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Bioisosteres and Scaffold Hopping in Medicinal Chemistry

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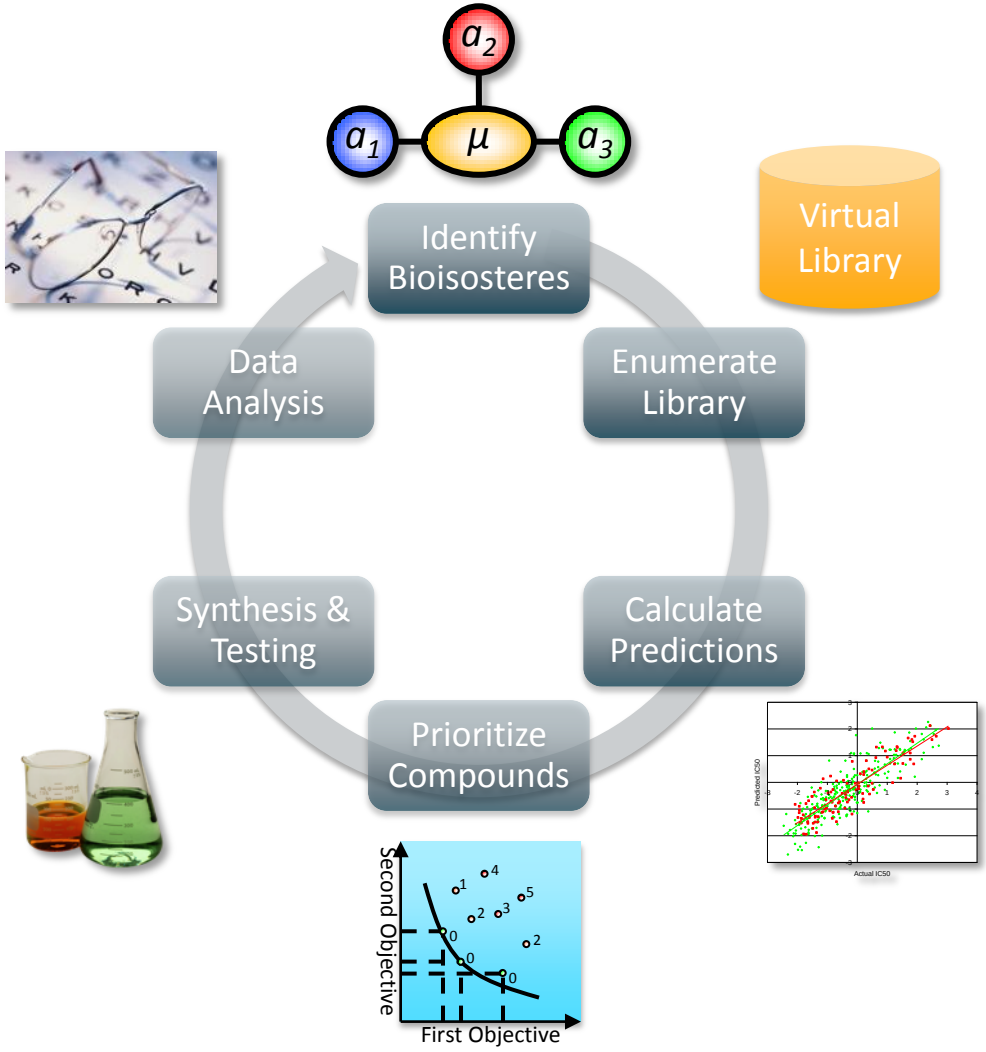
The Institute of Cancer Research, London

Chemoinformatics Strasbourg Summer School 2014
Thursday 26th June 2014

@nathanbroon

#CSSS2014

In Silico Medicinal Chemistry



1. Brown, N. (Ed.) *Bioisosteres in Medicinal Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2012**.
2. Brown, N. (Ed.) *Scaffold Hopping in Medicinal Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2013**.
3. Nicolaou, C. A.; Brown, N. Multi-objective optimization methods in drug design. *Drug Discovery Today: Technol.* **2013**, *10*, e427-e435.

What is a Bioisostere?

Bioisosteres

- Structural moieties with broadly similar shape and function
- Function should be biological but modulate other properties
- **Bioisosteric replacement**: replacement of functional groups

Molecular Scaffolds

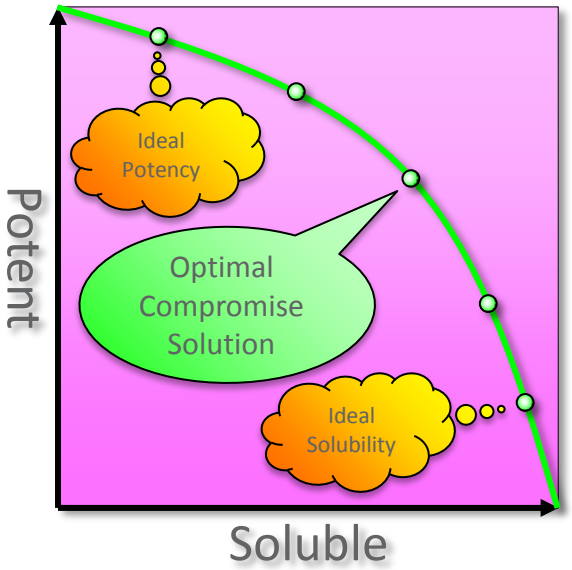
- *Subset of bioisosterism*
- Identification of the core functional or structural element
- **Scaffold hopping**: replacement of core element

The ***molecular interactions*** must be maintained

- Important to mimic **shape** and **function**

1. Langdon, S. R.; Ertl, P.; Brown, N. Bioisosteric Replacement and Scaffold Hopping in Lead Generation and Optimization. *Mol. Inf.* **2010**, *29*, 366-385.
2. Brown, N. Bioisosteres and Medicinal Chemistry. *Mol. Inf.* **2014**, *33*, 458-462.

Why Bioisosteres?



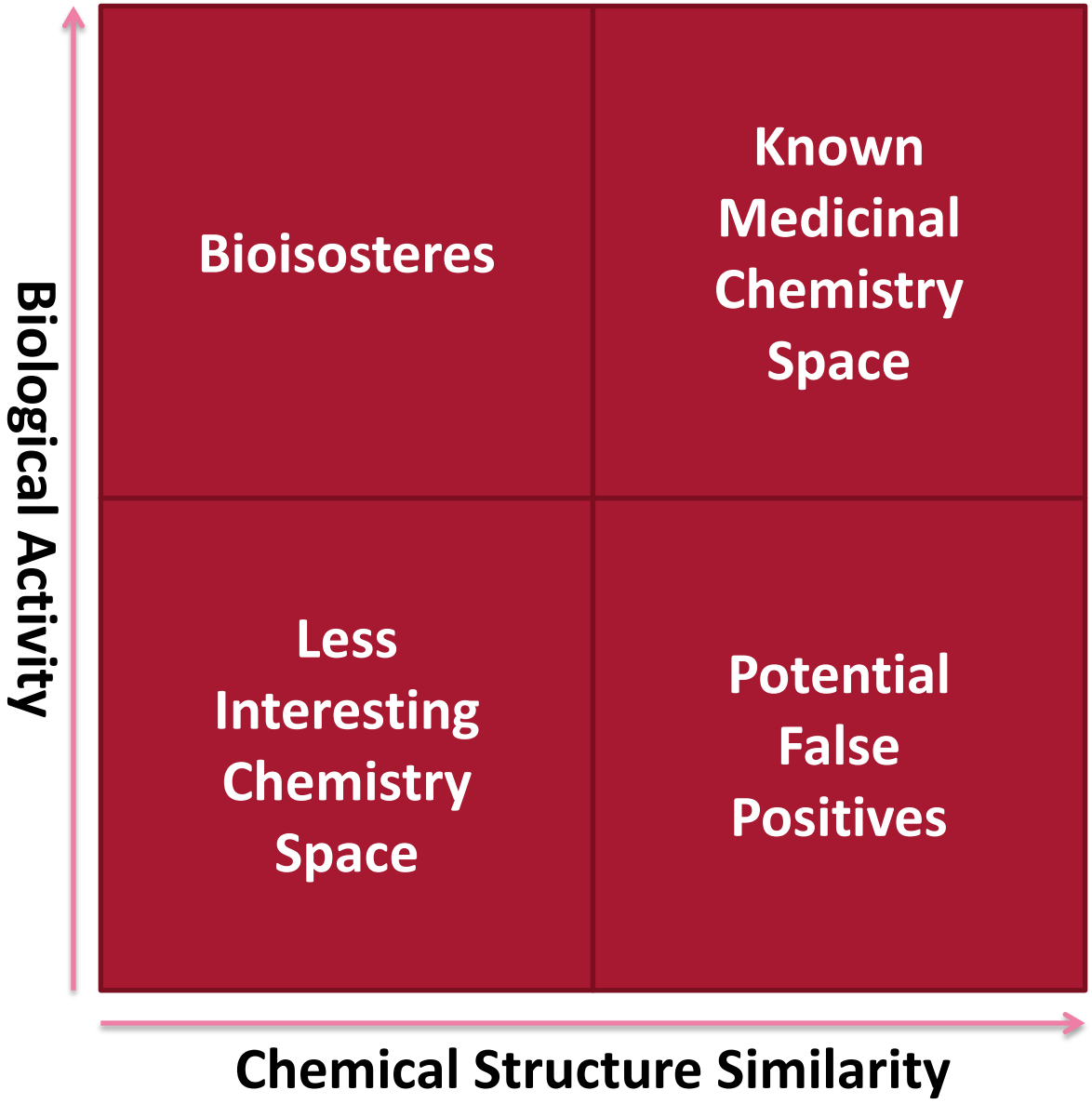
Many properties can be modulated with appropriate bioisosteres:

- Improved selectivity
- Fewer side effects
- Decreased toxicity
- Improved pharmacokinetics: solubility/hydrophobicity
- Increased metabolic stability
- Simplified synthetic routes
- Patented lead compounds

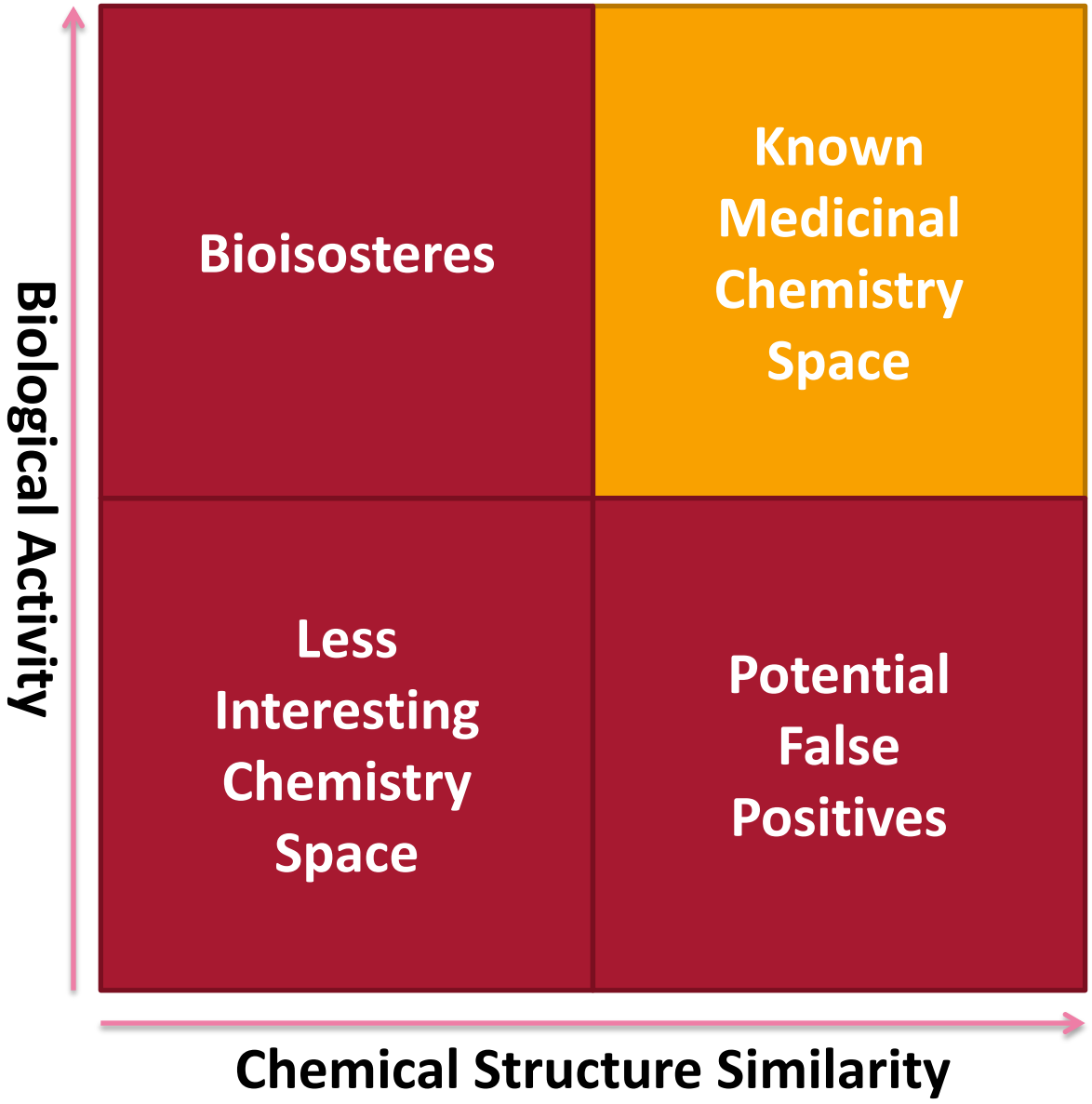
Drug Design is Inherently a Multiobjective Optimisation Problem

1. Nicolaou, C. A.; Brown, N. Multi-objective optimization methods in drug design. *Drug Discovery Today: Technol.* **2013**, *10*, e427-e435.

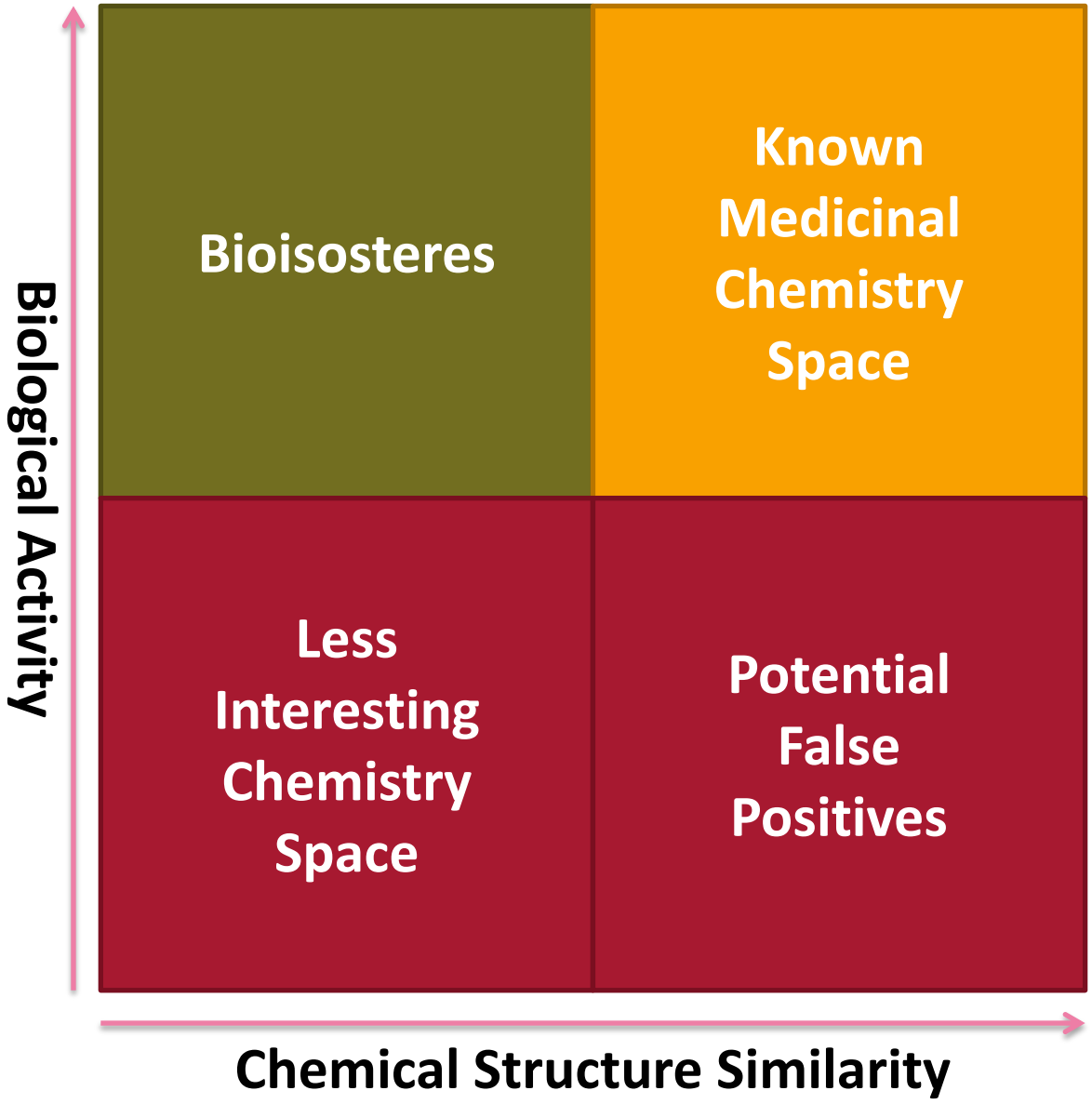
Why Bioisosteres?



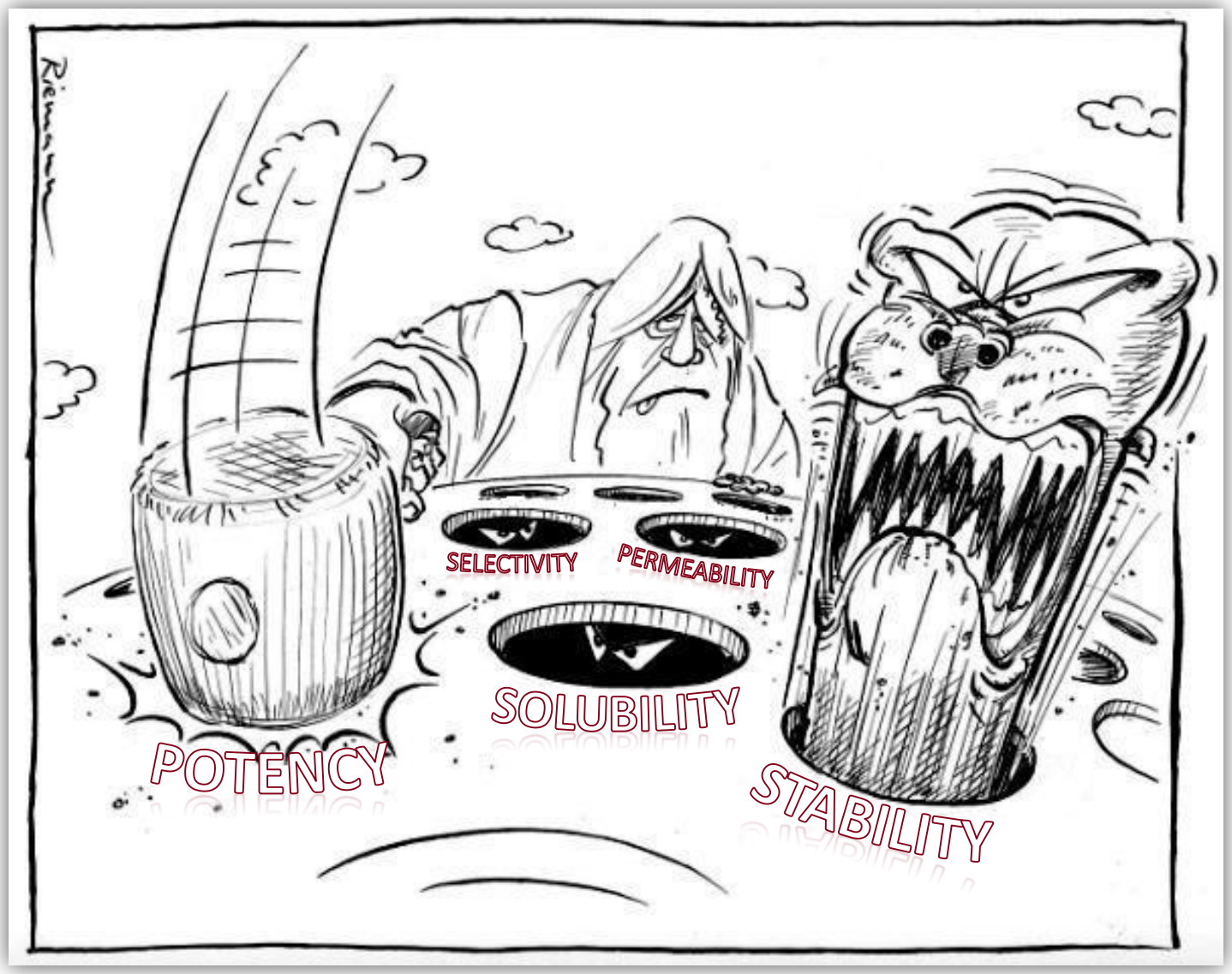
Why Bioisosteres?



Why Bioisosteres?



Why Bioisosteres?



1. Nicolaou, C. A.; Brown, N. Multi-objective optimization methods in drug design. *Drug Discovery Today: Technol.* **2013**, *10*, e427-e435.

Irving Langmuir, 1919

Irving Langmuir
1881 – 1957

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY.]

ISOMORPHISM, ISOSTERISM AND COVALENCE.

BY IRVING LANGMUIR.

Received June 30, 1919.

TABLE I.
List of Isosteres.

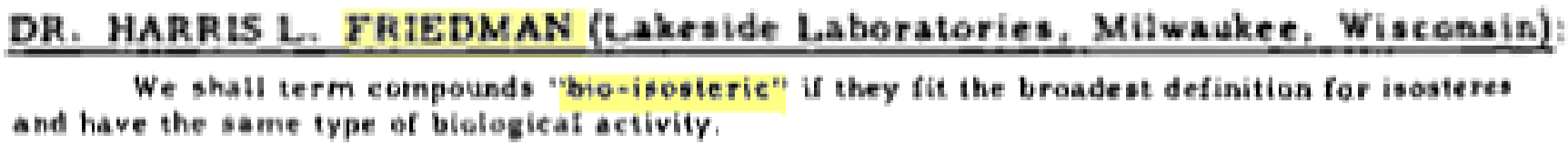
Type.	
1	H^-, He, Li^+
2	O^{--}, F^-, Ne, Na^+, Mg^{++}, Al^{+++}
3	S^{--}, Cl^-, A, K^+, Ca^{++}
4	Cu^+, Zn^{++}
5	Br^-, Kr, Rb^+, Sr^{++}
6	Ag^+, Cd^{++}
7	I^-, Xe, Cs^+, Ba^{++}
8	N_2, CO, CN^-
9	CH_4, NH_4^+
10	CO_2, N_2O, N_3^-, CNO^-
11	NO_3^-, CO_3^{--}
12	NO_2^-, O_3
13	HF, OH^-
14	ClO_4^-, SO_4^{--}, PO_4^{---}
15	ClO_3^-, SO_3^{--}, PO_3^{---}
16	SO_3, PO_3^-
17	$S_2O_6^{--}$, $P_2O_6^{----}$
18	$S_2O_7^{--}$, $P_2O_7^{----}$
19	SiH_4, PH_4^+
20	MnO_4^-, CrO_4^{--}
21	SeO_4^{--}, AsO_4^{---}

The octet theory of valence indicates that if compounds having the same number of atoms have also the same total number of electrons, the electrons may arrange themselves in the same manner. In this case the compounds or groups of atoms are said to be isosteric. Such compounds should show remarkable similarity in physical properties, that is, in those properties which do not involve a separation of the atoms in the molecule.

1. Langmuir, I. Isomorphism, Isosterism and Covalence. *J. Am. Chem. Soc.* **1919**, *41*, 1543-1559.

Harris L. Friedman, 1951

- Friedman first coined the term bio-isosteric in 1951:


DR. HARRIS L. FRIEDMAN (Lakeside Laboratories, Milwaukee, Wisconsin):

We shall term compounds "bio-isosteric" if they fit the broadest definition for isosteres and have the same type of biological activity.

- "We shall term compounds "bio-isosteric" if they fit the broadest definition for isosteres and have the same type of biological activity."

1. Friedman, H. L. Influence of isosteric replacements upon biological activity. NAS-NRS Publication No. 206, NAS-NRS, Washington, D.C., pp. 295-362, **1951**.

Craig W. Thornber, 1979

Isosterism and Molecular Modification in Drug Design

By C. W. Thornber
IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION, MERESIDE, ALDERLEY PARK, MACCLESFIELD, CHESHIRE, SK10 4TG

The element of a molecule being modified may have one or more of the following roles.

(i) *Structural*. If the moiety has a structural role in holding other functionalities in a particular geometry, parameters such as size and bond angle will be important. The moiety may be buried deep in the molecule and have little contact with the external medium.

(ii) *Receptor interactions*. If the moiety to be replaced is concerned with a specific interaction with a receptor or enzyme its size, shape, electronic properties, pK_a, chemical reactivity, and hydrogen bonding will be the important parameters.

(iii) *Pharmacokinetics*. The moiety to be replaced may be necessary for the absorption, transport, and excretion of the compound. In this case lipophilicity, hydrophilicity, hydrogen bonding, and pK_a are likely to be important.

(iv) *Metabolism*. The moiety may be involved in blocking or aiding metabolism. In this case chemical reactivity will be an important parameter. For example chloro and methyl substituents on a benzene ring may be interchangeable for certain purposes but the toluene derivative can be metabolized to a benzoic acid and may therefore have a shorter half-life or unexpected side effects.

(A) A given molecular modification may allow some, but probably not all of the parameters (*a*)—(*h*) to be kept the same.

(B) Whether the same or a different biological activity results from the replacement will be governed by the role(s) which that moiety fulfils in the molecule and whether parameters affecting that role have been disturbed.

(C) From (A) and (B) it follows that what proves to be a good bioisosteric replacement in one series of compounds will not necessarily be useful in another.

Table 1

1) *Univalent atoms and groups*

F, OH, SH, I, Br, NH_2, PH_2, Bu^t, Pr^i, Me, Cl

2) *Bivalent atoms and groups*

O, CO_2R, S, COSR, Se, $COCH_2R$, CH_2, CONHR, H—N—

3) *Tervalent atoms and groups*

—N=, —P=, —CH=, —As=

4) *Quadrivalent atoms*

—C—, —Si—

5) *Ring equivalents*

—CH=CH—, =C—H, S, =N— *e.g.* benzene: thiophen, *e.g.* benzene: pyridine

—O—, —S—, $—CH_2—$, —NH—

(*a*) Size.
(*b*) Shape (bond angles, hybridization).
(*c*) Electronic distribution (polarizability, inductive effects, charge, dipoles).
(*d*) Lipid solubility.
(*e*) Water solubility.
(*f*) pK_a.
(*g*) Chemical reactivity (including likelihood of metabolism).
(*h*) Hydrogen bonding capacity.

1. Thornber, C. W. Isosterism and molecular modification in drug design. *Progress in Drug Research* **1979**, *37*, 563-580.

Exploration *versus* Exploitation

Exploration

"... includes things captured by terms such as search, variation, risk taking, experimentation, play, flexibility, discovery, innovation."

All Exploration: "...the costs of experimentation without any of its benefits." Undeveloped ideas, little distinctive competence."

Exploitation

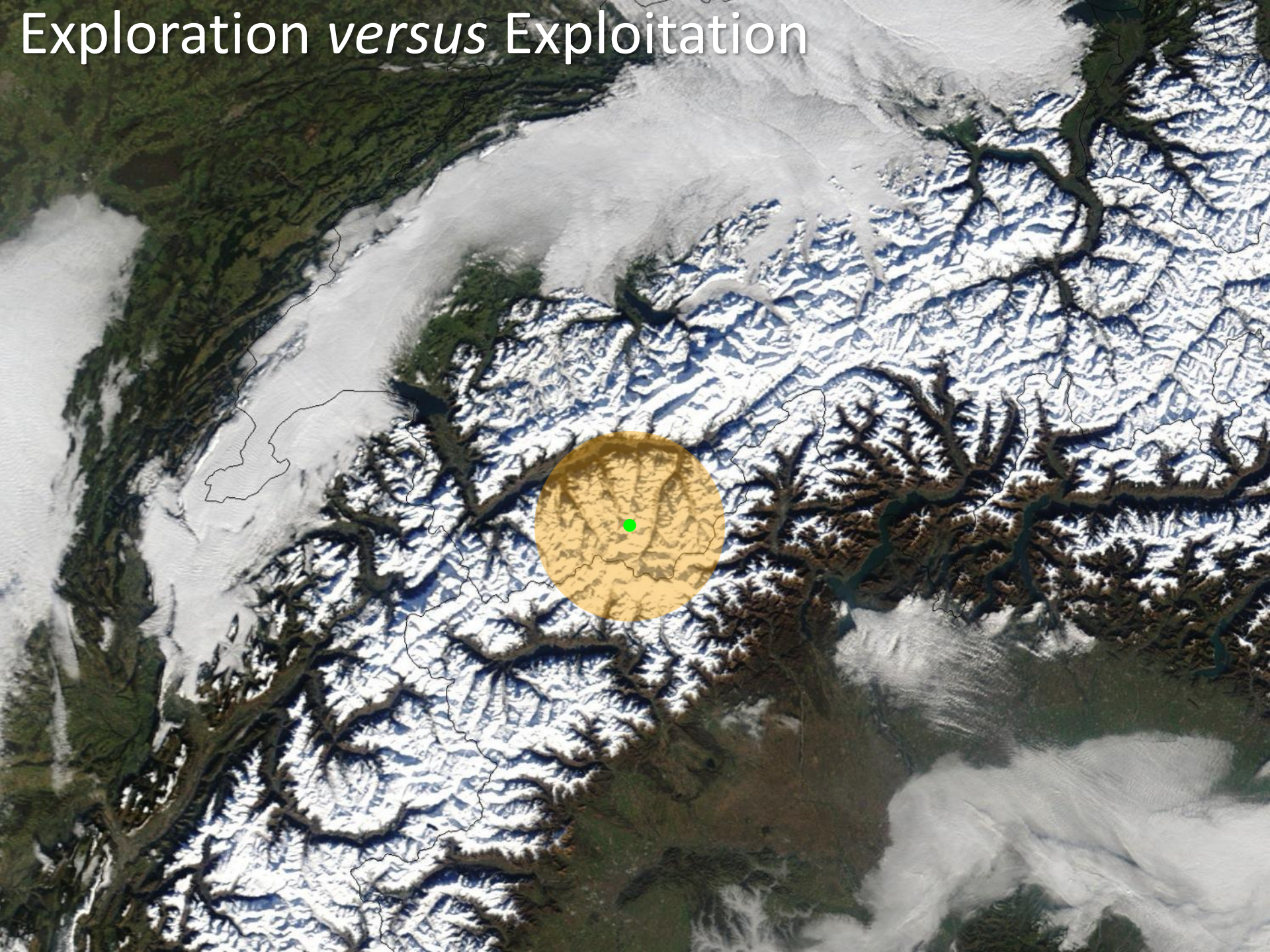
"... includes such things as refinement, choice, production, efficiency, selection, implementation, execution."

All Exploitation: "Locked-in to suboptimal equilibria (local maxima). Can't adapt to changing circumstances."

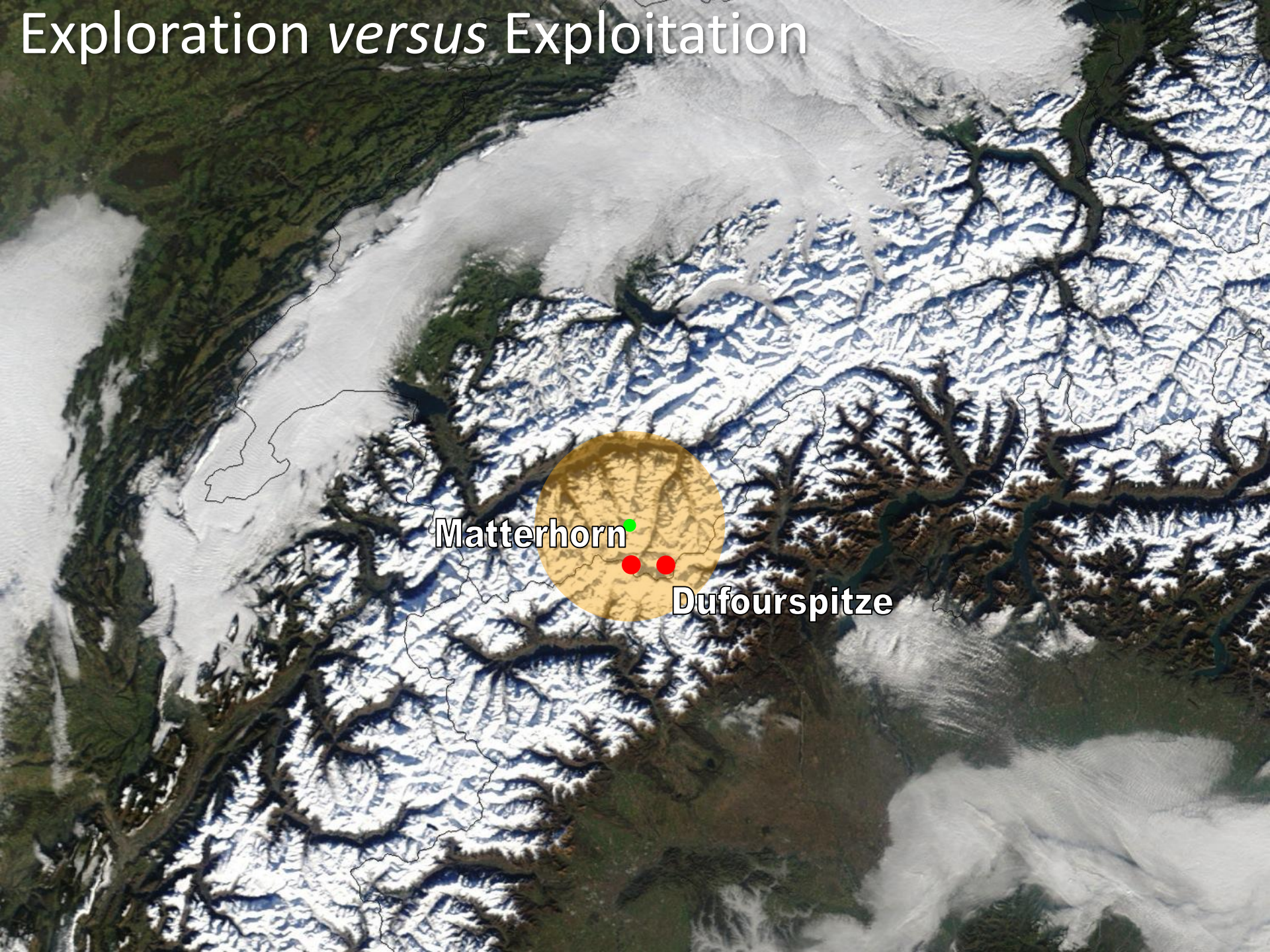
Feedback to exploitation occurs much more quickly. Increasing returns can lead to lock-in at a suboptimal equilibrium.
"...these tendencies to increase exploitation and reduce exploration make adaptive processes potentially self-destructive."

1. March, J. G. Exploration and Exploitation in Organizational Learning. *Org. Sci.* **1991**, *2*, 78-87.

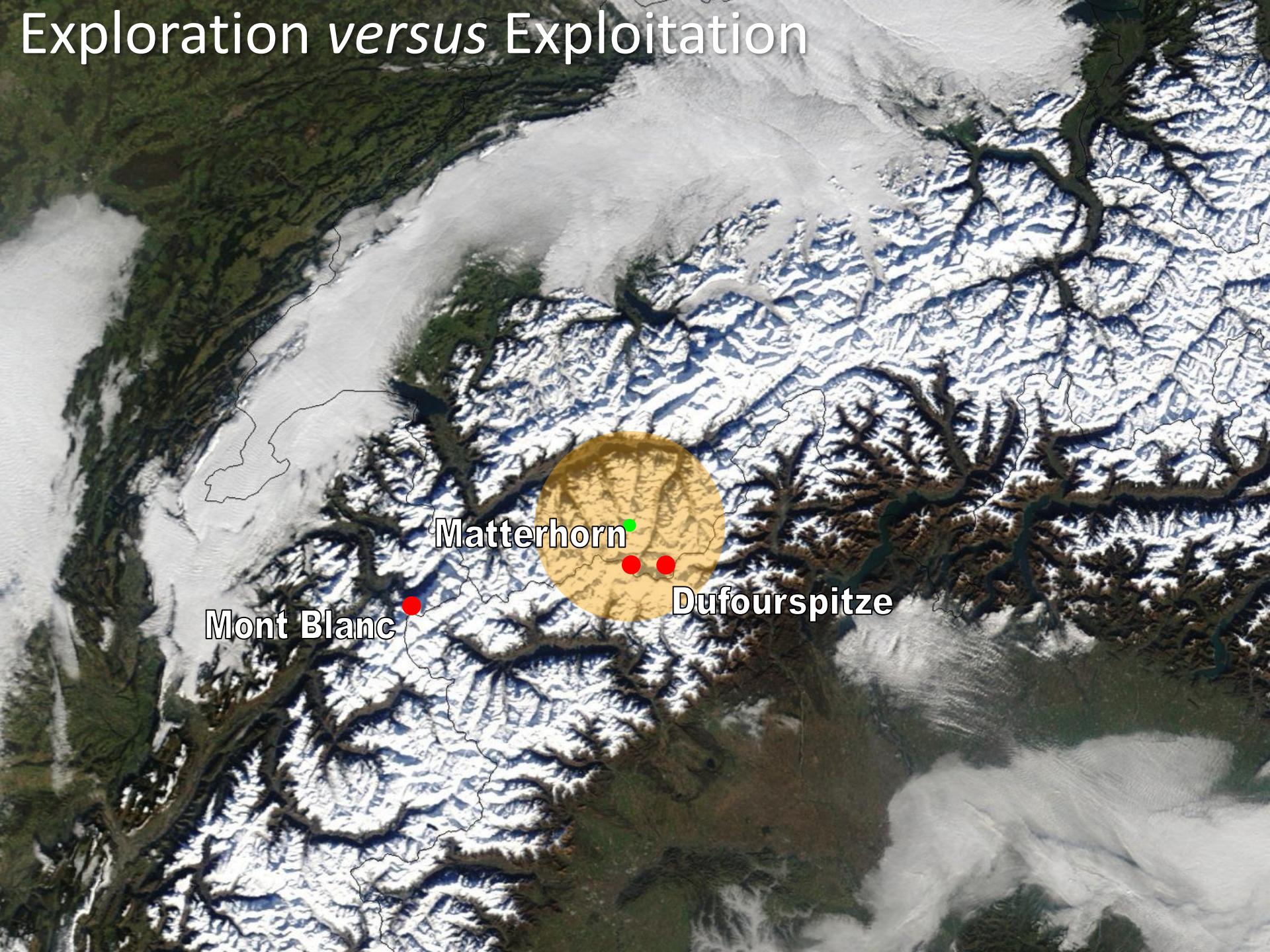
Exploration *versus* Exploitation



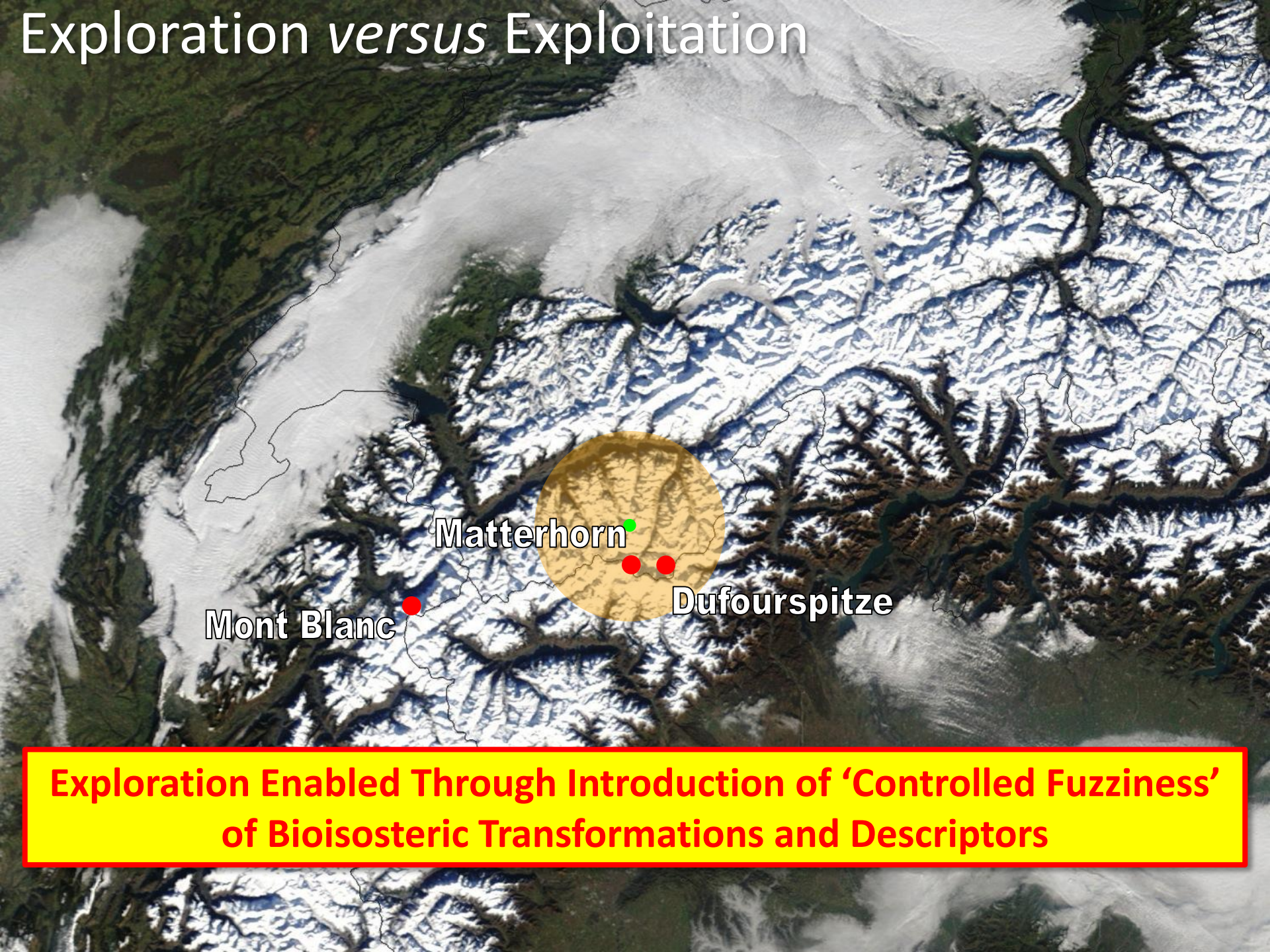
Exploration *versus* Exploitation



Exploration *versus* Exploitation



Exploration *versus* Exploitation



Exploration Enabled Through Introduction of ‘Controlled Fuzziness’ of Bioisosteric Transformations and Descriptors

Methods to Identify Bioisosteres

- **Databases**
  - BIOSTER
  - ChEMBL – Matched Molecular Pairs
  - Cambridge Structural Database (CSD)

- **Descriptors**
  - Physicochemical properties
  - Molecular Topology
  - Molecular Shape
  - Protein Structure

BIOSTER Database – István Ujváry

- Database of ~26,000 bioisosteric transformations
- Bio-analogous pairs mined from the literature:
  - Systematic abstracting since 1970
- Compound pairs represented as hypothetical reactions
  - ‘bioisosteric transformations’
  - Compatible with most reaction-searching software

BIOSTER—A Database of Structurally Analogous Compounds

István Ujváry

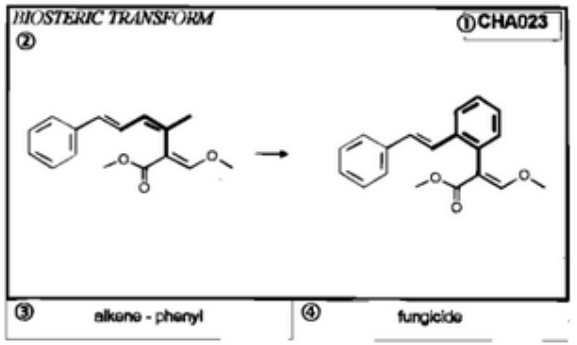
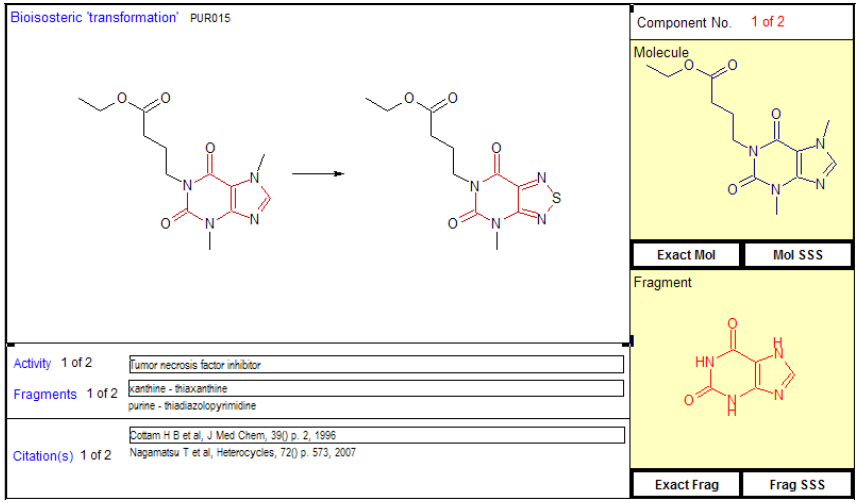


Fig. 1. Typical data form of *BIOSTER* database with field types as follows: ① ID code; ② structures of the biosteric transformation (biosteric fragments in the analogues are highlighted); ③ chemical fragment types relevant to transformation; ④ biological activity type related to the structures shown; ⑤ key references.



1. Ujváry, I. Bioster: a database of structurally analogous compounds. *Pesticide Science* **1997**, *51*, 92-95.
2. Distributed by Digital Chemistry: http://www.digitalchemistry.co.uk

Matched Molecular Pairs

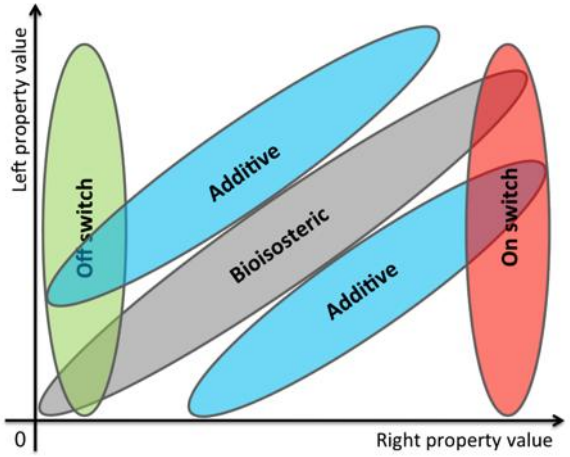
Journal of Medicinal Chemistry
PERSPECTIVE
pubs.acs.org/jmc

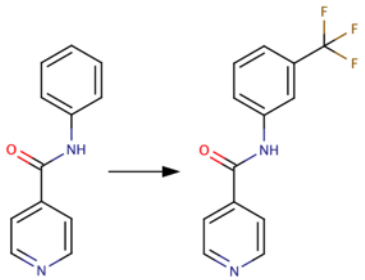
Matched Molecular Pairs as a Medicinal Chemistry Tool[†]

Miniperspective

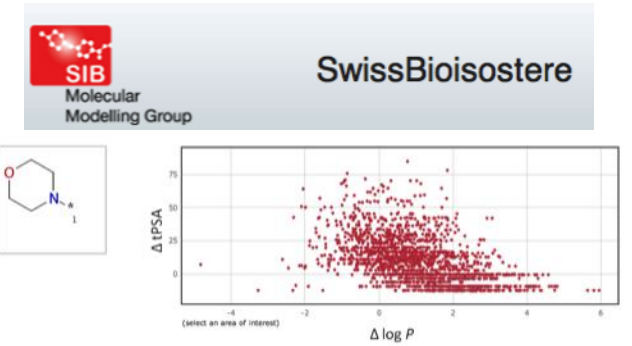
Ed Griffen,[†] Andrew G. Leach,[*,§] Graeme R. Robb,[§] and Daniel J. Warner[∥]

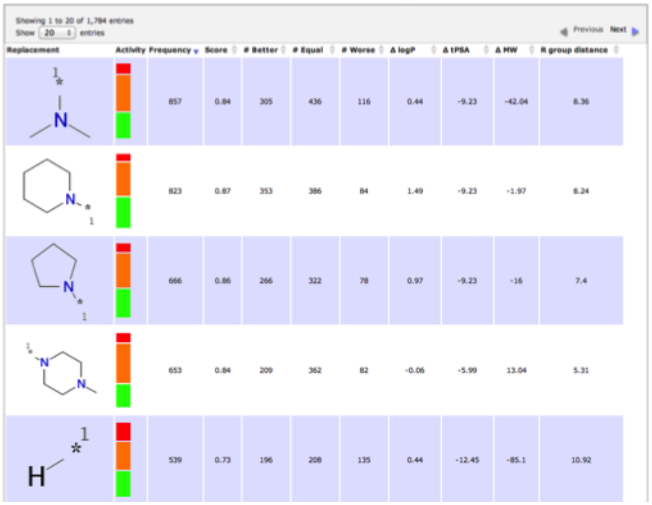
- Identification of molecules that differ in only one position
  - Can suggest structural changes to modulate biological or physicochemical properties





MMP Transformation:
$H >> CF_3$

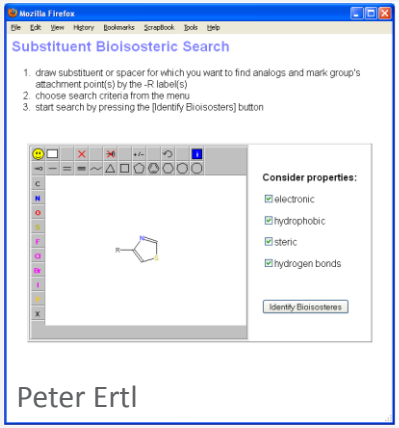


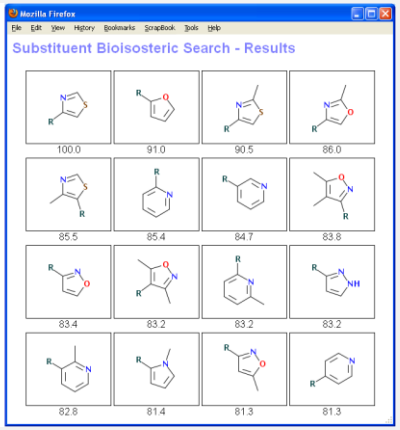


1. Kenny, P. W.; Sadowski, J. Structure Modification in Chemical Databases. In: *Chemoinformatics in Drug Discovery* (Ed. Oprea, T. T.). Wiley-VCH **2004**.
2. Griffen, E.; Leach A. G.; Robb, G. R.; Warner, D. J. Matched Molecular Pairs as a Medicinal Chemistry Tool. *J. Med. Chem.* **2011**, *54*, 7739-7750.
3. Wirth, M.; Zoete, V.; Michielin, O.; Sauer, W. SwissBioisostere: a database of molecular replacements for ligand design. *Nucleic Acids Research* **2012**.

Bioisosteric Similarity Methods

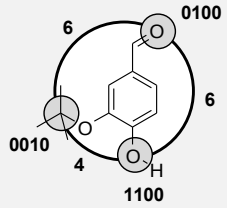
Physicochemical Properties





Peter Ertl

Molecular Topology



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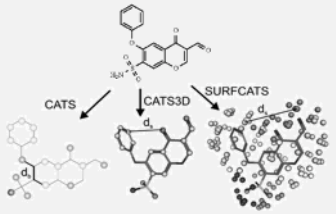
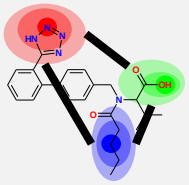
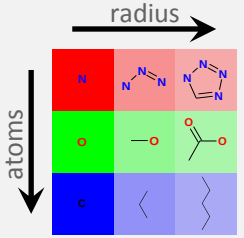
Similog



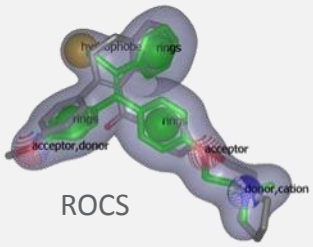
CATS



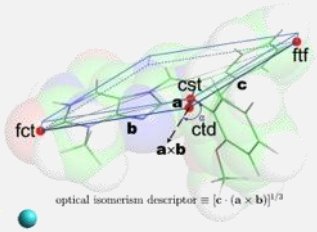


Hopfen

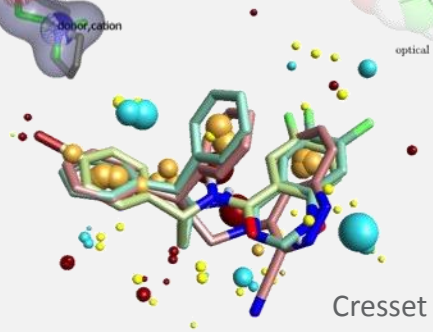
Molecular Shape



ROCS

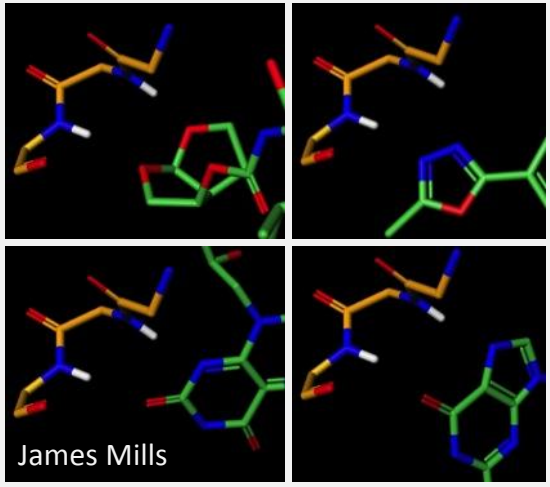


USR



Cresset

Protein Structure



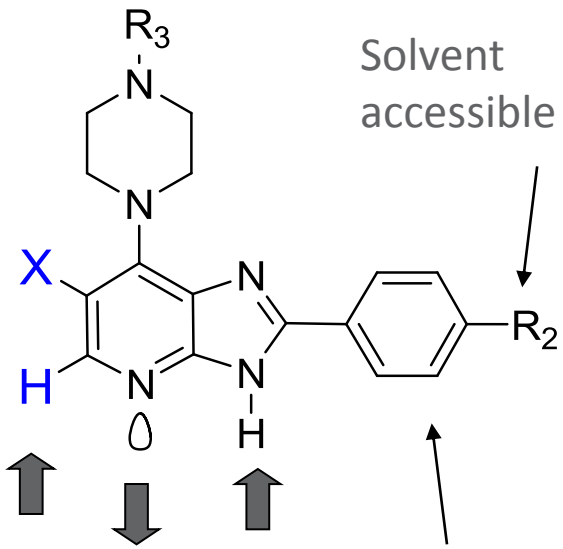
James Mills

Case Study: Bioisosteric Replacement

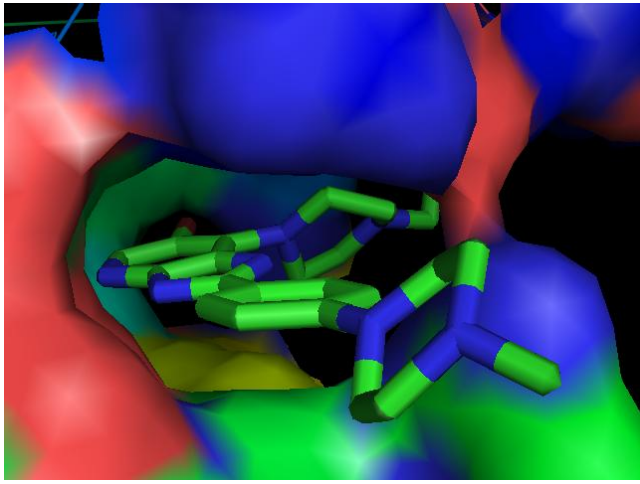
Benzyl-type linker optimal

X = Br, Cl, CN, CF_3 equivalent
X = H: 10 to 50 fold weaker
X = large group: inactive

Solvent accessible



Required

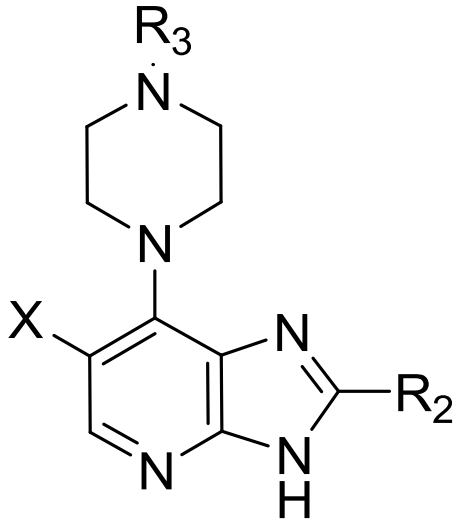


Butressed against hinge
***Ortho* substitution poor**
***Meta* tolerated but weaker**

320 Compounds already made: What is the learning?
Unbiased and objective analysis
Focus on enzyme potency and cell penetration

Generation of a Virtual Library

- Preferred R_2 and R_3 groups from Free-Wilson analysis.
  - Introduce other ideas from bioisosteric replacements
  - X = Cl, R_2 = 54, R_3 = 49
  - > 2600 possible compounds
- Filter to remove compounds that:
  - Have > 1 basic centre
  - Have TPSA > 100
  - Have AlogP > 3.5
  - Have MW > 520 Da.
  - Have > 2 HBD
- 1500 compounds remaining



Easy to generate ideas: Picking which ones to make is much harder

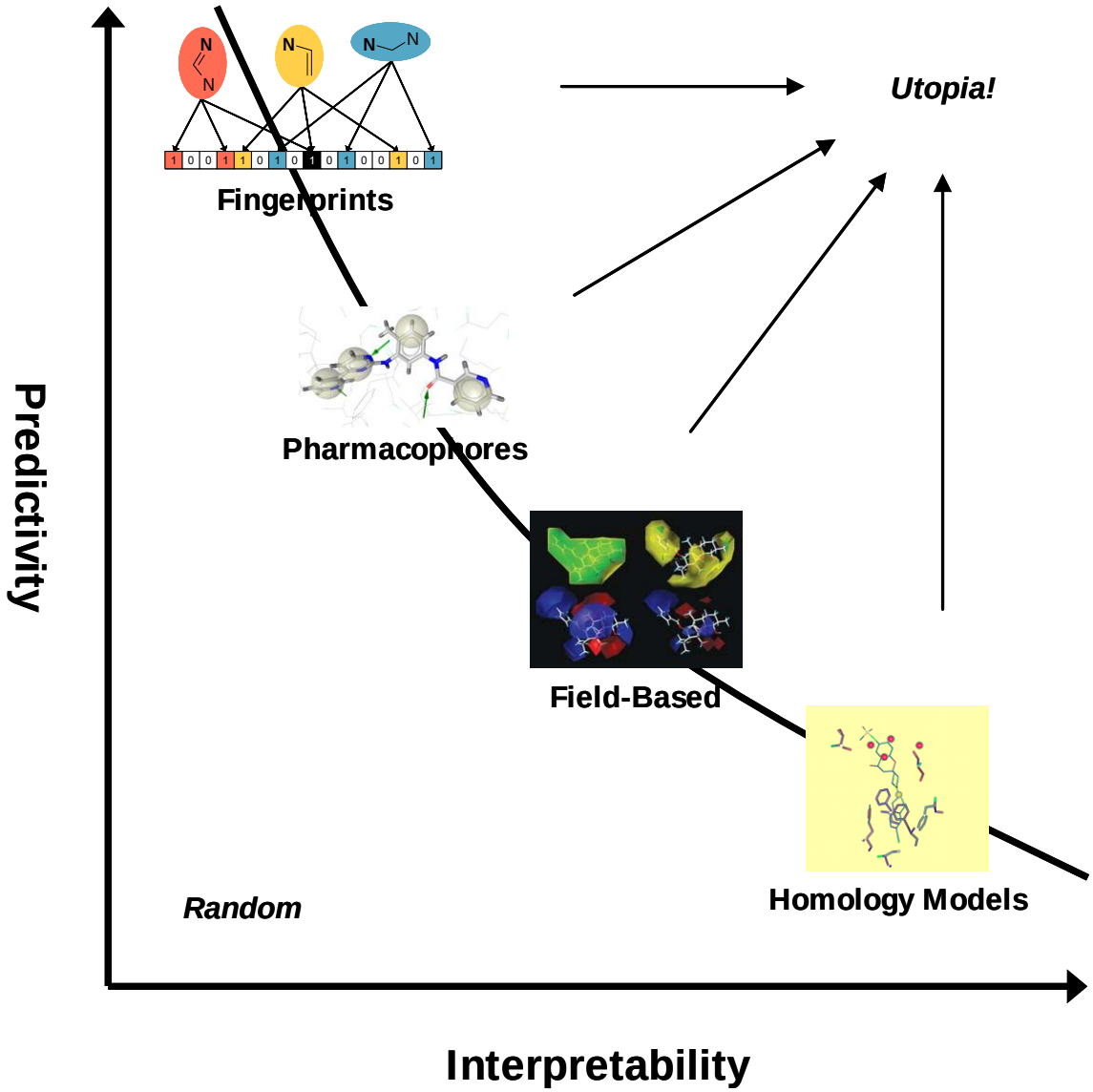
1868 – Properties a Function of Structure

- Alexander Crum Brown defined the following relationship between:
  - Φ, the physiological action, and
  - C, the chemical constitution of a molecule

$$\Phi = f(C)$$

1. Brown, A. C.; Fraser, T. R. On the connection between Chemical Constitution and Physiological Action. *J. Anat. Physiol.* **1868**, *2*, 224-242.

Predictive Modelling



1. Brown, N.; Lewis, R. A. Exploiting QSAR methods in lead optimization. *Curr. Opin. Drug. Discov. Devel.* **2006**, *9*, 419-424.

Predictive Modelling

Build naïve Bayesian model

FCFP_6 fingerprint molecular descriptors

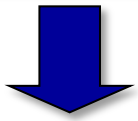
Active threshold set at:

- 10 nM for enzyme IC_{50}
- 300 nM for cell IC_{50}

Training set and test set (*n* = 320)

Molecules scored by predicted activity/inactivity

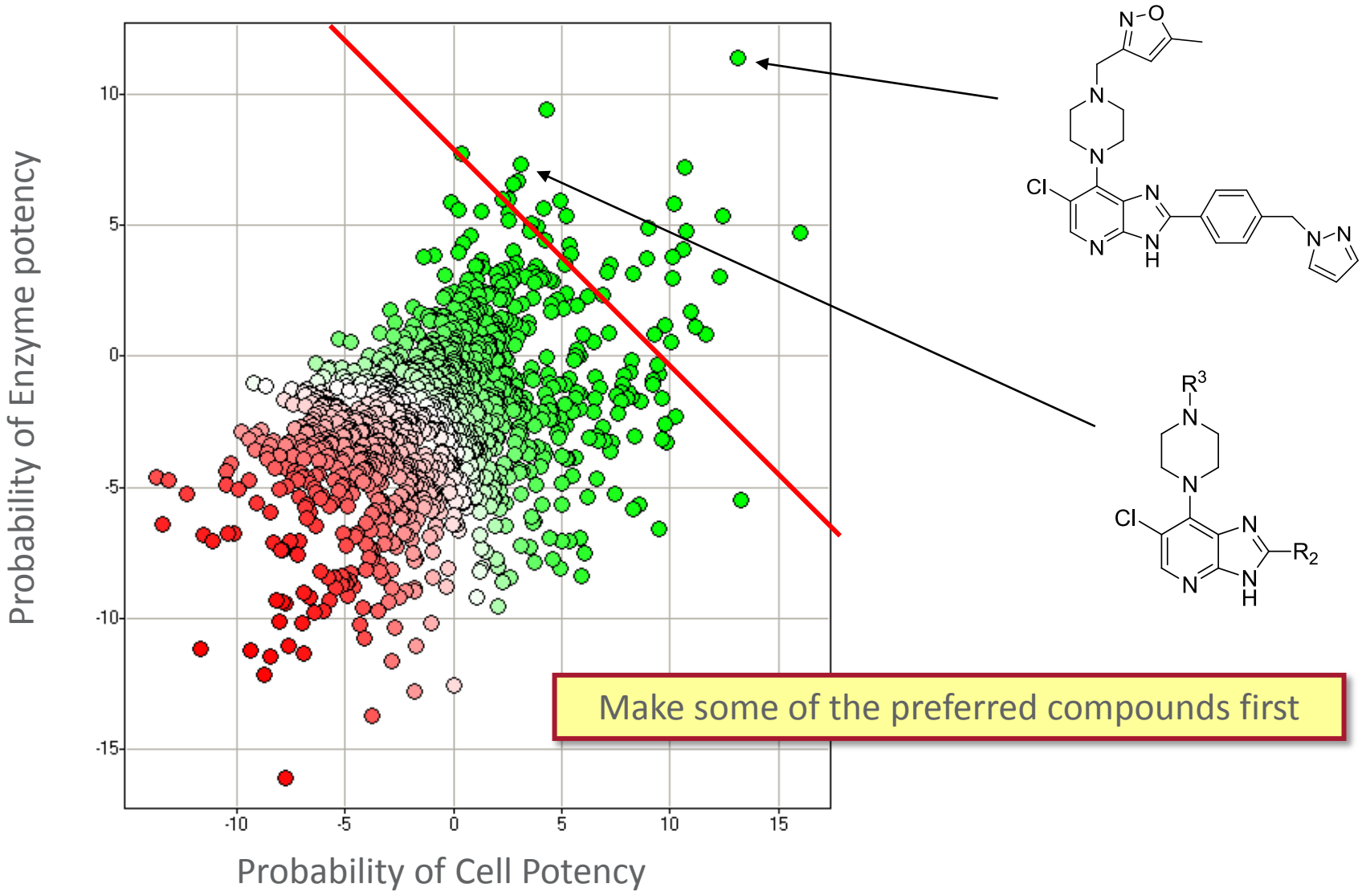
- Partition dataset into training and test sets
- Derive statistical models



Predict Activity for 1500 Virtual Molecules

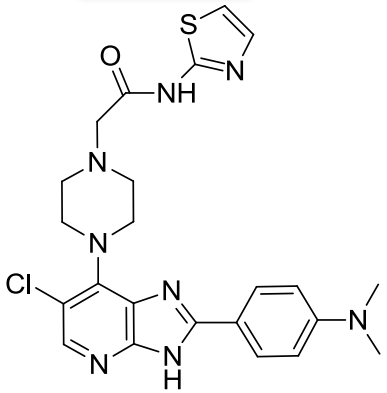
Prioritise the best molecules to make first

Predictions on Virtual Compounds



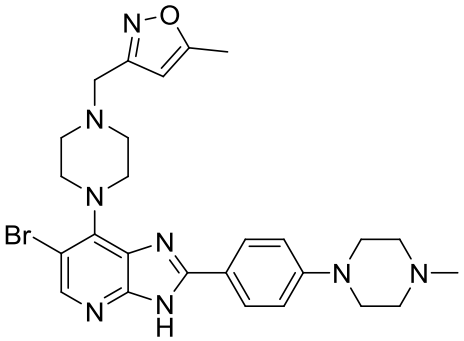
Example of Multiobjective Prioritisation Using Bioisosteric Replacements

Ligand



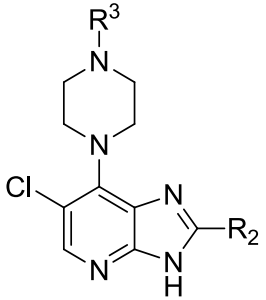
MW = 497
AlogP = 2.9
Aurora A = 42 nM
MLM unstable

Chemical Tool



MW = 551
AlogP = 4.1
FLT3 = 4 nM
Aurora A = 15 nM
MLM = 60% remaining
F = 100% mouse
HLM = 18% remaining
hERG IC_{50} = 3 uM

Potential Drug



MW = 456
logD = 3.8
FLT3 Ki = 6 nM
Aurora A Ki = 7 nM
MLM = 70% remaining
F = 100% (mouse)
HLM = 90% remaining
hERG IC_{50} > 30 uM

Optimal combination of R_2 and R_3 delivers desired profile

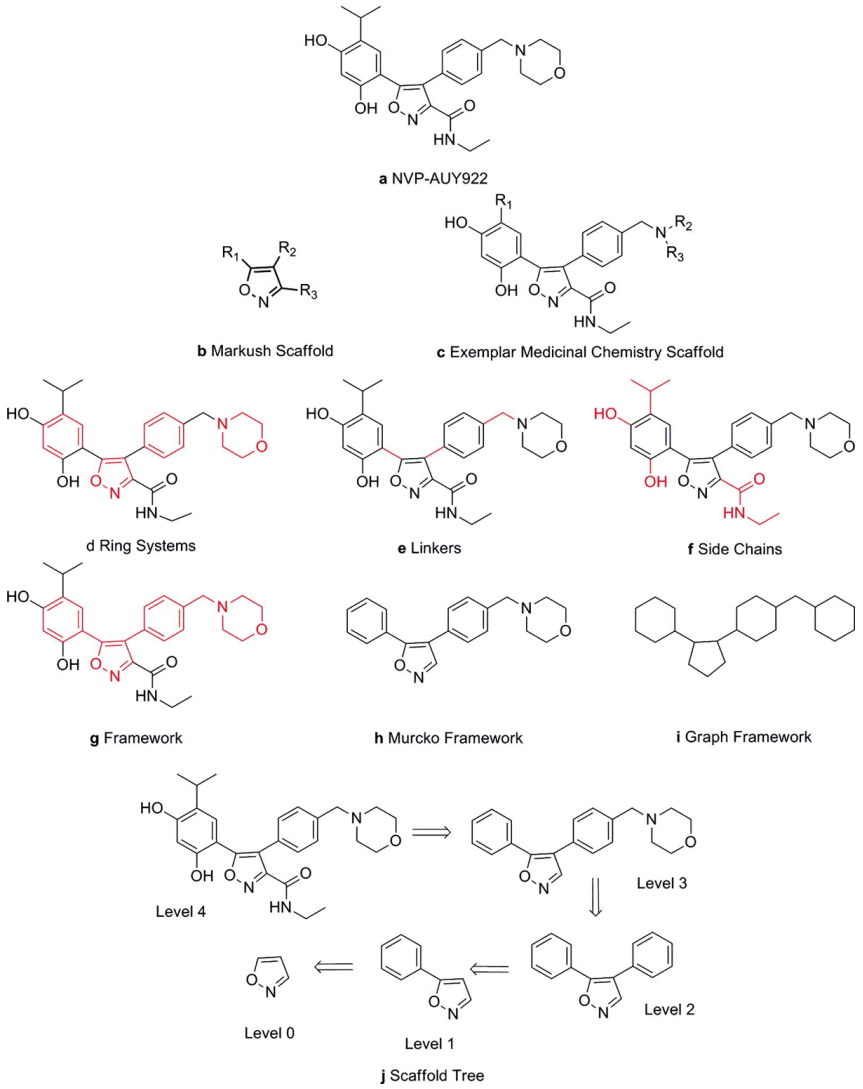
Case Study: Scaffold Hopping

Why do we need a definition?

- Scaffolds are often the synthetic invariant in lead optimization
- Library Analysis
  - Scaffold diversity
- Scaffold Hopping
  - Subset of bioisosteric replacement

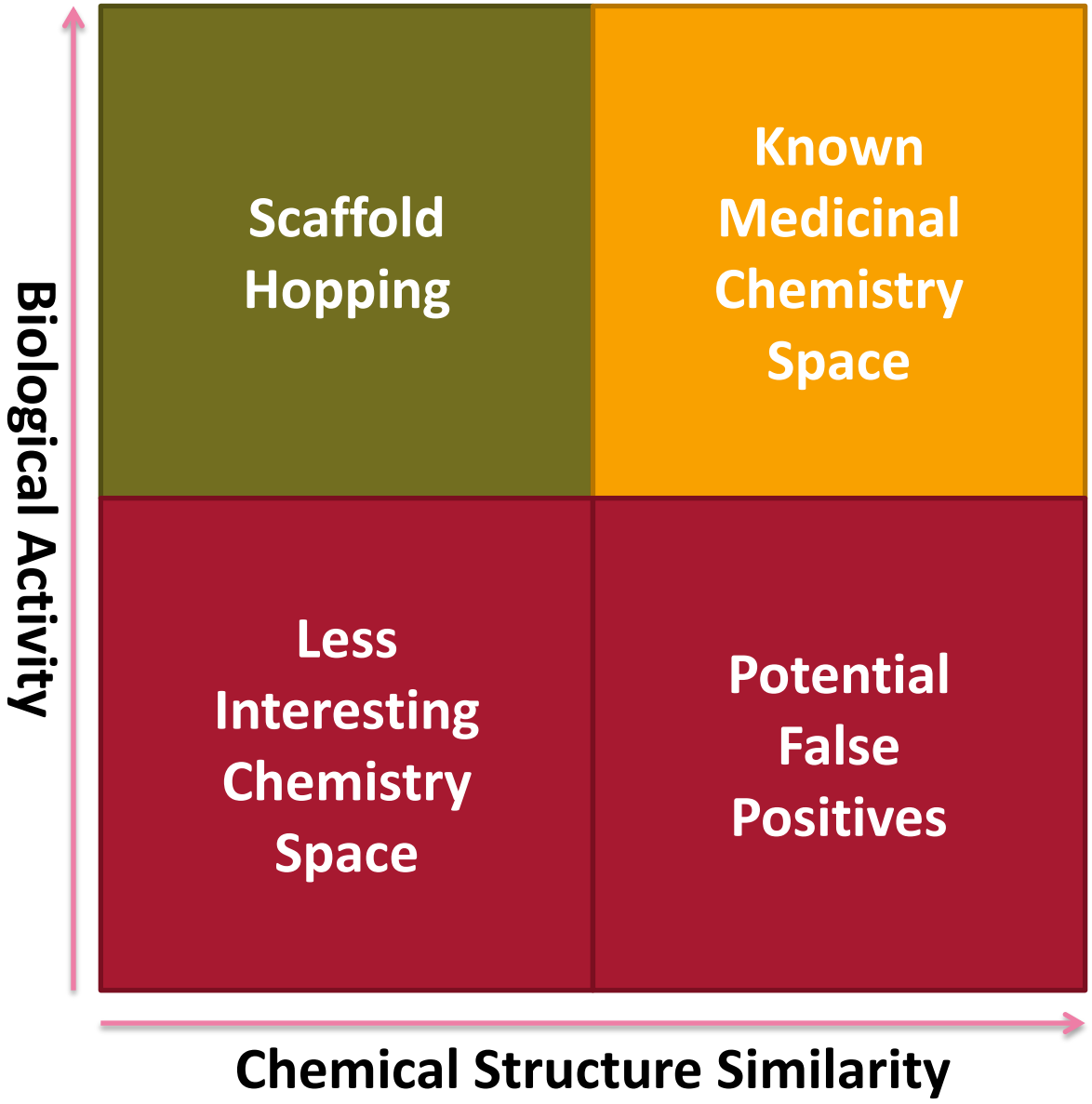
What do we need in a definition?

- Objective and invariant
  - Their definition derives solely from information in the molecule

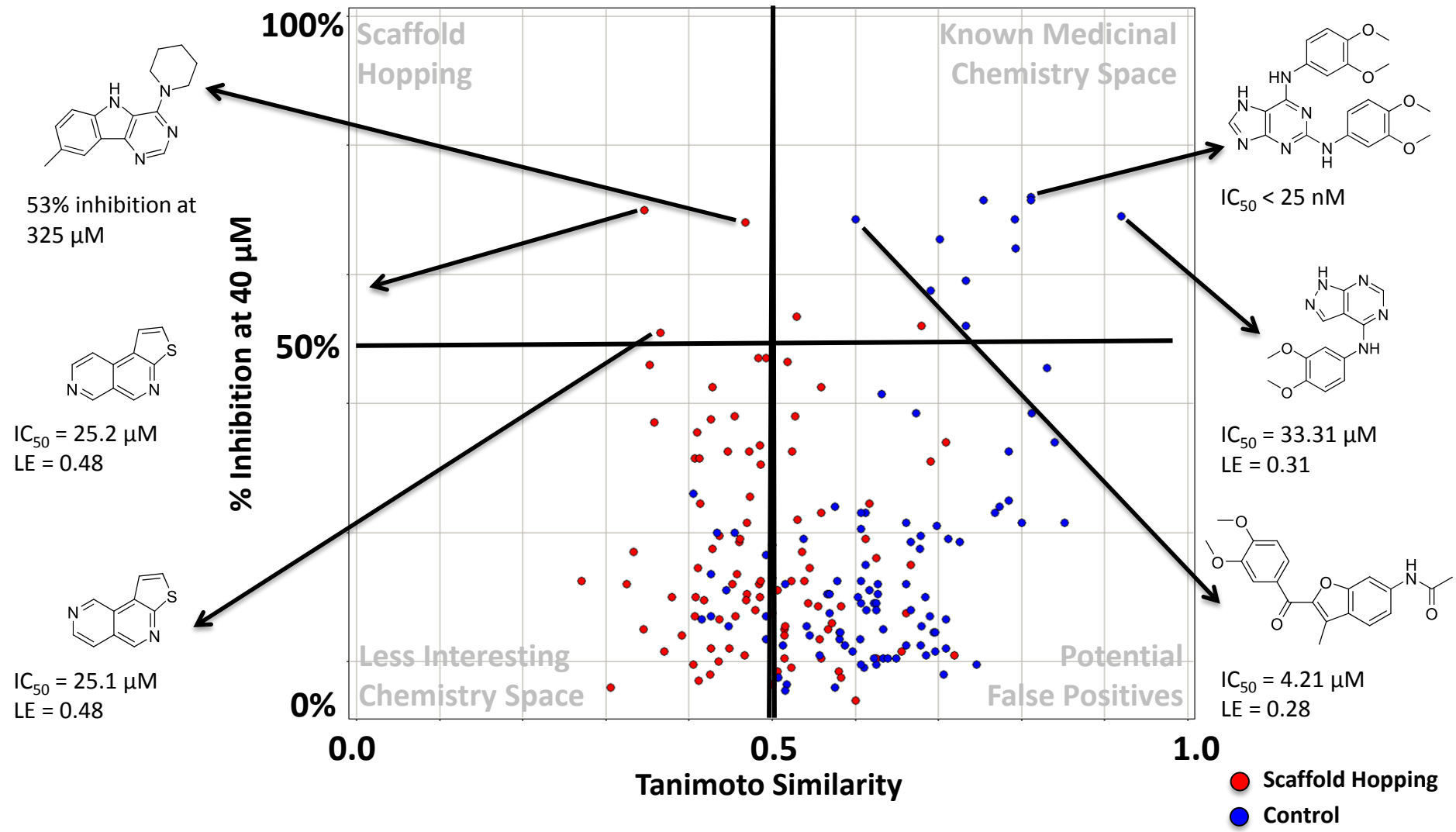


1. Langdon, S. R.; Brown, N.; Blagg, J. Scaffold Diversity of Exemplified Medicinal Chemistry Space. *J. Chem. Inf. Model.* **2011**, *51*, 2174-2185.

Case Study: Scaffold Hopping



Case Study: Scaffold Hopping



1. Langdon, S. R.; Westwood, I. M.; van Montfort, R. L. M.; Brown, N.; Blagg, J. Scaffold-focused virtual screening: Prospective application to the discovery of TTK inhibitors. *J. Chem. Inf. Model.* **2013**, *53*, 1100-1112.

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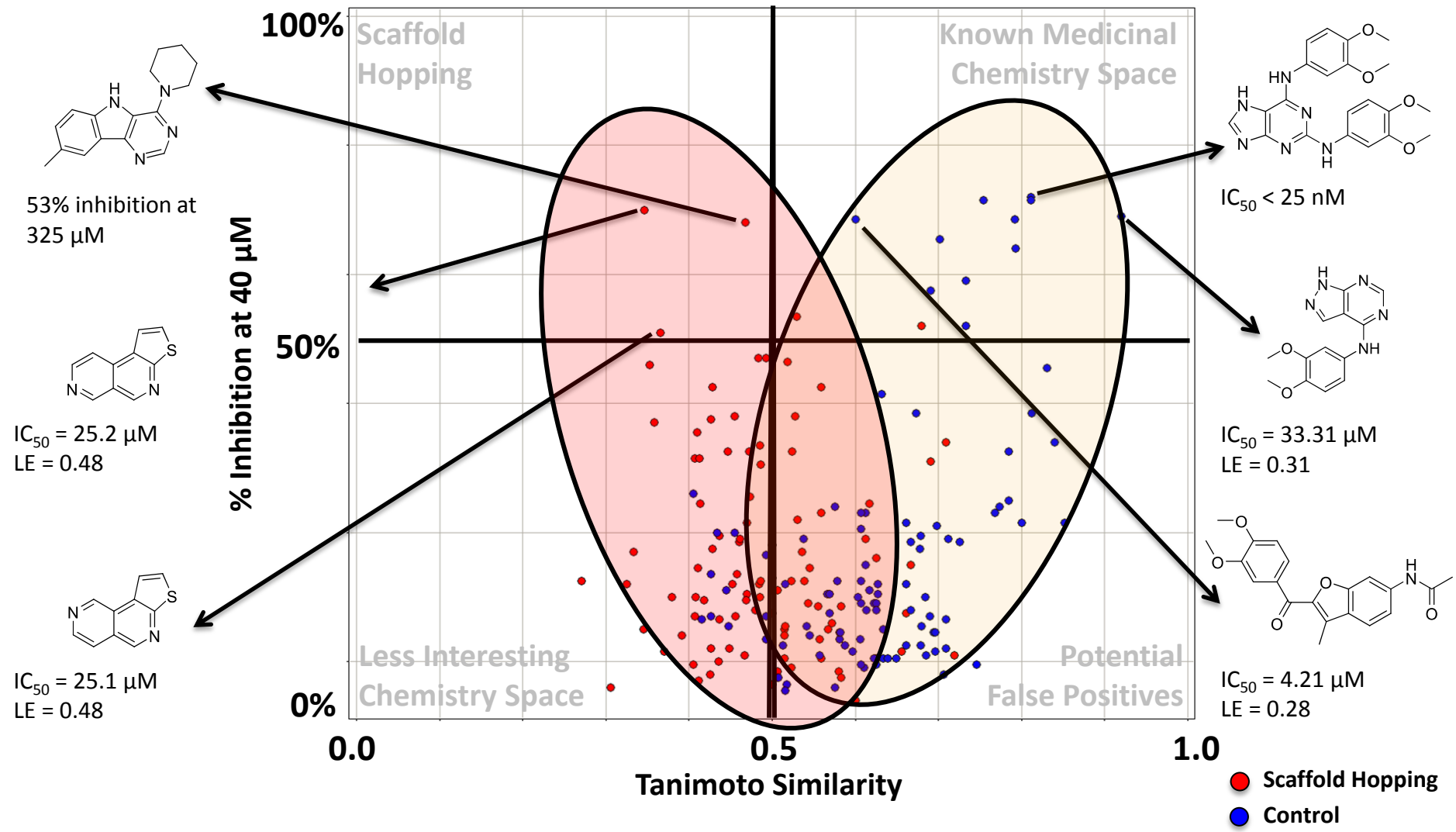

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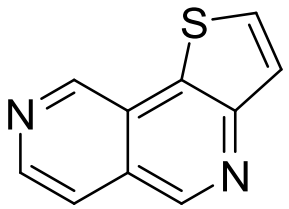
X-ray Co-crystal Structures



IC_{50} = 8.27µM
LE = 0.53

PDB: 4BHZ
Resolution = 2.85 Å

- Nine active SHv3 compounds have been soaked with TTK apo crystals
- Structures determined from X-ray crystallography
- Four active SHv3 compounds have been confirmed with co-crystal structures

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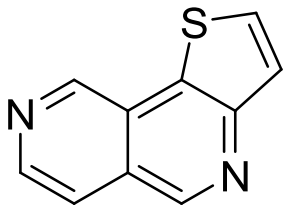

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Conclusions

Bioisosterism has seen more than a century of innovation

- Remains a difficult concept to define accurately, however…
- Databases of bioisosteric transforms routinely available
- Molecular descriptors allow for the exploration and validation of structurally disparate replacements

Scaffold Hopping is a subset of bioisosteric replacement

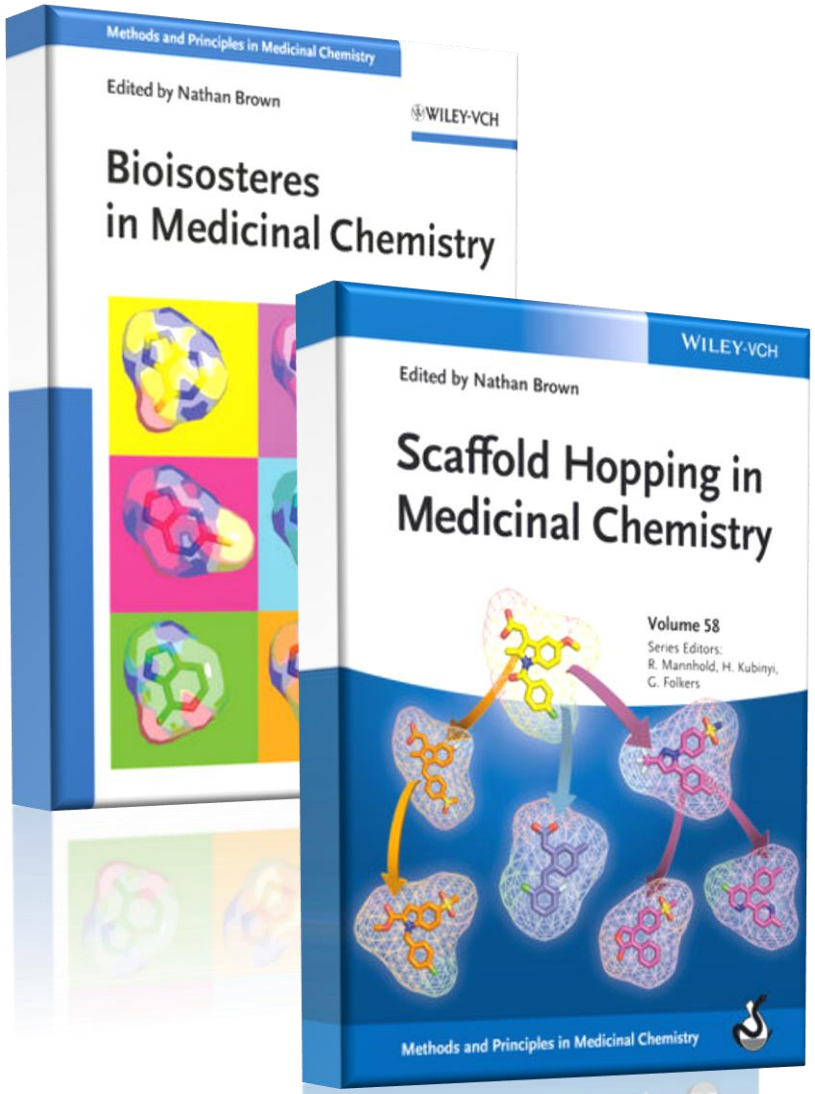
- Ability to successfully move away from problematic scaffolds
- Important to maintain exit vector geometries

Acknowledgements

CANCER RESEARCH UK

ICR The Institute of Cancer Research

Bioisosteres and Scaffold Hopping



- Principles of bioisosteres
- Scaffolds: Identification, Representation, Diversity, and Navigation
- Data Mining
- Methods
  - **Bioisosteres**: Physicochemical, Topology, Shape, Protein
  - **Scaffold Hopping**: CATS, Molecular Interaction Fingerprints
- Case Studies

Abbott, AstraZeneca, BMS, CCDC, Cresset, Digital Chemistry, EBI, Eli Lilly, ETH-Zurich, GSK, ICR, MRCT, Novartis, Pfizer, UCB Celltech, Bonn, Cambridge, Manchester, Sheffield, Strasbourg, Vanderbilt

1. Brown, N. (Ed.) *Bioisosteres in Medicinal Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2012**.
2. Brown, N. (Ed.) *Scaffold Hopping in Medicinal Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2013**.