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Identifying druggable disease-modifying gene products

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Many disease genes encode proteins that are difficult to target directly using small molecule drugs. Improvements in libraries based on synthetic compounds, natural products, and other types of molecules may ultimately allow some challenging proteins to be successfully targeted; however, these developments alone are unlikely to be sufficient. A complementary strategy exploits the functional interconnectivity of intracellular networks to find druggable targets lying upstream, downstream, or in parallel to a disease-causing gene, where modulation can influence the disease process indirectly. These targets can be selected using prior knowledge of disease-associated pathways or identified using phenotypic chemical and genetic screens in model organisms and cells. These approaches should facilitate the identification of effective drug targets for many genetic disorders.

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Disease and the druggable genome

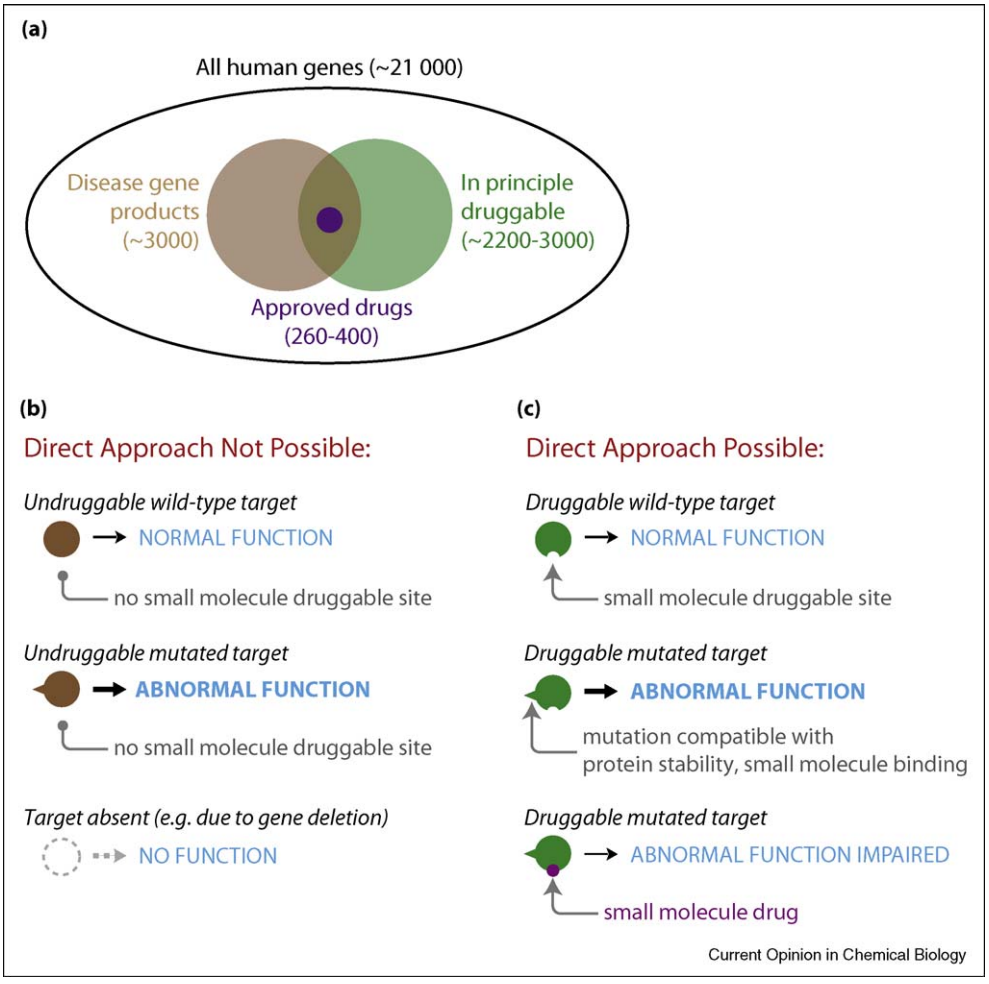
The development of drugs to combat human genetic disorders, including cancer and neurodegenerative disease, is a high priority. In recent years, new DNA sequencing and genotyping technologies have enabled the discovery of a slew of novel disease-causing mutations and disease-associated DNA sequence variants [1,2,3••,4,5]. Transforming this knowledge into a set of validated drug targets poses a significant challenge. It is sobering to consider that, to date, only ~2% of all predicted human gene products (260–400) have been successfully targeted with small molecule drugs [6,7] (Figure 1a). Partly, this may reflect the fact that only 10–15% of all human genes (2200–3000) are thought to be in principle 'druggable' (e.g. encode proteins similar in sequence to those that have already been targeted with small molecules) [8,9], and that the overlap between druggable genes and known disease genes is only on the order of 25% [10,11] (Figure 1a). Adding to the challenge, mutated human disease genes can give rise to protein targets that differ only subtly in structure or abundance compared to their wild-type counterparts or eliminate the production of a specific gene product altogether (e.g. owing to mRNA destabilization or gene deletion) (Figure 1b). These considerations suggest that few gene products, disease-associated or not, are likely to represent direct small molecule drug targets. How then can we find targets that are disease-specific, druggable, and that can be modulated with small molecule based drugs or other reagents to bring about a desired therapeutic effect? Here we review several strategies used to discover useful molecular targets for human genetic disorders.

Direct targeting of disease gene products

Conceptually, the simplest approach to treating a genetic disorder is to modulate the function of a disease-causing gene product directly (Figure 1c), as illustrated by the use of the small molecule imatinib (Gleevec) to inhibit the constitutively active kinase produced by the *BCR-ABL1* fusion gene found in patients with chronic myeloid leukemia [12]. The number of disease-associated gene products considered druggable is small (see above) but continues to slowly expand. For example, in early surveys, the disease-associated E3 ubiquitin ligase Mdm2, which is amplified in many cancers, was thought to be undruggable [8]. It has since been shown that the crucial Mdm2-p53 binding interface can be disrupted by the nutlin family of small molecule inhibitors, leading to stabilization of p53 and cancer cell death [13] (Figure 2a). These results suggest that extensive searching of existing chemotypes may yield direct modulators of additional disease gene products.

Both re-screening of existing chemotypes and *de novo* computationally assisted drug design [14] will be facilitated by new models of protein structures and protein-interaction interfaces. For example, starting with an existing model of the Jak3 tyrosine kinase domain, Sayyah *et al.* first used orthology modeling to develop a model of the Jak2 kinase domain, which is mutated in several cancers [15]. This model was then used to screen 20 000 known compounds *in silico* for those likely to bind adjacent to the ATP binding site and inhibit kinase activity [15]. This screen resulted in the identification of six candidate compounds, one of which, Z3, was subsequently shown to specifically inhibit Jak2 function in several cell culture and disease models [15] (Figure 2b). The application of similar approaches to other targets may

Figure 1



The druggable genome in relation to disease. **(a)** Venn diagram illustrating the relationship between all potential human proteins, those proteins that are in principle druggable (green), those proteins encoded by disease genes (brown), and those proteins targeted by approved therapeutics (purple). The size of the ovals approximates the number of gene products in each category. While not considered here, it should be noted that one gene may give rise to multiple gene products through alternate splicing. **(b)** Cartoon depicting disease gene products that are in principle undruggable, either because a suitable drug-binding fold is not present or because the disease-causing mutation eliminates protein production, and gene products that are druggable (e.g. accessible to a small molecule modulator). **(c)** Small molecule modulators of druggable targets could in principle act to either impair the abnormal function of a target resulting from a gain-of-function mutation or restore the impaired function of a target resulting from a partial loss-of-function mutation (not shown).
Part (a) is partly adapted from reference [11].

greatly decrease the amount of screening that needs to be performed in the future, and help characterize novel direct modulators of disease gene product function.

Exploiting the functional interconnectivity of biological systems to find alternate druggable targets

It is not always possible to target a disease gene product itself directly. However, normal and disease genes do not function in isolation: genes, gene products, and metabolites interact with one another to form functionally interconnected genetic, protein, and metabolic interaction networks of exquisite complexity [16–19]. Genetic diseases perturbing one or more genes alter the connectivity of these networks, as reflected in disease-specific patterns of gene expression, protein–protein interactions and metabolite production [20–22]. Changes in network connectivity induced by disease gene activity (or lack thereof) may expose unique genetic or chemical sensitivities due to a loss of biological redundancy, feedback regulation, and/or the upregulation or downregulation of alternate, druggable target genes [23,24,25••,26]. If suitable drugs are available to modulate these indirect targets, it becomes possible to exploit acquired chemical sensitivities to achieve a desired phenotypic outcome, such as cancer cell-selective cell death [27–29]. Indirect targets