activity: biotechnology can reduce the negative anthropogenic impact and promote ecosystem restoration through the means of bioremediation.

All these global trends form windows of opportunity for the accelerated development of biotechnologies. Many of them are significant for the development of the Russian biotech sector, some are not so important (e.g. population growth, deficiency of fresh water, and depletion of fossil natural resources). In any case, all these trends and challenges should be taken into account if Russia wants to participate in global value chains.

In parallel, the Russian biotech sector faces a number of limitations and weaknesses specific to the country:

- the critical lag in R&D and undeveloped production facilities;
- low demand for practical developments in biotechnology;
- a powerful lobby for the oil and gas sector;
- insufficient investment by businesses in biotechnological industry infrastructure;
- high barriers to entry on domestic and global biotechnology product markets;
- an ambiguous social attitude toward the use of genetically modified organisms;
- critical dependence on the technological import in some sectors using biotechnology production [10] (feed, enzymes, biomedical products and others).

In addition, nonmedical biotechnologies has relatively recently become a national priority in Russia [11]. In many respects, it is connected with the significant reserves of gas and oil, less attention to the environment than in developed countries, huge areas of arable

lands that promote extensive agriculture. However, the availability of separate competitive scientific teams, a broad resource base, large areas of arable land and forests are the windows of opportunities for the development of this area in Russia.

Progress in biotechnology sector

Biotechnology covers genetic engineering, cellular methods and technologies for the creation and use of genetically modified biological objects for production intensification or the creation of new kinds of products for various purposes. Modern biotechnological processes are based on recombinant DNA techniques, as well as on the use of immobilized enzymes, cells or cell organelles.

In Russia, in the near future, biotechnologies will be most in demand in the following markets: industrial bioproducts, biotechnological agricultural products, biofuel and bioenergy, food industry, biological environmental protection systems, biotechnological systems and products for the forestry sector and aquaculture [11]. In the light of progress in the field of biotechnology, the innovative products with radical effects will be in demand on global markets. Products with completely new properties or a multifold increase in technical and economic properties should be developed to tackle the challenges identified above. The most promising applications of biotechnologies on these markets are given below.

Russia has the potential for the development of the biotech sector, although the level of R&D in the majority of areas is lagging behind that in USA and leading EU countries. But there are several advanced applied research areas, where efforts can be focused. According to results of the study, seven thematic areas of applied research have been identified:

- industrial biotechnologies;
- energy biotechnologies;
- agricultural biotechnologies;
- food biotechnologies;
- environmental, forestry biotechnologies, aquabioculture.

Below these areas are described in more detail.

Industrial biotechnology

Biotechnologies can successfully substitute traditional chemical technologies and processes to produce biomaterials and organic synthesis products with unique properties, including new ones that do not exist in nature [12]. Replacing chemical production with biotechnological production will create high purity organic substances, including optically pure organic compounds for the synthesis of drugs, and reduce the cost of its production. New types of biomaterials due to their special characteristics will have a wide range of

applications. Some of them (e.g., bioplastics) will have valuable properties such as biodegradation, and this, in turn, will give impetus to the development of new biodegradable materials for medical and industrial applications.

The other way to produce biologically active compounds is the targeted modification of the producing organism's biosynthetic pathways using metabolic engineering techniques [13]. These technologies help to intensify the production of amino acids, vitamins, antibiotics, enzymes, recombinant proteins and other products and are more efficient than traditional ones (e.g. random mutagenesis) [14]. The most in-demand industrial bioproducts for long and short term are fodder additives (essential amino acids, vitamins, protein), enzymes, bioplastics, biopolymers and others.

The industrial biotech sector covers technologies for the production of industrial, agricultural and medical products both traditional (biologically active compounds, recombinant proteins, forage, etc.) and new ones (biopolymers, organic synthesis products, biodegradable plastics, etc.), using biosynthetic and biocatalytic processes, processes to obtain biomaterials, organic synthesis products from renewable raw materials (primary lignocellulose biomass and agricultural byproducts), new technologies for the production, isolation and purification of bioproducts and others [12]. The area of enzymes production for industrial and agricultural applications, which are now mostly supplied by foreign producers, will drive the development of industrial biotech area in the near future. The development of biotechnologies for the raw materials sector, such as microbial-enhanced oil recovery or metal bioleaching, is also in demand by the industry right now.

Bioenergy

The wide use of biofuels (including motor fuels) can transform existing energy markets. New bioenergy technologies will help to save non-renewable hydrocarbons, significantly expand the resource base of the economy, reduce greenhouse gas emissions and as a result reduce the negative impact of energy on the planet's climate [15]. The main directions of bioenergy's technological development are concerned with the improvement in energy efficiency, the biotransformation of carbon dioxide into motor fuel, the reduction of biofuel costs, the expansion of the supply base for its production, the improvement of quality (stability, environmental cleanliness) [16]. Since Russia has practically unlimited natural oil and gas resources, the development of the bioenergy sector will be initially driven primary by global biofuels markets.

Bioenergy development requires new technologies, including the conversion of lignocellulosic materials and agricultural waste into biofuels; environmentally friendly

biomass gasification technology and power generation units based on them; new methods of producing high-quality motor fuels from CO2 without photosynthesis; effective technologies of biogas production, including highly efficient microorganisms; new technologies of production of liquid motor fuels, including jet fuel, and components from vegetable raw materials; new technologies of biomass processing into high-quality solid fuel, and others. All these techniques are aimed at reducing production costs and increasing the energy output ratio of biodiesel and bioethanol.

Agriculture

Another sector where new promising biotechnologies can be implemented in the near future is agriculture. The Russian sector will continue to be an expensive one and lose in competitiveness to other countries without the development and introduction of biotechnological innovations. New varieties of crops and breeds of livestock animals can be produced by using molecular marker-assistant selection, doubled haploids technology, genetic engineering, genome editing and other methods [17]. Next-generation varieties and hybrids will be notable for high nutritional quality, high productivity (a larger size of fruit, reducing ripening time, etc.) and resistance to diseases and unfavorable weather conditions [9, 18]. New genomic technologies will bring new and better breeds of farm animals (e.g., those with the desired level of meat fatness) with rapid growth, which will contribute to the rational use of feed.

The development of agrobiotechnologies will be also focused on advanced methods for managing genetic resources of agricultural plants, animals and microorganisms. The other promising direction includes innovative biological techniques to protect plants and increase their productivity, and veterinary drugs.

Agricultural biotechnologies are aimed at increasing the efficiency of this sector and reducing crop losses [9]. Here R&D will concentrate on the development of genetic markers for selection, symbiotic plant-microbial systems for plant protection and growth stimulation, cloning techniques to replicate outstanding farm animal genotypes, plant genetic engineering and a methodology for the targeted modification of genomes ("genome editing"), the creation of new breeds and others. The development of the seed production industry within Russia is one of the highest priorities. Scientific interests in the veterinary field will be focused on the analysis of genomes of dangerous disease agents, studying the evolution and channels for the spread of infectious agents, identifying and studying mechanisms of resistance to pathogens. This knowledge can be used in new technologies for producing new preventive and therapeutic preparations based on research of the molecular mechanisms of pathogenicity and

immune response; the development of new test systems for high-performance detection of pathogens; recombinant vaccines against animal infectious diseases.

Food industry

The growing market of organic products will affect not only the agricultural sector, but also the food industry. The demand for "natural" food now prevails over the demand for genetically modified food in Russia. The uptake of transgenic products is limited due to the ambiguous attitude of society and the state, primarily because of the lack of objective information about its impact on human health and the environment in the long term. A similar situation occurs with the cultivation of test-tube meat [19]. This technology currently has a lot of limitations, however, in the future it has the potential to transform the sector of animal husbandry and increase the output of finished meat products. Development in this area may give a serious impetus for the creation of food and industrial crops with improved or new properties and often at a lower cost. As a result, one can expect a significant growth in agricultural production.

Plants and animals, including agricultural ones, can be used also as biofactories to produce recombinant proteins for industrial (enzymes, biopolymers, etc.) and medical (vaccines, antibodies, enzymes) use [20]. This technology is characterized by higher effectiveness and fewer costs than traditional ones based on using cell cultures from microorganisms or animals. The production of recombinant proteins in plants using viral systems, as well as in the milk of transgenic animals, can be noted as one of the most promising developments. The most important competitive advantage of Russian immunobiological drugs for veterinary practice is the use of local strains of pathogenic microorganisms. It can provide higher specificity for these products for their use in the Russian Federation and neighboring countries.

Safety evaluation systems for new and traditional food sources, ingredients, food processing technologies, functional food stuffs, baby food, diet and medical food, low allergenicity food, and biologically active additives will be in demand in food industry in the short and long term. Food biotechnologies will be developed in the following areas: the integrated safety evaluation of products; food protein technologies including the targeted production of protein compositions with specified properties and the deep conversion of by-products and waste from processing vegetable and animal raw materials; biotechnological approaches to the production of probiotics, prebiotics, synbiotics, enzymes and food ingredients; technologies for processing food raw materials and waste.

Environmental, forestry biotechnologies, aquabioculture

The use of biotechnologies for environmental applications is focused on the creation of pollution monitoring systems, the restoration of ecosystems using live organisms – bioremediators, protecting materials and technological objects from biocorrosion. The methods of cleaning up oil spills are most in demand. Today, bioremediation has been successfully used to protect soil and groundwater and land reclamation. In the short and long term scientists will focus their efforts on the development of new verified techniques for bio-testing and bioindication with increased sensitivity and selectivity to detect environmental pollution; biotechnologies for the purification of water, soil, and air; environmentally safe biocides for protection of process facilities from organisms-decomposers. Currently, not all technologies are commercially effective, but the dynamics of the process suggest that over the next 10-15 years, they will be introduced into mass production.

As in the USA and EU, [21] forestry biotechnologies will be concentrated on the creation of new varieties of arboreal plants with improved properties (texture of timber, resistance to pathogens, growth rate, etc.), microbiological protection of forests from pests and pathogens, promising biotechnological processes for the integrated processing of lignocellulose biomass and its individual components. At the moment the elimination of waste from woodworking enterprises in Russia is practically undeveloped, since significant investments are required for these purposes. There is a lack of capacities for deep biotechnological processing of wood, equipment and technologies for these purposes are missing. This sphere requires close attention from the state.

R&D in aquabioculture will be focused on the identification of new biologically active substances from marine organisms, cultivating cell lines of marine organisms, the producers of biologically active compounds, molecular selection of the objects for industrial aquaculture to make highly productive breeds [22]. These technologies correspond to the trend of the intensive development of recirculating aquaculture systems. In the future, algae can become a perspective source of biomass and be heavily used in the energy sector.

The development of the above-mentioned areas of applied research needs new methodological approaches that can form the scientific and methodological basis for biotechnology research. Progress in this direction can be provided by new genomic and post-genomic technologies, system, synthetic and structural biology, bioengineering and bioinformatics. The research agenda should concentrate on bioinformatics techniques to analyze genome, transcriptome and proteome data, the study of the structure of macromolecules and their components and modeling their structures in silico, metabolic

engineering of microbial cells and the development of models to create a synthetic cell, and other promising techniques.

Conclusion

Russia has access to unique natural resources, including an unlimited supply of many types of renewable raw materials, huge reserves of fresh water, fertile land, and therefore it has good potential for biotechnological development and integration into the global economy in this sphere. In order to ensure the long term social development and sustainability of the national economy, Russia should take a leading position and create a competitive sector of the bioeconomy, which along with the nanoindustry and information technologies should be the basis upon which the Russian economy is modernized.

At present Russia's share in the global market of biotechnology products is by far less than 0.1%, and for some segments, this share is near zero. That is why there is a strong need for the development of the biotechnology industry in the country and a need to enhance R&D activity in this area.

The concentration of available resources of the government and businesses on the development of the biotechnological sector could help in the search for answers to the challenges that Russia faces today or will face tomorrow. It will help to pick up on the current level of research activities, improve the quality of personnel training, make this area the engine of the economy and carry out the so-called new industrialization of the country, building a new, high-tech devices industry.

The realization of the identified R&D priorities will require the development of a detailed action plan, including the development of biotechnological infrastructure, the large-scale launching of the bioindustry in regions, the preservation and development of bioresource potential, the improvement of the legal, economic, informational and organizational bases.

References

1. OECD (2010) The Bioeconomy to 2030: Designing a Policy Agenda. Paris: OECD
2. National Academies of Sciences, Engineering, and Medicine (2016) Genetically Engineered Crops: Experiences and Prospects
3. Puping Liang et al. (2015) “CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes”, Protein & Cell. Volume 6, Issue 5, pp 363–372

4. Ministry of Education and Science of the Russian Federation; National Research University Higher School of Economics (2016) Russia 2030: Science and Technology Foresight. Moscow: HSE
5. The Russian Government (2012) "State programme for R&D development" Order № 2433-R of the 20th of December, 2012
6. Mikova N, Sokolova A (2014) Global Technology Trends Monitoring: Theoretical Frameworks and Best Practices. Foresight-Russia, vol. 8, no 4, pp. 64-83
7. Siegert M, Sitte J, Galushko A, Krüger M (2014) "Starting up microbial enhanced oil recovery" Advances in Biochemical Engineering / Biotechnology, vol. 142, pp. 1-94
8. David W. Pearce, R. Kerry Turner (1989). Economics of Natural Resources and the Environment. Johns Hopkins University Press
9. Yashveer S, Singh V, Kaswan V, Kaushik A, Tokas J (2014) "Green biotechnology, nanotechnology and bio-fortification: perspectives on novel environment-friendly crop improvement strategies", Biotechnology & Genetic Engineering Reviews, Vol. 30(1-2), pp. 113-26
10. Streltsova E (2014) Patent Activity in Biotechnology. Foresight-Russia, vol. 8, no 1, pp. 52-65
11. Technological Platform «Bioindustry and Bioresources» (2015) Strategic Research Agenda
12. National Research Council (2015) Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals. Washington (DC): National Academies Press (US)
13. Heux S, Meynial-Salles I, O'Donohue MJ, Dumon C (2015) "White biotechnology: State of the art strategies for the development of biocatalysts for biorefining". Biotechnology Advances. Vol. 33(8), pp. 1653-70
14. Weber T, Charusanti P, Musiol-Kroll EM, Jiang X, Tong Y, Kim HU, Lee SY (2015) "Metabolic engineering of antibiotic factories: new tools for antibiotic production in actinomycetes", Trends in Biotechnology. Vol. 33(1), pp. 15-26
15. Kilbane JJ II (2016) "Future Applications of Biotechnology to the Energy Industry" Frontiers in Microbiology
16. Hegde K, Chandra N, Sarma SJ, Brar SK, Veeranki VD (2015) "Genetic Engineering Strategies for Enhanced Biodiesel Production", Molecular Biotechnology, Vol.57(7), pp. 606-24

17. Hartung F, Schiemann J (2014) “Precise plant breeding using new genome editing techniques: opportunities, safety and regulation in the EU” Plant Journal, Vol. 78(5), pp. 742-52
18. Rossi M, Bermudez L, Carrari F (2015) “Стр: 14
Crop yield: challenges from a metabolic perspective”, Current Opinion in Plant Biology, Vol.25, pp. 79-89
19. Verbeke W, Sans P, Van Loo E (2015). "Challenges and prospects for consumer acceptance of cultured meat". Journal of Integrative Agriculture, vol. 14(2), pp. 285-294
20. Buyel JF (2015) “Process Development Strategies in Plant Molecular Farming”, Current Pharmaceutical Biotechnology, Vol.16(11), pp. 966-82
21. Häggman H, Raybould A, Borem A, Fox T, Handley L, Hertzberg M, Lu MZ, Macdonald P, Oguchi T, Pasquali G, Pearson L, Peter G, Quemada H, Séguin A, Tattersall K, Ulian E, Walter C, McLean M (2013) “Genetically engineered trees for plantation forests: key considerations for environmental risk assessmen”, Plant Biotechnology Journal. Vol. 11(7), pp. 785-98
22. Reen FJ, Gutiérrez-Barranquero JA, Dobson AD, Adams C, O'Gara F (2015) “Emerging concepts promising new horizons for marine biodiscovery and synthetic biology”, Marine Drugs. Vol. 13(5), pp. 2924-54

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