"THE MUST" OF THE DRUG DISCOVERY AND DEVELOPMENT IS – INTERDISCIPLINARITY

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ABSTRACT

The process of drug research and development has always been a challenge for many different professionals involved. In this process special emphasis has always been placed on the utilization of the state-of –the-art techniques through the interactions of experts from various fields. Nowadays, the approach of having single, narrow knowledge and background has been overcome. New researchers should be willing to acquire complimentary knowledge and skills through active communication with other professionals and learn about the ongoing application of advanced technologies that are evolving daily. Drug discovery process can serve as a model for implementing and providing evidence of this. The authors of this article, scientists with different backgrounds and expertise, were in the past actively involved in establishing new research facilities, in developing new systems, in acquiring new knowledge and ways of working within their institutes, universities and pharmaceutical industry. In such a way, they have demonstrated that there are no boundaries and limitations in knowledge sharing, particularly for the benefit of human health.

***Keywords**:* drug research & development; translational research; ADMET, toxicity; QSAR

INTRODUCTION

Discovery and development up to launching on the market of a new chemical entity (NCE) with targeted and precise therapeutically relevant response is very demanding, complex and expensive endeavour (Fig. 1).

New drug, either as first-in-class or follow-up, is a result of joint effort of experts of various disciplines. Within linear drug discovery paradigm (Fig. 1), the drug research and development (R&D) process commonly begins with selection of portfolio and validation of "druggable" that is therapeutically relevant biological target. This is than followed with revealing active molecule(s) and optimization of small molecule activity and pharmacokinetic (PK) properties, scale-up syn-

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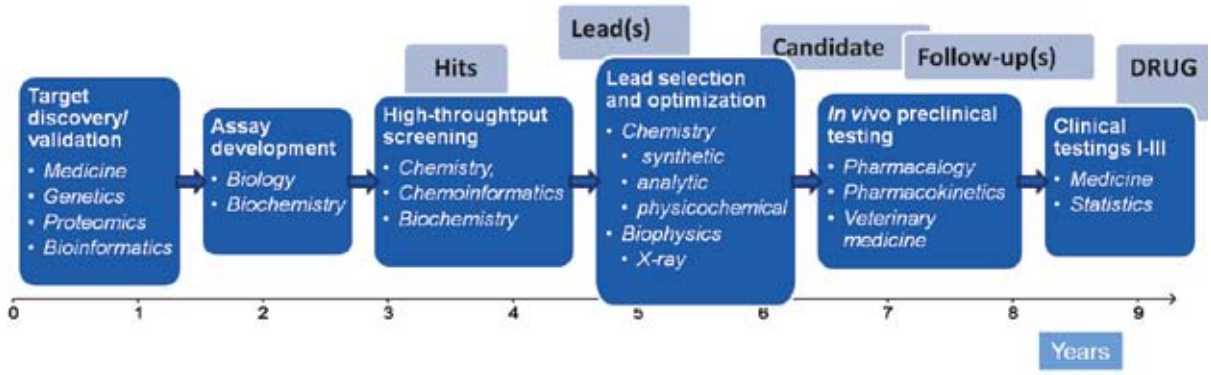

Figure 1. Collaborations of various experts during the complex process of drug discovery and development. Chemical compounds showing significant activity at various stages of the process should be properly denominated (e.g. hit, lead, candidate, drug) as soon as they are identified that possess the characteristics set in the therapeutic target profile (TPP).

thetic method and formulation before entering preclinical and clinical studies. Such an approach synergistically combines synthetic chemistry, *in vitro* screening, computational methods and *in vivo* animal models (including rigorous safety studies in various animal species) prior to the first-in-man testing in Phase I clinical trials.

The overall R&D process resulting with lunching new drug on market lasts up to 13.5 years[1]. It costs in average $1.8 billion and its cost progressively increases particularly due to more demanding regulatory requirements and increasingly cost-constrained healthcare systems. Consequently, new methodologies and partnerships of diverse businesses become more and more important for increasing efficiency and productivity of the R&D steps[1]. In this review, a brief description of contributions of Croatian researches in the field of chemoinformatics and chemical biology to these developments is presented.

Usage of predictive mostly knowledge-based techniques and approaches is one of most significant ways to reduce R&D cycle time and overall costs, particularly because of attrition (Fig. 2)[2,3]. Attrition in the clinical phases of development especially in Phases II and III, is the most important determinant of overall R&D efficiency and its decrease will strongly improve overall

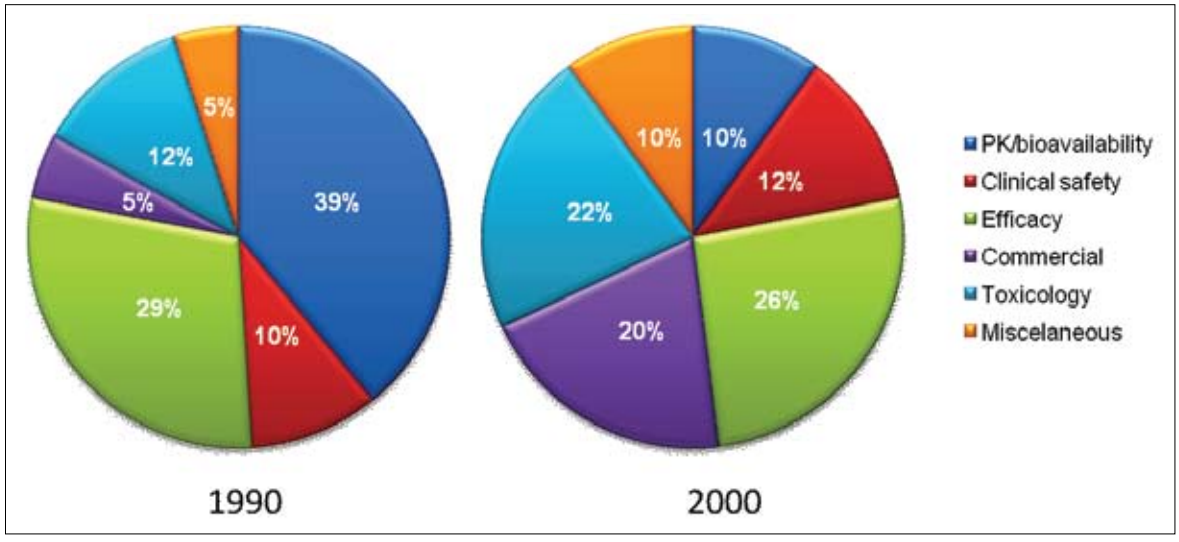

Figure 2. Main reasons for the compounds' attrition reported for 1990 and 2000.ii

pharmaceutical productivity and costs[1,2]. Around 60% of the total costs for each NCE launched is devoted to the clinical development (Phases I–III) (Fig. 1)[1].Common reasons for the attrition in the clinical phases are safety issues and lack of efficiency in man (Fig. 2). However, economic reasons are very often present, particularly if the drug does not meet the potential to treat large sub-populations of patients.

OPTIMIZATION OF ADME PROPERTIES

Poor PK properties such as low oral bioavailability or toxicity issues that are not predicted by animal pharmacology models or by preclinical ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) studies are often reasons for Phase I and Phase II attrition. Development and widespread early stage usage of models for predictions of (un)desirable ADME properties and toxicological liability reduce downstream attrition, particularly in clinical Phase I (healthy volunteers).

In 1991, ~40 % of failures of the candidate drugs came from poor oral bioavailability and PK properties (Fig. 2)[2]. Over the next decades, development and usage of *in vitro* experimental tools and *in silico* models to characterize ADMET profiles of compounds in early stages of the drug discovery process, significantly increase the success rate of discovery programs and turn-over of better candidates into drug development. At the present time, the practice is to adjust ADMET properties of molecules in parallel with the optimization of their primary pharmacological activity.

Application of *in silico* global ADMET models enables virtual screening of millions of compounds and identifying and filtering out molecules with unmet PK and safety related properties/activities that will eventually fail at later stages of the discovery process (Fig. 1). In the lead optimization stage pharmacological and pharmaceutical properties of a single or a few chemical series are optimized. Herein, local empirical or mechanistic models are major *in silico* tools which are improved in iterative process starting from *in silico* prediction, to chemical synthesis, to experimental testing and confirmation (secondary assay and/or *in vivo* tests in animals), and to model refinement. Such rational approach of selecting molecules in early hit identification, lead selection and optimization discovery stages with a greater chance of success makes basis for a 'fail early, fail cheap' strategy that has been widely accepted in the pharmaceutical industry.

ADMET profile of small chemical molecules is largely determined by molecular physicochemical properties, particularly aqueous solubility and membrane permeability[4]. These properties are both related to molecular lipophilicity. With the increase of lipophilic character, solubility of a molecule decreases, but its permeability through biological membranes like gastrointestinal tract or blood-brain barrier, generally increases regardless its chemotype[5]. In addition, too lipophilic molecules are also prone to cause toxicological effects[6]. Simple rules estimating lead- and drug-likeness of chemical compounds commonly include lipophilicity as significant parameter. Such rules serve as filters for removing compounds which are according to their lipophilicity and simple structural characteristics highly unlike to become stable, efficient and safe drugs.

Development of high-throughput screening (HTS) techniques enables fast, robust and reliable measuring of physicochemical properties for small molecules[5]. Measured data have been used for developing *in silico* predictive models which enable estimation of physicochemical and ADMET properties of chemical compounds prior their synthesis[7]. For example, molecular lipophilicity and membrane affinity are modelled experimentally by HPLC using C_{18} and immobilized artificial membrane (IAM) stationary phases, in terms of chromatographic hydrophobic index (CHI) and CHI IAM, respectively[5,8]. CHI and CHI IAM values can be used for estimation of accumulation and retention of compounds within the cells of various types[9]. The physicochemical properties can

be generally applied for screening compounds of various chemotypes. Similar trends as for "classic" compounds with molecular weight <500 Da, have been observed for relatively large macrolide "non-classic small" molecules (MW ~ 1000 Da)[5].

OPTIMIZATION OF TOXICOLOGICAL PROPERTIES

Toxicity issues particularly those which were not predicted by *in vitro* modelling are often reasons for eliminations of a lead compound development[10]. Over 90% of the market withdrawals were caused by drug toxicity[11].

We performed the modelling of carcinogenicity of a large set containing more than 911 different organic compounds, using Support Vector Machines (SVM) method combined with different variable selection methods, and by performing clustering of chemical and modelling on different overlapping substructure chemical classes[12,13]. To avoid the influence of high error in measuring the carcinogenic potency of chemical compounds, carcinogenicity data were selected from six different databases, taking into account the agreement of experimental data for one compound in different databases. The best SVM model with 250 descriptors, selected from initial set of 1500 descriptors, reaches the accuracy 80 % in classification of compounds as cancerogenic or non-cancerogenic [13]. The variable selection method was based on the highest correlation coefficients, and such an approach is named Correlation Coefficient (CC) method. The weakness of CC method is that in the selection of a descriptor its correlations with other ones are not taken into account. To avoid such a shortcoming of the model in the subsequent paper [13], we reduced the model complexity by introduction of more appropriate descriptor selection procedure based on sensitivity analysis that takes into account the relationships of a descriptor with the other ones, i.e. high inter-correlation between descriptors is penalized. The model had greater accuracy of 84 %, and included a significantly smaller number of descriptors [13]. The increase of accuracy from 80% to 84% can be considered as significant due to the size of data set, and the fact that improved model include a significantly smaller (for the factor 2 or 3) number of descriptors.

OPTIMIZATION AND MODELLING OF BIOLOGICAL ACTIVITY – MECHANISTIC APPROACH

Libraries of chemical compounds are pre-filtered in order to remove too lipophilic, toxic as well as unstable molecules. This is not only because of the reason to reduce attrition rates in downstream discovery phases, but also to minimize number of false positives in *in vitro* HTS assays[14]. If a molecular biological target has been assigned and if it is validated and its 3D structure known, virtual screening based on molecular docking method can be applied prior to the corresponding *in vitro* screening of the compounds library[15,16]. Resulted enrichment of tested set by active compounds, considerably increases speed and efficiency and reduces costs of HTS, and thus of the drug discovery process in general.

On another side, approaches based on known structures and activities of active molecules (inhibitors, agonists, antagonist), enable one to build (quantitative) structure-activity relationships ((Q)SAR). The obtained QSAR models can be used to predict activities of compounds which are similar to those in training sets[17,18]. In such a way, the potential new biological targets and therapeutic indications of available drugs can be predicted indicating their potential "re-allocation" for another indication and anticipating their eventual side effects[19].

It is important that the predictive QSAR model is simple, with clear structural interpretation, and also robust, what is determined by modelled activity and by types of molecular descrip-

tors used for model building. We present here an overview of our results obtained in modelling experimental *in vitro* antioxidant activities of flavonoids.

There are many papers that have investigated the antioxidant activity of flavonoids, and many analyses have been made to establish the relationship between radical scavenging activity (RSA) of flavonoids and their structure[20]. It is established that RSA of flavonoids depends mainly on the substitution pattern of the hydroxyl groups, that is, on the availability of phenolic hydrogens and on the possibility of stabilizing the resulting flavonoid phenoxyl radicals[21-23]. The ability of a flavonoid to form intramolecular hydrogen bonds between hydrogen belonging to a OH group and other neighbouring OH or keto (C=O) groups, is also related to the RSA of flavonoid. When these structural features were coded into numerical indicator descriptors having value '1' if a certain group is present and '0' otherwise, on a set of 29 or 28 flavonoids, the very good linear two-descriptor models were obtained, with correlation coefficients $r > 0.95$[23]. Similar requirements on flavonoids' structure 'having high antioxidant activity were established earlier by Bors *et al.*[21] and by Rice-Evans *et al*. in their vastly cited paper[22]. The structural requirements considered essential for effective radical scavenging by flavonoids are the presence of 3',4'-dihydroxy group in the B ring and/or the presence of the 3-OH group in the C ring (Fig. 3[24-27]). In addition, the 5-OH group in combination with a 4-oxo moiety and C2–C3 double bond may increase the radical scavenging activity[21].

In our recent studies[17,20,24,25] we tried to co-relate these structural features with minimal Bond Dissociation Enthalpy (BDE), the most important chemical parameter that describes the ability of H-atom abstraction from (or the H-atom donating ability by) flavonoids through homolytic breaking the O-H bond[28]. This single-step mechanism is known as hydrogen atom transfer (HAT). Density Functional Theory (DFT) calculations for compounds of the size like flavonoids are relatively time-consuming and hence we also applied simpler semiempirical quantum chemistry methods[17,24].

In the two papers, semiempirical gas-phase calculations of BDE values for six data sets having between 23 and 40 flavonoids were performed by the PM3 (Parametrization Method 3)[24] and PM6 (Parametrization Method 6), implemented in the MOPAC2009™ software package methods[17,29]. In these studies reasonable good correlations were obtained between the minimal BDE values and RSA on data sets of 25 (r = 0.836, PM3 method)[24] and 40 flavonoids (r = 0.85, PM6 method)[17].

Working with several data sets of experimental RS activities from four different laboratories, we also wanted to test the dependence of the observed relationships on the experimental errors in measurement of RSA. Consequently, we also wanted to test the significance of RSA *vs.* BDE relationships through the comparison of correlation coefficient values obtained for different experimental data sets with the level of chance correlations. In Fig. 4 the content of Table 3 from ref.[17] is given, in order to illustrate considerable discrepancy in experimental determination of RSA of flavonoids. They can be seen for those molecules for which more than one measurements were found in literature such as e.g. the compound 56 (genistein), 57 (myricetin) and 60 (cyanidin).

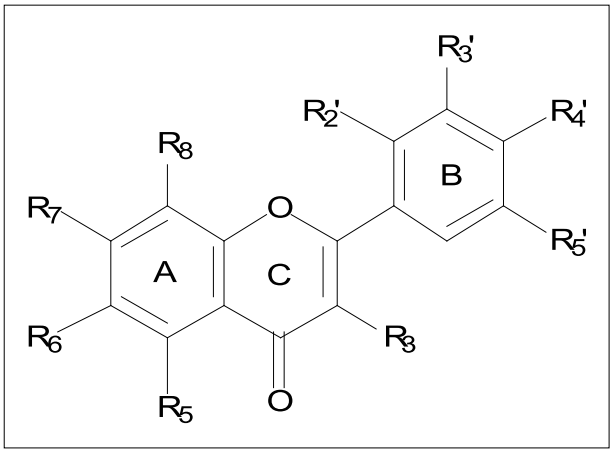

Figure 3. OH-substitution patterns of the series of flavonoids investigated.[x]

Furthermore, we calculated and compared semiempirical PM6 and DFT reaction enthalpies for the three reaction mechanisms for fla-

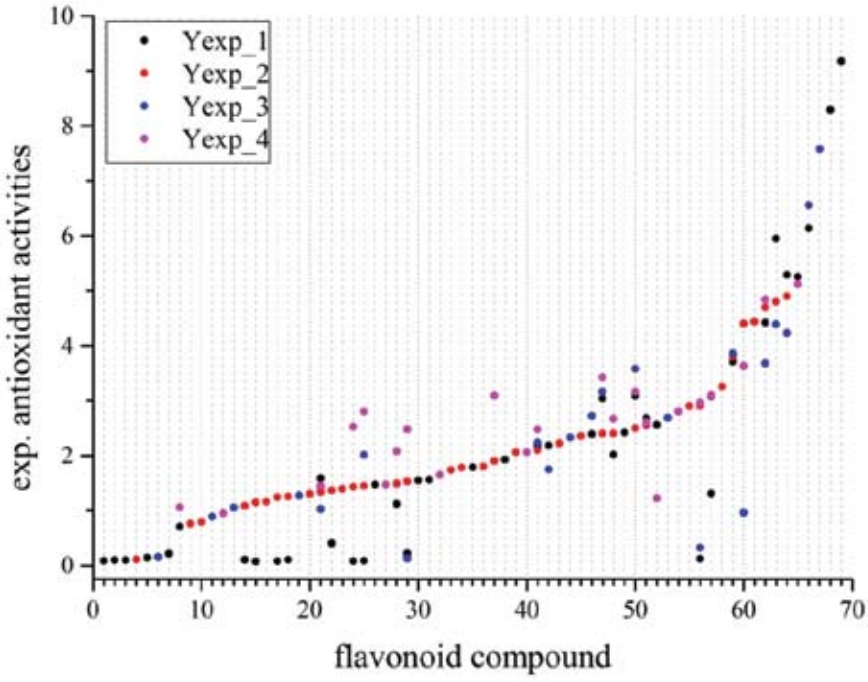

Figure 4. Four series of experimental antioxidant RS activities of 69 flavonoids measured in different laboratories.[17]

vonoid morin in different solvents (gas-phase, water, DMSO, benzene)[25]. It was shown that fast semiempirical PM6 method can mimic results obtained by means of DFT calculations. Similar results were obtained in the PM6 and DFT study of morin anion[26]. The study of flavonoid anions is important because at physiological pH=7.4, some flavonoids like quercetin can be present in the monoanion form, and it is supposed that in such a form they can fast react with free radicals.

TALKING ABOUT ATTRITION IN DRUG DISCOVERY: "WHY SO MUCH ATTRITION IN THE LATE PHASES OF THE DRUG DISCOVERY?"

During the early phases of the drug discovery process the main causes of attrition are efficacy *in vivo*, safety issues and economic reasons (Fig. 2). Major causes of high attrition rate in later, clinical phases concerns with drug safety and the necessity of demonstrating a highly desirable benefit-to-risk ratio and health outcome for new medicines[1]. Some therapeutic areas such as central nervous system (CNS) disorders and oncology, exhibit higher attrition rates than others[2]. The higher failure rates in these areas are in part due to modulating novel drug targets and to the lack of animal models with a strong capacity to predict human safety and efficacy.

Target identification and validation strongly affect effectiveness of a drug and patient benefit-to-risk ratio. They represent key factor and challenge in drug discovery process since it determines whole discovery process. Advances in genomics, proteomics and bioinformatics facilitate identification of new potential drug targets. However, a target must be "druggable" and validated for certain disease state and proof of principle (POC) clinical studies especially in Phase I, must be established by using biomarkers and surrogate or clinical endpoints of both efficacy and safety especially in oncology.

Due to substantial clinical and biological heterogeneity regarding cancers and other diseases, as well, to increase the benefit and reduce risks of a drug treatment, therapy should be personal-

ized or specifically tailored to specific patient populations. Such an approach puts focus on translational and personalized medicine and a more complete understanding of disease biology[30].

TRANSLATIONAL SCIENCE AND TRANSLATIONAL DISCIPLINES IN TODAY'S HEALTHCARE SYSTEM

Recognized as a need in the late 20th century and put in action in the first decade of the 21st century, translational science interconnects public scientific institutions, the academic community and industry (Fig. 5). It has resulted from the requirement for stronger bonds between fundamental research and clinical practice in order to facilitate more efficient discovery of new efficient and safe medicines.

Some of the challenges in the interrelationship between drug discovery and development and healthcare still remain to be tackled with great attention. They are:

- The need to better understand disease mechanisms;
- The need for harmonised methods for the handling and storage of tissue and data for use in biomarker development;
- The need for regulatory clarity as regards the qualification and validation of biomarkers as well as the approval of diagnostic tests;
- The need for a faster uptake of validated 'omics' technologies in clinical practice;
- The need for better training of healthcare professionals in the application of personalised medicines.

All these issues should be discussed by experts from industry, academia, clinics, regulatory authorities, health technology assessors and patient groups (Figs. 5 and 6). Interdisciplinarity, transdisciplinarity and multidisciplinarity is today's "must" in order to efficient overcome existing burdens in healthcare.

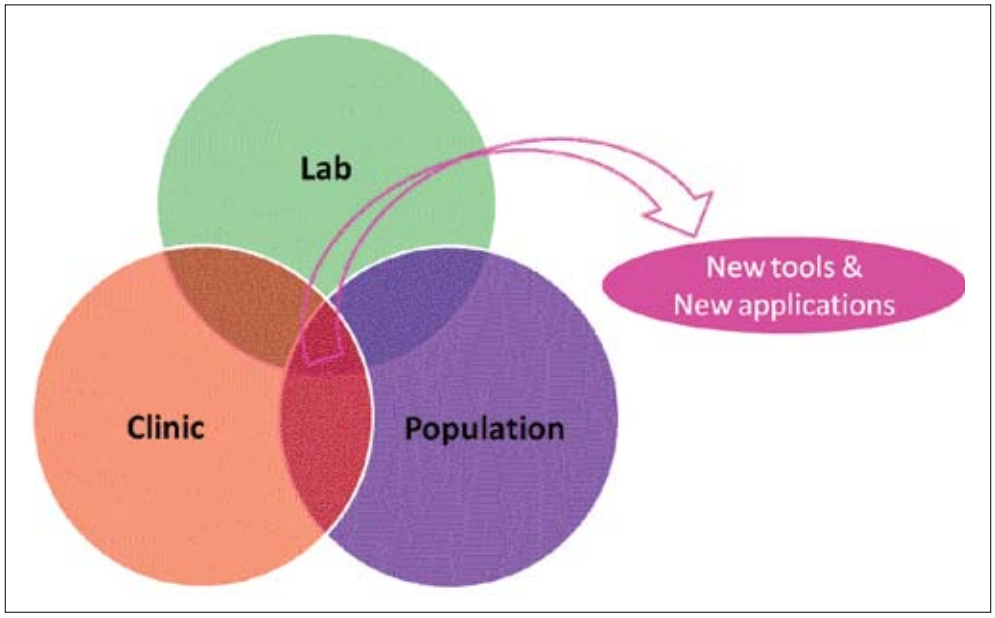

Figure 5. Translational science based on integration of basic laboratory research with clinical practice on properly pre-selected patient group will provide faster and more efficient public healthcare.

PHARMACEUTICAL INDUSTRY AND TRANSLATIONAL RESEARCH

Interest and support of the pharmaceutical industry for translational science is fully in accordance with the goal of discovering new drugs and cutting overall costs, primarily by reducing the duration of the research process and clinical trials of new chemical entities and new therapeutics (Fig. 1)[1].

Translational research in the early phases of drug development possesses the following main characteristics:

Enabling modelling and simulation to be fully applied in order to:

- ✓ Improve the reliability of cell and animal models,
- ✓ Evaluate the clinical meaning of specific therapeutic targets,
- ✓ Utilize mathematical models and simulations of biological behaviour of the testing compound.

Predictive medical research is yet another fast developing segment in the recent years, and it comprises part of drug research in this translational environment. The development of various predictive models is the best way to reduce the time for the development and attrition rate in the demanding clinical set-up. Mathematical modelling and simulations in order to select the right route of administration and appropriate dose for the clinical testing, before starting with the dose escalating studies, will significantly help all experts involved in these experiments. In addition, the use of predictive tools in determining the features of drug metabolism and its potential toxic effects are tools which can recount the defined and validated therapeutic targets to prognostics in best suited way[3].

Enabling more effective and productive utilisation of the relevant biomarkers:

- Discover biomarkers for use in early clinical trials,
- Define biomarkers responses at effective doses.

Biomarkers are of great assistance to researchers and clinicians in focusing research and choosing the right therapy[31]. The most important uses of biomarkers are the following: i) they are used as early indicators of efficacy in clinical practice or during clinical trials of drugs; ii) they guide the clinician in choosing an appropriate dose of medication for a particular patient; iii) certain biomarkers are used for establishing possible side effect and help define the therapeutic index of a drug and iv) they are of great help to pharmacologists as they are used to determine the efficacy of a drug as the function of its bioavailability.

On the basis of defining adequate biomarkers, it is possible to set up reliable clinical experimental models for conducting small, so-called exploratory studies[32], and the most important result of a well-defined procedure at these early stages is shorter duration and smaller extent of Phase II of clinical trials. This is the phase of clinical trials when the new drug is given to the patient for the first time, and on the basis of results obtained in this phase, it is possible to prove the rationale of the therapy and its efficacy and preliminary harmlessness. A significant reduction in Phase II of clinical trials, and possibly its complete elimination in the future and the launch of multi-centric testing right after the end of drug testing in Phase I would reduce the drug development time by several years.

Implementation of such activities requires collaboration and investment in knowledge by academic institutions, clinics, the industry, and also by regulatory agencies that issue licenses for the distribution and sales of drugs. All these procedures and successful interaction of existing knowledge require large multi- and trans-disciplinary teams of experts who know how to apply various tools and approaches like biosimulations, pharmacogenomics, proteomics and metabolonomics they have at their disposal, as shown in Fig. 6. It is a teamwork, accountability development and transparency of activities performed in the lab and the clinic, which ultimately result in good and consistent results.

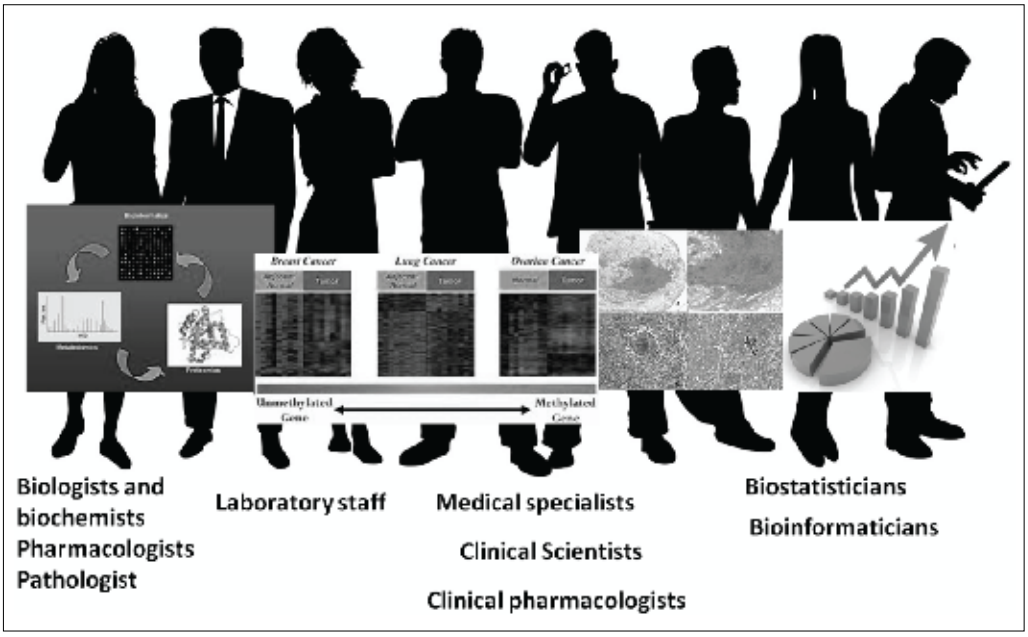

Figure 6. Collaboration of experts with diverse skills using variety of tools and approaches is basis of integrative translation medicine.

SOMEONE CALLS IT TAILORED, SOMEONE PRECISE, BUT IT IS ALL ABOUT – PERSONALIZED THERAPY!

Translational research can be applied in many areas of biological sciences and medicine. However, a special use has been found in the development of oncology drugs and in taking broad public health measures and activities for the prevention of chronic degenerative diseases, particularly metabolic diseases, whose key cause is the growing epidemic of obesity worldwide. It is translational science that is expected to play the key role in the introduction of personalized or tailored therapy. Personalised medicine is on the frontier of healthcare. It involves the use of molecular diagnostics to identify which patients are most likely to respond to specific medicines so that these medicines can be administered to them more effectively and with fewer side effects, and consequently healthcare systems across Europe will save money.

Personalised medicine poses a multitude of challenges. With the mapping of the human genome, a wealth of information has been generated about how humans differ from one another and how an individual's genetic make-up can influence his / her susceptibility to disease and response to new treatments. Genomics is only one of the new disciplines, called 'omics,' that seeks to define and explain the mechanisms of the human body (Table 1). Proteomics, or the large-scale study of proteins, is another one. There is also epigenomics, transcriptomics, metabolomics and metagenomics, just to name a few. Basic science is putting forward new theories about the causes, treatments and possible cures for disease at breath-taking speed.

HOW CAN THIS EXPLOSION OF KNOWLEDGE BE PUT TO WORK FOR BETTER HEALTHCARE?

The biggest potential of the personalized approach to medicine lies in the ability to seek solutions which are, from the very start, better fitted to different groups of patients compared to the so-called 'one size fit all' approach. Of course, the huge impact that the use of 'universal' drugs has played in people's health, particularly antibiotic therapy, cannot be completely dismissed.

It should be emphasized that the fact that several products have already been granted approval for use and application in targeted therapy, is the result of such systematic activity worldwide and in Europe. However, individual countries will have to assess for themselves whether improvements are necessary in order for products to become available to patients in a shorter period of time in the form of personalized therapy.

Last but not least, simple everyday habits like diet has considerably impact on prevention of many diseases[33]. It seems that holistic approach which takes into consideration every aspect of the patient will become the new stream in the healthcare policy.

Acknowledgements

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SAŽETAK

"Bitnost" otkrivanja lijekova i njihov razvoj je – interdisciplinarnost

Istraživanje i razvoj lijekova oduvijek je predstavljalo izazov za mnoge struke. Danas se posebno naglasak mora staviti na međusobno umrežavanje struke i tehnike. U tom smislu brojni znanstvenici koji su se donedavno usko bavili samo svojim područjem i ekspertizom, moraju biti spremni usvajati nove vještine kroz aktivnu komunikaciju s ostalim stručnjacima te učiti kontinuirano o primjeni naprednih tehnologija koje se svakodnevno razvijaju. Za takav model dobro nam može poslužiti proces razvoja lijeka. Znanstvenici okupljeni na ovom preglednom radu svojim su dosadašnjim radom i iskustvom doprinijeli uspostavi pojedinih tehnika i sustava, ali i novih načina rada unutar instituta, sveučilišnih institucija i farmaceutske industrije. Time su još jednom dokazali da ne postoje granice kada je konačni cilj primjena svih znanja u korist zdravlja čovjeka.

Ključne riječi: istraživanje i razvoj lijekova; translacijska istraživanja; ADMET, toksičnost; QSAR