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Impossible or Merely Difficult? Two Grand Challenges from a Biologist's Perspective

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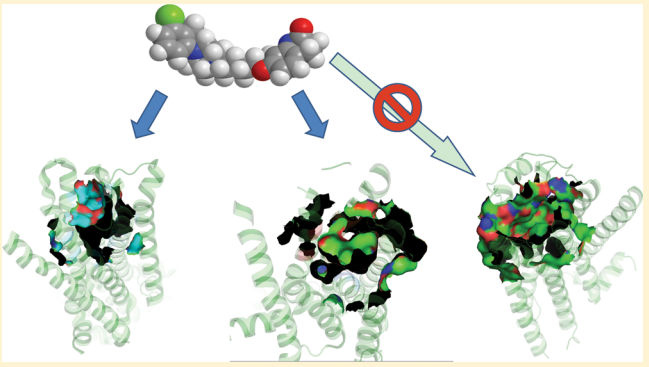
ABSTRACT: Here I propose two grand challenges for medicinal chemists: the deorphanization of orphan GPCRs via *in silico* methods and the design of multitarget drugs with enhanced safety and efficacy over current medications.



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Medicinal chemistry is a unique discipline straddling the interface of several sciences, including synthetic organic and inorganic chemistry, pharmacology, drug metabolism and distribution, toxicology, and systems and computational biology.[1] Ultimately, medicinal chemistry "*..is concerned with the invention, discovery, design, identification and preparation of biologically active compounds... (and) the interpretation of their mode of action at the molecular level ...*"[1] (emphasis mine). Here I will propose what might be considered to be "grand challenges" for medicinal chemistry based on the foregoing, made feasible from recent technological and conceptual breakthroughs.

Grand Challenge #1: Deorphanizing orphan GPCRs *in silico*. G-protein coupled receptors (GPCRs) represent the largest single target class for therapeutic drug discovery in the human genome.[2] Among the 900 or so GPCRs in the human genome, more than 50% represent so-called "orphan GPCRs" because validated endogenous ligands have yet to be identified. As recently highlighted by the awarding of the 2012 Chemistry Nobel Prize to Kobilka and Lefkowitz for their pioneering work on GPCR structure and function, the "deorphanization" of even a single GPCR is a notable achievement. Although many GPCRs remain orphans, considerable progress has been made in elucidating the structures of more than 70 GPCR–ligand complexes—mainly via X-ray crystallography.[3] Stevens and colleagues have estimated that 18% of nonolfactory GPCRs—including many orphan GPCRs—can now be faithfully modeled; and several studies suggest that, once modeled, they might be fruitfully interrogated by computer-assisted docking.[3] Given the steady growth in GPCR–ligand structure determination, one can anticipate that, within a decade, sufficient structural coverage and advances in modeling and computational docking of the GPCR-ome will be achieved so that most members could be computationally interrogated.

Here, the grand challenge is to identify the endogenous agonist for an orphan GPCR. At least two conceptual and technological roadblocks hinder this goal: (1) Modeling the active state of the binding pocket and (2) creating an *in silico* catalogue of putative endogenous ligands.

Can we accurately model the agonist-bound state of a GPCR for which we have neither ligands nor structure? Although adequate coverage of the GPCR-ome from a modeling perspective can be confidently predicted in the near term, most of the structures will probably continue to represent inactive receptor states with binding pockets that differ from those found of the agonist-bound active state. Certainly, many more agonist-bound states will need to be solved so that the research community can begin to appreciate the types of conformational changes within and outside the binding pocket that occur upon agonist binding. Simultaneously, advances in predicting and modeling agonist conformations—from both a ligand and side-chain perspective—of the binding pocket will be necessary. Thus, a significant aspect of this grand challenge will be to create and refine computational technologies so that they preferentially and faithfully extract or, as may often be the case, *infer* agonist ligands from large libraries of small drug-like molecules when a putative agonist structure is being interrogated.

Can we create an in silico *library encompassing all endogenous ligands?* GPCRs can be activated by a bewildering array of endogenous ligands including photons, ions, intermediary metabolites, fragrances, tastants, peptides, neurotransmitters, and autacoids.[4] To identify the potential endogenous ligands

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for an orphan GPCR, an in silico database including all of these is needed. Current databases such as the KEGG resource (e.g KEGG COMPOUND http://www.genome.jp/kegg/compound/) and PubChem (http://pubchem.ncbi.nlm.nih.gov/) provide annotation for both endogenous and exogenous bioactives (including peptides). Because many GPCR agonists represent intermediary metabolites, initiatives in metabolomics aiming to identify the universe of human metabolites (e.g., the "Human Metabolomics Library": http://www.metabolibrary.ca/) will provide many useful structures for computationally interrogating GPCR active states. Although there have been substantial advances in both cataloguing and predicting endogenous bioactive peptides, we will need a large database of such peptides—along with predicted conformations and post-translational modifications—to reliably deorphanize peptide GPCRs *in silico*.

Clearly, deorphanizing even a single orphan GPCR-ome by *in silico* or physical methods represents a considerable achievement, as exemplified by studies wherein the orphan peptide osteocalcin was demonstrated to regulate male fertility via the orphan GPCR GPRC6A.[5] Genome-wide deorphanizing GPCRs along with all other druggable targets (see for instance ref 6 for a pertinent non-GPCR deorphanization success) thus remain a grand challenge for medicinal chemists and biologists.

Grand Challenge No. 2: Purposeful creation of therapeutically superior multitarget drugs. For many years it has been evident that, for complex diseases, single-target agents are frequently therapeutically inferior to multitarget drugs.[7,8] This can be most clearly demonstrated by comparing the average weight loss induced by various antiobesity agents (Figure 1), although similar arguments can be made for other complex diseases, including schizophrenia, depression, various cancers, and so on.[8] As can be seen, the combination drugs phentermine/topiramate (which together target biogenic amine and glutamatergic neurons), fenfluramine/phentermine (which in combination target serotonin receptors and biogenic amine neurons), and bupropion/naltrexone (which collectively target biogenic amine neurons and opioid receptors) all induced weight loss equal to or greater than 10% in effectiveness trials as compared to an average weight loss of between 2 and 3% with placebo.[9] By contrast, with the exception of phentermine (an amphetamine derivative), the more selective drugs sibutramine (which inhibits reuptake of norepinephrine, serotonin, and, to a lesser extent, dopamine), lorcaserin (a 5-HT_{2C} serotonin agonist), rimonabant (a CB-1 cannibinoid antagonist), and orlistat (which inhibits the absorption of fat) induce a modest ~5% or less weight loss.[9]

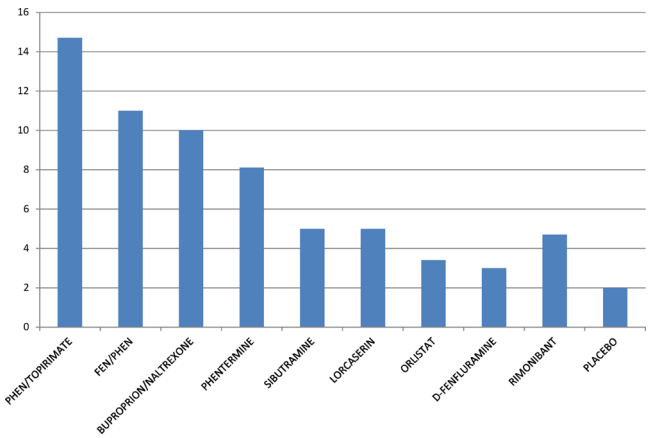

Figure 1. Comparative weight loss of antiobesity drugs. Shown is the average % weight loss at maximum effective dose of approved and investigational antiobesity drugs along with average % weight loss by placebo (data derived from ref 9). The phentermine/topirimate combination (marketed as Qnexa) and lorcaserin (marketed as Belviq) were approved by the US FDA in 2012 for treating obesity. Sibutramine was voluntarily withdrawn from the market in 2010, and rimonabant was withdrawn from the European market in 2009, while racemic fenfluramine and D-fenfluramine were voluntarily withdrawn in 1998. Phentermine, buproprion, naltrexone, topiramate, and orlistat all remain US FDA approved medications, though only phentermine and orlistat are US FDA-approved for obesity.

Here, creating a superior antiobesity medication that selectively engages predefined sets of molecular targets is an example of the broader grand challenge of targeted polypharmacology. Given the relatively modest activity of a 5-HT_{2C} serotonin receptor agonist and a reuptake inhibitor, for instance, one might wish to design a dual-acting 5-HT_{2C} agonist/norepinephrine reuptake inhibitor. Here, in addition to challenges associated with achieving the requisite on-target pharmacology, it would be important to avoid interaction with off-targets such as the 5-HT_{2B} serotonin receptor to prevent drug-induced valvular heart disease[10] and the H1-histamine receptor, which is associated with drug-induced weight gain .

Although rationally designing multitarget agents is challenging, and some might assert impossible, quite recent successes in large-scale predictions of off-target drug actions[11] as well as advances in the design of drugs with defined polypharmacologic profiles for neuropsychiatric[8] and oncologic[12] indications augur well for this grand challenge. Again, these sorts of successes will continue to be catalyzed by large open-source databases of small molecule pharmacology such as ChEMBL (https://www.ebi.ac.uk/chembl/), PubChem, and KiDB (http://pdsp.med.unc.edu/kidb.php) . As well, one can envision using small molecule-based docking on multiple targets simultaneously or sequentially to identify candidate small molecules with requisite polypharmacological profiles. Obviously, there are many potentially useful drugs that are effective because they have many therapeutic targets, yet there use is precluded because they also hit one or a few critical off-targets. Thus, it should be possible to computationally screen large compound databases for similar compounds that target the therapeutic molecule but not the off-targets. This approach would reduce the chemical space that needs to be investigated.

Although meeting these two grand challenges would have seemed impossible a few years ago, the cited spectacular successes in computationally intensive medicinal chemistry and systems pharmacology now make these feasible.

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■ REFERENCES

(1) Wermuth, C.; Ganellin, C.; Lindberg, P.; Mitscher, L. Glossary of Terms Used in Medicinal Chemistry. *Pure Appl. Chem.* **1998**, *70*, 1129−1143.

(2) Hopkins, A. L.; Groom, C. R. The druggable genome. *Nat. Rev. Drug Discovery* **2002**, *1*, 727−30.

(3) Stevens, R. C.; Cherezov, V.; Katritch, V.; Abagyan, R.; Kuhn, P.; Rosen, H.; Wuthrich, K. The GPCR Network: a large-scale collaboration to determine human GPCR structure and function. *Nat. Rev. Drug Discovery* **2012**.

(4) Allen, J. A.; Roth, B. L. Strategies to discover unexpected targets for drugs active at g protein-coupled receptors. *Annu. Rev. Pharmacol. Toxicol.* **2011**, *51*, 117−44.

(5) Oury, F.; Sumara, G.; Sumara, O.; Ferron, M.; Chang, H.; Smith, C. E.; Hermo, L.; Suarez, S.; Roth, B. L.; Ducy, P.; Karsenty, G. Endocrine regulation of male fertility by the skeleton. *Cell* **2011**, *144*, 796−809.

(6) Hermann, J. C.; Marti-Arbona, R.; Fedorov, A. A.; Fedorov, E.; Almo, S. C.; Shoichet, B. K.; Raushel, F. M. Structure-based activity prediction for an enzyme of unknown function. *Nature* **2007**, *448*, 775−9.

(7) Roth, B. L.; Sheffler, D. J.; Kroeze, W. K. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat. Rev. Drug Discovery* **2004**, *3*, 353−9.

(8) Besnard, J.; Ruda, G. F.; Setola, V.; Abecassis, K.; Rodriguiz, R. M.; Huang, X. P.; Norval, S.; Sassano, M. F.; Shin, A. I.; Webster, L. A.; Simeons, F. R.; Stojanovski, L.; Prat, A.; Seidah, N. G.; Constam, D. B.; Bickerton, G. R.; Read, K. D.; Wetsel, W. C.; Gilbert, I. H.; Roth, B. L.; Hopkins, A. L. Automated design of ligands to polypharmacological profiles. *Nature* **2012**, *492*, 215−20.

(9) Kabra, D.; Kabra, U.; Tschop, M.; Hoffmann, S. Pharmacological treatment of obesity. *Sleep loss and obesity* **2012**, 203−225.

(10) Roth, B. L. Drugs and valvular heart disease. *N. Engl. J. Med.* **2007**, *356*, 6−9.

(11) Keiser, M. J.; Setola, V.; Irwin, J. J.; Laggner, C.; Abbas, A. I.; Hufeisen, S. J.; Jensen, N. H.; Kuijer, M. B.; Matos, R. C.; Tran, T. B.; Whaley, R.; Glennon, R. A.; Hert, J.; Thomas, K. L.; Edwards, D. D.; Shoichet, B. K.; Roth, B. L. Predicting new molecular targets for known drugs. *Nature* **2009**, *462*, 175−81.

(12) Dar, A. C.; Das, T. K.; Shokat, K. M.; Cagan, R. L. Chemical genetic discovery of targets and anti-targets for cancer polypharmacology. *Nature* **2012**, *486*, 80−4.