Phenotypical versus target-based screening in CNS disorders: New directions for much-needed breakthroughs

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The IUPHAR/BPS guidetopharmacology.org, is a freely available knowledgebase on all drug targets quality-controlled by 90 subcommittees of 860 expert scientists for NC-IUPHAR. However, the explosion of potential molecular targets for drugs has not been accompanied by marked clinical success in the therapies in psychiatric and neurological disorders. In many cases, drug discovery programs underestimate sources of complexity and the number of experimental variables, which are difficult to transpose from lab to lab. Furthermore, human spontaneous mutations in disease are underestimated. Fortunately, some of these variables converge on key nodes where epigenetics, ageing, metabolism and inflammation may switch protein phenotype in cells by splicing, and switch cellular signalling, so these nodes may become key targets, albeit not necessarily, molecularly, being the precipitating event. The ratio of one gene/one protein underestimates alternative splicing - particularly for humans, where gene number is low. Recent knowledge changes old concepts which had been (and are still being) used for drug discovery. For example, both in real and virtual screening, gene sequences are used to encode real and virtual protein structures: one to one. Yet the pathophysiological interest is in variability and multiplicity - complex but crucial. Thus, target and phenotypical screening represents a delicate balance for drug discovery which can only be defined on a case-by-case basis. Furthermore, recent human evolution differentiated us from other non-human primates by an increase in brain and muscle metabolism to run, which is not taken into account in drug discovery. I will show how 1) the 22M€ IMI Newmeds psychiatry consortium demonstrated that multiple molecular initiating events can impact common medical psychiatric diagnoses and 2) metabolomic and transcriptomic analysis of 'impossible diseases' such as amyotrophic lateral sclerosis (ALS) can yield new therapeutic targets.