ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Targets for Hematologic Malignancies

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H&O Why is the prospect of targeting genes considered undruggable a particularly relevant line of research?

JB I am not fond of the term *undruggable*. Undruggable confers a sense of impossibility, which glamorizes certain targets or, worse, intimidates scientists who might quite feasibly develop successful direct-acting inhibitors. No target is undruggable. There are simply targets that have yet to be drugged, and these targets represent a milestone in ligand discovery. In that regard, they may require the development of new technologies, such as new chemical methodologies or ligand discovery assay technologies. These important advances developed for one intractable target create opportunities for the community to successfully approach other targets. It is very important that we rally around difficult targets so that such efforts may lead to historic advances in drug discovery, and also enable the community more broadly.

Many of the most pressing targets of cancer drug discovery are classified as undruggable targets. The most important disease genes in all of cancer—*p53*, *KRAS*, and *c-Myc*—are perceived to be beyond the immediate reach of conventional approaches in ligand discovery. Nothing in the field is more important than developing direct-acting therapeutics that correct these somatic alterations.

H&O What are super-enhancers, and what is known about their role in cancers/hematologic malignancies?

JB My laboratory works to develop small molecules that modulate pathways of gene expression or that exert so-called *gene control*. In working to understand the specific transcriptional consequences of a drug we developed for a general chromatin regulator, bromodomain containing 4 (BRD4), we teamed up with Dr. Richard Young, a leading scientist in the field of eukaryotic transcriptional biology at the Whitehead Institute. Over the last 2 years, we have been working to understand at the level of the chromatin structure how the genome-wide consequences of bromodomain inhibition yield specific transcriptional responses.

We reasoned that BRD4 might accumulate asymmetrically within the human epigenome, such that displacement above BRD4 would have selective local consequences at gene bodies adjacent to these regions of asymmetry. Indeed, this is what we found.

We estimate that 3% of enhancers in the cell bind 40–50% of all BRD4. These are known as super-enhancers, which are massive concentrations of transcriptional activators and co-activator proteins that promote transcription of master regulatory transcription factors and other critical determinants of cell states.

H&O What is JQ1, and what has your recent research uncovered regarding its ability to inhibit *c-Myc* expression in multiple myeloma cells?

JB JQ1 is a first inhibitor of BET bromodomains, synthesized in my lab and reported together with the laboratory of Stefan Knapp in 2010. JQ1 is a triazolo-diazepine which competitively binds to the acetyl-lysine recognition pocket, displacing bromodomains from chromatin.

In our broad studies of the JQ1 molecule, we have consistently identified a selective inhibitory effect on the *c-Myc* transcriptional pathway in cancer. This was most apparent in multiple myeloma, an incurable malignancy of plasma cells.

Using translational models of multiple myeloma for mechanistic studies, we have demonstrated that bromodomain inhibition with JQ1 acts to inhibit the function of *c-Myc* by abrogating chromatin-dependent signal transduction from this master regulator. This prompts cell cycle arrest and cellular senescence, leading to a favorable antiproliferative effect in model systems.

H&O What are the potential implications of these findings for the discovery of cancer therapeutics directed at components of super-enhancers?

JB The development of JQ1 and subsequent development of bromodomain inhibitors by other skilled groups firmly establishes the feasibility of inhibiting epigenetic reader proteins with efficient, cell-permeable small molecules. The development of first- and now second-generation bromodomain inhibitors based on JQ1 has implications for the discovery of cancer therapeutics directed at components of super-enhancers in diverse tumor types.

H&O What are the biggest remaining challenges?

JB The central challenge of cancer drug discovery concerns the development of inhibitors for the true pathologic causes of cancer: *c-Myc*, *KRAS*, and other master oncogenes that have evaded coordinated efforts in ligand discovery for decades.

The deep and broad annotation of somatic alterations in cancer genomes identifies incredible heterogeneity, which is chilling from the standpoint of cancer drug discovery. In these data sets, however, we still consistently observe a high frequency of somatic alteration of these master regulatory factors. We therefore must assemble as a community around the challenge—difficult as it may be—of developing inhibitors of these dominant cancer-causing pathways.

Additional challenges exist as well. We must commit to providing the chemical tools realized through modern efforts in drug discovery as broadly as possible within our own research community. To exemplify a more open-source approach to drug discovery, we have endeavored to provide the JQ1 bromodomain inhibitor to all laboratories worldwide, at whatever dose is needed to address their scientific questions. Through this activity, we have observed firsthand the power of open innovation in drug discovery. This approach will likely expedite the discovery and development of targeted therapeutics in a broad range of diseases.

H&O What does the future hold?

JB Science is moving at an incredible and inspiring pace. The revolution in genome medicine will hopefully prompt a parallel revolution in drug discovery that will deliver incisive chemical tools and important molecularly-targeted therapeutics capable of broadly impacting human health. It is very reasonable to expect that the current creative and competitive environment to drug discovery will continue to realize the potential of modern molecular medicine.

Suggested Readings

Lovén J, Hoke HA, Lin CY, et al. Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell*. 2013;153:320-334.

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Lin CY, Lovén J, Rahl PB, et al. Transcriptional amplification in tumor cells with elevated c-Myc. *Cell*. 2012;151:56-67.

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