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Commentary

Predicting response to new drugs in AML from simulation modelling: Value of the BEAT AML project as a validation resource

The recent approval of a number of mutation-specific targeted therapies for acute myeloid leukemia (AML) by the United States Food and Drug Administration, including midostaurin and quizartinib for *FLT3* mutations, enasidenib for relapsed cases with *IDH2* mutations and ivosidenib for *IDH1* mutations, has revitalized interest in mutation-directed approaches in a heterogeneous myeloid malignancy that has not seen progress in treatment options for several decades[1]. Based on the number of novel agents currently under clinical development and the complex molecular and biological heterogeneity of AML, the number of novel mutation-specific therapies are likely to accelerate in the near future. However, assigning an effective targeted therapy to a given patient's molecular profile in the outpatient setting is not trivial and will likely require an expert tumor board, expedited diagnostic profiling, and a clinically-integrated bioinformatics team. Emerging reports suggest (i) clinicians are not necessarily well-trained in the interpretation of sequencing data [1] and (ii) tumor boards often rely adopt a "matching one mutation to one drug", as outlined in a typical sequencing report from a leading tumor sequencing company such as Foundation Medicine [2], that may potentially miss the summation of combinatorial effects of mutations and copy number alterations in a given patient. Indeed, a recent report suggests tumor boards analyzing sequencing data are not more effective in prolonging survival of cancer patients compared to physician's choice [3]. Do we need better drugs or are we not matching the right drug to the right patient?

A report by Dusbosky et al. in this issue of *Leukemia Research* attempts to bridge the gap between available molecular data at a routine leukemia service (namely karyotype and recurrent somatic mutations) and predicting the response to a novel investigational agent in AML by mathematically modelling combinational effects. The study was a collaboration between Cellworks Research (a biological pathway-simulation analytics company headquartered in Bangalore, India & San Jose, California), the Beat AML investigators from Oregon Health and the Cogle laboratory from the University of Florida. The investigational agent used as a prototype for the simulation predictions was JQ1, a first-in-class bromodomain extra-terminal (BET) inhibitor. A number of BET inhibitors including CPI-0610, OTX 015, ABBV-075, PLX-51107 and I-BET-762 are currently being tested in multiple phase I/II clinical trials in AML (NCT02158858, BCT01713582, NCT02683395) and other cancers (NCT02391480, NCT01943851). Predominantly a service-based data simulation company, Cellworks have invested time and labor deriving differential equations that mimic core cellular processes based on manually curating and aggregating published experimental data which according to the paper include 112 central pathways, 75,000 reactions and 3300 cancer-specific genes. The output of their analytic platform is focused on two key biological variables: a proliferation index derived from CDK4-CCND1, CDK2-CCNE, CDK2-CCNA and CDK1-CCNB1 and a viability index (derived from predictions of survival proteins AKT1, BCL2, MCL1, BIRC5, BIRC2 and XIAP and apoptosis derived from predictions of caspases, PUMA and cleaved PARP). Whether modeling the behavior of this limited set of proteins is sufficient to predict response to a targeted therapy in AML is not clear (for instance BCL2A1 is not an output variable) but one can be sure the algorithms will continue to improve iteratively. The strength of this report is due to the direct comparison of CellWorks predictions with experimental data from 100 genotyped primary patient samples treated with JQ1 recently made available through the Beat AML Project [4]. Recent progress in assessing similar in silico prediction tools has been limited by inadequate functional data sets of well annotated clinical samples. As part of the functional annotation, Beat AML tested each of these samples to inhibition by JQ1 in vitro. Encouragingly, the simulations had a high positive predictive power and correctly predicted 84 out of 89 of the samples that were inhibited by JQ1 at concentrations less than 2.7 μM with a sensitivity of 97% and positive predictive value of 94%. The concentration of 2.7 μM was chosen as a pharmacokinetic correlate of in vivo maximal serum concentration. Samples with chromosomal aberrations del 7q, monosomy 7, trisomy 8 or del 5q were predicted and confirmed to be JQ1 responders as well as samples with mutations in *RAS*, *TET2* and *IDH1*. Some of these responding lesions were not unexpected and should be picked up by an astute tumor board: c-myc is on chromosome 8 and an increased gene dosage in +8 cases are likely to be sensitive to JQ1. However other lesions such as del 5q were less obvious, highlighting the critical role of cytogenetic abnormalities or copy number amplification (as well as somatic mutation) in determining response to epigenetic-based therapies.

The Beat AML study is a massive effort to correlate molecular profiles of AML with *ex vivo* drug screening results. These results, open to researchers and clinicians via a user-friendly portal (http://www.vizome.org), should enable rapid progress in predicting mutation-specific responses to targeted therapies. Beat AML includes whole-exome, RNA sequencing (RNA-Seq), and *ex vivo*drug screening (using 122 small molecule inhibitors) on 672 tumor samples from 562 patients (275 de novo) with detailed clinical annotations. Exome sequencing has revealed novel mutations that had not been previously reported in AML, in addition to a higher representation of mutated genes, such as *SRSF2*, in de novo patients compared to TCGA-AML. *Ex vivo* drug screening was performed by plating 10,000 cells per well into three, 384-well plates containing gradients of 122 small-molecule inhibitors. These agents targeting the majority of the tyrosine kinome, in addition to pathways such as MAPK, PI3K-AKT-MTOR, CDKs, HDAC, STAT, and RAF. By correlating all samples with joint RNA-Seq and drug screening, Tyner

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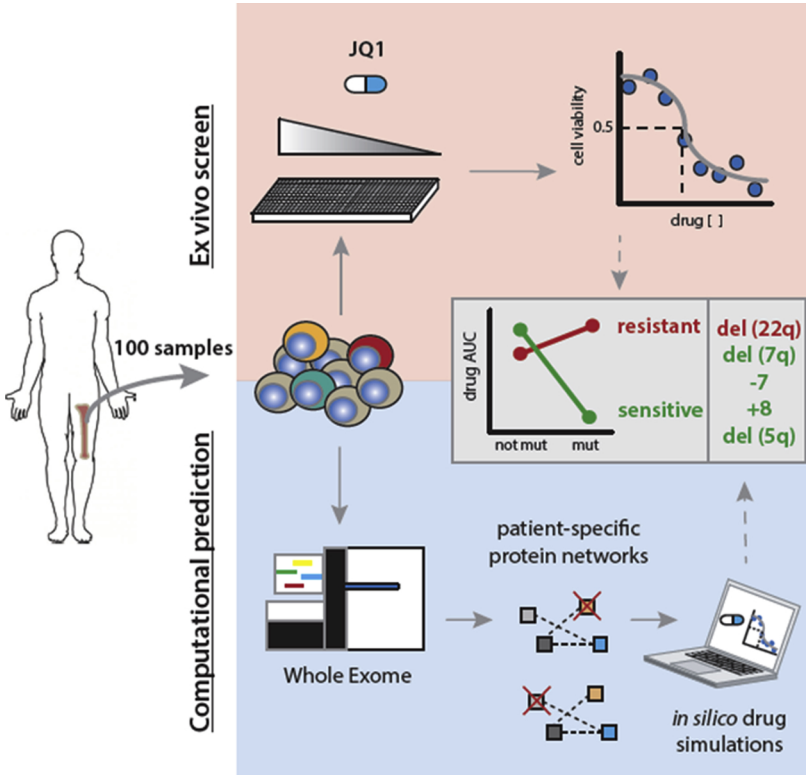

Fig. 1. Computational simulations may assist predicting responses to novel drugs in AML by integrating molecular data such as copy number and somatic mutations. Cytogenetic and somatic mutation data from 100 patient samples collected as part of the Beat AML was used to simulate drug responses to the bromodomain inhibitor JQ1 and compared to experimentally validated responses with high positive predictivity. Similar algorithms can potentially assist tumor banks and clinical investigators in predicting best responders to drugs of known pathway modulation.

et al. defined gene expression signatures that were predictive of drug response or resistance. While the *ex vivo* screening was not necessarily performed in physiological media conditions with canonical myeloid cytokines or stroma, the results showed striking differences in drug sensitivity in both diagnostic and relapse samples. Furthermore, Beat AML demonstrated definitively that mutation co-occurrence can dramatically alter drug response phenotypes. For instance, co-occurring *BCOR* and *RUNX1* mutations show increased sensitivity to JAK family kinase inhibitors compared to *BCOR* mutations alone. As highlighted by Dusbosky et al., simple inputs such as cytogenetic/ copy number data plus targeted mutation sequencing results can successfully predict in vitro responses to targeted therapies such as JQ1. The question is whether we currently know enough about growth, apoptosis and epigenetics to be confident of our own computational algorithms. Future studies will no doubt determine whether other inputs such as gene expression or mutant allele frequency can further improve this refinement using Beat AML or other functional datasets as a surrogate gold-standard until phase III trials show clinical efficacy. Finally, prospective trials of *in silico* prediction tools vs physician's choice will be critical in establishing in silico prediction as a "new normal" (see. Fig. 1).

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