AstraZeneca
IMED Biotech Unit

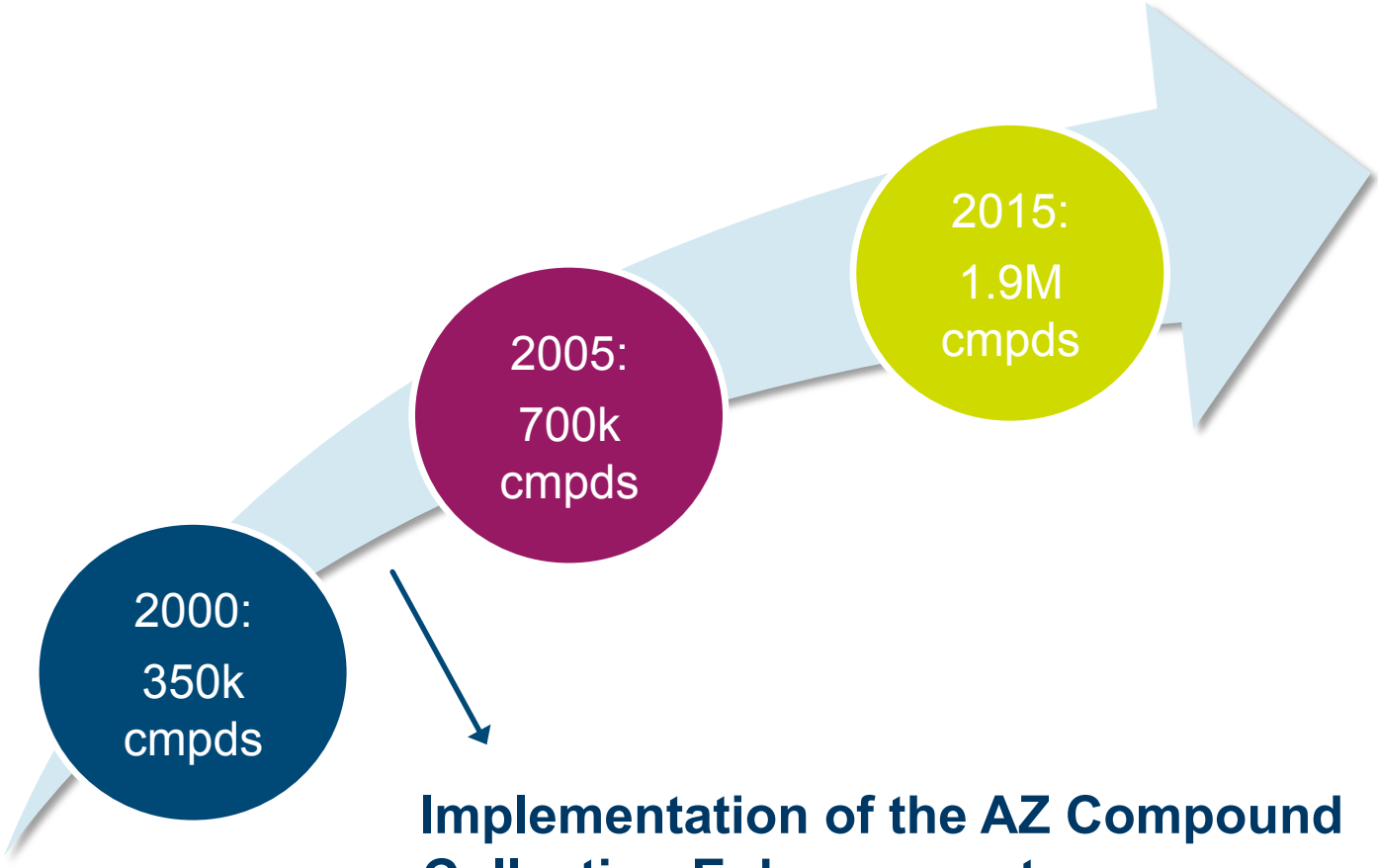
crease value of screening collection through
ben-innovation

ry Kogej
nal Sciences, Computational Chemistry

21th April 2017

gh Throughput Screening

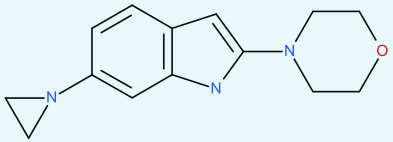
S = screen hundred thousand – several million compounds on a given biological target
S remains one of main methods to **discover novel chemical equity** and remains the **benchmark for lead generation**



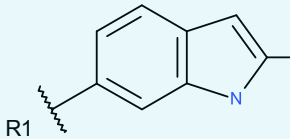
Implementation of the AZ Compound Collection Enhancement programme (CCE programme)

CE library design rationale

Project cmpd



Chemical lib



2003
Target Class Libraries

2008
Diversity Libraries

2012
Biologically Relevant Lib.

Target class libraries → **addressing target class specific requirements**

Diversity libraries → **based on novel chemistry and novel scaffolds**

Biologically relevant libraries → **linked to known bioactive features**

>5000 libraries designed by >200 AZ chemists

ompound & Library Design Criteria

”Small” Library - 100-200 cmpds

Physchem properties*

- pre 2012 strictly to follow ”Ro4,5” guideline
- since 2012 also bRo5 allowed

Predicted solubility high >100 µM

Novel to AZ (IP space)

No predicted tox and safety alerts

- no hERG, phospholipidosis, genotox, reactive metabolite warning

The drug likeness prediction of drugs, leads, fragments, and building blocks.

	MW (Da)	log *P*	Number of H donors	Number of H acceptors	PSA (Å
Drugs (Ro5)	<500	<5	<5	<10	<140
Leads (Ro4)	<400	<4	<4	<8	<120
Fragments (Ro3)	<300	<3	<3	<6	<60
Building blocks (Ro2)	<200	<2	<2	<4	

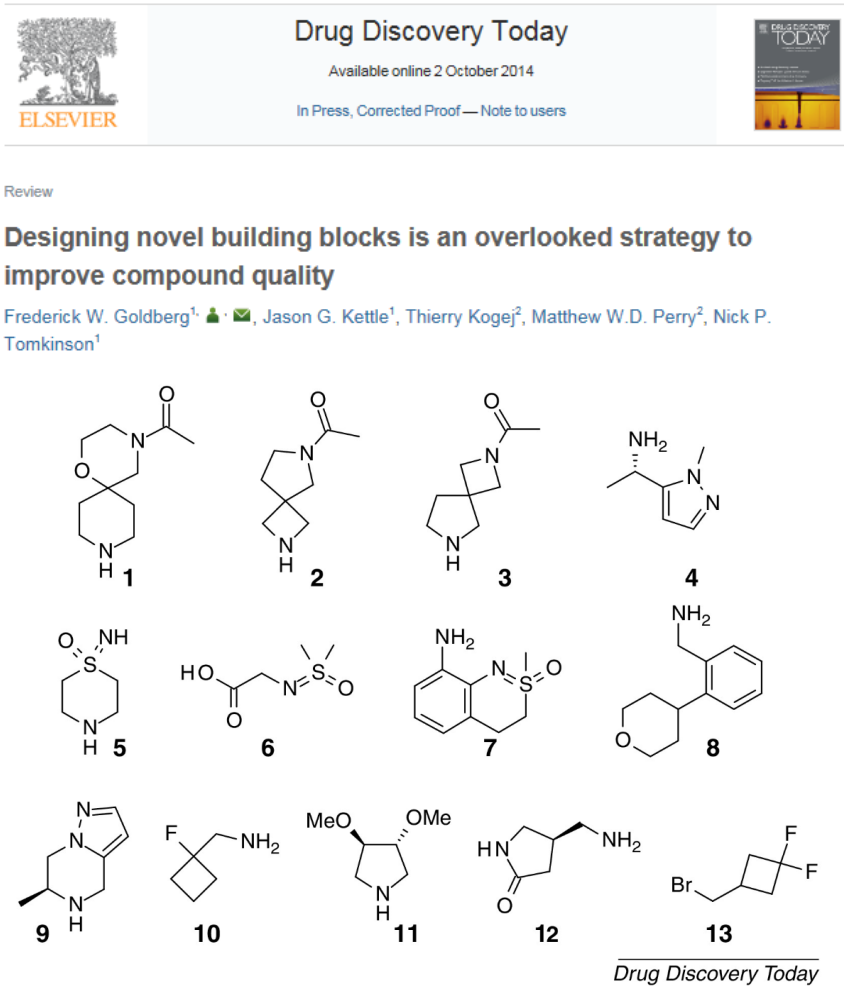
Z Proprietary Building Blocks

Internal programme initiated in 2009 with the goal to design proprietary building blocks to enhance and speed up exploration of chemical space

Compounds

- have one common reactive group
- are small reagents
- are not commercially available
- are medchem relevant

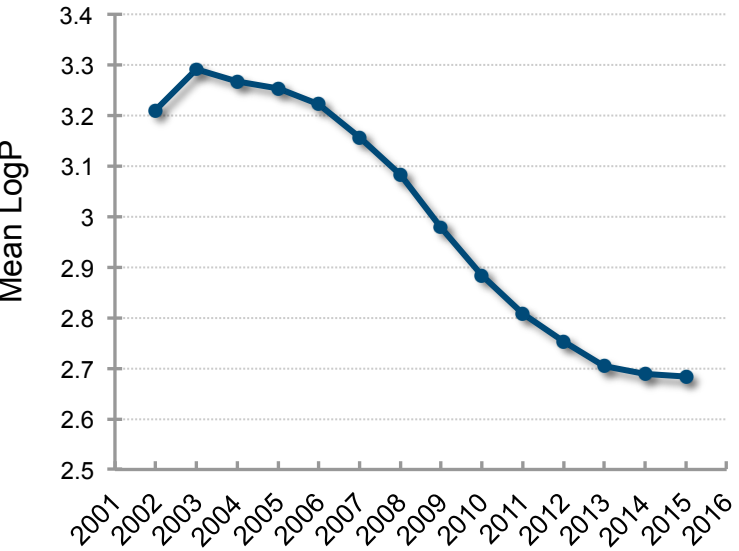
4k reagents incorporated in >70k library compounds



F.W. Goldberg et al., Drug Discovery Today 2015, 20, 11–17
F.W. Goldberg et al., Tetrahedron 2014, 70, 6613-6622
Y. Chen et al., Synthesis 2015, 679-691

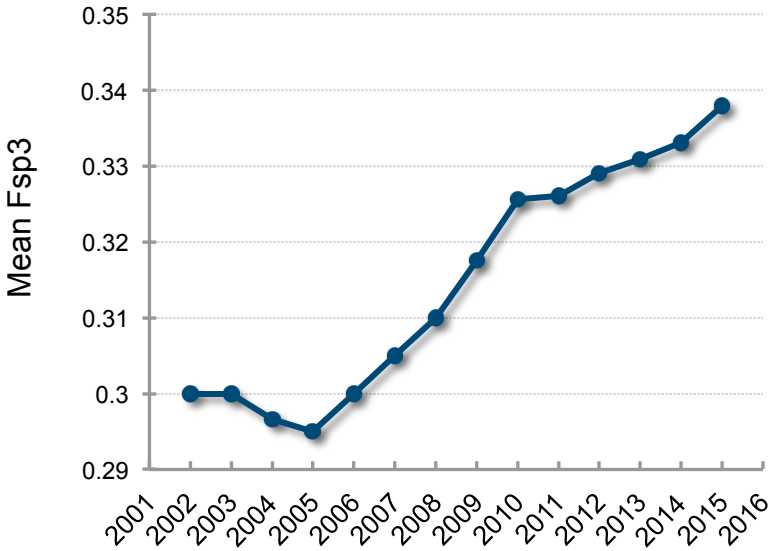
hanging Compound Properties Over Time
ipophilicity and Molecular Complexity

Mean clogP since 2002



Mean Fsp^3 since 2002*

Fsp^3 = # sp3-hybridized carbons / total carbon count



6752 *J. Med. Chem.* **2009,** *52,* 6752–6756
DOI: 10.1021/jm901241e

Journal of Medicinal Chemistry Article

Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success

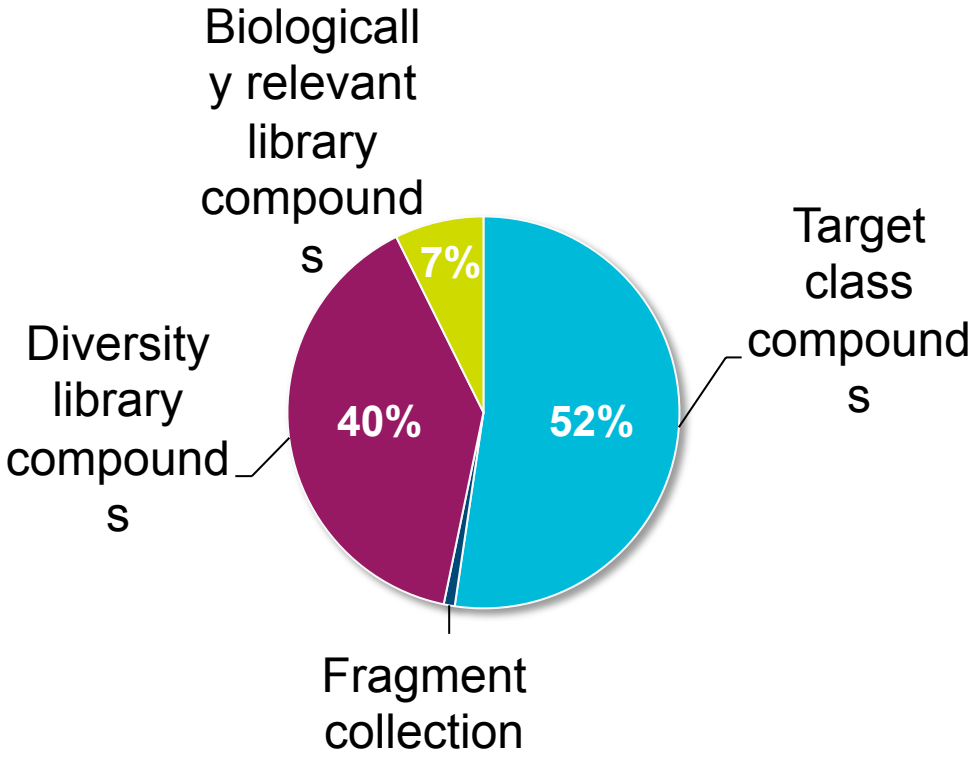
Frank Lovering,*,† Jack Bikker,‡ and Christine Humblet§

Wyeth Research, Chemical Sciences, †200 Cambridgepark Drive, Cambridge, Massachusetts 02140, ‡401 North Middletown Road, Pearl River, New York 10965, and §865 Ridge Road, Monmouth Junction, New Jersey 08543

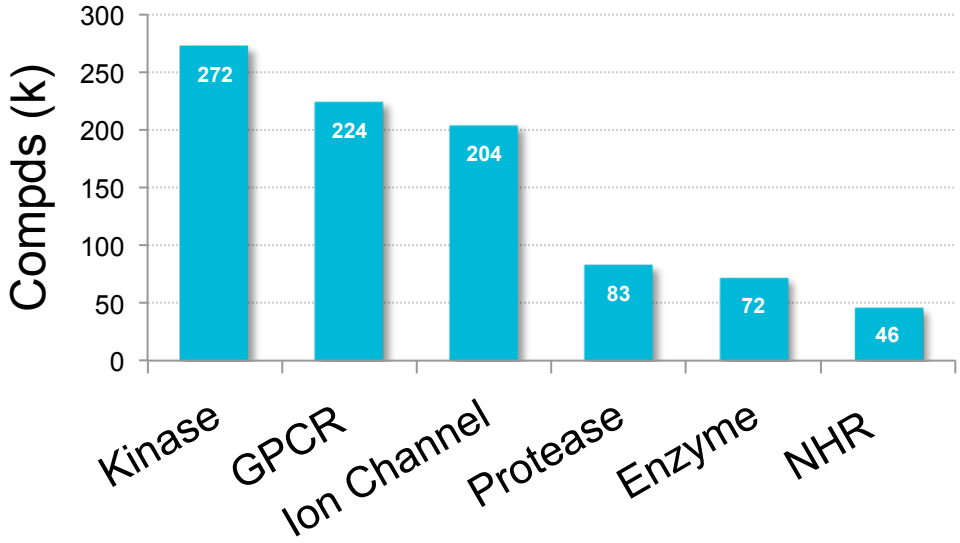
Received August 19, 2009

The medicinal chemistry community has become increasingly aware of the value of tracking calculated

CE library collection composition*



Target Class Subsets

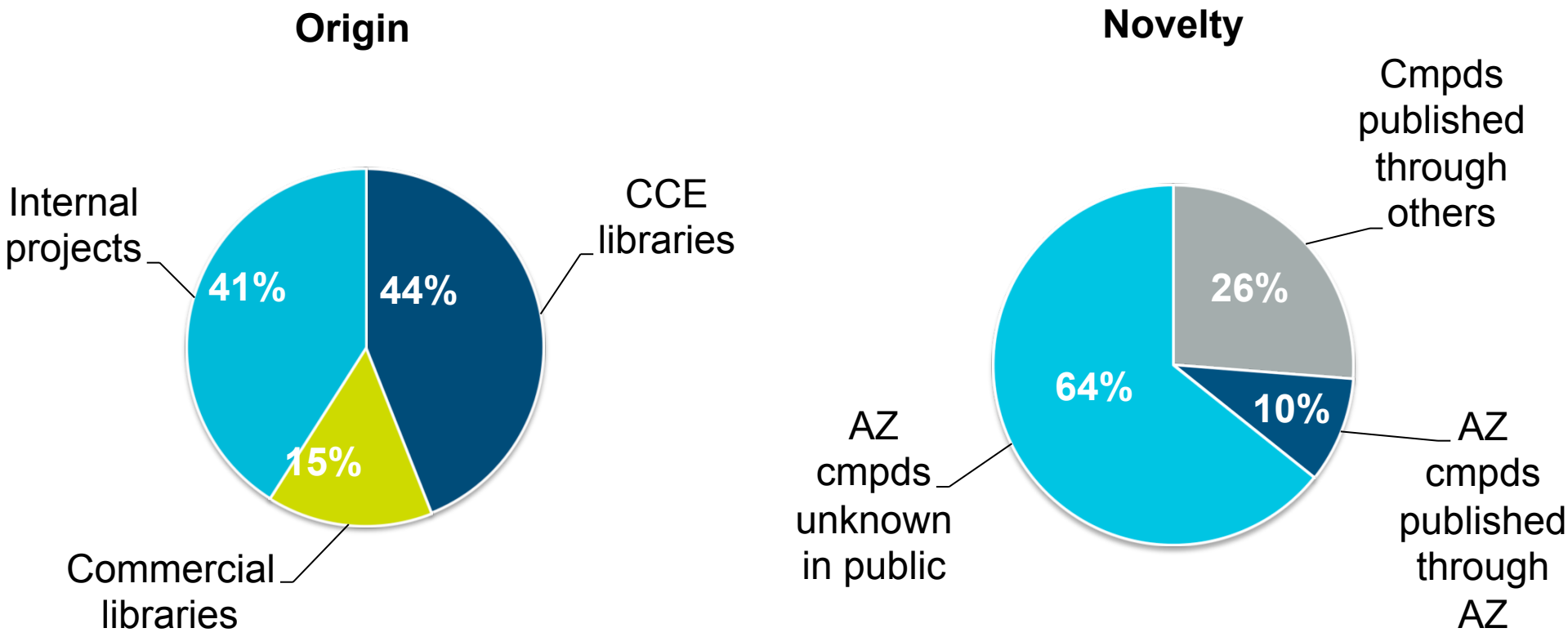


Biologically Relevant Subsets

- Peptidomimetics
- Secondary structure mimetics
- Diketopiperazinones
- Nicotine Adenine Dinucleotide mimetics
- Nucleotide mimetics
- Carbohydrate mimetics
- Macrocycles
- Epigentic ligands

015

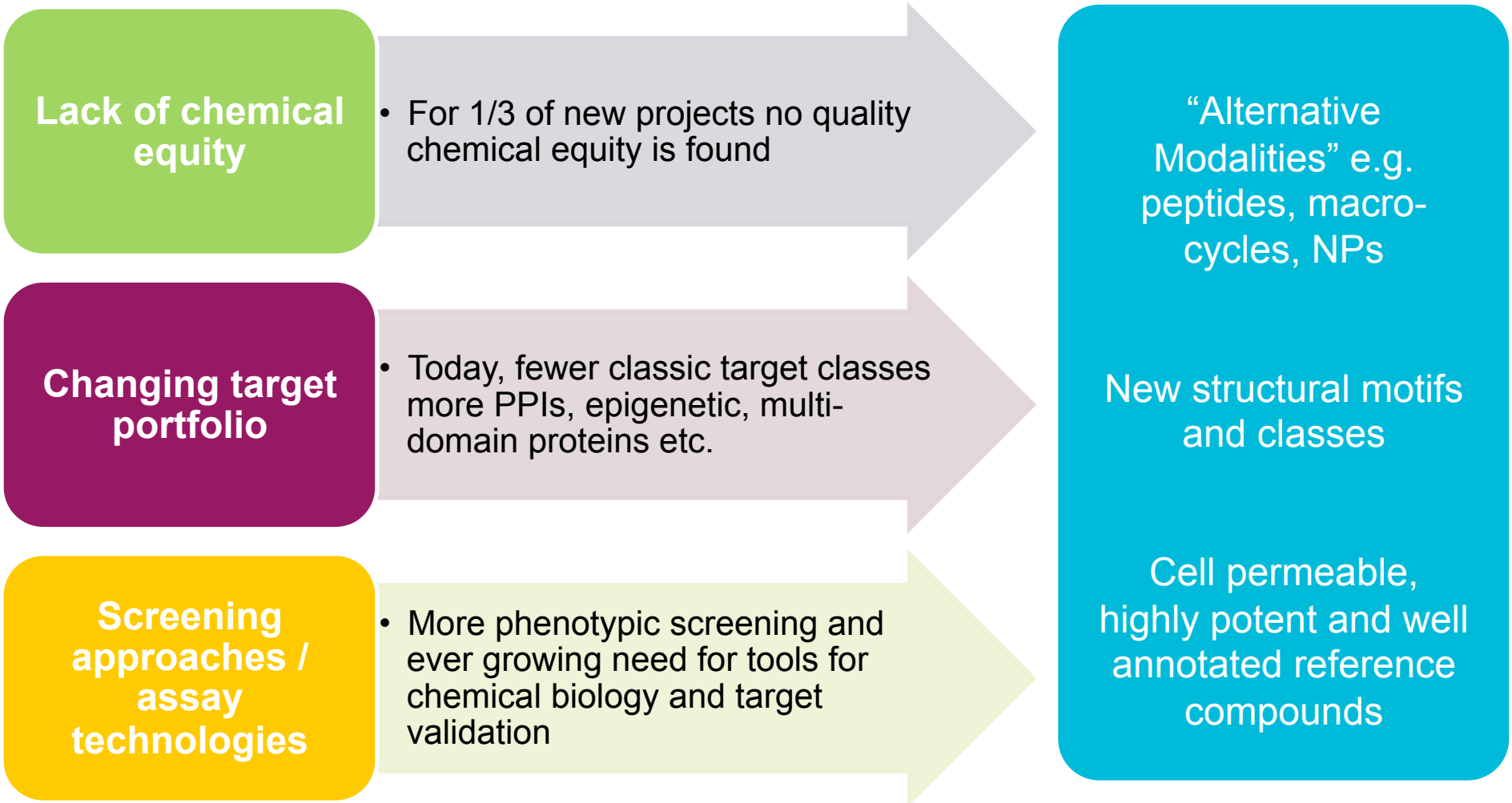
ompound Origin & ‘Novelty’



Focus on internal library design led to significant proportion of AZ compounds not disclosed externally*

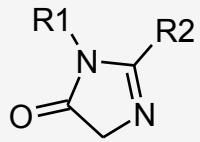
* according internal database of >86M published cmpds, AZ collection 2015

o we still need to enhance our collection?



rtual library

Scaffold/core



Reagents

R1 = primary amine
R2 = carboxylic acid

~4.2K library scaffolds
~20 000 reactions
extracted from ELN

30K pre-filter reagents

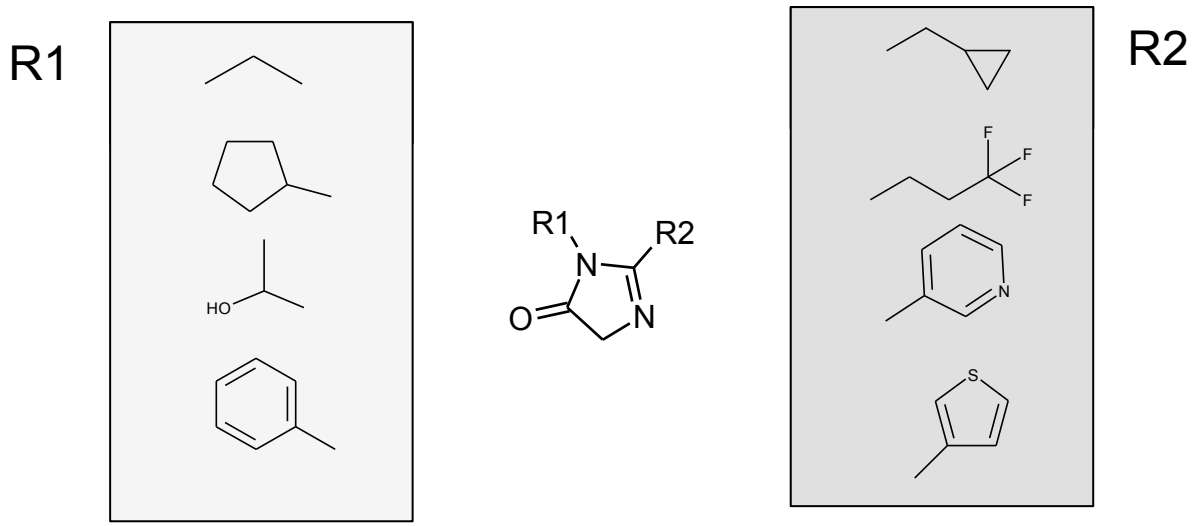
(ACD, Pharmaron, SRI)

”10^{15} Virtual compounds”

Impossible to fully enumerate
- Disk storage
- Search issue

rtual library - Similarity search

sis product approach*: Search in the R1+R2 space instead of R1 x R2

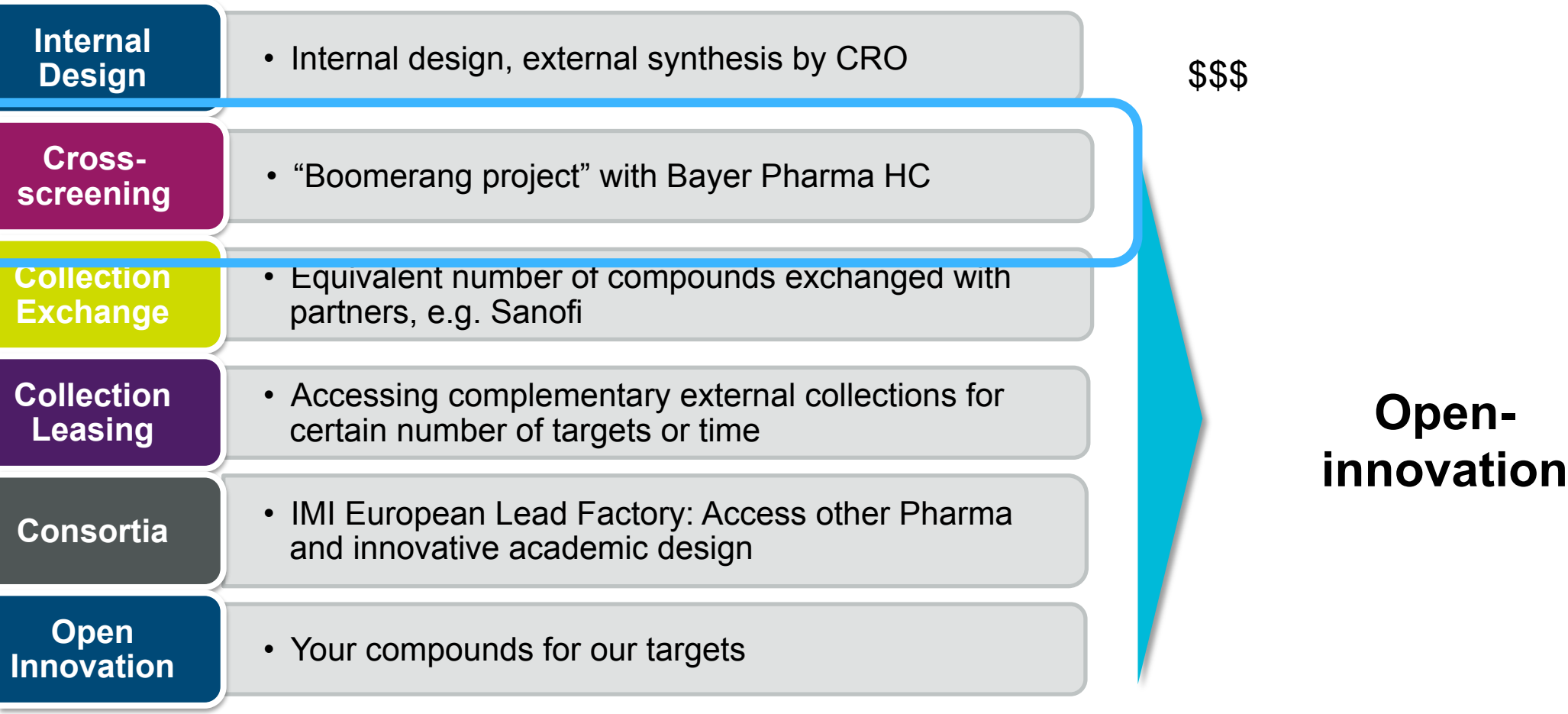


(R1 x R2) compounds
(R1 + R2) compounds

ow to search in 10^{15} virtual cmpds
everal 2D fingerprints to compare similarity between queries and the VL cmpds

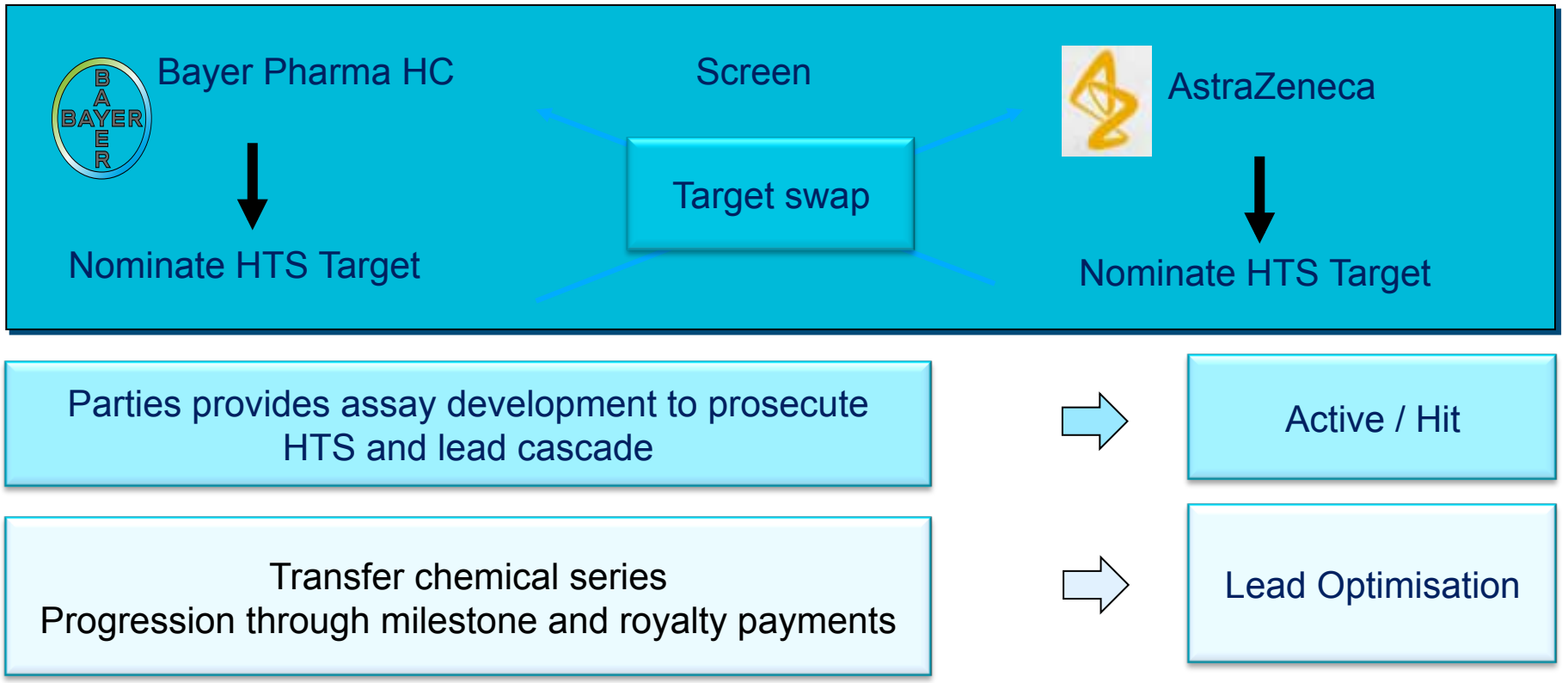
mated recycling of chemistry for virtual Screening and library Design
Vainio, T Kogej, F Raubacher. Journal of chemical information and modeling, 2012, 52, 1777-1786

lany ways to access novel chemistry

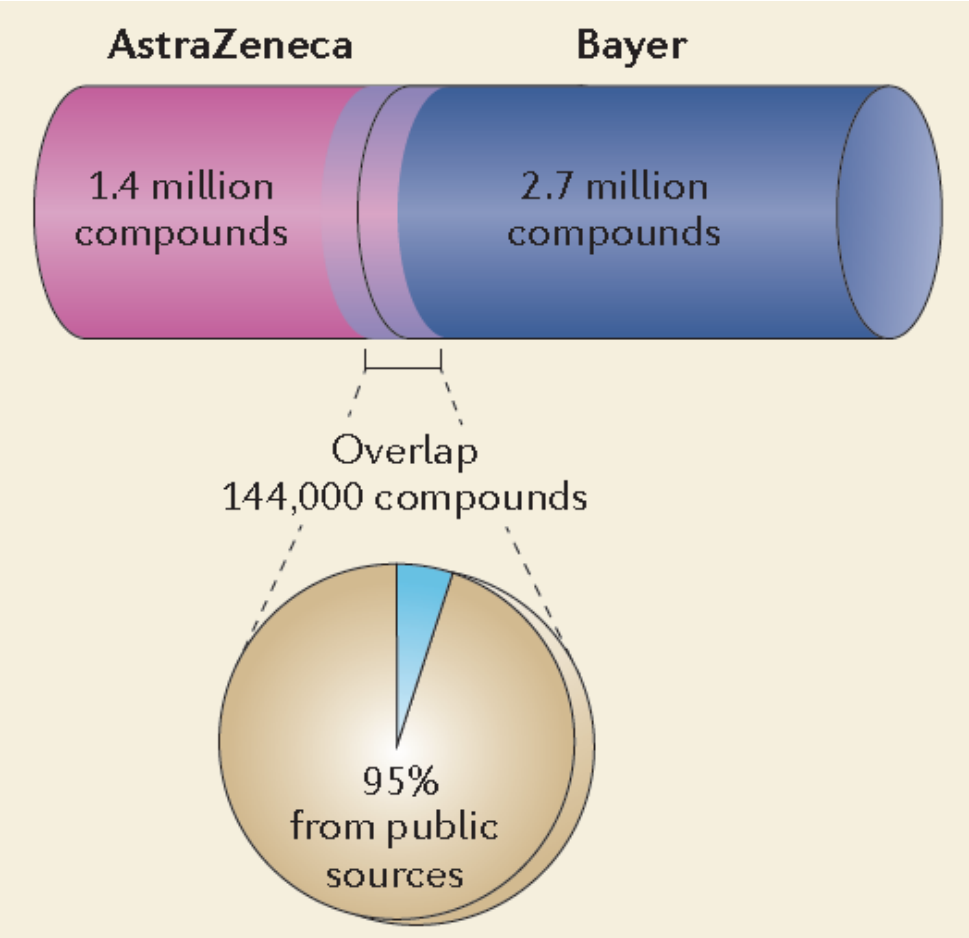


ayer Pharma HC - AstraZeneca ‘Boomerang’ project
a successful example of peer-peer collaboration

Pioneering Joint initiative established between AstraZeneca and Bayer in 2010 (alliance xtended until 2016), based on mutual trust and shared values
Enables both parties to seek chemistry starting points not available in their internal collections



verlap of Bayer Pharma HC and AstraZeneca collection dentical fingerprints



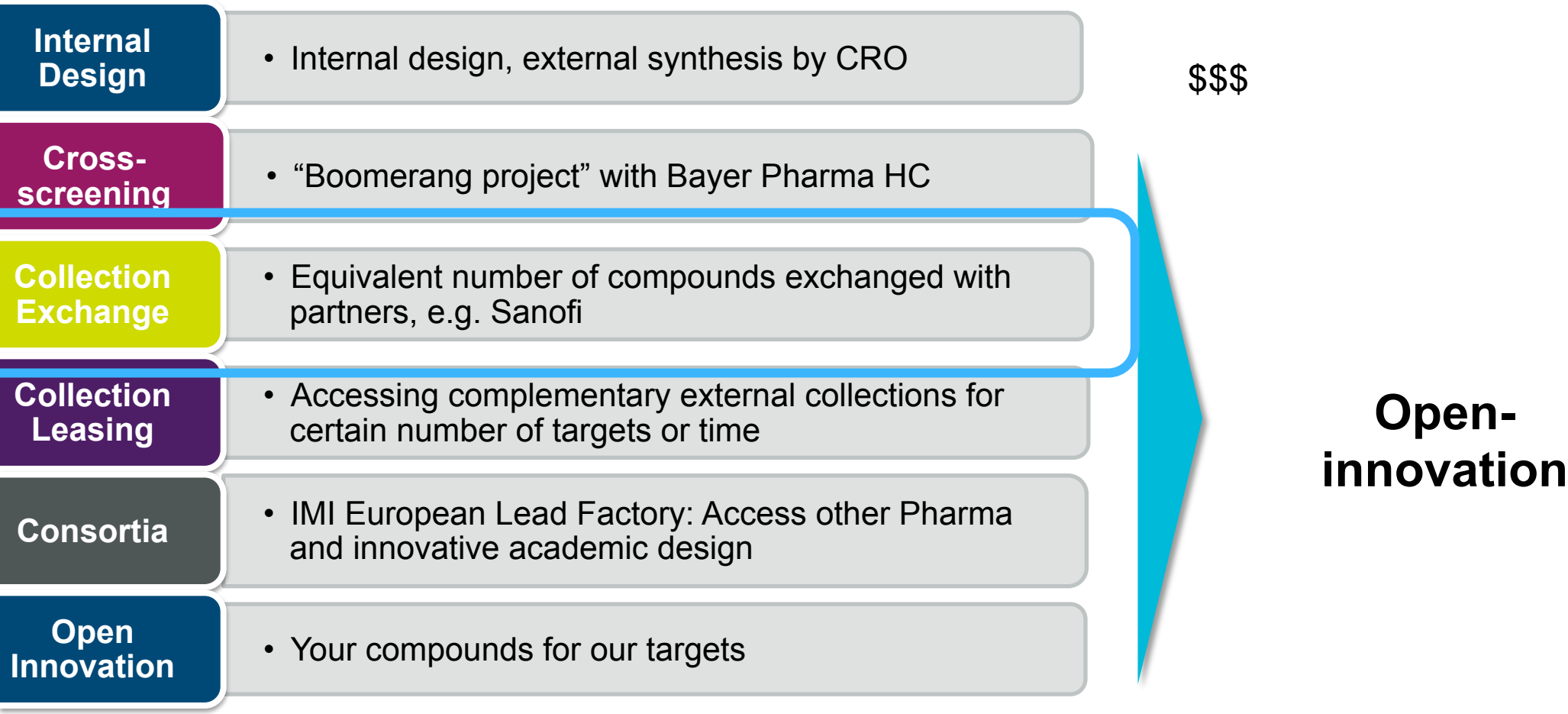
- 3.3% of the total collection (Bayer + AZ is overlapping*)
- 95% of the overlap are public domain compounds

⇒ Screening of > 4.2 Millions unique cmpds

*) As we are not sharing structures for analysis the overlap is based on exact match of molecular fingerprints (ECFP4). This is an overestimate of identity as a small fraction of non-identical compounds will have the same fingerprint

Big pharma screening collections: more of the same or unique libraries? The AstraZeneca-Bayer Pharma AG case
Kogej T, Blomberg N, Greasley PJ, Mundt S, Vainio MJ, Schamberger J, Schmidt G, Huser J. Drug discovery today (2013).

lany ways to access novel chemistry



ollection exchanges

rinciple: *quid pro quo* exchange of compounds
o cash payments
o royalties

Identify set of compounds suitable for sharing

ot AZ patents
ot restriced by other alliances
ot in active projects
gh quality physical sample and
fficient amount (no stock depletion)

Join meeting

2 ICore7, 8 threads, SSD
2 days (including travel)

Physically exchange t samples

2 days
Standalone computer (not network, clusters)
Isolated room
Sharing structures

straZeneca: Sanofi exchange

210k novel screening compounds
200 µL of 10 mM solution (>10y HTS)

Strong relationship foundation for future collaboration

Positive example of cross Pharma collaboration

FINANCIAL TIMES

Sanofi-AstraZeneca chemicals swap takes open route to R&D

The deal — the biggest of its kind among major pharmaceuticals groups — highlights an increased openness to co-operation in an industry criticised in the past for secrecy and beggar-thy-neighbour practices.

The Daily Telegraph

AstraZeneca and Sanofi agree novel drugs-sharing deal

Britain's AstraZeneca and French pharmaceutical company Sanofi have agreed a landmark deal to share data - for free - in the hope that it could lead to breakthrough treatments for disease.

SCRIP Intelligence

Is AstraZeneca/Sanofi Library Exchange Open Innovation's Future?

THE WALL STREET JOURNAL.

Drug Giants Seek Edge By Sharing Secrets

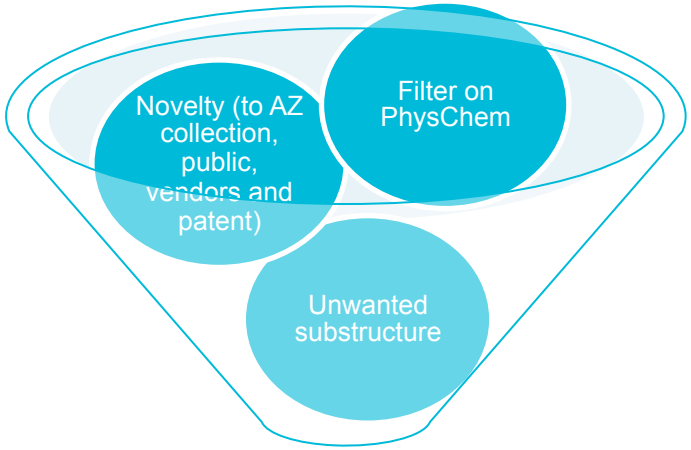
AstraZeneca PLC and Sanofi SA have agreed to share thousands of their proprietary chemical compounds with each other, an unusual deal that shows the creative lengths to which pharmaceutical companies will go to pursue new drugs.

REUTERS

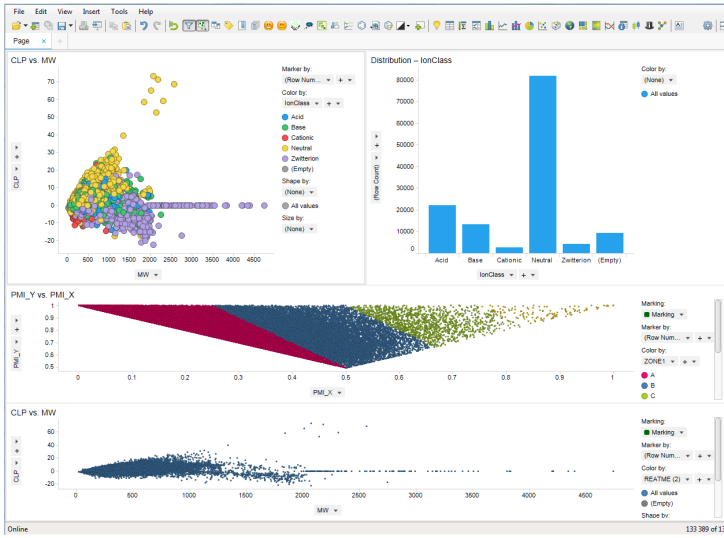
Sanofi, AstraZeneca swap compounds in new twist on open drug R&D

lection process

”Filtering OUT”



Result visualization



ue annotation”

- Fingerprint

imilarity to iterature, atent active cmpds

iversity to Z collection

Intrinsic molecular properties

Desirable Physchem (lead-likeness,…)

“3D” (FSp3, PMI)

Modelling

Model likeness (Bayesian) - Natural-Product

2D substructures

Macrocycles

Kinase cores

Specific scaffolds

3D Virtual Screening

β-turn

α-Helix

PPI

Clustering, grou

visual inspecti

Final selectio

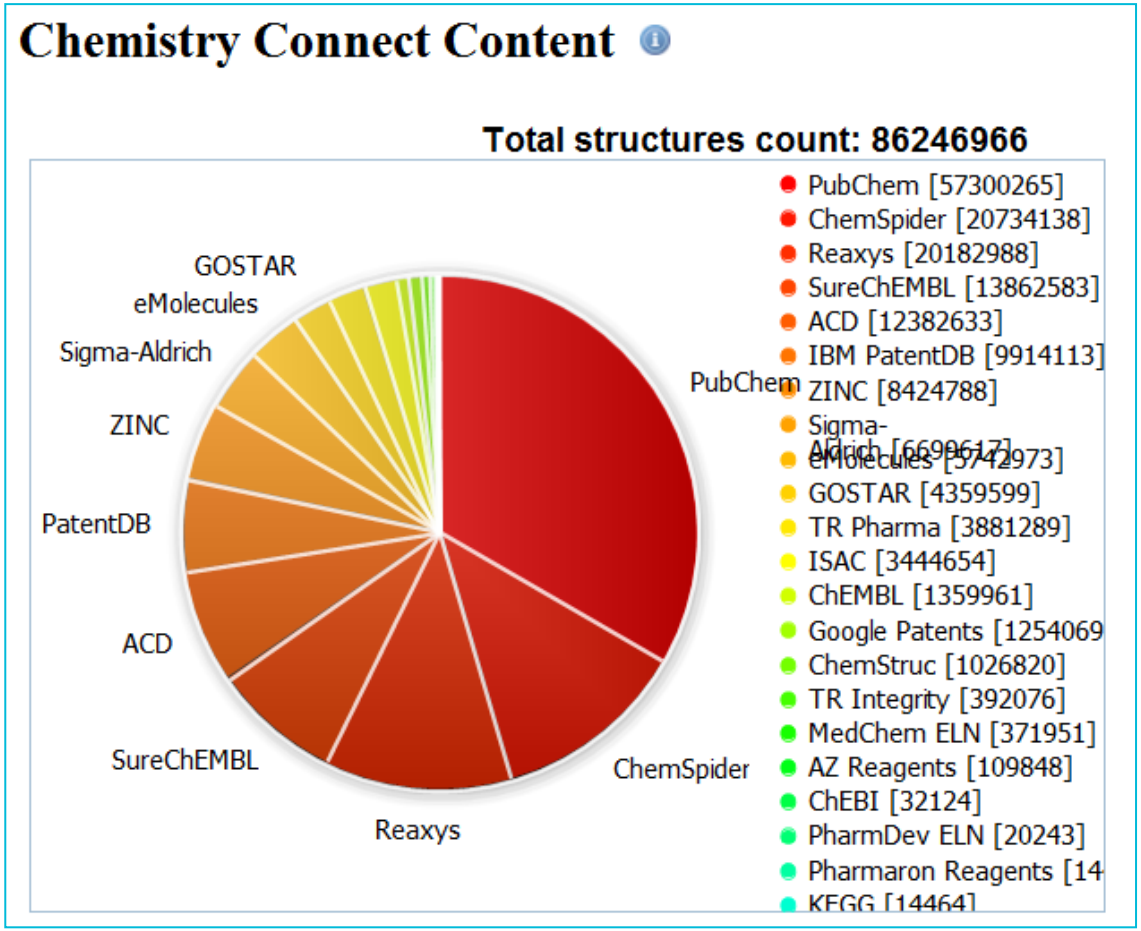
heminformatics assessment of external collections

ovelty

gh interest in Sanofi
opriatory compounds

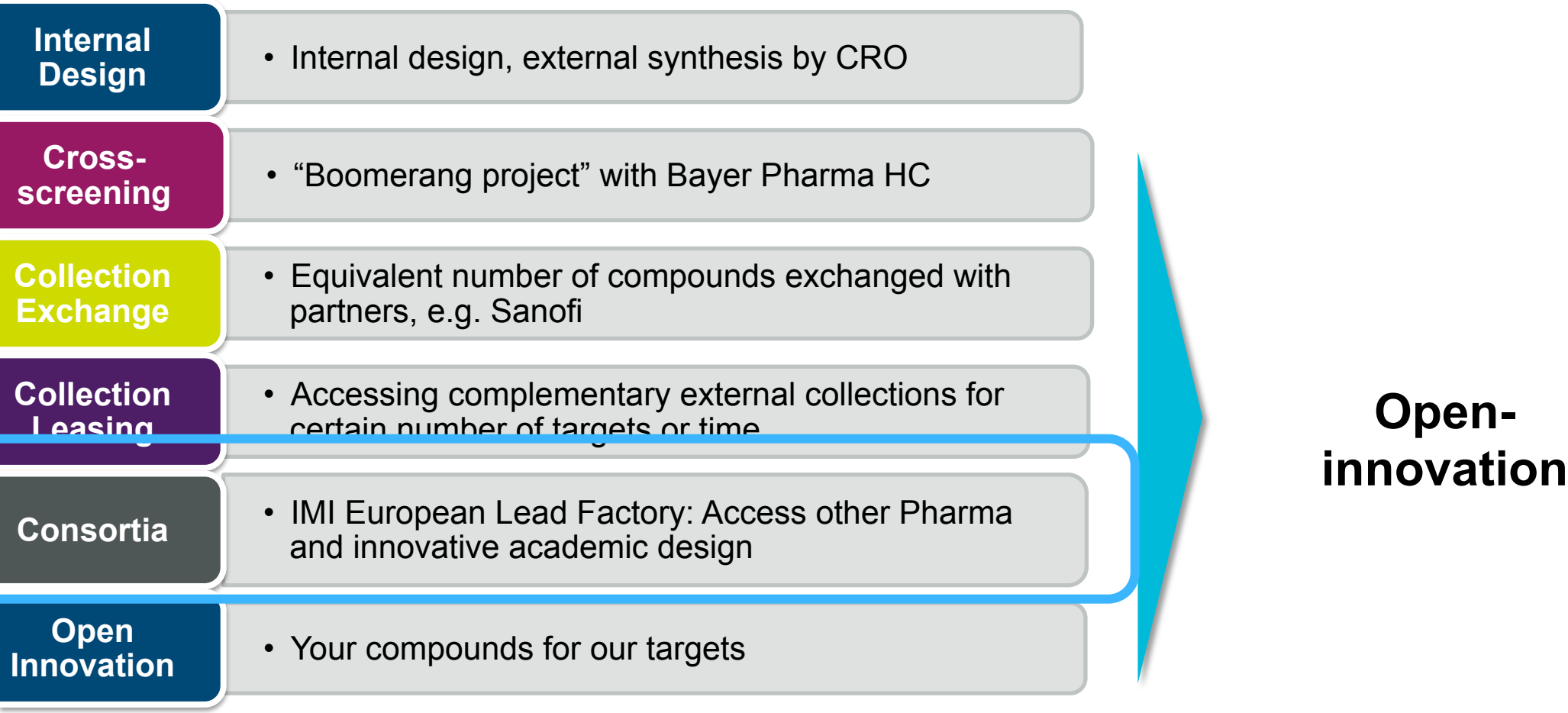
w in interested in
blically available compounds

gh interest in ”tool compounds”



Making every SAR point count: the development of Chemistry Connect for the large-scale integration of structure and bioactivity data.
Muresan S, Petrov P, Southan C, Kjellberg MJ, Kogej T, Tyrchan C, Várkonyi P, Xie PH. Drug Discov Today. 2011, 16, 1019-30

lany ways to access novel chemistry



uropean Lead Factory

ncept: Collaborative public-private partnership aiming to deliver innovative drug discovery starting points

- 30 international partners and 150 employees
- Academia, small-medium-large companies
- Access to up to 500,000 novel compounds

cess

Proposer:
Target-assay

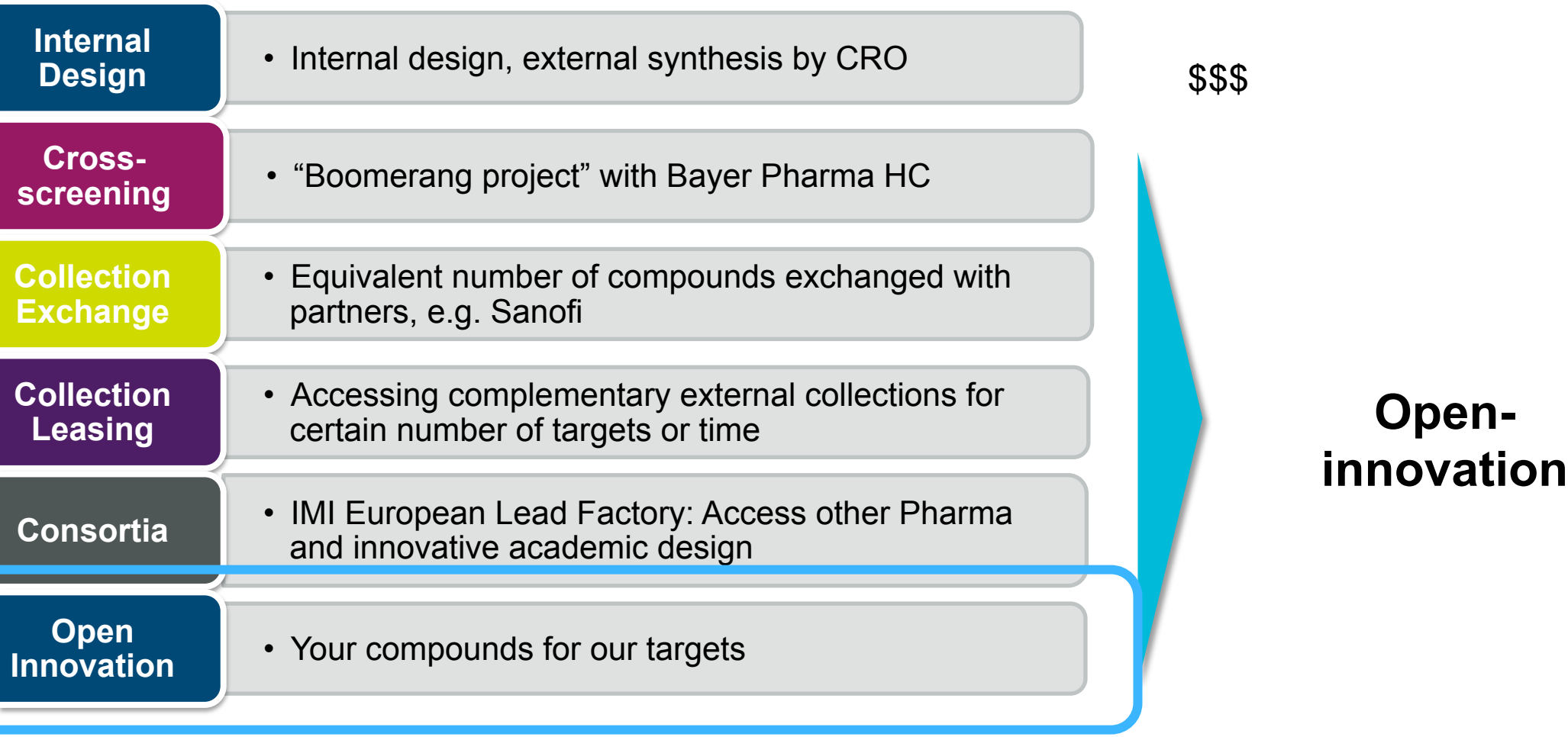
→ Committee agreement

→ HTS screening

→ Hit validation
Activity, chemistry
purity

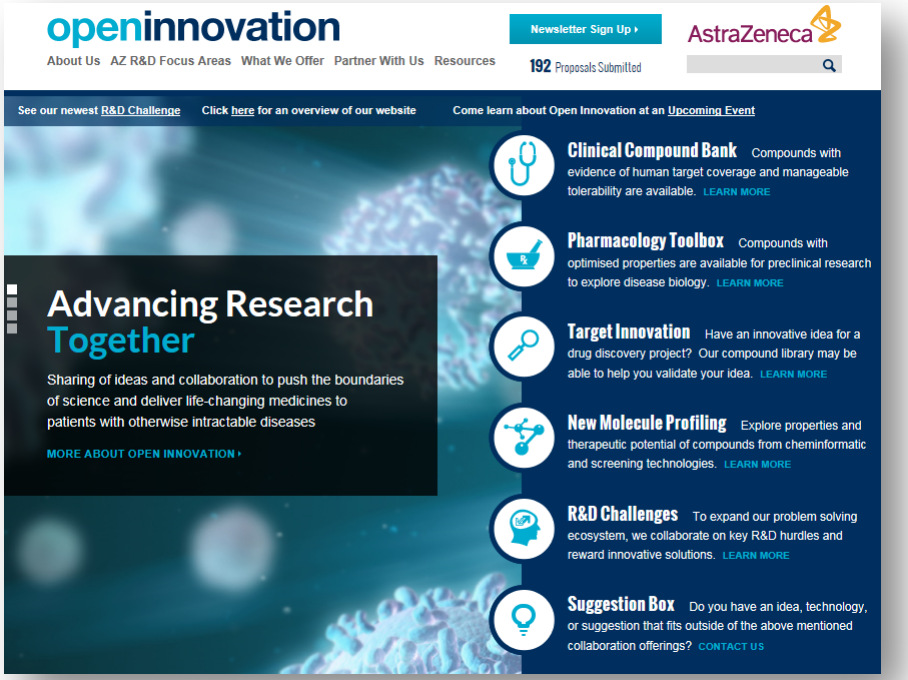
→ Up to 50 hits
Returned to
The proposer

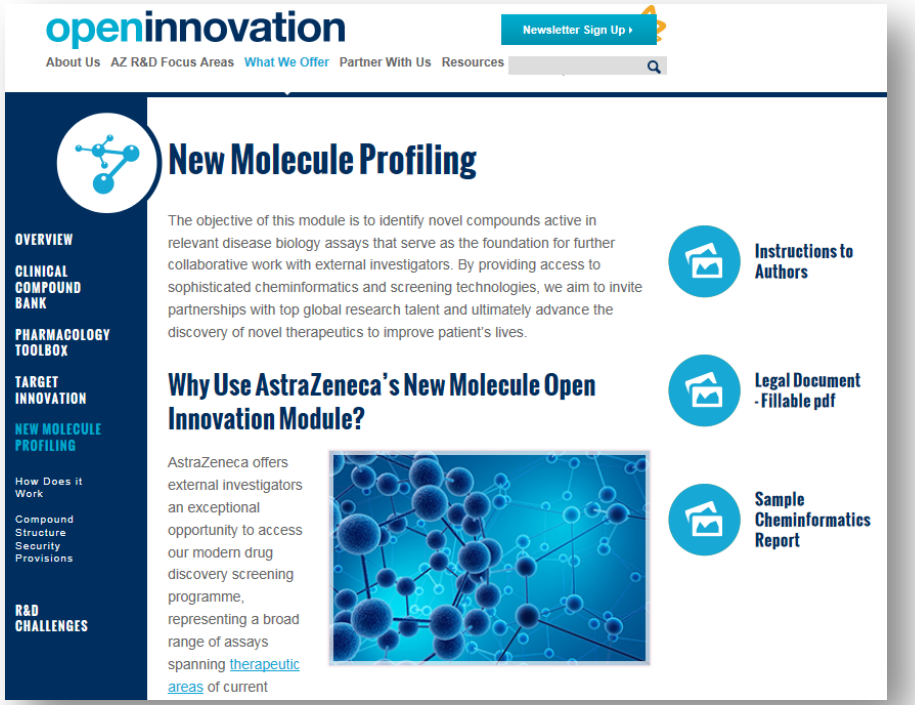
lany ways to access novel chemistry



Z Open Innovation: New Molecule Profiling

Your molecules are welcome!



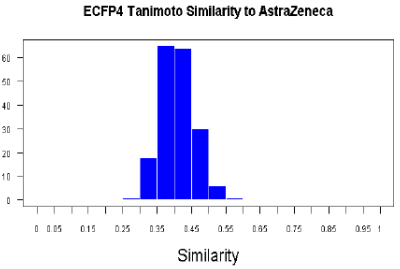


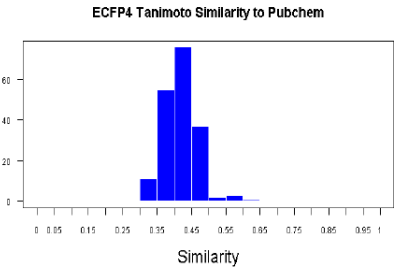
More under

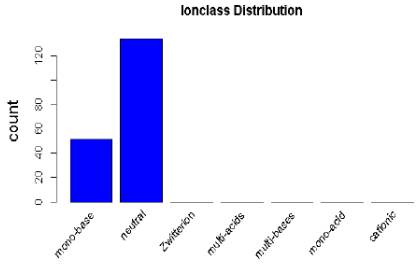
http://openinnovation.astrazeneca.com

heminformatic report

Similarity

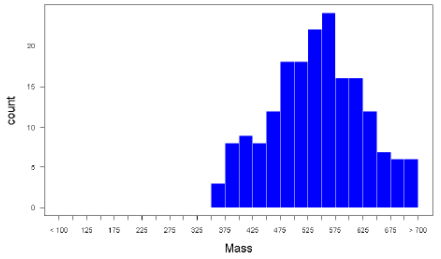


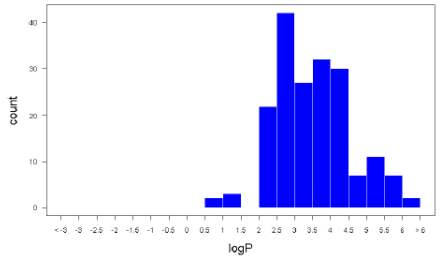


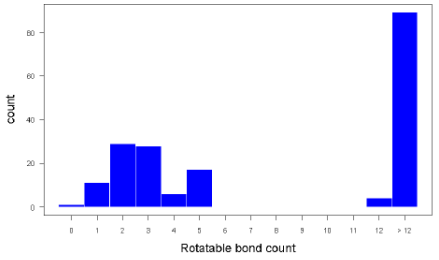


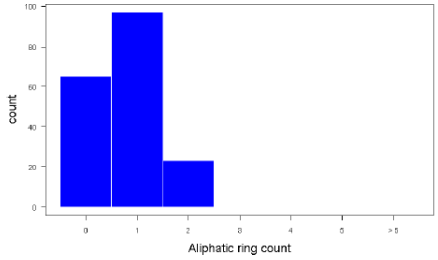
Main considerations for recommendation:
- Novelty
- Molecular complexity
- "Drug discovery friendly"

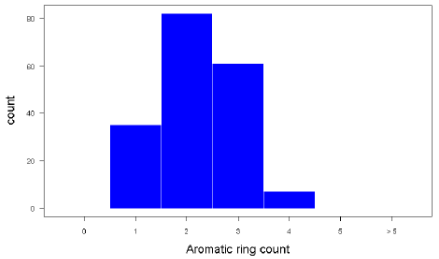
Physchem properties

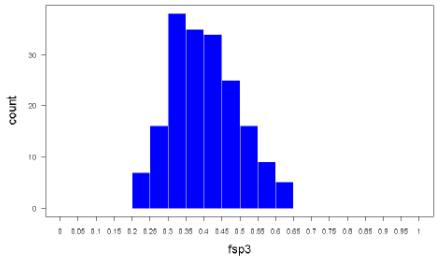


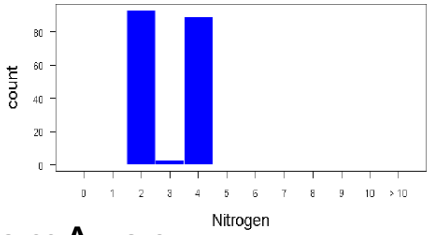


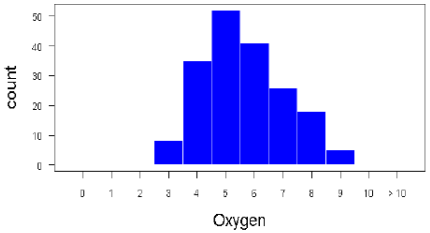












Structure filters

GenoTox	Count	Percentage
No	185	100.00%
Yes	0	0.00%

Reactive metabolite	Count	Percentage
No	185	100.00%
Yes	0	0.00%

Risk level	Count	Percentage
No Risk	74	40.00%
Risk	111	60.00%
All Known explosives	0	0.00%

Controlled	Count	Percentage
No	185	100.00%
Yes	0	0.00%

When	Metals and metalloids
After standardization	[ ]
Before standardization	[ ]

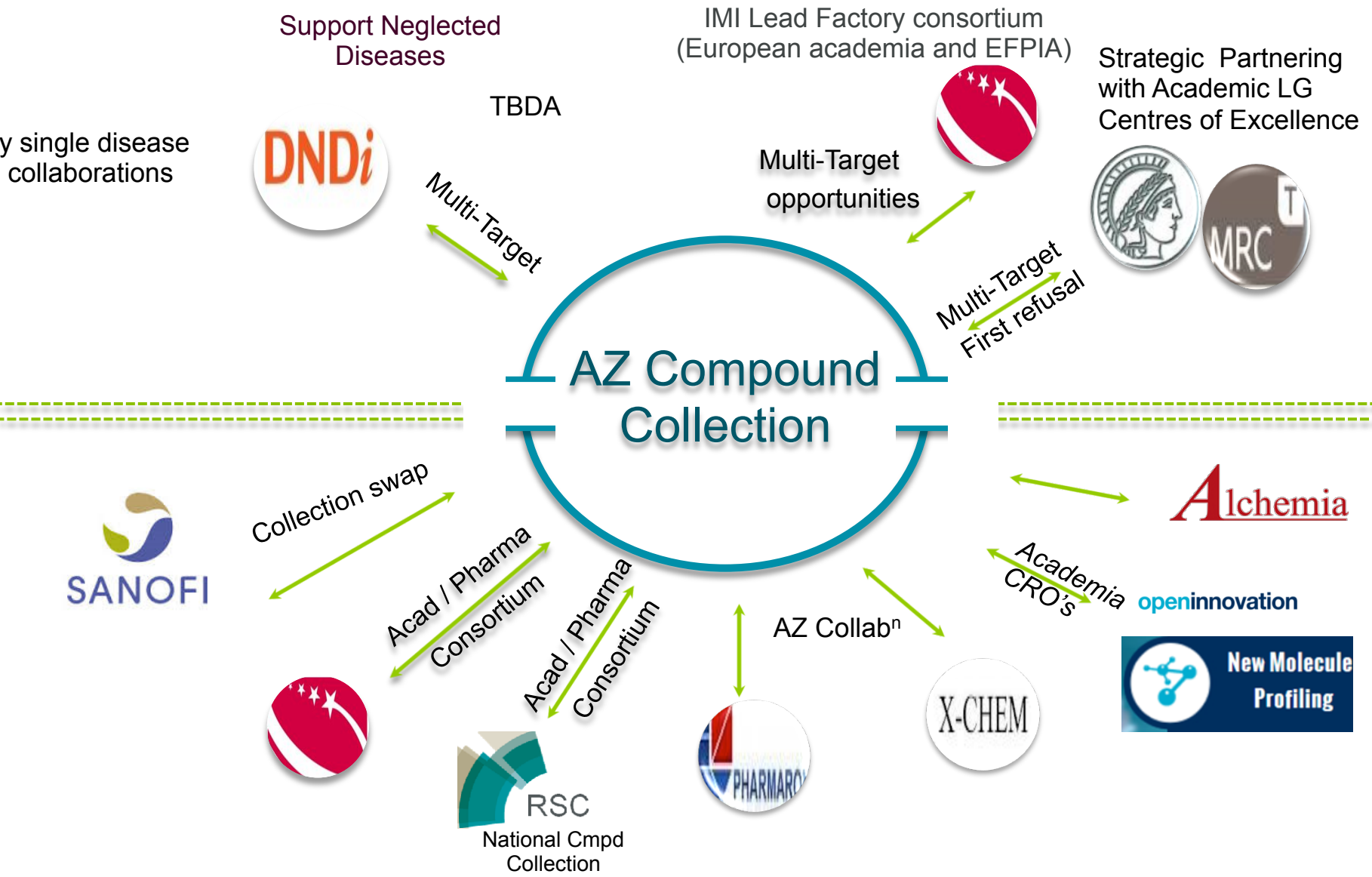
With the collaboration of ChemAxon

lany ways to access novel chemistry

Internal Design	• Internal design, external synthesis by CRO
Cross-screening	• “Boomerang project” with Bayer Pharma HC
Collection Exchange	• Equivalent number of compounds exchanged with partners, e.g. Sanofi
Collection Leasing	• Accessing complementary external collections for certain number of targets or time
Consortia	• IMI European Lead Factory: Access other Pharma and innovative academic design
Open Innovation	• Your compounds for our targets ↕ • Our compounds for your targets

Open-innovation

ternal Discovery Platform



Increase value of screening collections

Innovative chemistry: Increase diversity & quality of leads

ummary

- Continuous need to evolve internal compound collection and enabling **access to external compounds**
- Effort to capitalize on the validated library chemistry via “virtual library”
- Open Innovation platform great opportunity for academia and research institutes **to get their compounds screened by AZ** or to access our collection for their screens
- Increase value of screening collection by exposing it to externally identified innovative targets

With special thanks to…

HTS:

Mark Wigglesworth

Martina Fitzek

Marian Preston

Carolyn Blackett

Dave Murray

Kirsty Rich

Matt Collier

OI:

Craig Wegner

Pam Hill

Hitesh Sanganee

Discovery Sciences:

Mike Snowden

Steve Rees

Dave Smith

Michael Kossenjans

Selmi Nidhal

David Andrews

Clive Green

Kevin Cross

Ian Sinclair

John Cuff

Phil Spencer

Abdul Ingar

Rick Davies

,

Computational Chemistry:

Ola Engkvist

Hongming Chen

Isabella Feieberg

BD:

Iain Comely

Terry Reed

Duncan Young

Vicki Foster

IMED

Fred Goldberg,

Lena Ripa