BCI Pharma

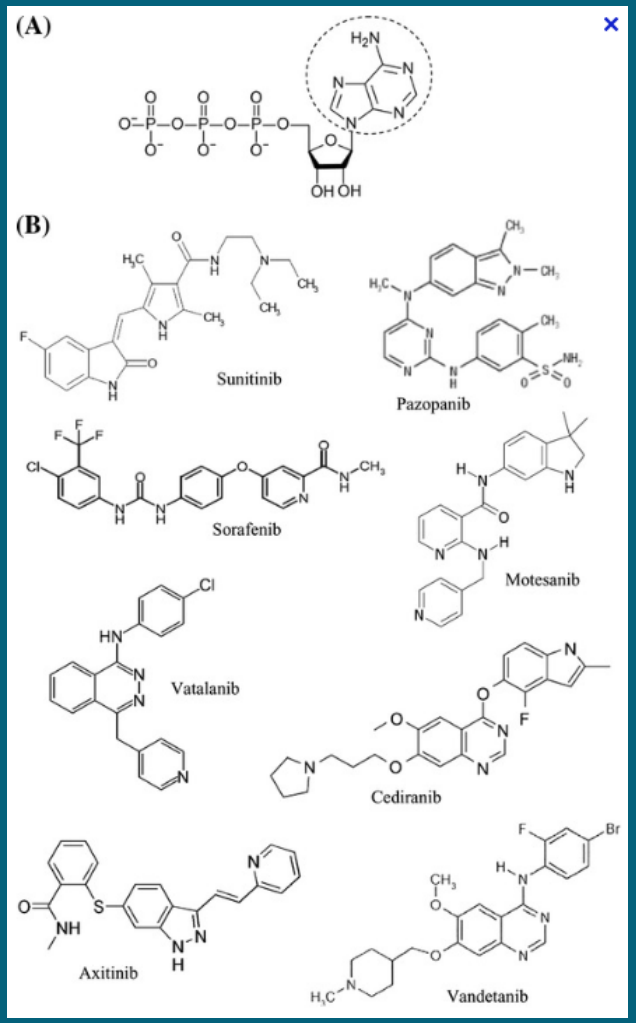
Update kinase project

Internal Library business

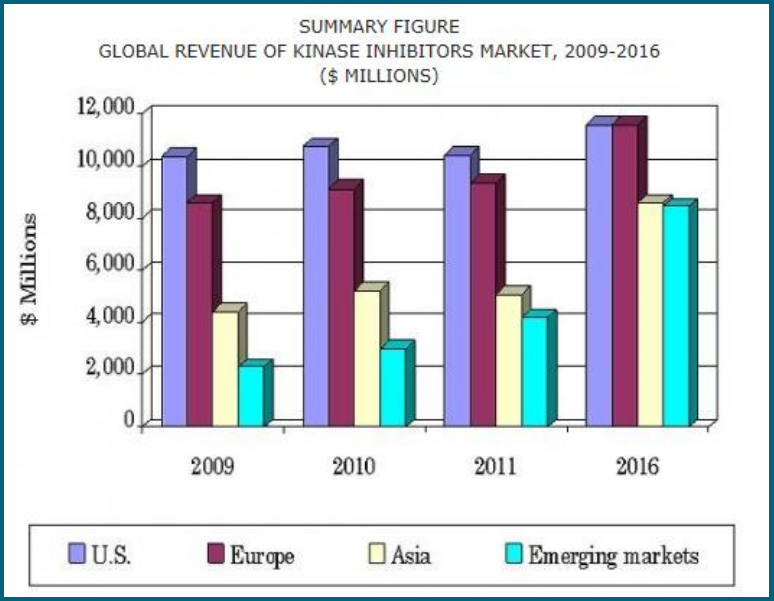
- Our primary focus:
  - Innovative Kinase Inhibitors Library
- 20 FDA approved Kinase Inhibitors
- 500 kinases; 20 have been explored
- Major issue:
  - Lack of chemical diversity

→ Urgent need for new scaffold

Major issue = lack of chemical diversity; IP crowded



Kinase Inhibitor, a Gold mine



Kinase inhibitor market is giant and will continue to grown

- http://www.bccresearch.com/market-research/biotechnology/kinase-inhibitors-global-markets-bio053c.html

Past and Future of Kinases Inhibitors

Past = Cancer

Future =

Immune-mediated disease:
Rheumatoid arthritis, psoriasis,
inflammatory bowel disease and MS
SYK (Spleen Tyrosine Kinase), JAK, IKK2
BTK (Bruton Tyrosine Kinase), PI3K, Src, ABL

Anti-infectives disease:
Anti bacterial
Biotin carbo, Hist kin, Pyr
Anti viral

CNS:
Alzheimer, stroke, Parkinson
Gsk3,DAPK1, ROCK1 and MLCK, LRRK2

Ophtamology
VEGF

Metabolic disease
Type 1 diabetes
PGGFR, Rho-kinase, MAPK, PAS

Pain:
Trk, P38, IkB

Cardiovascular
SPAK

Kinase Inh and CNS disease

Depression:
PKC, GSK-3beta
MARK, MKP-1

Parkinson:
LRRK2, PINK1
GRK6, PKC delta

Sleep disorder:
Casein kinase (CK1 delta/Epsilon
GSK-3

Anxiety:
ERK, MAPK,

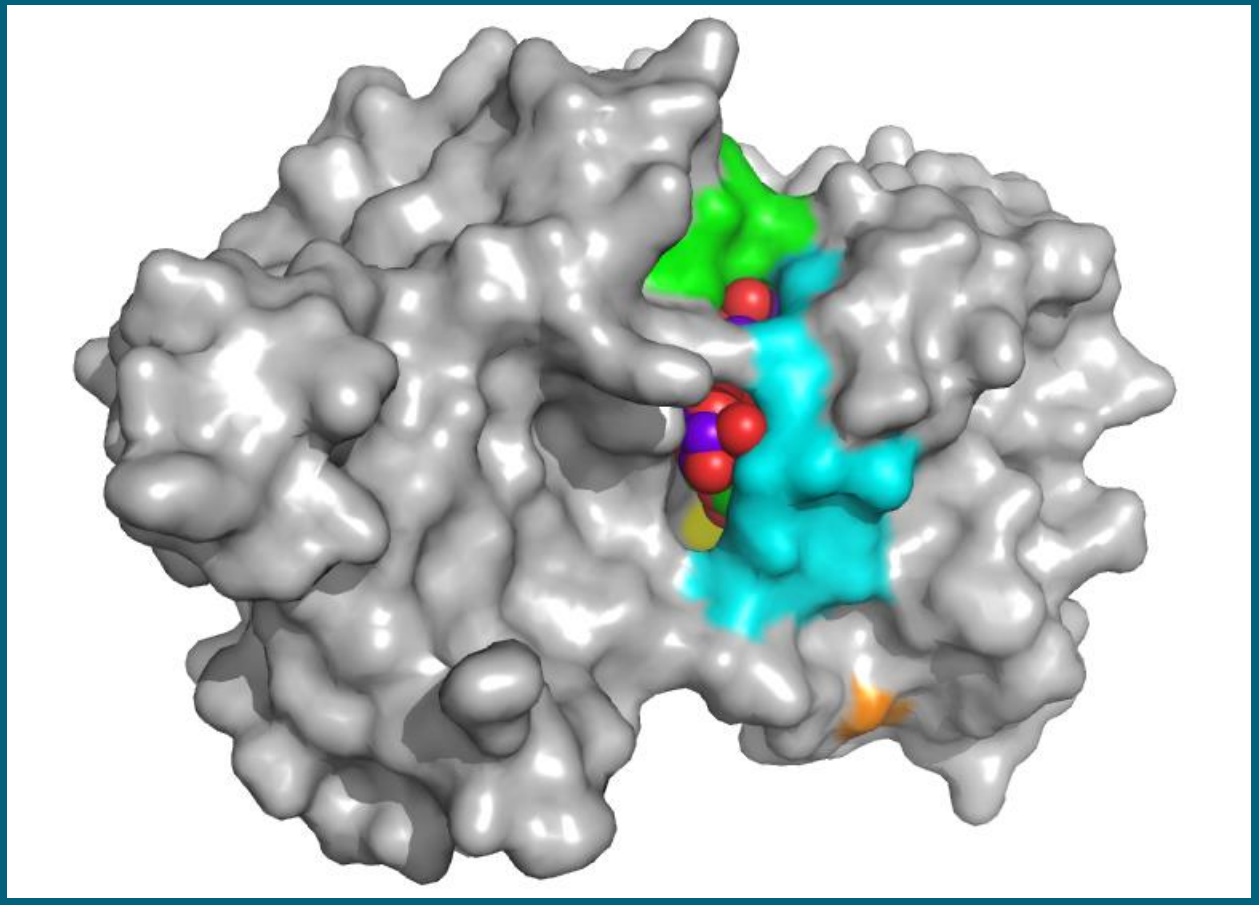
Alzheimer :
eIF2A(GCN2), Src, AMPK(+), Fyn, PKR,
GSK-3b

Huntington:
MAPK(PKP-1/DUSP1)
IKKbeta, DGK; AMPK

We offer

- 3 innovative kinase inhibitor libraries (BiKin1-3)
  - Type I,II,III kinase inhibitor
- 500 compounds each
- 20mg of powder
- BiKin 1-2 are ready to be shipped
- Bikin 3 completed Q1 2015

Molecular modeling results



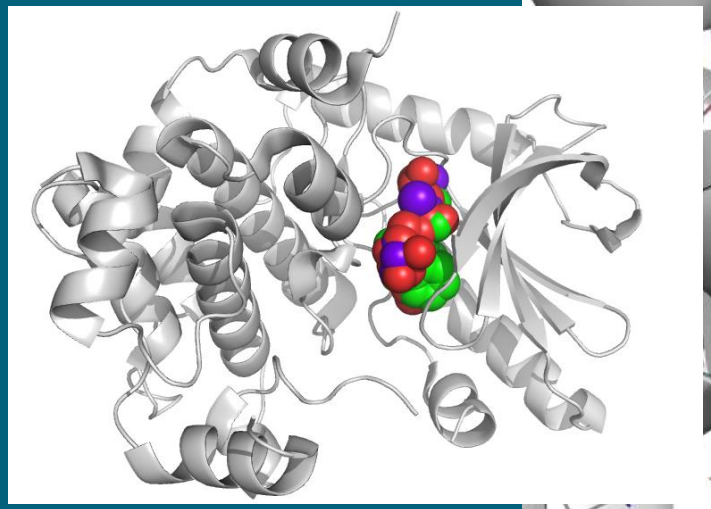
Protein:
Green - Hinge
Cyan - G-rich loop
Yellow – DFG motif
Orange – Phosphorylation

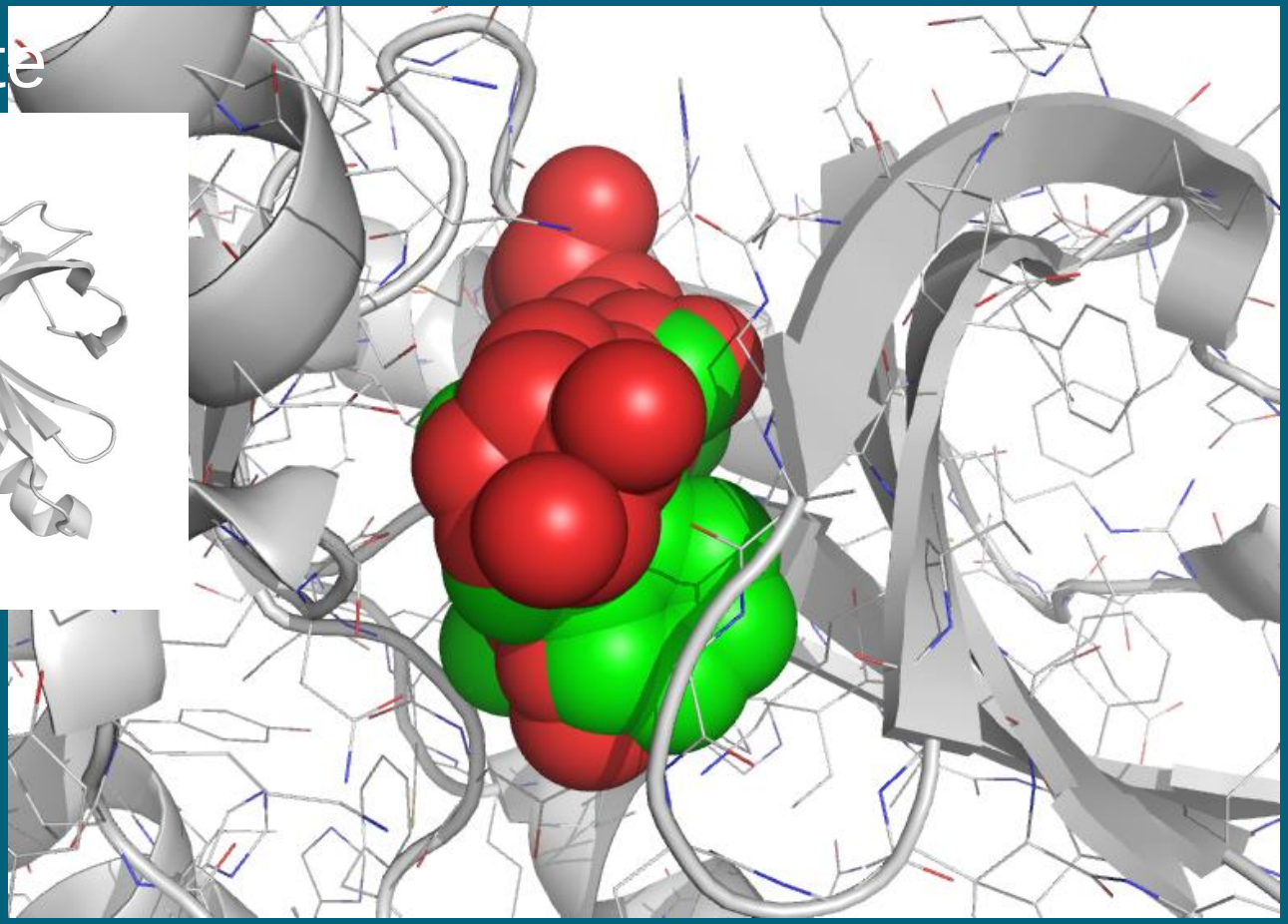
Ligands VDW:
Purple - X-ray
Green – BCI
Red – BCI

Molecular modeling results

BCI molecules

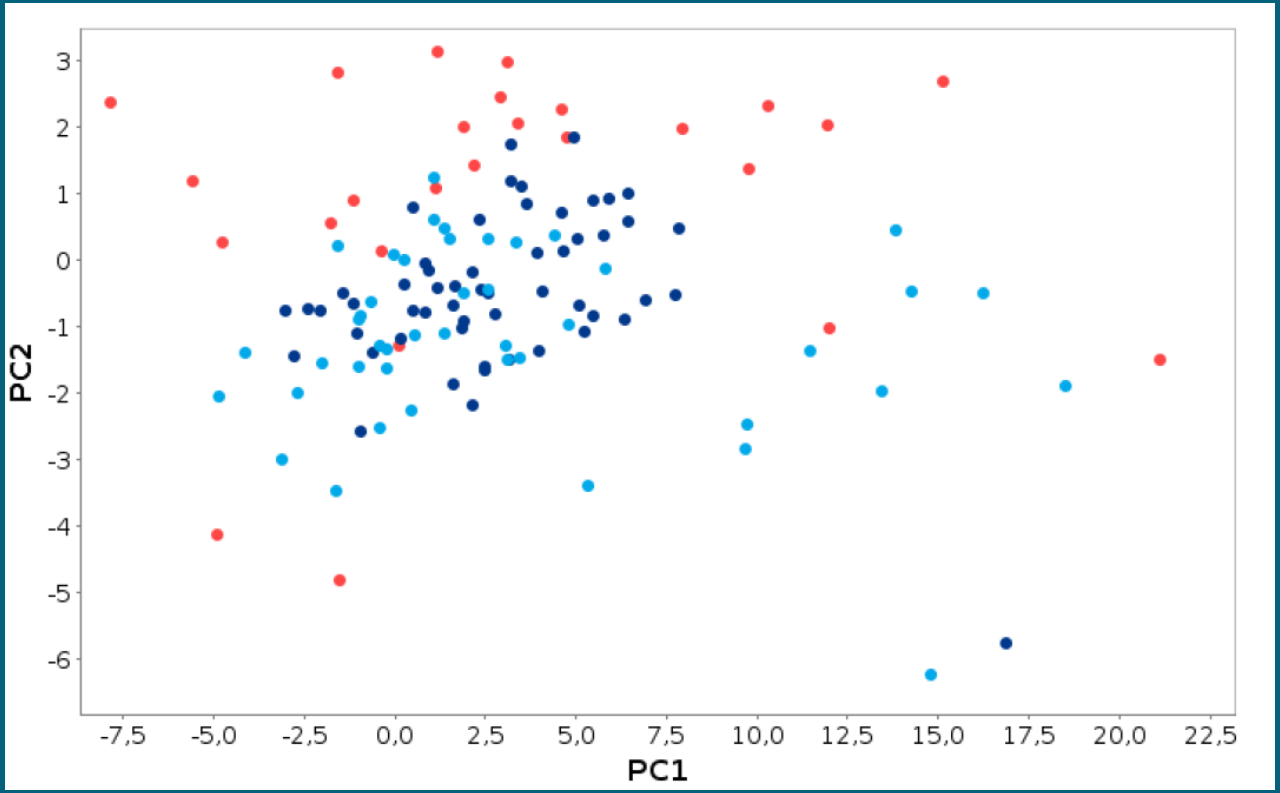
Active site





Ligands VDW:
Purple - X-ray
Green – BCI
Red – BCI

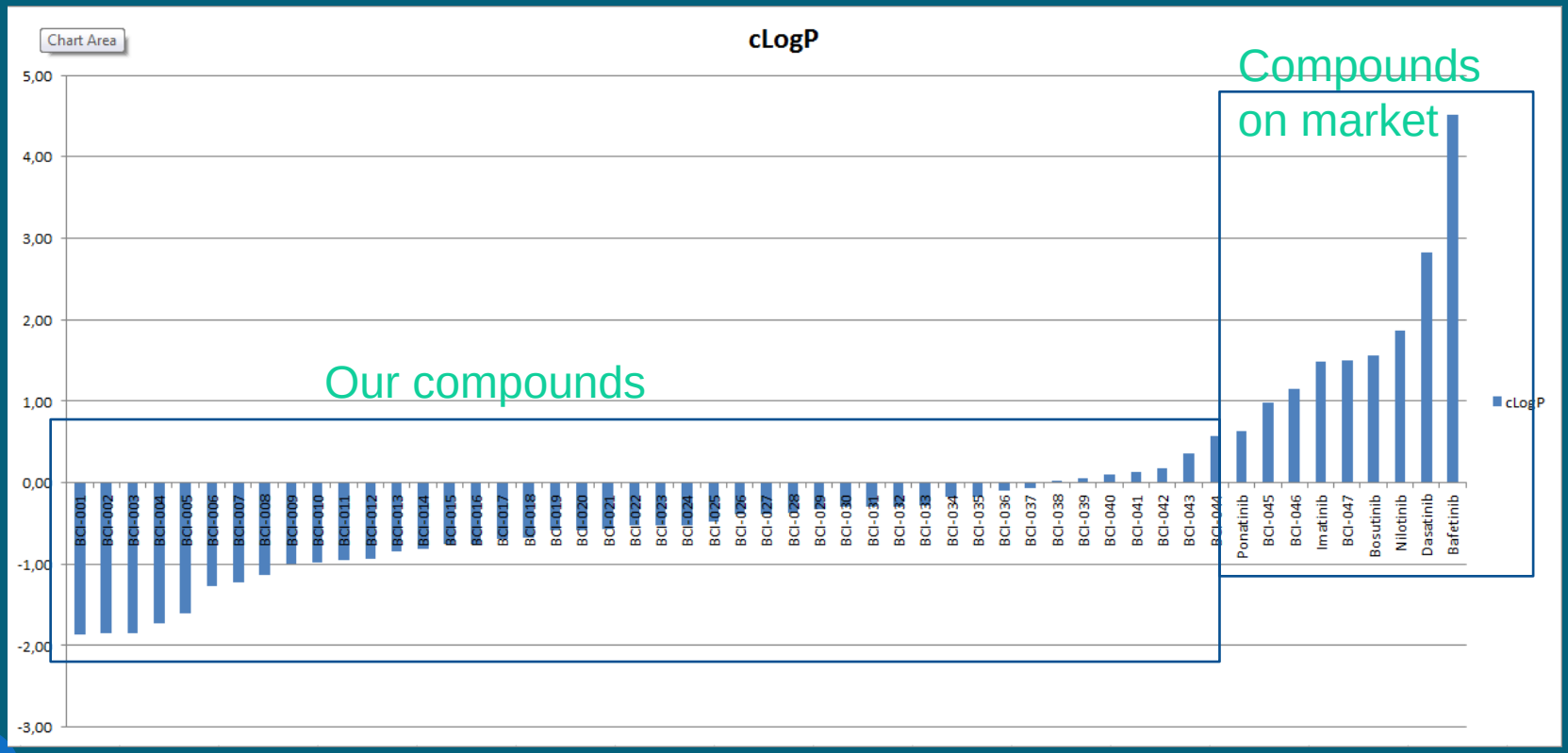
BCI Pharma solves low chem diversity of kinase inhibitors



Blue (light and dark) = chemical space of BCI Pharma kinase inhibitor
Red = chemical space of approved (FDA) kinase inhibitors.

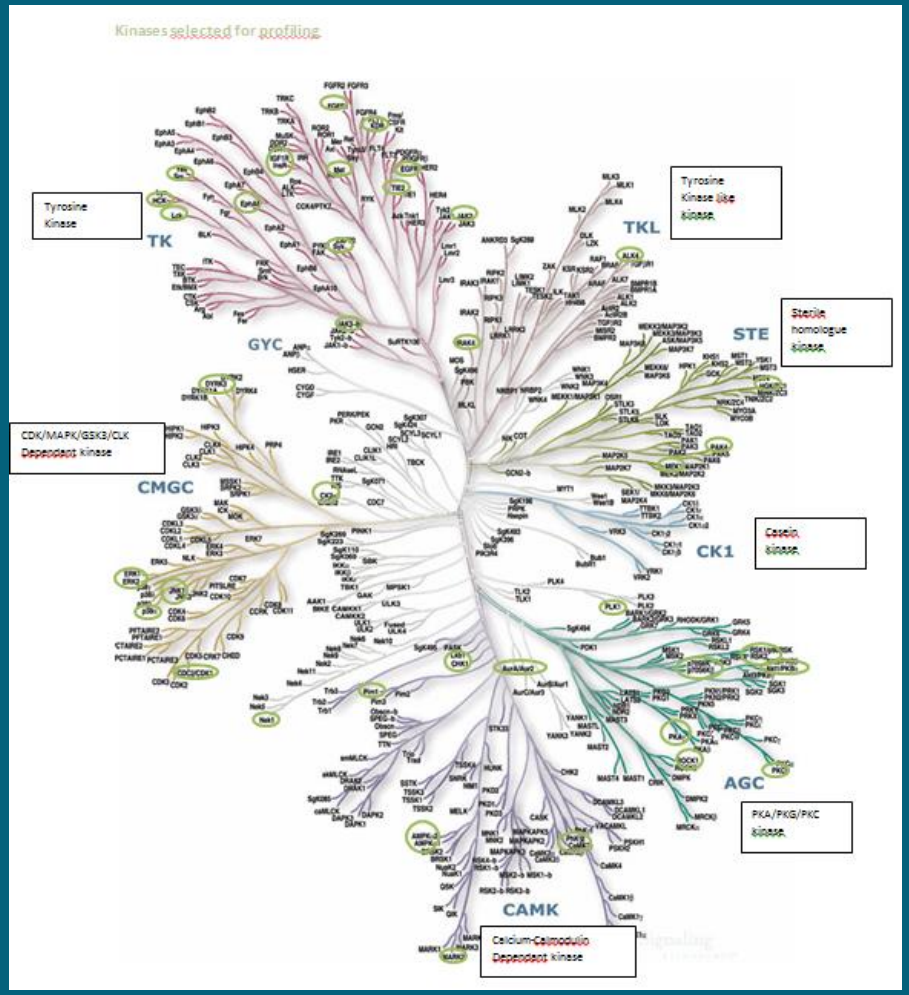
Promissing chemPhys properties cLogP of the kinase library

- The following scheme (cLogP (Y axis) versus compounds (X axis)) shows that our kinase library inhibitors is less lipophilic than commercial ones.



Biological results

kinases used (green circle) for profiling of cpds (% inh at 10uM)

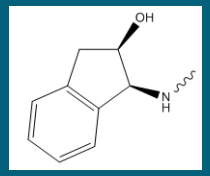


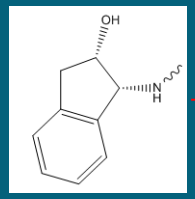
Goal= validate activity of kinase inhibitor

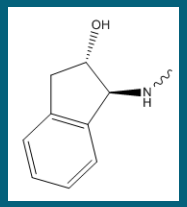
Screening against X kinases

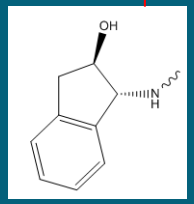
In vitro results of Bikin 1

Isomers (4) of BCI-004; % Inh at 10uM



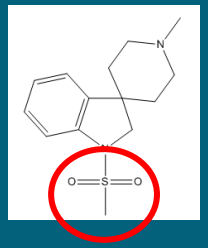






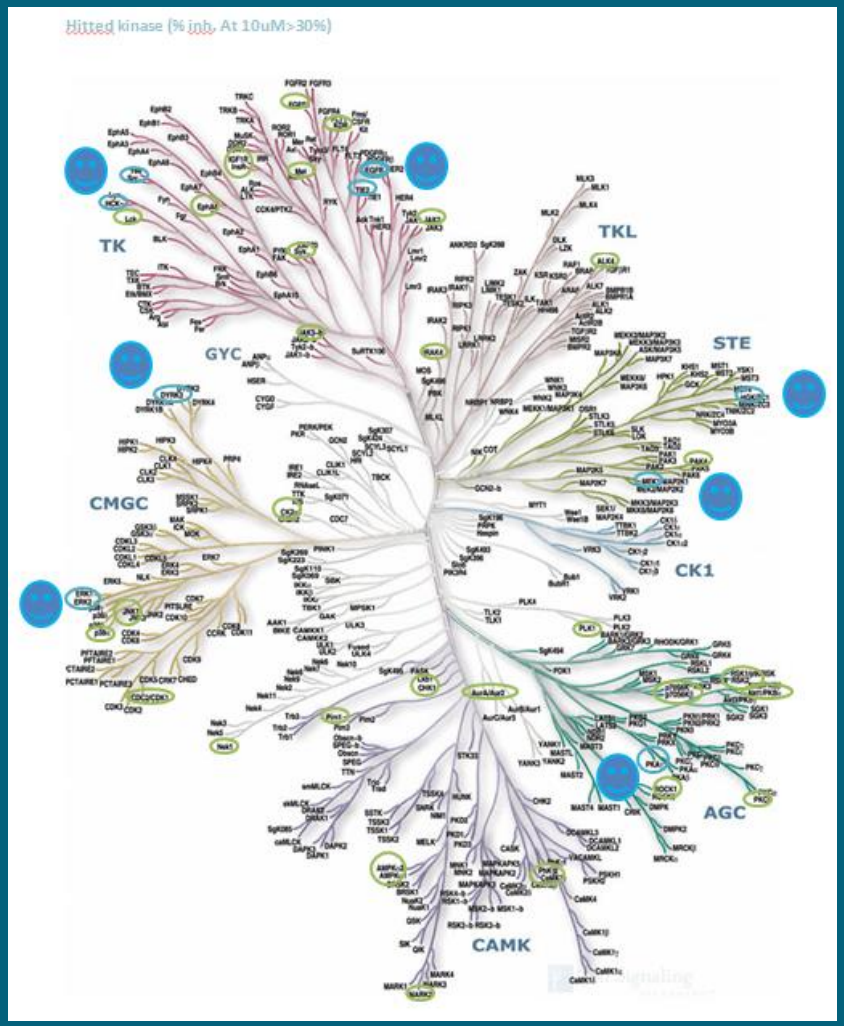
Compounds	MAP2K1 (MEK1)	MAPK1 (ERK2)	MAPK3 (ERK1)
BCI-004	59	43	37
BCI-106	89	75	66
BCI-107	40	27	26
BCI-108	73	54	49

Small SAR around Carb98= BCI-054; % Inh at 10uM



Compounds	MAP4K4 (HGK)	LCK	Src	Tie 2
BCI-054	83	64	56	50
BCI-112	03	16	12	01
BCI-110	5	89	76	26
BCI-111	14	80	50	91
BCI-128	13	84	62	41

BiKin I covers big part of kinome



Activity founded

Born to cure and innovate

Keep in mind

- BiKin I is:
- Really based on a **new scaffold**
  = New IP
  - Low MW
  - Good cLogP
  - Minor chemical modification changes **selectivity** profile
  - Amenable to fast synthesis, upscale
  - No tox issue expected

In vitro results of Bikin 2

Best results of Bikin2

Screening on 28 kinases, % Inh at 10uM
14 compounds tested

Compounds	FLT3	LCK	SRC
BCI-000138	83	27	21
BCI-000140	55	23	11
BCI-000141	66	21	9
BCI-000143	71	15	8
BCI-000147	44	65	41
BCI-000151	77	27	10

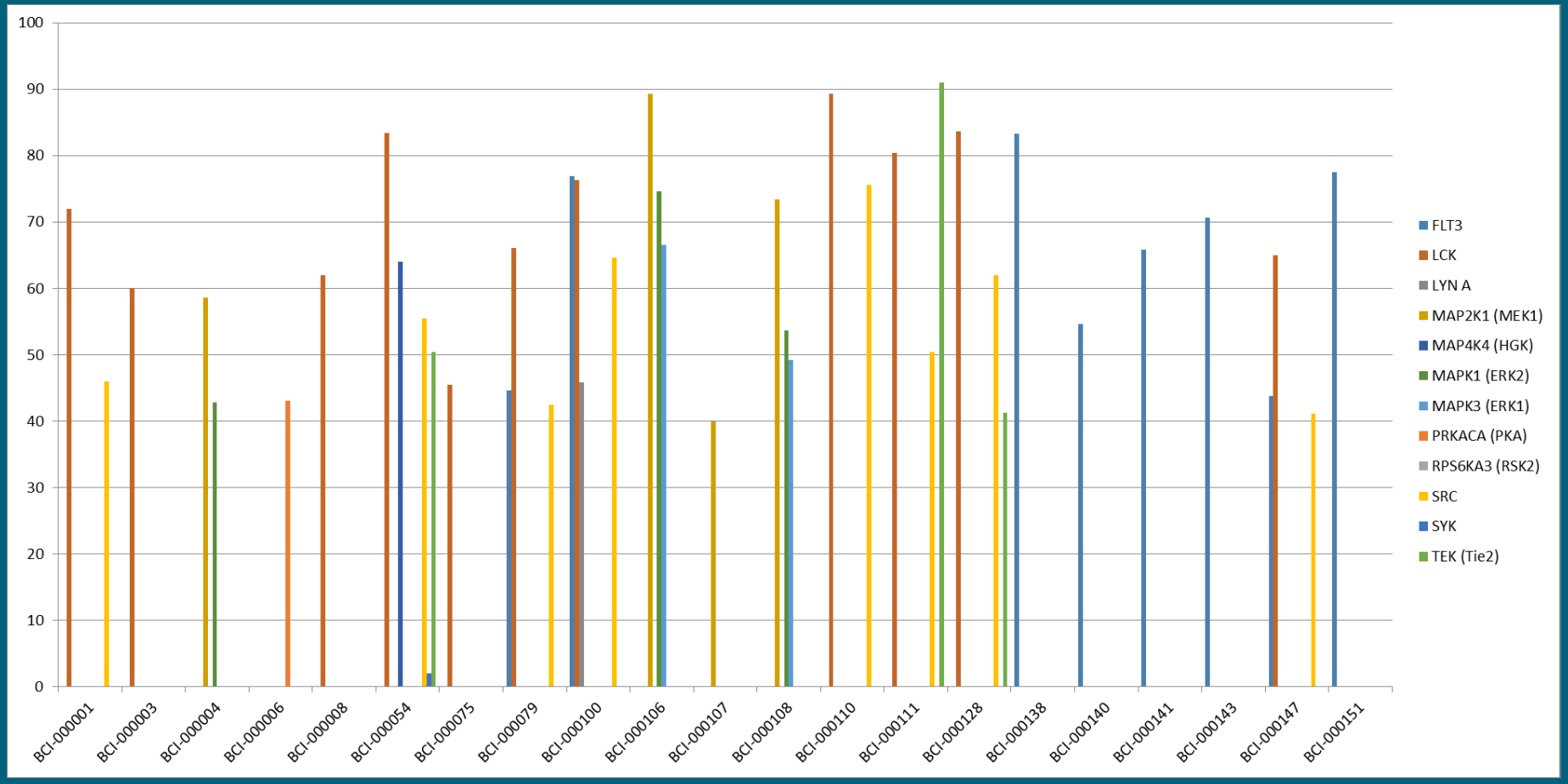
Analysis of Bikin2 results

- On the 14 compounds tested 6 (~50%) shown an inhibition > 50%
- Good activity and selectivity of Bikin 2 compounds active on FLT3 and its mutant.
- No activity on KIT, JAK2, weak on PDGFRA a very similar kinase to FLT3=> good selectivity.
- IC(50) value inversely proportionnal to ATP (data confirm)

[ATP] (uM)	IC50 (nM)
10	2512,477
100	486,663
500	162,662

Best results of BiKin 1 and 2

In vitro Results higher than 30% inhibition at 10uM



Take home message

- Our scaffold
  - Occupy a new chemical space
  - is a real potent kinase inhibitor
- So minor structural modification changes activity profile➔ selectivity can be achieved.

Next steps

- We are looking for
  - Partners to collaborate on a kinase project
  - Clients to acquire our Innovative kinase libraries
  - Don’t miss the opportunity to
    - Have access to a great IP space
    - Collaborate with a company having huge expertise
  - Contat us:
    - Dominique.surleraux@bci-pharma.com
    - +33674267334

How can we collaborate

- You define your kinase:
  - We offer our libraries to be screened and then Hit→Lead→Pre-clinical candidate
  - +
  - We design from our scaffold selective inhibitor for your selected kinase

- ➔ We maximize the chance to discover a potent and selective kinase inhibitor