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EDITORIAL

Current dichotomy between traditional molecular biological and omic research in cancer biology and pharmacology

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Abstract

There is currently a split within the cancer research community between traditional molecular biological hypothesis-driven and the more recent "omic" forms or research. While the molecular biological approach employs the tried and true single alteration-single response formulations of experimentation, the omic employs broad-based assay or sample collection approaches that generate large volumes of data. How to integrate the benefits of these two approaches in an efficient and productive fashion remains an outstanding issue. Ideally, one would merge the understandability, exactness, simplicity, and testability of the molecular biological approach, with the larger amounts of data, simultaneous consideration of multiple alterations, consideration of genes both of known interest along with the novel, cross-sample comparisons among cell lines and patient samples, and consideration of directed questions while simultaneously gaining exposure to the novel provided by the omic approach. While at the current time integration of the two disciplines remains problematic, attempts to do so are ongoing, and will be necessary for the understanding of the large cell line screens including the Developmental Therapeutics Program's NCI-60, the Broad Institute's Cancer Cell Line Encyclopedia, and the Wellcome Trust Sanger Institute's Cancer Genome Project, as well as the the Cancer Genome Atlas clinical samples project. Going forward there is significant benefit to be had from the integration of the molecular biological and the omic forms or research, with the desired goal being improved translational understanding and application.

Key words: Omic; Molecular biology; Pharmacology; Cancer; Integration

Core tip: This editorial describes the current split in approach, required expertise, and interpretation between the traditional molecular biological field, and the more recent "omic" approaches to cancer biology and pharmacology. The advantages and limitations of each of these disciplines are discussed and contrasted, highlighting their opposing approaches and mentalities.

The necessity of their efficient integration for the purpose of interpreting both cell line and clinical sample data is argued, especially when trying to project translationally into the clinic.

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PROBLEM OF INTEGRATION OF TRADITIONAL MOLECULAR BIOLOGICAL *VS* "OMIC" RESEARCH

The integration of the traditional molecular biological hypothesis-driven approach with the more recent "omic" forms or research for the purpose of providing translational insight is perhaps the premiere problem for cancer researchers today. How one views these two disparate forms of data impacts both the design and interpretation of biological and molecular pharmacological studies, and subsequently their prospective translational application. However, the two disciplines are by their nature in many ways mirror image opposites of one another, each with their own culture, assumptions, and requirements of expertise. This divergence has in the past, and continues at present to be an impediment to their successful merging.

MOLECULAR BIOLOGICAL APPROACH

The molecular biological approach to research has been dominant for years. It has provided innumerable contributions in the fields of biology, molecular biology, pharmacology, and cancer[1-3]. The mindset of those in the field is rooted in their training, in which questions are ideally distilled down to single alteration-single response formulations that are addressed at the bench experientially. This approach typically requires years of carefully constructed, sequential, narrowly focused studies to explore, confirm, or repudiate their hypothesis. Addressing questions in this fashion allows one to provide quantitative assessments regarding the influence of a specific change on an outcome. The advantages of this approach include understandability, exactness, simplicity, and testability. Typically, improved understanding of one aspect of a pathway also generates testable hypothesis regarding up or downstream events.

However, the use of isogenic systems to focus on specific responses also has important limitations. As molecular events typically occur within the context of pathways, influential events that might occur either upstream or downstream within the salient pathway are typically ignored. Of course, the more complex integration of influences from disparate pathways is also left out. If some single or small number of cell lines is being used to carry out the tests, then the results may be specific for those cell lines used, and less informative in other settings with significant variation. As one tries to apply these results translationally, one immediately encounters the inherent limitation of patients not being isogenic systems. For this reason, to propose that understanding either a patients cancer, or predicting their pharmacological response in the clinic can be successfully done based on an one-gene or one-molecular change type of analysis is likely to provide at best transient insight and benefit, in addition to being the exception to the (more complex) rule. A specific example of this using a dominant molecular event is provided by the BRAF V600E mutation, which provides a useful indicator for efficacious response to vemurafenib in melanoma[4,5]. However, even this unusually robust indication is typically short-lived in its usefulness, as alterations in the tumors undergoing treatment with BRAF inhibitors limit its affective treatment window to some period of months, generally followed by recurrence, often at the same locations[6].

"OMIC" APPROACH

The omic approaches to research, meanwhile, have their own set of advantages and disadvantages. On the positive side, data generated using technology such as array comparative genomic hybridization, transcript microarrays, mass spectrophotometrical proteomic analysis, exome sequencing, cell line screens, or broad spectrum patient sample compendiums view things in the broader context[7-13]. These more inclusive approaches provide the advantage of generating much larger amounts of usable data, allowing the consideration of multiple alterations simultaneously, both in those genes that one might expect to be altered, as well as in those whose involvement is completely unexpected. When the studies include multiple cell lines or patient samples, they also allow cross-sample comparisons to be made. This, of course, allows one to ask directed questions, while simultaneously making novel and potentially important discoveries and observations in totally unexpected areas. A single well-designed omic project can and does typically yield multiple potentially important observations and hypothesis, due to the large amount of data generated.

Unfortunately, there are multiple disadvantages inherent in these approaches as well. By their nature, the omic forms of data necessitate new forms of expertise just to process, and provide basic interpretation and access. These forms of expertise include computer science, statistics, mathematics, and more recently, bioinformatics. When added to the need to understand the results in the context of biology, including the detailed implications of the specific molecular alterations found, both the individual researcher as well the field in general are presented with the need for combinations of cross-disciplinary expertise that are rarely found. In the design

and implementation phase of studies, significant care needs to be taken with issues of quality control and reproducibility. This is necessary to assure the ability to meaningfully compare and interpret data across numerous samples harvested at different times, either from the clinic or cell lines. What cell line or clinical sample to select, their number, how they are handled, and what assay types to perform are all central considerations. For pharmacological studies, which compounds or drugs are selected, their number and type, the conditions under which they are used, and assay type are all key. Once the data assessment and interpretation phase is entered, there are multiple algorithmic approaches that may be used, with their choice being influenced by the data type, the question being asked, and the expertise and biases of the researcher. Correlations, linear regressions, classical statistics, information-theoretic algorithms, and machine learning all have contributions to make in the handling and interpretation of this data[4,14-20]. Additional complexity is then added as multiple forms of data are integrated[21-26]. Finally, algorithmic integration of biological knowledge into the mathematical approach is likely necessary, although this field is in its infancy[27,28].

MOVING FORWARD WITH THE INTEGRATION OF TRADITIONAL MOLECULAR BIOLOGICAL *VS* "OMIC" RESEARCH

So at the current time, integration of the molecular biological and omic disciplines is problematic. Increasing that tension is that the research community as it is constituted today, both at the bench and editorially, is dominated by those with traditional molecular biological training and understanding. This has lead to some reluctance to either accept or understand the omic forms of research. It has even been proposed that the large-scale omic projects are jeopardizing progress in traditional molecular biology due to competition for the research dollar[29].

However, attempts are ongoing throughout the research community to better interpret, integrate, and apply both these forms of data simultaneously[30]. Success may be had by starting with experimental data, and expanding its interpretation by overlaying omic data. This was done in the study of the affect of DNA methylation on E-cadherin expression using standard experimental approaches, and then assessing its influence in the context of multiple regulatory parameters using omic data[31,32]. Conversely, one may start with omic data, and verify its implications with standard experimental approach. This was done with the omic observation that SLFN11 transcript levels had a strong correlation to several drug activities, followed by the use of experimental approaches to prove its causality[33,34].

Both the molecular biological and omic forms of research will be necessary in order to interpret the results of the large cell line screens, including the Developmental Therapeutics Program's NCI-60, the Broad Institute's Cancer Cell Line Encyclopedia, and the Wellcome Trust Sanger Institute's Cancer Genome Project[10-12]. These screens are designed to provide the omic basis for improving the understanding of molecular pharmacology in cancer from the cell line level. Omic analysis has already provided multiple potentially important associations from these databases, including: (1) the association of MEK inhibitor efficacy with AHR expression in NRAS mutant cell lines; (2) a potential affect on the MET inhibitor PHA665752 by amplifications in MET; (3) sensitivity to PARP inhibitors in EWS-FLI1 translocation-containing cells; and (4) the activities of the DNA-damaging bleomycin, zorbamycin, and peplomycin with ATAD5 mutations[4,5,35,36]. All of these omic associations will require traditional molecular biological experimental follow-up to verify or disprove whether they are causal. All insights gained from both the molecular pharmacological and omic approaches will be both useful and necessary for understanding the cells phenotypic differences and establishing a solid basis for drawling inferences. The cell line screens will certainly continue to provide hypotheses and useful study cases going forward. An example of this is the melanoma line LOXIMVI, which while containing the well studied BRAF V600E mutation, still has reduced sensitivity to vemurafenib when compared to the other cell lines containing the mutation, and is thus a potentially useful study case for patient relapse or resistance to that drug.

As one projects to patient samples, such as those found in The Cancer Genome Atlas (TCGA) both molecular biological and omic forms of research will again be necessary as one attempts to provide interpretation[13]. TCGA is designed to provide a base for omic analysis of clinical samples, providing data on some about 9939 patients from 33 cancer types. It provides both molecular and patient therapeutic information. Omic analysis of this data has already provided multiple potentially important associations, including: (1) targets for pharmacological intervention in squamous cell cancer including FAT1, MLL2, TGFRBR2, HLA-A, and NFE212; (2) a potentially clinically relevant association between elevated levels of CX43 in glioblastoma tumor samples and temozolomide resistance; and (3) multiple FDA-approved drug targets of metabolic vulnerabilities[37-39]. As was the case for the cell line screens, these omic associations will require traditional experimental follow-up to verify or disprove their causality.

Going forward, considering the daunting set of challenges facing the researcher, it should be clear that all insights derived from both the traditional molecular biological and omic approaches will be both desirable and necessary to make sense of the complex and overlapping challenges that exist. As progress is made in these areas, one hopes that making patient treatment decisions based on that patient's complex

molecular profile will become the norm. An integrated vision for the molecular biological and omic approaches will be helpful if not necessary to that end.

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