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Drug Repurposing: New Uses for Old Drugs or Systems Biomedicine?

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University of Strasbourg, 27 June - 1 July 2016

THE 5TH ANNUAL

Drug Repositioning, Repurposing and Rescue Conference

Arrowhead PUBLISHERS | CONFERENCES

Chicago, Illinois USA
June 21-22, 2016

Featured Speakers

Matthew DeSilva, CEO, **Notable Labs**

Daphna Laifenfeld, Ph.D., Director, Personalized and Predictive Medicine and Big Data Analytics, **Teva Pharmaceuticals**

Aytekin Oto, MD, Professor of Radiology, Section Chief, Abdominal Imaging, Chief of Body MRI, **The University of Chicago**

Larry Sklar, Ph.D., The Maralyn S. Budke and Robert E. Anderson Distinguished Endowed Chair in Cancer Drug Discovery, Director, UNM Center for Molecular Discovery, **The University of New Mexico School of Medicine**

Marty St. Clair, Ph.D., Clinical Virology, **ViiV Healthcare**

About the Conference

Join us in Chicago, where we will highlight the latest developments in the fields of drug repositioning, repurposing and rescue. This conference continues to serve as a global meeting place for those engaged in efforts to further drug development through new means of collaborations, including patient advocacy efforts and industry/academic /government cooperation.

Key Themes at This Year's Conference

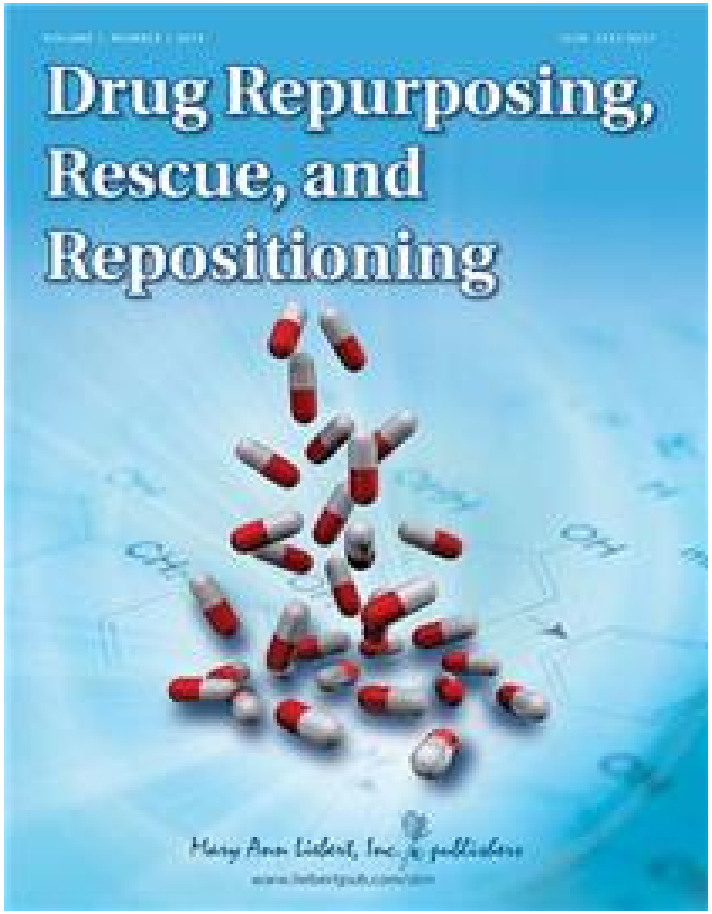
PATIENT ADVOCACY EFFORTS
Emphasis on and engagement with patient advocacy groups, who are investing in drug repositioning efforts to an unprecedented degree

NEW PARTNERSHIPS
The conference will explore how new partnerships between various groups, including government, industry and academia are teaming up to advance repurposing efforts

COMMERCIAL CASE STUDIES
Leaders in drug repositioning will discuss their successes, failures and the way forward

COLLABORATIVE EFFORTS
Government/Academic/Industry Collaborations will be explored and highlighted in order to determine how

http://www.drugrepositioningconference.com/index/



A New Journal for the Drug Repurposing Community

Hermann A.M. Mucke, PhD

European Editor, Drug Repurposing, Rescue, and Repositioning.
H.M. Pharma Consultancy, Wien, Austria.

Dear reader:

What you are holding in your hand—or what you are looking at on your screen—is the premier issue of the first journal that is exclusively dedicated to new medical uses of known pharmaceutically active compounds: *Drug Repurposing, Rescue, and Repositioning.*

So, another peer-reviewed journal for the medical sciences. Why should this be necessary? Hundreds exist already.

INTERDISCIPLINARY BROADNESS DEMANDS HIGH-LEVEL INTEGRATION

To be sure, it is not as if there were no proper opportunities to publish quality articles addressing drug repurposing. Pertinent articles appear in life sciences journals that specialize in medicinal chemistry, systems biology, molecular modeling, has been missing until now. The product you are looking at is the first coordinated and well-supported attempt to remedy this.

OPTIMAL RESOURCE UTILIZATION IS NOT RECYCLING

Several common myths need to be dispelled before experts from so many diverse fields can collaborate with maximum efficacy. Number one is that drug repurposing, rescue, and repositioning is an inherently defensive concept, promoted by pharmaceutical companies to recoup at least part of their investments in the development of their failed late-stage drug candidates, or in drugs that had to be removed from the market for safety reasons. While such things do happen, this is only the "*rescue*" part of the story—and probably the least significant one in economic terms.

Nor is the *repositioning* of marketed drugs something as simple as what business developers call a line extension—such as expanding the approval of a cancer drug to include additional tumor types. Rather, drug repositioning implies the use in a different disease class, and while this often exploits

http://www.liebertpub.com/overview/drug-repurposing-rescue-brand-repositioning/627/

DRUG REPURPOSING NEWS

Astellas continues IT-enabled Drug Repurposing Deal Drive with Excelra hook-up

June 10th 2016, Posted By: Drug Repurposing Portal

Astellas Pharma has struck its third drug repurposing agreement of the past 6 months. The latest collaboration sees Astellas start working with Excelra, an Indian informatics company that has landed 8 similar deals on the strength of its drug repurposing database and accompanying algorithms. For Excelra, the deal with Astellas marks an advance in its attempts to establish itself as a standalone business.

News | Methods | Funding | Collaborations

http://drugrepurposingportal.com/drug-repurposing-news.php

Why DRP? - Society point of view.

Several benefits could arise from repurposing of the launched drugs, such as:

- **finding new therapies for unmet medical needs;**
- **finding more efficacious therapies;**
- **replacing expensive with inexpensive drugs;**
- **substituting safer drugs for drugs with unwanted effects.**

National Comprehensive Cancer Network (NCCN) estimated that 50-75% of drugs have been used through off-label prescription in USA (Drug Discovery Today, 2014, 19: 637-644).

National Center for Advancing Translational Sciences (NCATS, NIH) has invested $575 million budget on drug rescuing and repurposing.

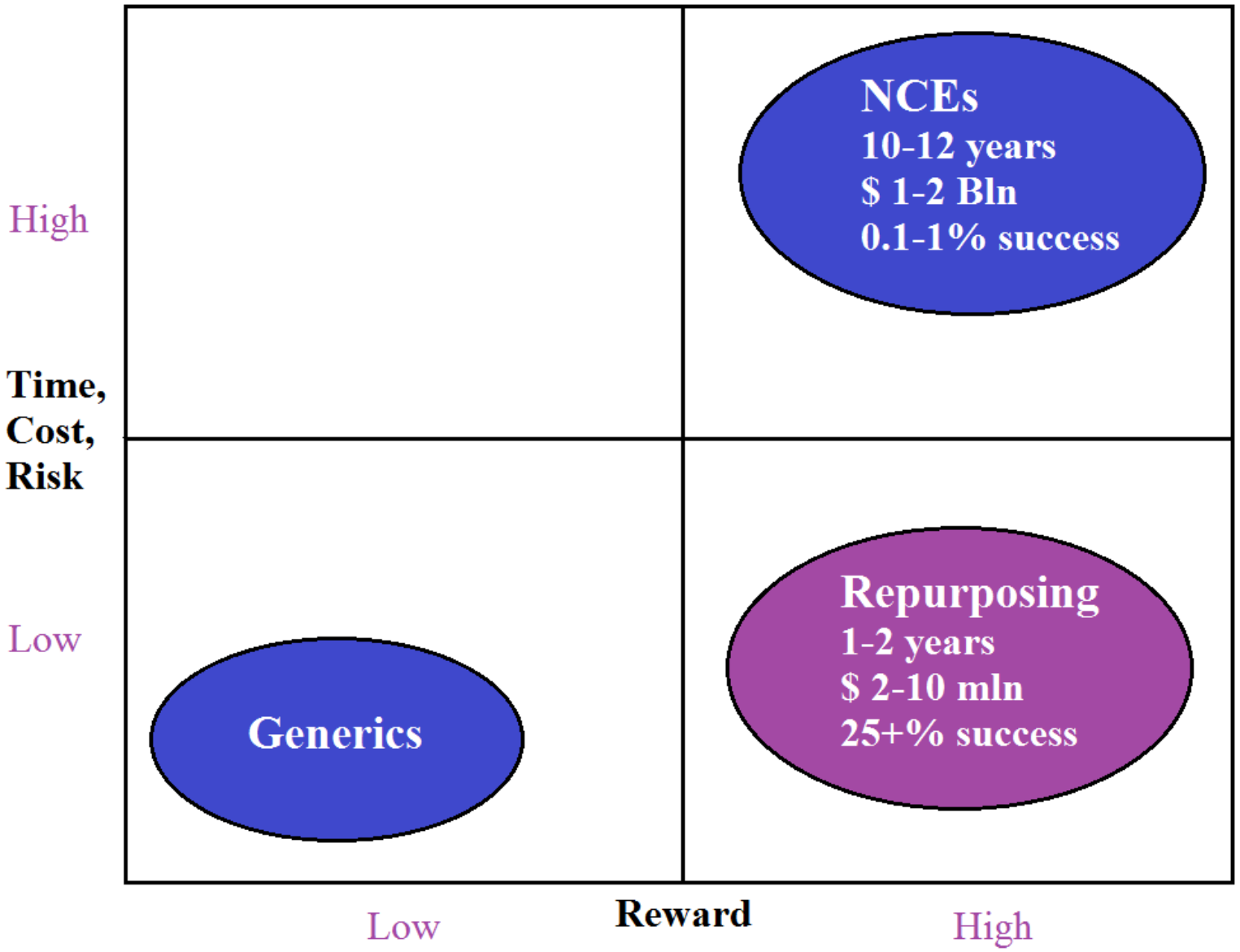
Center for World Health & Medicine (CWHM, NIH) has initiated to provide a screening platform for identification of drugs for rare/neglected diseases (Sci. Translat. Med., 2011, 3: 80ps16).

Why DRP? - Industry point of view.

- **Successfully repositioned drugs enter the market 3-5 years faster than a conventionally developed drug and as a consequence generate income sooner.**
- **Success rates for repurposed drugs are higher and costs are lower than *de novo* R&D.**
- **It is estimated that over 2,000 failed drugs are sitting on companies shelves and that this number grows at the rate of 150-200 drugs per year.**
- **The science to evaluate new diseases continues to evolve so that science led repurposing (rather than random screening) is a viable business model.**
- **Repositioning is expected to generate up to $20 billion in annual sales in 2012.**

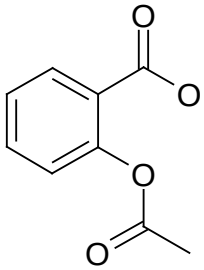
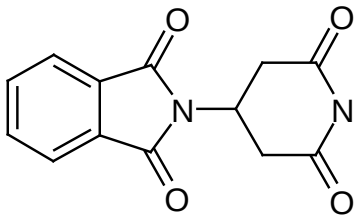
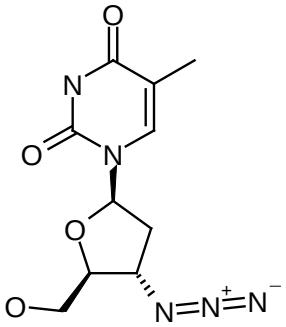
Thomson Reuters

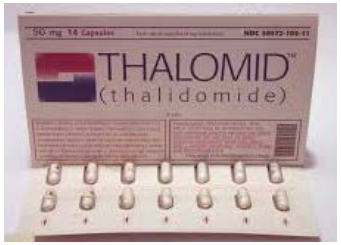
DRP: Time/Cost/Risk values

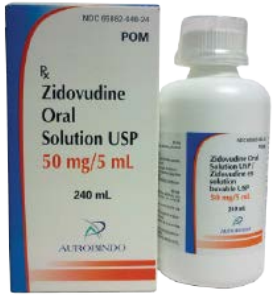


Ashburn T.T. and Thor K.B., 2004; Cavalla D., 2009; Flower D.R., 2013; Naylor S. and Schonfeld J.M., 2014.

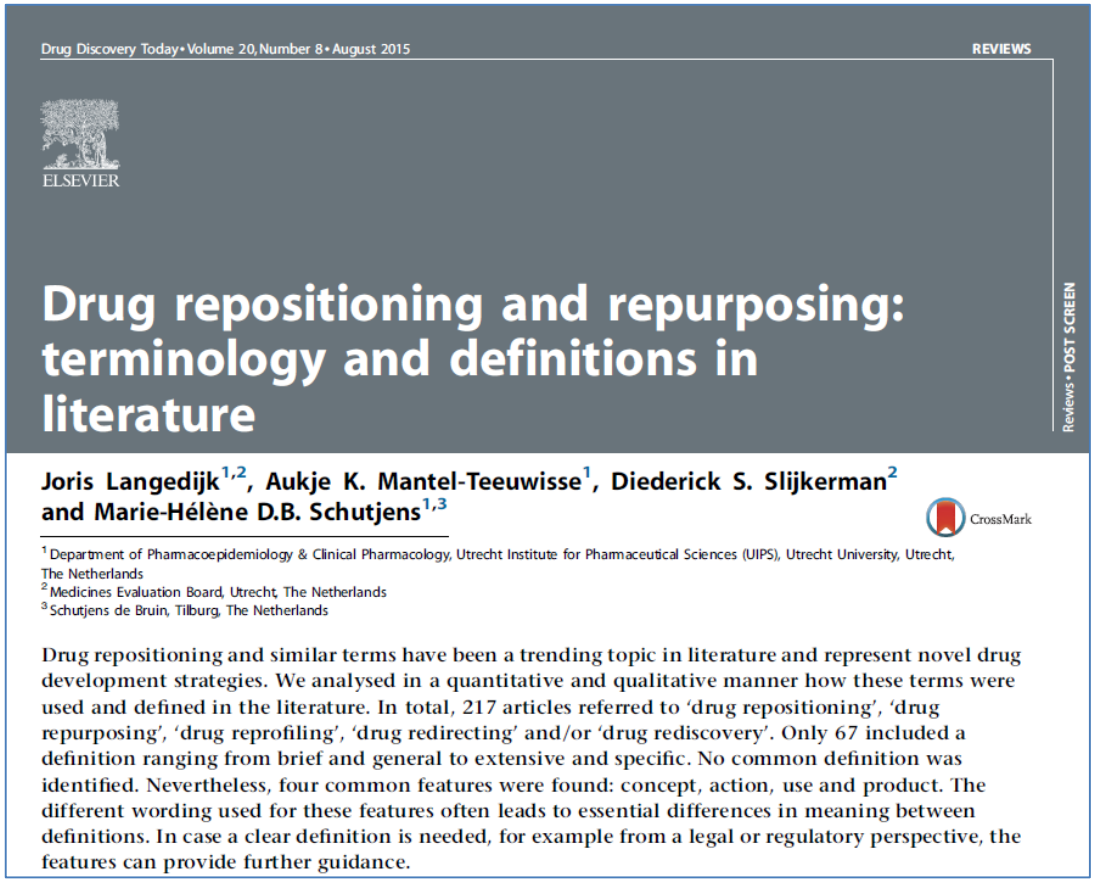
Some examples of drug repurposing

Drug	Primary indication (year)	Repurposed indication (year)
 Acetylsalicylic acid	NSAID (1897)	Antithrombotic (1956)
 Thalidomide	Sedative (1957)	Antileprosy (1998), Antitumor (2006)
 Zidovudine	Cancer (1964)	HIV/AIDS (1987)





Drug repurposing (DRP): terminology and definitions



Drug Discovery Today • Volume 20, Number 8 • August 2015 REVIEWS

ELSEVIER

Drug repositioning and repurposing: terminology and definitions in literature

Reviews • POST SCREEN

Joris Langedijk[1,2], Aukje K. Mantel-Teeuwisse[1], Diederick S. Slijkerman[2] and Marie-Hélène D.B. Schutjens[1,3]

[1] Department of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
[2] Medicines Evaluation Board, Utrecht, The Netherlands
[3] Schutjens de Bruin, Tilburg, The Netherlands

Drug repositioning and similar terms have been a trending topic in literature and represent novel drug development strategies. We analysed in a quantitative and qualitative manner how these terms were used and defined in the literature. In total, 217 articles referred to 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' and/or 'drug rediscovery'. Only 67 included a definition ranging from brief and general to extensive and specific. No common definition was identified. Nevertheless, four common features were found: concept, action, use and product. The different wording used for these features often leads to essential differences in meaning between definitions. In case a clear definition is needed, for example from a legal or regulatory perspective, the features can provide further guidance.

Drug repositioning

OR

Drug repurposing

OR

Drug reprofiling

OR

Drug redirecting

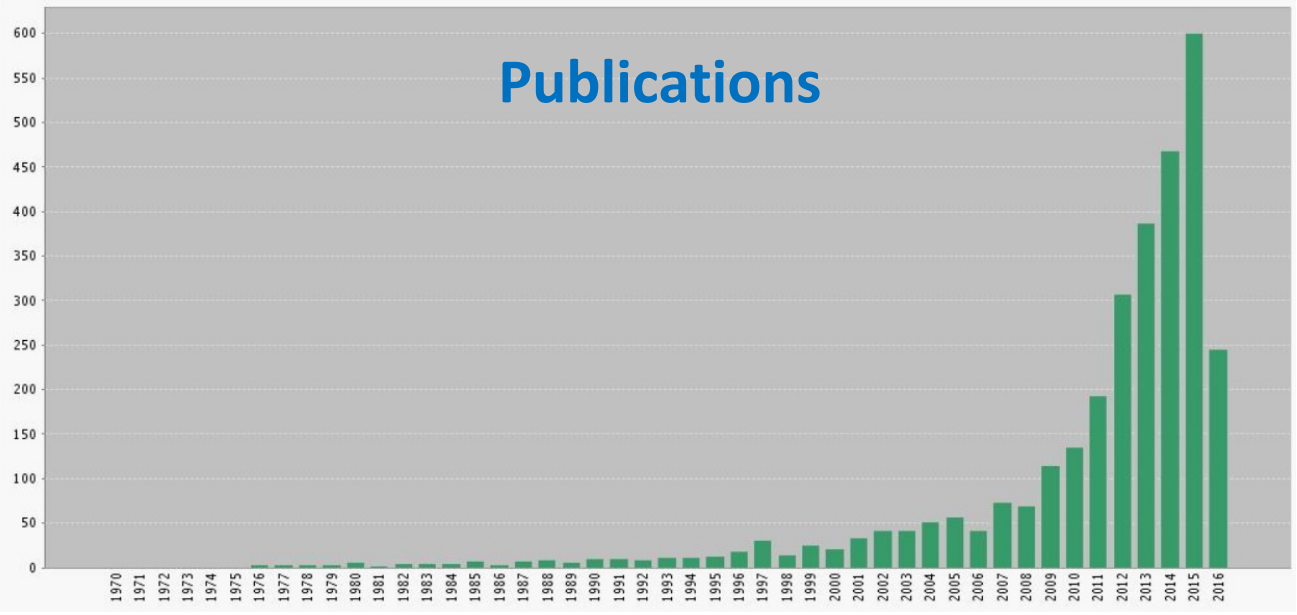
OR

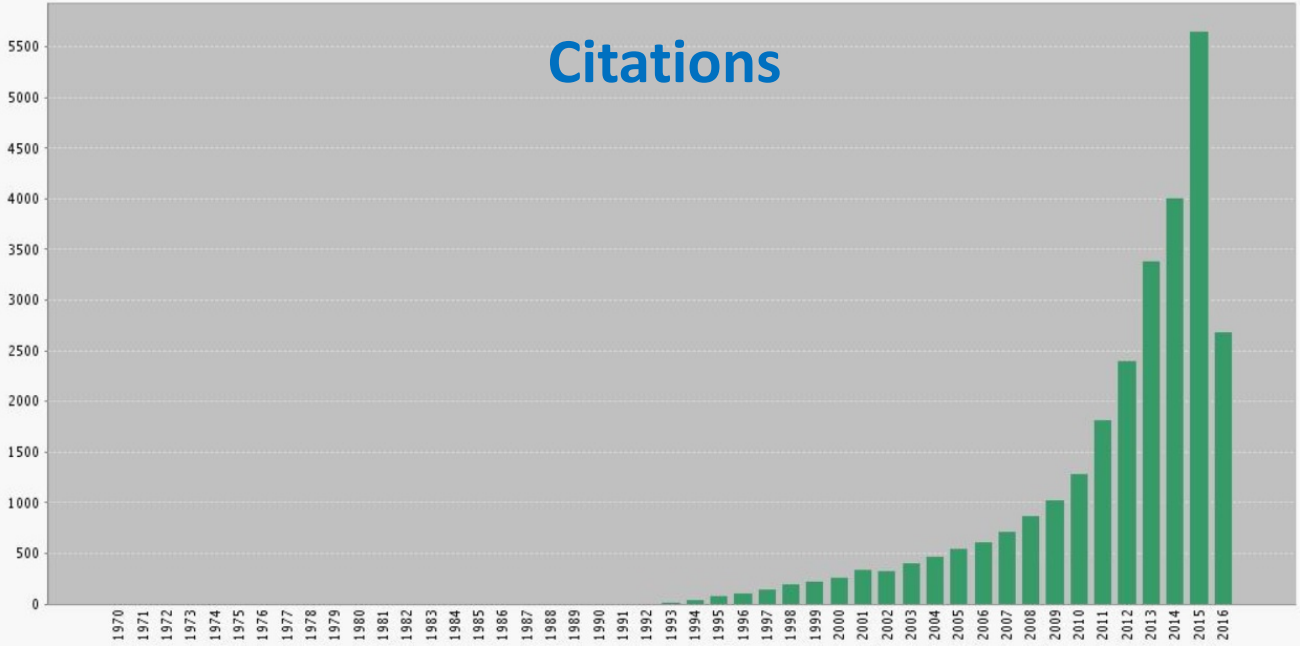
Drug rediscovery

No common definition was identified. Nevertheless, four common features were found: concept, action, use and product. The different wording used for these features often leads to essential differences in meaning between definitions.

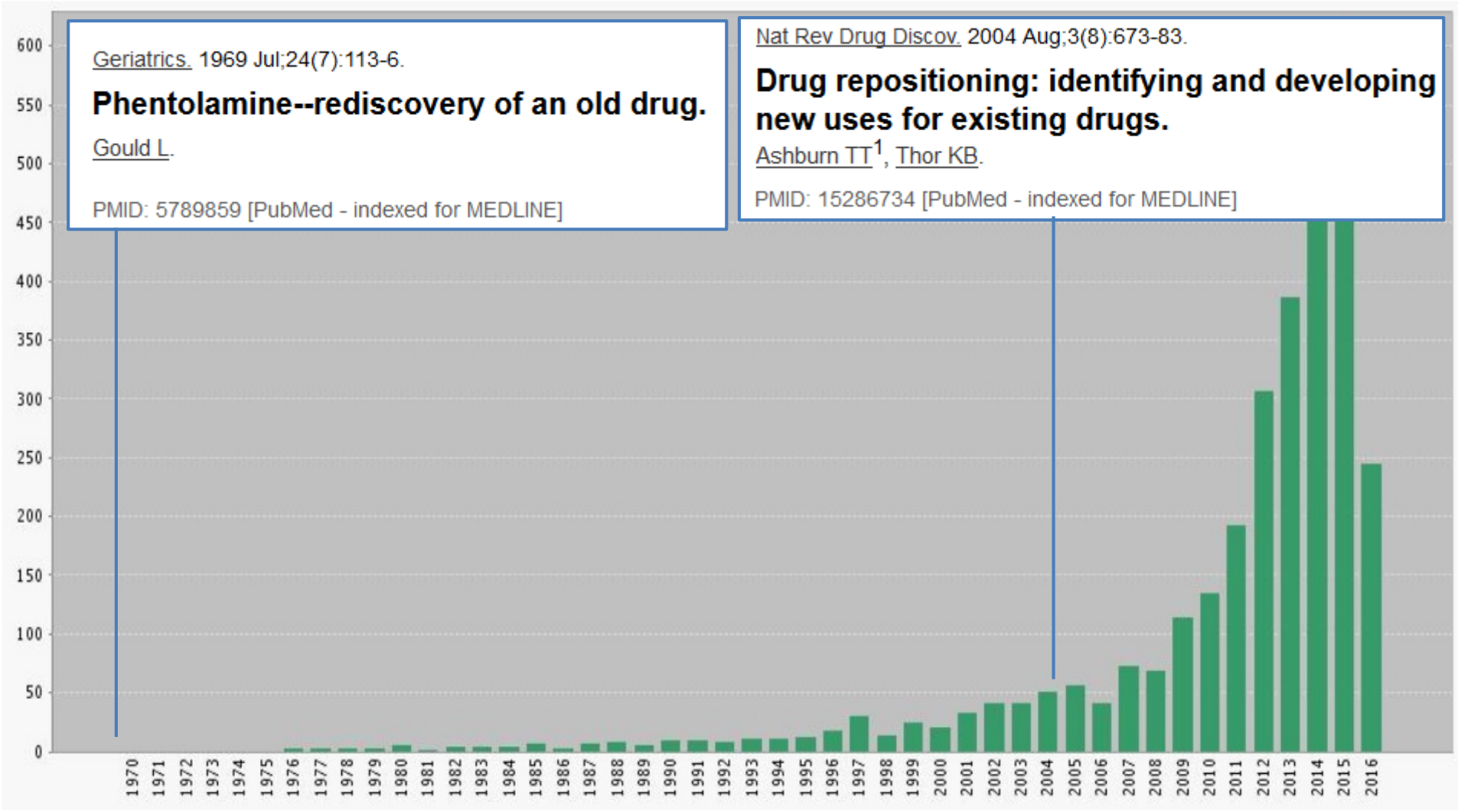
Before 2004 no articles about drug repositioning were found started to increase after 2010 in particular.

Search for DRP in Web of Science core collection





Some examples of the relevant publications



Publications on drug repurposing covered by Web of Science

Phentolamine—rediscovery of an old drug

LAWRENCE GOULD, M.D.
Director, Cardiac Catheterization Laboratory
Misericordia–Fordham Hospital
BRONX, NEW YORK

Phentolamine has long been considered to be an alpha-adrenergic blocking agent which produces arteriolar dilation unaccompanied by any primary cardiac effect. It is primarily used as a screening test for the detection of pheochromocytoma. Recent work in our laboratory has demonstrated that the drug has far greater clinical application.

Thanks to the favor of Marc Nicklaus, CADD Group, LCB, CCR, NCI/NIH.

More examples of the relevant publications

No such terms as:

Drug repositioning

OR

Drug repurposing

OR

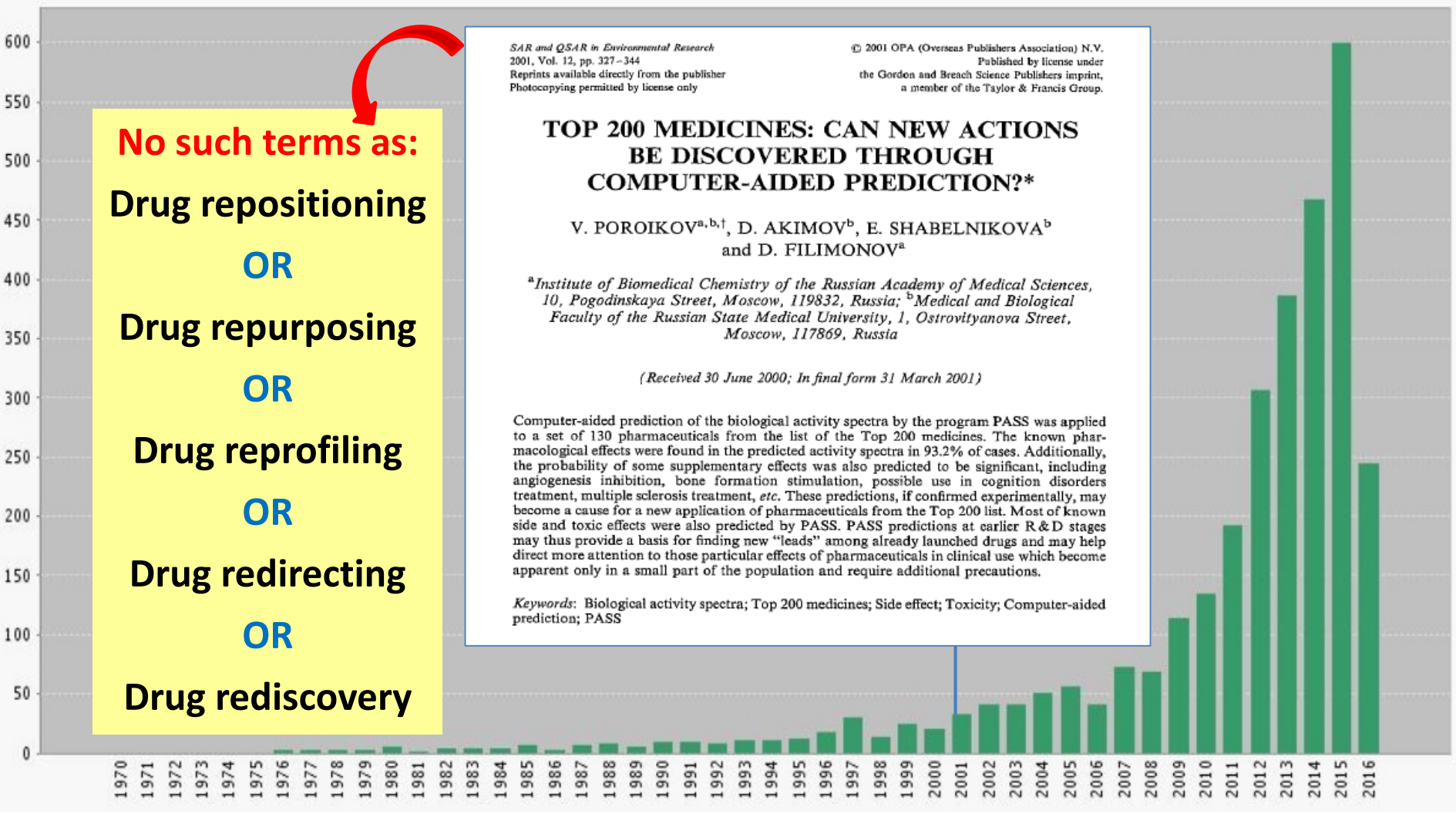
Drug reprofiling

OR

Drug redirecting

OR

Drug rediscovery



SAR and QSAR in Environmental Research
2001, Vol. 12, pp. 327–344
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TOP 200 MEDICINES: CAN NEW ACTIONS BE DISCOVERED THROUGH COMPUTER-AIDED PREDICTION?*

V. POROIKOV[a,b,†], D. AKIMOV[b], E. SHABELNIKOVA[b] and D. FILIMONOV[a]

[a]*Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, 10, Pogodinskaya Street, Moscow, 119832, Russia;* [b]*Medical and Biological Faculty of the Russian State Medical University, 1, Ostrovityanova Street, Moscow, 117869, Russia*

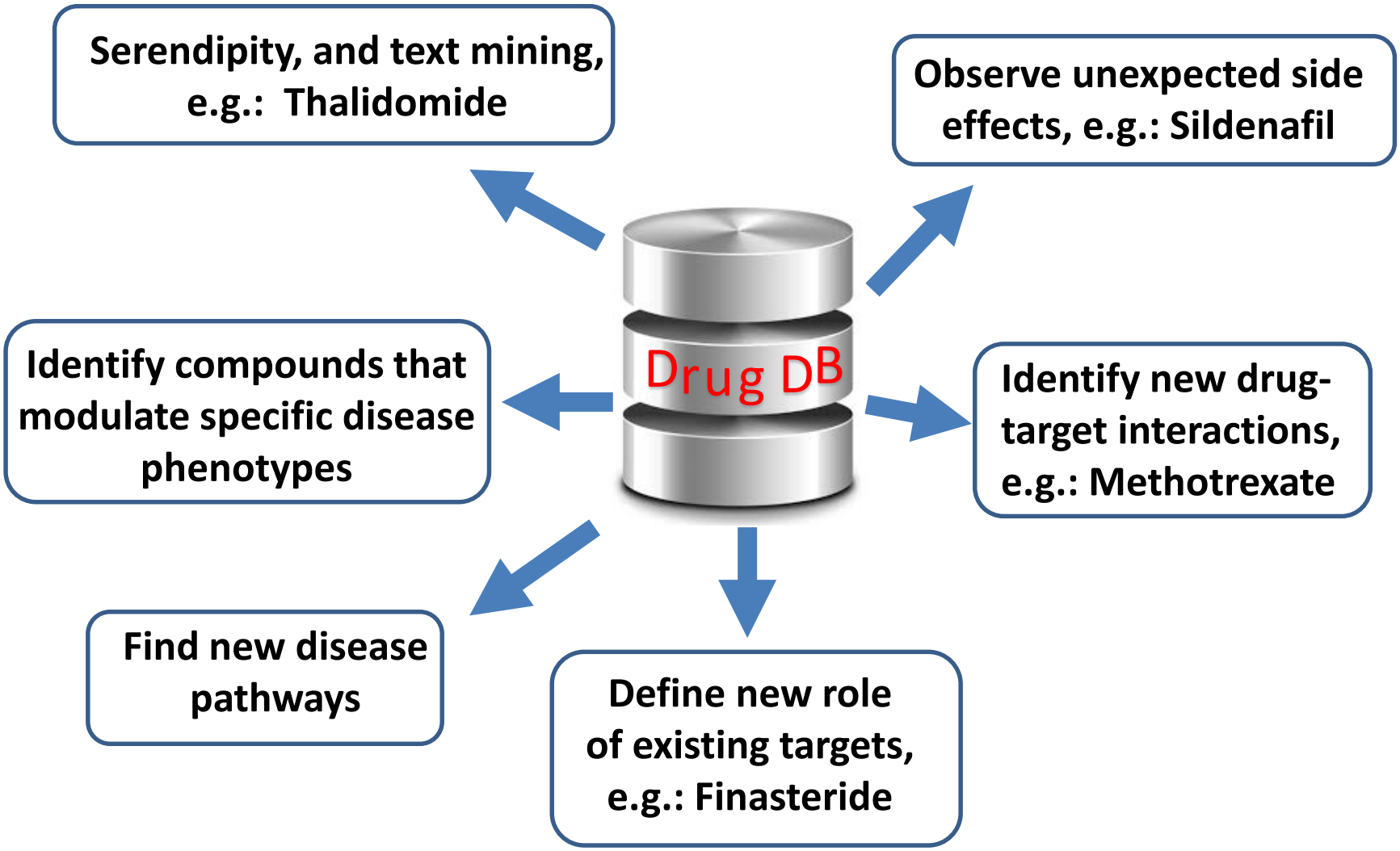
(Received 30 June 2000; In final form 31 March 2001)

Computer-aided prediction of the biological activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacological effects were found in the predicted activity spectra in 93.2% of cases. Additionally, the probability of some supplementary effects was also predicted to be significant, including angiogenesis inhibition, bone formation stimulation, possible use in cognition disorders treatment, multiple sclerosis treatment, *etc.* These predictions, if confirmed experimentally, may become a cause for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were also predicted by PASS. PASS predictions at earlier R&D stages may thus provide a basis for finding new "leads" among already launched drugs and may help direct more attention to those particular effects of pharmaceuticals in clinical use which become apparent only in a small part of the population and require additional precautions.

Keywords: Biological activity spectra; Top 200 medicines; Side effect; Toxicity; Computer-aided prediction; PASS

Publications on drug repurposing covered by Web of Science

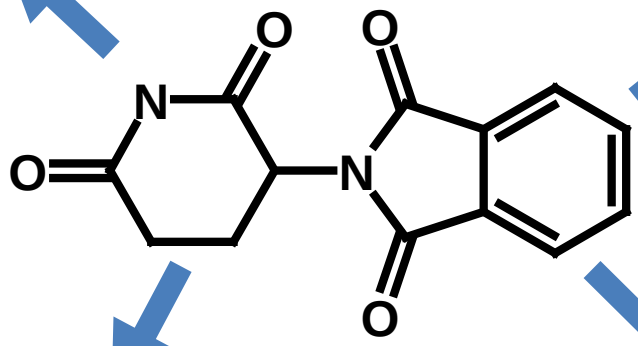
DRP: How it happens?



Thalidomide: discoveries by serendipity

Sedative, Morning sickness in pregnant women treatment - 1957

Erythema nodosum laprosum Treatment (agonizing inflammatory condition of leprosy) – 1998 (1964)

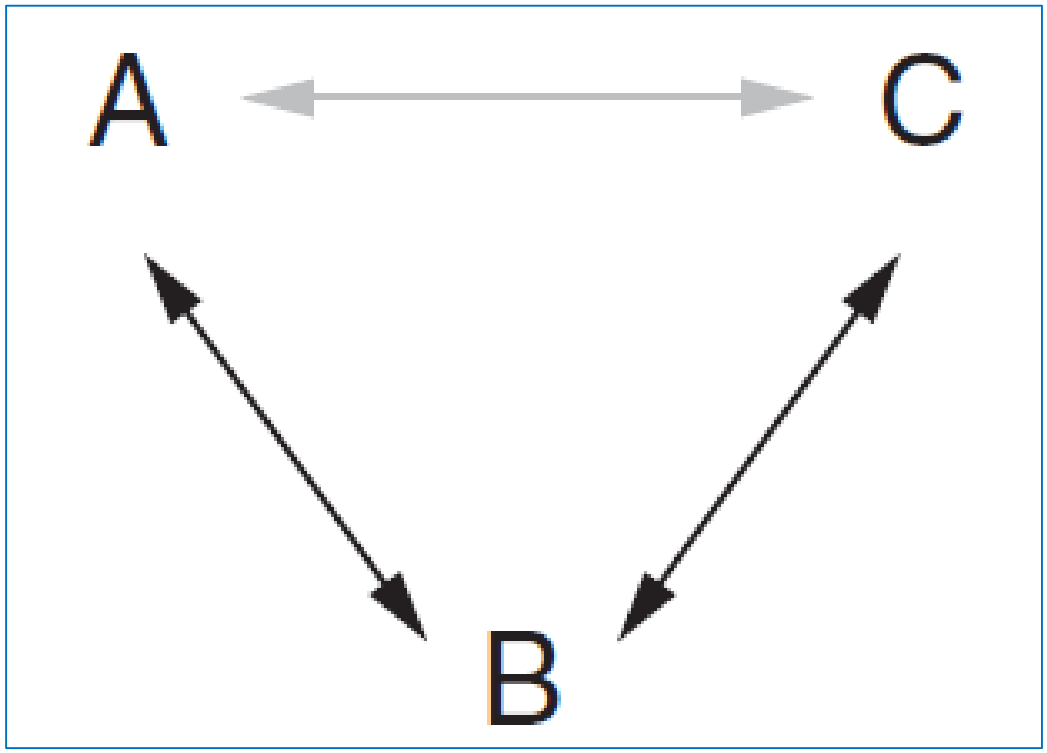


Teratogenic, Skeletal birth defects in children – early 60s (Withdrawn)

Antiangiogenic – 1994; Multiple myeloma off-the-label treatment - 1998

Baek M.-C. et al. Pharmacol. Res., 2015, 99: 185–193.
Ashburn T.T., Thor K.B. Nat. Rev. Drug. Discov, 2004, 3: 673-683.

Text mining: Literature-based discovery



Swanson's ABC model of discovery.

If concepts A and B are reported to be related to one set of publications and concepts B and C are reported to be related to another set, then A and C might be indirectly related to each other.

Swanson, D.R. (1990) Medical literature as a potential source of new knowledge. Bull. Med. Libr. Assoc. 78, 29–37.

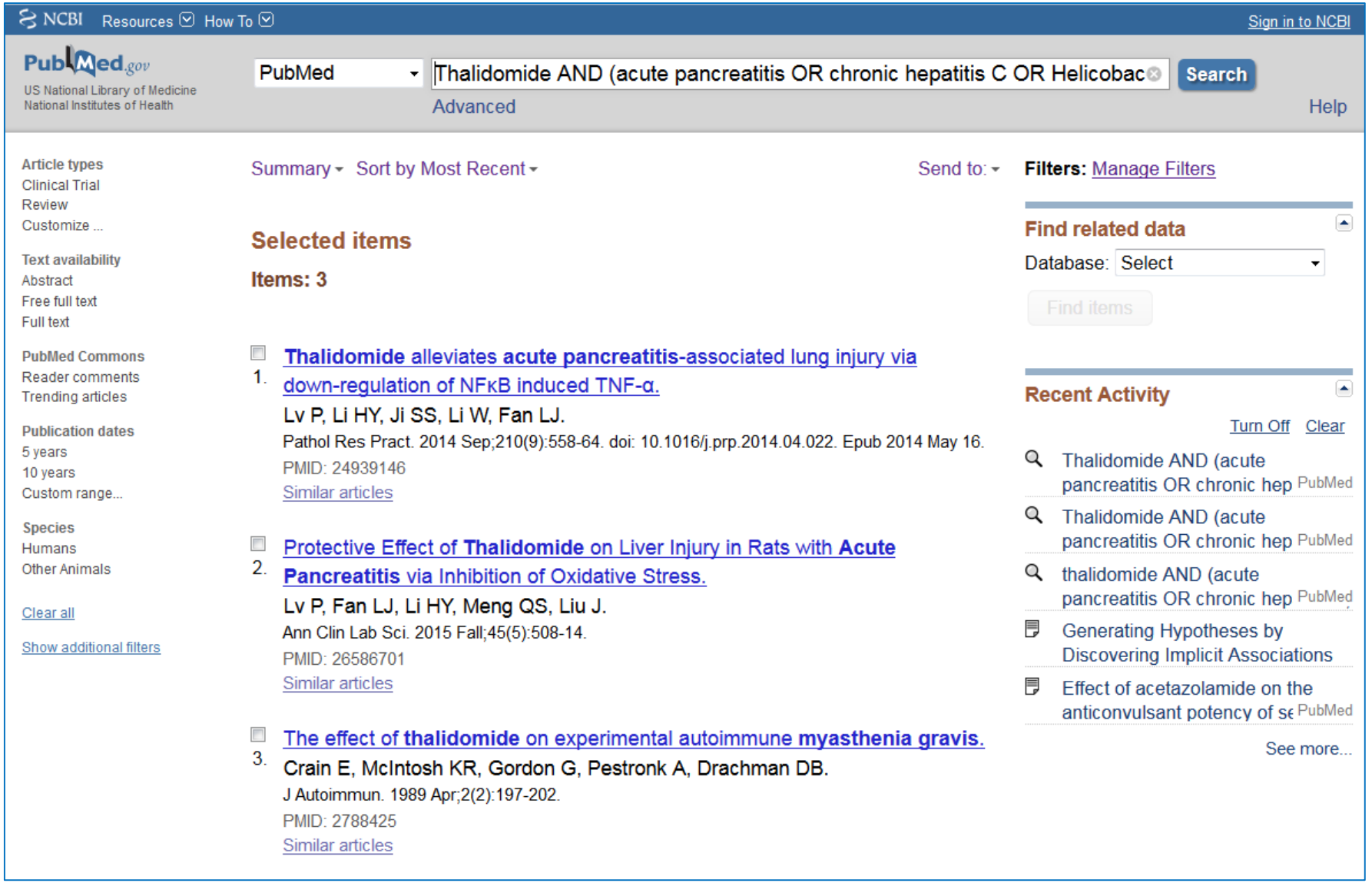
Case Report ■

Generating Hypotheses by Discovering Implicit Associations in the Literature: A Case Report of a Search for New Potential Therapeutic Uses for Thalidomide

MARC WEEBER, PHD, REIN VOS, MD, PHD, HENNY KLEIN, PHD,
LOLKJE T. W. DE JONG-VAN DEN BERG, PHD, ALAN R. ARONSON, PHD,
GRIETJE MOLEMA, PHD

We find solid bibliographic evidence suggesting that thalidomide might be useful for treating acute pancreatitis, chronic hepatitis C, *Helicobacter pylori*-induced gastritis, and myasthenia gravis. However, experimental and clinical evaluation is needed to validate these hypotheses and to assess the trade-off between therapeutic benefits and toxicities.

Search in PubMed provides some evidences



NCBI Resources How To Sign in to NCBI

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | Thalidomide AND (acute pancreatitis OR chronic hepatitis C OR Helicobac | Search
Advanced Help

Article types
Clinical Trial
Review
Customize ...

Text availability
Abstract
Free full text
Full text

PubMed Commons
Reader comments
Trending articles

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Clear all

Show additional filters

Summary Sort by Most Recent Send to:

Filters: Manage Filters

Selected items

Items: 3

1. Thalidomide alleviates acute pancreatitis-associated lung injury via down-regulation of NFκB induced TNF-α.
Lv P, Li HY, Ji SS, Li W, Fan LJ.
Pathol Res Pract. 2014 Sep;210(9):558-64. doi: 10.1016/j.prp.2014.04.022. Epub 2014 May 16.
PMID: 24939146
Similar articles

2. Protective Effect of Thalidomide on Liver Injury in Rats with Acute Pancreatitis via Inhibition of Oxidative Stress.
Lv P, Fan LJ, Li HY, Meng QS, Liu J.
Ann Clin Lab Sci. 2015 Fall;45(5):508-14.
PMID: 26586701
Similar articles

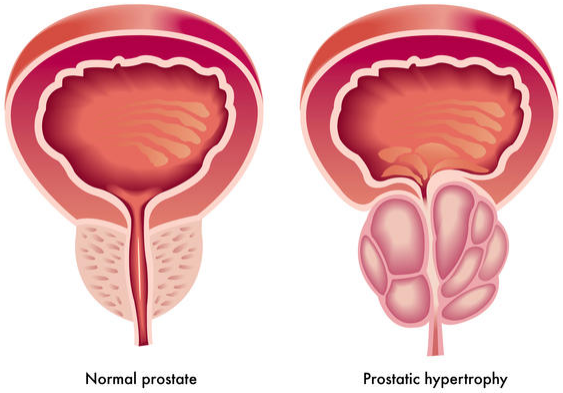
3. The effect of thalidomide on experimental autoimmune myasthenia gravis.
Crain E, McIntosh KR, Gordon G, Pestronk A, Drachman DB.
J Autoimmun. 1989 Apr;2(2):197-202.
PMID: 2788425
Similar articles

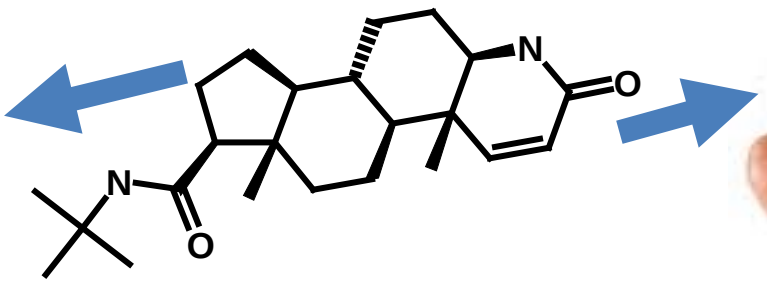
Find related data
Database: Select
Find items

Recent Activity
Turn Off Clear
Thalidomide AND (acute pancreatitis OR chronic hep PubMed
Thalidomide AND (acute pancreatitis OR chronic hep PubMed
thalidomide AND (acute pancreatitis OR chronic hep PubMed
Generating Hypotheses by Discovering Implicit Associations
Effect of acetazolamide on the anticonvulsant potency of se PubMed
See more...

Define new role of existing targets: Finasteride

5-alpha-reductase inhibitor, Benign prostatic hyperplasia - 1992 (Proscar; Merck)





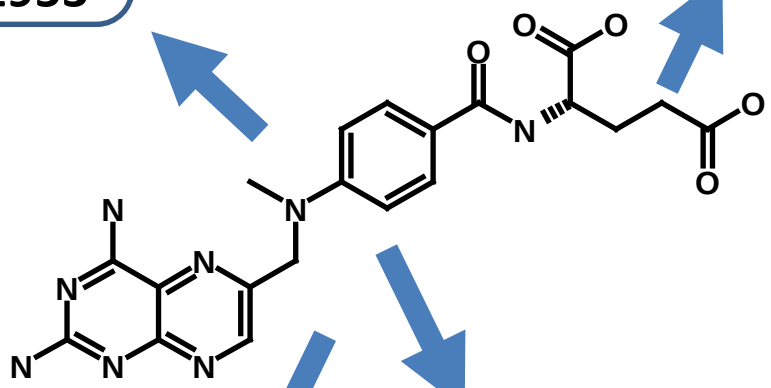
5-alpha-reductase inhibitor, Hair loss treatment - 1997 Propecia (with a fivefold lower dose), had worldwide sales of US $239 million in 2003

Ashburn T.T. and Thor K.B. Nat. Rev. Drug. Discov., 2004, 3: 673-683.

One of the major reason for DRP is drug promiscuity: Methotrexate as an example

Antineoplastic (Acute leukemia), Dihydrofolate reductase inhibitor - 1953

Antiarthritic - 1954

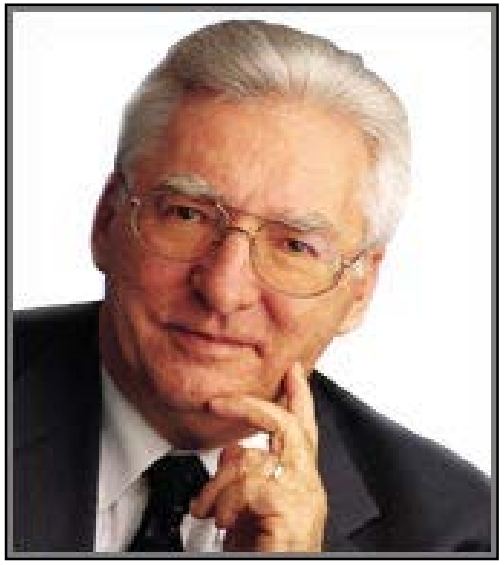


Osteosarcoma, breast cancer, acute lymphoblastic leukemia, and Hodgkin lymphoma - 1988

NF-κB and TNF-α signaling pathway inhibitor, antiangiogenic, antiinflammatory - 2010

Gupta S.C. et al. Trends Pharmacol. Sci., 2013, 34: 508-517.
Tobinick E.L. Drug News & Perspectives, 2009, 119-125.

Multitargeted Drugs: The End of The "One-Target-One Disease Philosophy?"



(1933-2015)

update | discussion forum

DDT Vol. 9, No. 19 October 2004

For many years, clinicians have treated patients by combinations of drugs with different pharmacotherapeutic actions. It is being recognized that a balanced modulation of several targets can provide a superior therapeutic effect and a favourable side effect profile compared to the action of a selective ligand.

In a recent issue of *Drug Discovery Today*, Morphy *et al.* [1] discuss the opportunities and advantages associated with the design of ligands that act on two (or more) specific targets in an article entitled 'From magic bullets to designed multiple ligands'.

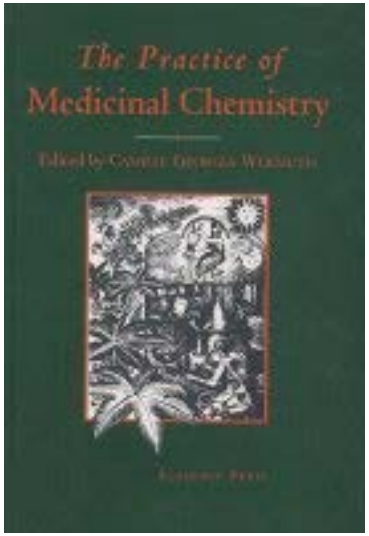
Several highly specific drugs that have only one target have clearly proven the usefulness of monotarget medicine. conjunction with amoxicillin, and in the treatment of Parkinson's disease, where L-4-dihydroxyphenylalanine (DOPA) is concomitantly administered with DOPA-decarboxylase and catechol-*O*-methyltransferase inhibitors. The risk with combination therapies is that the use of multiple drugs introduces problems with pharmacokinetics, toxicity and patient compliance. To circumvent these difficulties, and after a truly rational computer-generation of DM ligands should not be based on the interactions of structural elements, but rather the comparison and association of true pharmacophores.

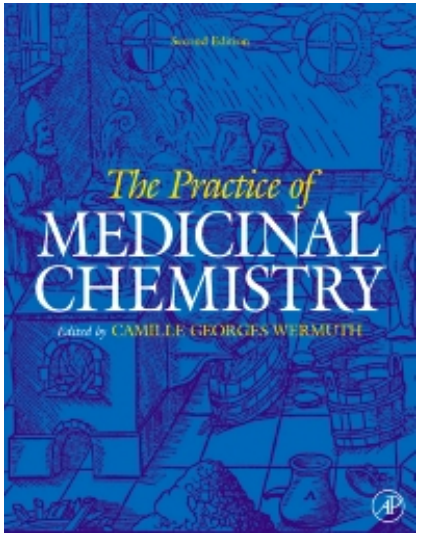
The second approach (screening approach) to DM ligands is based on the screening of large libraries for the two relevant bioassays. The substantial screening of a large number of compounds, which therefore have a

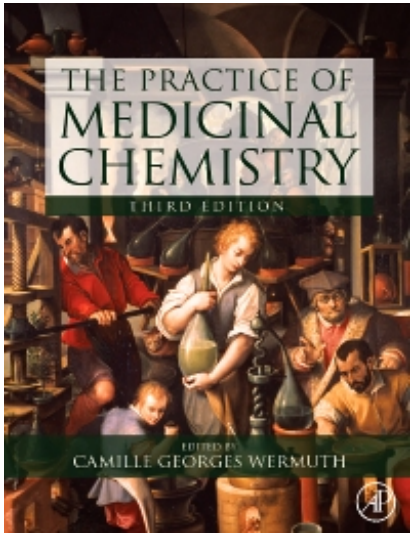
"In conclusion, the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value compared with monotarget formulations".

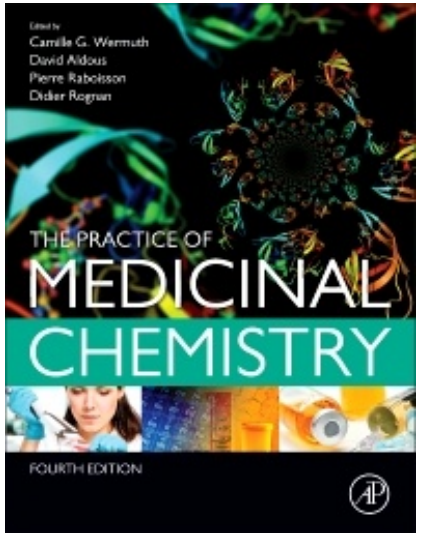
Camille George Wermuth. *Drug Discovery Today*, 2004, 9.

The Practice of Medicinal Chemistry
4th Edition, Elsevier, 2015.









Disclaimer. **No advertisement, only proper tribute to a remarkable man and scientist.**

If we can predict by the current chemoinformatics tools the most probable targets for the existing drugs?

Yes, we can!

Both structure-based and ligand-based methods may be applied for this purpose: (Q)SAR, pharmacophore sets, inverse docking, etc.

However, not all methods are freely available.

Some freely available computational tools for DRP

PASS (Prediction of Activity Spectra for Substances)

Poroikov V. et al. *Automatic Documentation and Mathematical Linguistics*, 1993, 27: 40-43.
Filimonov D. et al. *Experimental and Clinical Pharmacology*, 1995, 58: 56-62.
Lagunin A. et al. *Bioinformatics*, 2000, 16: 747-748. (www.way2drug.com/passonline)
Filimonov D. *Chemistry of Heterocyclic Compounds*, 2014, No. 3, 483-499.

SEA (Similarity Ensemble Approach)

Keiser M.J. et al. *Nat. Biotech.*, 2007, 25:197-206. (sea.bkslab.org/)

PharmMapper

Liu X. et al. *Nucl. Acids Res.*, 2010, 38, W609-W614. (59.78.96.61/pharmmapper/)

DRAR-CPI

Luo H. et al. *Nucl. Acids Res.*, 2011, 39, W492-W498. (cpi.bio-x.cn/drar/)

TargetHunter

Wang L. et al. *AAPS J.*, 2013, 15: 395-406. (www.cbligand.org/TargetHunter/)

SuperPred

Nickel J. et al. *Nucl. Acids Res.*, 2014, 42: W26-31. (prediction.charite.de/)

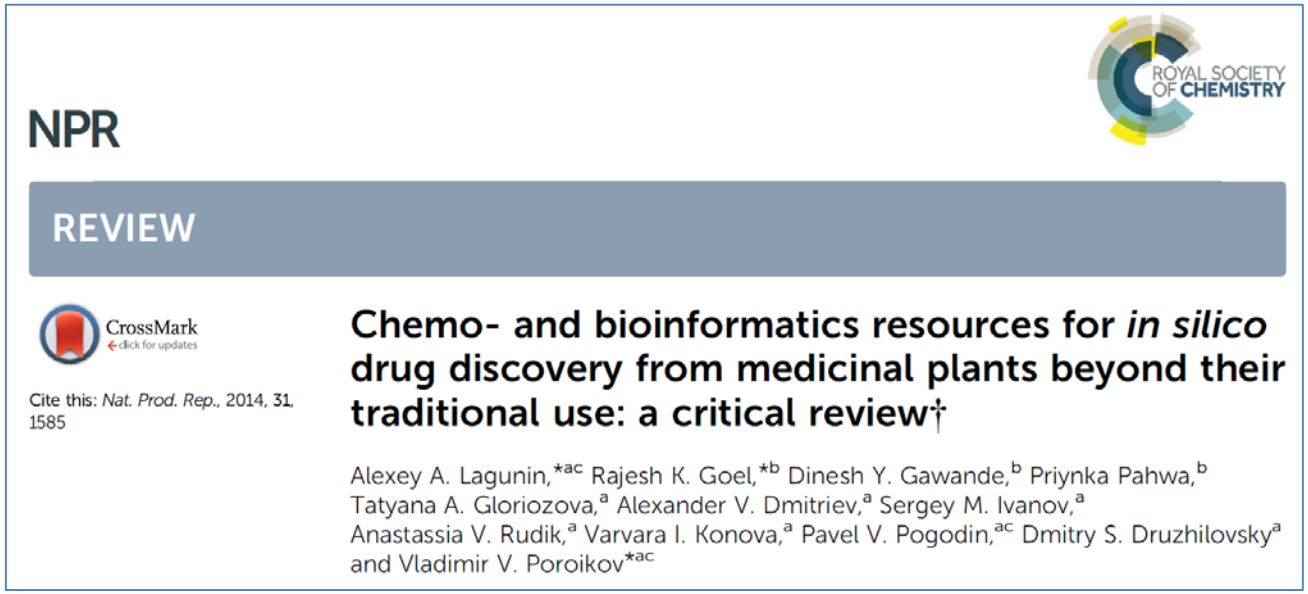
SwissTargetPrediction

Gfeller D. et al. *Nucl. Acids Res.*, 2014, 42, W32-W38. (www.swisstargetprediction.ch/)

ChemProt 3.0

Kringelum J. et al. *DataBase*, 2016, 2016: bav123. (potentia.cbs.dtu.dk/ChemProt/)

More info about the computational resources:



NPR

ROYAL SOCIETY OF CHEMISTRY

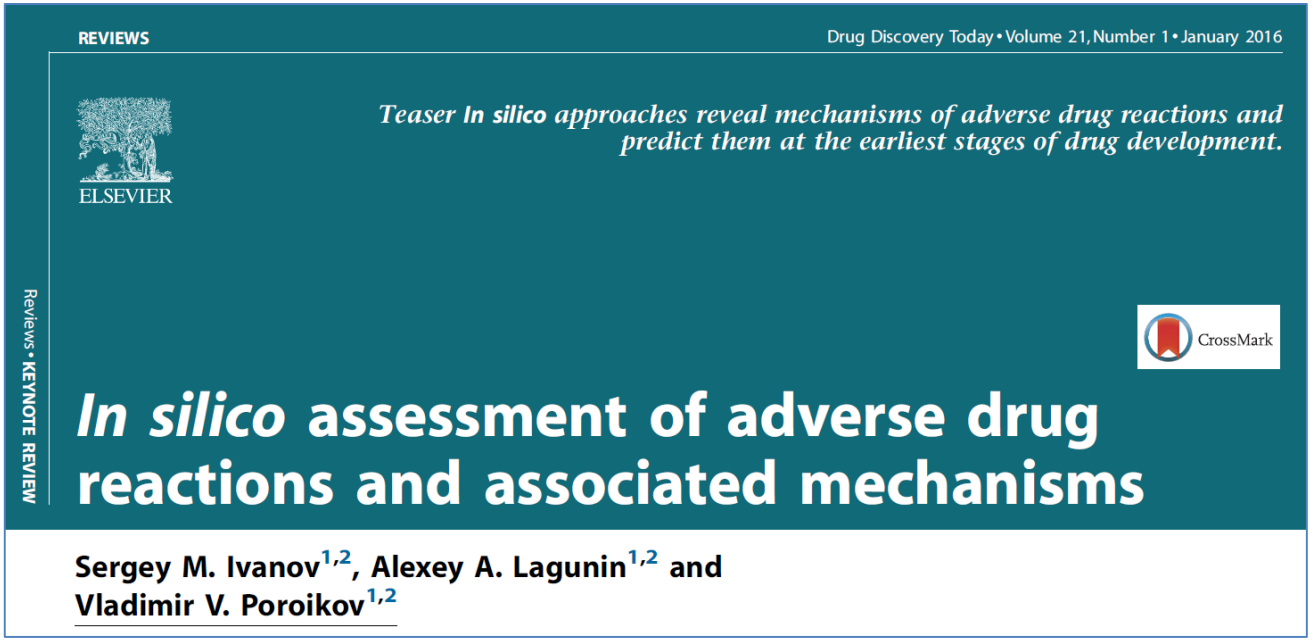
REVIEW

CrossMark click for updates

Cite this: *Nat. Prod. Rep.*, 2014, 31, 1585

Chemo- and bioinformatics resources for *in silico* drug discovery from medicinal plants beyond their traditional use: a critical review†

Alexey A. Lagunin,*[ac] Rajesh K. Goel,*[b] Dinesh Y. Gawande,[b] Priynka Pahwa,[b] Tatyana A. Gloriozova,[a] Alexander V. Dmitriev,[a] Sergey M. Ivanov,[a] Anastassia V. Rudik,[a] Varvara I. Konova,[a] Pavel V. Pogodin,[ac] Dmitry S. Druzhilovsky[a] and Vladimir V. Poroikov*[ac]



REVIEWS

Drug Discovery Today • Volume 21, Number 1 • January 2016

ELSEVIER

Teaser **In silico** *approaches reveal mechanisms of adverse drug reactions and predict them at the earliest stages of drug development.*

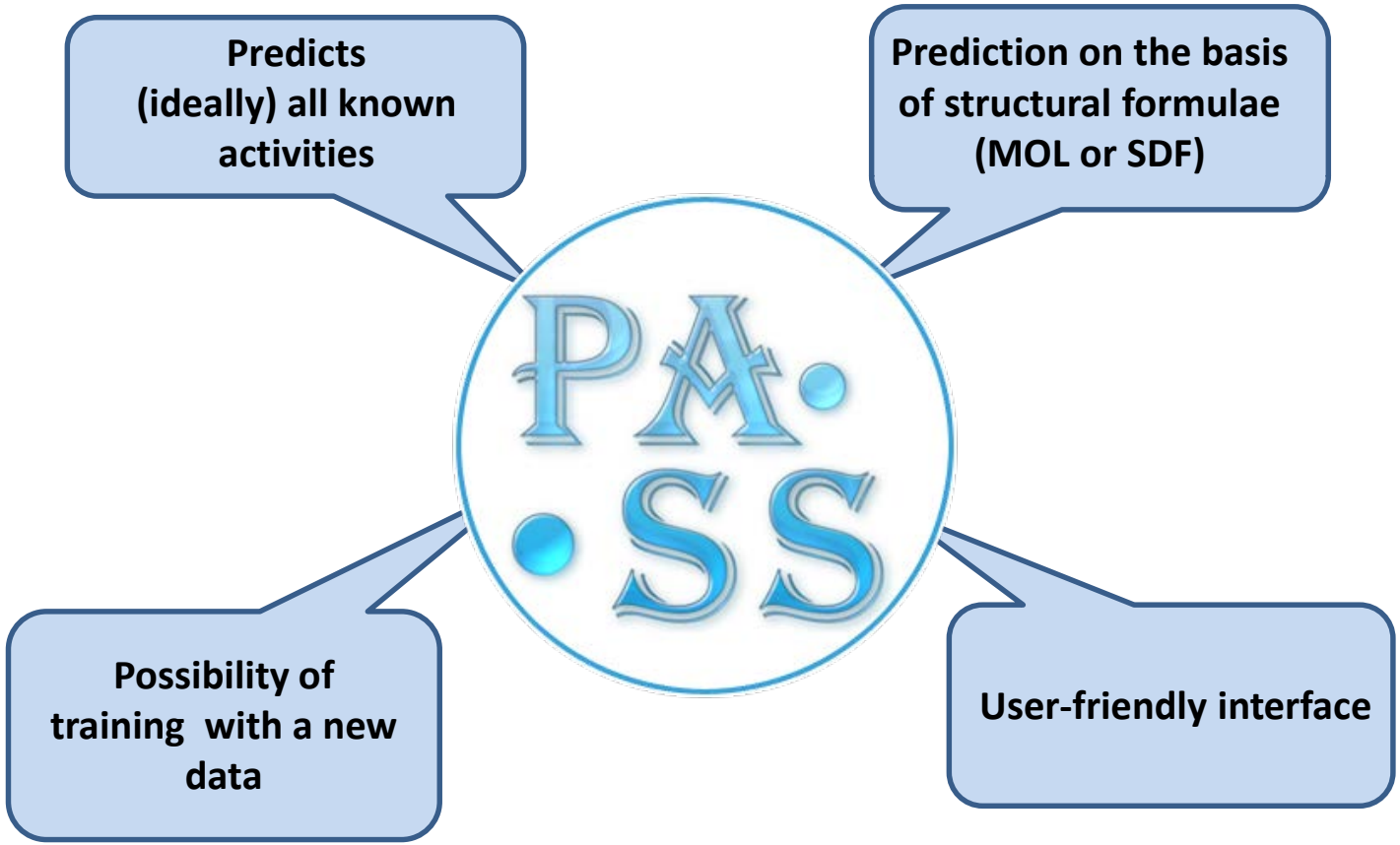
CrossMark

Reviews • KEYNOTE REVIEW

In silico assessment of adverse drug reactions and associated mechanisms

Sergey M. Ivanov[1,2], Alexey A. Lagunin[1,2] and Vladimir V. Poroikov[1,2]

Requirements for a computer program evaluated biological activity profiles (spectra)

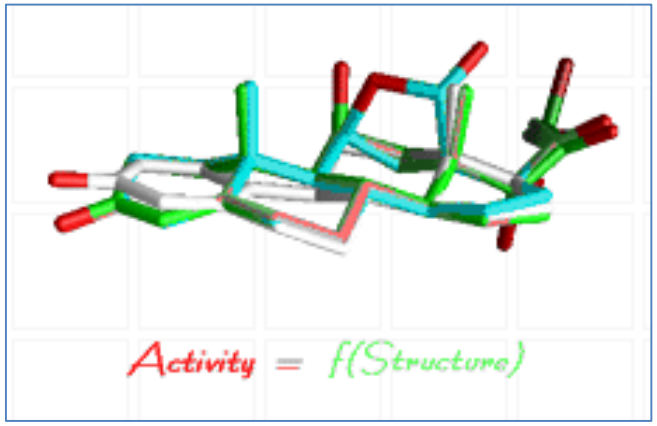


Biological activity spectra of organic compound

Biological activity is one of the most important characteristics of organic compound, which provides the basis for its use in therapeutic purposes. Biological activity reflects the result of interaction between the substance and biological object, and depends on substance structure and properties, biological object (species, sex, age), and mode of action (administration route, dose). Biological activity spectrum of an organic compound is the set of different kinds of biological activity that reflect the results of the compound's interaction with various biological entities. It represents the "intrinsic" property of a substance depending only on its structure. This is a qualitative characteristic property of a substance that depends only on its molecular structure.

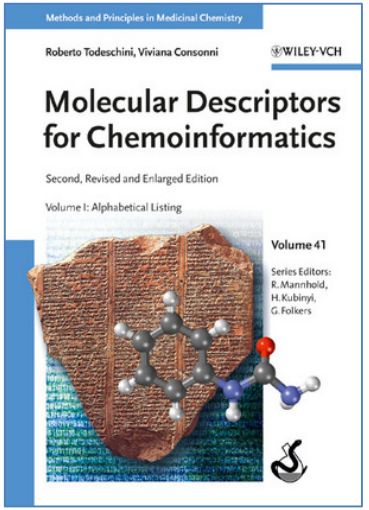
Poroikov V. et al. *Automatic Documentation and Mathematical Linguistics*, 1993, 27: 40-43.
Filimonov D. *Chemistry of Heterocyclic Compounds*, 2014, No. 3, 483-499.

Structure-activity relationships: (Q)SAR



Molecular descriptors

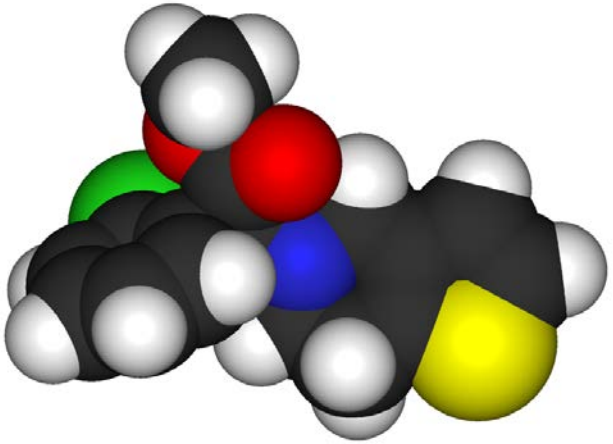
Sub-structural (-COO, -NH2, -OH, C6H5, и др.); physical-chemical (molecular weight, melting point, IR frequencies, chemical shifts in NMR, etc.); molecular connectivity, Wiener indices, Balaban indices, hydrophobicity constant, pKa, van der Waals volume, Log P, water solubility, etc. (several thousand).

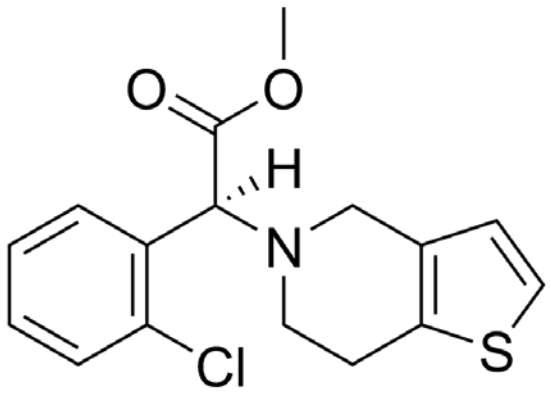


Mathematical methods

Multiple linear regression (MLR); non-linear regression; partial least squares (PLS); regression on principal components (PCR); artificial neural networks (ANN); similarity matrices; genetic algorithms; support vector machine (SVM); cluster analysis (CA); discriminant analysis; etc.

Chemical structure representation





The spatial configuration of the free uncharged molecules in the ground state in a vacuum is a necessary and sufficient description of its structure.

The use of this molecular structure description requires substantial computational resources for molecular modeling and/or quantum-chemical calculations.

However, the basis of all calculations is the traditional structural formula.

Thus, the structural formula uniquely determines all properties of the organic molecule.

Influence of the environment?

- Structural formula determines, at least, potential “intrinsic" properties of the molecule.

Neighborhoods of atoms descriptors

The most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the correspondence between particular atoms of the ligand and the target.

MOLECULAR BIOLOGY

QUANTUM CHEMISTRY

QUANTUM FIELDS THEORY

D.A. Filimonov

$$M = V + VgM = V + VgV + VgVgV + VgVgVg + \ldots$$

$$M_i = V_i + V_igM = V_i + V_ig(M_1 + M_2 + \ldots + M_m)$$

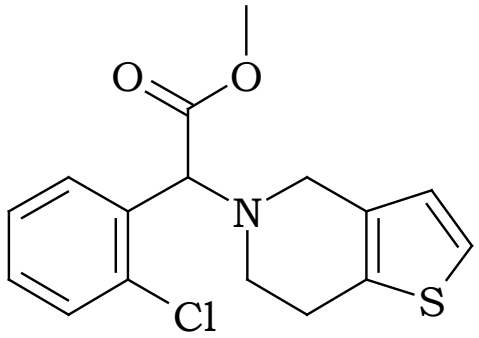
Descriptors are based on the concept of atoms' of molecule taking into account the influence of the neighborhoods:

MNA - **M**ultilevel **N**eighborhoods of **A**toms
QNA - **Q**uantitative **N**eighborhoods of **A**toms
LMNA - **L**abeled **M**ultilevel **N**eighborhoods of **A**toms

Filimonov D.A., Poroikov V.V. *In: Chemoinformatics Approaches to Virtual Screening.* Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 2008, 182-216.
Filimonov D.A. et al. *SAR and QSAR Environ. Res.*, 2009, 20: 679-709.
Rudik A.V. et al. *J. Chem. Inform. Model.*, 2014, 54: 498–507.

Substance representation: Clopidogrel

Structural formula



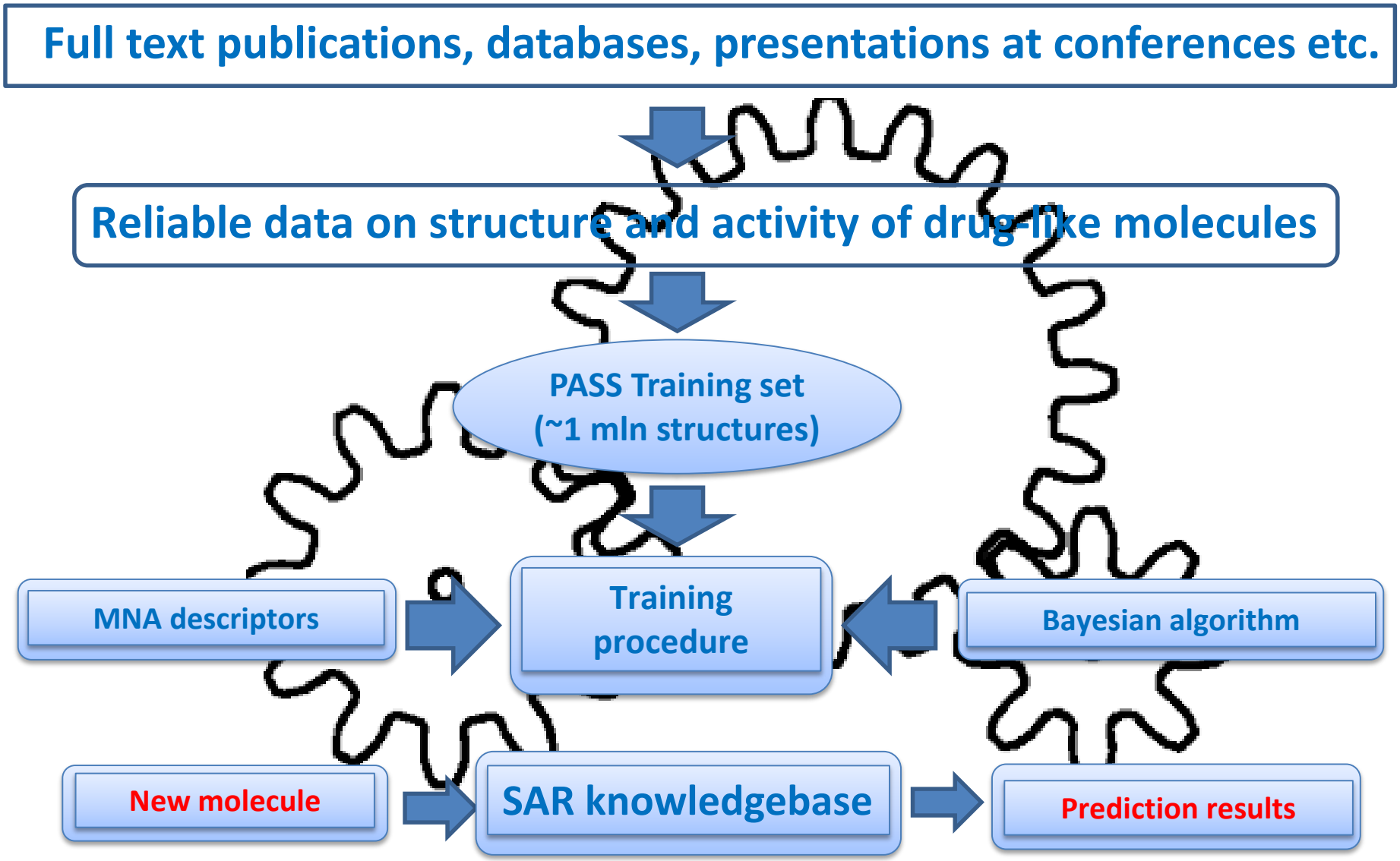
Activity Spectrum

Abdominal pain
Acute neurologic disorders treatment
Agranulocytosis
Allergic reaction
Anaphylaxis
Anemia
Angioedema
Angiogenesis inhibitor
Antianginal
Antiarthritic
Anticoagulant
Antineoplastic
Antipsoriatic
Antithrombotic
. . .
112 known activities in PASS SAR Base

MNA Descriptors (1st and 2nd levels)

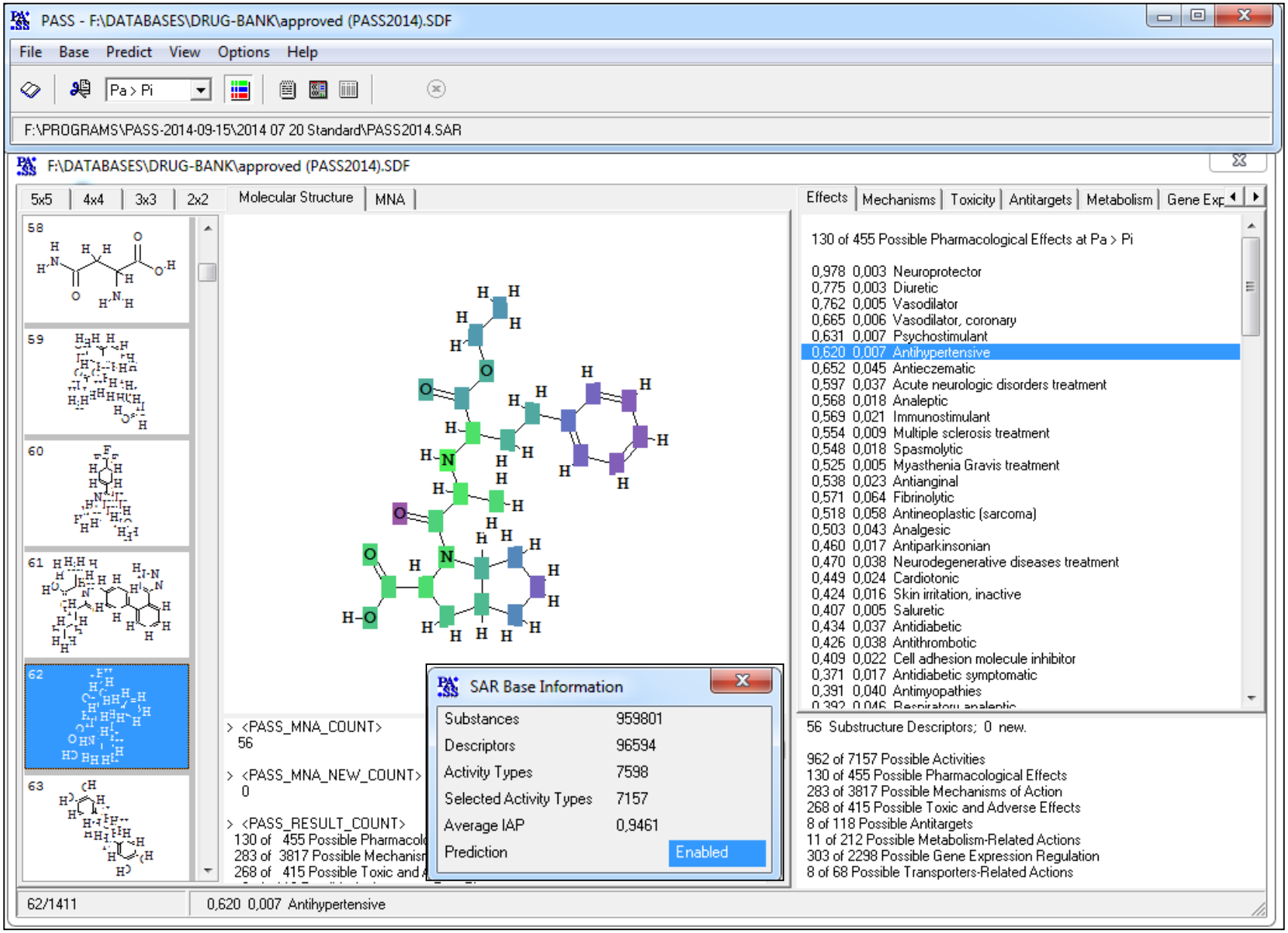
HC	C(C(CCC)C(CC-H-H)S(CC))
CHHHO	C(C(CCC)C(CS-H)-H(C))
CHHCC	C(C(CCC)N(CC-C)-H(C)-H(C))
CHHCN	C(C(CCS)C(CC-H)C(CN-H-H))
CHCC	C(C(CCS)C(CN-H-H)-H(C)-H(C))
CHCCN	C(C(CC-H-H)N(CC-C)-H(C)-H(C))
CHCS	C(C(CC-H)C(CC-H)-H(C))
CCCC	C(C(CC-H)C(CC-C)-H(C))
CCCS	C(C(CC-H)C(CC-C)-Cl(C))
CCCCl	C(C(CC-H)C(CC-Cl)-H(C))
CCOO	C(C(CC-H)C(CC-Cl)-C(CN-H-C))
NCCC	C(C(CC-H)S(CC)-H(C))
OC	N(C(CN-H-H)C(CN-H-H)-C(CN-H-C))
OCC	S(C(CCS)C(CS-H))
SCC	-H(C(CC-H))
ClC	-H(C(CC-H-H))
	-H(C(CN-H-H))
	-H(C(CS-H))
	-H(-C(CN-H-C))
	-H(-C(-H-H-H-O))
	-C(C(CC-C)N(CC-C)-H(-C)-C(-C-O-O))
	-C(-H(-C)-H(-C)-H(-C)-O(-C-C))
	-C(-C(CN-H-C)-O(-C)-O(-C-C))
	-O(-C(-H-H-H-O)-C(-C-O-O))
	-O(-C(-C-O-O))
	-Cl(C(CC-Cl))

PASS: Prediction of Activity Spectra for Substances

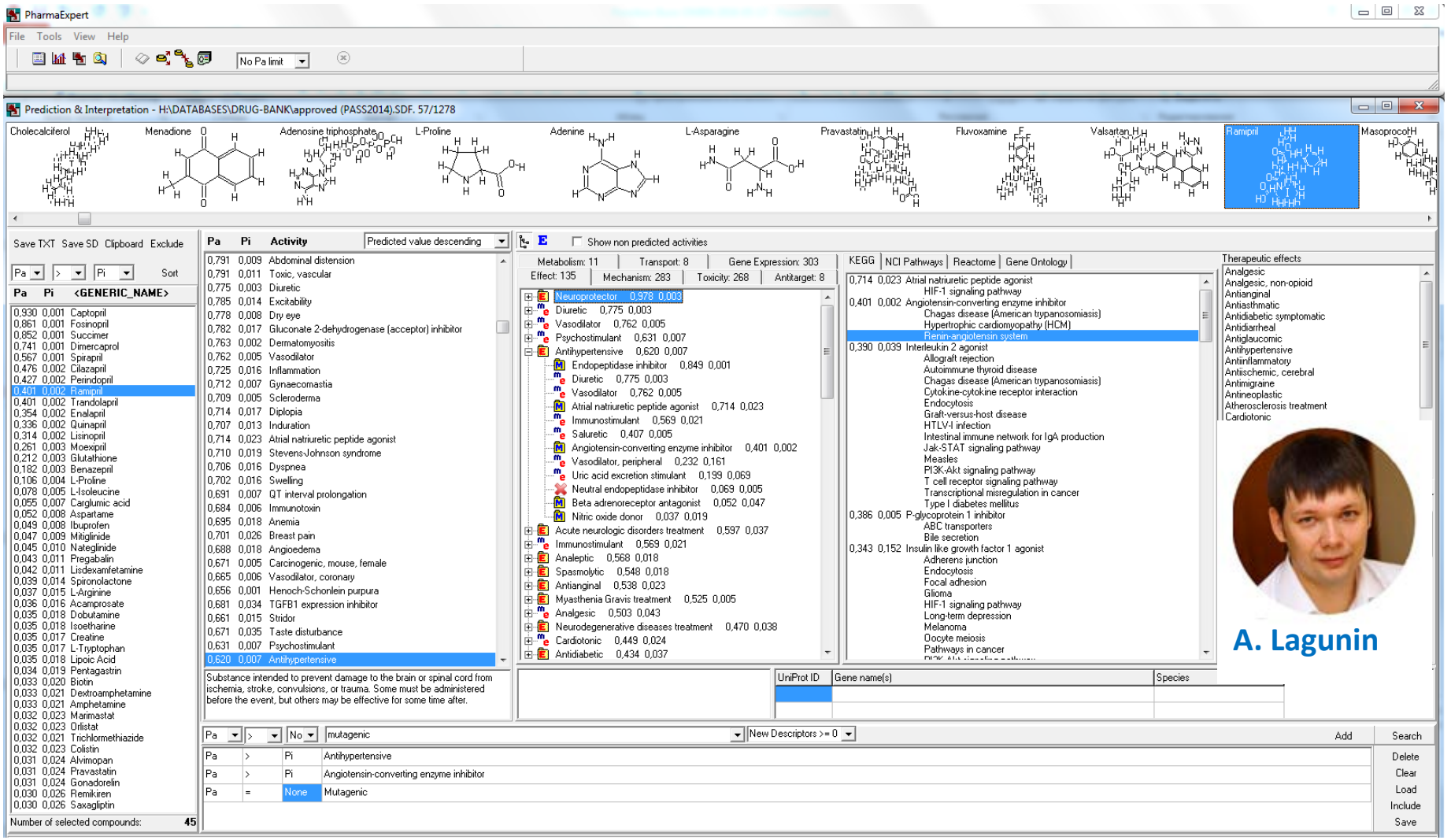


Filimonov D.A. et al. *Chem. Heterocycl. Comps.*, 2014, **50**: 444-457.

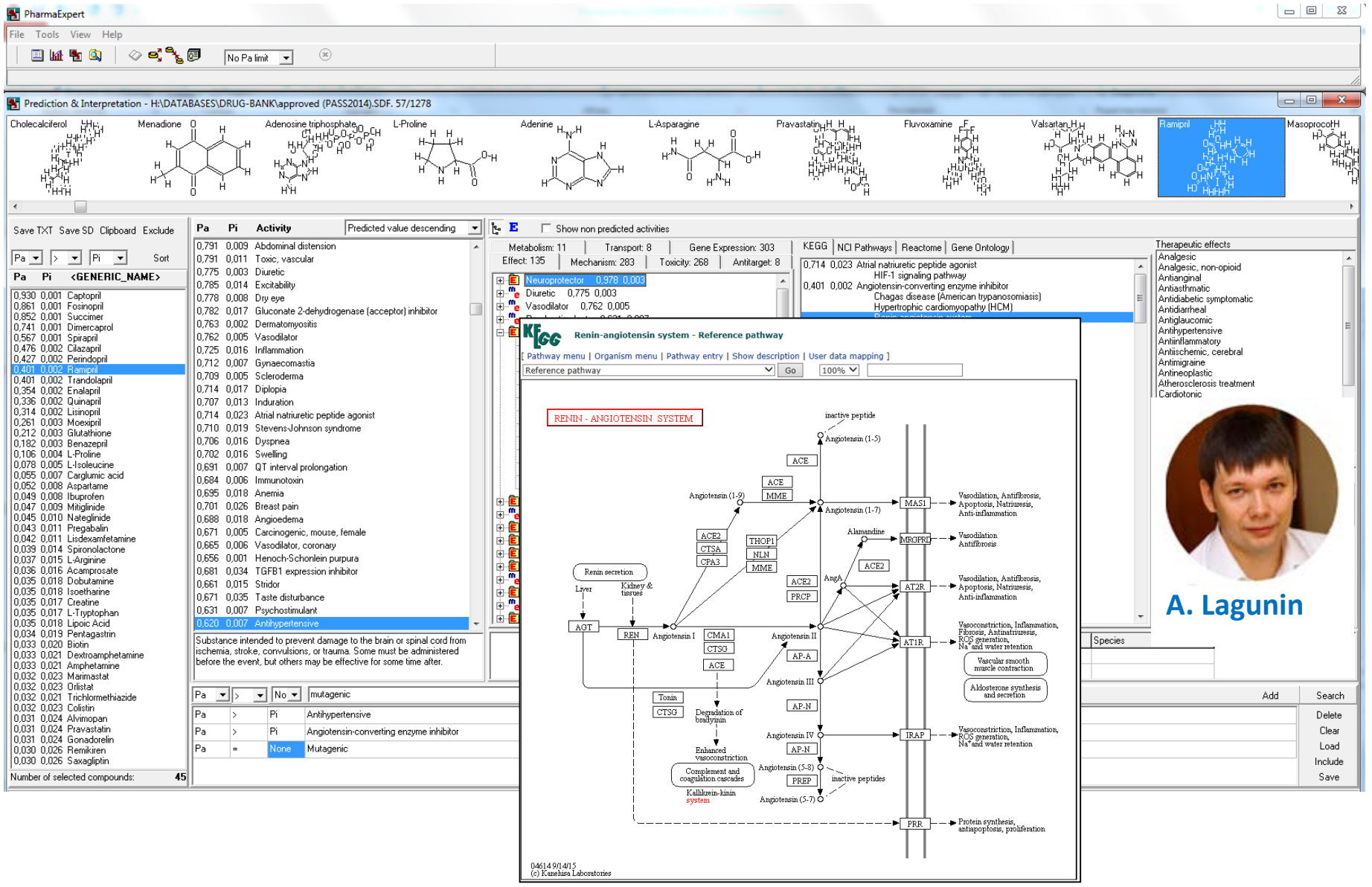
Example of prediction for Ramipril



PharmaExpert: Interpretation of the prediction results



PharmaExpert: Interpretation of the prediction results



Web-services based on our methods

www.way2drug.com/Projects.php

D. Druzhilovsky

A. Rudik

A. Zakharov

Some examples of practical applications of biological activity spectra prediction

Athina Geronikaki,
AUT, Greece

Finding molecules with needed effects and MOA
Cur. Top. Med. Chem., 2015, 16: 441.

Marc Nicklaus,
NCI/NIH, USA

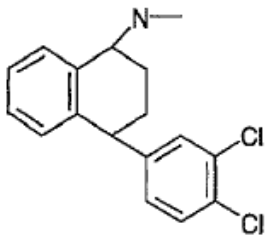
Search for multitarget drugs
J. Med. Chem. 2008, 51: 1601.

Drug reporpusing
Pharm. Chem. J. 2011, 45: 605.

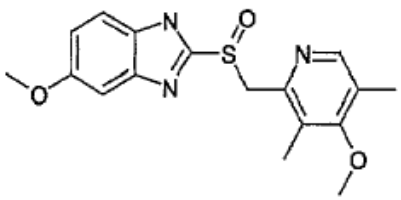
Rajesh Goel,
PU, India

Estimating drug-drug interactions for phytoconstituents of medicinal plants
Nat. Prod. Rep., 2014, 31: 1585.

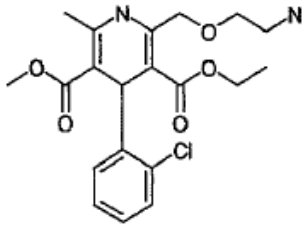
Sergey Kryzhanovsky,
Inst. of Pharmacol., Russia



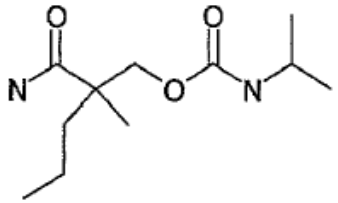
Sertraline
Adrenergic transmitter uptake inhibitor (0.770)
Antiparkinsonian (0.609)
Leukopoiesis inhibitor (0.582)
Cocain dependency treatment (0.560)
Acute neurologic disorders treatment (0.541)



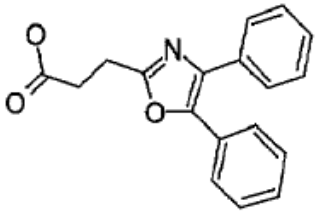
Omeprazole
TNF-alpha release inhibitor (0.658)
Atherosclerosis treatment (0.541)



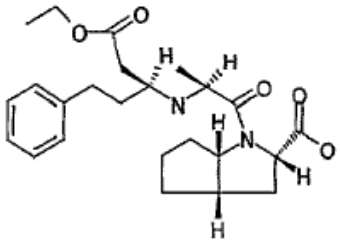
Amlodipine
Antineoplastic enhancer (0.608)
Multiple sclerosis treatment (0.508)



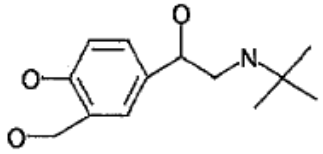
Carisoprodol
Angiogenesis inhibitor (0.569)
Multiple sclerosis treatment (0.549)



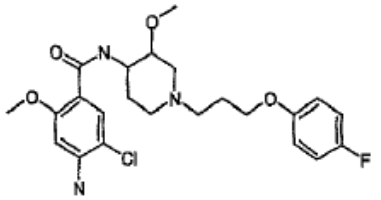
Oxaprozin
Bone formation stimulant (0.785)
Interleukin 1 antagonist (0.640)



Ramipril
Multiple sclerosis treatment (0.589)
Cognition disorders treatment (0.562)
Antiarthritic (0.454)



Albuterol
Antiobesity (0.784)



Cisapride
Irritable Bowel syndrome therapy(0.720)
Rhinitis treatment (0.524)

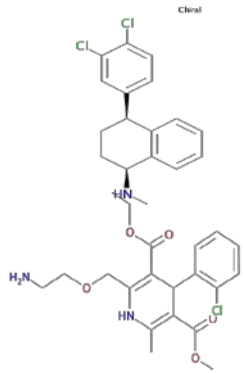
FIGURE 3 Examples of biological activities predicted de novo for some pharmaceuticals from the Top 200 list, which may become a reason for a new application. Pa values are given in brackets.

Poroikov V.V. et al. SAR & QSAR Environ. Res., 2001, 12: 327-344.

Drug repositioning based on PASS prediction

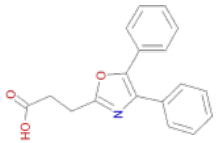
In 2001 we published predictions of new effects for 8 medicines from the list of Top200 Drugs [1].

Which predictions are confirmed? (informational search, September 2014)

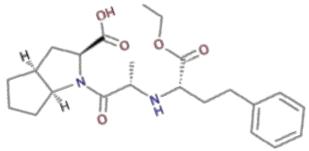


Sertraline — **Cocain dependency treatment** — **+** — [2]

Amlodipine — **Antineoplastic enhancer (moderate BCRP/ABCG2 inhibitor)** — **+** — [3]



Oxaprozin — **Interleukin 1 antagonist (Inhibitor of production of Interleukin 1β)** — **+** — [4]



Ramipril — **Antiarthritic** — **+** — [5]

1. Poroikov V. et al. SAR and QSAR Environ. Res., 2001, 12: 327-344.

2. Mancino M.J. et al. J. Clin. Psychopharmacol., 2014, 34: 234–239.

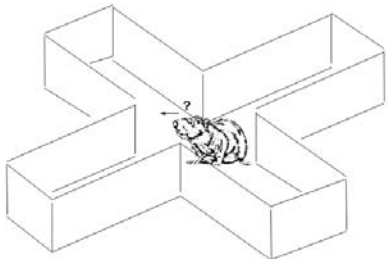
3. Takara K. et al. Mol. Med. Rep., 2012, 5: 603-609.

4. Rainsford K.D. et al. Inflammopharmacology, 2002, 10: 85–239.

5. Shi Q. et al. Arthritis Res. Ther., 2012, 14: R223.

Nootropic effect in some antihypertensive drugs?

Name	Pa (Nootropic effect), %
Captopril	44,6
Enalapril	65,5
Lisinopril	61,8
Perindopril	60,9
Quinapril	65,1
Ramipril	63,3
Monopril	30,9
Piracetam	81,7
Amlodipin	-
Hydrochlorothiazide	-



Perindopril in dose of 1 mg/kg, and quinapril and monopril in doses of 10 mg/kg improved the patrolling behavior in the maze, like piracetam and meclofenoxate (in doses of 300 and 120 mg/kg, respectively).

BMJ Open 2013;**3**:e002881 doi:10.1136/bmjopen-2013-002881

Geriatric medicine

Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia

Yang Gao[1,2], Rónán O'Caoimh[1], Liam Healy[1], David M Kerins[3,4], Joseph Eustace[5], Gordon Guyatt[6], David Sammon[2], D William Molloy[1,7]

+ Author Affiliations

Correspondence to

Professor D William Molloy; w.molloy@ucc.ie

Published 22 July 2013

Kryzhanovskii S.A. et al. *Pharm. Chem. J.*, 2012, 45: 605-611.

Let's validate the available computational tools for DRP

PASS (Prediction of Activity Spectra for Substances)

Poroikov V. et al. *Automatic Documentation and Mathematical Linguistics*, 1993, 27: 40-43.
Filimonov D. et al. *Experimental and Clinical Pharmacology*, 1995, 58: 56-62.
Lagunin A. et al. *Bioinformatics*, 2000, 16: 747-748. (www.way2drug.com/passonline)
Filimonov D. *Chemistry of Heterocyclic Compounds*, 2014, No. 3, 483-499.

SEA (Similarity Ensemble Approach)

Keiser M.J. et al. *Nat. Biotech.*, 2007, 25:197-206. (sea.bkslab.org/)

PharmMapper

Liu X. et al. *Nucl. Acids Res.*, 2010, 38, W609-W614. (59.78.96.61/pharmmapper/)

DRAR-CPI

Luo H. et al. *Nucl. Acids Res.*, 2011, 39, W492-W498. (cpi.bio-x.cn/drar/)

Calculation is not finished yet (>1 month).

TargetHunter

Wang L. et al. *AAPS J.*, 2013, 15: 395-406. (www.cbligand.org/TargetHunter/)

SuperPred

Nickel J. et al. *Nucl. Acids Res.*, 2014, 42: W26-31. (prediction.charite.de/)

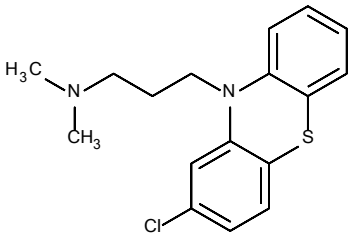
SwissTargetPrediction

Gfeller D. et al. *Nucl. Acids Res.*, 2014, 42, W32-W38. (www.swisstargetprediction.ch/)

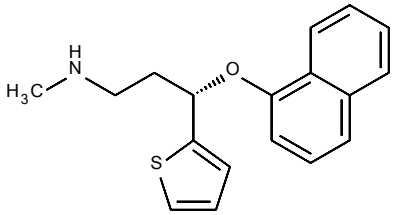
ChemProt 3.0

Kringelum J. et al. *DataBase*, 2016, 2016: bav123. (potentia.cbs.dtu.dk/ChemProt/)

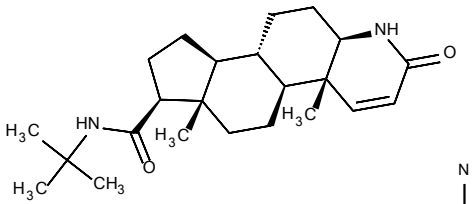
Molecules for validation of DRP computational tools



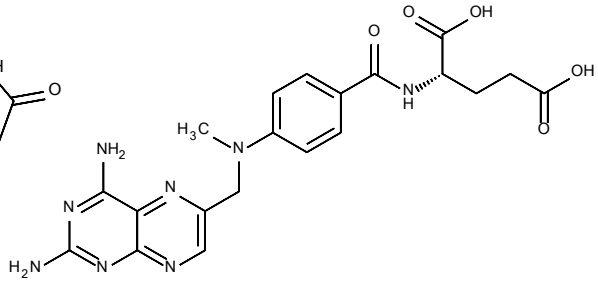
Chlorpromazine



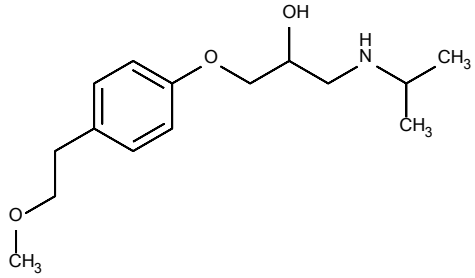
Duloxetine



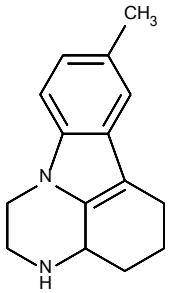
Finasteride



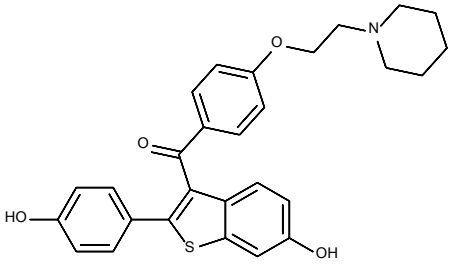
Methotrexate



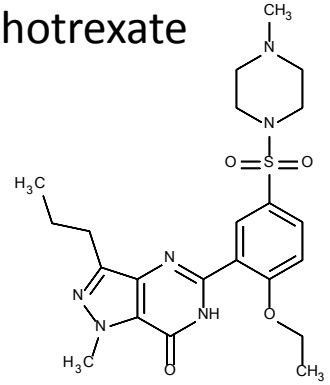
Metoprolol



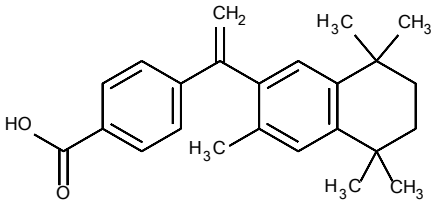
Pirlindol



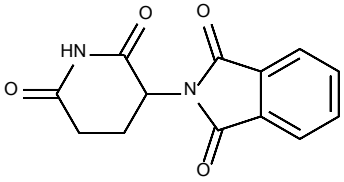
Raloxifene



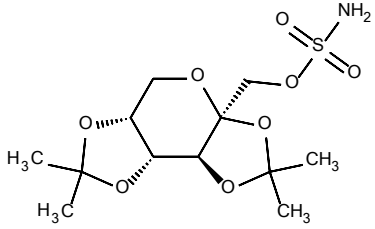
Sildenafil



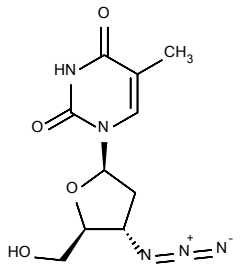
Targretin



Thalidomide



Topiramate



Zidovudine

Biological activity of compounds from validation set

Drug	Original indication	Repurposed indication
Chlorpromazine	Anti-emetic/antihistamine	Non-sedating tranquillizer
Duloxetine	Antidepressant	Stress urinary incontinence
Finasteride	Benign prostatic hyperplasia	Hair loss
Methotrexate	Acute leukemia	Osteosarcoma, breast cancer, Hodgkin lymphoma
Metoprolol	Migraine prophylaxis	Antihypertensive, Congestive heart failure
Pirlindol	Depression	Multiple sclerosis
Raloxifene	Invasive breast cancer	Osteoporosis
Sildenafil	Angina	Male erectile dysfunction
Targretin	Cancer	Alzheimer disease
Thalidomide	Sedative, nausea preventing	Leprosy, multiple myeloma
Topiramate	Epilepsy	Obesity
Zidovudine	Cancer	HIV/AIDS

Prediction of the original indications

Drug	ChP	SEA	PhM	STP	SP	TH	PASS
Chlorpromazine	+	+	--	+	+	+	+
Duloxetine	+	+	--	+	+	+	+
Finasteride	+	+	+	+	+	+	+
Methotrexate	+	+	+	+	+	+	+
Metoprolol	+	+	--	+	+	+	+
Pirlindol	+	--	+	--	--	--	+
Raloxifene	+	+	+	+	+	+	+
Sildenafil	+	+	+	+	+	+	+
Targretin	+	+	+	+	+	+	+
Thalidomide	--	--	--	--	--	--	+
Topiramate	+	--	--	--	--	--	+
Zidovudine	+	--	--	--	--	--	+

ChP – ChemProt 3.0; SEA – Similarity Ensemble Approach; PhM – PharmMapper; STP- SwissTargetPrediction; SP – SuperPred; TH – Target Hunter; PASS – Prediction of Activity Spectra for Substances.

Prediction of the repurposed indications

Drug	ChP	SEA	PhM	STP	SP	TH	PASS
Chlorpromazine	--	--	--	--	--	--	+
Duloxetine	--	--	--	--	--	--	+
Finasteride	--	--	--	--	--	--	+
Methotrexate	--	--	--	--	--	--	+
Metoprolol	+	+	--	+	+	+	+
Pirlindol	--	--	--	--	--	--	+
Raloxifene	+	+	+	+	+	+	+
Sildenafil	--	--	--	--	--	--	+
Targretin	--	--	--	--	--	--	+
Thalidomide	+	--	--	--	--	--	+
Topiramate	--	--	--	--	--	--	+
Zidovudine	+	+	--	--	--	--	+

ChP – ChemProt 3.0; SEA – Similarity Ensemble Approach; PhM – PharmMapper; STP-- SwissTargetPrediction; SP – SuperPred; TH – Target Hunter; PASS – Prediction of Activity Spectra for Substances.

Ranking of the predictions

Original indications

PharmMapper (6/12) < Target Hunter (8/12) = SuperPred (8/12) =

SwissTargetPrediction (8/12) = SEA (8/12) < ChemProt (11/12) < PASS (12/12)

Repurposed indications

PharmMapper (1/12) < Target Hunter (2/12) = SuperPred (2/12) =

SwissTargetPrediction (2/12) < SEA (3/12) < ChemProt (3/12) << PASS (12/12)

Ranking of predictions in the list (original indications)

Drug	ChP	SEA	PhM	STP	SP	TH	PASS
Chlorpromazine	209	20	--	11	11	6	66
Duloxetine	21	2	--	2	1	1	12
Finasteride	14	4	101	2	1	2	2
Methotrexate	11	1	39	5	1	2	7
Metoprolol	1	1	--	2	3	1	12
Pirlindol	1	--	19	--	--	--	2
Raloxifene	4	1	10	2	2	1	13
Sildenafil	85	1	52	2	4	2	5
Targretin	16	1	1	4	1	1	96
Thalidomide	--	--	--	--	--	--	78
Topiramate	5	--	--	--	--	--	1
Zidovudine	6	--	--	--	--	--	14

ChP – ChemProt 3.0; SEA – Similarity Ensemble Approach; PhM – PharmMapper; STP- SwissTargetPrediction; SP – SuperPred; TH – Target Hunter; PASS – Prediction of Activity Spectra for Substances.

Ranking of predictions in the list (repurposed indications)

Drug	ChP	SEA	PhM	STP	SP	TH	PASS
Chlorpromazine	--	--	--	--	--	--	105
Duloxetine	--	--	--	--	--	--	20
Finasteride	--	--	--	--	--	--	105
Methotrexate	--	--	--	--	--	--	19
Metoprolol	1	1		3	1	1	12
Pirlindol	--	--	--	--	--	--	1
Raloxifene	4	1	10	2	1	1	6
Sildenafil	--	--	--	--	--	--	3
Targretin	--	--	--	--	--	--	1095
Thalidomide	3	--	--	--	--	--	8
Topiramate	--	--	--	--	--	--	26
Zidovudine	34	2	--	--	--	--	19

ChP – ChemProt 3.0; SEA – Similarity Ensemble Approach; PhM – PharmMapper; STP-- SwissTargetPrediction; SP – SuperPred; TH – Target Hunter; PASS – Prediction of Activity Spectra for Substances.

Ranking of the predictions (taking into account the positions in the list)

Original indications

Target Hunter < SuperPred < SwissTargetPrediction < SEA < PharmMapper < PASS < ChemProt

Repurposed indications

Target Hunter = SuperPred < SEA < SwissTargetPrediction < PharmMapper < ChemProt < PASS

Clopidogrel: predicted vs. known activities

Abdominal pain
Acute neurologic disorders treatment
Agranulocytosis
Allergic reaction
Anaphylaxis
Anemia
Angioedema
Angiogenesis inhibitor
Antianginal
Antiarthritic
Anticoagulant
Antineoplastic
Antipsoriatic
Antithrombotic
Anxiety
Arthralgia
Atherosclerosis treatment
Back pain
Behavioral disturbance
Blindness
Bronchoconstrictor
Cardiotoxic
Cataract
CCL4 expression enhancer
CCL5 expression enhancer
Chest pain
Colic
Colitis
Conjunctivitis
Consciousness alteration
Constipation
Cough
CYP2 substrate
CYP2C substrate
CYP2C19 inhibitor
CYP2C19 substrate
CYP2C9 inhibitor
CYP3A substrate
CYP3A4 substrate
Cytochrome P450 inhibitor
Dermatitis
Dermatologic
Dizziness
Drug eruption
Dyspepsia
Emetic
Eosinophilia
Erythema
Erythema multiforme
Exanthema
Flatulence
GP IIb/IIIa receptor antagonist
Hallucinogen
Headache
Heart failure
Hematotoxic
Hemorrhage
Henoch-Schonlein purpura
Hepatic failure
Hepatitis
Hepatotoxic
Hypertensive
Hyperthermic
Hypotension
Infection
Insomnia
Lassitude
Leukopenia
Lichen planus
Lichenoid eruption
Malaise
Menstruation disturbance
Myalgia
Nausea
Necrosis
Nephrotoxic
Neuroprotect
Neutropenia
Ocular toxicity
Pain
Pancreatitis
Pancytopenia
Platelet aggregation inhibitor
Platelet antagonist
Pruritus
Pulmonary embolism
Purinergic P2 antagonist
Purinergic P2T antagonist
Purinergic P2Y antagonist
Purinergic P2Y12 antagonist
Purinergic receptor antagonist
Purpura
Renal colic
Reproductive dysfunction
Rhinitis
Sensory disturbance
Serum sickness
Shock
Sinusitis
Sleep disturbance
Stomatitis
Syncope
THBS1 expression enhancer
Thrombocytopenia
Toxic
Toxic epidermal necrolysis
Toxic, gastrointestinal
TP53 expression enhancer
Urticaria
Vasculitis
Vertigo
Vision disturbance

Blue – predictions coincided with the experiment.
Black – unpredictable activities.
Red – unpredicted activities.

"Not all repositioning projects that work on paper are really feasible," says Tudor Oprea, a bioinformatics researcher at the University of New Mexico in Albuquerque who monitors the field in addition to doing his own repositioning work. For instance, he says, side effects that would be acceptable for a life-threatening disease might not be acceptable for a chronic one. And the standard business case for repositioning — that costs are slashed because safety tests are already in the bag — works only if the dose and mode of administration remain similar. If the new disease requires a significantly higher dose, the drug will have to go through phase I trials again. In the end, says Oprea, development costs can be similar to those for a new molecule".

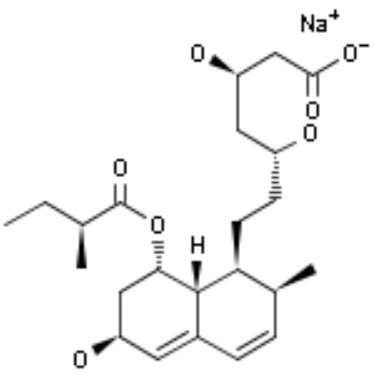
NICOLA NOSENGO 314-316 | NATURE | VOL 534 | 16 JUNE 2016

Let me remind you that our knowledges in life sciences are rather incomplete

'That's Dr Arnold Moore. He's conducting an experiment to test the theory that most great scientific discoveries were hit on by accident.'

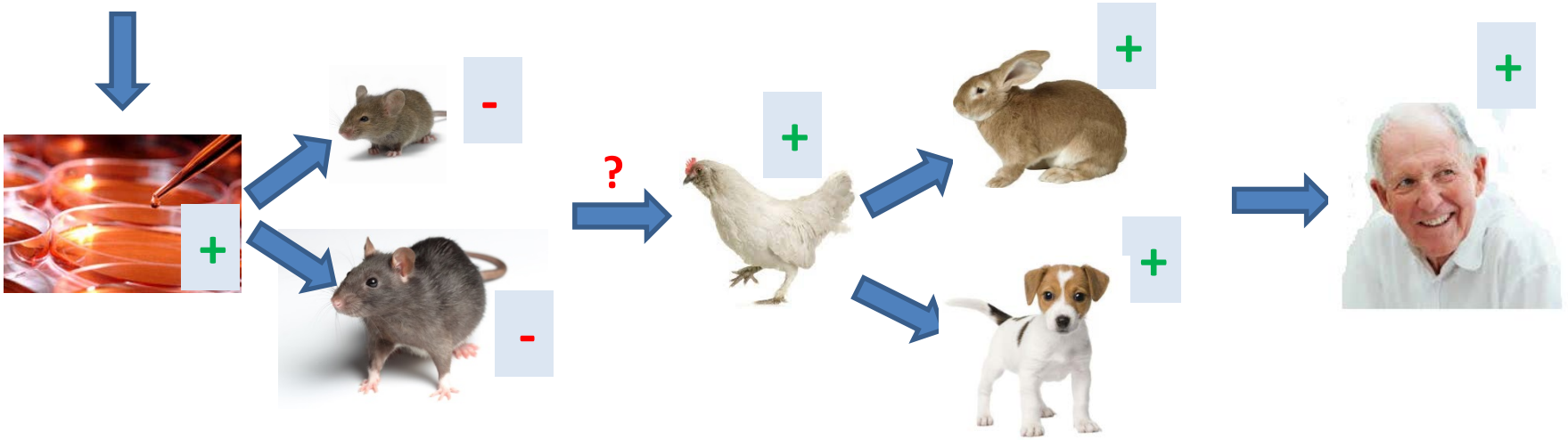
Drawing by Hoff ; © 1957
The New Yorker Magazine, Inc.

The history of Pravastatin development by Sankyo



HMG-CoA reductase inhibitor

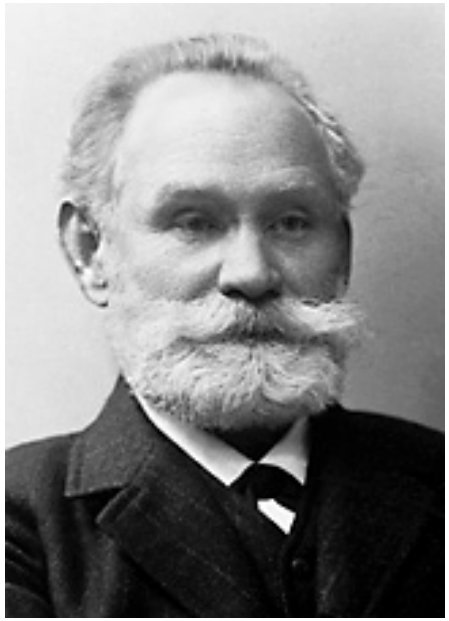
CS-514, pravastatin - derivative ML236B (compactin), which was extracted from fungies *Penicillium citrinum* in 1970 by Sankyo Pharma Inc. In 1989 Pravastatin sodium was registered as hydroxymethylglutaril-CoA-reductase inhibitor for treatment of familial hypercholesterolemia and hyperlipidemia. In 2005 Pravachol (Pravastatin sodium) became blockbuster in US with annual sales 1,3 billion dollars.



Diabetes Res Clin Pract. 1986 Jun;2(3):179-81.

Effect of CS-514, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, on lipoprotein and apolipoprotein in plasma of hypercholesterolemic diabetics.

Yoshino G, Kazumi T, Kasama T, Iwatani I, Iwai M, Inui A, Otsuki M, Baba S.



Ivan Pavlov

The Nobel Prize in Physiology or Medicine 1904 was awarded to Ivan Pavlov "in recognition of his work on the physiology of digestion, through which knowledge on vital aspects of the subject has been transformed and enlarged".

"On the vast territory of medical knowledge pharmacology seems, one may say the border, where there is a particularly lively exchange of services between the natural scientific basis of medicine, physiology, and medical knowledge - therapy, and where therefore particularly felt the mutual usefulness of one knowledge to another. Pharmacology, studying animal drug action by using physiological methods, improving therapy, puts it on a rational solid ground; on the other hand, the treatment indication, subjected to laboratory analysis, often leads to the discovery of the such physiological phenomena that would remain undetected for a long time with pure physiological study."

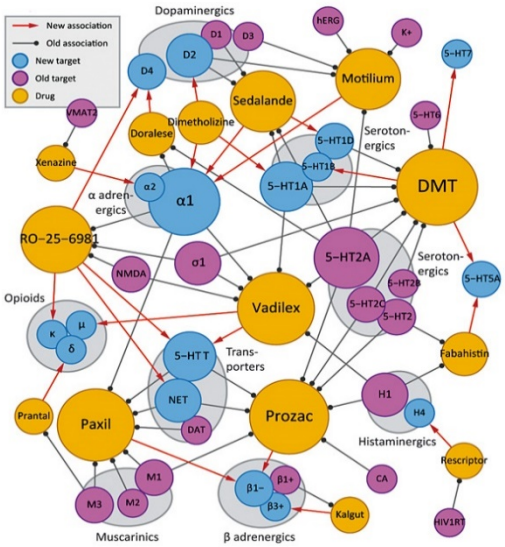
No matter, where you start from…

Target

Personality

Ligand

Disease



Feature Endeavour Vol. 37 No. 3
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SciVerse ScienceDirect

Understanding life together: A brief history of collaboration in biology

Niki Vermeulen[1,*], John N. Parker[2] and Bart Penders[3]

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Manchester M13 9PL, UK
[2]Barrett, The Honors College, Arizona State University, P.O. Box 871612, Tempe, AZ 85287, USA
[3]Department of Health, Ethics & Society, School for Public Health and Primary Care (CAPHRI), Maastricht University,
P.O. Box 616, 6200 MD Maastricht, The Netherlands

Abstract

The history of science shows a shift from single-investigator 'little science' to increasingly large, expensive, multinational, interdisciplinary and interdependent 'big science'. In physics and allied fields this shift has been well documented, but the rise of collaboration in the life sciences and its effect on scientific work and knowledge has received little attention. Research in biology exhibits different historical trajectories and organisation of collaboration in field and laboratory – differences still visible in contemporary collaborations such as the Census of Marine Life and the Human Genome Project. We employ these case studies as strategic exemplars, supplemented with existing research on col-

Hood and Auffray *Genome Medicine* 2013, **5**:110
http://genomemedicine.com/content/5/12/110

Arch Bronconeumol. 2011;47(1):35-40
ARCHIVOS DE BRONCONEUMOLOGIA
www.archbronconeumol.org

Review

P4 Medicine: the Future Around the Corner

Patricia Sobradillo,[a,b,c,*] Francisco Pozo,[a,d] Álvar Agustí[a,b,c,e]

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[b]Instituto del Tórax, Hospital Clínic, Universidad de Barcelona, Spain
[c]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[d]Hospital 12 de Octubre, Madrid, Spain
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Biotechnology Journal
DOI 10.1002/biot.201200242 Biotechnol. J. 2012, 7, 938–939

Editorial:
Systems biology and personalized medicine – the future is now

During the past decades, we have witnessed extraordinary advances in experimental and

converge through implementation of systems biology approaches combining advanced imaging data to ept of systems or edicine one step

genomic analysis converge through of systems bio- ersonalized medi- ality.

a focus on the detection and treatment of disease to the prevention of disease occurrence based on the analysis of individual characteristics, **Ralph Snyderman** [3] discusses how this can help reduce the high burden of chronic diseases. **Larry Smarr** [4] then shares his decade-long personal experience in quantifying his personal health state through regular quantitative monitoring of his own body,

Advanced Drug Delivery Reviews 65 (2013) 905–911

EDITORIAL

Participatory medicine: a driving force for revolutionizing healthcare

Leroy Hood[1*] and Charles Auffray[2*]

Healthcare is undergoing a profound revolution as a consequence of three contemporary thrusts: systems medicine [1-4], big data and patient involvement in their own health through social networks. This convergence is leading to a medicine that is predictive, preventive, personalized and participatory (P4) [4-7]. The first three Ps, predictive, preventive and personalized, were delineated in the early 2000s [1,2], whereas the fourth P, participatory, was added later. To achieve a participatory health-

individual's network disease-perturbed state information will prov mechanisms, new appr peutics, and a platform

Participatory medici
Implementation of P4 major objectives. First,

Contents lists available at SciVerse ScienceDirect
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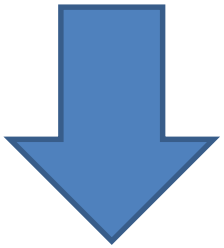
journal homepage: www.elsevier.com/locate/addr

Delivering systems pharmacogenomics towards precision medicine through mathematics☆

Drug Repurposing: New Uses for Old Drugs or Systems Biomedicine?



Drug Repurposing: New Uses for Old Drugs and Systems Biomedicine.

Summary

- **Drug repurposing is a promising way for finding new medicines.**
- **“Not all repositioning projects that work on paper are really feasible” (T. Oprea).**
- **Chemoinformatics methods help to identify the most prospective directions of research.**
- **There are still some “rooms”, to improve the existing and develop novel computational methods for DRP.**
- **Drug repurposing provides opportunities for both finding new uses of old drugs and development of the systems biomedicine.**

Acknowledgements to the key persons and to the financial support of our long-term efforts

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Alexey Zakharov, Ph.D.

МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ РОССИЙСКОЙ ФЕДЕРАЦИИ

РОССИЙСКИЙ НАУЧНЫЙ ФОНД
ПОДДЕРЖКА И РАЗВИТИЕ

RFBR RUSSIAN FOUNDATION FOR BASIC RESEARCH

Sk Сколково

And to many other colleagues who participate(d) in our projects

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UBC

AstraZeneca

Thank you for your kind attention!

We are open for collaboration.

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