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

Vladimir Poroikov

Institute of Biomedical Chemistry
Pogodinskaya Str. 10, Bldg.8, 119121, Moscow, Russia
E-mail: vladimir.poroikov@ibmc.msk.ru

University of Strasbourg, 27 June - 1 July 2016
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
A New Journal for the Drug Repurposing Community

Hermann A.M. Muecke, 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/
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.
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

- **High Time, Cost, Risk**
  - **NCEs**
    - 10-12 years
    - $1-2 Bln
    - 0.1-1% success

- **Low Time, Cost, Risk**
  - **Generics**

- **Low Reward**
  - **Repurposing**
    - 1-2 years
    - $2-10 mln
    - 25+% success

Some examples of drug repurposing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary indication (year)</th>
<th>Repurposed indication (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>NSAID (1897)</td>
<td>Antithrombotic (1956)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Cancer (1964)</td>
<td>HIV/AIDS (1987)</td>
</tr>
</tbody>
</table>
Drug repurposing (DRP): terminology and definitions

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

**Phentolamine--rediscovery of an old drug.**
Gould L.


PMID: 5789859 [PubMed - indexed for MEDLINE]

**Drug repositioning: identifying and developing new uses for existing drugs.**
Ashburn TT¹, Thor KB.


PMID: 15286734 [PubMed - indexed for MEDLINE]

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.

GERIATRICS, July 1969 113

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

Publications on drug repurposing covered by Web of Science
DRP: How it happens?

- Serendipity, and text mining, e.g.: Thalidomide
- Observe unexpected side effects, e.g.: Sildenafil
- Identify compounds that modulate specific disease phenotypes
- Find new disease pathways
- Define new role of existing targets, e.g.: Finasteride
- Identify new drug-target interactions, e.g.: Methotrexate
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

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.

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

   Lv P, Li HY, Ji SS, Li W, Fan LJ.
   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.
   PMID: 26588701
   Similar articles

3. The effect of thalidomide on experimental autoimmune myasthenia gravis.
   Crain E, McIntosh KR, Gordon G, Pestronk A, Drachman DB.
   PMID: 2788425
   Similar articles
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

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

- Antineoplastic (Acute leukemia), Dihydrofolate reductase inhibitor - 1953
- Osteosarcoma, breast cancer, acute lymphoblastic leukemia, and Hodgkin lymphoma - 1988
- NF-κB and TNF-α signaling pathway inhibitor, antiangiogenic, antiinflammatory - 2010
- Antiarthritis - 1954

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. In conjunction with amoxicillin, and in the treatment of Parkinson’s disease, where L-3,4-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”.

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)**

**SEA (Similarity Ensemble Approach)**

**PharmMapper**

**DRAR-CPI**

**TargetHunter**

**SuperPred**

**SwissTargetPrediction**

**ChemProt 3.0**
More info about the computational resources:

**Review**

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

Alexey A. Lagunin, Rajesh K. Goel, Dinesh Y. Gawande, Priynka Pahwa, Tatyana A. Glorioso, Alexander V. Dmitriev, Sergey M. Ivanov, Anastasia V. Rudik, Varvara I. Konova, Pavel V. Pogodin, Dmitry S. Druzhilovsky, and Vladimir V. Poroikov

**Review**

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

In *silico* assessment of adverse drug reactions and associated mechanisms

Sergey M. Ivanov, Alexey A. Lagunin, and Vladimir V. Poroikov
Requirements for a computer program evaluated biological activity profiles (spectra)

- Predicts (ideally) all known activities
- Prediction on the basis of structural formulae (MOL or SDF)
- Possibility of training with a new data
- User-friendly interface
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.

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.
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.

\[
M = V + VgM = V + VgV + VgVgV + VgVgVg + \ldots \\
M_i = V_i + V_i gM = V_i + V_i g(M_1 + M_2 + \ldots + M_m)
\]

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

- **MNA** - Multilevel Neighborhoods of Atoms
- **QNA** - Quantitative Neighborhoods of Atoms
- **LMNA** - Labeled Multilevel Neighborhoods of Atoms


Substance representation: Clopidogrel

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
Reliable data on structure and activity of drug-like molecules

PASS: Prediction of Activity Spectra for Substances

Full text publications, databases, presentations at conferences etc.

PASS Training set
(~1 mln structures)

MNA descriptors

Training procedure

Bayesian algorithm

SAR knowledgebase

New molecule

Prediction results

Example of prediction for Ramipril
PharmaExpert: Interpretation of the prediction results

A. Lagunin
PharmaExpert: Interpretation of the prediction results
Web-services based on our methods

www.way2drug.com/Projects.php
Some examples of practical applications of biological activity spectra prediction

Athina Geronikaki, AUT, Greece
Search for multitarget drugs

Rajesh Goel, PU, India

Marc Nicklaus, NCI/NIH, USA

Sergey Kryzhanovsky, Inst. of Pharmacol., Russia

Finding molecules with needed effects and MOA

Drug repurposing

Estimating drug-drug interactions for phytoconstituents of medicinal plants
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.
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)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>Cocain dependency treatment</td>
<td>+</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Antineoplastic enhancer (moderate BCRP/ABCG2 inhibitor)</td>
<td>+</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Interleukin 1 antagonist (Inhibitor of production of Interleukin 1β)</td>
<td>+</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Antiarthritic</td>
<td>+</td>
</tr>
</tbody>
</table>

Nootropic effect in some antihypertensive drugs?

<table>
<thead>
<tr>
<th>Name</th>
<th>Pa (Nootropic effect), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>44,6</td>
</tr>
<tr>
<td>Enalapril</td>
<td>65,5</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>61,8</td>
</tr>
<tr>
<td>Perindopril</td>
<td>60,9</td>
</tr>
<tr>
<td>Quinapril</td>
<td>65,1</td>
</tr>
<tr>
<td>Ramipril</td>
<td>63,3</td>
</tr>
<tr>
<td>Monopril</td>
<td>30,9</td>
</tr>
<tr>
<td>Piracetam</td>
<td>81,7</td>
</tr>
<tr>
<td>Amlodipin</td>
<td>-</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>-</td>
</tr>
</tbody>
</table>

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).

Let’s validate the available computational tools for DRP

PASS (Prediction of Activity Spectra for Substances)

SEA (Similarity Ensemble Approach)

PharmMapper

DRAR-CPI
Calculation is not finished yet (>1 month).

TargetHunter

SuperPred

SwissTargetPrediction

ChemProt 3.0
Molecules for validation of DRP computational tools

Chlorpromazine

Duloxetine

Finasteride

Methotrexate

Metoprolol

Pirlindol

Raloxifene

Sildenafil

Targetretin

Thalidomide

Topiramate

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>ChP</th>
<th>SEA</th>
<th>PhM</th>
<th>STP</th>
<th>SP</th>
<th>TH</th>
<th>PASS</th>
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<tbody>
<tr>
<td>Chlorpromazine</td>
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<td>Finasteride</td>
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<td>Raloxifene</td>
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<td>Sildenafil</td>
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<td>Targretin</td>
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<td>Thalidomide</td>
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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

<table>
<thead>
<tr>
<th>Drug</th>
<th>ChP</th>
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</table>

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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ChP</th>
<th>SEA</th>
<th>PhM</th>
<th>STP</th>
<th>SP</th>
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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
Hemorrhage
Henoch-Schonlein purpura
Hepatic failure
Hepatitis
Hepatotoxic
Hypertensive
Hypertensive
Hypotension
Infection
Insomnia
Lassitude
Leukopenia
Lichen planus
Lichenoid eruption
Malaise
Menstruation disturbance
Myalgia
Nausea
Necrosis
Nephrotic
Neuroprotect
Neutropenia
Ocular toxicity
Pain
Pancreatitis
Pancytopenia
Platelet aggregation inhibitor
Platelet antagonist
Pruritus
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
Syncpe
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.”
Let me remind you that our knowledges in life sciences are rather incomplete.
The history of Pravastatin development by Sankyo

CS-514, pravastatin - derivative ML236B (compactin), which was extracted from fungi *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.


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

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.

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".
No matter, where you start from...
Understanding life together: A brief history of collaboration in biology

Niki Vermeulen¹,*, John N. Parker² and Bart Penders³

¹Centre for the History of Science, Technology and Medicine, University of Manchester, Simon Building, Brunswick Street, Manchester M13 9PL, UK
²Barrett, The Honors College, Arizona State University, P.O. Box 871612, Tempe, AZ 85287, USA
³Department 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 collab-

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

During the past decades, we have witnessed extraordinary advances in experimental and theoretical biology that have paved the way for the development of systems biology approaches. Combining advanced imaging data with clinical and genetic information has led to the identification of new pathways and metabolites that were previously unknown. This convergence of technologies has enabled the development of personalized medicine, where treatment is tailored to the individual's genetic makeup.

Participatory medicine: a driving force for revolutionizing healthcare

Leroy Hood* and Charles Auffray*

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 healthcare system, technical and societal challenges must be addressed, including the secure sharing of individual's network disease-perturbed state information will prove mechanisms, new appraoches, and a platform

Delivering systems pharmacogenomics towards precision medicine through mathematics

* Correspondence: leroy.hood@nih.gov and charles.auffray@nih.gov

Advanced Drug Delivery Reviews 65 (2013) 905–911
Drug Repurposing: New Uses for Old Drugs or Systems Biomedicine?

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

Tatyana Gloriozova, M.Sc.
Alexey Lagunin, Dr. Sci.
Dmitry Filimonov, Ph.D.
Dmitry Druzhilovskiy, Ph.D.
Alexey Zakharov, Ph.D.

And to many other colleagues who participate(d) in our projects
Thank you for your kind attention!

We are open for collaboration.

Please, address your questions to:

vladimir.poroikov@ibmc.msk.ru

or

vvp1951@yandex.ru