Success stories de la Chimiothèque Nationale

Microglia Anti-inflammatories

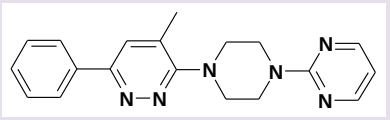
Potential indication : Alzheimer disease

Investigators : Jacques Haiech + Martin Watterson

Teams : UMR7200 - Laboratoire d'Innovation Thérapeutique, Illkirch
University of Chicago, USA

Library screened : National chemlib Strasbourg subset, 3600 compounds

1999: Phenotypic screen on Strasbourg platform (PCBIS)
Hit to lead (Strasbourg/Chicago) ⟶ MINOZAC



2001 : target identification (kinases)

2002 : in vivo efficacy of mouse Alzheimer model

2003 : Patents - Licences to Transition Therapeutics, then Elan
Phase II clinical trial

Development stopped

patents :

- Anti-inflammatory and protein kinase inhibitor composition and method of use. WO03018563, 6 mars 2003.
- Anti-inflammatory and protein kinase inhibitor compositions and related methods for downregulation of detrimental cellular responses and inhibition of cell death. US2003176437, 18 Septembre 2003.

Publications :

- Ligand modulation of glial activation : cell permeable, small molecule inhibitors of serine-threonine protein kinases can block induction of interleukin 1,3 and nitric oxide synthase II. D.M. Watterson, S. Mirzoeva, L. Guo, A. Whyte, J.J. Bourguignon, M. Hibert, J. Haiech, L.J. Van Eldik. Neurochem. Intern., 2001, 39, 459-468.
- Homodimerization of the death-associated protein kinase catalytic domain: development of a new small molecule fluorescent reporter. Zimmermann M, Atmanene C, Xu Q, Fouillen L, Van Dorsselaer A, Bonnet D, Marsol C, Hibert M, Sanglier-Cianferani S, Pigault C, McNamara LK, Watterson DM, Haiech J, Kilhoffer MC. PLoS One, 2010, 5, e14120.

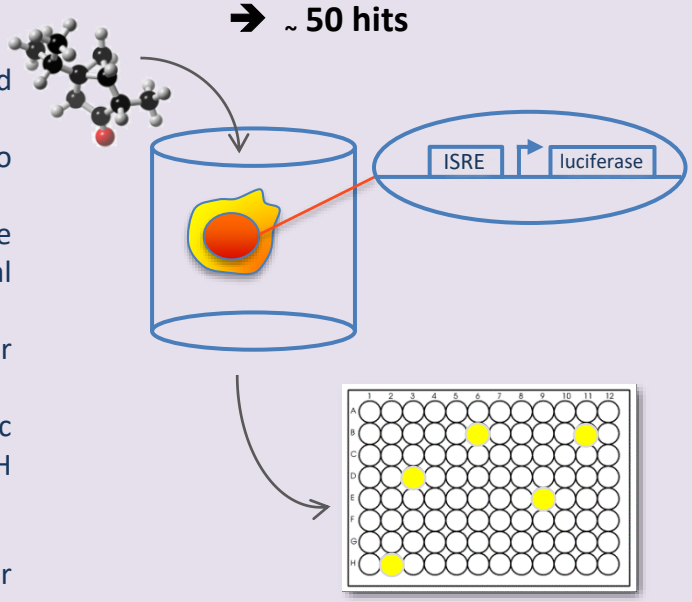
Success stories de la Chimiothèque Nationale

Stimulators of Interferon Genes and broad-spectrum antivirals

Project leader: **Pierre-Olivier Vidalain** (UMR 3569, Paris)
Teams: - Institut Pasteur (UMR 3523, Paris)
H. Munier-Lehmann and Y. Janin
- Institut Curie (UMR3666, Paris)
D. Dauzonne
- Institut Pasteur (UMR 3569, Paris)
F. Tangy

Screened chemical libraries:
- French National Chemical library (~ 25,900 compounds)
- Prestwick (1,200 compounds)
- Chemical Diversity (~ 14,000 compounds)
- Chem-X-Infinity (10,000 compounds)

➔ ~ **50 hits**



2008-2011: Cell-based screening for interferon-inducers and measles virus inhibitors
2013: target identification (DHODH belonging to the *de* novo pyrimidine biosynthesis pathway)
2009-2015: hit validation – structure-activity studies on three chemical series derived from the French National Chemical library – ADME/Tox studies
2015-2016: evaluation of compounds *in vivo* for their antiviral effect
2020: IPP/CNRS-A017 certification by the Structural Genomic Consortium as a chemical probe for the human DHODH (potent, selective, and cell-active inhibitor)

2021…: ongoing maturation on other therapeutic applications

2 patents (2010 et 2014)
10 articles:

- Lucas-Hourani M, Dauzonne D, Jorda P, Cousin G, Lupan A, Helynck O, Caignard G, Janvier G, André-Leroux G, Khiar S, Escriou N, Desprès P, Jacob Y, Munier-Lehmann H, Tangy F, Vidalain PO. PLoS Pathog. 2013;9(10):e1003678.
- Munier-Lehmann H, Lucas-Hourani M, Guillou S, Helynck O, Zanghi G, Noel A, Tangy F, Vidalain PO, Janin YL. J. Med. Chem. 2015;58(2):860-77.
- Lucas-Hourani M, Dauzonne D, Munier-Lehmann H, Khiar S, Nisole S, Dairou J, Helynck O, Afonso PV, Tangy F, Vidalain PO. Antimicrob. Agents Chemother. 2017;61(10).

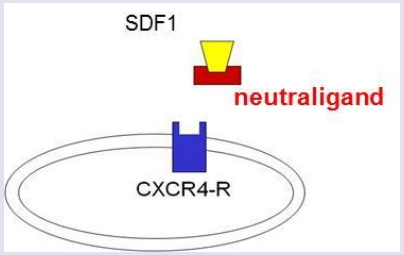
Success stories de la Chimiothèque Nationale

Chemokine neutrligands (1)

Applications : Inflammation – pain, asthma, dermatitis, WHIM, cancer, etc.

Investigators : **J-L Galzi, N Frossard, M Hibert, D Bonnet**

Teams : UMR7200 - Laboratoire d'Innovation Thérapeutique, Illkirch
UMR 7242 - Biotechnologie et signalisation cellulaire, Illkirch



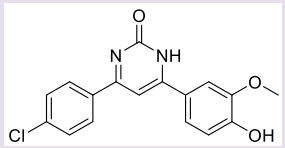
Library screened:

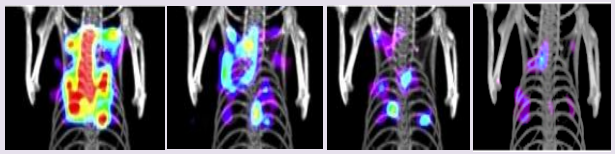
- Strasbourg set of Nat[al] lib : 6000 compounds
- Prestwick : 1200 compounds

2009 : Molecular screening (***FRET***) - Strasbourg (PCBIS)
2010 : New Concept - ***Neutraligand***
2010-2017 : hit to lead, prodrug, antedrug
2010-2018 : In vivo efficacy on several animal models

- In vivo activity on pain, asthma, dermatitis, lupus, WHIM, etc.
- Pet Scan with iodinated analog

2017 : Patent





Maturation SATT Conectus – Industrial partner contact for Pain

Patent : 2017

Publications :

Neutralizing endogenous chemokines with small molecules. Principles and potential therapeutic applications. Hachet-Haas M. et al. Pharmacol Therapeut 2010, 126, 39-55.

Prodrugs of a CXC Chemokine-12 (CXCL12) Neutraligand Prevent Inflammatory Reactions in an Asthma Model in Vivo Gasparik V et al. ACS Med Chem Lett 2012, 3, 10-14

An antedrug of the CXCL12 neutraligand blocks experimental allergic asthma without systemic effect in mice. Daubeuf F. et al. J Biol Chem. 2013 288(17):11865-76.

A strategy to discover decoy chemokine ligands with an anti-inflammatory activity. Abboud D. et al. Sci Rep. 2015 Oct 7;5:14746.

Success stories de la Chimiothèque Nationale

Modulation of alternative splicing

Proposing therapeutic approaches for viral and inflammatory diseases

Project leader : Jamal Tazi

Teams : UMR 5535 (IGMM Montpellier)
UMR 9187-U1196 (Institut Curie Orsay)

Screened chemical library :

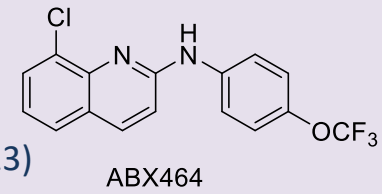
- Subset of the Institut Curie Chemical Library (2500 compounds)

2002… : In vitro screening, validation on cell lines, patient cells

2005-2008 : Hit-to-lead optimization (ANR)

2008 : Creation of start-up Splicos (which became Abivax in 2013)

2015 : ABX464 mode of action and start of clinical trials



ABX464

Success of ABX464 in clinical phase II for HIV and ulcerative colitis (UC) indications
2024: Clinical phase III underway for UC and clinical phase IIb planned for Crohn's disease

Patents : WO2005 023255 (1st hit IDC16); WO2009 087238 (hit-to-lead)…

Publications : Soret, J.; Bakkour, N.; Maire, S.; Durand, S.; Zekri, L. ; Gabut, M.; Fic, W.; Divita, G.; Rivalle, C.; Dauzonne, D.; Nguyen, C.H.; Jeanteur, P.; Tazi, J. Selective modification of alternative splicing by indole derivatives that target serine-arginine-rich protein splicing factors *Proc. Natl. Acad. Sci.* **2005**
Bakkour, N.; Lin, Y.-L.; Maire, S.; Ayadi, L.; Mahuteau-Betzer, F.; Nguyen, C.H.; Mettling, C.; Portales, P.; Grierson, D. S.; Chabot, B.; Jeanteur, P.; Branlant, C.; Corbeau, P.; Tazi, J. Small-molecule inhibition of HIV pre-mRNA splicing as a novel antiretroviral therapy to overcome drug resistance *PLoS Pathogens* **2007**; **…**

Success stories de la Chimiothèque Nationale

Inhibition of CK2 and Pim-1 protein kinases

Oncology application

Project leader : Claude Cochet

Teams : INSERM U1036 BIG-BCI CEA (Grenoble)
Institut Curie Orsay et Paris

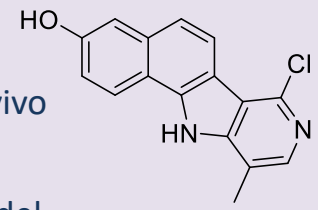
Screened chemical library :

• Institut Curie Chemical Library (6560 compounds)

2003 : Enzymatic screening carried out on the CMBA platform (CEA Grenoble)
Identification of 6 active compounds grouped into 3 families (arylsalicylaldehydes, difuran dicarboxylic acids and benzopyridoindoles)

2008-2013 : SAR studies, docking. Proof of concept in vitro and ex-vivo

Proof of concept in human glioblastoma xenograft mouse model



Compound 18

Patent : WO2011 013002

Publication : Prudent R., Moucadel V., Lopez Ramos M., Aci S., Laudet B., Mouawad L., Barette C., Einhorn J., Einhorn C., Denis J.N., Bisson G., Schmidt F., Roy S., Lafanechère L., Florent J.-C., Cochet C., Expanding the chemical diversity of CK2 inhibitors, *Mol Cell Biochem* **2008**

- Prudent R., Lopez Ramos M., Moucadel V., Barette C., Grierson D., Mouawad L., Florent J.-C., Lafanechère L., Schmidt F., Cochet C., Salicylaldehyde Derivatives as New Protein Kinase CK2 Inhibitors, *Biochim. Biophys Acta* **2008**

- Prudent, R.; Moucadel, V.; Nguyen, C.H; Barette, C.; Schmidt, F.; Florent, J.-C.; Lafanechere, L.; Sautel, C. F.; Duchemin-Pelletier, E.; Spreux, E.; Filhol, O.; Reiser, J.-B.; Cochet, C.; Antitumor activity of pyridocarbazole and benzopyridoindole derivatives that inhibit protein kinase CK2, *Cancer Research* **2010**

- López-Ramos M., Prudent R., Moucadel V., Sautel CF., Barette C., Lafanechère L., Mouawad L., Grierson D., Schmidt F., Florent JC., Filippakopoulos P., Bullock AN., Knapp S., Reiser JB. and Cochet C., New potent dual inhibitors of CK2 and Pim kinases: Discovery and structural insights, *FASEB Journal* **2010**

Success stories de la Chimiothèque Nationale

Inhibition of Aurora protein kinases

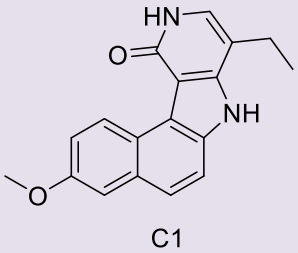
Oncology application

Project leader : Annie Molla

Teams : U823 (Grenoble)
UMR9187/U1196 Institut Curie Orsay

Screened chemical library :

• Institut Curie Chemical Library (6560 compounds)



C1

2003 : Enzyme screening carried out on the CMBA platform

Identification of 14 active compounds, including 6 belonging to the benzopyridoindole family

2009 : Proof of concept in mice carrying the H358 tumour (NSCLC) with C1

2013 : Synthesis of water-soluble benzopyridoindolones (C3, C4)

2014 : C1 treatment sensitises glioma stem cells to radiotherapy

2015 : Water-soluble C5M benzopyridoindolone -> multikinase inhibitor with interesting preclinical features, proven efficacy in xenograft mice.

Patents : WO2011 131636, WO2012 163934

Publications: Hoang T.M., Favier B., Valette A., Barette C., Nguyen C.H., Lafanéchère L., Grierson D. S., Dimitrov S., Molla A., Benzo [e]pyridoindoles, novel inhibitors of the aurora kinases, *Cell Cycle* ***2009*** - Le Ly, TT., Vu, H.L., Naud-Martin, D., Bombled, M., Nguyen, C.H., and Molla A.,New hydrosoluble benzo[e]pyridoindolones as potent inhibitors of aurora kinases, *Chem. Med. Chem*. **2013** - Le L.-T.-T., Vu H.-L., Nguyen C.-H., Molla A., Basal aurora kinase B activity is sufficient for histone H3 phosphorylation in prophase, *Biology Open*, **2013** - Hoang T.-M.-N., Vu H.-L., Le L.-T.-T., Nguyen C.-H., Molla A., In vitro high throughput screening, what next ? Lessons from the screening for Aurora kinase inhibitors, *Biology*, **2014** - Minata M., Gu C., Joshi K., Nakana-Okuno M., Hong C., Nguyen C.-H., Kornblum H. I., Molla A., Nakano I.,Multi-kinase inhibitor C1 triggers mitotic catastrophe of glioma stem cells mainly through MELK kinase inhibition, *Plos One*, **2014** - Le L.-T.-T, Couvet M., Favier B., Coll J.-L., Nguyen C.-H., Molla A., Discovery of benzo[e]pyridoindolones as kinase inhibitors that disrupt mitosis exit while erasing AMPK-Thr172 phosphorylation on the spindle, *Oncotarget,* **2015**

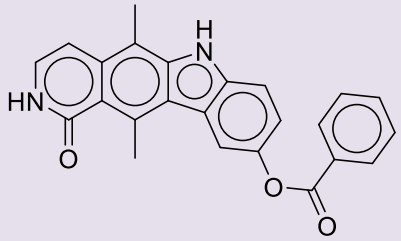
Success stories de la Chimiothèque Nationale

Microtubule stabilization

Oncology application

Project leader : **Laurence Lafanéchère**

Teams : Plateforme CMBA (iRTSV, Grenoble)
UMR 9187-U1196 (Institut Curie Orsay)



Liminib

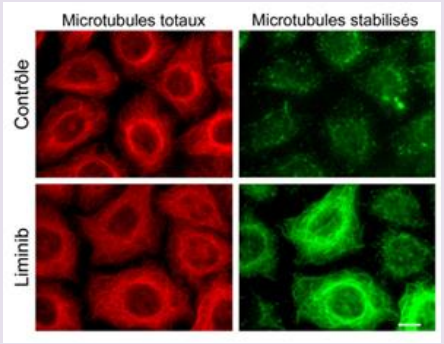
Screened chemical library :

• National Chemical Library (11920 compounds)

2005… : Phenotypic screening on microtubule stabilisation/destabilisation
Identification of the Liminib "hit" and target using the LIM kinase hit

Tested on a 66 kinase panel involved in the regulation of the cytoskeleton. Only active on NEK11 and MLK1 and LIMK1 (the highest inhibition) & LIMK2. Tested on 45 additional different kinases (ATP-competitive kinase inhibition): no significant interaction.

IC_{50} (LIMK1)= 50nM & IC_{50} (LIMK2)= 75nM



2013 : Creation of a Cellipse start-up
2015 : Preclinical phase
2020 : Closure of the start-up

Patent : WO2010 095042

Publications : Renaud Prudent, Emilie Vassal-Stermann, Chi-Hung Nguyen, Catherine Pillet, Anne Martinez, Chloé Prunier, Caroline Barette, Emmanuelle Soleilhac, Odile Filhol, Anne Beghin, Glaucio Valdameri, Stéphane Honoré, Samia Aci-Sèche, David Grierson, Juliana Antonipillai, Rong Li, Attilio Di Pietro, Charles Dumontet, Diane Braguer, Jean-Claude Florent, Stefan Knapp, Ora Bernard, Laurence Lafanechère Pharmacological Inhibition of LIM Kinase Stabilizes Microtubules and Inhibits Neoplastic Growth *Cancer Research* **2012** - Prudent, R., Vassal-Stermann, E., Nguyen, C.H., Mollaret, M., Viallet, J., Castan, A., Barette, C., Pillet, C., Martinez, A., Soleilhac, E., Feige, J-J., Billaud, M., Florent J-C., and Lafanechère, L., Azaindole derivatives are inhibitors of microtubule dynamics, with anticancer and anti-angiogenic activities, *Br. J. Pharmacol*. **2013**

Success stories de la Chimiothèque Nationale

Reduction in the metastatic spread of cancer cells

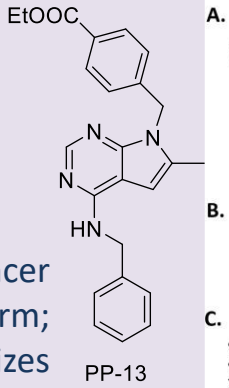
Oncology application

Project leaders : Benoît Busser et Amandine Hurbin

Teams : UMR5309-U1209 (Grenoble)
UMR9187-U1196 (Institut Curie Orsay)

Screened chemical library :

- Institut Curie Chemical Library (7520 compounds)

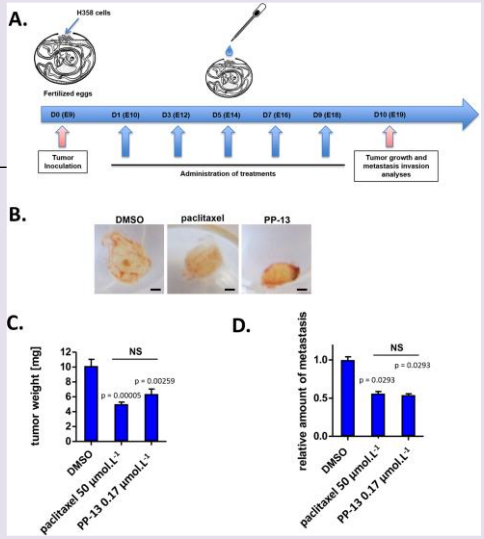


PP-13

2006 : Cellular screening (non-small cell lung cancer cells) carried out on the CMBA platform; identification of a PP-13 hit that destabilizes microtubules.

2017 : Proof of concept in ovo with PP-13. Reduction of metastatic invasion with a low concentration treatment (130 nmol.L^{-1})

2019 : Proof of concept in an orthotopic breast cancer model (mouse) with PP-13
Reduction in tumour size and metastatic spread without significant toxicity



PP-13 inhibits tumour growth and cell dissemination in vivo. H358 NSCLC cells were xenografted on a chick embryo chorioallantoic membrane (CAM). After treatment with vehicle (0.5% DMSO), paclitaxel (50 µmol.L^{-1}) or PP-13 (170 nmol.L^{-1}), tumours were excised and weighed. (A) Schematic representation of the assay principle. (B) Representatives pictures of tumours at the end of the different treatments. Bar = 1 mm. (C) Effects of treatments on the H358 tumour weight (means ± SEM of ≥16 samples). (D) Effects of treatments on H358 metastasis in the lower CAM (means ± SEM of 15 samples)

Publications: Gilson, P.; Josa-Prado, F.; Beauvineau, C.; Naud-Martin, D.; Vanwonterghem, L.; Mahuteau-Betzer, F.; Moreno, A.; Falson, P.; Lafanechère, L.; Frachet, V.; Coll, J-L; Fernando Díaz, J.; Hurbin, A.; Busser B. Identification of pyrrolopyrimidine derivative PP-13 as a novel microtubule-destabilizing agent with promising anticancer properties *Scientific Reports* **2017**

Pauline Gilson, Morgane Couvet, Laetitia Vanwonterghem, Maxime Henry, Julien Vollaire, Vladimir Baulin, Marco Wernerc Anna Orlowska, Véronique Josserand, Florence Mahuteau-Betzer, Laurence Lafanechère, Jean-Luc Coll, Benoit Busser, Amandine Hurbin The pyrrolopyrimidine colchicine-binding site agent PP-13 reduces the metastatic dissemination of invasive cancer cells in vitro and in vivo *Biochemical Pharmacology* 160 (**2019**) 1–13

Success stories de la Chimiothèque Nationale

Interaction with CD45, an important target of protein phosphatase in the treatment of acute myeloblastic leukaemia (AML)

Oncology application

Project leader : Ronan Quéré

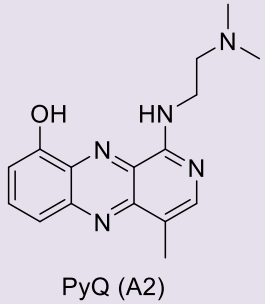
Teams : UMR866 (Dijon)
UMR9187/U1196 Institut Curie Orsay

Screened chemical library :

• Institut Curie Chemical Library (7400 compounds)

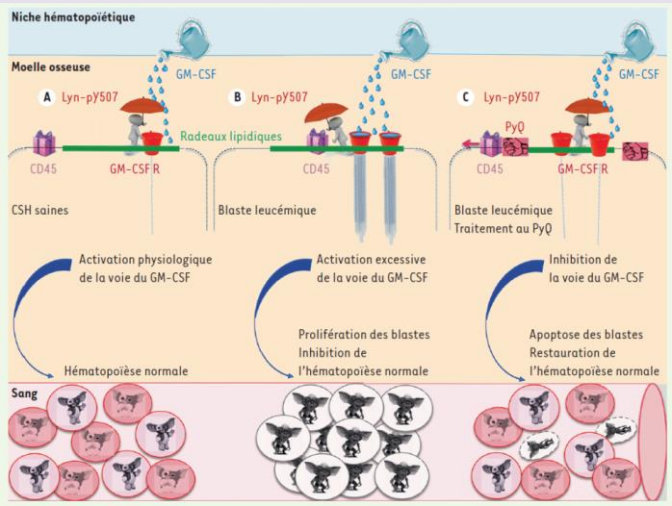
2012 : In vitro screening on leukemia and hematopoietic cells

Identification of 3 active compounds belonging to the Pyrido[4,3-b]quinoxaline family PyQ



PyQ (A2)

2015 : Proof of concept in a mouse model of AML: *PyQ blocks leukemic development*



Patent : WO2015 028622

Publications : Laetitia Saint-Paul, Chi-Hung Nguyen, Anne Buffière, Jean-Paul Pais de Barros, Arlette Hammann, Corinne Landras-Guetta, Rodolphe Filomenko, Marie-Lorraine Chrétien, Pauline Johnson, Jean-Noël Bastie, Laurent Delva, Ronan Quéré CD45 phosphatase is crucial for human and murine acute myeloid leukemia maintenance through its localization in lipid rafts *Oncotarget*, **2016** - Saint-Paul L, Nguyen CH, Bastie JN, Delva L, Quéré R. CD45 phosphatase, a relevant target for the treatment of acute myeloid leukemia, *Med Sci*, **2016**

Success stories de la Chimiothèque Nationale

Inhibiteurs de cellules déficientes en cytidine désaminase (CDA)

Oncology application

Project leaders : **M. Amor-Guéret, F. Mahuteau-Betzer**

Teams : UMR3348 - Intégrité du génome, ARN et Cancer, Institut Curie, Orsay
UMR9187 – Chimie et Modélisation pour la Biologie du Cancer, Institut Curie, Orsay

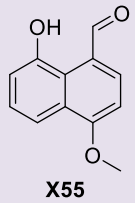
Screened chemical library :

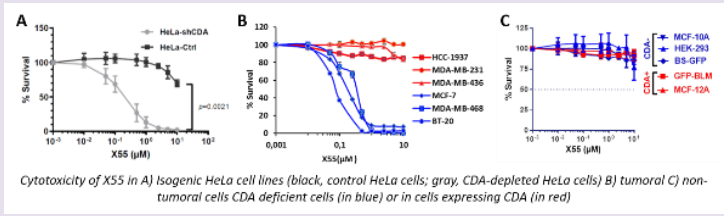
- Institut Curie Chemical Library (8560 compounds)

2012 : Screening on isogenic cell pair HeLa-shCDA (CDA-deficient)/Hela-Ctrl (CDA-proficient) on the CMBA platform (CEA Grenoble) -> Identification of 1 hit X55

2018-2021 : Hit-to-Lead optimisation

2021 : Patent





Cytotoxicity of X55 in A) Isogenic HeLa cell lines (black, control HeLa cells; gray, CDA-depleted HeLa cells) B) tumoral C) non-tumoral cells CDA deficient cells (in blue) or in cells expressing CDA (in red)

2022 : Lead formulation for per os administration

2023 : In vivo Proof-Of-Concept, TechMedIll platform, PCBIS, Illkirch

2024 : Study of the effect of X55 on the proteome in order to identify the signaling pathways engaged by the target of this molecule - Collaboration with Human Proteome Project (HPP)

Patent : Amor-Guéret M., Mameri H., Beauvineau C., Mahuteau-Betzer F., Naphthalene derivatives useful in the treatment of cancer, EP21305572, 2021, WO2022.

Publication :

H. Mameri, G. Buhagiar-Labarchède, G. Fontaine, C. Corcelle, C. Barette, R. Onclercq-Delic, C. Beauvineau, F. Mahuteau-Betzer and M. Amor-Guéret. Cytidine deaminase deficiency in tumor cells is associated with sensitivity to a naphthol derivative and a decrease in oncometabolite levels. *Cellular and Molecular Life Sciences*, **2022**, 79:465 - doi.org/10.1007/s00018-022-04487-9

Success stories de la Chimiothèque Nationale

Antiviral agents against SARS-CoV-2

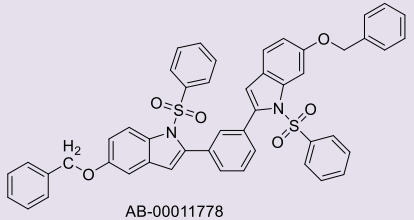
Applications: antiviral activity

Project leader : **V. Parissi**

Teams : UMR5234 – Microbiologie Fondamentale et Pathogénicité, Bordeaux
UMR9187 – Chimie et Modélisation pour la Biologie du Cancer, Institut Curie, Orsay
UMR7311 - Institut de Chimie Organique et Analytique, Orléans

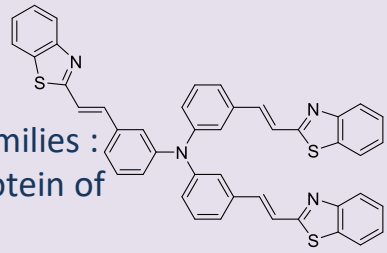
Screened chemical library :

- National Chemical Library (CN): 70000 compounds
- Mu.Ta.Lig. Virtual Chemotheca : 60000 compounds
- Inhibitors of Protein-Protein Interactions Database : 1956 compounds
- ZINC Chemical Library: 7000 compounds


AB-00011778

2020 : In silico screening on a molecular model of the interaction between the viral protein spike S and the cellular receptor ACE2 -> 110 compounds selected

10 compounds of CN tested *in vitro* and *in cellulo*


AB-00047476

2 compounds identified in the bis-indolylpyridine and triphenylamine families :

- ✓ blocks the infectivity of lentiviral vectors pseudotyped with the S protein of SARS-CoV-2
- ✓ Direct inhibitory effect on the S/ACE2 association
- ✓ Inhibition of viral replication: EC50 between 0.1 and 5 µM depending on the cell line.

2021 : Patent

Patent : Parissi V., Sousa S., Lapaillerie D., Delelis O., Meertens L., Gallois-Montbrun S., Teulade-Fichou M.-P., Lartia R., Bordeau G., Pharmaceutical composition, its use as a drug and new compounds, especially for treating sars-cov-2 infection, EP21306521, 2021

Publication :

Selection of Bis-Indolyl Pyridines and Triphenylamines as New Inhibitors of SARS-CoCellular Entry by Modulating the Spike Protein/ACE2 Interfaces, D. Lapaillerie et al., *Antimicrobial Agents and Chemotherapy*, August **2022** Volume 66 Issue 8

Success stories de la Chimiothèque Nationale

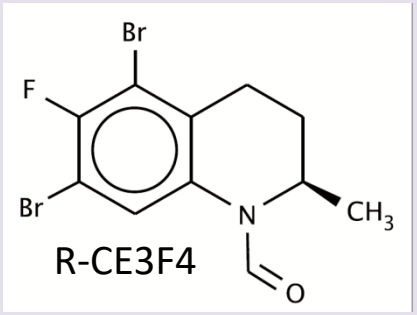
Identification of New Epac1 inhibitor

Development of new potential therapeutic drug to prevent cardiac hypertroph

Leader : **Frank Lezoualc'h**
Teams: INSERM UMR-1048, Univ Toulouse
CIBLOT, Univ Paris-Saclay

Screening of Chemical Library chimiothèque nationale essentielle:
CNE (640 compound : 1 hit)

2010-2013: Primary screen (Biochemical assay) and secondary screen (cellular assay), IC50 determination, new synthesis of inhibitor and confirmation, molecular mechanism (uncompetitive inhibitor), synthesis of analogs, SAR, identification of active enantiomer, specificity toward Epac1 versus Epac2 and PKA



R-CE3F4

2014-2020: Specificity of Epac1 by inactivation of Epac1 gene, in vivo studies, molecular mechanism by RMN, new biologicals effects, encapsulation

2020-2024: Optimization of in vivo efficacy in experimental models of heart failure – Characterization of mechanism of action by crystallography - POC in vivo in cardio-oncology

Patents 2012, 2014 and 2017**, non exclusive licence :** Tocris

Main publications :

2023: Sartre C et al. Nature com 14:4157.
2023: Mazevet et al. Elife. 2023 Aug 8;12:e83831.
2018 : Boulton S et al. J Am Chem Soc. 140, 9624.
2017 : Fazal L. & al., Circ Res. 120:645.
2014 : Bisserier M. & al., Biochem Soc Trans. 42, 257-264.
2012 : Courilleau D. & al., J. Biol. Chem. 287, 44192−44202.

Success stories of the National Chemical Library

NBD-EGFR & Electrophilic Stress

Screening of EGFR receptor modulators and elucidation of their mode of action in cancer

Head : **Pr. Vehary SAKANYAN**

Teams : Université de Nantes, IICiMed, EA1155.
Université Paris Cité, UMR8601, LCBPT

2010: Initial touch from NCI (USA) Screening of the NCI chemical library on small molecule chips. Discovery of nitro-benzoxadiazole (NBD) as an EGFR activator.

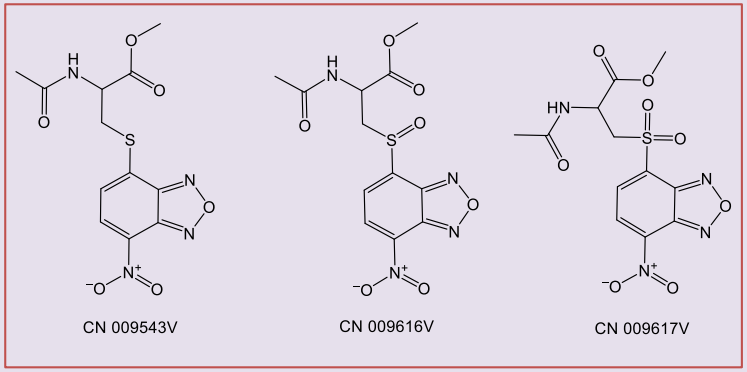
2011: Virtual screening of NBD structural analogues available in the CN database. Selected Hits = 3 NBD compounds synthesized in 2000 as inhibitors of nitrile hydratase (NHase), a metalloenzyme involved in the conversion of Nitrile to Amide.

2012-15: Verification of purity, synthesis of new batches, synthesis of new analogues and fluorescence studies

Expected: Targets in the cancer proteome

Screened chemical library:

NCI Chemical Libraries (Diversity Set II Library)
1364 compounds ➔ 20 selected compounds
➔ 1 Hit confirmed
3 CN analogues of the main hit from NCI



Résultats majeurs

- ✓ Discovery of NBDs as EGFR activating
- ✓ New EGFR activation mechanism
- ✓ Multiple targets for the NBD backbone
- ✓ New concept of electrophilic stress in cancer

Patent : « Puces à petite molécules » FR2927170A1 (2008)

Publis : Scientific Reports (2014), 4, 3977
Scientific Reports (2016), 6, 21088
Ann. Clin. Exp. Metabol. (2016) 1(1), 1006
High-Throughput (2018) 7(2), 12

Success stories of the Chimiothèque Nationale

SeaBeLife Biotech (Startup)

Identification and valorization of new polypharmacological inhibitors of necrotic cell death (necroptosis and ferroptosis), with various therapeutic applications

Scientists:

M. T. Dimanche-Boitrel & S. Bach

Teams : IRSET INSERM U1085 de Rennes, Station Biologique de Roscoff (KISSf & UMR8227), ICBMS UMR5246 - Université Lyon 1

2013: Primary screening at Kissf facility

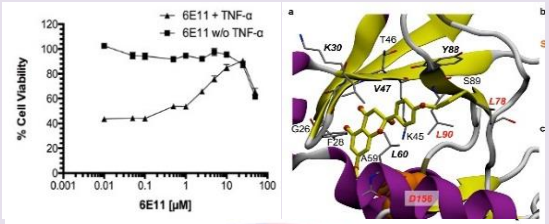
2014: Hit confirmation and discovery of 2 families of active compounds, first patent applications

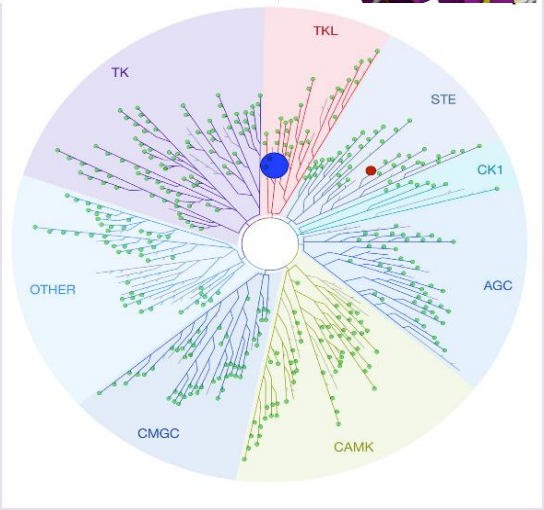
2017: Maturation project GREF_HEPATO_PRES (SATT Ouest Valorisation) and synthesis of +150 analogues of hits by ICBMS Chemical Library (A. Comte) and ICBMS -LCO2 team (Pr. P. Goekjian)

2019: Creation of **SeaBeLife Biotech** (www.seabelife.com) proof of concept on various cell death models and realization of toxicity studies, adme, in vivo.

In-house ICBMS chemical library (A. Comte) **screened:**

+3000 compound ➔ 10 primary hits





Ongoing: (late 2024) Regulatory preclinical development before the start of a phase 1 clinical trial on a first drug candidate

SeaBeLife

Patents: applicative patents (WO2017/064217, WO2018/073321) and patents protecting new compounds (WO2017/064216, WO2022/157392)

Publications: *Sci. Rep.* **2017**, 7, 12931, *FEBS J.* **2017**, 18, 3050, *Sci. Rep.* **2022**, 24, 5118.

Startup: SeaBeLife Biotech, CEO Dr. Morgane Rousselot (created in March 2019, staff of 8 people in April 2024)

CNRS • SORBONNE UNIVERSITÉ Station Biologique de Roscoff
www.sb-roscoff.fr

irset Institut de recherche en santé, environnement et travail
www.irset.org

UNIVERSITÉ DE LYON — icb ms UMR 5246
www.icbms.fr

Inserm La science pour la santé From science to health
www.inserm.fr

cnrs
www.cnrs.fr

OUEST VALORISATION Ressources d'innovation
www.ouest-valorisation.fr

Success stories de la Chimiothèque Nationale

TSL2-SMA

Spinal muscular atrophy (SMA): correction of SMN2 gene expression by targeting TSL2 loop of mRNA

Promoter : **Pr. L. Scapozza** **(Université de Genève)**

Teams : Université de Genève, Université de Lausanne, Université de Lyon (ICBMS – UMR CNRS 5246), Université de Francfort, Université de Valence, IRB Barcelone and Hoffman La Roche

Compound library screened:

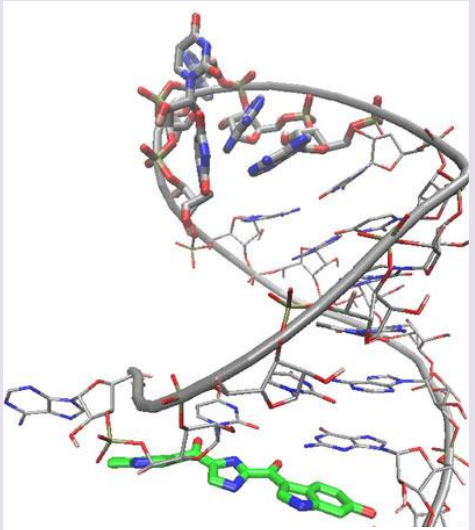
- Subset of the UMR 5246 - ICBMS in-house compound library (300 compounds)
  - ➔ 4 primary hits

2014 : Compounds primary screening

2015 : Identification of best hit «**PK4C9**» (natural product homocarbonyltopsentin) and validation in biological assays

2016 : re-synthesis of hit for various studies (in vitro and in vivo évaluation, NMR, MoA, selectivity (RNA-seq), cytotoxicity,…)

2017 : Creation of a binding model between **PK4C9** and the TSL2 loop of SMN2 gene mRNA



Model of binding mode between homocarbonyltopsentin and RNA TSL2 loop

2017-2019: Hit optimization and chemical synthesis by ICBMS compound library and SMITh Team (A. Comte and Pr. B. Joseph) in collaboration with Université de Genève (Pr. L. Scapozza)

Publication : Garcia-Lopez, A.; Tessaro, F.; Jonker, H. R. A.; Wacker, A.; Richter, C.; Comte, A.; Berntenis, N.; Schmucki, R.; Hatje, K.; Petermann, O.; Chiriano, G.; Perozzo, R.; Sciarra, D.; Konieczny, P.; Faustino, I.; Fournet, G.; Orozco, M.; Artero, R.; Metzger, F.; Ebeling, M.; Goekjian, P.; Joseph, B.; Schwalbe, H.; Scapozza, L. *Nat. Commun*. **2018**, *9*, 2032

UNIVERSITÉ DE GENÈVE
www.unige.ch

UNIL | Université de Lausanne
www.unil.ch

UNIVERSITÉ DE LYON
icbms UMR 5246
www.icbms.fr

GOETHE UNIVERSITÄT FRANKFURT AM MAIN
www.goethe-university-frankfurt.de

VNIVERSITAT DE VALÈNCIA
www.uv.es

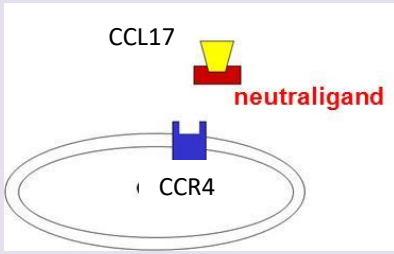
IRB BARCELONA INSTITUTE FOR RESEARCH IN BIOMEDICINE
www.irbbarcelona.org

Roche
www.roche.com

Success stories de la Chimiothèque Nationale

Chemokine neutraligands (2)

Applications : dermatitis (dermocosmetics)



Investigators : **J-L Galzi, N Frossard, P Bernard**

Teams : Green Pharma SAS, Rue du Titane, Orléans
UMR 7242 - Biotechnologie et signalisation cellulaire, Illkirch

Library screened:

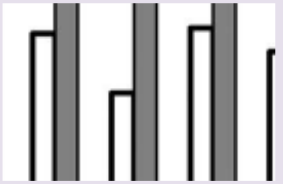
- GreenPharma natural compounds: 640 compounds

2013 : New screening assay TRIC (Abboud et al.2015)

2014-2015 : hit characterization (theophyllin analog)

2010-2018 : In vivo efficacy on several animal models

- In vivo activity on pain, asthma, dermatitis, lupus, WHIM, etc.
- Pet Scan with iodinated analog

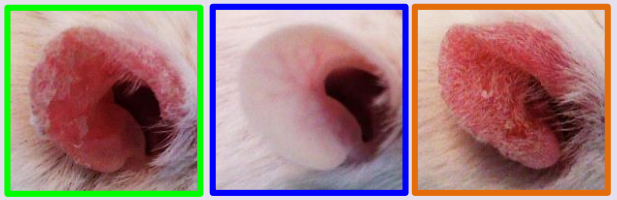


2017 : Patent

2024: Randomized double blind **Clinical study** on moderate dermatitis

Marketing the active ingredient

Dermatitis model +GPN 279 +Theophyllin



Patent : 2014

Publications : Neutralizing endogenous chemokines with small molecules. Principles and potential therapeutic applications. Hachet-Haas M. et Pharmacol Therapeut 2010, 126, 39-55.

A strategy to discover decoy chemokine ligands with an anti-inflammatory activity. Abboud D. et al. Sci Rep. 2015 Oct 7;5:14746.

Galzi, JL., Abboud, D., Frossard, N., Do, Q.T., Bernard, P. Composition contenant au moins un inhibiteur de certaines chimiokines, son procédé d'obtention et son utilisation en dermocosmétique pharmaceutique (INPI 14/02163 and INPI 14/02162, septembre 2014) extension in progress

Coïc A, Himbert, F., Do, Q.T., Galzi, J.L., Frossard, N., Guillaumet, G., Saguet, T., Bonnet, P., Bernard, P. (2024). Randomized double-blind placebo-controlled cosmetic trial of a topical first-in-class Neutraligand targeting the chemokine TARC/CCL17 in mild-to-moderate atopic dermatitis, International journal of cosmetic scienceDOI: 10.1111/ics.12948

Success stories de la Chimiothèque Nationale

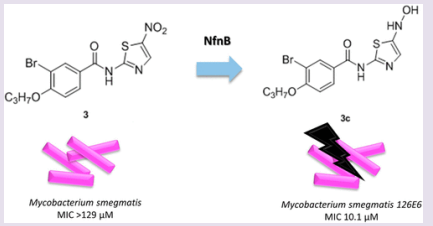
Antimycobacterial compounds

Project leaders: N. Alonso, B. Gicquel & H. Munier-Lehmann

Teams : Institut Pasteur, Unité de Génétique Mycobactérienne, Paris
Institut Pasteur, Unité de Chimie et Biocatalyse, CNRS UMR3523, Paris
UMR9187, Chimie et Modélisation pour la Biologie du Cancer, Institut Curie, Orsay

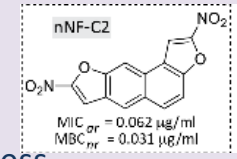
Screened chemical libraries:

- French National Chemical library (36,000 compounds)



2014: Screening on *Mycobacterium aurum*

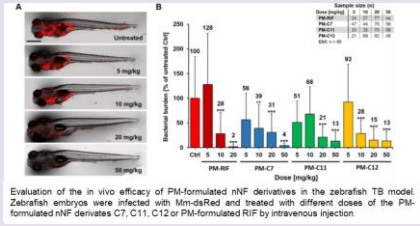
2015-2016: 3 nitrothiazolylbenzamide derivatives active against NTM (non-tuberculous mycobacteria)[1]



2015: 14 nNFs (nitronaphthofuran) active against *M. tuberculosis*

2018-2021: Demonstration of nNFs activation through the SigH/Mrx22 stress response pathway[2]

2019-2021: Proof of concept in zebrafish via formulation of lipophilic nanoparticles[3]



Articles :

[1] Nitazoxanide Analogs Require Nitroreduction for Antimicrobial Activity in *Mycobacterium smegmatis*, Buchieri M.; Cimino M.; Rebollo-Ramirez S.; Beauvineau C.; Cascioferro A.; Favre-Rochex S.; Helynck O.; Naud-Martin D.; Larrouy-Maumus G.; Munier-Lehmann H.; Gicquel B., J. Med. Chem., 2017, 60, 7425−7433

[2] SigH stress response mediates killing of *Mycobacterium tuberculosis* by activating nitronaphthofuran prodrugs via induction of Mrx2 expression, L. Cioetto-Mazzab, F. Boldrin, C. Beauvineau, M. Speth, A. Marina, A. Namouchi, G. Segafreddo, M. Cimino, S. Favre-Rochex, S. Balasingham, B. Trastoy, H. Munier-Lehmann, G. Griffiths, B. Gicquel, M. E. Guerin, R. Manganelli, and N. Alonso-Rodrıguez, Nucleic Acids Research, 2023, 51, 144-165

[3] The zebrafish embryo as an *in vivo* model for screening nanoparticle-formulated lipophilic anti-tuberculosis compounds, N.-J. Knudsen Dal, M. Tobias Speth, K. Johann, M. Barz, C. Beauvineau, J. Wohlmann, F. Fenaroli, B. Gicquel, G. Griffiths, and N. Alonso Rodriguez, Disease Models & Mechanisms, 2022, 15 (1): dmm049147

The National Library
Success Stories

Nonsense Mutation Correction in Human Diseases

A therapeutic approach for genetic diseases involving nonsense mutations

PI : **Fabrice Lejeune**

Teams : UMR 8161 (IBL – Lille)
UMR 7245 (MNHN - Paris)

Screened libraries:

- Prestwick (1200 compounds : no HIT)
- Essential Chemical Library (640 compounds : no HIT)
- The National Extract Library (15500 extracts : **4 HITs**)

Lepista inversa

© MNHN - Chimiothèque

Development (SATT Lutech) – POC

2012 – 2014 : Screening, isolation and characterization of the active compound in the fungal extract, and bioassays
2014 – 2017 : Validation on cell lines and patient cells
2017 – 2020 : Measurement of the effective concentration
2020 – 2023 : Mode of Action and *in vivo* validation in mouse models

2021 : Creation of the startup **Genvade Therapeutics** (Lille)

French Patent deposited in 2016 et **International Patent** in 2017

Publications :

- Leroy C., Spellier S., Charlene-Essonghe N. et al. Use of 2,6-diaminopurine as a potent suppressor of UGA premature stop codons in cystic fibrosis, *Molecular Therapy*, 31(4), 970-985 (**2023**)
- Trzaska C., Amand S., Bailly C. et al. 2,6-Diaminopurine as a highly potent corrector of UGA nonsense mutations, *Nature Communications*, 11, 1509-1520 (**2020**)
- Benhabiles H., Gonzalz-Hilarion S., Amand S., Bailly C. et al. Optimized approach for identification of highly efficient correctors of nonsense mutations in human diseases, *PLoS ONE*, 12(*11*), e0187930 (**2017**)

Success stories de la Chimiothèque Nationale

BIODOL

FLT3 negative allosteric modulators for the treatment of neuropathic pain

Laboratoire d'innovation thérapeutique
LIT | UMR 7200 de l'Université de Strasbourg et du cnrs
http://medchem.unistra.fr

institute for neurosciences montpellier
http://www.inmfrance.com

BIODOL THERAPEUTICS
http://www.biodol.eu

PI : **Didier Rognan**

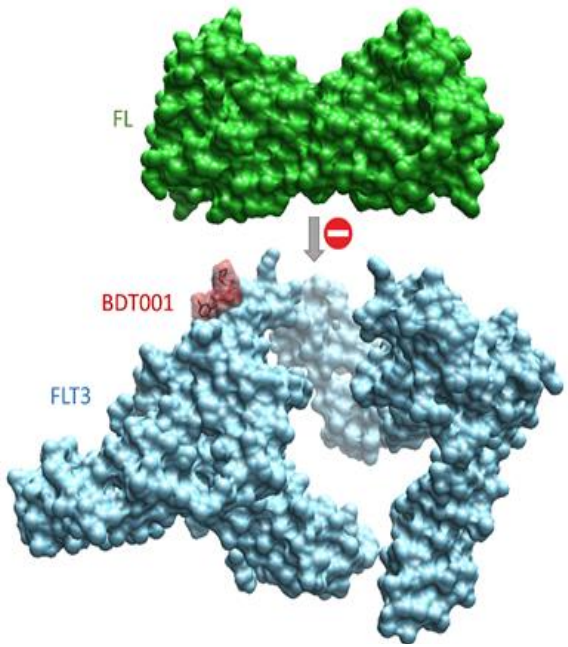
Teams : LIT (UMR7200, Illkirch): D. Rognan
PCBIS (UMS3286, Illkirch): P. Villa
INM (U1051, Montpellier): J. Valmier
ICR (UMR7273, Marseille): P. Vanelle

Jui-Dec.2016: primary screen
Jan-Mar.2017: confirmation at two concentrations
Mar-Jui.2017: IC50 determination (Evotec plates)
➔11 hits (chemical series)
Aou-Nov.2017: IC50 confirmation (powder)
2018-2022: Hit to lead optimization of two chemical series
2023: Regulatory preclinical development

Ongoing: Phase 1 clinical trials

WO2016016370AEP22306531
Rivat et al. Nature Commun, 2018, 9, 1042
Hany et al. ACS Chem Biol, 2022, 17, 709-722
Jouvenel et al. bioRxiv 2023.03.16.532971

Compound Library:
National Cpd Lib. (48.320 compounds)
➔ 1.473 primary hits



A molecule selected by computer screening and then optimized by medicinal chemistry (BDT001) prevents the binding of FL to FLT3. This innovative anti-FLT3 immediately and lastingly reduces neuropathic pain caused in rodents(© Didier Rognan, UMR7200)

1 Maturation: SATT AxLR
2 ANR : BIODOL (PRC) et NEUROPATH (PRCE)
1 Startup : BIODOL Therapeutics (Montpellier & Strasbourg)

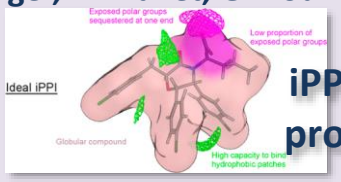
Success stories de la Chémoinformatique

Data-driven approaches to drug design on protein-protein interactions

Applications : Cancer, Infectious diseases, inflammation, etc.

Project leaders : O. Sperandio, B. Villoutreix, R. Torchet, F. Mareuil, H. Ménager, V. Mallet, G. Bouvier, C.B. Ciambur

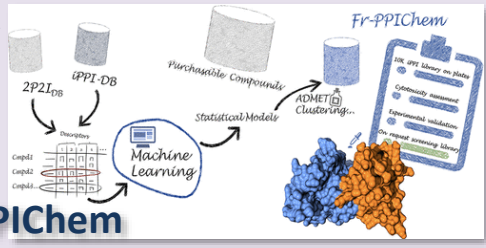
Teams : U973 Mti - Molécules thérapeutiques *in silico*
UMR3528 - Bioinformatique Structurale – Institut Pasteur
USR 3756 - HUB – Département de Biologie Computationnelle



iPPI 3D profiles

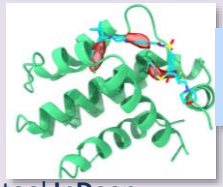
Collection of PPI modulators to train machine learning tools and facilitate drug design

2010 : First national machine learning model to design PPI-focused chemical libraries [1,2]
2013 : Release of **iPPI-DB** v1, a database of PPI modulators [3]
2014 : Identification of specific 3D characteristics for PPI modulators [4]
2016 : Rendez-vous between chemical space and pocket space of PPI targets [5]
2016 : Release of **iPPI-DB** v2 [6]
2017 : Identification of privileged substructures to modulate PPI targets [7]



Fr-PPIChem

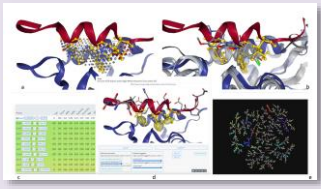
2020 : Use of iPPI-db data to co-design of the **Fr-PPIChem** [8]
2021 : Release of **iPPI-DB** v3. Release of innovative crowdsourcing maintenance interface and a pocket-centric interface [9]



2022 : Use of iPPI-DB data to develop the deep learning tool **InDeep** that predicts functional binding sites within PPI targets [10]
2023 : Development of a target-centric mode for iPPI-DB data to develop the deep learning tool **InDeep**
2024 : Development of Protein Interaction Explorer within iPPI-DB data to explore the PPI pocketome

Toolbox to drug design PPI targets

- InDeep[Net] : https://indeep-web-main.gpu.pasteur.cloud/
- iPPI-DB : https://ippidb.pasteur.fr/



PIE

1. Sperandio O, Reynès CH, Camproux AC, Villoutreix BO. Drug Discov Today. 2010 Mar;15(5-6):220-9
2: Reynès C, Host H, Camproux AC, Laconde G, Leroux F, Mazars A, Deprez B, Fahraeus R, Villoutreix BO, Sperandio O. PLoS Comput Biol. 2010 Mar 5;6(3):e1000695
3: Labbé CM, Laconde G, Kuenemann MA, Villoutreix BO, Sperandio O. Drug Discov Today. 2013 Oct;18(19-20):958-68.
4: Kuenemann MA, Bourbon LM, Labbé CM, Villoutreix BO, Sperandio O.J Chem Inf Model. 2014 Nov 24;54(11):3067-79.
5: Kuenemann MA, Labbé CM, Cerdan AH, Sperandio O.Sci Rep. 2016 Apr 1;6:23815.
6: Labbé CM, Kuenemann MA, Zarzycka B, Vriend G, Nicolaes GA, Lagorce D, Miteva MA, Villoutreix BO, Sperandio O.Nucleic Acids Res. 2016 Jan 4;44(D1):D542-7.
7: Bosc N, Kuenemann MA, Bécot J, Vavrusa M, Cerdan AH, Sperandio O.J Chem Inf Model. 2017 Oct 23;57(10):2448-2462.
8: Bosc N, Muller C, Hoffer L, Lagorce D, Bourg S, Derviaux C, Gourdel ME, Rain JC, Miller TW, Villoutreix BO, Miteva MA, Bonnet P, Morelli X, Sperandio O, Roche P. ACS Chem Biol. 2020 Jun 19;15(6):1566-1574.
9: Torchet R, Druart K, Ruano LC, Moine-Franel A, Borges H, Doppelt-Azeroual O, Brancotte B, Mareuil F, Nilges M, Ménager H, Sperandio O. Bioinformatics. 2021 Jan 8;37(1):89-96.
10: Mallet V, Checa Ruano L, Moine Franel A, Nilges M, Druart K, Bouvier G, Sperandio O.Bioinformatics. 2022 Feb 7;38(5):1261-1268.
11. Moine-Franel, A., Mareuil, F., Nilges, M., Ciambur, C. B. & Sperandio, O. A comprehensive dataset of protein-protein interactions and ligand binding pockets for advancing drug discovery. Sci Data 11, 402 (2024).

Success stories de la Chémoinformatique

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DOI: 10.1002/minf.202200208

RESEARCH ARTICLE

molecular informatics

French dispatch: GTM-based analysis of the Chimiothèque Nationale Chemical Space

Polina Oleneva | Yuliana Zabolotna | Dragos Horvath | Gilles Marcou | Fanny Bonachera | Alexandre Varnek

Laboratoire de Chémoinformatique, UMR7140 CNRS/UniStra, University of Strasbourg, Strasbourg, France

Correspondence
Alexandre Varnek, Laboratoire de Chémoinformatique, UMR7140 CNRS/UniStra, University of Strasbourg, 4 rue Blaise Pascal, 67081, Strasbourg, France.
Email: varnek@unistra.fr

Abstract

In order to analyze the Chimiothèque Nationale (CN) – The French National Compound Library – in the context of screening and biologically relevant compounds, the library was compared with ZINC in-stock collection and ChEMBL. This includes the study of chemical space coverage, physicochemical properties and Bemis-Murcko (BM) scaffold populations. More than 5 K CN-unique scaffolds (relative to ZINC and ChEMBL collections) were identified. Generative Topographic Maps (GTMs) accommodating those libraries were generated and used to compare the compound populations. Hierarchical GTM («zooming») was applied to generate an ensemble of maps at various resolution levels, from global overview to precise mapping of individual structures. The respective maps were added to the ChemSpace Atlas website. The analysis of synthetic accessibility in the context of combinatorial chemistry showed that only 29,7% of CN compounds can be fully synthesized using commercially available building blocks.

KEYWORDS
ChEMBL, chemical space, chimiothèque Nationale, Generative Topographic Mapping, ZINC