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# SYNTHETIC BIOLOGY IN PERSPECTIVE

## BIOLOGIA SYNTETYCZNA

***Summary**: Towards the end of the XXth century, genetics expanded its scope not only in the field of structure and mechanisms of heredity, owing to progress in nucleic acid research including efficient sequencing and reassembly methods, but in acquiring precise tools which enable construction of new forms of life. Synthetic biology marks a radical change in practices of genetic manipulation from random mutations followed by selection, to design of specific DNA transformations attainable by application of genetic engineering methods. Mastering enzymatic gene splicing procedures and chemical synthesis of polynucleotides allowed perceiving macromolecules of life as "parts" or "bricks" amenable to specification, cataloguing and also fit for applications commensurable with the rules of engineering. The purpose of synthetic biology is to apply defined macromolecular constructs (abstracted from living matter or synthetic) as modules for construction of devices, sensors or switches, which can ultimately be integrated into self-sustained systems. Target applications of synthetic biology products ranges from biotechnological manufacturing of energy, fuels, chemicals, food and pharmaceuticals, through marker sensors and diagnostic devices, to various classes of therapeutics like antibodies, vaccines, probiotic microbes or modified immune cells. Thus, synthetic biology becomes an integral part of the prospective switch from present industrial reality to circular bioeconomy, which is the greatest challenge facing humanity.*

***Keywords**: bioeconomy, bioengineering, biotechnology, xenobiology, biotransformations, biological constructs and devices, genetically modified organisms*

***Streszczenie**: Na przełomie stuleci genetyka zyskała, w wyniku dogłębnych badań nad kwasami nukleinowymi, nowe specyficzne narzędzia modyfikacji materiału genetycznego, nieporównywalnie skuteczniejsze od wykorzystywanych uprzednio przypadkowych mutacji z następczą selekcją. W wyniku rozwoju różnych form biotechnologii, korzystających z narzędzi inżynierii genetycznej wyłoniła się (najpierw w formie postulatywnej) biologia syntetyczna, zakładając wykorzystanie funkcjonalnych biomakromolekuł jako elementów zamiennych (cegiełek lub podzespołów) do projektowania i konstrukcji większych modułów, systemów a wreszcie organizmów, spełniających z góry zadane założenia metaboliczne. Zadaniem biologii syntetycznej jest zapewnienie dostępności (docelowo w skali procesów przemysłowych) układów biologicznych zdolnych do korzystnego przetwarzania energii (szczególnie solarnej), transformacji składników biomasy w niskoemisyjne paliwa, półprodukty chemiczne, biopolimery oraz składniki żywności i leków. Inne zastosowania biologii syntetycznej koncentrują się w obszarze ochrony zdrowia; projektowane obecnie konstrukty będą spełniać role markerów i sensorów dla diagnostyki, probiotyków dla profilaktyki oraz przeciwciał, szczepionek a nawet celowo reprogramowanych komórek (np. układu immunologicznego) dla terapii lub medycyny rekonstrukcyjnej.*

***Słowa kluczowe**: bioekonomia, bioinżynieria, biotechnologia, ksenobiologia, biotransformacje, konstrukty biologiczne, organizmy genetycznie modyfikowane*

## Introduction

There is a general tendency to perceive the anthropocene period of the earth history in a dual and controversial perspective: as a rise of triumphant technical civilization able to support and sustain (at least thus far) large and dynamically growing populations, versus grim catastrophic perspective of inevitable global planetary damage caused by basically the same anthropogenic factors which stem from global industrialization.

It seems natural to look in time of predictable crisis towards Science as an ultimate guiding light, for general strategy as well as for particular technical solutions. Alas, many intellectualists share an opinion that scientific knowledge tends to be mismanaged by political forces, adding to already defined technical risk factors of industrial civilization [1-3]. Also, paradoxically, there are not clear cut and unanimous answers to simple questions about causative human factors in phenomena like global warming, though other visible environmental damages are easily attributable to industrial wastes, which cause legitimate public concerns deserving to be treated with the utmost caution [4-6]. The industrial double-edge sword seems to have drawn much attention recently, with experts suggesting that currently existing branches of manufacture can be made much safer, environment and human-friendly, basically by some gradual introduction of suitable laws and regulations [7-8]. However, it is reasonable to point out that history of civilization abounds in quantum leaps, which evoke new cycles based on exploitation of radical scientific and technological innovations.

In the life sciences domain we are currently experiencing, apart from incredible burst of information related technologies, remarkably dynamic translation of material manufacturing processes from synthetic organic chemistry to a novel realm of

*Fig. 1. Green Chemistry pricipals.*
*Source: www.buddhajeans.com/encyclopedia*

synthetic biology (SynBio), which emerged from more traditional disciplines as biochemistry, genetics, and classical biotechnology, with notable help of genetic engineering [9-11]. Based on already developed methodologies, it can be predicted that large sectors of production focused on such materials as fuels, polymers, chemical intermediates, pharmaceuticals, cosmetics, food additives and even nutrients, will transit from category of chemical processes to the most advanced new forms of biotechnology.

New bioeconomy, which is already present in the EU programs and regulations will rely to a large extent, on implementing SynBio principles for newly designed biological systems specialized in realizing complex biogenetical and metabolic sequences for mass production of organic materials [12-14]. It should be remembered that such transition from chemical to biological technologies, which in principle should help preservation of natural resources and slowing down environmental degradation, became feasible owing to fundamental discoveries made by generations of the 20th century scientists [15], among which some towering figures from Polish academic circles deserve particular attention as SynBio co-founders.

## The era of omnipotent chemistry

Modern chemistry, armored by atomic and molecular theories, and supplemented with potent analytical tools, as well as plethora of methods (chemical reactions) for bond making and bond breaking, is less than two centuries old. Within that time, it has managed (with considerable help of equipment designed based on physical phenomena) to provide basic methodologies for identification, quantification, and structural analysis of compounds and composite materials found in surrounding environment. Moreover, driven by an ancient idea of metal transmutation, it strived from the beginning, to create new substances, based on mineral as well as organic natural resources.

From the time of serendipitous transformation of inorganic ammonium isocyanate salt into typically organic urea molecule, discovered by F. Wöhler in 1828 (by which date some hundreds of pure compounds of natural origin, like organic acids and their salts, alkaloids and their salts, glycosides and their components, etc., were already known) the collection of individual low molecular weight entities has grown to ca. $10^8$ compounds, supplemented by rather difficult to assess number of new polymeric materials. Thus, chemistry demonstrated unprecedented ability to create previously nonexistent forms of matter, as well as facility to obtain by assembling from simpler elements, even the most complicated structures made by living organisms [16-18].

The total synthesis of complex organic molecules of natural origin, such as alkaloids, isoprenoids and acetogenins became initially a hallmark of academic excellence, but were soon followed by industrial achievements such as technical syntheses of biogenic amines, vitamins, hormones, antibiotics and their synthetic pharmaceutical mimetics and congeners [18-19]. The key role of discoveries in the field of catalysis (evolving from metal complexes, to biocatalysis and organocatalysis, along to newly created principles of Green Chemistry) has been underlined as evidence of catalytic chemical processes efficiency, crucial for economical and environmental reasons [20].

Mastering organic synthesis, involving many thousands of reactions and complex networks of competing pathways seemed particularly well suited for engagement of informatic tools to support choice of synthetic schemes for experimental validation. Fundamental concept of rethrosynthetic analysis, designed by R. Woodward and E.J. Corey [21-22] proved invaluable as a tool

*Fot. 1. E. J. Corey (left) and Robert B. Woodward (right) at a conference in Uppsala, Sweden*
*Source: researchgate.net*

for generations of synthetic chemists, but remained surprisingly recalcitrant to integration with current functional chemoinformatics. Basic methodological crisis in the field has been only recently overcome by valiant effort of Bartosz A. Grzybowski, who founded ingenious, powerful system of computer aided multistep chemical syntheses, called Chematica [23].

This breakthrough development is particularly valuable for planning multistep syntheses of pharmaceutical active substances, which involve decision making based not only on synthetic literature references but also on intellectual property status of target compounds as well as their intermediates [24]. Based on these successes in creating molecules of life, as well as newly designed materials to perform specific functions, chemistry has claimed central place among life sciences and material sciences. Moreover, structural representations commonly used in traditional chemistry became adapted as lingua franca for all molecular structure and molecular dynamics descriptions [25].

Accordingly, the extensive span of chemical disciplines participation in the leading breakthrough technologies striving for new materials, processes and devices to be applied for example for energy production, conversion and storage, is a matter of continuous experts debate [26-27]. Following the famous R. Feynman's advice concerning need for miniaturization, chemistry has already stepped down towards nanotechnology, microfluidics, microreactors, nanoswitches, microdevices etc. At this end the convergence of traditionally divided "two cultures" of chemistry and biology [28] becomes inevitable as they both in principle concern the molecular architecture perceived in a functional perspective.

## Emergence of systems biology, chemical biology, and functional derivative – synthetic biology

In short, synthetic biology constitutes application of engineering principles to biology. Since it is a relatively new field of research, which spans over more established disciplines like genetics, biotechnology and molecular biology, it is easier to present its goals and methodology through recall of some milestones in evolution of modern life sciences.

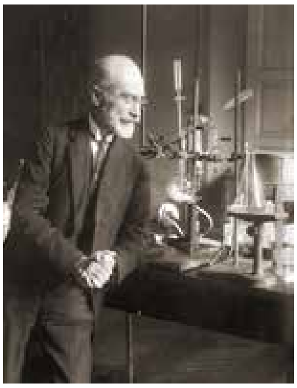
The most significant advancement of biology leads from Mendel's observation of heredity principles, through formulation of theory of evolution, to modern genetics described in terms of nucleic acids biosynthesis and replication. Although a book entitled "La biologie synthetique", which coined up the wording appeared in Paris as early as 1912 [29], it was some decades before the matter of heredity got recognized as a defined chemical substance - DNA, and elucidation of its structure led to formulation heterocyclic base complementarity and pairing hypothesis.

As a result, the study of nucleic acid formed the foundation of molecular biology and modern genetics, soon followed by birth of the recombinant DNA technology known as genetic engineering, which aims at manipulating transcription and translation processes with tools developed by biochemistry [9, 11, 30]. Practices of the surrounding living matter alteration are as old as humanity, known in form of selective breeding of plants and animals, but also in form of food and beverages making such as bread, beer, vinegar and wine, processes presently classified as microbial biotransformations. On a long way from tribal tradition to modern time molecular description of various aspects of life, countless discoveries were made out of which a handful extracted from the vibrant pool of the XX century Wien-Kraków-Lwów academic school, pioneering life sciences and philosophy studies in many fields, will be recalled.

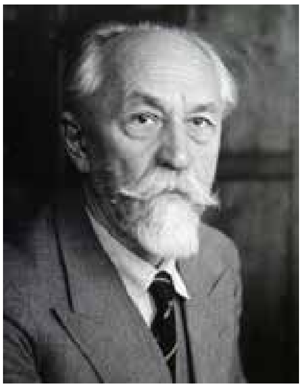
Scientists like the founder of sociology of experimental research Ludwik Fleck, physiologists: Marceli Nencki and Leon Marchlewski, biochemists: Jakub Parnas and Kazimierz Funk, and microbiologist

*Fot. 2. Ludwik Fleck*
*Source: www.researchgate.net*

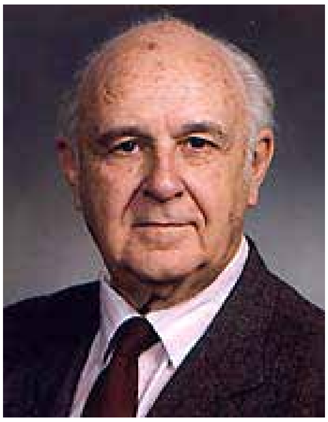
*Fot. 3. Leon Marchlewski*
*Source: www.en.wikipedia.org*



*Fot. 4. Marceli Nencki*
*Source: www.prenumeruj.forumakademickie.pl*



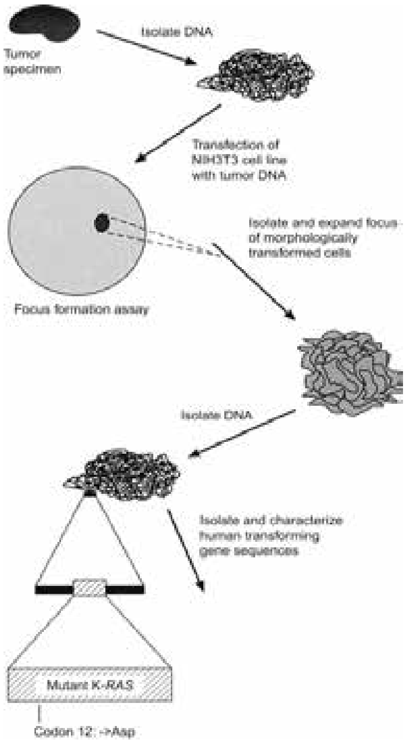
*Fot. 5. Waclaw Szybalski*
*Source: www.news.wisc.edu*



Rudolf Weigl inspired some generations of gifted disciples such as Ernest Sym (pioneer of enzymatic biotechnology), Hilary Koprowski (inventor of the polio vaccine) and Wacław Szybalski (geneticist, researcher of bacteriophage lambda and DNA transfection), who made profound contribution to establishing molecular foundations of biology. Ludwik Hirszfeld, prized for his discoveries concerning ABO blood group system deserves special mention, as a scientist of the mainstream research towards molecular markers of heredity.

In 1974, Wacław Szybalski posed the question: "What next?" to scientists involved in practicing genetic engineering, and suggested development of methods leading to design and assembly of new biological systems executing predetermined tasks, which he called synthetic biology (SynBio), as the answer [31-33].

*Fig. 2. DNA Transfection.*
*Source: www.ScienceDirect.com*



Apparently, the time was ripe for such idea to catch on, with some basic tools of molecular biology already in place to advance genetic engineering applications. Soon, dynamic accumulation of biological knowledge in form of consecutive "omics" – genomics, proteomics, metabolomics, glycomics, lipidomics, etc., led to the idea of systems biology, attempting to describe life as a network of biochemical processes of metabolic and regulatory nature [34-35].

After almost two centuries of reductionism, biology became ready for a conceptually new era of reconstructive activities along bottom up assembly lines, based on newly available subcellular or macromolecular constructs. SynBio embraces both: molecular modifications of existing biological parts at sub-systemic level, and creating radically novel constructs, designed to perform desired tasks, thus entering somewhat dreaded field of "synthetic life". One of the simplest examples of SynBio in action is the genetic code expansion, by including non-protein aminoacids for manufacture of artificial polypeptides [15]. Design and de novo construction of biological devices such as molecular switches, regulatory circuits, logical gates, oscillators, signal inducers and transformers, molecular motors, sensors, etc., (sometime included into nanotechnology field [36]) illustrate scope for new applications [37-38].

Research towards microorganisms with synthetic genomes, and in particular search for constructs equipped with only minimal self-supportive genetic assembly, has been already advanced to the stage of synthetic yeast chromosome completion, and creation of Synthia, the first synthetic bacteria [39]. Institutionalized academic SynBio is doing well – the first department dedicated to the field – in the US Lawrence Berkeley National Laboratory commenced in 2003; since that time several global conferences have been organized (MIT, Cambridge, MA, 2004; UCB Berkeley, CA 2006; Zurich, CH, 2007; Hong Kong, China, 2008; Stanford Univ., CA, 2011), and new research groups mushroomed around the globe, following initiatives like iGEM competition (in which Warsaw University team participates regularly; [40]), addressed to young undergraduate enthusiasts of the modern biology and biotechnology. Certain security concerns on possible dual use of SynBio, even if reasonable, are not likely to stop its conceptual and methodological progress heading towards new scientific advancements [41-42].

However, the synthetic biology label is associated in public perception mainly with genetically modified organisms (GMO), which evoke a great deal of contempt among social activist. Meanwhile, EU definition of genetically modified as organisms whose "genetic material has been changed in a way that does not occur under natural conditions through cross-breeding or natural recombination" has to accommodate such novel concepts as: genetically engineering machines, genomically designed organisms, genomically edited organisms, genomically recoded organisms, and chemically modified organisms, to keep pace with expanding field of SynBio [42].

Commercial development and applicability of these new advancements require legal market authorizations, which rely entirely on a state of local legislation. Unfortunately in the EU market region situation is complicated by restrictive GMO regulations, which are largely based on outdated state of knowledge. During the last two decades variety of new breeding techniques (NBT; particularly in the field of plant biology and agriculture) emerged, for which legal status in view of current EU GMO legislature has not been clearly defined. These are genome editing techniques, based on oligonucleotide directed mutagenesis (ODM), and site directed nucleases (SDM), among which clustered regularly interspaced short palindromic repeats – the CRISPR/Cas9 system, has gained great popularity as the most useful tool for inducing precise mutations [43]. Lasting debate on the legal status of these new useful plant breeding procedures negatively affects competitive abilities of the European agricultural enterprises, as recently pointed out by T. Twardowski [44-45].

## Synthetic biology as maturing operational system for advancement of bioeconomy

The previous century industrial advancements, such as introduction of new man made materials for construction, transportation, energy, communication, agriculture, medicine, pharmaceuticals, etc., generated by modern chemical industry, were welcomed by general public until recently, when the environmental impact of mass industrialization became a subject of general debate. Chemical industry invested much effort in modernization its processes, and academic movement of "green chemistry" proved very helpful in educating new generations of environmentally conscious citizens and customers. It seems evident, however, that fulfillment of "no emission" and "zero waste" postulates is beyond technical capacity of current manufacturing technologies, which are chiefly based on exhaustible oil and coal resources.

Bioeconomy, operated as a closed circuit, becomes an urgent need as at least a partial replacement for environmentally damaging industries. This need is global and already well pronounced in development strategies for Europe [45-46]. Thus far bioeconomy governance concerns primarily biomass conversion into the following array of products, arranged according to increasing mass unit value: energy and heat; fuels; bulk and platform chemicals; biopolymers; food and feed; pharmaceuticals, nutraceuticals and cosmetics.

Traditional biotechnologies, like fermentation, have already paved the way to perception of synthetic chemical reaction sequences as prospective biotransformations, which can be carried out catalytically, without turn to excessive process conditions. Enzymatic catalysis has extended its scope from engineering more stable and organic solvent tolerant natural proteins for industrial use, to the entirely new field of chemically modified biocatalysts obtained by "chemical evolution" [47], which found immediate application in pharmaceutical industry. Cell-free biotransformations are intensely exploited for syntheses of drug active substances and/or their key intermediates [48].

Basically, both principal lines of SynBio concentration on actions: a) from parts through modules, to devices and systems, and b) on natural biological information flow from transcription to translation exploration for new functionalities of products, are of great interest and value to sustainable biotechnology, which is presently focused on biorefinery technologies, securing when combined with new agro business well over 2 trillion Euro in annual turnover. Many other multibillion businesses arouse from traditional biotechnologies, which started as selected microorganism strain fermentation designed to manufacture a single overexpressed metabolite but constantly evolved striving for higher product titers by application of more efficient, eventually genetically modified organisms.

Current impact of biotransformations, carried out with constantly increasing SynBio protocols ratio, on industrial manufacturing of organic materials earlier available from chemical synthetic processes, like fuels, polymers, chemical intermediates and drug components already becomes critical. Modern biotechnologies cover global demand for aminoacids, organic acids (including hydroxyacids needed for biodegradable polymers), vitamins, hormones, antibiotics, enzymes, nucleosides and nucleotides, alcohols and polyols.

Apart from already mentioned medicinal products SynBio is instrumental in manufacturing secondary metabolites often used as pharmaceutical intermediates, phytochemicals for food, nutraceutical or cosmetic applications, and therapeutic proteins such as enzymes, antibodies and vaccines. Outside of molecular therapeutics category, biological devices are increasingly applied in diagnostics, while cellular therapies are still of rather limited utility.

In November 2015, more than 700 experts from around 80 countries which met in the first Global Bioeconomy Summit in Berlin, recognized that a sustainable bioeconomy should make defined contributions to achieving the United Nations Sustainable Development Goals (SDG ; United Nations. 17 goals to Transform Our World. https://www.un.org/sustainabledevelopment/).

The final document of the summit particularly stressed on the SDGs related to food security and nutrition (Goal 2), healthy lives (Goal 3), water and sanitation (Goal 6), affordable and clean energy (Goal 7), sustainable consumption and production (Goal 12), climate change (Goal 13), oceans, seas and marine resources (Goal 14), terrestrial ecosystems, and biodiversity preservation (Goal 15), but it is also very relevant for sustainable economic growth (Goals 8 and 9) and sustainable cities (Goal 11).

A few years later it can be concluded that role of SynBio in the SDG attainment ought to be significant. Artificial photosynthesis needs to be mastered, along with new bioprocesses for clean energy and clean fuels. Current advances in research on organisms biogenetically engineered for exactly these purposes prove that such goals are in principle realistic, if not readily attainable. During the last decade a number of process technologies employing multi-enzymatic reaction systems were implemented for industrial scale manufacturing of drug intermediates [48] with notable example of artemisinin – a model secondary plant metabolite derived antimalarial drug, for which the key intermediate – artemisinic acid, could be obtained by bioengineered bacteria (E. coli) or yeasts [49].

In fuel and energy sectors some projects have been advanced, which already demonstrated some capability for biocatalytic water into atom splitting – a highly endoenergetic process, which requires temperatures in excess of $1000^0$C to get completed in a chemical laboratory. Hydrogen regarded as a clean fuel, is currently obtained mainly from natural gas, constituting an important industrial commodity with ca. 100 billion USD value market.

Research on alternative methods for hydrogen manufacturing has brought up some "green" solutions, including water splitting

*Fig. 3. United Nations - 17 goals to Transform Our World. Source: www.un.org/sustainabledevelopment*

in: photocatalytic, photo-electrochemical, photobiological, and microbial electrolysis cell exploiting ways. In one of prospective new processes, based on enzymatic generation of NADPH molecules from glucose 6-phosphate, generation rate of 310 milimole of H2 from 1L volume reactor per hour was achieved [50], when the biomimetic electron transport was facilitated by additional organic mediator and supplementary oxidoreductase. Admittedly, photoreactive devices for water splitting, which are constructed based on inorganic nanocomposites may offer some immediate advantages but all efforts towards sustainable bioeconomy deserve attention and systemic support [51] .

## Concluding remarks

Currently over 85% energy needs worldwide is covered by fossil fuels (oil, coal and natural gas), which constitute a finite resource, illustrating dramatic need for new bioeconomy based on renewal biomass, solar energy etc. Research on systems biology points to vast resources of biosphere which can be responsibly exploited for development of novel technologies built on bioengineering principles.

SynBio fits well in this perspective as a multipurpose toolbox capable of delivering materials, molecular devices, functional subcellular modules, marker sensors, switches and indicators as "parts" for design of more complex systems with manufacturing, signaling, diagnostic and therapeutic functions. Interesting and useful synergy is expected from combining such high-tech platforms as SynBio, metabolomics, nanotechnology and microfluidics, on the way to manufacturing of novel functional materials efficiently, in closed technological circuits.

Among many successful applications of SynBio, metabolic pathways engineering procedures stand out, with shining examples of optimized, validated and implemented processes for energy, chemical intermediates, biopolymers and pharmaceutical active substances (including biologicals) manufacturing [52]. More complex therapeutic systems, like DNA and RNA constructs, probiotic microorganisms and modified human cells are on their way towards clinical applications [53-55]. Recent global gathering of experts (Global Bioeconomy Summit, 18-20 April 2018, Berlin) states in its report: "A key driver of bioeconomy innovation is the rapid development in the life sciences, in combination with digitization, and the convergence of key technologies in applications.

Promising innovations have for example been developed from genomics, applying big data analysis, and artificial intelligence as well as bio-, neuro- and nanotechnology. Such high-tech applications provide a huge potential in the various areas of bioeconomy and for sustainable development." It seems obvious that in order to achieve target circular bioeconomy, coordinated effort is needed, with focus on international cooperation and special stress on propagation of technical information through media and social channels. Unavoidable widespread application of genetic and metabolic engineering on the way towards bioeconomy, calls for extensive continuous education of all population segments, in order to avoid generating spontaneous contesting of GMO in general, based entirely on prejudice and ignorance.

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