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Upcoming ACS Webinars®

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ACS Chemistry for Life®

Thursday, May 1, 2014

"Cannabis Chemistry 101"

Christopher Hudalla, Ph.D., ProVerde Laboratories

Jeff Kiplinger, Ph.D., Founder and President of Averica Discovery Services

Thursday, May 8, 2014

"Surviving and Succeeding in Grad School"

Sam Pazicni, Assistant Professor of Chemistry, University of New Hampshire

Patricia Simpson, Director of Academic Advising and Career Services, University of Illinois Urbana-Champaign

Next in the Drug Discovery Series!

Thursday, May 29, 2014

"Lead Optimization – Building Efficacy & Safety" Session 4

Dr. Craig Lindsley of Vanderbilt University

Dr. Joe Fortunak of Howard University

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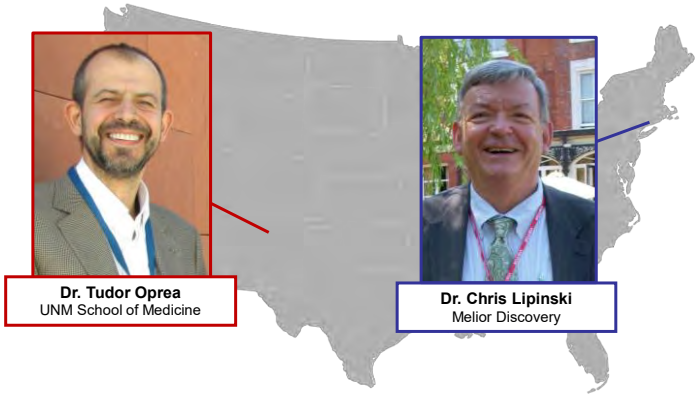
2014 Drug Discovery Series

Session 3: Key Concepts in Identifying Drug Leads



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Key Concepts in Identifying Drug Leads

Tudor I. Oprea
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DTU Center for Biological Sequence Analysis
Lyngby, Denmark

Sahlgrens Academy Dept of Rheumatology & Inflammation
Research, Gothenburg Sweden

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ACS Webinars® 2014 Drug Discovery Series, Session 3

What You Will Learn

- Leads as drug prototypes: Lessons from the past may guide the present
- Rule-of-Five, Lead-like and Rule-of-three criteria: How to narrow the search space
- Drug-likeness is a deceiving concept, and lead-like criteria are context dependent
- Always seek multiple lead series; choosing the smallest lead may be of benefit

Note: all hyperlinks are valid as of 4/22/14

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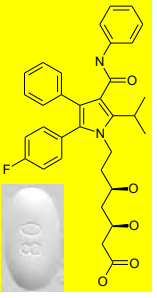
What is a Drug?

- Drugs (medicines) are well defined entities in the clinical usage: a substance used to alter symptoms, kill microbes, balance metabolism or hormones, etc.
- However, *drugs are an ill-defined entity when it comes down to chemistry:* there are no clear features that should be included in a drug.
- If you work for a car factory, you can work on features because you understand the “car” concept.
- *In drug discovery, we go by trial and error.*



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But …what IS a drug?!

- It is easier to define what a drug is *not:* it should not contain reactive moieties *(exceptions exist!)*, heavy metals *(exceptions exist!)*, be too large/small, etc.
- Most definitions do not address issues like active ingredients, dose strength, formulation, combinations, etc
- To complicate the issue, Big Pharma executives use *economic factors* when defining a (blockbuster) drug*:*
- The Cost Of Creating A New Drug Now $5 Billion, Pushing Big Pharma To Change* [numbers just go up…]
- By this definition, fewer than 50 medicines can make the cut (none that will cure tuberculosis or malaria)

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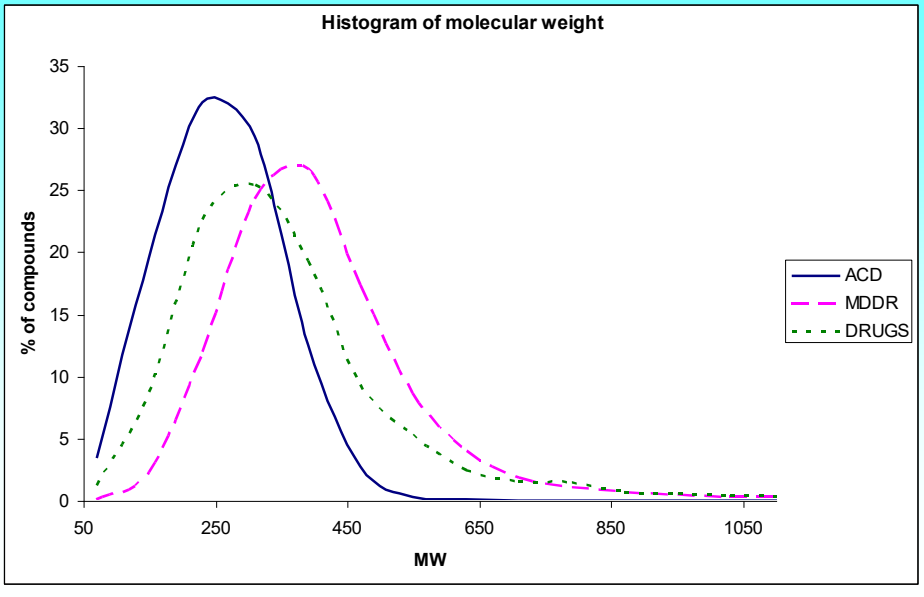
*according to Forbes Magazine

In Pursuit of Drug-likeness

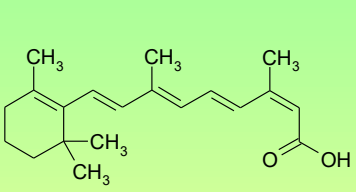
- Can we look at drugs and understand what differentiates them from other sets of structures?
- To date, most publications treated this as a binary discrimination problem, e.g., ACD (“non-drugs”) vs. MDDR or WDI (“drug-like”) datasets
- A “drug” should match a look-up list (only approved drugs are classified as such); we then used the multi-class approach, to discriminate between ACD (non-drugs), MDDR (drug-like) and DRUG (launched) [1]
- Few recognize that drug-likeness is not an intrinsic property of chemicals (i.e., regulatory agencies vote to attribute or remove the “drug” quality), and models can offer guidelines, not answers [2]

[1] O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387–1394
[2] O. Ursu, A. Ryan, A. Goldblum & T.I. Oprea, WIRE Comp Mol Sci 2011 1:760-781

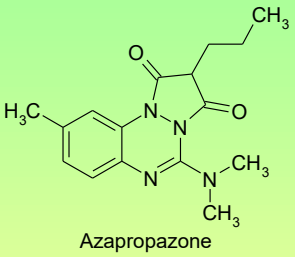
Size Matters



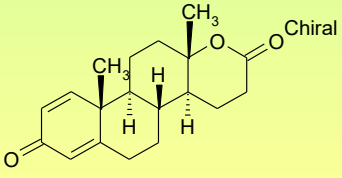
What Do These Drugs Have in Common?



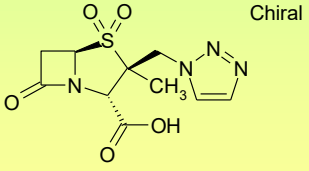
Isotretinoin; 13-cis-retinoic acid



Azapropazone



Testolactone



Tazobactam

Audience Trivia Question

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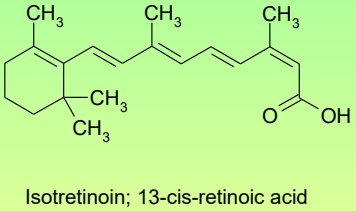
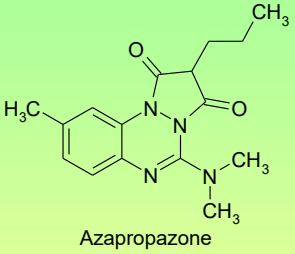
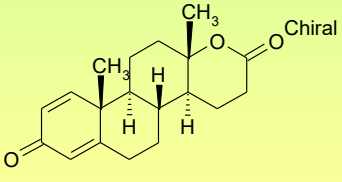
What Do These Drugs Have in Common?



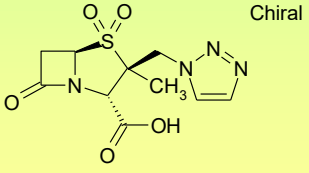
Isotretinoin; 13-cis-retinoic acid



Azapropazone



Testolactone



Tazobactam

Roughly the Same MW, ~300.5

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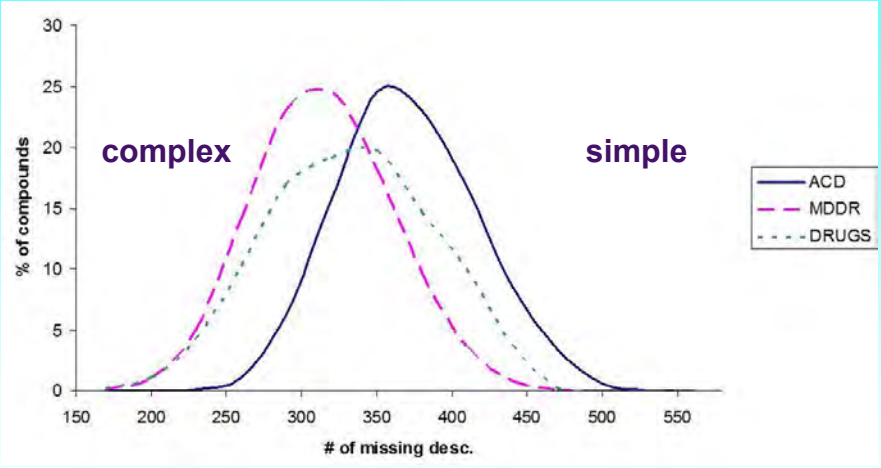
Simplicity Can Discriminate – or Does it?!



Counting the presence of chemical features ("keys") separates ~90% of DRUGS (180 fingerprint bits ON, max 480 keys turned OFF) from ACD (max 30 ON, and up to 530 keys OFF). However, MDDR molecules are somewhat more complex than drugs.

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O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Take Home Message 1

- We chose to separate DRUGS from MDDR since the purpose is to understand aspects that are "drug-like", not "MDDR-like"
- Even after size correction (via MW) it is difficult to ignore the role of molecular complexity:
- **Drugs are on average more complex** (i.e., more features turned "on") **compared to chemical reagents**
- However, many chemicals not in therapeutic use are quite complex as well, so in fact machine learning models are over-trained to discriminate "simple" from "complex".
- Is that really "drug-likeness"? Or is it a simplicity-detector?
- *Caveat emptor*, drug-like computations offer no guarantee that the molecule(s) in question may be drugs

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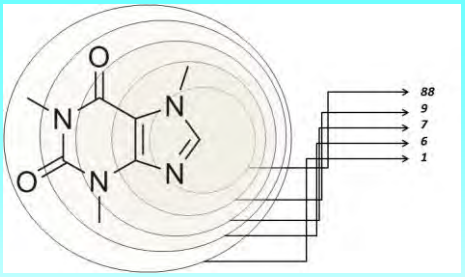
Exhausting Fingerprints Space



Fragmentation of molecules up to 5 bonds radius (e.g., caffeine)

Fragment occurrence ratios (OR) were computed based on fragmentation of all chemicals from DRUGS and ACD

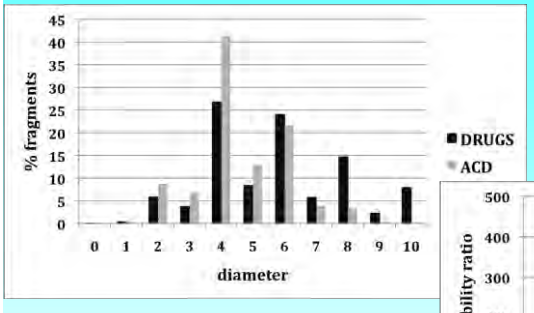
Datasets:

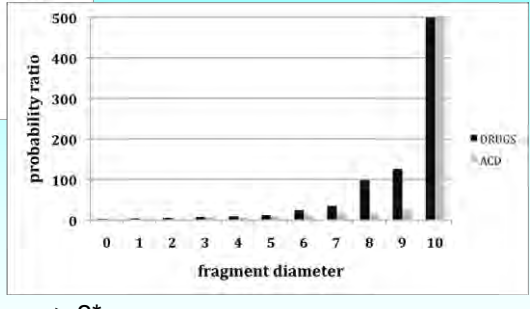
ACD 2002.1 (178,011 compounds) vs. DRUGS (3,823 compounds)

External prediction: MDDR 2006.2 (169,277 compounds after removing duplicates from ACD & DRUGS)

O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Fragments Distributions & Ratios



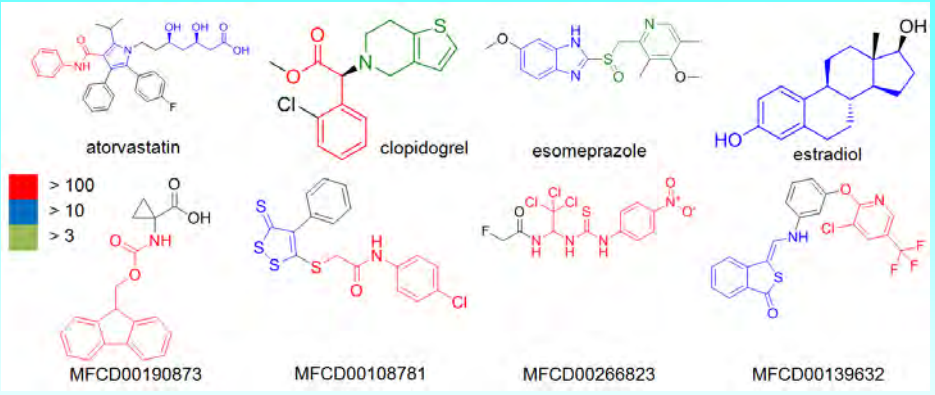


88,037 DRUGS fragments
12,970 fragments w/ OR ≥ 3
11,016 fragments w/ probability $p_{DRUGS} \geq 2^{*}p_{ACD}$

1,360,790 ACD fragments
7,215 fragments w/ OR ≥ 3
4,954 fragments w/ probability $p_{ACD} \geq 2^{*}p_{DRUGS}$

O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Fragments Occurrence: Examples



This color-coded illustration points out how different fragment occurrence is perceived and evaluated by *machines* (not individuals). Many may think that the bottom row molecules are drug-like. They contain fragments predominantly found in ACD.

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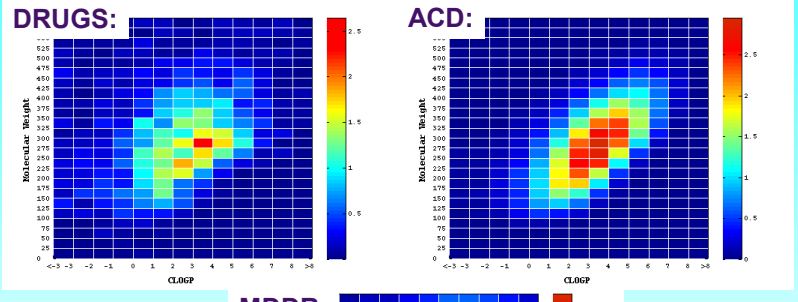
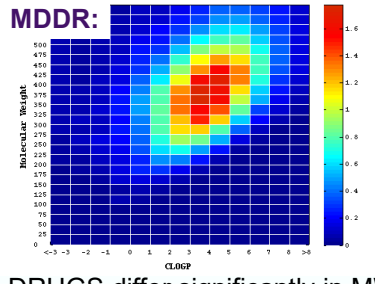
O. Ursu, A. Ryan, A. Goldblum & T.I. Oprea, WIRE Comp Mol Sci 2011 1:760-781

MW and CLOGP



DRUGS @ 90%:
MW = 562.04
CLOGP = 5.48

MDDR @ 90%:
MW = 646.07
CLOGP = 6.68



ACD @ 90%:
MW = 417.28
CLOGP = 5.55

Because ACD and DRUGS differ significantly in MW distribution, we introduced the optional rule, MW ≤ 600 in the DLF (drug-like filter)

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O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Rule of Five Enforcement

Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings☆

Christopher A. Lipinski*, Franco Lombardo, Beryl W. Dominy, Paul J. Feeney

Central Research Division, Pfizer Inc., Groton, CT 06340, USA

Received 9 August 1996; accepted 14 August 1996

Abstract

Experimental and computational approaches to estimate solubility and permeability in discovery and development settings are described. In the discovery setting 'the rule of 5' predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (MWT) is greater than 500 and the calculated Log P (CLogP) is greater than 5 (or MlogP > 4.15). Computational methodology for the rule-based Moriguchi Log P (MLogP) calculation is described. Turbidimetric solubility measurement is described and applied to known drugs. High throughput screening (HTS) leads tend to have higher MWT and Log P and lower turbidimetric solubility than leads in the pre-HTS era. In the development setting, solubility calculations focus on exact value prediction and are difficult because of polymorphism. Recent work on linear free energy relationships and Log P approaches are critically reviewed. Useful predictions are possible in closely related analog series when coupled with experimental thermodynamic solubility measurements.

Keywords: Rule of 5; Computational alert; Poor absorption or permeation; MWT; MLogP; H-Bond donors and acceptors; Turbidimetric solubility; Thermodynamic solubility; Solubility calculation

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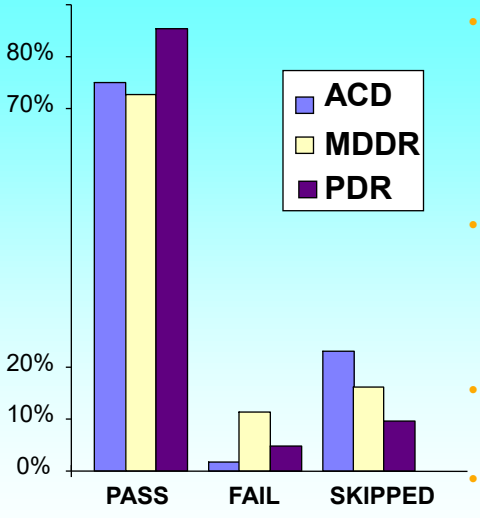
C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Adv. Drug. Deliv. Rev. 1997, 23, 3-25

Rule of Five & Drug-Likeness



- World-wide drug discovery programs apply **the Rule of 5: MW ≤ 500, cLogP ≤ 5, H-don ≤ 5, H-acc ≤ 10**. Any 2 violations → poor %Oral
- **The Rule of 5 is not for "druglikeness".** Its use is intended as filter in early HTS hit analysis/discovery.
- Though applied literally, Ro5 was derived from drugs
- … thus, it cannot be directly applied to leads.

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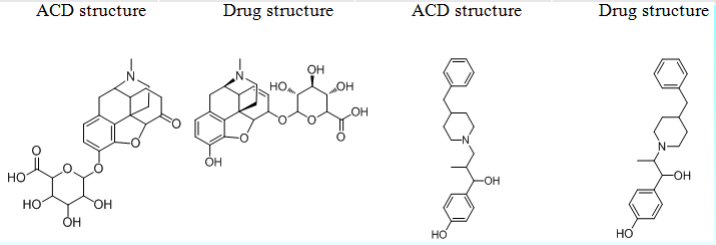
T.I. Oprea, *J Comput-Aided Mol Des* 2000 14, 251-264

Drug-likeness: Results Using Filters

FILTER	ACD (pass)	DRUGS (pass)	MDDR (pass)
DLF	**39.65%**	87.05%	78.45%
DLF + MW	**40.17%**	78.81%	65.64%



- Almost 40% of ACD structures pass the DLF, which proves that *ACD is far from perfect as a surrogate for "non-drugs"*
- The DLF-compliant ACD subset has properties (LogP, MW, PSA) similar to DRUGS, not MDDR (see paper for details)

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O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Take Home Message 2

- Rule of Five is not a "drug-like" criterion/filter
- ACD (reagents) served as the "non-drugs" reference since 1998, *yet ~40% of ACD compounds are similar to drugs*
- We used ACD 2002.1 as "non-drugs" to maintain compatibility with earlier work (key druglike references pre-date 2002)
- Newer updates of chemical catalogs deliberately shift towards "drug-like" chemicals. Chemical vendors modify their catalog offering in order to attract pharmaceutically-oriented customers

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O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

To Summarize Drug-Likeness by Structure

- Molecular fragments from ~3800 drugs were compared to ~178,000 ACD chemicals. This resulted in 15,970 fragments: 11,016 from drugs and 4,954 from ACD, respectively.
- Using DLF + MW, 78.81% of DRUGS, 40.17% of ACD, 65.64% of MDDR and 52.04% of pesticides pass the DLF
- There is a danger in relying non-discriminately on machine learning techniques that artificially separate “drugs” from “non-drugs”.
- Recall “drug” is a man-attributed quality

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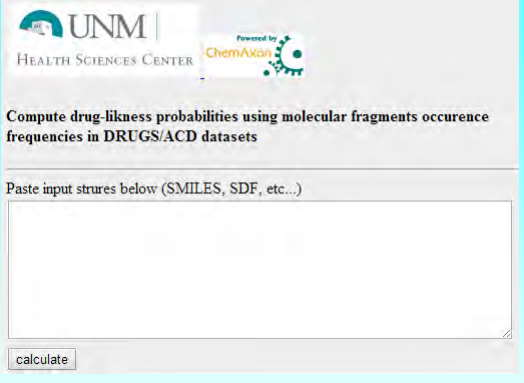
O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Take Home Tool 1



The 11,016 drug fragments and 4,954 ACD fragments are encoded into the DLF tool on-line (free to use):

http://pasilla.health.unm.edu/tomcat/drug-likeness

DLF does not use machine learning, i.e, ACD is not a negative label.

As the time-capsule illustrates, learning (incl. ML) relies on models. As such, DLF is not a “model-free” system (this is an old epistemic issue). *All models need updates…*

Time Capsule:

75 drugs approved *after we developed DLF* are classified as follows:

21 as ACD (28%)

47 as DRUG (62.67%)

7 as “unknown” (9.33%)

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O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

What is a Lead?

- Many compounds are *hits* or *actives*, or even chemical probes

…but not all become leads

- Leads are prototypes that meet well-defined criteria in drug discovery projects:
- validated biological activity (both in primary and secondary screens) against known targets [or well understood phenotypic screens], and must be part of a compound series (with SAR if possible)
- must be patentable, and display good initial ADMET profile.

T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308-1315

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Is There A Leadlike Space?

- There is a general consensus that lead discovery is an essential goal that **proceeds** drug discovery
- The only way to analyze the nature of leads is to examine structures that, ***historically*****,** were leads.
- Can these structures provide an objective link between lead-space and drug-space?
- Lead structures are often disclosed in a series (SAR), making it difficult to pinpoint a particular compound
- Furthermore, *a drug can have 1 or more leads*
- *a lead can be a drug*
- *a lead can result in several drugs*

T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308-1315

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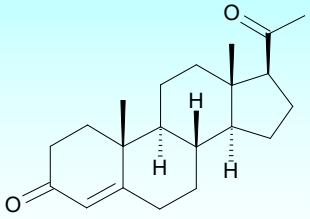
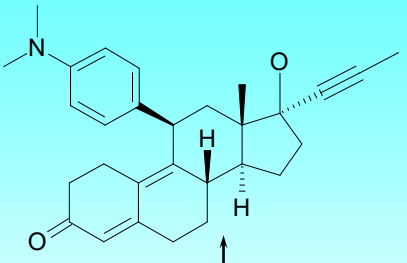
Leads 1: Mifepristone

Drug with multiple leads:

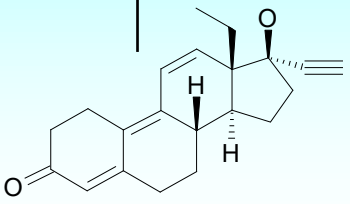
Mifepristone originates from progesterone and RU2323



Progesterone



RU486



RU2323

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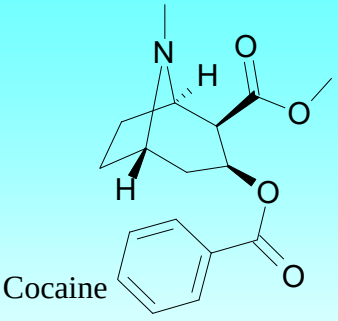
T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308-1315

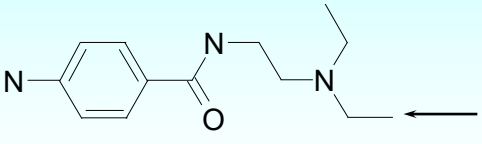
Leads 2: Cocaine

Drugs that are leads:

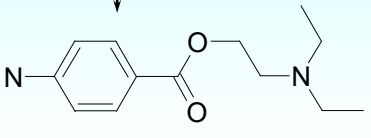
Cocaine (local anesthetic) was the lead for procaine (local anesthetic) which was, in turn, the lead for procainamide (antiarrhythmic)



Cocaine



Procainamide



Procaine

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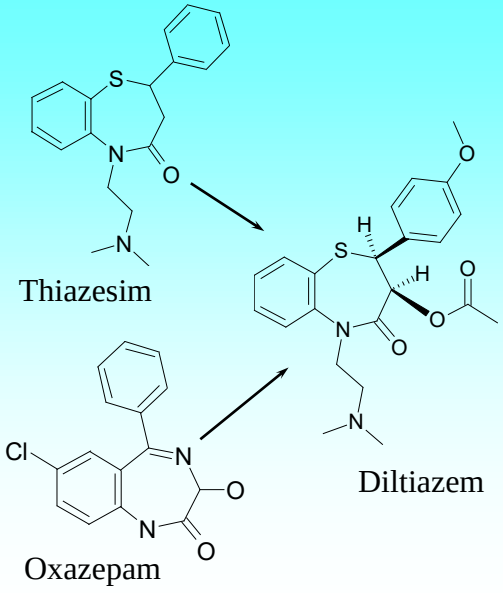
T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308-1315

Leads 3: Diltiazem

Classes of leads that have generate drugs with diverse medical applications:

benzodiazepines are a well described class of leadlike structures that resulted in several drugs, ranging from CNS agents (hypnotics, anxiolytics) to calcium channel blockers and ACE inhibitors

40 launched benzodiazepines with ATC codes; 12 currently lack ATC codes (52 total)



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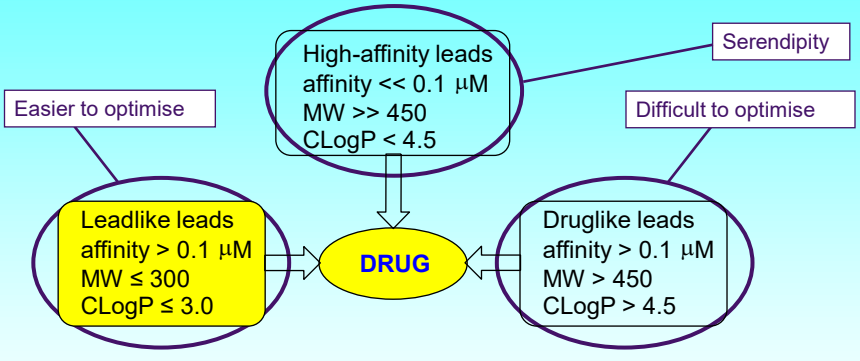
T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308-1315

Common Sources for Leads in Drug Discovery



One needs to distinguish "leadlike" leads from other sources of lead structures, e.g., natural products that are high-affinity compounds (NPY or taxol are leads!) or from "druglike" leads that are marketed structures (e.g., salbutamol or HTS actives from "normal" combichem)

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S.J. Teague, A.M. Davis, P.D. Leeson & T.I. Oprea, *Angew. Chem.*, 1999, 38, 3743-3748

Suggested Properties for Good Leads

The following properties could be considered for lead-likeness:

- **Cheminformatics-driven criteria:**
  - MW ≤ 460, -4 ≤ ClogP ≤ 4.5 (-4 ≤ $logD_{74}$ ≤ 4), $LogS_w$ ≥ -5, H-don ≤ 5, H-acc ≤ 9 (a subset of the to Ro5 criteria)
  - Non-terminal Flexible Bonds ≤ 9, Nr. Rings ≤ 4 (relate to complexity)
- **Pharmacokinetics-driven criteria:**
  - %F ≥ 30, CL ≤ 30 mL/min/kg (use 10 for humans) (related to rat pharmacokinetics)
  - K_D ≥ 100 μM for drug-metabolizing enzymes (avoid drug-drug interactions)
  - no acute toxicity, no carcinogenicity, etc.
- The exact cut-off values are subject to change

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M.M. Hann & T.I. Oprea, *Curr. Opin. Chem. Biol.*, 2004, 8, 255-263

Property Cut-off Values for Leads Approved Drugs 2010-2014 Only

The following median property values were observed for N=70 drugs approved between 1/1/2010 and their corresponding lead structures (N = 73):

- **Properties from earlier slide:**
  - MW ≤ 460, -4 ≤ ClogP ≤ 4.5 (-4 ≤ $logD_{74}$ ≤ 4), $LogS_w$ ≥ -5, H-don ≤ 5, H-acc ≤ 9
  - Non-terminal Flexible Bonds ≤ 9, Nr. Rings ≤ 4
- **Same Properties Derived from New Drugs:**
  - MW ≤ 440, ClogP ≤ 4.74, $LogS_w$ ≥ -4.63, H-don ≤ 5, H-acc ≤ 9
  - Non-terminal Flexible Bonds ≤ 9, Nr. Rings ≤ 4
- The cut-off values did not change significantly in 10 years, which implies that the concept remains valuable
- *Caveat Emptor:* It does not work well with natural products

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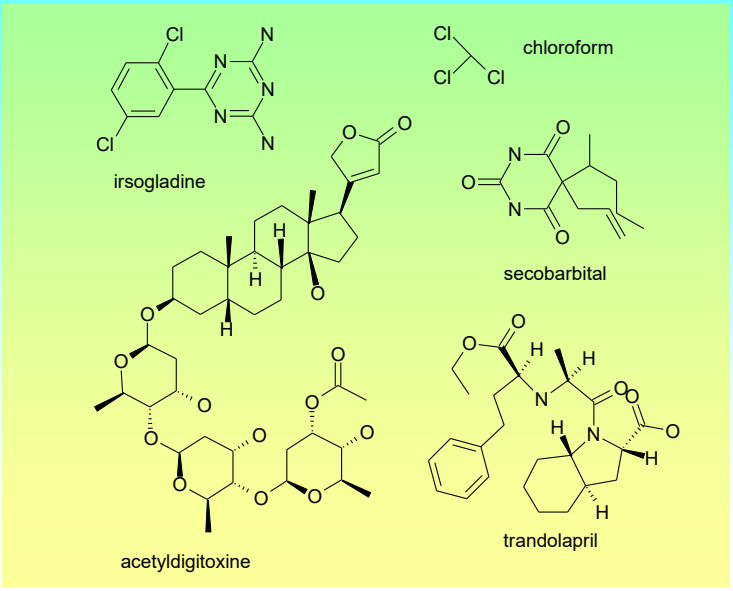
C. Bologa, O. Ursu, T.I. Oprea, *unpublished*

What Do These Drugs Have in Common?



Audience Trivia Question

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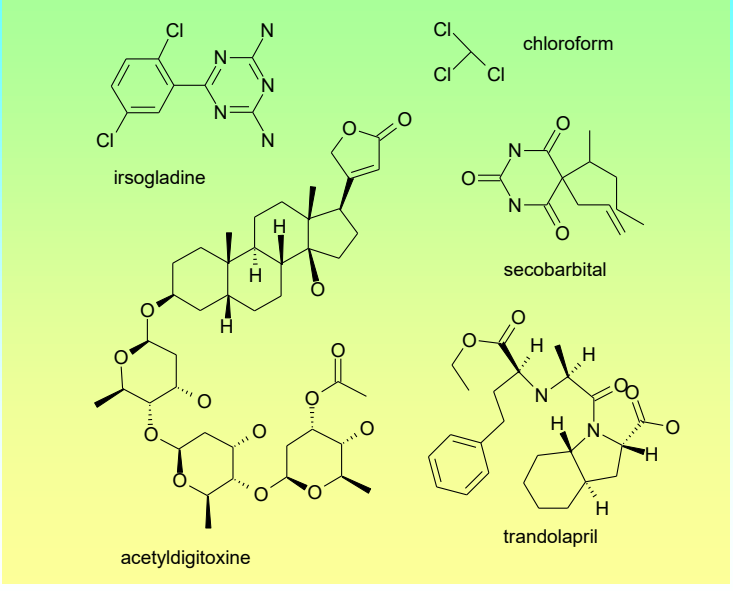
What Do These Drugs Have in Common?



The same measured LogPo/w, 1.97

42

Rule of Three: Fragments, Anyone?

We carried out an analysis of a diverse set of fragment hits that were identified against a range of targets. The study indicated that such hits seem to obey, on average, a 'Rule of Three', in which molecular weight is <300, the number of hydrogen bond donors is ≤3, the number of hydrogen bond acceptors is ≤3 and ClogP is ≤3. In addition, the results suggested NROT (≤3) and PSA (≤60) might also be useful criteria for fragment selection. These data imply that a 'Rule of Three' could be useful when constructing fragment libraries for efficient lead discovery.

References

1 Hann, M. *et al.* (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* 41, 856–864

2 Oprea, T.I. (2001) Is there a difference between leads and drugs? A historical perspective. *J. Chem. Inf. Comput. Sci.*

5 Veber, D.F *et al.* (2002) Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* 45, 2615–2623

6 Clark, D.E. and Picket, S.D. (2000) Computational methods for the prediction of drug-likeness. *Drug Discov. Today* 5, 49–58

7 Teague, S.J *et al.* (1999) The design of leadlike combinatorial libraries. *Angwe. Chemie Int. Ed.* 38, 3743–3748

8 Carr, R. and Jhoti, H. (2002) Structure-based screening of low-affinity compounds. *Drug Discov. Today* 7, 522–527

9 Erlanson, D.A. *et al.* (2000) Site-directed ligand discovery. *Proc. Natl. Acad. Sci. U. S. A.* 97, 9367–72

10 Vetter, D. (2002) Chemical microarrays, fragment diversity, label-free imaging by plasmon resonance-a chemical genomics approach. *J. Cell. Biochem.* 39, 79–84

Miles Congreve, Robin Carr, Chris Murray and Harren Jhoti
Astex Technology Ltd
436 Cambridge Science Park
Milton Road, Cambridge

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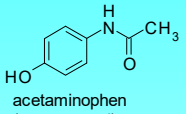
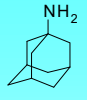
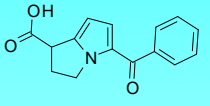
How Many Ro3-Compliant Drugs?



acetaminophen
(paracetamol)
IC_{50} = 4.31 (COX-2)
other targets:
TRPV1
CB1
FAAH
CAR (antitarget)



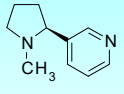
amantadine
IC_{50} = 5.0 (NMDA)
other targets:
D1
D2
M2 (influenza virus)



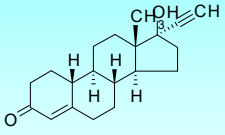
ketorolac
IC_{50} = 9.72 (COX-1)
IC_{50} = 7.12 (COX-2)
other targets:
N/A

mexiletine
IC_{50} = 5.48 ($Na_v1.4$)
IC_{50} = 4.27 ($Na_v1.5$)
other targets:
N/A

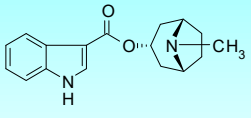
morphine
K_i = 9 (μ-opioid)
K_i = 7.3 (κ-opioid)
K_i = 6.9 (d-opioid)
other targets:
EC_{50} = 6.86 (NK1)



nicotine
K_i = 8.74 (α4β2-nAChR)
Ki = 6.73 (a3b4-nAChR)
Ki = 7.85 (a3b2-nAChR)
other targets:
K_i = 5.7 (a7-nAChR)
K_i = 7.4 ($K_v4.3$)
antitarget:
IC_{50} = 5.35 (CYP2A6)



norethindrone
ED_{50} = 11.26 (PR)
IC_{50} = 7.12 (AR)
other targets:
N/A



tropisetron
K_i = 7.96 (5-HT_3)
K_i = 6.85 (5-HT_4)
other targets:
N/A

Ro3 criteria: MW ≤ 300; ClogP ≤ 3; HDO ≤ 3; HAC ≤ 3; RTB ≤ 3; PSA ≤ 60 Å^2

307 out of 3953 "organic" drugs (of which 164 have ATC codes)

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T.I. Oprea, unpublished

How Many Lead-like Drugs?

- An analysis on 3,953 small molecule organic drugs (launched world-wide; not corrected for "status", formulation or any other property) reveals that using the
- **Cheminformatics-driven criteria:**
  - MW ≤ 460, -4 ≤ ClogP ≤ 4.5 (-4 ≤ $logD_{74}$ ≤ 4), $LogS_w$ ≥ -5, H-don ≤ 5, H-acc ≤ 9
  - Non-terminal Flexible Bonds ≤ 9, Nr. Rings ≤ 4
- …2327 drugs (~58.9%) pass the computational criteria
- … 2994 drugs (~75.74%) have zero Ro5 violations (all Ro5 criteria are observed)
- … 3629 drugs (~91.8%) have one or no Ro5 violations (Ro5 compliant)

Note: We use ChemAxon for descriptor calculation, except for $LogS_w$ (Igor Tetko's ALogPS program); H-acc is "sum of N+O"

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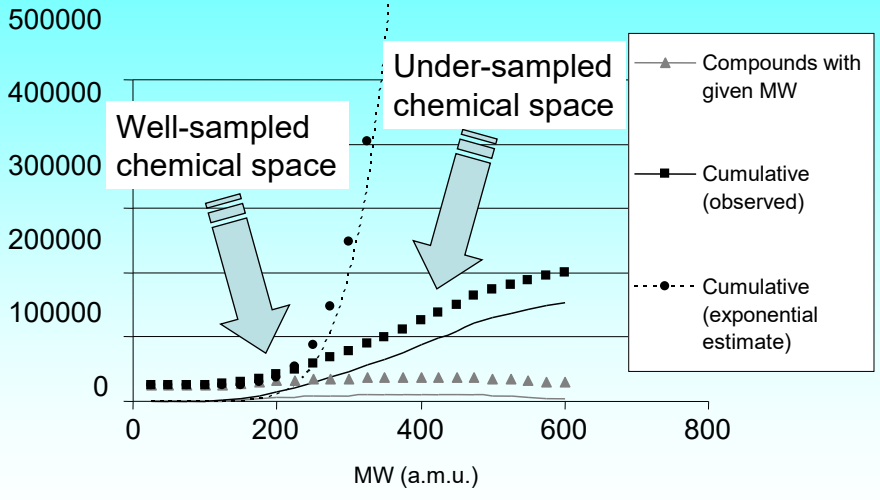
T.I. Oprea, unpublished

Current Chemical Space Sampling



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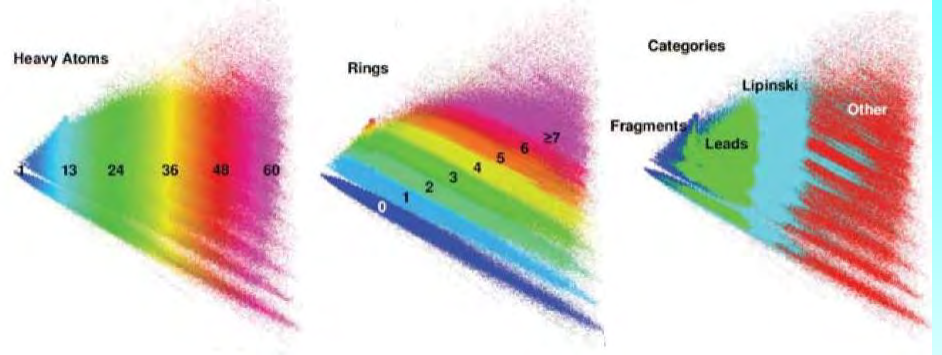
M.M. Hann & T.I. Oprea, *Curr. Opin. Chem. Biol.*, 2004, 8, 255-263

Theoretical Chemical Space Sampling



- Chemical space of PubChem (<= 60 atoms) & GDB-13 (66,647,914 molecules total). Descriptor maps are color-coded by average descriptor value (nr atoms and rings).
- Category maps (right): Fragments, blue (Ro3, 32.5 million cpds); lead-like, green (Teague's, NOT Ro3; 2.7 million cpds); Ro5, cyan (not leads, not Ro3; 31.4 million cpds)

Adapted from Fig. 2.2 (pg 48) by J.L. Reymond, L. Ruddigkeit, M. Awale,
Chapter 2 in *Computational Chemogenomics*; E. Jacoby Ed., Pan Stanford Publishing, pp. 39-64, 2014

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Take Home Message 3

- Chemical space is significantly under-sampled as complexity and molecular weight increase
- Ro3 criteria (7.77% of drugs) are a subset of the lead-like criteria (58.9% of drugs), which are a subset of the Ro5 criteria (75.74% strict, 91.8% compliant)
- *Remember: drugs can be found outside this space*
- When multiple series are available (assuming all other criteria are satisfied): *Choose the simplest one*

… fewer moieties implies fewer pharmacophores, fewer liabilities and fewer side-activities

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O. Ursu & T.I. Oprea, J. Chem. Inf. Model. 2010, 50:1387-1394

Take Home Tools 2

app description		powered by
BadApple	bioactivity datamining associative promiscuity pattern learning engine	ChemAxon
Convert	convert mol formats	ChemAxon
Depict	depict molecules	ChemAxon
JSME	JavaScript molecular editor, by P. Ertl & B. Bienfait	peter.ertl.com
MolCloud	molecule clouds (algorithm by P. Ertl & B. Rohde, Novartis)	ChemAxon
Ro5	Lipinski Rule of 5 analysis	ChemAxon, VCCLAB/eADMET
Sim2d	2D similarity	ChemAxon
SmartsFilter	smarts filtering with built in Glaxo, Blake, and Oprea smarts sets	ChemAxon

SMARTSFILTER helps eliminate unwanted substructures

BADAPPLE learns from “frequent hitters” found in the Molecular Libraries Screening program, and flags promiscuous compounds

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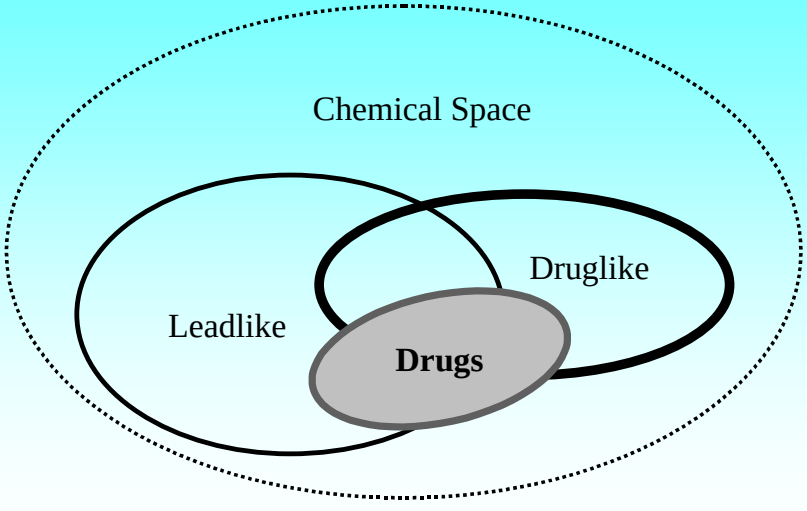
J.J. Yang, O. Ursu & T.I. Oprea, unpublished

Drugs are not always Leadlike or Druglike



50

T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson *J. Chem. Inf. Comput. Sci.*, 2001, 41, 1308-1315

No Rule in Drug Discovery is Absolute

- This paper* challenges the general desire to find simple rules and guidelines to reduce attrition due to toxicity and clinical safety.
- An analysis of 150 AstraZeneca development compounds fails to observe published guidelines (aka “filters”) and their ability to identify compounds with safety liabilities.
- “None of the current guidelines were able to discriminate compounds that successfully reached Phase II.”
- A large portion of the 2009–2011 approved drugs “would never have reached patients if these guidelines had been applied at an early stage”

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* D. Muthas, S. Boyer, C. Hasselgren, *Med. Chem. Commun.* **2013**, 4:1058–1065

Acknowledgments:
Cristian Bologa & Oleg Ursu (UNM)

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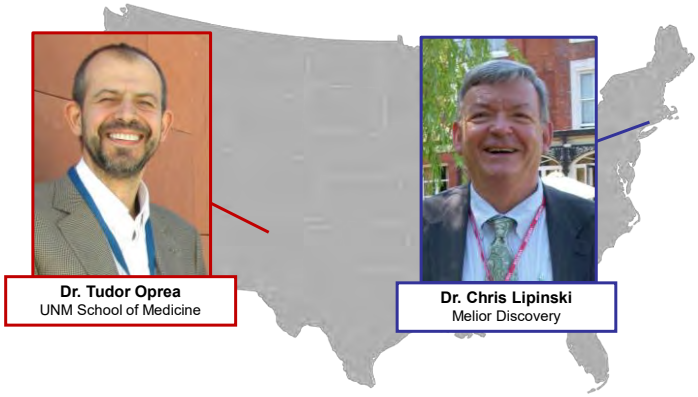

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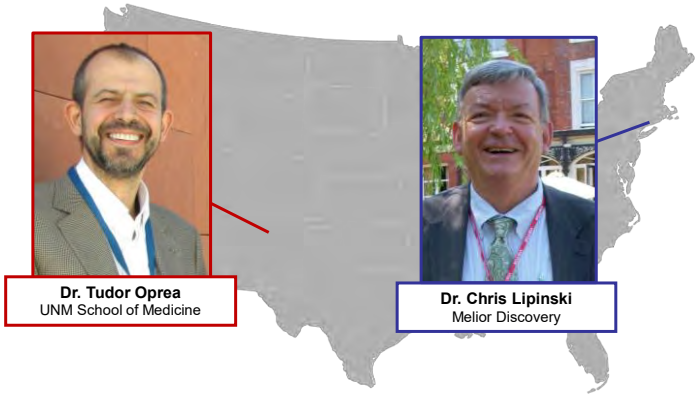

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