The future of red biotechnology

Tailor-Made Medicine

ALEKSANDRA MAŁYSKA
University of Medical Sciences, Poznań
aleksandra.malyska@wp.pl

TOMASZ TWARDOWSKI
Technical University of Łódź
Institute of Bioorganic Chemistry, Poznań
Polish Academy of Sciences
twardows@ibch.poznan.pl

Aleksandra Małyska is a 5th-year student of biotechnology at the University of Medical Sciences in Poznań, and a 2nd-year student of psychology at the Adam Mickiewicz University. Her interests lie mainly in the social aspects of biotechnology, in particular how people's understanding influences their acceptance of innovative technologies

Prof. Tomasz Twardowski is a researcher at the Institute of Bioorganic Chemistry in Poznań and the Biotechnology Department at the Technical University of Łódź. He specializes in the problems of protein biosynthesis regulation. His secondary area of interest lies in social and legal aspects of biotechnology

Until recently, researchers strove to develop drugs with the broadest possible applications. However, thanks to pharmacogenomics, in the future medicine will be tailor-made to each patient

Over fifty years ago, Watson and Crick proposed the structure of DNA based on X-ray crystallography research carried out by Rosalind Franklin. Just under ten years ago the Human Genome Project published the first draft of the human genome at the cost of three billion USD. By 2009 re-sequencing an individual human genome cost well below 100,000 USD. Over thirty years ago Dr. Sidney Pestka, working at the Roche Institute of Molecular Biology, Nutley, New Jersey, proposed the mode of action of interferon. Under its trade name Roferon-A, interferon is now one of the most frequently prescribed biopharmaceuticals, with annual sales of the order of hundreds of millions of Swiss Francs.

Those scientific achievements have had an immeasurable influence on the uses of innovative biopharmaceuticals and methods in medicine. These breakthrough discoveries have contributed to an irreversible change in the perception and use of diagnostics in contemporary treatment of many illnesses. Today, in addition to the well-established types of physical and chemical examination and our growing understanding of biochemical processes occurring in the body, we now have at our fingertips state-of-the-art diagnostics and therapies based on the molecular pathomechanisms of illnesses. A gradual change is occurring in the treatment strategies that have been used for years, based on the format: specific pathogenic factor → pathogenesis → illness.

Same case in each case?

Although the discovery of specific pathogens revolutionized medicine in the 19th and 20th centuries, making it possible to create pharmaceuticals essential to treat certain illnesses, generally improve health, or extend patients' lives, nowadays more attention is being paid to the lower than expected success of those medications. Their efficacy tends to fall between 25–62%. Such variation may result from different, difficult to predict responses to the same therapy within a population of patients with the same illness, hence in cases that are seemingly the same.

Significant differences are also noted with regard to the safety of administered pharmaceuticals. Intrapopulation variation, which determines the different responses to the same dose of a given drug, can lead to dangerous and undesirable side effects. In 1994 there were 1.8 million hospitalizations and over 100 deaths caused by such side effects in the US alone. Changing this will require implementing a fully innovative, individualized approach to illness and its treatment in patients.

Therapy and diagnostics must be closely linked when establishing a treatment regime for an individual patient

Personalized medication

For a long time researchers sought to fit one drug to as large a population of patients as possible, and identify the opportunities of using it to treat several different illnesses. Put simply, they aimed for the broadest pos-

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Thanks to the development of molecular techniques, the concept of personalized medicine has become a reality. It involves administering a medication optimally chosen for a concrete patient at the optimal times

sible application for each drug. Today it is standard practice to place more weight on selecting the most appropriate drug and setting an optimal dose not just for each illness, but also for each given patient. Following selection based on sex, age, race and general health condition it is now the norm to carry out laboratory tests to establish individual risk factors (such as cholesterol levels and blood pressure in suspected heart and circulatory disorders) as well as an analysis of family history of illness. However, all these factors only help in establishing the patient's susceptibility to certain illnesses, rather than providing more specific information. They can be defined as making best use of the readily-available, routinely-used biochemical methods for precise diagnosis.

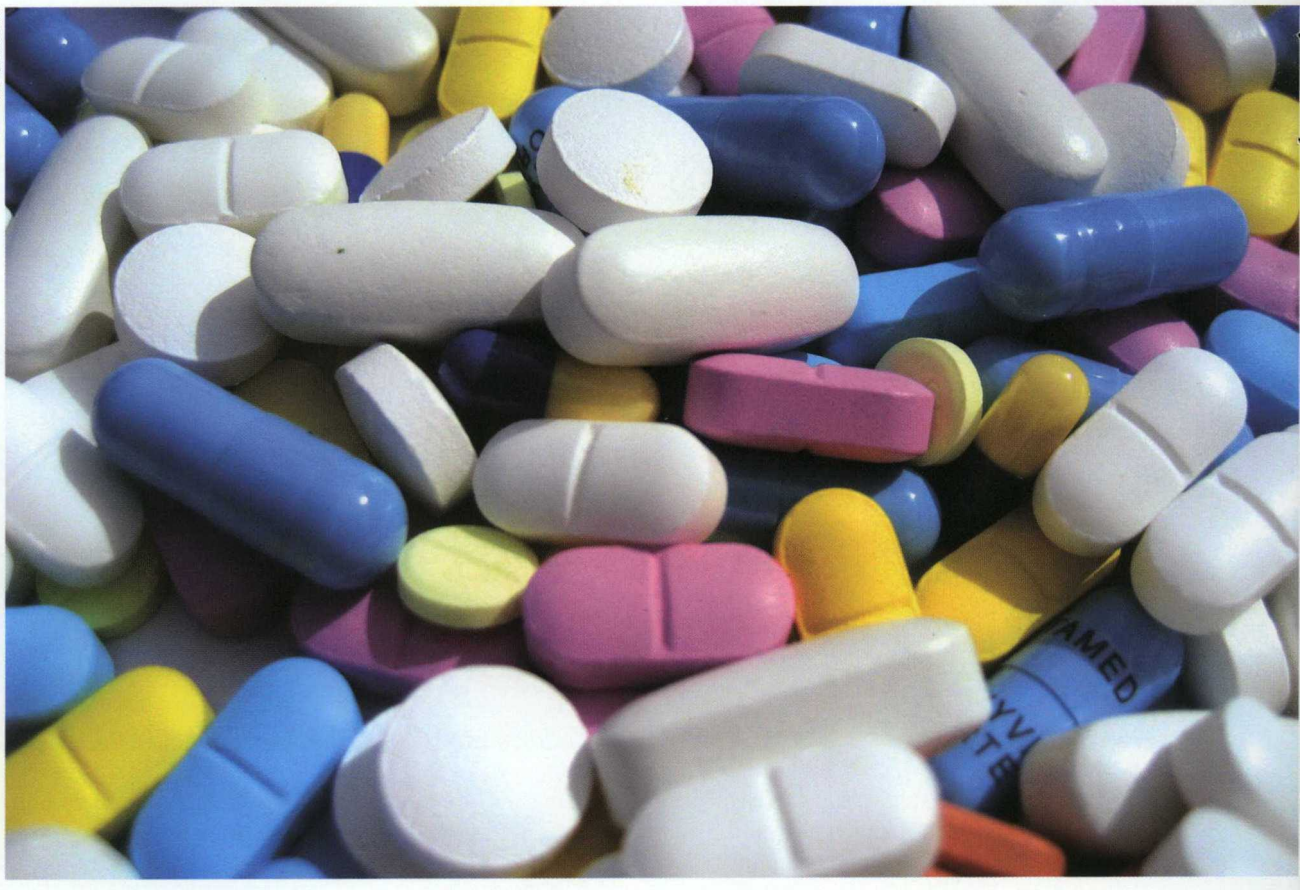
This practice can be extended further into the concept of personalized medicine: selecting and administering a precise medication at an appropriate time to each patient. This is becoming possible thanks to the latest diagnostic tools that utilize molecular biology techniques to analyze genomes of bacteria or humans.

Using biomarkers

Biomarkers are essential for defining the progress of an illness in a given patient and predicting its likely course, as well as individual response to treatment. Biomarkers are indicators of biological or pathogenic processes or pharmacological responses to therapeutic intervention (*Biomarkers Definitions Working Group*).

In oncology the most commonly used biomarkers are enzymes and hormones linked with tumors. They can be detected using biochemical tests, although their presence is not always indicative of the presence of a specific tumor. For example, an increase in the levels of the prostate-specific antigen (PSA) indicates a high likelihood of a prostate tumor being present, but it can also be a result of a mild hyperplasia. Similarly, raised levels of the carcinoembryonic antigen (CEA) are characteristic in between 60-90% of colon cancer cases and 50-80% of pancreatic cancers.

Thanks to the rapid development of molecular diagnostic techniques, it is possible to monitor the course of many illnesses by studying differences in the structures of nucleic acids. DNA biomarkers include chromosome aberrations, single nucleotide polymorphisms (SNPs), a change in the number of copied DNA fragments, or differences in the degree of methylation of promoter regions. RNA biomarkers include



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For a long time researchers attempted to use a single drug to treat as many patients as possible – they strove for the broadest possible application for each drug. Today's standard is to individually select the medication and the optimum dosage not just for the given illness, but also for the specific patient

differences in the transcription levels, or RNA molecules that take part in regulation. Research shows that using a biomarker that defines the degree of DNA methylation may be a factor in differentiating between prostate cancer from mild hyperplasia.

Bringing biomarkers to market

Bringing biomarkers into general use must be preceded by thorough analyses of their safety in patients, reliability, efficacy, and the financial implications of their use in diagnostics. In the US, the steps involved in introducing a new biomarker include: identification of relevant information in the patient's biological material (using DNA microarrays, gene chips, restriction fragment length polymorphisms (RFLP) and others, depending on type), establishing possible applications, and finally clinical and analytical validation. The final stage must be carried out if the biomarker is to be approved by the FDA for clinical use, although it can be bypassed if it is to be used purely for research. The final decision regarding bringing a biomarker to market lies with the Center for Medicaid & Medicare Services (CMS), responsible for carrying out an analysis of costs versus benefits including societal aspects.

Future of theranostics

Personalized medicine is closely linked with several clinical applications, and is most advanced in oncology and infectious diseases. In the latter case, defining the genotype of the virus (HIV, hepatitis B and C) and establishing the viremic concentration play a crucial role in selecting an appropriate therapy, predicting its efficacy, discovering any drug resistance and any necessary modifications of the treatment. Researchers have even suggested introducing a new term "theranostics," which stresses the close links between therapy and diagnostics when the course of treatment is being determined for individual patients. Efforts to promote this new coinage show how far advanced the introduction of personalized medicine is in various branches of medicine. Some scientists are no longer debating whether such medicine

will be used at all, but when its use will become widespread in clinical practice.

Societal benefits and costs

Alongside the high hopes and optimism brought by the prospect of "made to measure" medicine, there are also some ethical concerns. The most frequently cited examples revolve around personal data protection, potential discrimination by insurance firms or employers against people who have a tendency towards certain illnesses, or personal stigma. These may become deciding factors in whether this novel treatment strategy ultimately gains societal acceptance, therefore they should be put forward for thorough discussion, eventually leading to concrete legislative measures. Doubts may also arise because of the potential costs of introducing personalized medicine. In this instance it is essential to take a close look at the problems of efficacy and safety of current therapies, and the intentions and options in investing in innovative technologies. In this specific instance it is very important to stress that a significant part of the diagnostic costs should be recompensed through targeted and effective therapeutics. Contemporary biopharmaceuticals (hormones, interferons and interleukins) are very expensive, and yet ineffective, and therefore unnecessary (or badly dosed) use of expensive drugs is wasteful. The application of proteomics and transcriptomics to personalized medicine will make it possible to optimize the possibilities of medicine in both economic and social aspects.

Medicine 2050

The personalization of medicine is an irreversible process whose benefits can already be observed, and whose potential benefits cannot be overstated. This is excellently illustrated by a communication from the European Commission on 10 December 2008, which includes a declaration of support for scientific research in pharmaceutical development: "With the emergence of new technologies like pharmacogenomics and patient-specific modelling and disease simulators, personalised medicine is now on the horizon. In the long term, doctors may be able to use genetic information to determine the right medicines, at the right dose and time. This field is already affecting companies' business strategies, the design of clinical trials and the way medicines are prescribed. Although it is too early to say whether 'omics' technologies will indeed revolutionize the sector, the Commission closely monitors the area and will reflect on how it can support its development." As one of its main aims, the Commission set 2010 as a deadline for presenting a report on possible applications of "-omics" technologies in scientific research and in the development of novel pharmaceuticals. We cannot predict what medicine will be like in 2020 or 2050, although we can be certain that it will be quite different from what it is today. The scientific, economic, and social circumstances all indicate that "tailor-made" medicine is likely the way of the future. ■

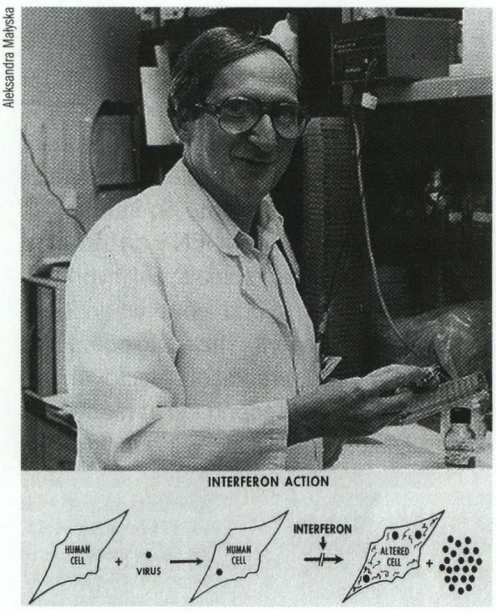
Further reading:

Snyderman R., Yoediono Z. (2006). Prospective care: a personalized, preventative approach to medicine. *Pharmacogenomics, 7*, 5-9.

Ludwig J.A., Weinstein J.N. (2005). Biomarkers in cancer staging, prognosis and treatment selection. *Nature Reviews Cancer, 5*, 846-856.

Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions - Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector, (COM 2008) 666, final version.

Aleksandra Małyska



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