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ANTICANCER DRUGS

Advancing precision medicine *in silico*

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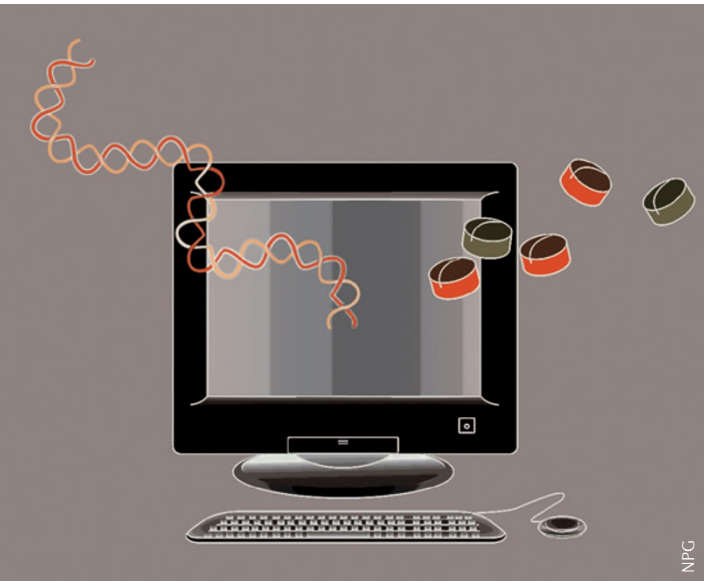
Large-scale cancer genomics data have been collected by several initiatives in recent years, in the hope of revealing molecular drivers of cancer that can be therapeutically targeted. Using sequence data from nearly 7,000 tumours, Lopez-Bigas and colleagues have identified 475 driver genes, many of them novel, as well as numerous repurposing opportunities for existing drugs.

The authors used data from The Cancer Genome Atlas, combined with sequencing data from other studies. About one-quarter of the identified driver genes encoded factors required for chromatin regulation, ubiquitin-mediated protein degradation, and splicing and RNA processing. Thus far, few anticancer agents have been developed that target these pathways. A subset of 76 driver genes, which the authors termed 'major cancer drivers', carried mutations that were found at high frequencies within clones from each individual tumour, suggesting that these genes confer a strong survival advantage.



Changes in copy number and gene fusion events were also incorporated into the data set (see The Cancer Drivers Database available at the Intogen website). When gene mutations, copy number alterations and fusions were considered together, 90% of tumours in the cohort had at least one identifiable, putatively causal genetic change.

The authors then collated information on which of these alterations are targeted by therapeutic agents — either approved or in development — to create a Cancer Drivers Actionability Database (see the Intogen website). These drugs targeted a total of 96 of the 475 driver genes.

After filtering the data to exclude repurposing that had not worked in the clinic, the authors determined which drugs might be useful for which patients. Only 5.9% of these patients could be prescribed a tumour-specific, genotype-targeted agent *in silico*. Nearly one-half of these patients had ERBB2 amplifications, for which there are three approved drugs.

The authors then considered how each of these approved drugs could be repurposed, and stratified these according to feasibility. 'Tier 1' repurposing involved using the compounds either for tumour types or indications other than those approved by regulatory agencies. 'Tier 2' involved using drugs that target a different type of alteration (but within the same protein), a different but connected gene (with evidence that this targeting can kill tumours with the patient's mutation) or drugs that bind the mutated protein more strongly than they bind their primary target. 'Tier 3' repurposing included mild off-target repurposing (drugs that bind the mutated protein strongly, but with less affinity than they bind their primary targets).

Using these strategies, 40.2% of patients could be prescribed one of the US Food and Drug Administration (FDA)-approved drugs in the Cancer Drivers Actionability Database, and one-half of these potential prescriptions would be due to Tier 1 repurposing. Most of these Tier 1 repurposing cases involved kinase inhibitors, and were for treating thyroid carcinoma, glioblastoma or lung adenocarcinoma. An additional 33.1% of the nearly 7,000 patients that would not benefit from approved drugs could be treated with drugs in clinical trials.

A subset of genes that have driver mutations in more than 5% of tumours of at least one cancer type but with no targeted therapeutic were prioritized for drug discovery on the basis of their potential druggability. The resulting 25 targets include 13 that are not well-established cancer-associated gene products and that have roles in cell adhesion, migration, cytoskeletal remodelling and other core biological processes.

Overall, this study highlights new areas of opportunity for advancing precision cancer medicine, and provides databases that could be useful in exploiting these opportunities.

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ORIGINAL RESEARCH PAPER Rubio-Perez *et al. In silico* prescription of anticancer drugs to cohorts of 28 tumour types reveals targeting opportunities. *Cell* **27**, 382–296 (2015)

WEB SITE

Intogen website: http://www.intogen.org/downloads