The changing world of drug development

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Abstract: Cancer drug development is undergoing a substantial shift nowadays. The underlying drivers are multi-factorial. On the one side, drug development is performed more rationally than ever, profiting from the scientific advances in molecular biology in general and the elucidation of the various "omes" from genome to metabolome in particular. On the other side, it is based on enormous technological progress, e.g., in the field of genome sequencing, and in that of adequate handling of the resulting plethora of data. The high attrition rate of oncologic drugs under development in the past and the pressure from the side of the payers make it necessary to find permanently new answers for and adaptations of the process of drug development. In this context, it is necessary to respect arguments and views from the various perspectives of all the relevant stakeholders. Together with a group of international experts from different perspectives of drug development, this special issue will illustrate the respective role of patients, laboratory, clinical trials, drug companies, regulatory bodies, and also the economic principle in drug development, aiming at facilitating drug research in the near future.

Keywords: Cancer drug development; translational research; biomarker; stratified medicine; personalized medicine

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A report of the Institute of Medicine (IOM) screamed alarm while pointing to attrition rates, especially high for antitumoral drug development (1,2). In principle, output is dependent on the methodologies, procedures, and principles used to produce results. According to Heisenberg's uncertainty principle, the instruments used for measurement and the measurement procedure itself exert potential influence on the results (3). In this context, it is to be expected that newly developed instruments and methods used in basic science will have impact on drug discovery and development. Thus, molecular biology and molecular genetics on the one side and technologies such as reverse-phase protein arrays (RPPA), microarray-based measurement of copy number, whole-exome sequencing, sequencing of micro-RNA, microarray gene expression analysis, and finally, next generation sequencing have led to a dramatic change in applied clinical research via progress in basic science on the other side (4). They revealed areas of a before unknown world comparable to the huge step by the invention of the microscope allowing insights into the micro-cosmos or that of the telescope allowing to shift the horizon to other constellations. The eternal and ultimate goal of drug development is to identify and to apply the best treatment in terms of efficacy, safety, and tolerability to the individual patient; in the past via an "one size fits all approach" requiring large population-based trials to overcome heterogeneity and accepting small differences, nowadays via the "stratified approach" representing the best treatment for the average patient based on pre-selected characteristics in order to overcome low frequency phenomena, and finally in the future via a "personalized approach", i.e., the best treatment for a given individual based on maximum patient and tumor characterization (5).

How far we have gone is summarized in the contribution

of Christophe Le Tourneau and co-workers presenting and dissecting both, the actually already terminated and the on-going clinical trials aiming at finding out whether at all and at trying to answer to what extent this goal has already been accomplished. In a first step, the authors give an insight into screening programs using molecular profiling of the tumors in order to offer patients the most individual treatment available, but on the base of the not yet proven assumption that treatment according to molecular profiling yields better treatment outcome. In a second step, the authors are conceptually discriminating two distinct types of personalized medicine trials: trials stratified according to either molecular alterations or tumor types and algorithm-based trials evaluating merely a treatment algorithm instead of drugs' efficacy. For both types of personalized medicine trials, there exist non-randomized and randomized examples. The status of these comprehensively presented trials has to be taken as an indirect proof that we are on the best way of personalizing cancer medicines, but we have obviously not reached this goal as of yet.

One requirement for personalizing the anticancer treatment is fulfilled by Sumithra Mandrekar and Daniel Sargent with their contribution on appropriate drug designs. They have to tackle with the schizoid situation that personalizing in its extreme exegesis represents n=1 trials based on the adequate biomarker, whereas the statistical identification of predictive biomarkers derives only from randomized trials, ideally with interaction design, requiring large patient populations. Although the call for biomarkers for drug development is ubiquitous, there exist only scarce examples in clinical routine that fulfill the requirements of their validation. Neither HER2 testing for the anti-HER2 agent selection nor KRAS testing for the epidermal growth factor receptor (EGFR)-directed monoclonal antibody therapy have reached the highest level of evidence for prospective validation to represent a predictive marker, although HER2 is over-expressed in about 20% of the breast cancer population and KRAS is mutated in more than half of the patient population with colon cancer. In their review, Mandrekar and Sargent focus on actual and novel trial designs aiming at personalizing medicine in the context of early phase trials for initial marker validation, a prerequisite for early drug development.

Another tool influencing the outcome of drug development are the preclinical models used. The sentence by George Box "all models are wrong, but some are useful" can also be applied to the use of cell lines and further to *in vivo* models for drug development (6). Nevertheless, the use of molecular genetics in cell line panels of several hundred cell lines representing a biomarker discovery platform to guide rational cancer therapeutic strategies has led to the identification of new genomic markers of drug sensitivity and has proven a good correlation of mutated genes associated with cellular response to available drugs. Jens Hoffmann critically reviews the pros and cons of the correlation of *in vitro* and *in vivo* models as well as the pros and cons of patient-derived xenograft models (PDXs) and finally alludes to genetically engineered mouse models (GEMMs), respectively, representing altogether an integrative preclinical development program suitable for the purpose of new drug development nowadays.

For rational drug development, translational research, covered by the contribution of Sophie Doisneau-Sixou and Nadia Harbeck, is as important as the new taxonomy of cancer based on profound knowledge of molecular biology, notably on numerous molecularly-based disease markers such as the genome, transcriptome, proteome, metabolome, lipidome, epigenome, and finally the activitome as comprehensively summarized by Goldstein *et al.* (7,8). The authors exemplify that importance while providing a comprehensive overview of the respective development in breast cancer. The target characterization as well as the identification of the appropriate patient population via "enrichment" biomarkers represent the main focus for translational research during drug development. The early development of bioassays is important, and it may be substituted in the future by a more holistic approach, such as next generation sequencing, detecting therewith multiple genomic events in a single sample. Whereas the establishment of a bioassay allows selecting patients for a single new drug study, the latter approach allows allocating patients to combination drug trials. The development of drug combinations is essential for facing the various forms of tumor heterogeneity such as intra-tumoral, inter-metastatic or intra-metastatic heterogeneity and for facing the occurrence of secondary resistance to monotherapy (9). In order to incorporate high-dimensional molecular data into translational and clinical research, a respective powerful computational infrastructure and expertise in systems biology are mandatory. Homeostasis both, in normal cells and in cancer cells, is sustained by a complex network of redundantly activated or inactivated pathways. Therefore, the integration of systems biology should help develop new "network" therapeutic strategies (5,10).

A specific tool reviewed by Vikram Bollineni *et al.* which is still in its infancy regarding drug development is functional

and molecular imaging. Functional imaging allows in a non-invasive way to get repetitively and timely the 3-dimensional quantitative information on the dissemination of drugs, their success or failure in reaching the presumed target and is capable of visualizing heterogenous metabolic processes. Different tracers dispose on advantages and dis-advantages concerning their distribution, target specificity or adequacy for the differential reflection of metabolic processes. The methodology can also be used for patient selection/enrichment and for response evaluation, usually even before morphologic changes can be detected by conventional non-isotope-based imaging methodologies. In order to get applicable in a multi-center setting which is usually used in drug development, the validation of this highly sophisticated methodology is still to be provided. The formation and activities of the Positron Emission Tomography (PET) Study Group of the European Organisation for Research and Treatment of Cancer (EORTC) is a step in this direction having issued recommendations for PET imaging for the purpose of response assessment.

The Radiation Oncology Group (ROG) of the EORTC chaired now by Philippe Maingon and formerly by Vincent Grégoire has performed several practice changing trials leading to the establishment of radio-chemotherapy as new standard of care for preoperative treatment of rectal cancer, definite therapy of anal cancer, for glioblastoma, for the postoperative setting of head and neck cancer and, in combination with hormonal therapy, for locally advanced prostate cancer (11). Much less is known concerning the integration of targeted drugs into combined modality treatments. Philippe Maingon *et al*. identified processes that can be used as potential targets for radio-sensitization, such as DNA repair, or defects in cell cycle checkpoints. Drugs interfering with them may increase radio-sensitivity. The PI3K-AKT-NFkappaB-MAPK pathway is mediating radio-resistance and can be pharmaco-therapeutically influenced. A further reason for radio-resistance is hypoxia. Several new approaches to be tested are presented and discussed. The authors underline that for developing new combined modality treatment a methodologically highly developed and quality controlled network of advanced high-tech laboratories and clinical departments devoted to early phase trials with integrated new imaging modalities is indispensable. Such a network has been established in form of the Synergy of Targeted Agents and Rationale (STAR) initiative of the EORTC.

Unlike all other stakeholders of the drug developmental process, an academic research organization like the EORTC, represented in this contribution by Yan Liu, Denis Lacombe and Roger Stupp, is not restricted to drug development, but covers also combined treatment development, respectively. Common genetic alterations can sometimes predict sensitivity to therapy across multiple tumor types tested in the so-called basket trials. A scenario going far beyond is the initiative of the EORTC of establishing the Screening Platforms for Efficient Clinical Trial Access (SPECTA), meanwhile consisting of several tumor-related subsets, namely SPECTAcolor for colorectal cancer, SPECTAlung, SPECTAbrain, SPECTAmel or SPECTAprostate, respectively. The integration of functional imaging groups into the drug developmental process on the base of quality assurance was an early contribution of academic applied cancer research heavily supported and stimulated by the EORTC. Although being an academic research organization, the EORTC is anticipating a pay for performance scenario (12). Along this perception, it is defending the performance of methodologically robust, practice-relevant clinical trials comprising optimized phase II trials based on strong biologic rationales and cleverly selected endpoints allowing smaller, faster, and less expensive pivotal trials, both types accepting only larger differences versus control than in the past. The EORTC presents extremely open for new models of cooperation with the various stakeholders (13).

Susan Galbraith, now responsible for the Oncology Innovative Medicines Unit of AstraZeneca, shares an optimistic view starting with the allusion on the miserable success rates in the 1990's, underlining the importance of the understanding of the genetic aberrations in each patient's cancer at diagnosis and at progression in order to adapt the development of targeted drugs and ending-up with a proposal of a completely unorthodox business model of cooperation for the future. To better illustrate the change of paradigm while developing molecularly targeted agents (MTAs), the not always lucky development of gefitinib, the first MTA in solid tumors, is presented pars pro toto to demonstrate in a sober and open way how new knowledge based on novel technology can influence a more rational development. Personalized medicine trials represent also for industry an attractive new form of drug development, although the time of the blockbuster business model has gone therewith. Susan Galbraith finally makes a commitment to "open innovation" concerning the company's drug discovery. The last step in the direction of a new business model is the opening of an "oncology toolbox", i.e., sharing compounds with investigators from

academia for preclinical research.

The new approach of Medicine Adaptive Pathways to Patients (MAPPs) promoted by the European Federation of Pharmaceutical Industries and Associations (EFPIA), represented by Duane Schulthess and co-workers, merits to be mentioned explicitly (14). According to these MAPPs, in a first step of drug development a commercial marketing authorization will be provided only for a patient group who has access to new therapeutic agents, while validating simultaneously additional clinical endpoints. Thus, trials to assess efficacy as well as effectiveness including health technology assessments can be performed in an efficient way with regard to time and resources. An on-going challenge for early drug development results from the lack of resources invested in the analytical validation of predictive biomarkers.

Progress in basic and translational research as outlined is of great impact on the drug registration process by the regulatory bodies, the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). According to the results of The Cancer Genome Atlas Network perspective, the genomic profiles detected let shift away from characterizing cancers by the organ of their origin to their characterization based on their genetic aberrations such as mutations or to integration of molecular characterization into conventional tumor characterization (4,15). But, so far approval by the regulatory bodies is still based on efficacy in specific disease areas. Cross cancer molecular similarities justify the performance of basket trials with targeted or pathway selective drugs. In order to anticipate therapeutically the development of resistances and to find an adequate reaction to the intra-cancer heterogeneity, the development of drug combinations is of key importance (16,17). A FDA Co-Development Guidance of two or more new investigational drugs for use in combination is regulating such developments under specific conditions, mainly based on a strong biologic rationale, representing therewith a step in the right direction. A delicate discussion has been started on the consequences of regulatory risk-aversion for public health and on a healthy change of attitude towards a justifiable degree of acceptance of risk and uncertainty by regulators showing tolerance in allowing drugs onto the market without having excluded any possible toxicity (14). These and many more aspects are touched upon by Iordanis Gravanis and co-authors.

The high attrition rates in drug development for cancer are also highlighted by Nils Wilking and co-workers. While drug development is clearly a scientifically driven process on the one side, it is economically driven on the other side. Since the established way of generating data on large patient populations demonstrating often only small differences in outcome has shown to be not sustainable for even highly developed economies any further, also the pharmaceutical industry is eagerly looking for new business models. Some enterprises already by now have themselves established sequencing platforms for the identification of drug candidates active in small cohorts of patients only, therewith reacting to the splitting of tumor entities into small fragments (18). Since developments of non-blockbusters are costly and therefore, the drugs sold at high prices, health care providers tend more and more to link reimbursement of drug costs to the demonstration of benefit for the individual patient (19).

Last but not least, we are confronted with the patients' voice in person of the patient advocate Peter Kapitein which is the most authentical one what patients' expectations concerns. It certainly gives us the feedback that patients may gain a very deep insight into the entire complexity of the drug development process, and it is legitimate if they keep their perspective as potential users of the outcome of that drug developmental process. Therefore, we have also to respect their sometimes sober criticism. Nonetheless, this view is very pragmatic when patients are asking for speeding-up the drug developmental process that is so often delayed by partly unnecessary and even counter-productive administrative hurdles. Especially, the overwhelming safety attitude should be adapted, i.e., normalized to patients' needs (14).

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