CCBIO Opinion

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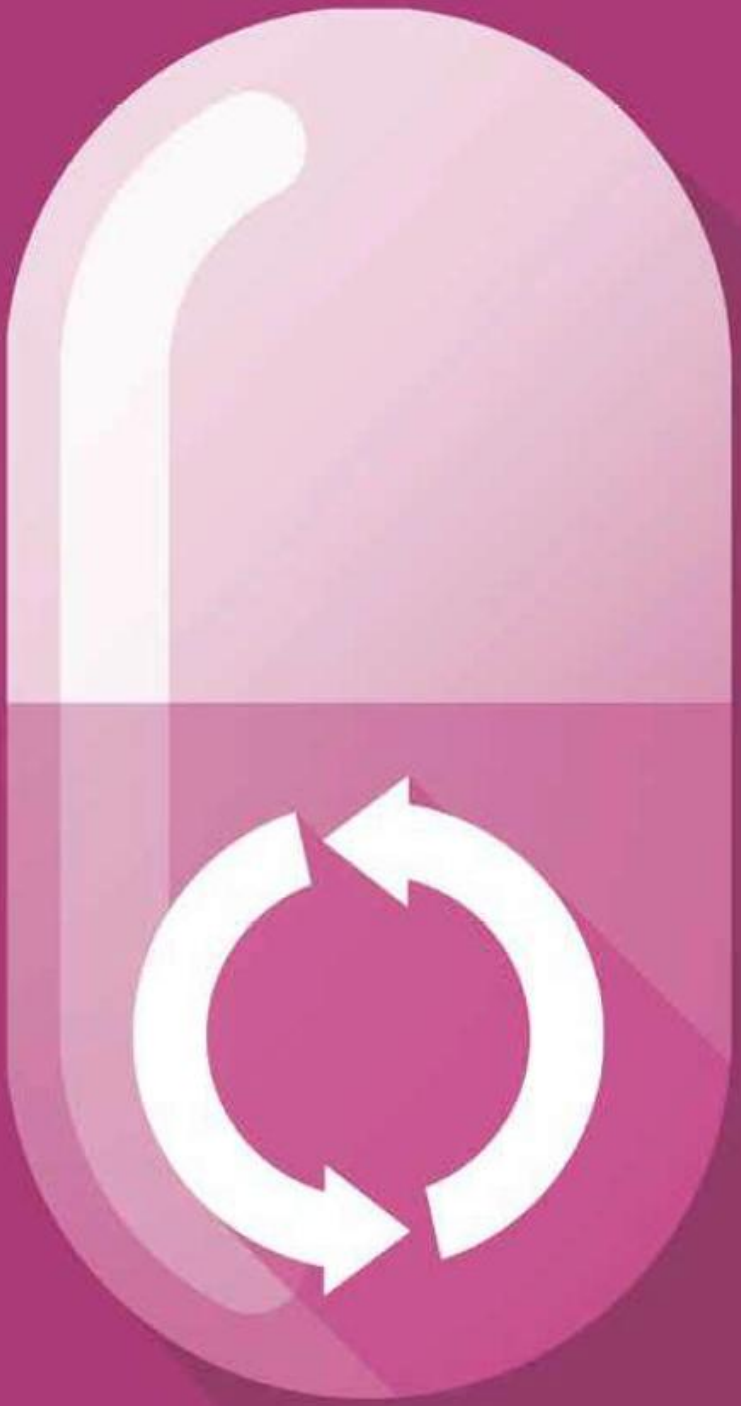

Repurposing Drugs for Cancer Therapy

Repurposing is a recognized strategy in drug discovery and development where a drug already approved for human use, is screened for new effects and new targets. Repurposing is potentially fruitful because we already know that these drugs are introduced to and distributed in the organism with acceptable and known side effects. It is also often the case that "new substances" which are promising in cell culture, and even in animal models, fail the requirements for absorption, distribution, acceptable side effects and efficiency when they are later tested in the human body.

Based on 1578 FDA-approved (Food and Drug Administration, USA) drugs and drugs in late clinical development, the number of druggable molecules is estimated to 667 among more than 21 000 genes and 1.5 million proteins and isoforms expressed. If an optimal use of these drugs could be exploited across a wider range of diseases, this would expand the therapeutic toolbox considerably. There are several examples of useful repurposing internationally and in our groups.

Thalidomide presents one interesting example. This drug was developed as an anti-emetic and sleeping pill in the late 1950s, resulting in catastrophic occurrence of birth defects when used during pregnancy. Promoted by patient advocacy groups, thalidomide was tested nearly 50 years later with effect against multiple myeloma and stimulated research into thalidomide analogs. One such analog, lenalidomide, was particular effective in myelodysplasia lacking one copy of the 5q chromosome and provided an example of so-called synthetic lethality with 5q deletion. Cereblon, an E3 ubiquitin ligase, was identified as the molecular target of lenalidomide.

In a different approach, our group tested the anti-leukemic effect of the old anti-convulsant and mood stabilizing agent valproic acid in combination with all-trans retinoic acid and theophylline in acute myeloid leukemia, aiming for a combined effect that resulted in increased differentiation and programmed cell death of tumor cells. Novel low-toxic combinations with valproic acid are in development for evaluation in clinical trials.

Our research group employed a fluorescent reporter to screen FDA-approved drug panels for compounds that could inhibit WNT/β-catenin signaling, a pathway that is commonly aberrantly activated in cancer. Several small molecular candidate compounds were found to inhibit activated β-catenin signaling and were next characterized using a method called DARTS. This is a method to identify the molecular target of the compound. The compound axitinib, previously approved as a VEGFR inhibitor against kidney cancer, was found to bind and stabilize the E3 ubiquitin ligase SHPRH, leading to subsequent degradation of activated β-catenin in the cell nucleus. Further testing revealed that axitinib could selectively inhibit WNT/β-catenin signals in both zebrafish and mouse models with reduced tumor development in the mice. Repurposing is not, however, straightforward. Careful design of the screening and evaluation assays is important. Small molecule substances might have more than one molecular target in the cells. The drug concentration required to achieve a desired pharmacological effect can vary strongly between targets. Consequently, if a substantially higher drug concentration is required for a new pharmacological effect, a new preclinical evaluation will be necessary in addition to a new clinical evaluation of toxicity and side effects. At one end of the spectrum, repurposing has the potential to bring old drugs rapidly into new use. At the other end of the spectrum, repurposing could serve to discover leading compounds that could be chemically modified in order to increase target affinity and reduce necessary dosing and toxicity.

The major challenge of cancer therapy today is therapeutic effect in metastatic cancer and surgically non-resectable tumors. A deeper understanding of tumor cell clonal evolution has followed increasing understanding of disease heterogeneity. Therapy of advanced cancer urgently needs a greater toolbox. Repurposing may be one important strategy to increase the number of therapy responders in cancer.

Repurposing may need regulatory steps to move forward, securing approved indications, safety data and allowing insurance reimbursement. An effective moderate cost clinical development plan may be needed to collect sufficient documentation to allow approval of old drugs for new indications. ••