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Expansion of the druggable genome in the IUPHAR/BPS Guide to PHARMACOLOGY and other drug target resources: a key substrate for future medicines

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Introduction The landmark concept of the druggable genome (DG) defines the landscape of successful and potential new targets for human diseases (1). This is becoming increasingly data-supported by publications that expand the range of proteins with activity-modulating starting points. As an expert-curated online database of approved, clinical or research level pharmacological targets and their molecularly defined ligands, the IUPHAR/BPS Guide to PHARMACOLOGY (GtoPdb) provides its own internal statistics on DG coverage (2). As a DG-relevant cross-reference in UniProtKB/Swiss-Prot, we are joined by the additional target-to-chemistry resources of DrugBank, ChEMBL and BindingDB. This work compares overlaps and differences, functional coverage as well as cumulative target expansion of the data-supported DG between these four key databases.

Methods. Comparative analysis of these four resources was initiated via the UniProt query interface. Intersects and differentials were generated using the online Venny tool. Gene Ontology (GO) categories for selected protein identifier lists were displayed using the PANTHER resource. Further details, such as coverage by 3D structures, were analysed via the UniProt interface.

Results. While exact numbers will be updated for the presentation, in order of their mention above, the human Swiss-Prot cross reference counts were 1496, 2336, 3303 and 2462, respectively. This produced an outer limit total of 4223 (representing 21% of the canonical human proteome of 21,136) but the four-way consensus drops to 738. This core set thus has a well-corroborated likelihood of tractability for small molecule drug discovery or possibly biologics. These metrics underline the differential coverage of these sources but encouragingly, the consensus had increased from 568 two years ago. Analysis by GO categories indicates the different data capture selectivity and curatorial stringencies between the sources. Results will also be presented on coverage of structures, pathways and diseases for consensus sets as determined by additional UniProt queries.

Conclusions. The four resources compared here provide accessible, complementary and cumulative coverage of the DG. As we know, this does not obviate the major challenges of target validation. However, increasing delineation of the DG expands the number of potential starting points for the development of new medicines.

References

(1) Oprea et al. (2018), Nat *Rev Drug Discov*. doi: 10.1038/nrd.2018.14.
(2) Harding, *et al*. (2018), *Nucl. Acids Res.* **46** (Database Issue), D1091-D1106. doi: 10.1093/nar/gkx1121.