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Slicing and dicing curated protein targets: analysing the drugged, druggable and tractable.

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A hallmark of the Guide to PHARMACOLOGY database (GtoPdb) is expert curation of ligand-target binding data (PMID 24234439). Ligands include approved medicines, clinical candidates, drug research leads, receptor ligands and tool compounds. Mechanistic relationship mapping has now grown to ~1300 human proteins, ~5500 small molecules, ~1200 peptides ~50 clinical antibodies and ~12000 binding constants (e.g. IC50, Ki or Kd). This facilitates analysis of molecular pharmacology from both the ligand and target perspectives. Results are presented here for the drugged, druggable (i.e. with leads) and tractable (i.e. at least some chemical starting points) target landscape. This is defined by our own high-stringency data capture but can be compared with other sources. Our recent UniProt cross-links enable detailed target analysis, together with Venn diagram generation, the PANTHER resource for Genome Ontology (GO) and pathway analysis. We have used these to explore differences between our ~ 300 primary targets of approved drugs, the set of ~ 950 targets with quantitative binding data and a further ~ 350 proteins with non-quantitative but pharmacologically important interactions. Utility is demonstrated by analysing our own linked Swiss-Prot set and comparing to other target-centric sources. For example, a query for proteins with transmembrane content give results of 68% for targets of approved drugs, 40% for non-quantitative interactions and an average of 56% for all 1300 human proteins. Comparative figures for DrugBank and ChEMBL target proteins were 42% and 45%, respectively. Additional data will be presented for GPCRs, channels, kinases, proteases, other target classes, secreted vs transmembrane proportions, intersects with pathway enzymes and links to Orphan Diseases genes. Results will also show GtoPdb utility for addressing drug R&D business questions. For example, we executed the following Boolean series: which targets have endogenous peptide interactions? (plus) exogenous synthetic peptide interactions? (plus) synthetic molecule interactions? (plus) are the targets of approved drugs? The four-way intersect produced 23 proteins for which pathways they were in could be determined using PANTHER. We also sliced target sets by ligand binding affinities (<0.1, <1.0, <10 and <100 nM). Not unexpectedly, this indicated receptor enrichment for each step of increased potency. This work also addresses the practical utility for tool compound acquisition (e.g. checking for the same or similar vendor compounds in PubChem) which can be followed up for target query sets. This enables the move from in silico analysis to experimental studies of target validation, pathway intervention points and functional genomics perturbations. This applies to all our annotated ligands and extends beyond ~300 approved (drugged) targets out to ~ 950 proteins covering possible future tractable targets with new pharmacology.