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Abstract	■.	

Personalized Medicine: Cutting Edge Developments

Hans P. Zenner and Mijo Božić

Abstract ■.

1 Introduction

A fundamental problem of classical medicine is that preexisting therapies, such as medications or medical devices are not effective in all affected individuals. For example, efficacy is limited to 38% for antidepressants, 50% for arthritis, 70% for Alzheimer's disease and only 74% for chemotherapy.[1] For suitable patients, personalized (or individualized) medicine should remedy this.

Modern personalized medicine can be described in several dimensions. These include the molecular dimension using so-called "omics" methods such as genomics, proteomics, metabolomics or bacterioomics. One result of the omics procedures may be the identification of biomarkers. These may allow the use of additional dimensions such as the functional-anatomical dimension. This may play a role in biomarker-specific imaging procedures or in the biomarker-based stratification of medical devices such as pacemakers or cochlear implants.

While the above methods involve stratification of the patients with respect to a pre-existing therapy procedure, tailored medicine means that the therapy is tailored specifically for the patient. The last dimension to address in this paper is the big data dimension.

[1] LEOPOLDINA statement (2014).

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2 Molecular Dimension

Using high throughput methods like NGS the "omex" methods of the molecular dimension of personalized medicine perform a broad search for a **biomarker as a target.** This should allow a predictive test for the efficacy or toxicity of a preexisting treatment, usually of a drug or a medical device.

An important clinical application is the avoidance of adverse reactions. The drug Vemurafenib is used in malignant melanoma, where it acts as a BRAF inhibitor. However, it can produce spinaliomas as a side effect. With the help of genomics-based identification of RAS mutations prediction of the individual risk for skin carcinomas may be possible.[2]

In the prediction of the therapeutic efficacy, gene variants may play a role in determining changes in drug metabolism, drug delivery, or excretion. Statins serve to reduce the level of cholesterol. However, they are effective only after uptake into the liver. This requires transport proteins. Gene variants of these transport proteins may reduce the transport of statins.[3] Tamoxifen may be used after the surgery of estrogen receptor positive breast carcinomas for the prevention of recurrences and metastases. However, the efficacy of tamoxifen requires enzymatic conversion. Thus, in cases of defects of the genes responsible for the production of these enzymes (10% of European women are affected), the medication may be less effective.[4]

An important target of oncological drugs is tyrosine kinase (TK). The TK antibody trastuzumab (Herceptin) can be used for breast tumors if there is an HER2 gene expression disorder.[5] Vemurafenib is used for malignant melanoma (MM) when it is a BRAF-V600E-mutated or BRAF-V600K-mutated MM.

Another important target is the hedgehog pathway, which plays a role in skin cancer basal cell carcinoma. Different proteins and their genes like the hedgehog protein (PCTH1 gene) and smoothened protein (SMO gene) may play a role. Therapeutic approach is a hedgehog protein inhibition e.g. by small molecules.

In particular, the genomics approach partly together with genom editing methods[6] has made a significant contribution to finding an entry into clinical care of **gene therapy.** This includes application to the eye for the retina in Weber amaurosis and the vestibular organ. Phase I/II studies on the treatment of monogenetic hereditary eye diseases by gene therapy are e.g. for x-linked Chronic Granulomatosis, for ADA-SCID ("Adenosine Deaminase Deficient Severe Combined Immunodeficiency") and for Wiskott-Aldrich Syndrome.[7] Cochlea, heart muscle, spinal cord, kidney, cartilage and lung are also expected as target organs.

[2] Suh et al. (2013).

[3] Canestaro et al. (2012), pp. 158–174.

[4] Goetz (2018), pp. 102–105.

[5] Slamon et al. (1989), pp. 707–712; Slamon et al. (2001), pp. 783–792.

[6] Karimian et al. (2019).

[7] Anliker et al. (2015), pp. 11–12.

Molecular personalized medicine my not only play a role for drug application but also for the **indication for medical devices**. Technologically this is also based on targeted gene capture and high-throughput sequencing. An example is the stratification of a few months old totally deafened newborn for early pediatric cochlear implantation (CI). Instead of the usual single-gene diagnostics, high-throughput sequencing can sequence all known genes for deafness (currently about 110, in the future probably around 200) in parallel. If genetic deafness is suspected, the molecular cause can be elucidated in more than 50% of cases.[8] Frequently found of gene disorders may be linked to connexin, KCNQ4 or OTOF. Depending on the affected gene and its functional significance the chances of success for cochlear implantation may also be limited (e.g., for the gene TMPRSS3). Conversely, for a purely sensory and non-neuronal genetic cause, the functional prognosis for cochlear implantation is favorable (e.g., for the GJB2 or MYO7A genes). If it is an early childhood auditory neuropathy, the molecular genetic analysis of the gene OTOF, which encodes the protein otoferlin, can be helpful. Otoferlin is important for the control of an ion channel of hair cells, which in turn plays a role in frequency coding.[9] The mutational analysis of connexin 26 in bilateral high-grade deafness and deafness plays a widespread role.[10] Missing or inadequate expression leads to disruptions in gap junctions of the inner ear.[11] The human genetic analysis of the gene encoding connexin 26 is therefore often used for the indication of early childhood cochlear implantation.[12] In addition, the routine analysis of the DFNA2 gene, which codes for the ion channel KCNQ4 in hair cells, is emerging. KCNQ4 is an important ion channel that plays an indispensable role at the end of the transduction cycle.[13] Its absence can lead to deafness and may thus contribute to the early childhood indication of a cochlear implant.[14] Further, in the future, all known Usher genes can be examined early for changes in to early identify the Usher syndrome at the onset of deafness or early onset of vision problems, especially in childhood.[15] In this way, the indication for a cochlear implant can be made in good time so that a communication ability is maintained despite deafness and blindness.[16]

In the area of inherited heart disease, namely dilated cardiomyopathy, there is evidence for the installation of an ICD (Implantable Cardioverter Defibrillator) in the

[8]Friese et al. (2015), pp. 428–433.
[9]Friese et al. (2015), pp. 428–433.
[10]Brown and Rehm (2012).
[11]Qu et al. (2012), pp. 245–250.
[12]Black et al. (2011), pp. 67–93.
[13]Gitter et al. (1986), pp. 68–75.
[14]Walter et al. (2011).
[15]Yang et al. (2012), pp. 1165–1183.
[16]Loundon et al. (2003), pp. 216–221.

presence of a mutation in the LMNA gene. Patients with long QT syndrome and mutations in the genes KCNH2 or SCN5A can also receive an ICD early on.[17]

3 Functional-Anatomical Dimension of Individualization

Modern imaging techniques contribute to the anatomical dimension of personalized medicine. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) provide the ability to display the distribution of a radiolabeled biomarker (tracer) on an individual molecular target in a patient's body three-dimensionally (3D).[18] This applies, for example, to receptors. Using these approaches individualized biomarker-based image localization, for example of tumors, is possible, which may play an important role in individualized radiotherapy.

Equally based on imaging techniques an important patient stratification for medical devices consists in the consideration and use of the individual anatomy. A typical example is cochlear implantology. The consideration of the individual anatomy is technologically based on the high-resolution digital imaging combined with the functional topodiagnostics of modern audiometry allowing mapping the individual frequency card of the patient on the measured total length of the cochlea. Depending on the extent of the functional SNHL the individually distorted area along the cochlea can be calculated. This results in the selection of an electrode length matched to the individual residual hearing function.

4 Tailored Medicine

Tailored medicine has been available in a conventional manner for many years, when prostheses and implants for skull reconstruction, orthopedic implants or even dental implants and cardio-vascular stents are made individualized. Today, however, tailored medicine has reached new horizons and uses approaches derived from cellular and molecular medicine. In oncology by introducing a so-called chimeric antigen receptor (CAR) into T cells, CAR- expressing T cells are able to specifically bind to and destroy cancer cells in the patient.[19] In addition to the clinical success, however, these therapies sometimes also show severe side effects. This includes

[17] van Rijsingen et al. (2012), pp. 493–500; Priori et al. (2003), pp. 1866–1874; Priori et al. (2015), pp. 2793–2867.

[18] Schober and Heindel (2010), Bailey et al. (2015), pp. 595–608. Hicks and Hofman (2012), pp. 712–720; Weber (2006), pp. 3282–3292. Mankoff et al. (2014), pp. 525–528; Mankoff et al. (2016), pp. 47–56; Haberkorn et al. (2016), pp. 9–15.

[19] Maus et al. (2014), pp. 2625–2635.

e.g. the so-called cytokine release syndrome, in which patients show excessive inflammatory response with high fever, pulmonary edema and organ failure.

T cells can also be obtained as directed virus-specific T cells from donors by leukapheresis and subsequently purified after incubation with the corresponding virus peptides. Furthermore, genomic analyzes may identify neo-antigens and the associated DNA and RNA, which together with an X-point blockade should allow the production of neo-antigenic vaccines. Moreover, patients with severe viral infections, in whom conventional therapies are exhausted and no longer effective, can benefit from the transfer of virus-specific T cells as individualized medicine.[20]

A further approach of tailored medicine includes regenerative medicine that serves to restore the structure and function of destroyed cells, tissues and organs. As a rule, regenerative medicine targets certain cells, be they somatic or stem cells—natural or artificial—on which the restoration of tissues, organs and functions depends. On the one hand, the regenerative therapy is carried out directly in the patient's organism, e.g. genes, cell cycle inhibitors or activators, cell products or components or growth factors can be introduced either systemically or locally. The goal is cell and subsequent tissue regeneration by cell division or by cellular transformation.

Regeneration may include tissue engineering. Clearly individualized tissue engineering is not new. Ex vivo applications may include scaffold cell/tissue hybrids using, for example, a patient's own skin cells, brain cells, peripheral nerve cells, bone cells, cartilage cells, islet cells, sensory cells, heart cells, connective tissue or even tendons[21] to produce e.g. skin, heart valves or even stents. The underlying cell culture processes may be highly specialized and should enable rapid and qualitatively reproducible production of cells or tissues in large numbers.[22]

The possibility of reprogramming specialized differentiated body cells in personalized iPS cells has led to a significant paradigm shift.[23] On a therapeutic level, there are future opportunities for obtaining patient-derived stem cells for cell therapies and for use in somatic gene therapy. On the other hand, it should also be pointed out that iPS cells are usually derived from adult cells, thus kind of old cells are obtained, which may already be afflicted with mutations, which are then also contained in the iPS cells. It is also unclear to what extent an epigenetic "memory" of the initial cells in iPS cells has an effect on the differentiation of iPS cells.[24] From the ethical and

[20]Feucht et al. (2015), pp. 1986–1994. Tischer et al. (2014), p. 336.

[21]Frick et al. (2017), pp. 105–114; Tudorache et al. (2016a), pp. 89–97; Tudorache et al. (2016b), pp. 1228–1238; Flanagan et al. (2007), pp. 3388–3397; Koch et al. (2010), pp. 4731–4739; Weinandy et al. (2012), pp. 1818–1826; Moreira et al. (2014), pp. 741–748; Hess et al. (2010), pp. 3043–3053; Wiegmann et al. (2014), pp. 8123–8133; Dietrich et al. (2015), Fuehner et al. (2012), pp. 763–768; Schmitz and Grabow (2015), pp. 143–162; Soares and Moore (2015), Haude et al. (2016), pp. 2701–2709; Piazza and Cribier (2012).

[22]Lee et al. (2015), pp. 2379–2387; Egami et al. (2014), pp. 96–106; Fraunhofer (2016): http://www.ipa.fraunhofer.de/automatisierte_zellkultur.html.

[23]Hou et al. (2014), pp. 179–188.

[24]acatech POSITION (2017).

regulatory point of view iPS cells are not subject e.g. to the German Embryo Protection Act (Embryonenschutzgesetz—EschG). They also do not fall under the regulations of the German Stem Cell Act (Stammzellgesetz—StZG). The handling of iPS cells is therefore not regulated by law; although they are pluripotent, as determined in par. 3 no. 1 StZG for stem cells. However, to be covered by the provisions of the StZG, they would have to have been obtained from embryos (par. 3 no. 2 StZG) and would have been pluripotent at the time they were obtained from the embryos (par. 3 no. 1 in conjunction with no. 2 StZG). In fact, the latter requirement is lacking because iPS cells become pluripotent only through reprogramming. They are not taken from embryos in their capacity as pluripotent cells.

5 Big Data

Final dimension is the big data dimension produced by digitized medicine. Increasingly digitized data from an individual patient is available through, for example, imaging, laboratory analysis, or functional examinations. Merging and processing of huge amounts of data enables individualized organ modeling such as mathematical cardiac models. Such a personalized model may be based on a patient's myocardial cell and their ion channels and the interaction of the cells in the heart tissue. Then the whole organ may be considered and finally the organ may be embedded in the circulation and the body.[25]

Such a model may allow determining the individual impact of individual ionic channel variant and relevant drugs on heart electrophysiology, pumping function and the entire cardiovascular system.[26] Other examples are organ models of the ear which allow subtraction of the middle ear physiology to thereby capture parameters of the inner ear from the eardrum.

Further modeling may include models of tumor growth and influence of tumor growth by cytostatics and ionizing radiation, models of human circulation for anesthesia, models of bones and joints for orthopedics and surgery, models of respiration and gas exchange in the lung, models of sugar metabolism for diabetes patients, and models of electrolyte balance for dialysis patients.[27]

[25] acatech POSITION (2017).
[26] acatech POSITION (2017).
[27] acatech POSITION (2017).

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