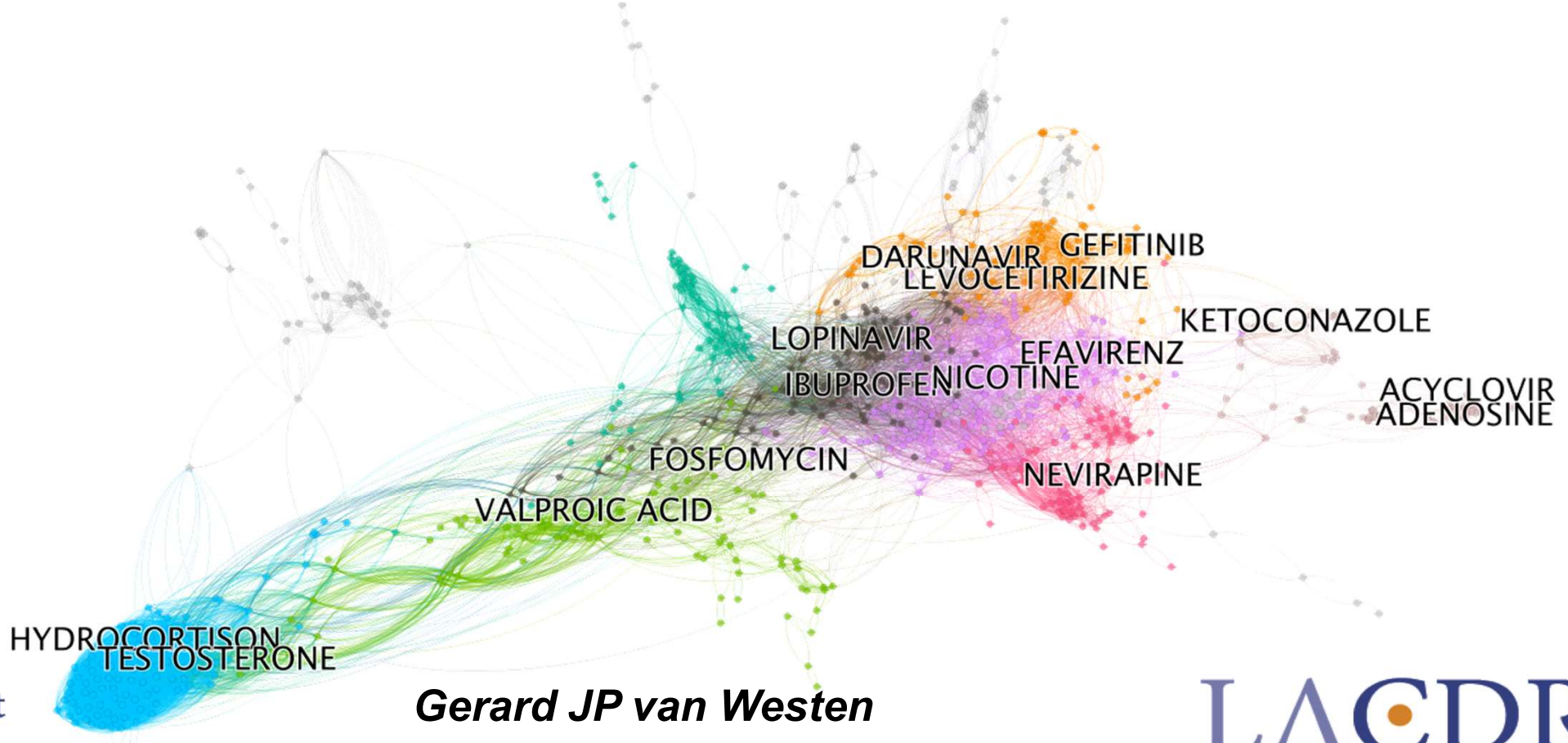
# *Computational Drug Discovery*

*arget prediction, mode-of-action elucidation, virtual screening,* ***molecular structure genera***





Universiteit Leiden
The Netherlands

***Gerard JP van Westen***


*SAILS Kick off*

LACDR

Unilever janssen NWO Applied and Engineering Sciences

# Quick intro on myself

MSc in biopharmaceutical sciences (2007)

PhD in Chem/Bioinformatics (2007 – 2012)

- Computational chemistry
- Medicinal Chemistry in Leiden
- Personal Grant from Janssen

# Quick intro on myself

MSc in biopharmaceutical sciences (2007)

PhD in Chem/Bioinformatics (2007 – 2012)

Postdoc at European Bioinformatics Institute (2012 – 2015)

- ChEMBL group
- Marie Curie Fellowship

# Quick intro on myself

MSc in biopharmaceutical sciences (2007)

PhD in Chem/Bioinformatics (2007 – 2012)

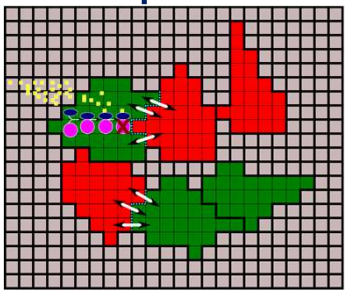
Postdoc at European Bioinformatics Institute (2012 – 2015)

Assistant Professor in Leiden (2015 - …)

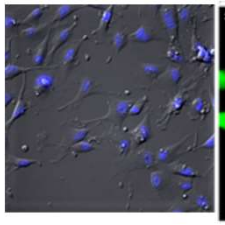
- LACDR & LIACS
- Drug Discovery and Safety
- Data Driven Drug Discovery network (D4N, www.d4n-leiden.nl)
- ***Center for Computational Life Sciences (www.ccls-leiden.nl, with Dr. Emmerich)***

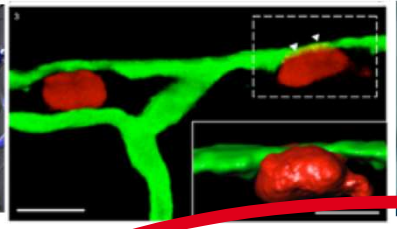
# g Discovery and Safety

## 6. Image-Based Computational Biology

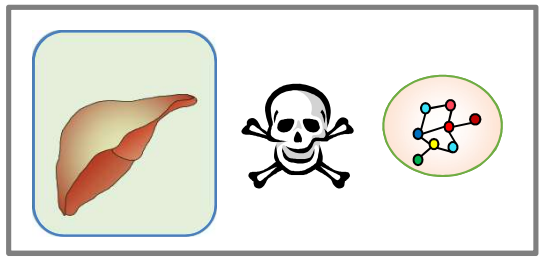


## 1. Cancer Drug Target Discovery



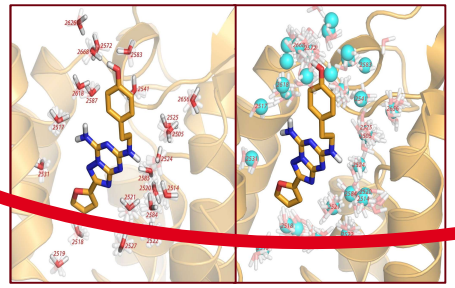


## . Cancer Therapeutics
## nd Drug Safety

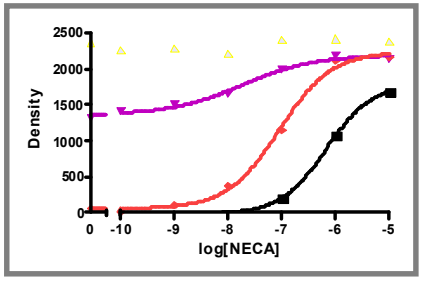


*Establish Concepts for Drug Discovery Cycle*

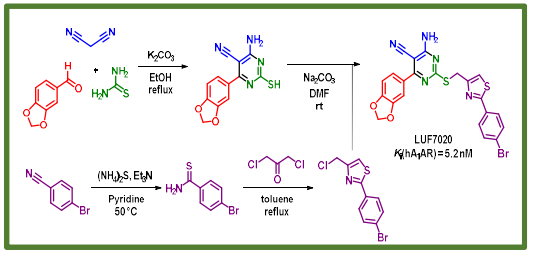
## 2. Computational Drug Disco



## 4. Receptor Pharmacology




## 3. Medicinal Chemistry




# at is ChEMBL?

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

## Synthesis, Pharmacological Characterization, and Docking Analysis of a Novel Family of Diarylisoxazoles as Highly Selective Cyclooxygenase-1 (COX-1) Inhibitors

Paola Vitale,[†,#] Stefania Tacconelli,[§,⊥,#] Maria Grazia Perrone,[†,#] Paola Malerba,[†] Laura Simone,[†] Antonio Scilimati,[*,†] Antonio Lavecchia,[*,‡] Melania Dovizio,[§,⊥] Emanuela Marcantoni,[§,⊥] Annalisa Bruno,[∥,⊥] and Paola Patrignani[*,§,⊥]

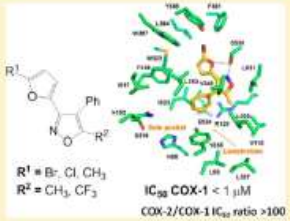
[†]Dipartimento di Farmacia-Scienze del Farmaco, Università degli Studi di Bari "A. Moro", Via Orabona 4, 70125 Bari, Italy

[‡]Dipartimento di Farmacia, "Drug Discovery" Laboratory, Università di Napoli "Federico II", Via D. Montesano 49, 80131 Napoli, Italy

[§]Department of Neuroscience and Imaging, [∥]Department of Medicine and Aging, "G. d'Annunzio" University, and [⊥]Center of Excellence on Aging (CeSI), Chieti, Italy

Supporting Information

**ABSTRACT:** 3-(5-Chlorofuran-2-yl)-5-methyl-4-phenylisoxazole (**P6**), a known selective cyclooxygenase-1 (COX-1) inhibitor, was used to design a new series of 3,4-diarylisoxazoles in order to improve its biochemical COX-1 selectivity and antiplatelet efficacy. Structure−activity relationships were studied using human whole blood assays for COX-1 and COX-2 inhibition in vitro, and results showed that the simultaneous presence of 5-methyl (or -$CF_3$), 4-phenyl, and 5-chloro(-bromo or -methyl)furan-2-yl groups on the isoxazole core was essential for their selectivity toward COX-1. **3g**, **3s**, **3d** were potent and selective COX-1 inhibitors that affected platelet aggregation in vitro through the inhibition of COX-1-dependent thromboxane (TX) $A_2$. Moreover, we characterized their kinetics of COX-1 inhibition. **3g**, **3s**, and **3d** were more potent inhibitors of platelet COX-1 and aggregation than **P6** (named **6**) for their tighter binding to the enzyme. The pharmacological results were supported by docking simulations. The oral administration of **3d** to mice translated into preferential inhibition of platelet-derived $TXA_2$ over protective vascular-derived prostacyclin ($PGI_2$).




### INTRODUCTION

Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) catalyze the first step of the biosynthesis of prostanoids from arachidonic acid (AA).[1] Different from COX-2 gene that is mainly inducible, COX-1 is a housekeeping gene constitutively expressed in almost all mammalian tissues and cells.[1] However, the expression of COX-1 can be regulated in some circumstances, such as during development.[2] In physiological conditions, COX-1 is highly expressed in the gastrointestinal (GI) tract and platelets,[3,4] where it is involved in the generation of cytoprotective prostaglandin (PG)$E_2$ and platelet proaggregatory thromboxane (TX) $A_2$, respectively.[1]

COX-1 plays a role in several pathological conditions such as thrombosis, atherosclerosis, and tumorigenesis.[5−10] Importantly, platelet COX-1 is the target of one of the most efficacious antithrombotic agents used for prevention of vascular occlusive events, i.e., aspirin.[11]

Aspirin irreversibly acetylates Ser529 and Ser516 of COX-1 and COX-2, respectively,[12] leading to irreversible enzyme inactivation. Because of pharmacokinetics features (i.e., short half-life of 20 min) and pharmacodynamics features (higher potency to inhibit COX-1 than COX-2), low doses of aspirin (75−100 mg once daily) act by affecting platelet COX-1 activity while they cause only a marginal and transient inhibitory effect on COX-2 and extra-platelet cellular COX-1. Low doses of aspirin cause an almost complete suppression (≥95%) of platelet $TXA_2$ generation ex vivo, persisting throughout the dosing interval (i.e., 24 h).[11,13] This is a fundamental requisite to obtain an antiplatelet effect,[14] since even tiny concentrations of $TXA_2$ may activate platelets and importantly they synergize with other platelet agonists.[15] The antiplatelet effect of aspirin is strictly related to platelet turnover.[11,12] Thus, enhanced platelet turnover rate detected in some cardiovascular (CV) conditions, such as diabetes, might decrease the efficacy of the drug to halt almost completely platelet $TXA_2$ generation.[16] Moreover, we have recently shown that platelets contain COX-1 mRNA and the enzymatic machinery for protein synthesis; thus, these anucleated megacaryocyte fragments are able to synthesize de novo COX-1 in response to platelet activation in vitro.[17] Thus,

Received: December 28, 2012
Published: May 7, 2013

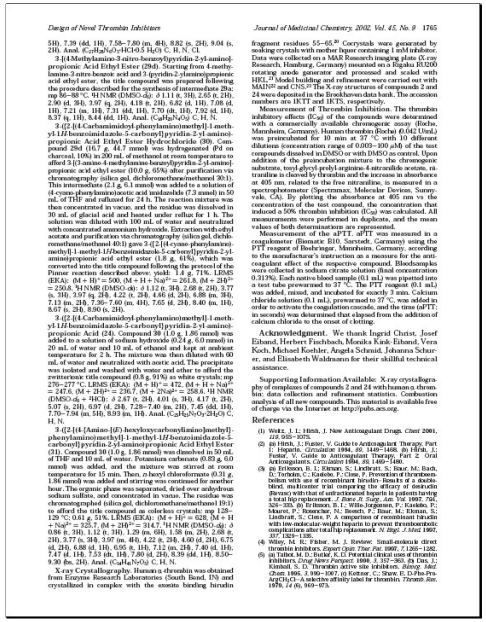


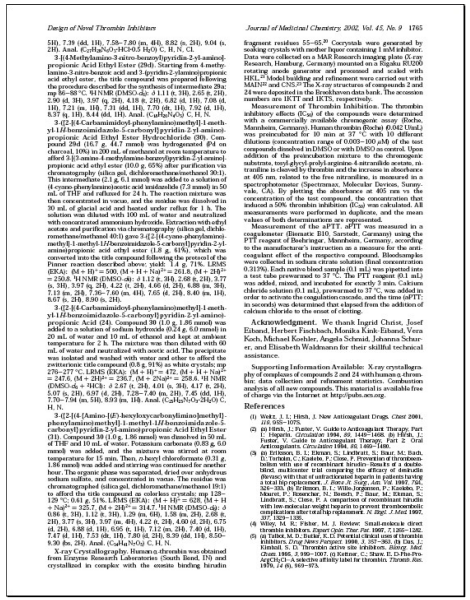


dx.doi.org/10.1021/jm301905a | J. Med. Chem. 2013, 56, 4277−4299

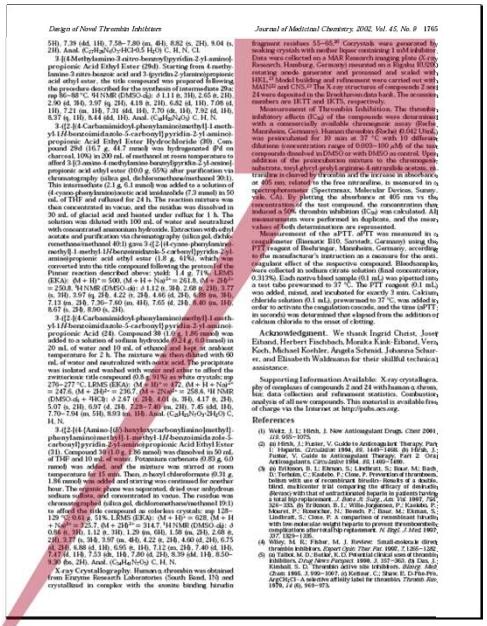
*/www.ebi.ac.uk/chembl/*

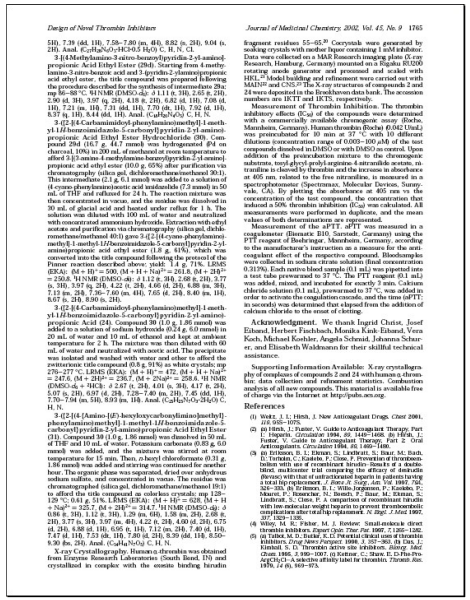
# at is ChEMBL?

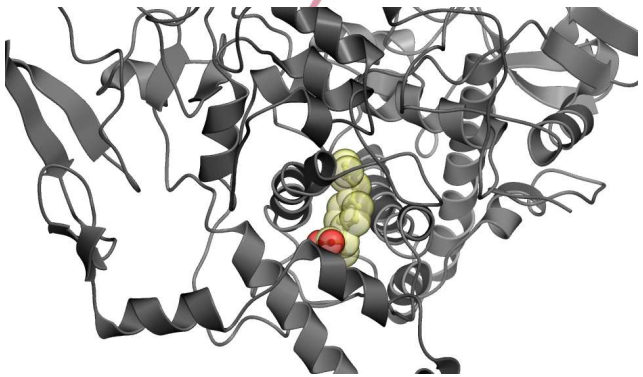




# at is ChEMBL?



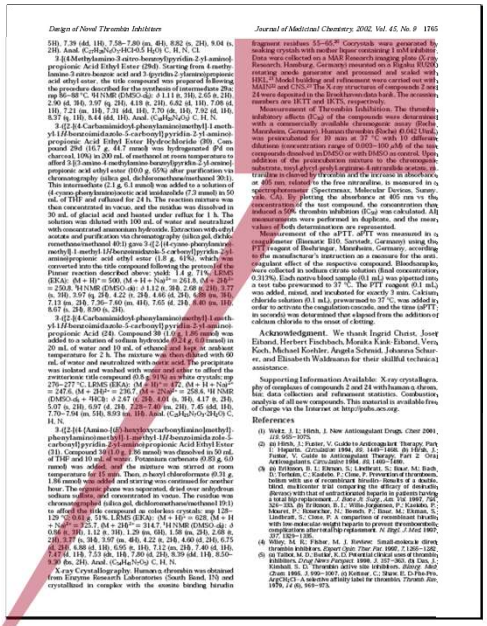


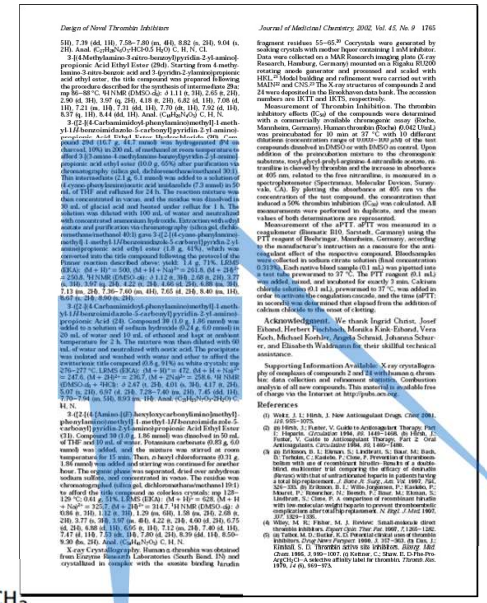


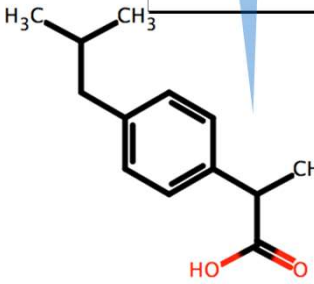
Affinity to COX-1

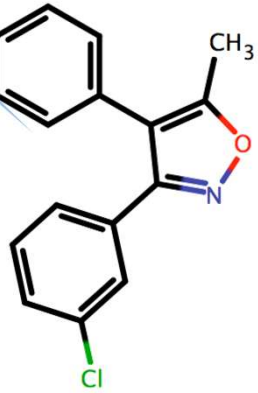
*ed from J.P. Overington*
*//www.ebi.ac.uk/chembl/*

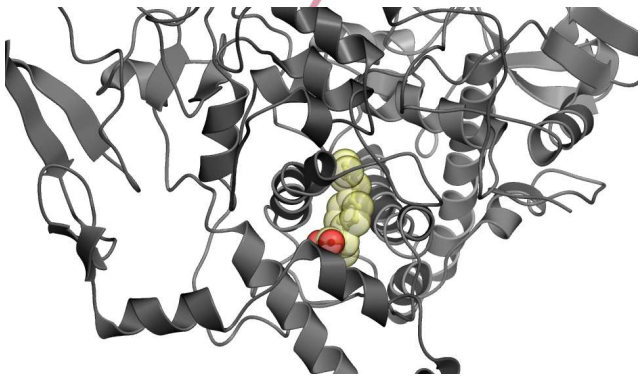
# at is ChEMBL?







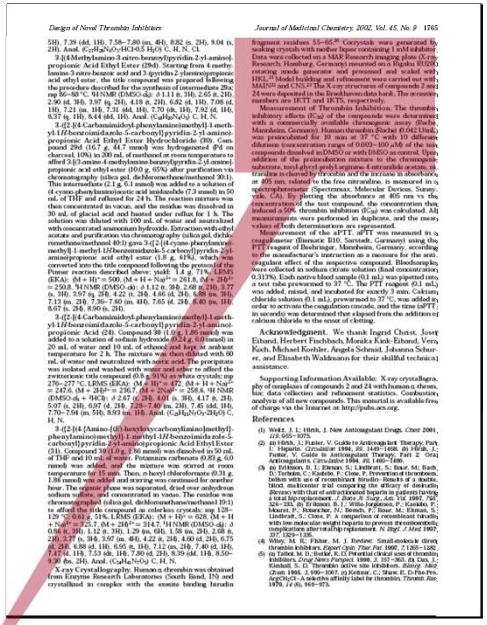


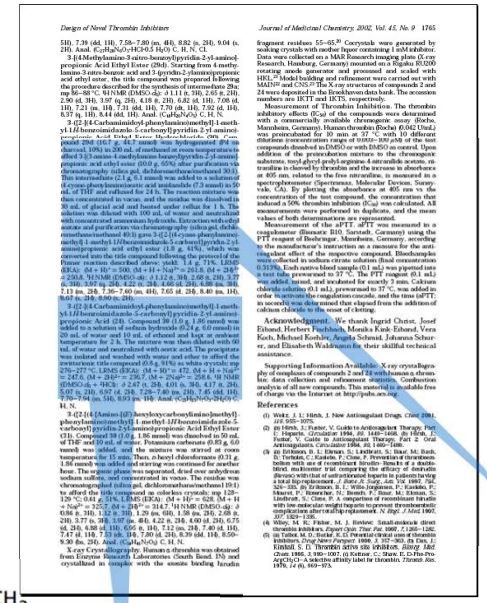


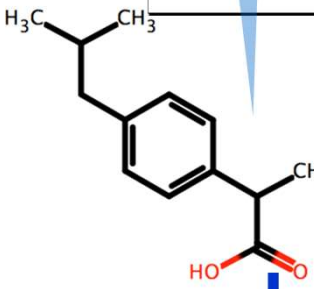
Affinity to COX-1

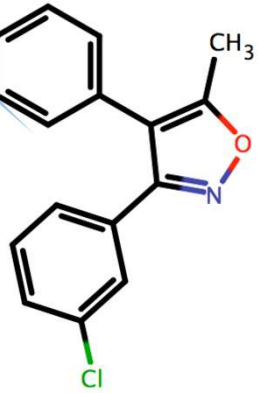
*ed from J.P. Overington*
*//www.ebi.ac.uk/chembl/*

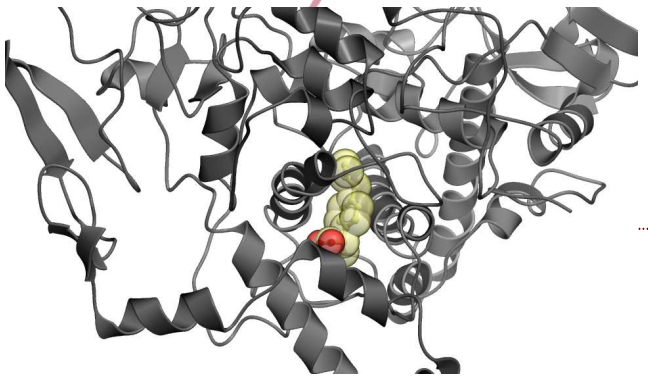
# at is ChEMBL?











Affinity to COX-1

$IC_{50}$=290 nM

$IC_{50}$=270 nM

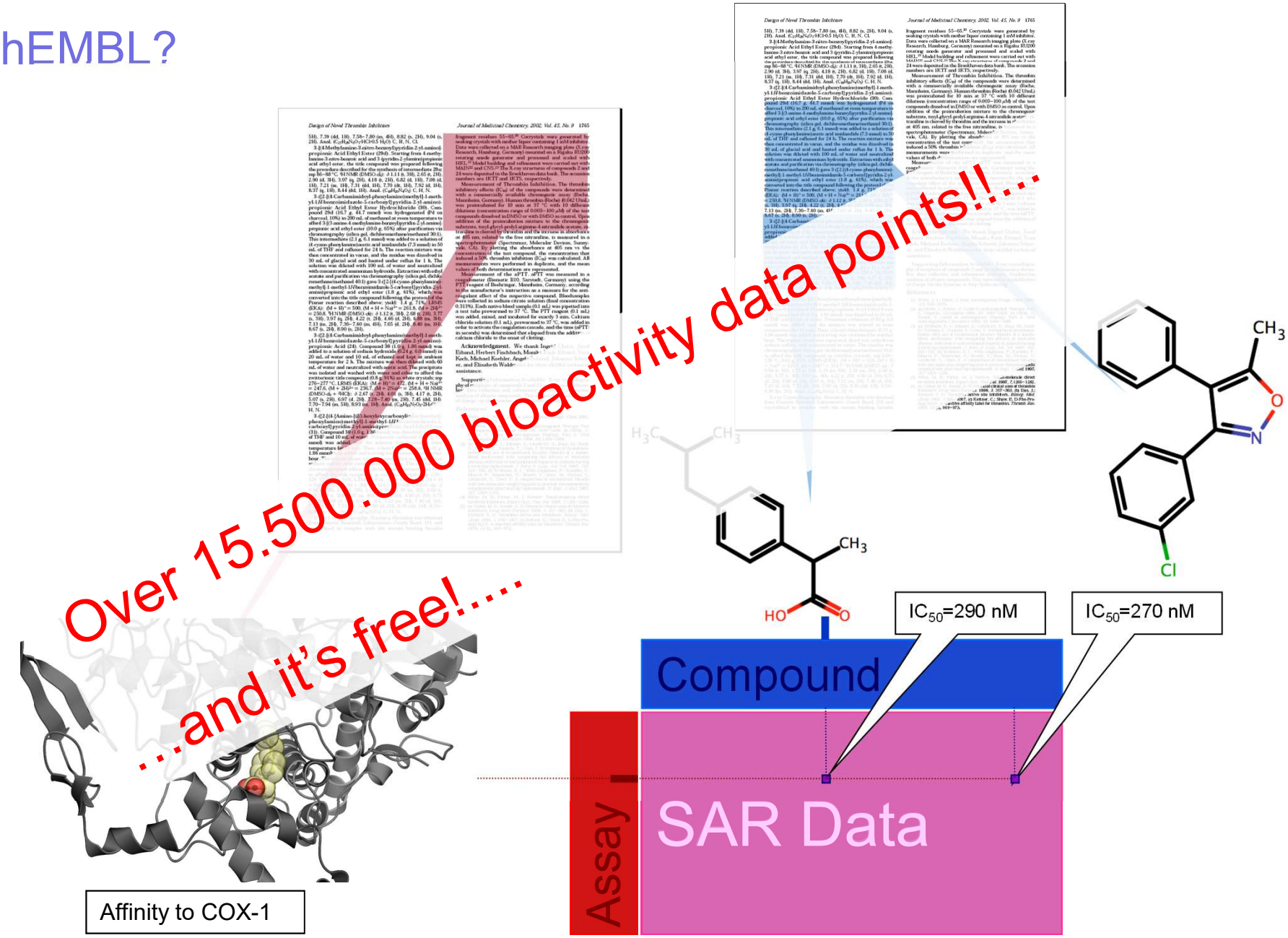
Compound

Assay

SAR Data

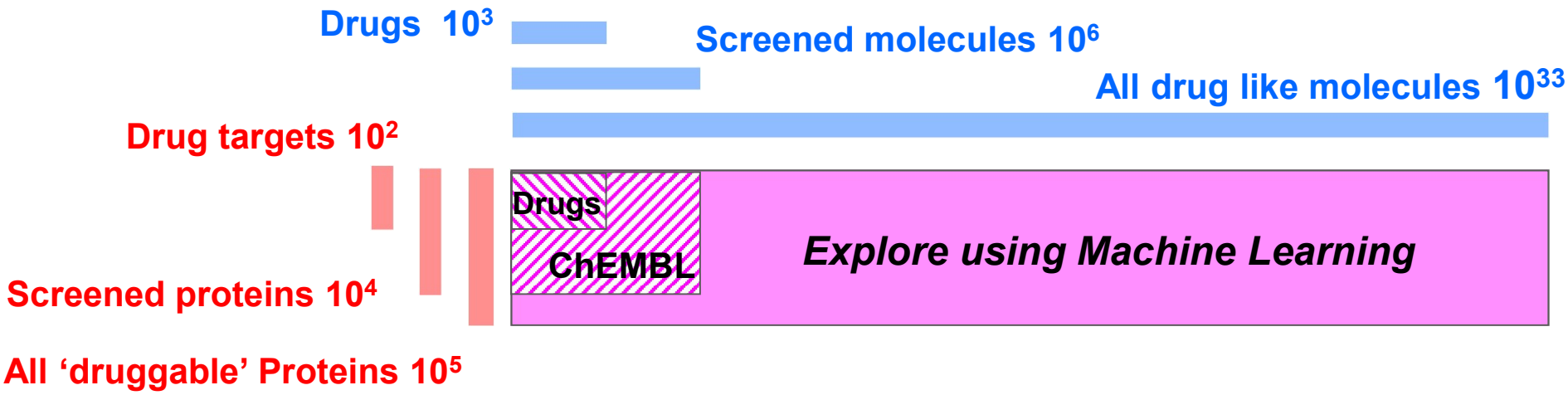
*ed from J.P. Overington*
*//www.ebi.ac.uk/chembl/*

# at is ChEMBL?



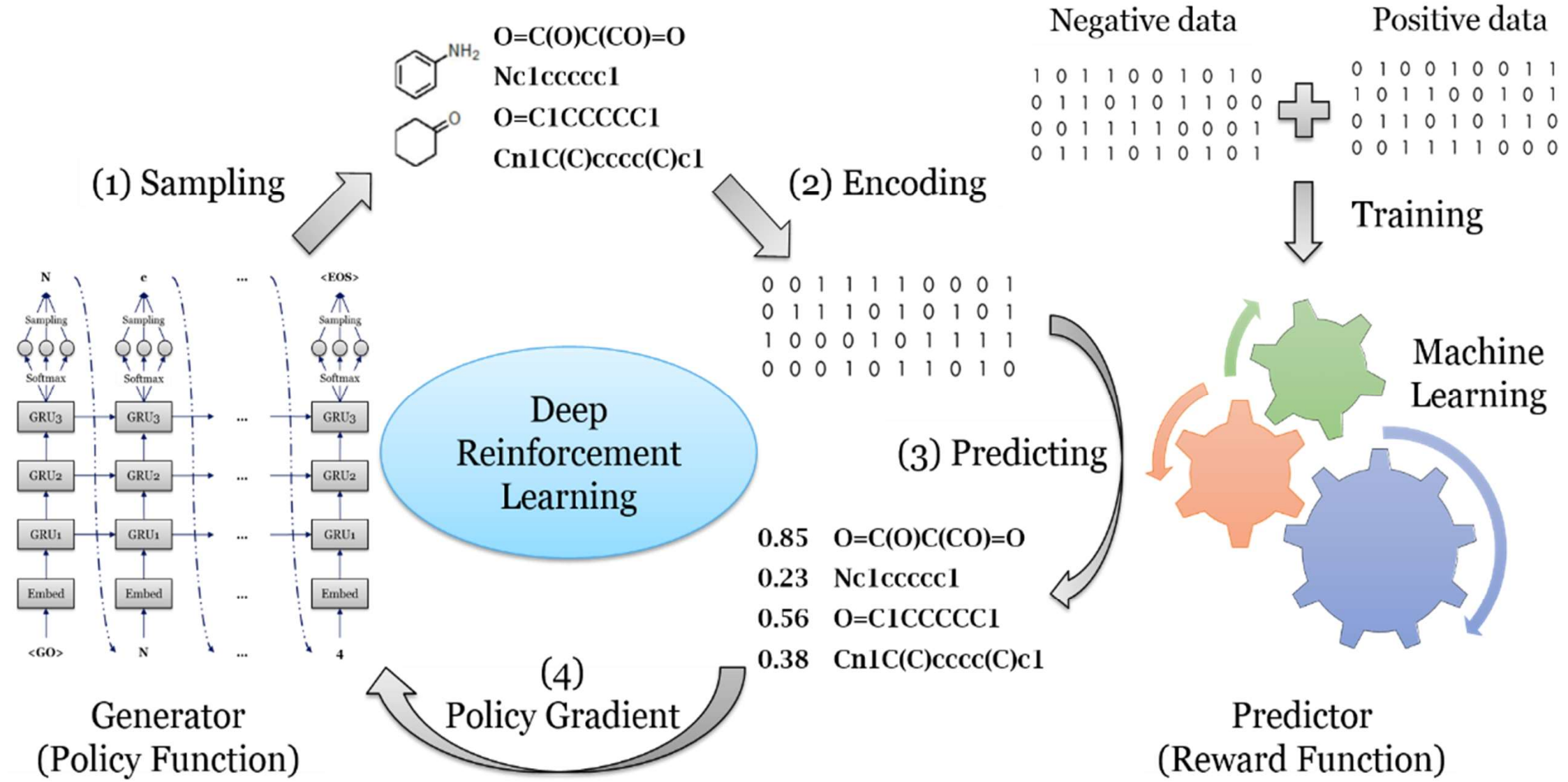

*ed from J.P. Overington*
*//www.ebi.ac.uk/chembl/*

# e challenge…




*mond, J.-L.; (**2015**) Acc. Chem. Res., 48, 722.*
*man, H.M.; et al. (**2012**) Structure, 20, 391.*
*[3] Polishchuk, P.G.; (2013) J. Comput. Aided. Mol. Des., 27, 675*
*And J.P. Overington*

# Exploring ‘Drug-Like’ Chemical Space




, K. Ye, et al, (2019), J Cheminform, Accepted

## Challenges

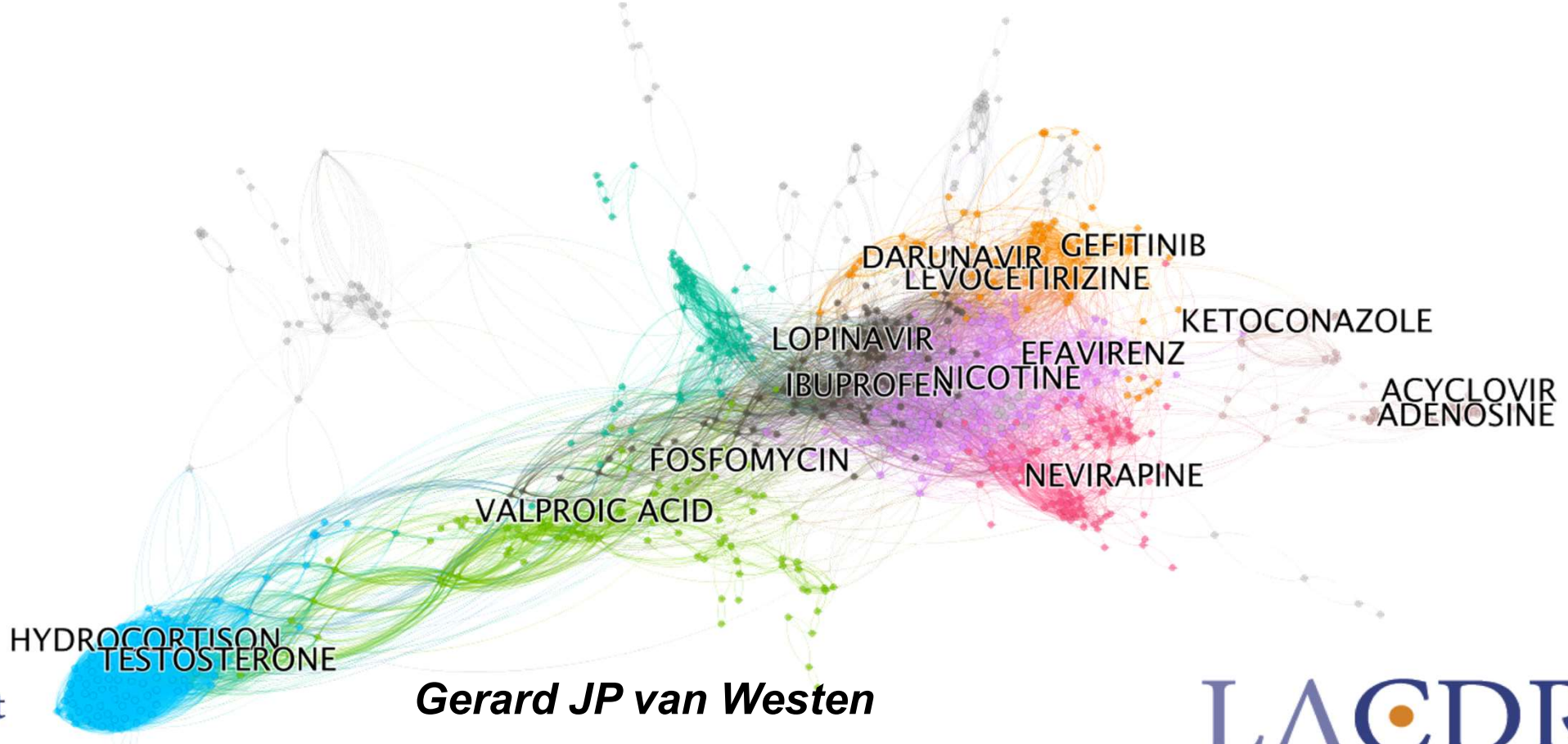
- Target description for side-effect prediction

- Bias in the data (ligand size, explored proteins, etc..)
  - Models will display tendency to regress to the mean for extremes
- Errors in the data (experimental errors and annotation errors)
- Sparseness of the data
  - Typical coverage is 2%...
- Synthesizability
  - Can molecules suggested by the computer be generated?


The data is out there ...

# *Machine Learning in Drug Discovery*

*Off-target prediction, mode-of-action elucidation, virtual screening, molecular structure*





Universiteit Leiden
The Netherlands

**Gerard JP van Westen**


*SAILS Kick off*

LACDR

Applied and Engineering Sciences

***Storage is cheap*,***
***computing power is cheap*,***
***measurements are easy** .. (and cheap*)..***

***…scientific data is becoming open / public…***

***…every research project can profit from data / analytic***

*vely compared to historic prices*
*ld also be taken with a grain of salt and is relative to history…*