

## RESEARCH HIGHLIGHT

# How Can Network-Pharmacology Contribute to Antiepileptic Drug Development?

Mauricio Emiliano Di Ianni, Alan Talevi

*Medicinal Chemistry, Department of Biological Sciences, Faculty of Exact Sciences, National University of La Plata (UNLP) - La Plata (B1900AJI), Buenos Aires, Argentina*

Correspondence: Alan Talevi

E-mail: [alantalevi@gmail.com](mailto:alantalevi@gmail.com)

Received: December 09, 2013

Published online: February 18, 2014

---

**Network-pharmacology is a field of pharmacology emerging from the observation that most clinical drugs have multiple targets, contrasting with the previously dominant *magic bullet* paradigm which proposed the search of exquisitely selective drugs. What is more, drug targets are often involved in multiple diseases and frequently present co-expression patterns. Therefore, useful therapeutic information can be drawn from network representations of drug targets. Here, we discuss potential applications of drug-target networks in the field of antiepileptic drug development.**

**Keywords:** drug-protein networks; network analysis; epilepsy; drug repositioning ; drug repurposing

*Molecular & Cellular Epilepsy* 2014; 1: e30. doi: 10.14800/mce.30; © 2014 by Mauricio Emiliano Di Ianni, et al.

---

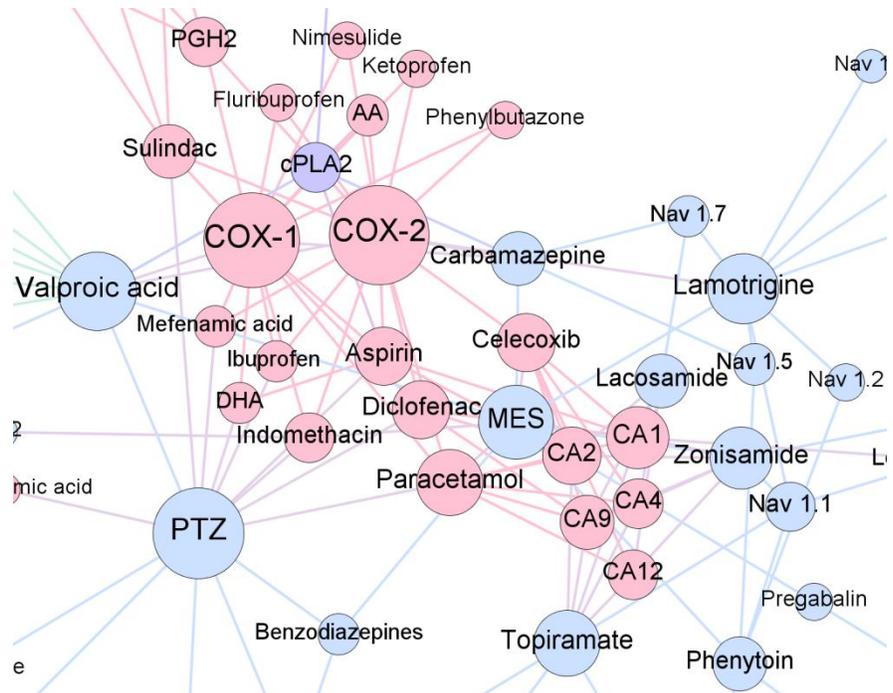
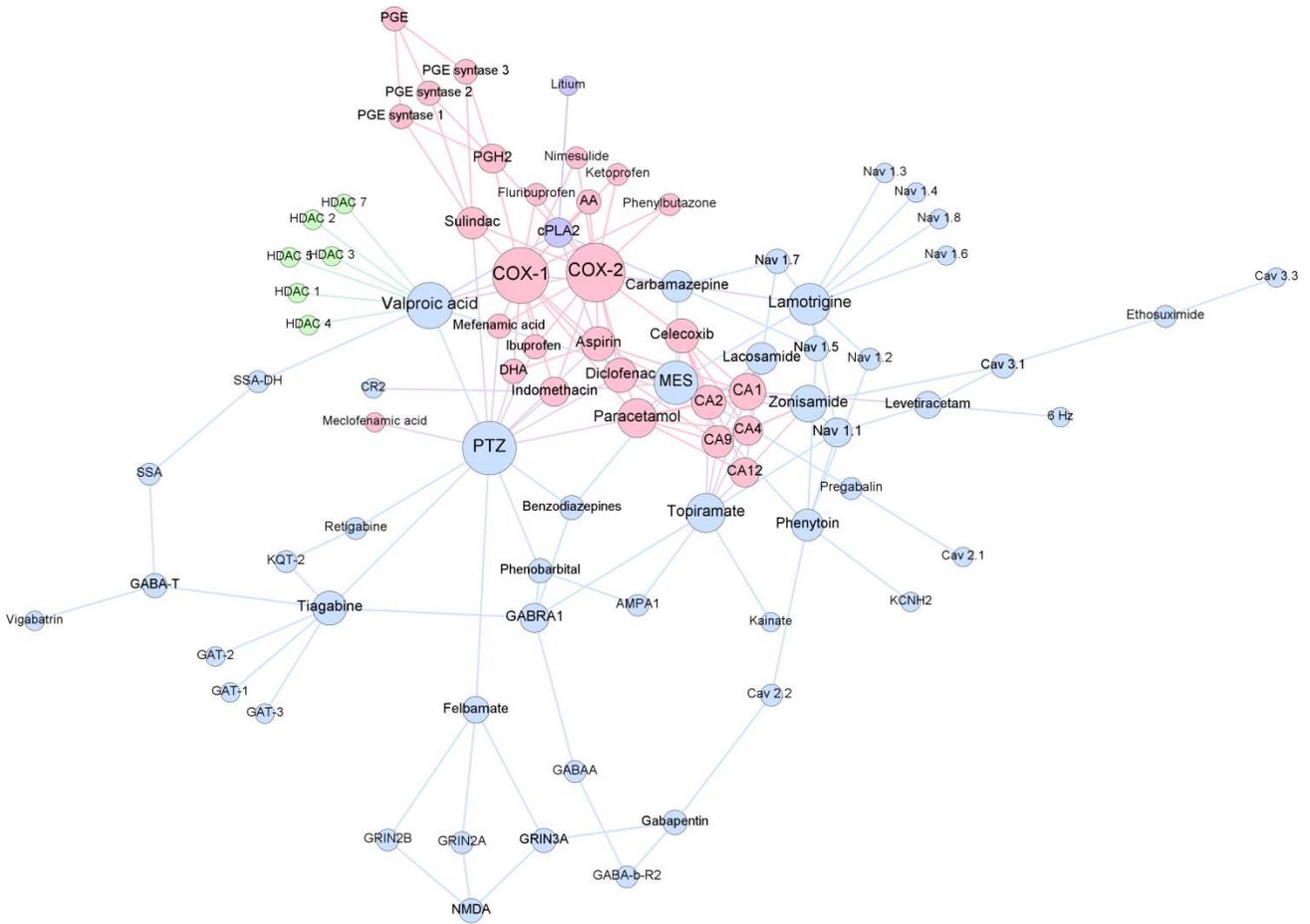
## Introduction

Two decades ago, the prevailing paradigm in the drug discovery field proposed the development of maximally selective ligands acting on a single disease target. Selectivity and potency were thus essential aspects to decide whether a drug candidate would progress into further development phases. Such reductionist approach was founded on two notions: a) highly specific drugs would avoid off-target side-effects, thus leading to safer therapeutics and; b) at least some diseases could be adequately treated using a single target intervention (“*one gene, one drug, one disease*” paradigm). However, recent discoveries have challenged the earlier paradigm in favor of a more holistic approach in line with the philosophy of systems biology.

First, most of the approved drugs interact with more than one target<sup>[1]</sup>. Drugs developed or discovered using “black box”, phenotypic screens are in fact, frequently, multi-functional (multi-target) therapies, with more and

more action mechanisms being uncovered each day<sup>[2]</sup>. Second, multi-target drugs usually affect their targets only partially, that is, they present only low affinity interactions with many of their targets<sup>[2]</sup>. Contrary to previous beliefs, low-affinity multifunctional drugs may represent an advantage: weak links may stabilize the systems, buffering changes after system perturbations. Third, due to redundant functions and compensatory mechanisms, phenotypes are robust, i.e. resilient to perturbation<sup>[3]</sup>.

Under this novel perspective, disease can be regarded as a breakdown of the robustness of normal physiological systems and the re-establishment of also robust (and potentially progressive) disease states<sup>[1]</sup>. This modern conception of disease might well sound familiar in the area of epilepsy: acquired epilepsy is typically initiated by a brain insult followed by a silent period during which molecular, biochemical and cellular alterations (including adaptive remodeling of neural circuits) occur in the brain and eventually lead to the recurrent spontaneous seizures



**Figure 1.** Drug-target network considering antiepileptic, anti-inflammatory and mood stabilizer drugs (up) and a zoom in on the interface between antiepileptic and anti-inflammatory agents.

that characterize the chronic condition<sup>[4-6]</sup>. It has been suggested that the degree of neural reorganization during epileptogenesis might be linked to the tractability of chronic disorder<sup>[6, 7]</sup>.

In the light of the observation that redundancy and compensatory mechanisms limit the phenotypic impact of single perturbations to biological systems, disease will more probably manifest whenever multiple perturbations occur simultaneously. Remarkably, those disorders with significant unmet clinical needs are etiologically complex and often involve a combination of environmental and intrinsic factors (e.g. Alzheimer disease, epilepsy, cancer)<sup>[8, 9]</sup>.

There are many good reasons to consider applications of drug-target networks in the field of antiepileptic drug discovery. Inconclusive but persuasive evidence suggests that some refractory patients may achieve seizure remission on poly-pharmacy, with isobolographic studies in animals and clinical experience indicating that combinations of drugs with distinct primary action mechanisms tend to be beneficial<sup>[10-13]</sup>. On the other hand, the normal function of neural networks may be more likely preserved by multiple small adjustments than by a single, strong perturbation, reducing not only the likelihood of central side-effects but also the induction of counter-regulatory processes related to drug resistance<sup>[14]</sup>. Furthermore: many currently used antiepileptic drugs are in fact unintended multi-target agents -from a drug-protein network analysis perspective, antiepileptic agents are highly connected nodes that bridge several targets-<sup>[12, 14]</sup> and much interest has been given to the broader range of therapeutic effects possessed by many antiepileptic drugs<sup>[15, 16]</sup>.

### The potential contribution of drug-target network to epilepsy

Today, scientific information is produced at an unprecedented rate. Before it can be regarded as knowledge (and thus exploited) such information must be organized. Particularly, the ligand-drug and protein-protein interactomes (i.e. the set of molecular interactions) have revealed themselves so complex that they often have to be either summarized or condensed through the use of manageable representations, or explored with the help of computational resources. Networks deal with complexity by simplifying complex systems: system elements are represented as nodes while relationships between nodes are represented as edges<sup>[17]</sup>. In such representation -strongly linked to mathematical Graph Theory- functional and dynamic features of the nodes are often lost and emphasis is given to the connectivity between the nodes, i.e. the topological

architecture of the net.

The general philosophy of network science is then to drive attention to the wood, not the trees. Drug-protein networks have a number of practical applications which goes from rational drug repurposing (finding second medical uses of already known drugs) to prediction of side-effects<sup>[18, 19]</sup>.

Figure 1 shows a partial representation of a *drug-protein-animal model* network focused on antiepileptic drugs; this network is currently under development within our research group. It is intended to guide drug repurposing (either to propose new indications for antiepileptic drugs or to reposition drugs from other therapeutic categories as antiepileptics), and to predict potential safety issues of antiepileptic drug candidates. To the moment, it includes three node types: a) approved drugs; b) drug targets that are either directly or indirectly modulated by such drugs and; c) animal models used in phase I of the NIH's Anticonvulsant Drug Development Program. It is possible, however, to expand the network by including drug candidates under investigation or withdrawn drugs and additional seizure or epilepsy models, in the future. In the figure, the nodes have been distributed in arbitrary modules (distinctively colored according to the original therapeutic indication of the included drugs); identification of topological models through network clustering algorithms blind to the function of individual nodes will be performed once the whole network is completed. In order to illustrate the potential of the network we have isolated the modules that correspond to non-steroidal anti-inflammatory agents (red), antiepileptic drugs (blue) and bipolar disorder therapies (purple). Essentially, two approaches can be used to capture interactions between the nodes<sup>[17]</sup>. The first involves compilation and curation of existing experimental data available in the literature. The second consists of predicting (often with the help of cheminformatic and bioinformatic tools) the interactions. More details on these approaches and a clear illustrative example are presented separately in the next section of the article. Interactions shown in Figure 1 have emerged from curated literature and from the Supertarget database<sup>[20]</sup>. Since all the edges have been established from experimental data, we have weighted them all alike; however, important additional information could be obtained by considering other types of bridges and by incorporating a weighting scheme which reflects either the strength of the interaction (e.g. using inhibition constants as references) or its nature (experimental versus predicted interactions). The sizes of the nodes are proportional to their degrees.

There is solid scientific ground to choose the connection between inflammation and epilepsy to illustrate the potential of the drug-network approach. Contributing factors to epilepsy such as trauma, malignancies and infections are accompanied by different levels of central nervous system inflammation and abundant evidence points to the role of inflammation in epilepsy generation and exacerbation<sup>[21-23]</sup>. Note the profuse connectivity and the presence of hubs (highly connected nodes, here represented as larger nodes) in the interface between antiepileptic and anti-inflammatory agents. The inclusion of nodes representing animal models of seizure (MES, scPTZ and 6 Hz) has been critical to detect the relative abundance of nodes in this region, which reflects the fact that many approved non-steroidal anti-inflammatory drugs have shown either anticonvulsant or proconvulsant effects in both MES and scPTZ tests<sup>[24-29]</sup>. The molecular basis of such effects remains largely unexplored. The inhibition of inflammatory mediators through downregulation and/or inhibition of cytosolic phospholipase A2 (cPLA2) and cyclooxygenase (COX) isoforms (and the consequent reduction of proinflammatory cytokines) by chronic administration of carbamazepine, valproate and lamotrigine have been postulated as mechanisms of actions that may be involved in the effectiveness of these antiepileptic agents on bipolar disorder<sup>[30-32]</sup>; these actions are shared with classical bipolar disorder treatment (lithium) and justify the ongoing clinical trials of aspirin (which decreases pro-inflammatory mediators synthesis and stimulates anti-inflammatory signals) as a treatment for bipolar disorder<sup>[33]</sup>. Another interesting observation is that both antiepileptic and anti-inflammatory agents share actions on different carbonic anhydrase (CA) isoforms. It has been demonstrated that some CA isoforms may play a role in experimental febrile seizure exacerbation<sup>[34]</sup>, while inhibition of CA isozymes is linked to weight loss<sup>[35,36]</sup>. Randomized clinical trials have recently been performed to establish the efficacy of topiramate and zonisamide as anti-obesity treatments<sup>[37,38]</sup>. In late 2012, a combination of topiramate and phentermine gained FDA approval for the treatment of obesity.

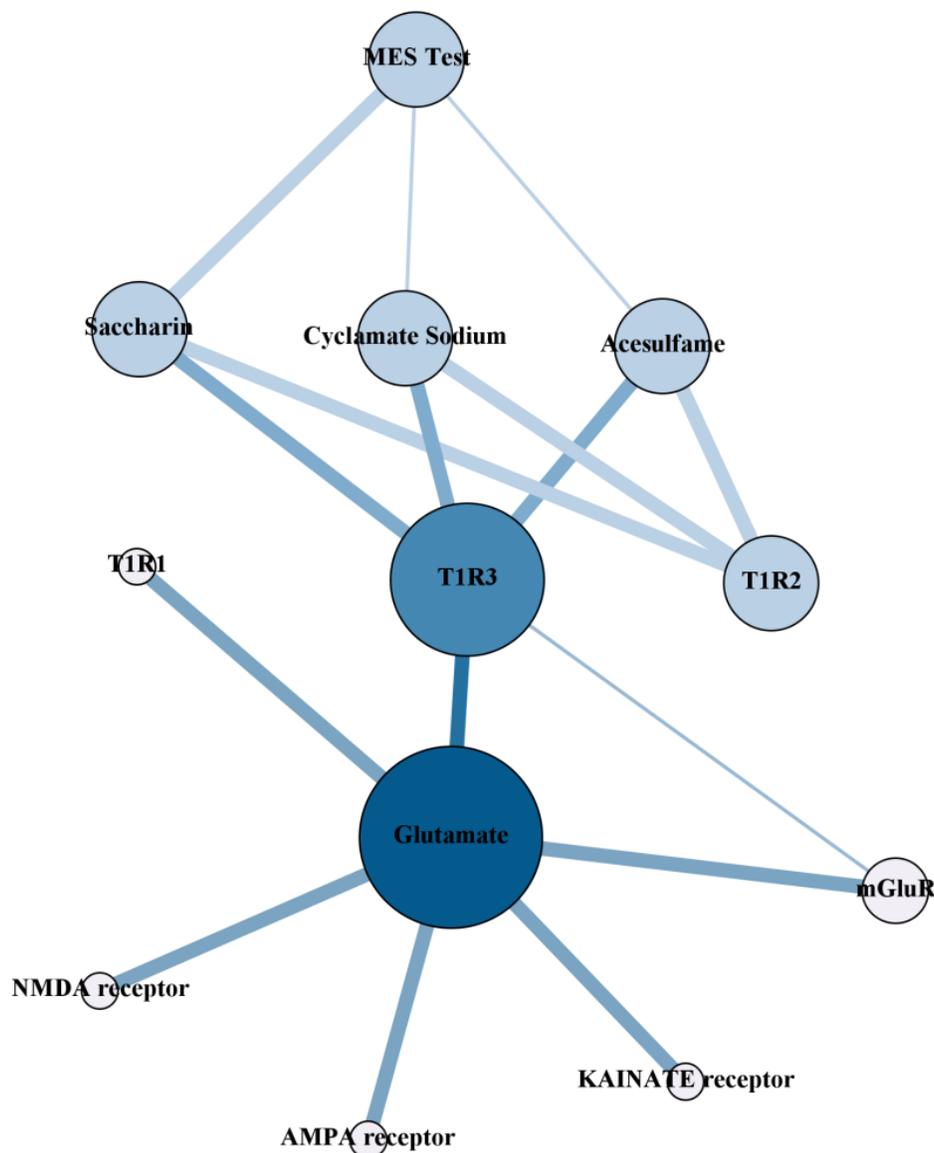
Finding regular links (patterns) between certain therapeutic categories pose relevant questions in the field of drug discovery and drug repositioning. E.g. should in-development anticonvulsant candidates be systematically screened as CA inhibitors or anti-inflammatory agents? In such case, should both acute and chronic models be used? Is it worth screening therapeutics from other categories related to antiepileptic drugs (e.g. anti-obesity

drugs, anti-inflammatory agents) as potential anticonvulsants? As a matter of fact, our group has shown a growing interest in testing our anticonvulsant prototypes as CA inhibitors during the last few years, with encouraging results<sup>[39,40]</sup>.

### **Different approaches to establish links between drugs and targets**

So far, the observations derived from Figure 1 are merely descriptive, since to the moment the network only condensates available experimental data. So... how can network analysis be used to develop new knowledge?

A helpful example to answer this question has recently been presented in the 2012 report from Talevi et al. on anticonvulsant effect of non-nutritive sweeteners<sup>[41]</sup>. A previously reported descriptor-based QSAR model<sup>[42]</sup> predicted that a number of artificial sweeteners (acesulfame, cyclamate, saccharin) might have anticonvulsant effect in the MES test. Subsequent bibliographic revision showed that one of them, saccharin, had already been tested in MES test in 1979 with positive results<sup>[43]</sup>. The model's predictions were later validated experimentally, and both cyclamate and acesulfame showed protective effects in the MES test. The results made us wonder whether a structural link could exist between the sweet taste receptor and one or more molecular targets of antiepileptic drugs. Literature revealed that a family of proteins named T1R is the major mediator of the sweet and umami responses in mammals<sup>[44,45]</sup>. Sweet flavor is elicited by a heterodimer formed by T1R2 and T1R3, while umami flavor is detected by the combination of T1R1 and T1R3. Noteworthy, one of the main stimuli sensed by the umami receptor is no other than glutamate, and response to glutamate flavor is totally abolished in T1r3 KO mice<sup>[46]</sup>. We searched for similar sequences to T1R3 in the NCBI non-redundant protein database, in order to investigate the possible link between T1R3 and molecular targets of antiepileptic drugs. BLAST showed that several of the significantly aligned sequences corresponded to metabotropic glutamate receptors (mGlu) from different species, among them rat, mouse and human. Interestingly, subtypes of mGlu that were retrieved in the BLAST search (mGluR1 and mGluR5) are upregulated in epileptogenesis and kindling models of epilepsy, and in patients with complex partial seizures<sup>[47-49]</sup>. They are also linked to augmented activity of NMDA receptors, release of arachidonic acid, excitotoxicity and neuronal injury<sup>[50-51]</sup>. A synthesis of the previous analysis is depicted in the network of Figure 2. The relationships that had been experimentally



**Figure 2.** The thick lines in the network illustrate experimentally corroborated links; the thin lines correspond to cheminformatic (cyclamate-MES test, acesulfame-MES test) and bioinformatic (T1R3-mGluR) predictions. The first two predictions were later validated experimentally.

established previously to the report from Talevi et al. are presented as thick edges, while the associations that were predicted with computational (cheminformatic, bioinformatic) tools are presented as thin edges.

The previous example integrates the three general strategies to establish unknown (non-experimental) interactions between network nodes: a) cheminformatic predictions (e.g. predictions from automatic machine learning algorithms, molecular docking or molecular similarity searches); b) bioinformatic predictions (e.g. sequence alignment, functional relationships established from gene-order conservation, and others) and; c) literature analysis. This later approach relies on Swanson's ABC model. Briefly, Swanson's ABC model describes the possibility of linking different scientific disciplines through intermediate (shared) concepts<sup>[52]</sup>. Consider three separate scientific concepts A, B and C,

where A is reported to be linked to B in one set of publications and B is reported to be related to C in other, while A is not reported to be directly associated to C. The relationships A-B and B-C allow inferring that A may be indirectly related to C. The unknown A-B-C relation may constitute a new finding. A practical and elegant example of the application of Swanson's ABC model in the field of network-based drug discovery is presented in ref. [18], where the importance of a predicted relationship between two nodes depends on the shared node count and the shared node weight, and this shared node weight depends, in turn, of the connection probability.

## Conclusions

Due to the multifactorial nature of epilepsy, and having in mind that most antiepileptic drugs are in fact multi-target (multifunctional) agents, it is highly probable

that drug-protein analysis will provide exciting advances in the field of antiepileptic drug discovery. Many antiepileptic drugs have already gained approval for other therapeutic indications, which suggests that development and analysis of drug-protein networks focused on antiepileptic drugs may reveal or reinforce connections between antiepileptic drugs and members of other therapeutic categories. Such knowledge might be useful to guide systematic screening of second or further medical applications of antiepileptic drugs and screening of drugs from other categories in seizure and/or epilepsy models. Prediction or explanation of side effects to antiepileptic drugs may also emerge from network analysis.

### Conflict of interest

The authors declare no conflict of interest related to this article.

### Acknowledgement

M. E. Di Ianni, is a National Council of Scientific and Technical Research (CONICET) fellowship holder. A. Talevi is a member of the Scientific Research Career at CONICET. A. Talevi thanks the National Agency of Scientific and Technological Promotion (ANPCyT) for the PICT 2010-2531 grant.

### References

1. Yildirim MA, Goh KI, Cusick ME, László B, Vidal M. Drug-target network. *Nat Biotechnol* 2007; 25: 1119-1126. <http://dx.doi.org/10.1038/nbt1338> PMID:17921997
2. Mencher SK, Wang LG. Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). *BMC Clin Pharmacol* 2005; 5: 3. <http://dx.doi.org/10.1186/1471-2210-5-3> <http://dx.doi.org/10.1186/1472-6904-5-3> PMID:15854222 PMCID:PMC1090568
3. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 2008; 11: 682-690. <http://dx.doi.org/10.1038/nchembio.118> PMID:18936753
4. Löscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: experimental Approaches and translational Research. *Pharmacol Rev* 2010; 62: 668-700. <http://dx.doi.org/10.1124/pr.110.003046> PMID:21079040 PMCID:PMC3014230
5. Waldaum S, Patel M. Mitochondrial dysfunction and oxidative stress: a contributing link to acquired epilepsy? *J Bioenerg Biomembr* 2010; 42:449–55. <http://dx.doi.org/10.1007/s10863-010-9320-9> PMID:21132357 PMCID:PMC3102435
6. Fang M, Xi ZQ, Wu Y, Wang XF. A new hypothesis of drug refractory epilepsy: neural network hypothesis. *Med Hypotheses* 2011; 76: 871-876. <http://dx.doi.org/10.1016/j.mehy.2011.02.039> PMID:21429675
7. Talevi A, Bruno-Blanch LE. On the development of new antiepileptic drugs for the treatment of pharmacoresistant epilepsy: different approaches to different hypothesis. In *Pharmacoresistance in Epilepsy. From Genes and Molecules to Promising Therapies*, Edited by Rocha L & Cavalheiro EA, New York: Springer; 2013: 207-224. [http://dx.doi.org/10.1007/978-1-4614-6464-8\\_14](http://dx.doi.org/10.1007/978-1-4614-6464-8_14)
8. Talevi A, Bellera CL, Di Ianni M, Gantner M, Bruno-Blanch LE, Castro EA. CNS drug development – Lost in translation? *Mini Rev Med Chem* 2012; 12: 959-970. <http://dx.doi.org/10.2174/138955712802762356> PMID:22420574
9. Filmore, D.; Thayer, A. M.; Willis, R. C. Pipeline challenges. Major pharmaceutical and biotechnology companies take a variety of approaches to remain productive. *Modern Drug Discov* 2004;7: 28-34.
10. Brodie MJ, Covanis A, Gil-Nagel A, Lerche H, Perucca E, Sills GJ et al. Antiepileptic drug therapy: Does mechanism of action matter? *Epilepsy Behav* 2011; 21: 331-341. <http://dx.doi.org/10.1016/j.yebeh.2011.05.025> <http://dx.doi.org/10.1016/j.yebeh.2011.04.053>
11. Kwan P, Brodie MJ. Combination therapy in epilepsy: when and what to use. *Drugs* 2006; 66: 1817-1829. <http://dx.doi.org/10.2165/00003495-200666140-00004>
12. Lee JW, Dworetzky B. Rational polytherapy with antiepileptic drugs. *Pharmaceuticals* 2010; 3: 2362-2379. <http://dx.doi.org/10.3390/ph3082362>
13. Kaminski RM, Matagne A, Patsalos PN, Klitgaard H. Benefit of combination therapy in epilepsy: a review of the preclinical evidence with levetiracetam. *Epilepsia* 2009; 50: 387-397. <http://dx.doi.org/10.1111/j.1528-1167.2008.01713.x> PMID:18627416
14. Bianchi MT, Pathmanathan J, Cash SS. From ion channels to complex networks: magic bullet versus magic shotgun approaches to anticonvulsant pharmacotherapy. *Med Hypotheses* 2009;72: 297–305. <http://dx.doi.org/10.1016/j.mehy.2008.09.049> PMID:19046822
15. Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia* 2012; 53 (Suppl 7): 26-33. <http://dx.doi.org/10.1111/j.1528-1167.2012.03712.x> PMID:23153207

16. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nat. Med.* 2004; 10: 685-692.  
<http://dx.doi.org/10.1038/nm1074>  
PMid:15229516
17. Vidal M, Cusick ME, Barabási, AL. Interactome network and human disease. *Cell* 2011; 144: 987-998.  
<http://dx.doi.org/10.1016/j.cell.2011.02.016>  
PMid:21414488 PMCID:PMC3102045
18. Lee HS, Bae T, Lee JH, Kim DG, Oh Y, Jang Y et al. Rational drug repositioning guided by an integrated pharmacological network of protein, disease and drug. *BMC Syst Biol* 2012; 6: 80.  
<http://dx.doi.org/10.1186/1752-0509-6-80>  
PMid:22748168 PMCID:PMC3443412
19. Mizutani S, Pauwels E, Stoven V, Goto S, Yamanishi Y. Relating drug-protein interaction network with drug side effects. *Bioinformatics* 2012; 28: i522-i528.  
<http://dx.doi.org/10.1093/bioinformatics/bts383>  
PMid:22962476 PMCID:PMC3436810
20. Günther S, Kuhn M, Dunkel M, Campillos M, Senger C, Petsalaki E et al. SuperTarget and Matador: resources for exploring drug-target relationships. *Nucleic Acids Res* 2008; 36: D919-D922.  
<http://dx.doi.org/10.1093/nar/gkm862>  
PMid:17942422 PMCID:PMC2238858
21. Lorigados Pedre L, Morales Chacón LM, Orozco-Suárez S, Rocha L. Pharmacoresistant epilepsy and immune system. From Genes and Molecules to Promising Therapies, Edited by Rocha L & Cavalheiro EA, New York: Springer; 2013: 149-168.
22. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nat Rev Neurol* 2011; 7: 31-40.  
<http://dx.doi.org/10.1038/nrneurol.2010.178>  
PMid:21135885 PMCID:PMC3378051
23. Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. *Epilepsia* 2005; 46: 1724-1743.  
<http://dx.doi.org/10.1111/j.1528-1167.2005.00298.x>  
PMid:16302852
24. Wali RS, Patil PA. Aspirin and anticonvulsant interaction. *Indian J Physiol Pharmacol* 1995; 39: 77-79.  
PMid:7705877
25. Wallenstein MC, Mauss EA. Effect of prostaglandin synthetase inhibitors on experimentally induced convulsion in rats. *Pharmacology* 1984; 29: 85-93.  
<http://dx.doi.org/10.1159/000137996>
26. Shafiq N, Malhotra S, Pandhi P. Anticonvulsant action of celecoxib (alone and in combination with sub-threshold dose of phenytoin) in electroshock induced convulsion. *Methods Find Exp Clin Pharmacol* 2003; 25: 87-90.  
<http://dx.doi.org/10.1358/mf.2003.25.2.723681>  
PMid:12731453
27. Srivastava AK, Gupta YK. Aspirin modulates the anticonvulsant effect of diazepam and sodium valproate in pentylenetetrazole and maximal electroshock induced seizures in mice. *Indian J Physiol Pharmacol* 2001; 45: 475-480.  
PMid:11883156
28. Tayal V, Singh Kalra B, Chawla S. Effect of celecoxib on anticonvulsant activity of carbamazepine against maximal electroshock-induced convulsions in mice. *Methods Find Exp Clin Pharmacol* 2008; 30: 727-730.  
<http://dx.doi.org/10.1358/mf.2008.30.10.1316829>  
PMid:19271020
29. Dhir A, Naidu PS, Kulkarni SK. Effect of cyclooxygenase inhibitors on pentylenetetrazol (PTZ)-induced convulsions: possible mechanism of action. *Prog Neuro-Psycoph* 2006; 30: 1478-1485.  
<http://dx.doi.org/10.1016/j.pnpbp.2006.06.003>  
PMid:16844276
30. Gherlardini S, Tomita YA, Bell JM, Rapaport SI, Bosetti F. Chronic carbamazepine selectively downregulates cytosolic phospholipase A2 expression and cyclooxygenase activity in rat brain. *Biol Psychiatry* 2004; 56: 248-254.  
<http://dx.doi.org/10.1016/j.biopsych.2004.05.012>  
PMid:15312812
31. Bosetti F, Weerasinghe GR, Rosenberger TA, Rapaport SI. Valproic acid down-regulates the conversion of arachidonic acid to eicosanoids via cyclooxygenase-1 and -2 in rat brain. *J Neurochem* 2003; 85: 690-696.  
<http://dx.doi.org/10.1046/j.1471-4159.2003.01701.x>  
PMid:12694395
32. Rapaport SI, Basselin M, Kim HW, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. *Brain Res Rev* 2009; 61: 185-209.  
<http://dx.doi.org/10.1016/j.brainresrev.2009.06.003>  
PMid:19555719 PMCID:PMC2757443
33. Savitz J, Preskorn S, Teague TK, Devrets D, Yates W, Devrets W. Bipolar disorder and mechanisms of action of mood stabilizers. *BMJ Open* 2012; 2: e000643.  
PMid:22357572 PMCID:PMC3289990
34. Ruusuvaari E, Huebner AK, Kirilkin I, Yukin AY, Blaesse P, Helmy M et al. Neuronal carbonic anhydrase VII provides GABAergic excitatory drive to exacerbate febrile seizures. *EMBO J* 2013; 32: 2275-2286.  
<http://dx.doi.org/10.1038/emboj.2013.160>  
PMid:23881097 PMCID:PMC3746197
35. De Simone G, Supuran CT. Antiobesity carbonic anhydrase inhibitors. *Curr Top Med Chem* 2007; 7: 879-884.  
<http://dx.doi.org/10.2174/156802607780636762>
36. Supuran CT. Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity. *Expert Opin Emerg Dr* 2012; 17: 11-15.  
<http://dx.doi.org/10.1517/14728214.2012.664132>

PMid:22335448

37. Gadde KM, Kopping MF, Wagner HR 2nd, Yonish GM, Allison DB, Bray GA. Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med* 2012; 172: 1557-1564.

<http://dx.doi.org/10.1001/2013.jamainternmed.99>

PMid:23147455 PMCID:PMC3753218

38. Shin JH, Gadde KM. Clinical utility of phentermine/topiramate (Qsymia™) combination for the treatment of obesity. *Diabetes Metab Syndr Obes* 2013; 6: 131-139.

PMid:23630428 PMCID:PMC3626409

39. Gavernet L, Gonzalez Funes JL, Palestro PH, Bruno-Blanch LE, Esti ú GL, Maresca A et al. Inhibition pattern of sulfamide-related compounds in binding to carbonic anhydrase isoforms I, II, VII, XII and XIV. *Bioorg Med Chem* 2013; 21: 1410-1418.

<http://dx.doi.org/10.1016/j.bmc.2012.10.048>

PMid:23266178

40. Gavernet L, Gonzalez Funes JL, Bruno-Blanch L, Esti ú G, Maresca A, Supuran CT. Affinity of sulfamates and sulfamides to carbonic anhydrase II isoform: experimental and molecular modeling approaches. *J Chem Inf Model* 2010; 50: 1113-1122.

<http://dx.doi.org/10.1021/ci100112s>

PMid:20481572

41. Talevi A, Enrique AV, Bruno-Blanch LE. Anticonvulsant activity of artificial sweeteners: a structural link between sweet-taste receptor T1R3 and brain glutamate receptors. *Bioorg Med Chem Lett* 2012; 22: 4072-4074.

<http://dx.doi.org/10.1016/j.bmcl.2012.04.076>

PMid:22579423

42. Talevi A, Bellera, Bellera CL, Castro EA, Bruno-Blanch LE. A successful virtual screening application: prediction of anticonvulsant activity in the MES test of widely use pharmaceutical and food preservatives methylparaben and propylparaben. *J Comput Aided Mol Des* 2007; 21: 527-538.

<http://dx.doi.org/10.1007/s10822-007-9136-9>

PMid:17960329

43. Shkulev VA, Aboyan LS, Dzhagatspanyan IA, Akopyan NE, Mndzhoyan OL. Saccharin derivatives. *Pharm Chem J* 1979; 13: 144-147.

<http://dx.doi.org/10.1007/BF00780526>

44. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJP, Zuker CS. Mammalian sweet taste receptors. *Cell* 2001; 106: 381-390.

[http://dx.doi.org/10.1016/S0092-8674\(01\)00451-2](http://dx.doi.org/10.1016/S0092-8674(01)00451-2)

45. Chen QY, Alarcon S, Tharp A, Ahmed OM, Estrella NL, Greene TA et al. Perceptual variation in umami taste and polymorphism in TAS1R taste receptor genes. *Am J Clin Nutr* 2009; 90: 770S-779S.

<http://dx.doi.org/10.3945/ajcn.2009.27462N>

PMid:19587085 PMCID:PMC3136006

46. Lemon CH, Margolskee RF. Contribution of the T1r3 taste receptor to the response properties of central gustatory neurons. *J Neurophysiol* 2009; 101: 2459-2471.

<http://dx.doi.org/10.1152/jn.90892.2008>

PMid:19279151 PMCID:PMC2681431

47. Akiyama K, Daigen A, Yamada N, Itoh Y, Kohira I, Ujike H et al. Long-lasting enhancement of metabotropic excitatory amino acid receptor-mediated polyphosphoinositide hydrolysis in the amygdala/pyriform cortex of deep prepiriform cortical kindled rats. *Brain Res* 1992; 569: 71-77.

[http://dx.doi.org/10.1016/0006-8993\(92\)90370-O](http://dx.doi.org/10.1016/0006-8993(92)90370-O)

48. Keele NB, Zinebi F, Neugebauer V, Shinnick-Gallaher P. Epileptogenesis up-regulates metabotropic glutamate receptor activation of sodium-calcium exchange current in the amygdala. *J Neurophysiol* 2000; 83: 2458-2462.

PMid:10758147

49. Notenboon RG, Hampson DR, Jansen GH, van Rijen PC, van Veelen CW, van Nieuwenhuizen O et al. Up-regulation of hippocampal metabotropic glutamate receptor 5 in temporal lobe epilepsy patients. *Brain* 2006; 129: 96-107.

<http://dx.doi.org/10.1093/brain/awh673>

PMid:16311265

50. Skeberdis VA, Lan J, Opitz T, Zheng X, Bennett MV, Zukin RS. mGluR1-mediated potentiation of NMDA receptors involves a rise in intracellular calcium and activation of protein kinase C. *Neuropharmacology* 2001; 40: 856-865.

[http://dx.doi.org/10.1016/S0028-3908\(01\)00005-3](http://dx.doi.org/10.1016/S0028-3908(01)00005-3)

51. Lea PM, Custer SJ, Vicini S, Faden AI. Neuronal and glial mGluR5 modulation prevents stretch-induced enhancement of NMDA receptor current. *Pharmacol Biochem Behav* 2002; 73: 287-298.

[http://dx.doi.org/10.1016/S0091-3057\(02\)00825-0](http://dx.doi.org/10.1016/S0091-3057(02)00825-0)

52. Allen JW, Vicini S, Faden A. Exacerbation of neuronal cell death by activation of group I metabotropic glutamate receptors: role of NMDA receptors and arachidonic acid release. *Exp Neurol* 2001; 169: 449-460.

<http://dx.doi.org/10.1006/exnr.2001.7672>

PMid:11358458

53. Deftereos SN, Andronis C, Friedla EJ, Persidis A, Persidis A. Drug repurposing and adverse event prediction using high-throughput literature analysis. *WIREs Syst Biol Med* 2011; 3: 323-334.

<http://dx.doi.org/10.1002/wsbm.147>

PMid:21416632

**To cite this article:** Di Ianni M, Talevi A. How Can Network-Pharmacology Contribute to Antiepileptic Drug Development? *Mol Cell Epilepsy* 2014; 1: e30. doi: 10.14800/mce.30.