Success stories of structure-based drug discovery

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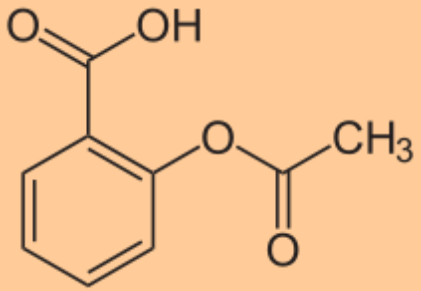
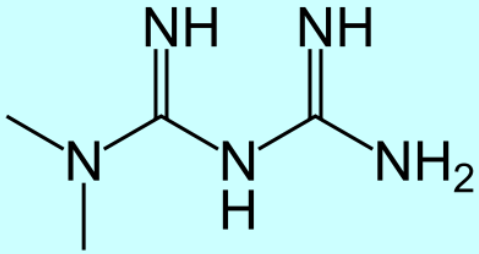
Nature is the best chemist



acetylsalicylic acid

(ASPIRIN – Bayer 1853**, 1899)**

- antipyretic
- analgesic
- anticoagulant
- pro-drug
- commercially, the most successful drug ever

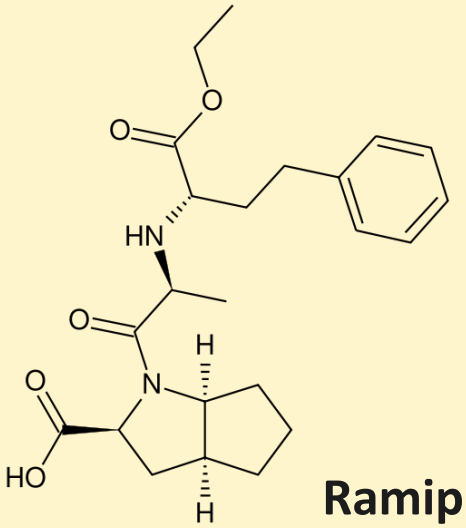


metformin

(**Glucophage** – Rona 1922, **1958**)

- antidiabetic

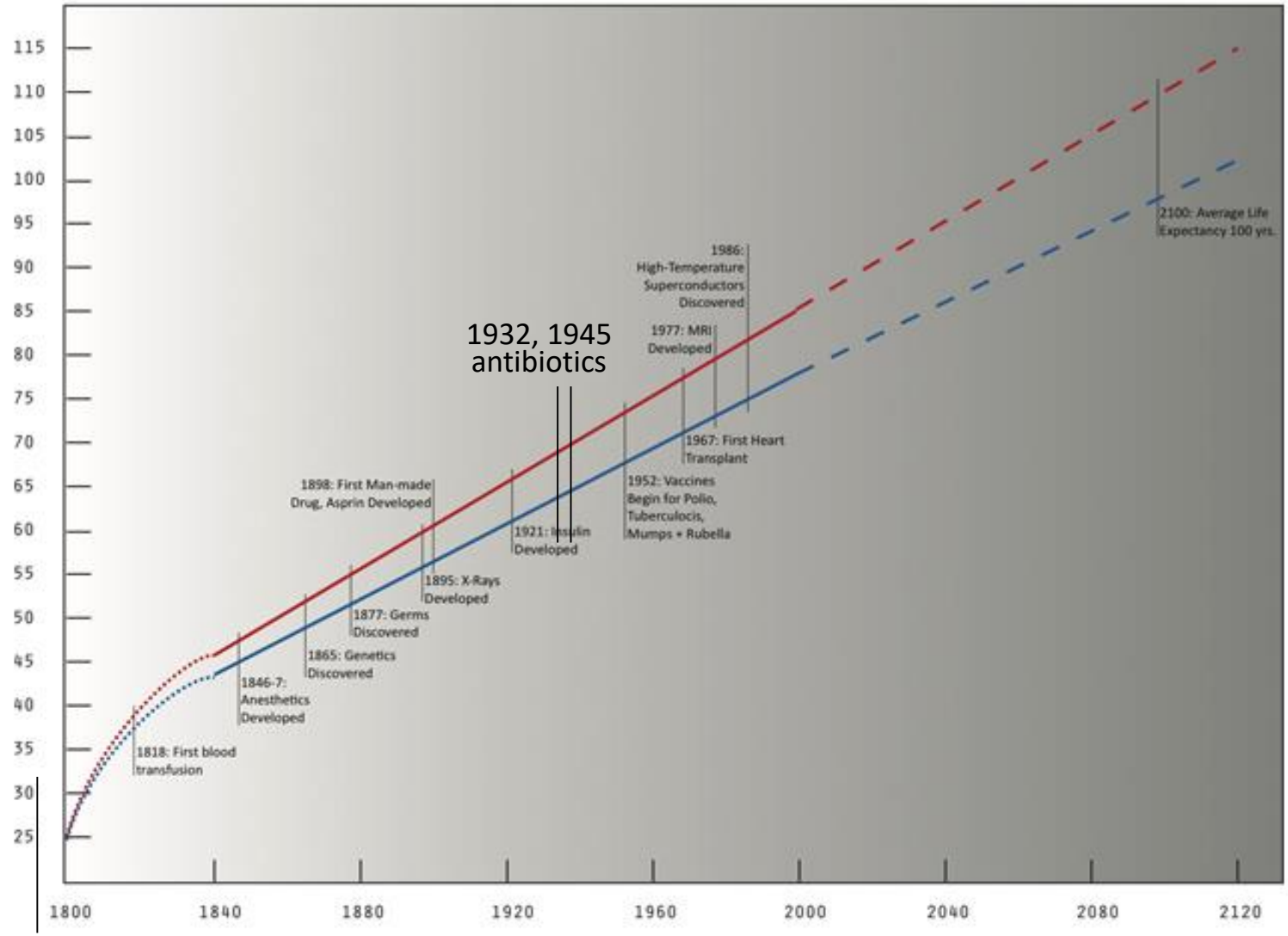
- antihypertensive
- inhibits Angiotensin Converting Enzyme (ACE)
- pro-drug
- designed from viper snake venom



Ramipril

(Altace – Aventis 1991**, 1991)**

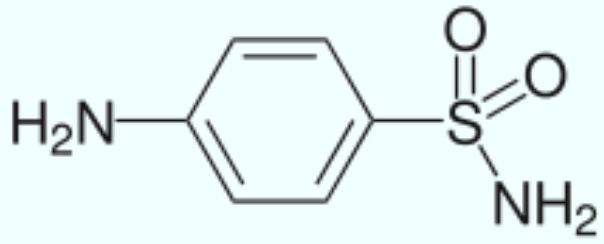
Discovery and life expectancy



1796 smallpox vaccine

History of the Food & Drug Administration (FDA)

- **1906 Food and Drugs Act** prohibited adulteration or misbranding of pharmaceuticals. Premarket approval of drugs not required - commercialization of hazardous or useless drugs were not prevented
- **1937** sulfanilamide formulation with untested solvent killed more than 100 people.
- **1938 Food, Drug, and Cosmetic Act** - evidence of **drug safety** required
- **1962** – required evidence of **effectiveness** through adequate **clinical trials**



Sulfanilamide
Antibacterial agent used in WW2

Chemist Lee Geismer looking over an New Drug Application (NDA) in the 1960s (fda.gov)

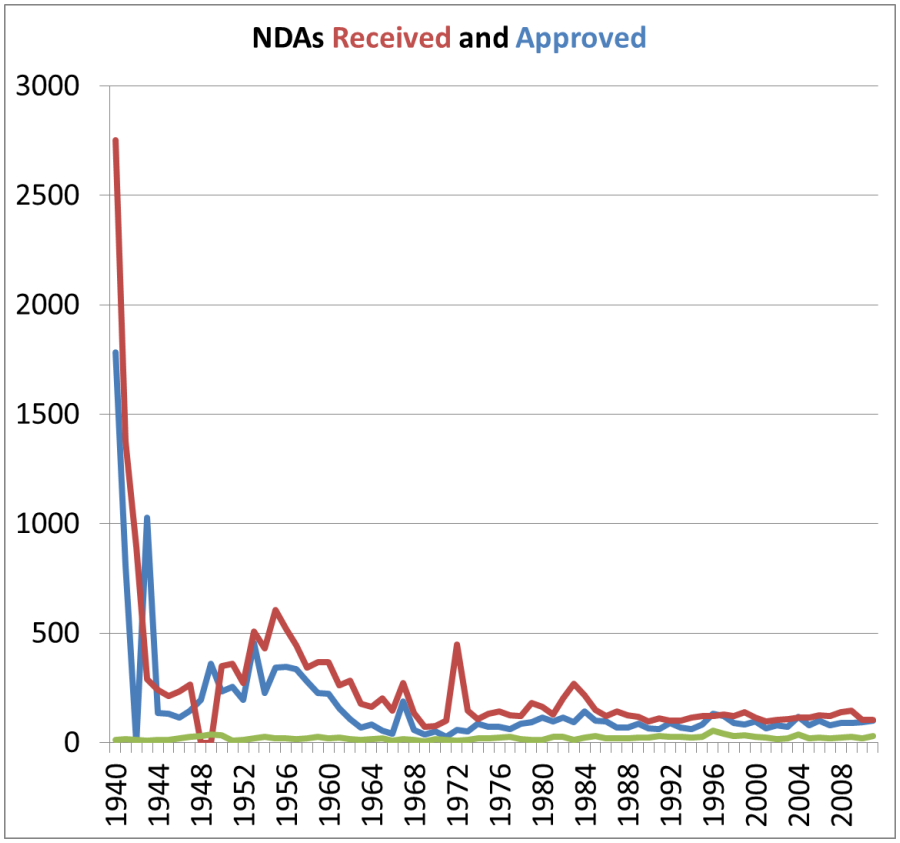
New Drug Application (NDA)

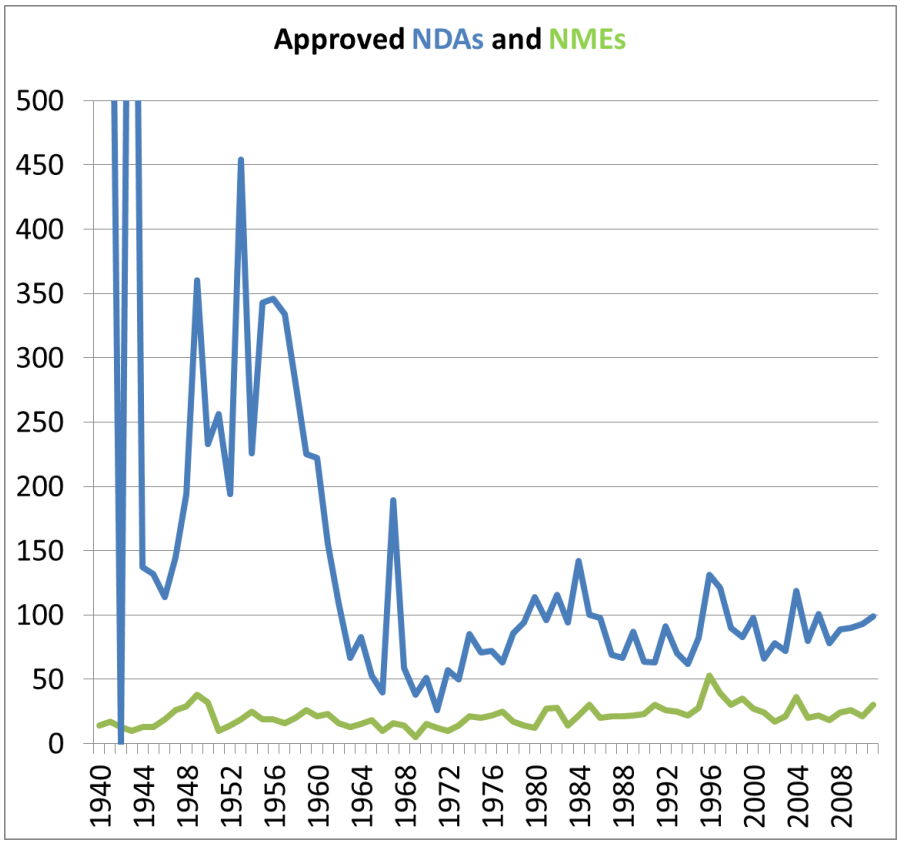
It's the **drug whole story**, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.

The goals of the NDA are to provide enough information to permit FDA reach key decisions, whether the drug:

- is **safe and effective in its proposed use(s**), and whether the **benefits of the drug outweigh the risks**
- the **proposed labeling (package insert) is appropriate**, and what it should contain
- the methods used in drug manufacturing and controls preserve the **drug's identity, strength, quality, and purity**

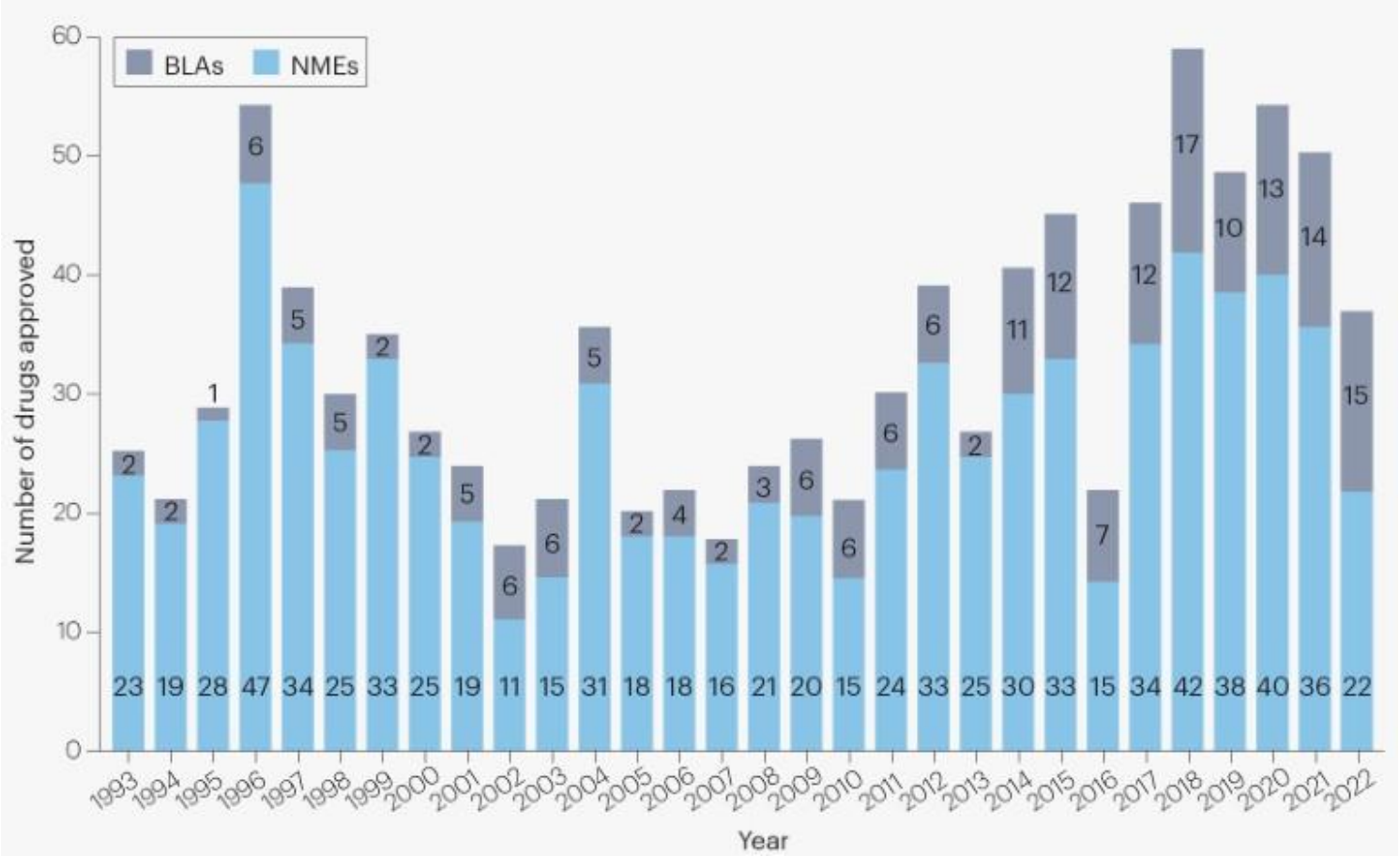
Summary of FDA New Drug Applications (NDAs)





- **Average submitted NDAs (1938 - 2011) 254.3/year**
- **Average approved NDAs (1938 - 2011) 168.9/year**
- **Average NMEs (1938 - 2011) 21.2/year**

Number of approved drugs by the US FDA



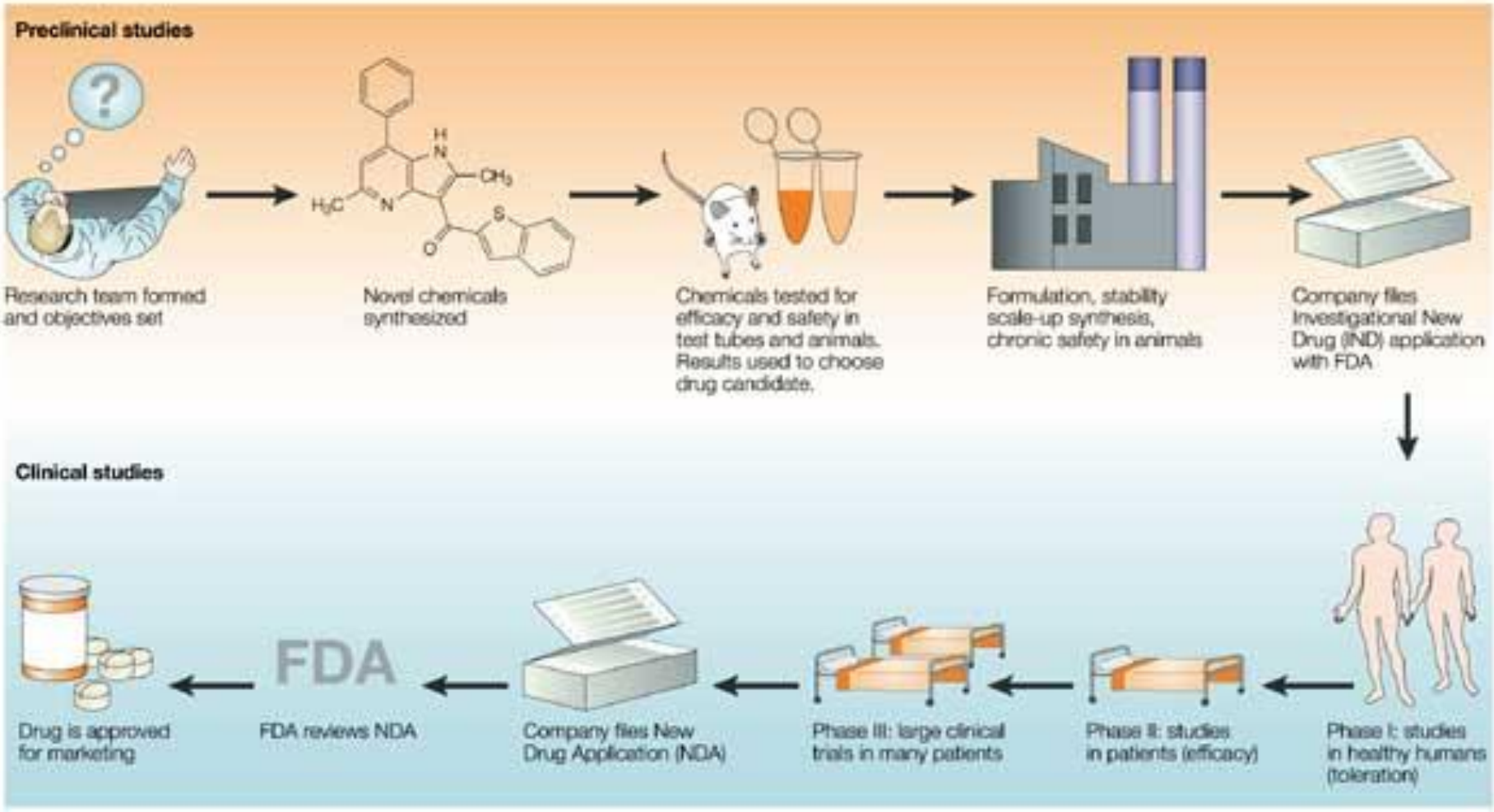
- 2007-2015: average 30 approved NMEs/year
- 2013-2022: average 43 approved NMEs/year

NME – New Molecular Entity

BLA – Biologics License Application

Mullard, A. (2023) 2022 FDA approvals. Nature Review Drug Discovery

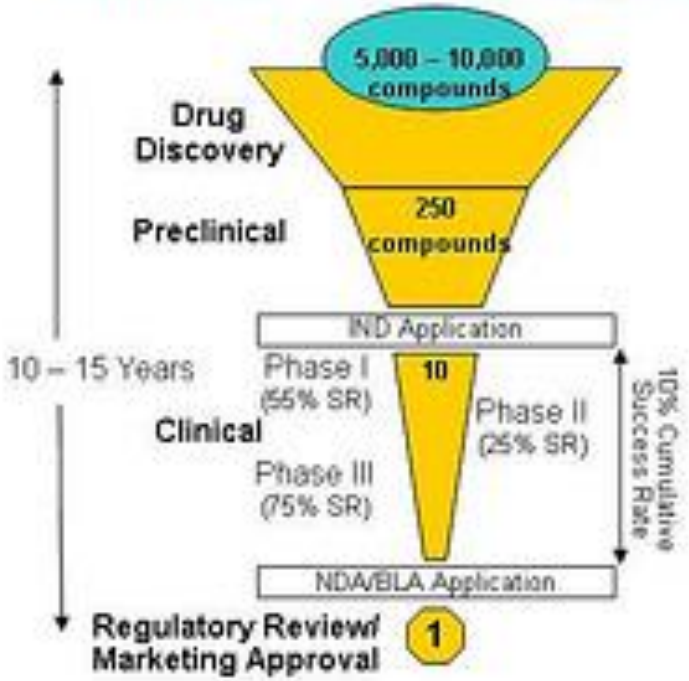
Stages of drug discovery



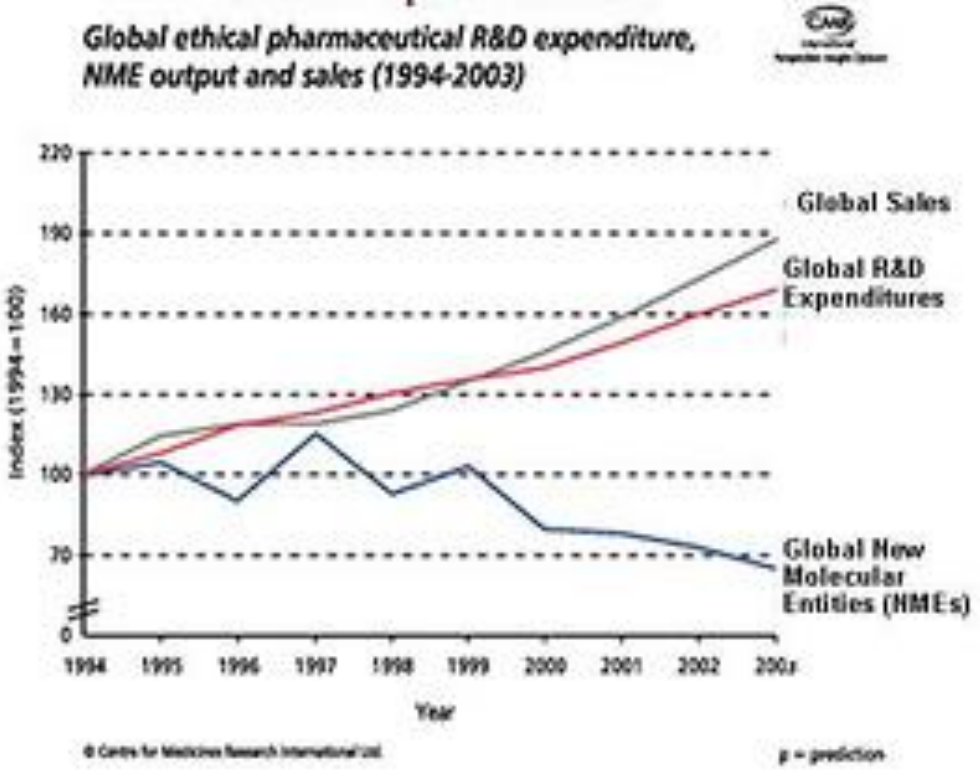
Jones, AW (2019) Perspectives in Drug Discovery

Big Pharma : Dramatic Decline in R&D Productivity

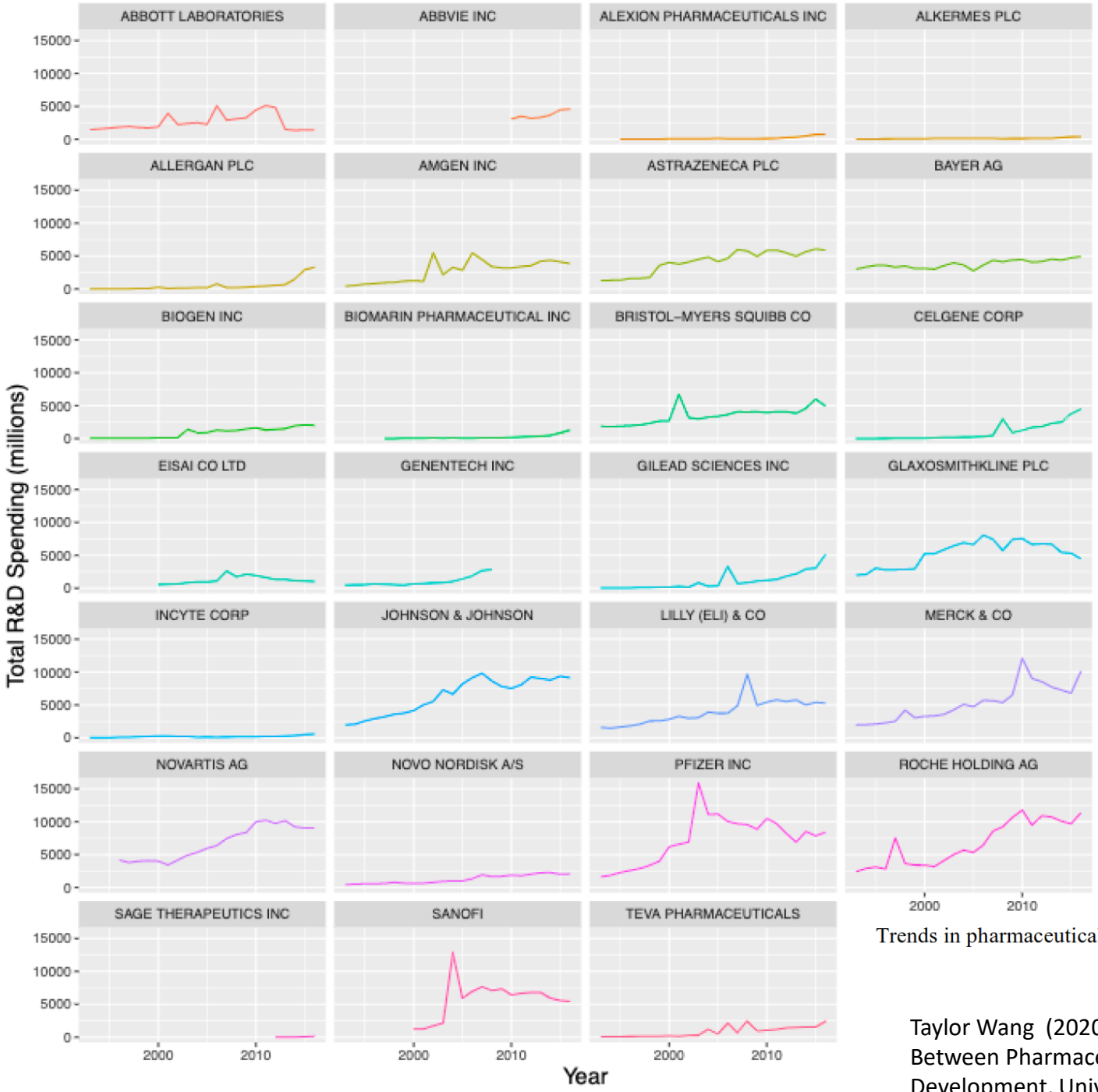
Attrition Remains Very High



Output Not Keeping Up With R&D Expenditures



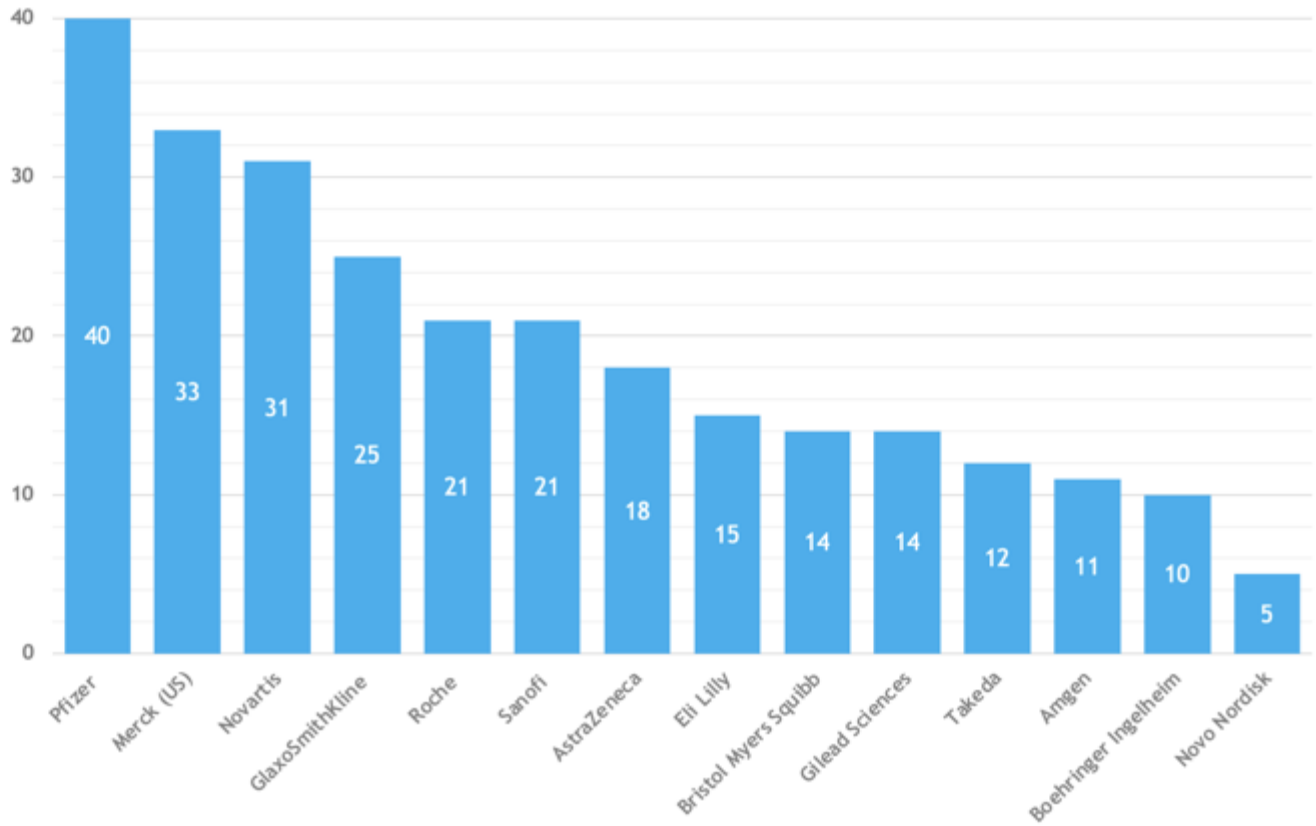
Source: PhRMA, CMR, Genentech, Booz Allen Hamilton: *The Global Innovation 1000*, 2006



Trends in pharmaceutical R&D expenses over time by Company

Taylor Wang (2020) Honor's Thesis: The Relationship Between Pharmaceutical R&D Spending and NME Development, University of California, Berkeley

Total NMEs 1999-2018



Total New Medical Entities by Pharma Company 1999-2018.
Modified from "R&D efficiency of leading pharmaceutical companies – A 20-year analysis"

Spending more in R&D does not mean more NMEs

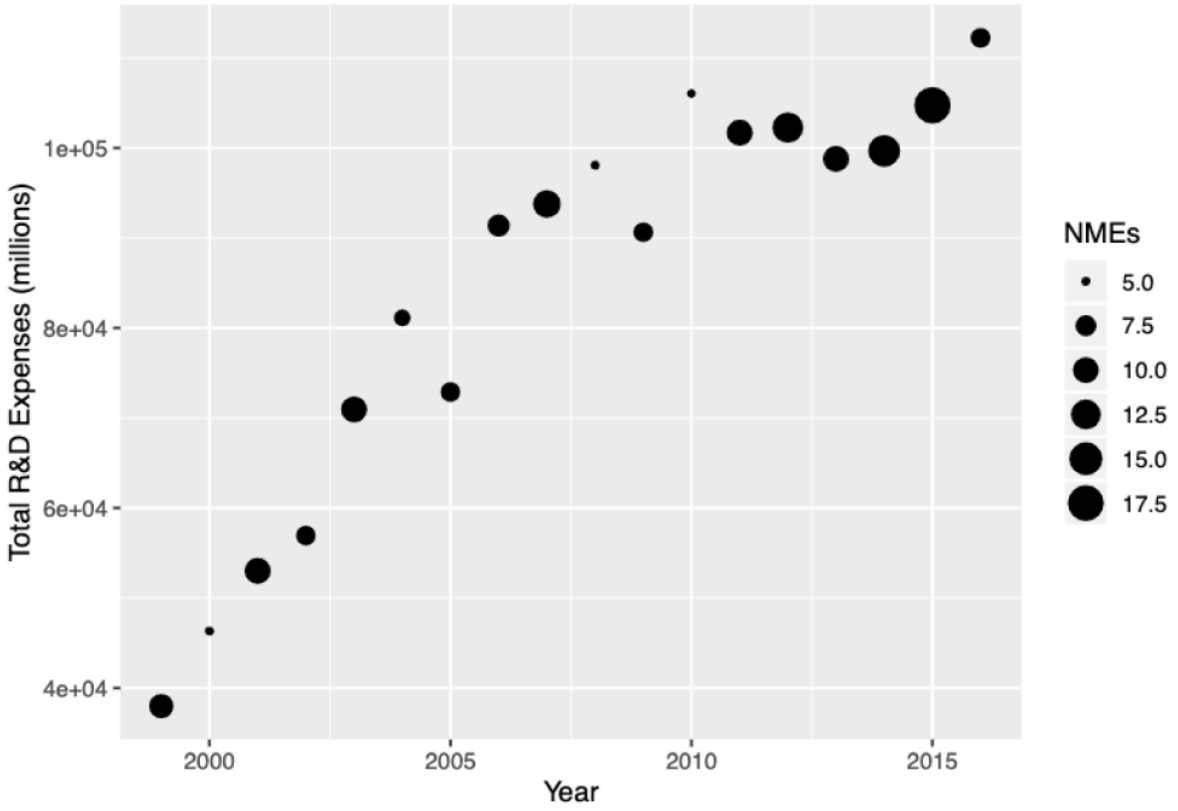
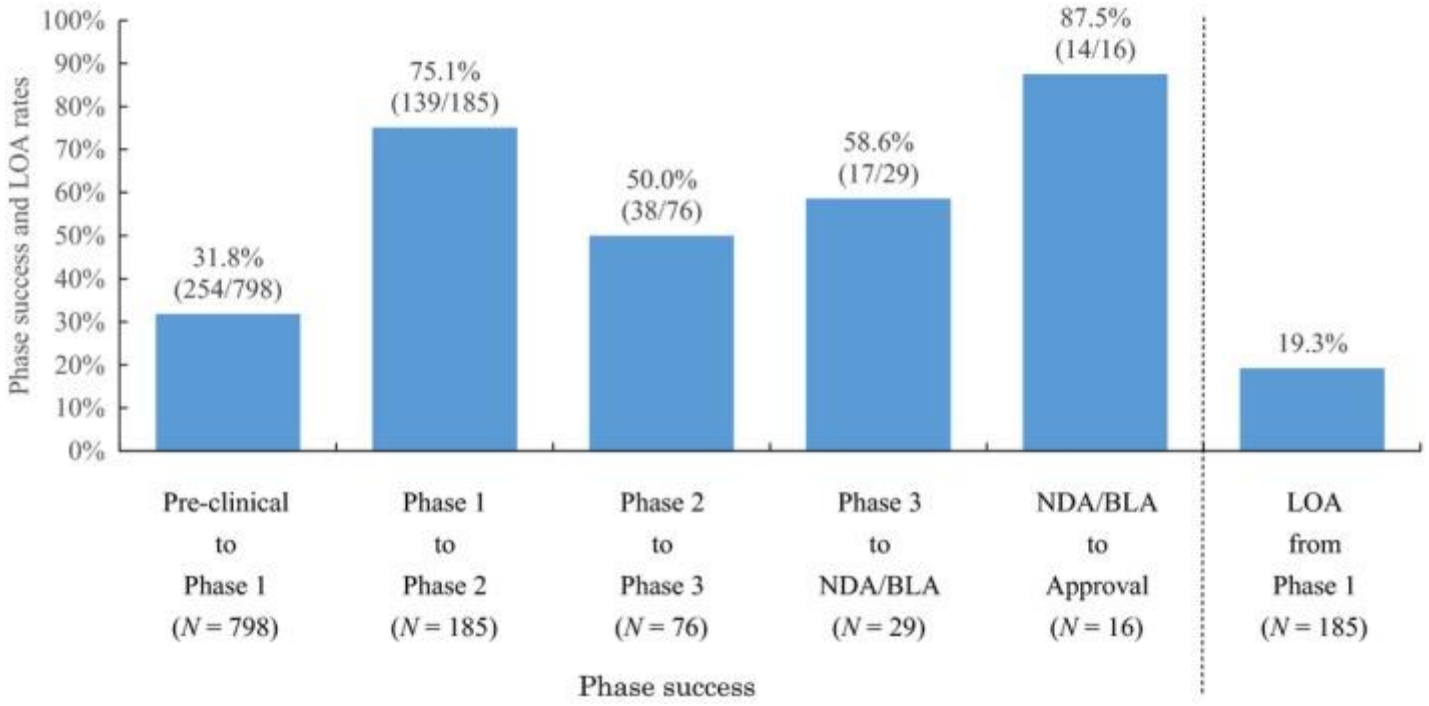


Figure 3: Total R&D expenditure from 1999-2016 by NME development

Taylor Wang (2020) Honor's Thesis: The Relationship Between Pharmaceutical R&D Spending and NME Development, University of California, Berkeley | Department of Economics

A submitted NDA has a high chance of approval



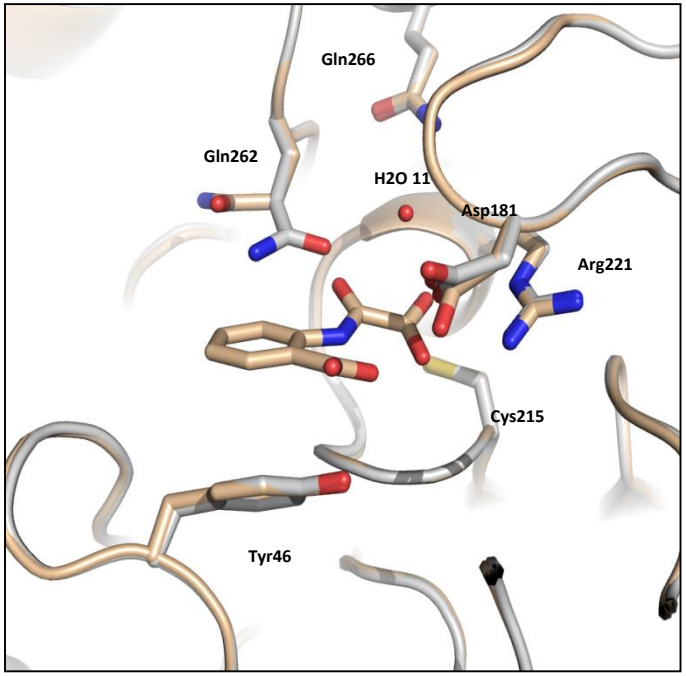
Phase success and likelihood of approvals (LOA) rates of academic drug discovery and development that was begun between 1991 and 2010. NDA/BLA, new drug application/biologics license application.

Takebe, T et al. (2018) The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development. Clin Transl Sci. Nov; 11(6): 597

Structure-based drug design (SBDD)

- Develop new drug candidates for a disease
- Protein target relevant for the disease
- Relies on knowledge of the protein 3D structure
- Find compounds that block (or enhance) protein activity by binding to:
  - catalytic site
  - allosteric site (better for selectivity)
- Structural information of protein-ligand interaction is used to develop new compounds with increased potency and selectivity

PTP1B co-crystallised with OBA



Examples of drugs developed using SBDD

- Dorzolamide (Merck, 1995) – first SBDD approved drug (anti-glaucoma agent; carbonic anhydrase inhibitor)

- Imatinib (Novartis, 2001) – first anti-cancer drug substantially different from previous anti-cancer drugs (inhibitor of the tyrosine kinase *bcr-abl*)

- Vemurafenib (Roche, 2011) – first FBDD approved drug (late stage melanoma; inhibitor of B-Raf (V600E)) - only 6 years from fragment to approval!

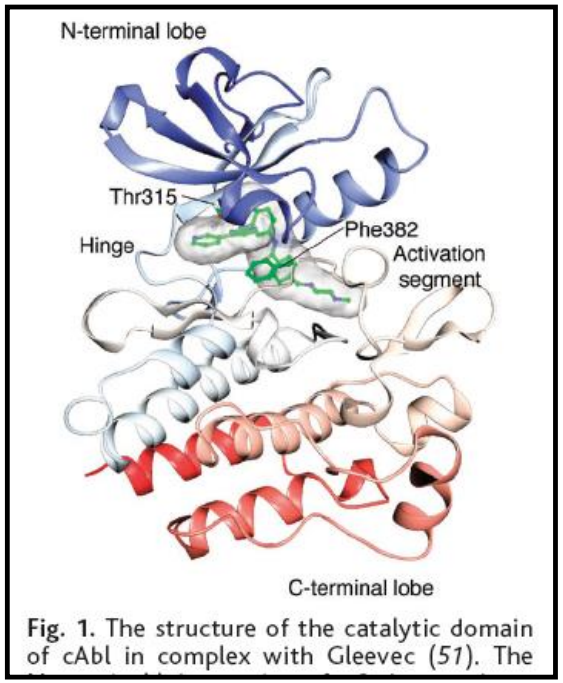
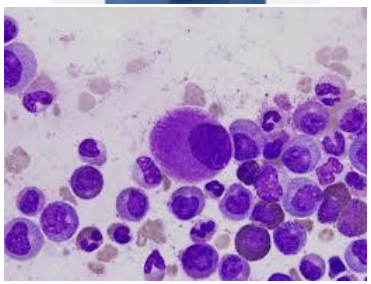
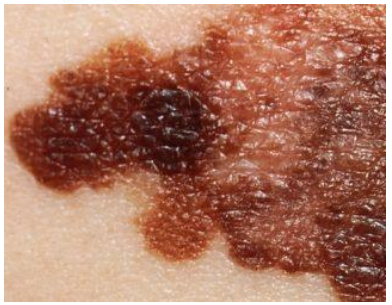
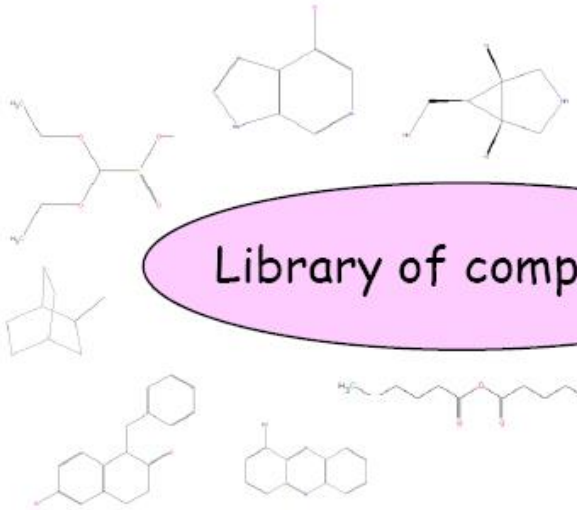


Fig. 1. The structure of the catalytic domain of cAbl in complex with Gleevec (*51*). The





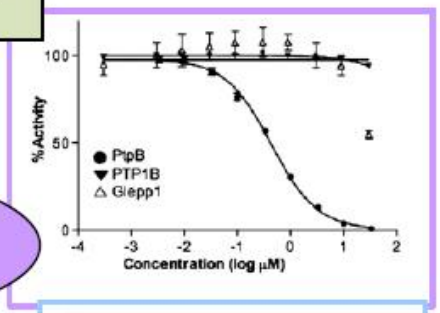
Structure-based drug discovery (SBDD)



Protein overexpression

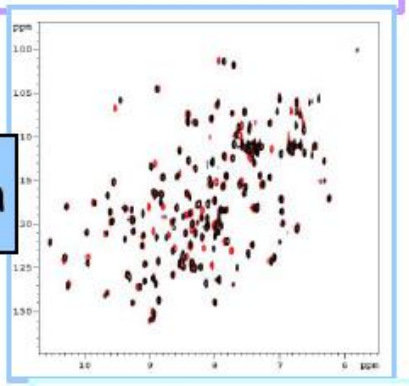
Library of compounds

Screening assay

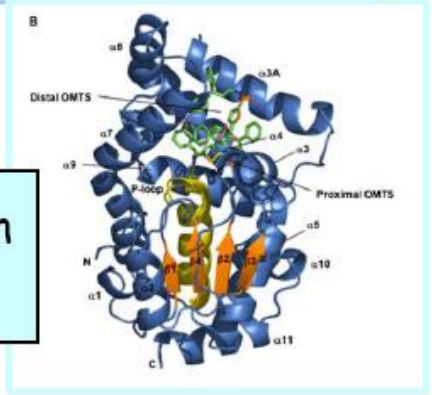


Hits

NMR screening/validation



Positive hits



3D structure determination protein-ligand complex

Optimization of ligand affinity and selectivity

+

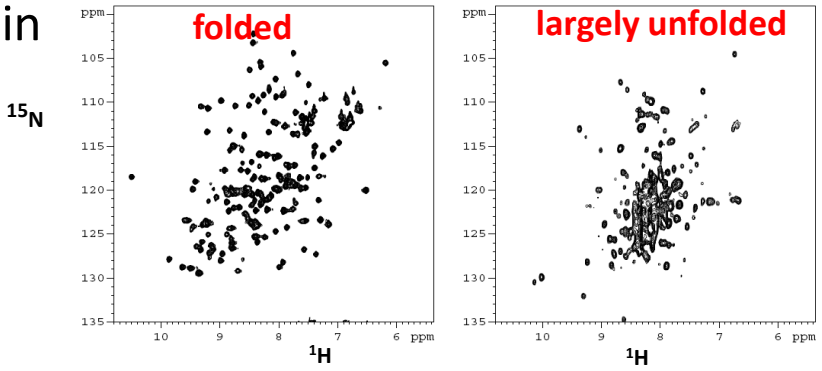
Early ADMET-PK

The essentials of a SBDD project

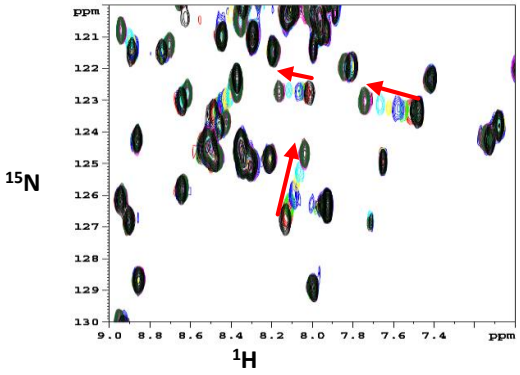
- **Protein:**
  - Easily overexpressed to high amounts
  - Stable (ideally can be frozen or lyophilised)
  - Folded
  - Suitable for structural biology: i.e. crystallised into robust (compound soaking) and high-symmetry crystals (reduced acquisition time)
- **Chemical library:**
  - High-purity (> 95%)
  - High amounts (up to 50 mg)
  - Highly soluble in DMSO and water
  - Without reactive or unstable molecules
- **Infrastructure and technology:**
  - Wet-lab with biophysical equipment
  - High-field NMR spectrometers
  - Crystallography facility and access to synchrotron
  - CryoEM facility
- **Chemistry support**

NMR in drug discovery

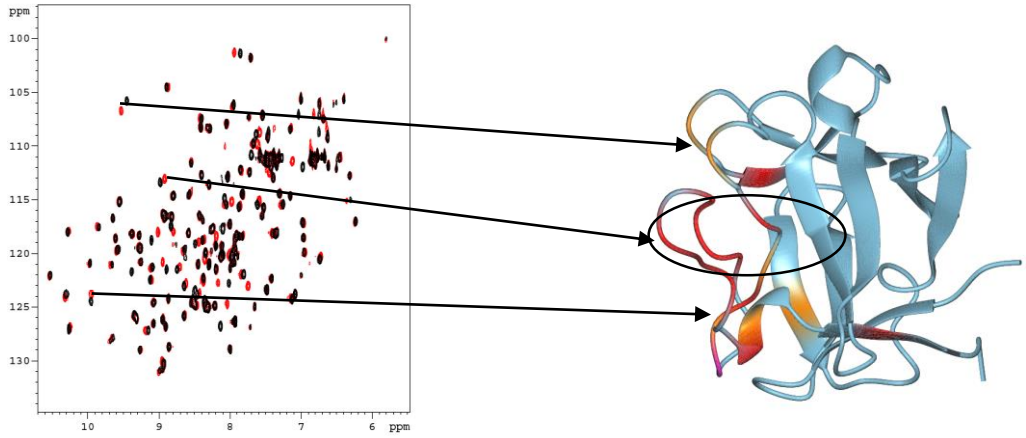
- Construct optimization of the target protein



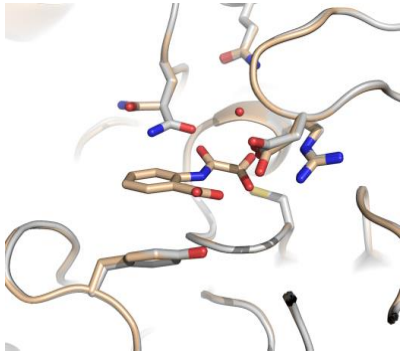
- NMR screening and hit validation



- Map the ligand-binding site

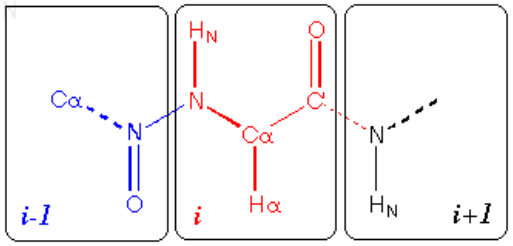


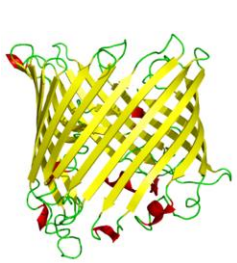
- Characterize the protein-ligand interaction

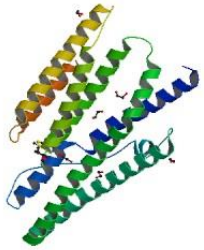


- Protein-ligand structure determination

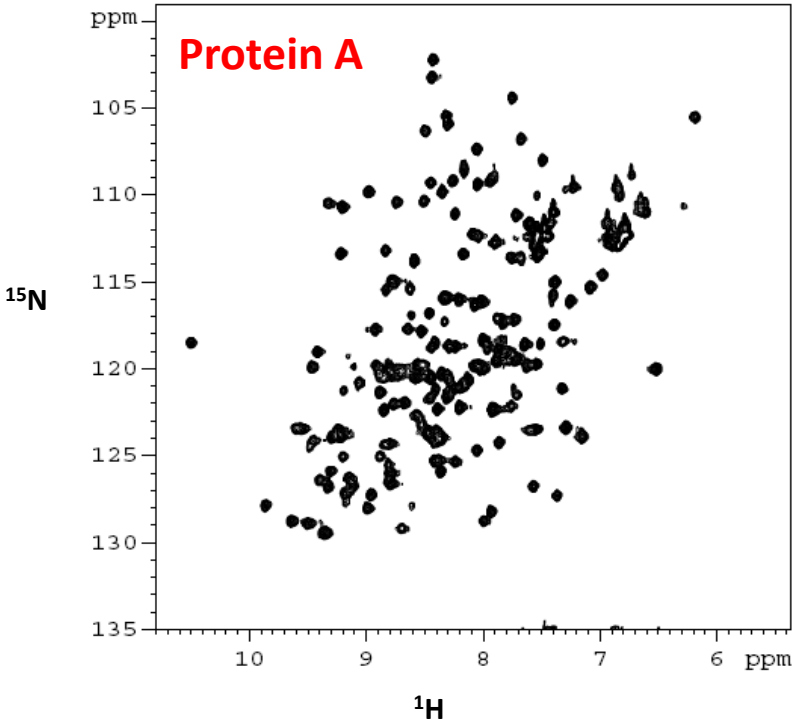
Is the protein folded?

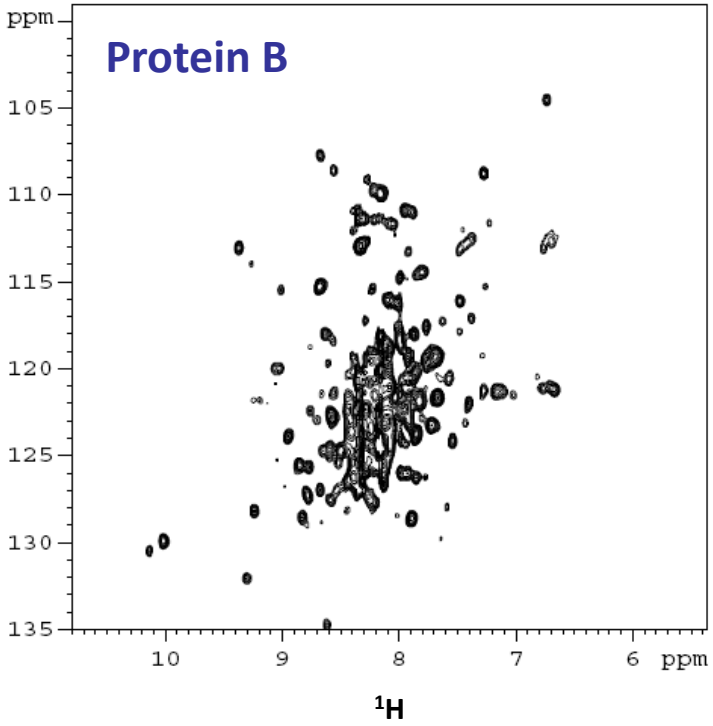






~ 200 amino acid residues





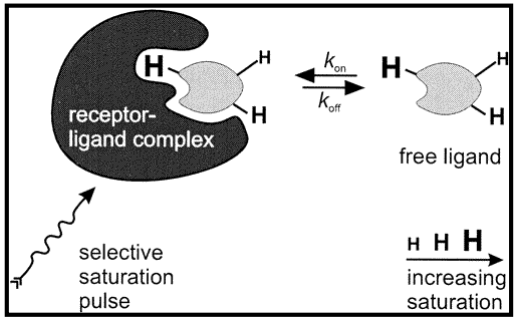
Nicely folded

Largely unfolded

⇒ Improve construct/NMR conditions

NMR screening and validation

- NMR detects ligand binding mM $\rightarrow$ nM
- Specific binding can be distinguished from unspecific binding
- False positive identification
- Different pH, salt, buffer or redox conditions can be chosen



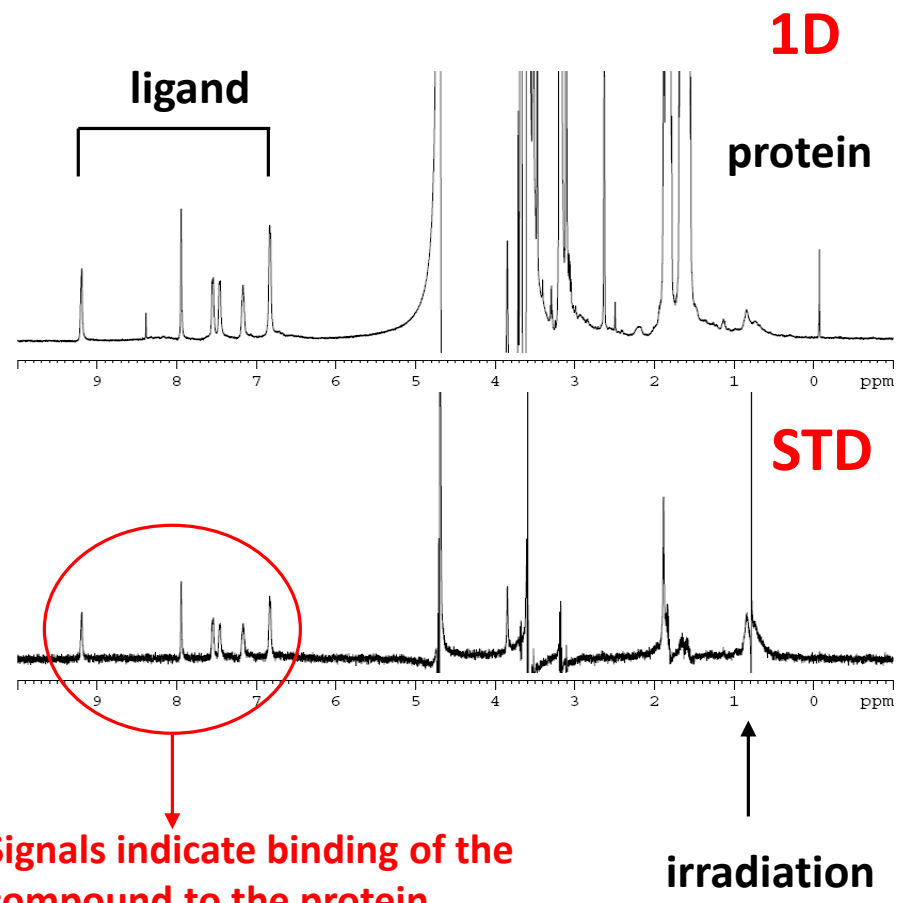
1D screening

Saturation Transfer Difference (STD) experiments

- Fast
- Unlabelled protein
- Low protein concentrations (~20 μM)
- Compound soluble in buffer (maximum DMSO levels 20%)
- Binding epitope can be inferred

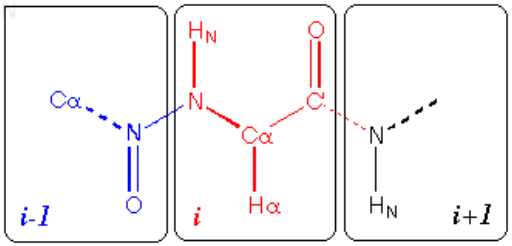
Problems:

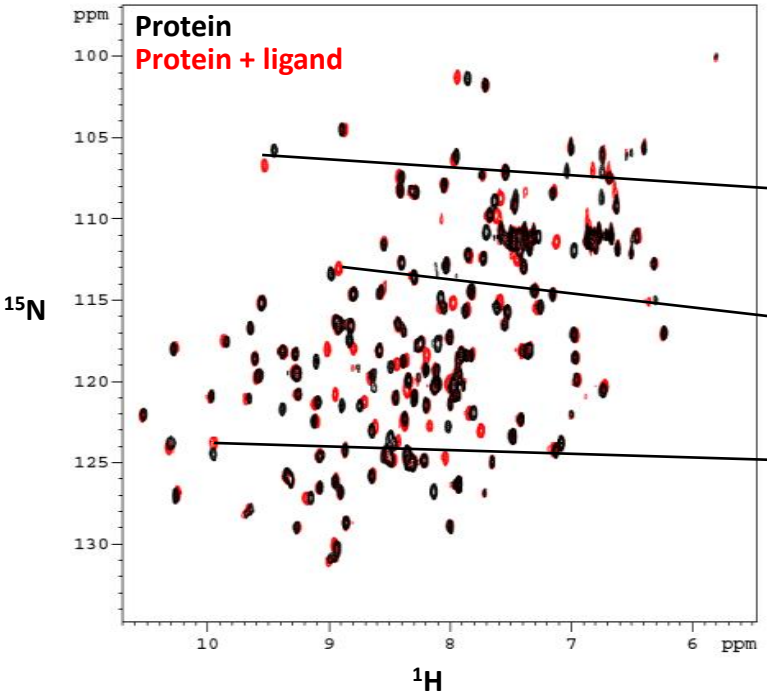
- STD signals but non-specific interaction
- No STD signals but specific binding

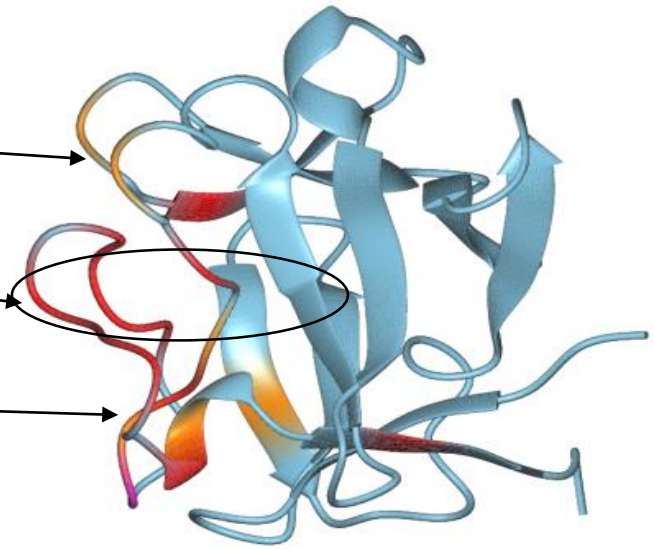


2D screening

- Identifies specific binding epitopes
- Requirements:
  - ^{15}N-labelled protein
  - Assignment and 3D structure of the protein

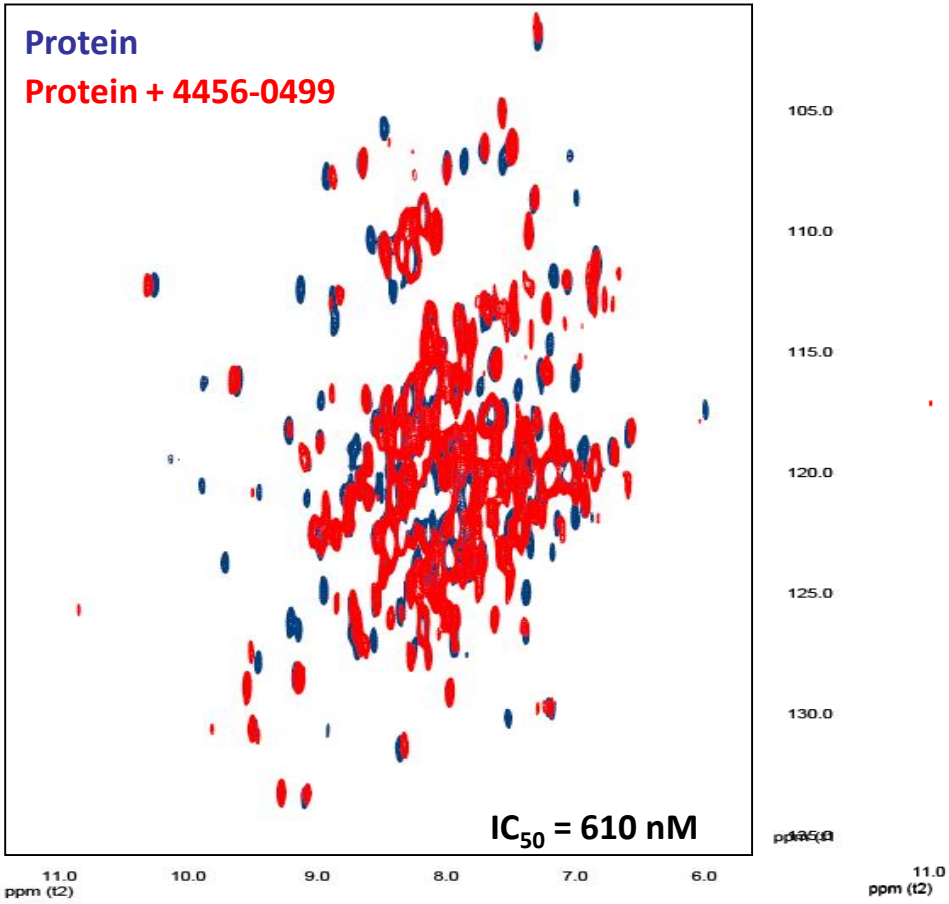






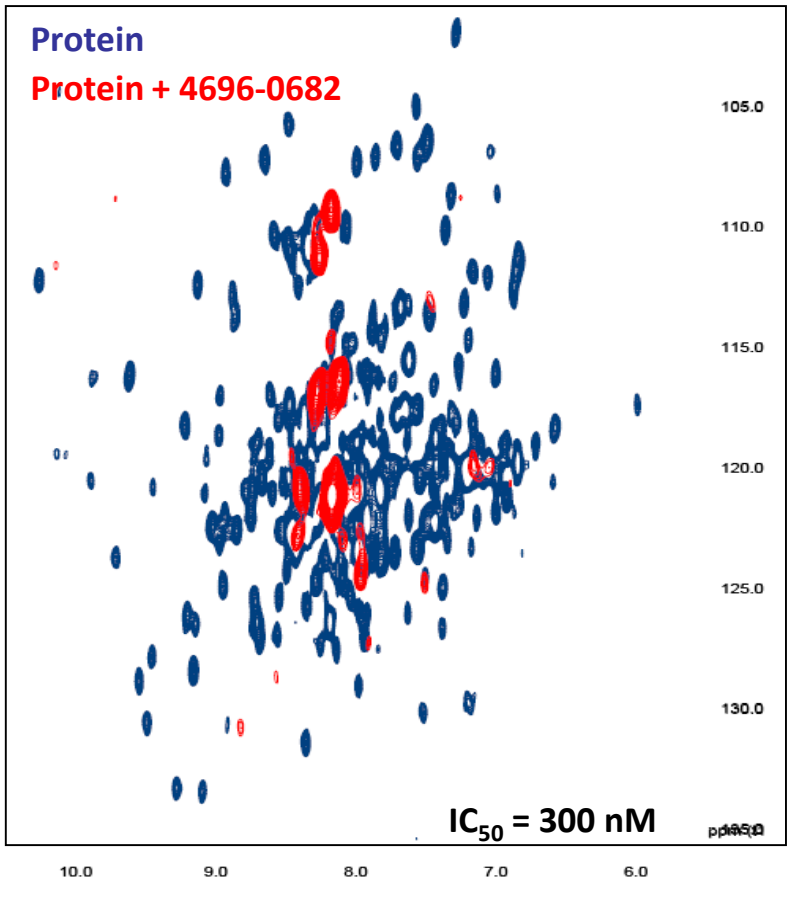
Chemical shift perturbations mapping

Hit validation



Significant shifts

Positive hit

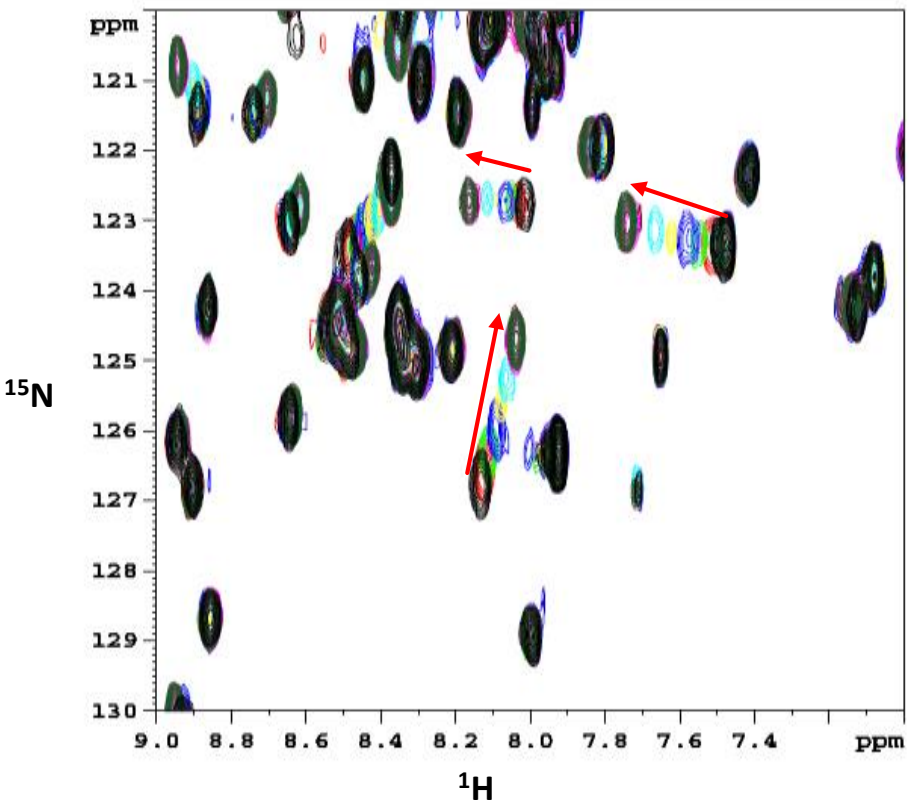


Protein precipitation

False positive hit

Characterizing protein-ligand interactions

Determining the protein-ligand affinity (K_D)



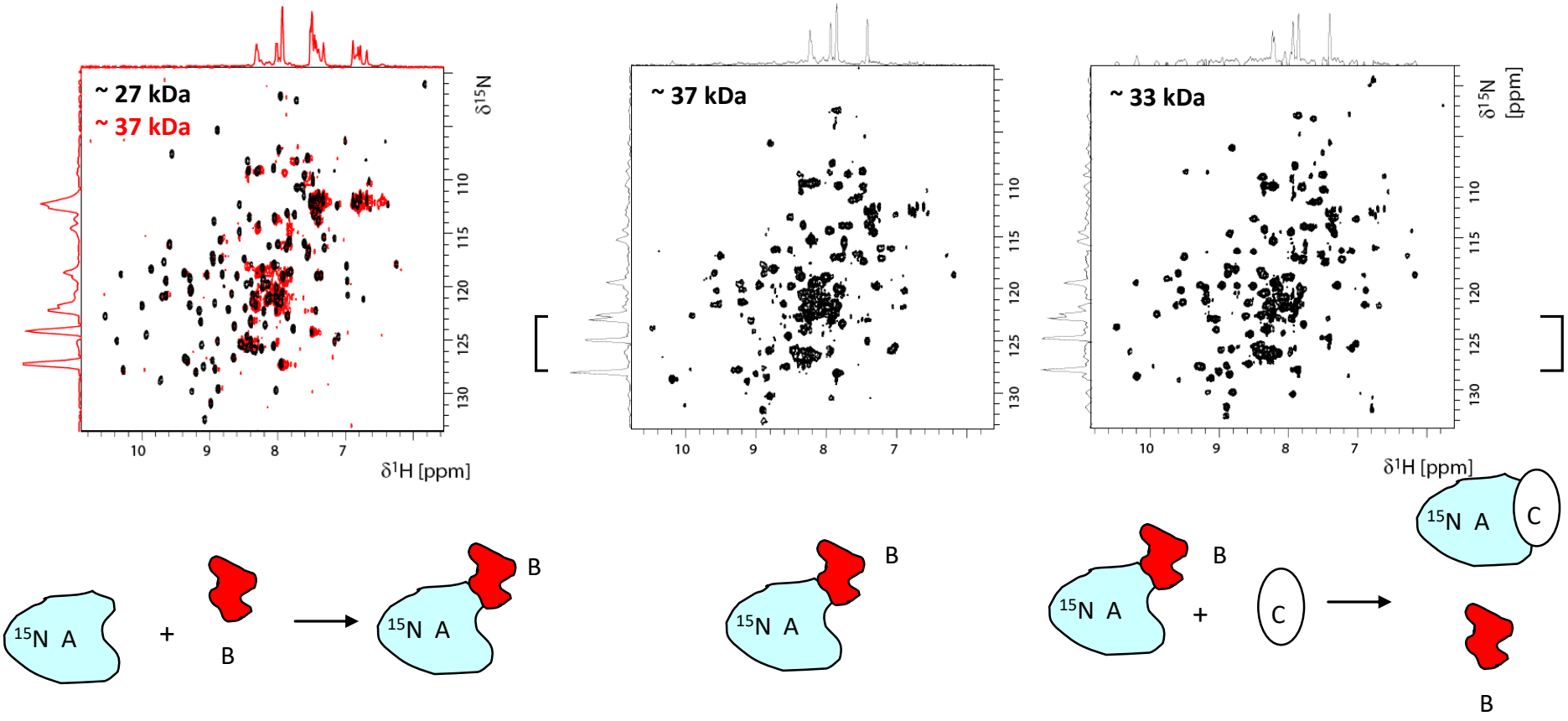
Ligand titration by NMR

Limitations:

- Simple systems
- Fast exchange
- mM → µM binding
- Higher affinities – other techniques *e.g.* ITC

Determining how the ligand exerts its action

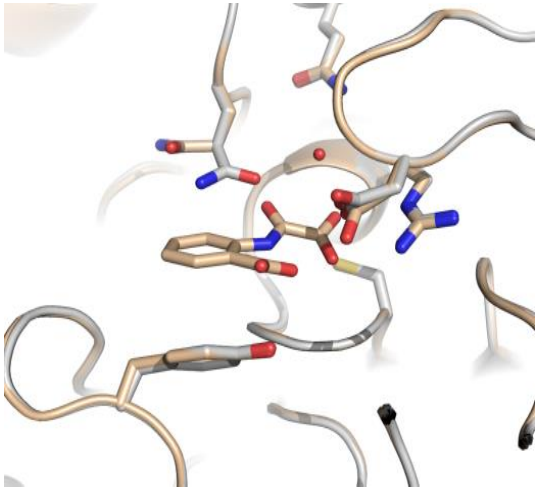
T_2 estimation



Inhibition of the interaction with biological partners

3D structure determination

- 3D structure determination of protein-ligand complexes
- High-resolution – fine details of ligand-protein interactions can be determined and used to improve affinity or selectivity of the compound
- **Crystallography**: fast (once you get crystals!)
- **NMR spectroscopy**: slow and limited to smaller complexes (< 100 kDa)
- **Cryo-EM:** limited to larger complexes (>100 kDa), resolution usually ~3 Å



FBDD drugs (June 2023)

Drug	Company	Target	Disease	FDA Approval
Asciminib	Novartis	BCR-ABL1	Cancer	2021
Erdafitinib	Astex/J&J	FGFR1-4	Cancer	2019
Pexidartinib	Plexxikon	CSF1R, KIT	Tumor	2019
Sotorasib	Amgen	$KRAS^{G12C}$	Cancer	2021
Vemurafenib	Plexxikon	$B\text{-}RAF^{V600E}$	Cancer	2011
Venetoclax	AbbVie/Genentech	Selective BCL-2	Cancer	2016

THE NMEs OF 2011

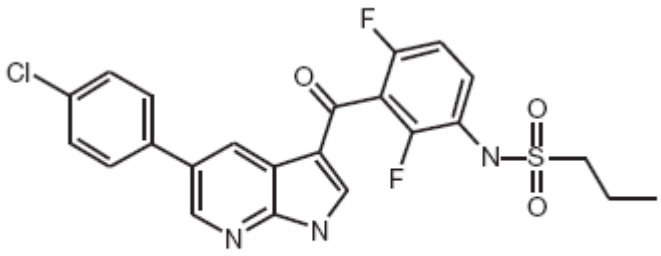
Drug Name	Active Ingredient	Date	What it's used for
Eylea	aflibercept	11/18	To treat wet (neovascular) age-related macular degeneration (AMD), a leading cause of vision loss and blindness in Americans ages 60 and older.
Erwinaze	asparaginase Erwinia chrysanthemi	11/18	For patients with acute lymphoblastic leukemia (ALL), who have developed an allergy (hypersensitivity) to E. coli derived asparaginase and pegapargase chemotherapy drugs used to treat ALL.
Jakafi	ruxolitinib	11/16	To treat patients with the bone marrow disease myelofibrosis.
Onfi	clobazam	10/24	For use as an adjunctive (add-on) treatment for seizures associated with Lennox-Gastaut syndrome in adults and children 2 years of age and older.
Ferriprox	deferiprone	10/14	Iron overload from blood transfusions in patients with thalassemia (genetic disorder causing anemia), who had an inadequate response to chelation therapy.
Xalkori	crizotinib	08/26	Certain patients with late-stage (locally advanced or metastatic), non-small cell lung cancers who express the abnormal anaplastic lymphoma kinase gene.
Firazyr	icatibant	08/25	For the treatment of acute attacks of a rare condition called hereditary angioedema (HAE) in people ages 18 years and older.
Adcetris	brentuximab vedotin	08/19	Hodgkin lymphoma and ALCL (systemic anaplastic large cell lymphoma).
Zelboraf	vemurafenib	08/17	To treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma, the most dangerous type of skin cancer.
Brilinta	ticagrelor	07/20	To reduce cardiovascular death and heart attack in patients with acute coronary syndromes (ACS).
Xarelto	rivaroxaban	07/01	To reduce the risk of blood clots, deep vein thrombosis (DVT), and pulmonary embolism (PE) following knee or hip replacement surgery.
Arcapta Neohaler	indacaterol inhalation powder	07/01	For the long term, once-daily maintenance bronchodilator treatment of airflow obstruction in people with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.
Nulojix	belatacept	06/15	To prevent acute rejection in adult patients who have had a kidney transplant.
Potiga	ezogabine	06/10	An add-on medication to treat seizures associated with epilepsy in adults.

CY 2011 New Molecular Entities (NMEs)

Drug Name	Active Ingredient	Date	What it's used for
Dificid	fidaxomicin	05/27	For the treatment of *Clostridium difficile*-associated diarrhea (CDAD).
Incivek	telaprevir	05/23	To treat certain adults with chronic hepatitis C infection.
Edurant	rilpivirine	05/20	Treatment of HIV-1 infection in adults who have never taken HIV therapy.
Victrelis	boceprevir	05/13	To treat certain adults with chronic hepatitis C.
Tradjenta	linagliptin	05/02	Addition to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Zytiga	abiraterone acetate	04/28	In combination with prednisone to treat patients with late-stage (metastatic) castration-resistant prostate cancer who have received docetaxel (chemotherapy).
Caprelsa	vandetanib	04/06	To treat adult patients with late-stage (metastatic) medullary thyroid cancer, ineligible for surgery who have disease that is growing or causing symptoms.
Horizant	gabapentin enacarbil	04/06	A once-daily treatment for moderate-to-severe restless legs syndrome (RLS).
Yervoy	ipilimumab	03/25	Late-stage (metastatic) melanoma, the most dangerous type of skin cancer.
Gadavist	gadobutrol	03/14	Magnetic resonance imaging (MRI) of the central nervous system.
Benlysta	belimumab	03/10	To treat patients with active, autoantibody-positive lupus (systemic lupus erythematosus) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs.
Daliresp	roflumilast	02/28	To decrease the frequency of flare-ups (exacerbations) or worsening of symptoms from severe chronic obstructive pulmonary disease (COPD).
Edarbi	azilsartan medoxomil	02/25	To treat high blood pressure (hypertension) in adults.
Viibryd	vilazodone HCl	01/21	To treat major depressive disorder in adults.
Natroba	spinosad	01/18	For the treatment of head lice infestation in patients ages 4 years and older.
Datscan	ioflupane i-123	01/14	An imaging drug used to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS).

First fragment-based drug approved 17/08/2011

The story of vemurafenib (ZELBORAF)



PLX4032

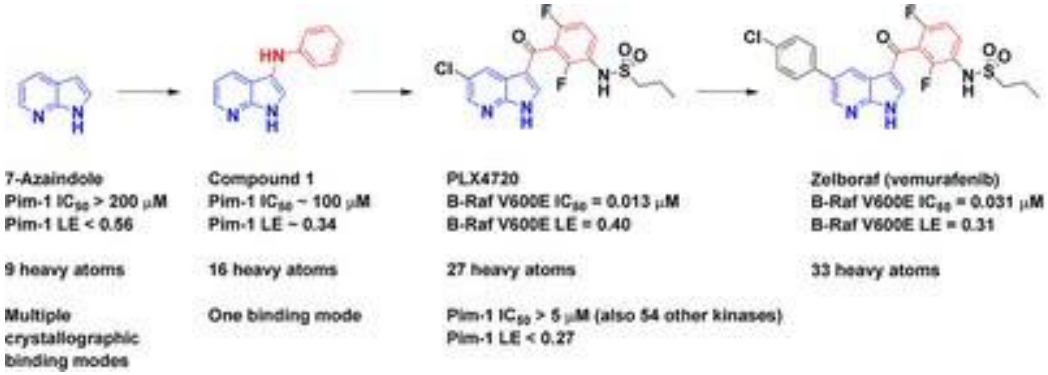
Vemurafenib=PLX4032

- Drug discovered at Plexxikon in partnership with Roche; Plexxikon acquired by Daiichi Sankyo
- 6 years from fragment to approval!

- Treatment of late stage melanoma
- Targets B-Raf (V600E), a Ser-Thr protein kinase
- 50% melanomas carry this mutation
- B-Raf most frequently mutated kinase in human cancers
- Increases survival by approximately 5 months longer
- $9400 /month

Compound evolution

- Initial screen of a 20000 compound library against the ATP-binding site of 3 kinases (Pim-1, CSK, p38)



7-Azaindole	Compound 1	PLX4720	Zelboraf (vemurafenib)
Pim-1 IC_{50} > 200 μM Pim-1 LE < 0.56	Pim-1 IC_{50} ~ 100 μM Pim-1 LE ~ 0.34	B-Raf V600E IC_{50} = 0.013 μM B-Raf V600E LE = 0.40	B-Raf V600E IC_{50} = 0.031 μM B-Raf V600E LE = 0.31
9 heavy atoms	16 heavy atoms	27 heavy atoms	33 heavy atoms
Multiple crystallographic binding modes	One binding mode	Pim-1 IC_{50} > 5 μM (also 54 other kinases) Pim-1 LE < 0.27	

Zelboraf (PLX4032) has better pharmacokinetic properties in dogs and monkeys than PLX4720

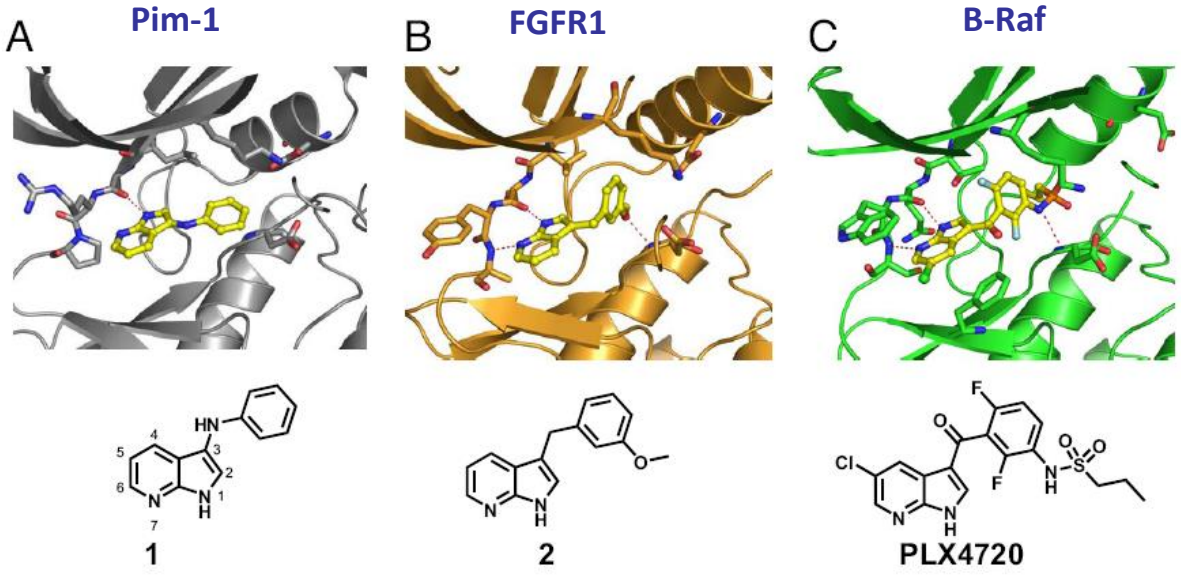


Fig. 1. Structures of individual compounds leading to the discovery of PLX4720 are shown. (*A*) The chemical structure of 3-aminophenyl-7-azaindole (compound 1) is shown beneath its costructure with Pim-1 kinase. (*B*) The chemical structure of 3-(3-methoxybenzyl)-7-azaindole (compound 2) is shown beneath its costructure with the kinase domain of FGFR1. (*C*) The chemical structure of PLX4720 is shown beneath its costructure with B-Raf kinase.

Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity.
Tsai J. et al. Proc Natl Acad Sci U S A. 2008 Feb 26;105(8):3041-6

PLX4720 binds preferentially to active B-Raf

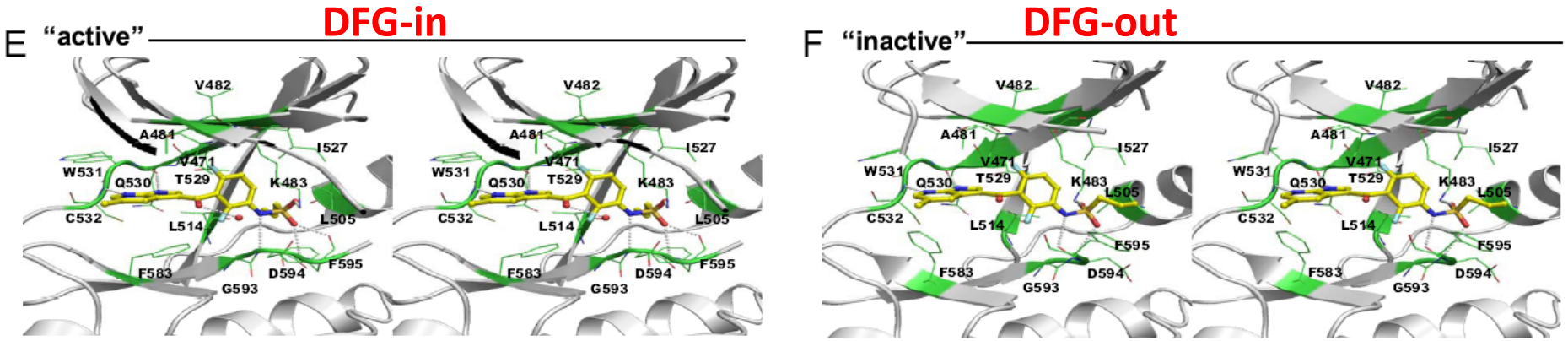
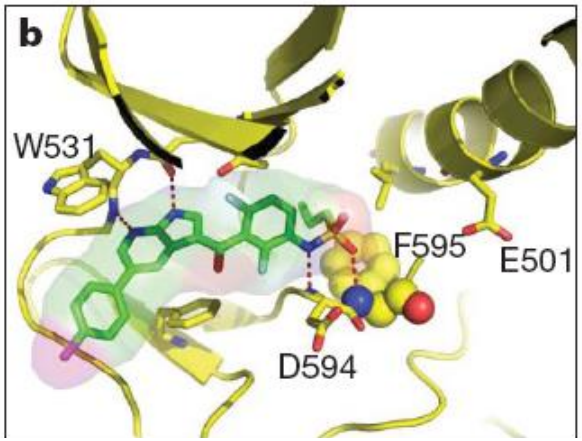


Fig. 2. Depiction of the three-dimensional structure of PLX4720 bound to B-Raf. (*A*) The structure of B-Raf^{V600E} bound to PLX4720 (yellow) is overlayed with an ATP model based on structures of ATP analogs in complex with other tyrosine kinases (orange). This view indicates that the PLX4720 scaffold overlaps with the adenine-binding site, but the tail of PLX4720 binds to a different pocket from the ATP ribose-triphosphate tail. The positions of the hinge, activation loop (A-loop), and phosphate-binding loop (P-loop) are also shown. (*B*) A surface representation shows PLX4720 binding to the B-Raf-selective pocket in the active conformation. (*C*) A surface representation shows PLX4720 binding to the kinase general pocket in the inactive conformation. (*D*) A close-up view shows the overlay PLX4720 bound to both active (green) and inactive (purple) conformations of the V600 protein, and PLX3203 (yellow) bound to V600E protein in the active kinase conformation. (*E*) A stereoview shows the specific interactions of PLX4720 to the active kinase conformation. In this conformation, the phenylalanine of the DFG loop is pointing in toward the compound-binding site. (*F*) A stereoview shows the specific interactions of PLX4720 to the inactive kinase conformation. In this conformation, the phenylalanine of the DFG loop is pointing away from the compound-binding site, and binding of PLX4720 is disfavored, leading to partial occupancy of this site even at the 1 mM compound concentration used in cocrystallography.

Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity.
Tsai J, *et al.* Proc Natl Acad Sci U S A. 2008 Feb 26;105(8):3041-6

B-Raf(V600E) in complex with PLX4032



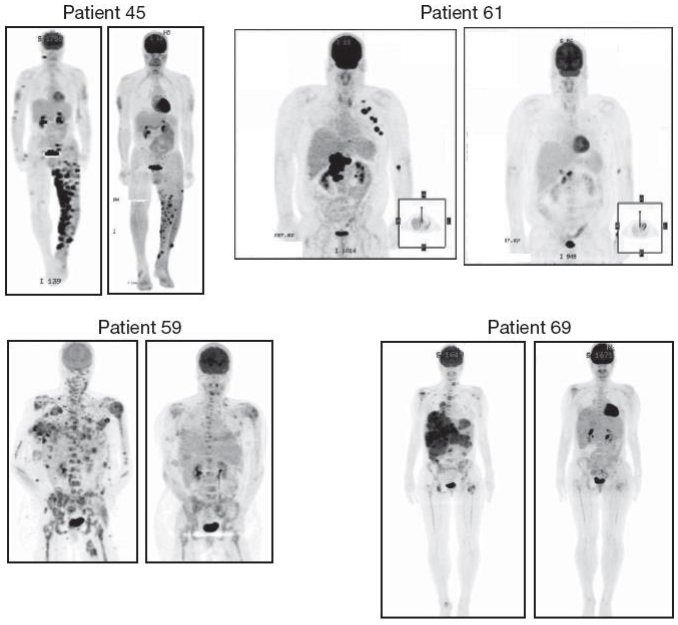


Figure 4 | Representative PET scans for patients taken pre-dose and following 2 weeks of dosing with PLX4032. Each of these image pairs demonstrates significant reduction in FDG uptake following PLX4032 treatment. Note that tumour regressions were later documented for each of these patients: best responses were 70% for patient 45, 70% for patient 59, 68% for patient 61 and 37% for patient 69.

Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Bollag G, *et al.* Nature. 2010, 467:596

Supplementary Table 1. Biochemical IC_{50} determinations of the kinase inhibitory activity of PLX4032 versus a panel of kinases

Assay	IC_{50} nM*
B-RAF-V600E	31
C-RAF	48
B-RAF	100
SRMS	18
ACK1	19
MAP4K5 (KHS1)	51
FGR	63
LCK	183
BRK	213
NEK11	317
BLK	547
LYNB	599
YES1	604
WNK3	877
MNK2	1717
FRK (PTK5)	1884
CSK	2339
SRC	2389

*A list of over 200 kinases minimally affected by PLX4032 is included below.
Note that all RAF enzymes and SRMS were assayed at an ATP concentration of 100 µM, while all other kinases in the table above were assayed at an ATP concentration of 10 µM.

Kinases with <20% Inhibition at 1 µM:
ABL1, ABL2, ADRBK1, AMPK_A2, ARK5, Aurora_A-C, BMX, CDC42_BPA, CAMK2A, CDK5_p35, CSF1R, DYRK1B, EPHA5, EPHA8, EPHB4, FES, FLT3, FYN, GSK3beta, JAK1, KDR, KIT, MAP4K2, MAPK3, MARK2, MARK4, MATK, MET, MINK1, NEK1, NEK2, PAK3, PAK6, PDGFRbeta, PHKG1, PKBalpha, PKC_beta_I, PKC_beta_II, PKC_delta, PKC_gamma, PKC_zeta, SRC, STK4, STK24

Kinases with <10% Inhibition at 1 µM:
ACVR1B_(ALK4), ADRBK2_(GRK3), ALK, AMPK_A1/B1/G1, ASK1, AXL, BRSK1_(SAD1), BrSK2, BTK, CAMK1, CAMK1D, CAMK2B, CAMK2D, CaMKIdelta, CaMKIIbeta, CaMKIIdelta, CaMKIIgamma,,CDC42_BPB, CDK1/CyclinB, CDK2/CyclinA, CDK2/cyclinE, CDK3/cyclinE, CDK5_p25, CDK6/cyclinD3, CDK7/CyclinH/MNAT1,CDK9/CyclinT1, CHEK1, CHEK2, CK1delta, CK1gamma1, CK1gamma2, CK1gamma3, CK2alpha2, CLK1, CLK2, CLK3, CSNK1A1, CSNK1D, CSNK1E, CSNK1G1, CSNK1G2, CSNK1G3, CSNK2A1, CSNK2A2, DAPK1, DAPK2, DAPK3_(ZIPK), DCAMKL2_(DCK2), DDR2, DMPK, DRAK1, DYRK1A, DYRK2, DYRK3, DYRK4, EEF2K, EGFR, EPHA1, EPHA2, EPHA3 EPHA4, EPHA7, EPHB1, EPHB2, EPHB3, ERBB2, ERBB4, FER, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT4, FRAP1, GCK, GRK4, GRK5, GRK6, GRK7, GSK3A, HCK, HIPK, HIPK2, HIPK3, HIPK4, IGF1R, IGF-1R, IKBKB, IKBKE IKKalpha, IKKbeta, INSR, INSRR, IRAK1, IRAK4, ITK, JAK2, JAK2_JH1_JH2, JAK3, JNK1alpha1, JNK2alpha2, LCK, LIMK1, LKB1, LOK, LTK, MAP2K1, MAP2K2, MAP2K6, MAP3K8, MAP3K9, MAP4K4, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK2, MAPK8, MAPK9, MAPKAPK2, MAPKAPK3, MAPKAPK5, MARK1, MARK3, MELK, MERTK, MKK7beta, MLCK, MRCKalpha, MRCKbeta, MST1R, MST4, mTOR/FKBP12, MUSK, NEK3, NEK4, NEK6, NEK7, NEK9, NLK, NTRK1, NTRK2, NTRK3, PAK2, PAK4, PAK7_(KIAA1264), PAR-1Balpha, PASK, PDGFRalpha, PDK1, PHKG2, PIK3CA/PIK3R1, PIK3CG, PIM1, PIM2, PIM-3, PKBbeta, PKBgamma, PKCalpha, PKCepsilon, PKCeta, PKCiota, PKCmu, PKCtheta, PKG1alpha, PKG1beta, PKN1, PLK2, PLK3, PRK2, PRKACA, PRKC PRKCE, PRKCH, PRKCI, PRKCN, PRKCQ, PRKD1, PRKD2, PRKG1, PRKG2, PRKX, PTK2, PTK2B, RET, RIPK2, ROCK1, ROCK2, ROS1, RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA4, RPS6KA5, RPS6KA6, RPS6KB1, SGK, SGK2, SGKI SIK, SNF1LK2, SNK, SRPK1, SRPK2, STK3, STK22B, STK22D, STK23, STK25, STK33, SYK, TAK1, TAO3, TAOK2, TBK1, TEC, TEK, TLK2, TXK, TYK2, TYRO3, ULK2, ULK3, VRK2, WNK2, WNK3, ZAP70

Problems: PLX4032 has low brain-blood barrier permeability

THE NOVEL DRUGS OF 2016

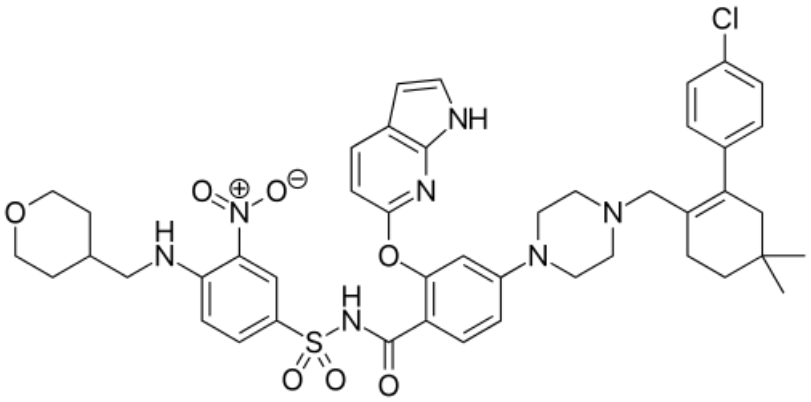
CDER's Novel Drug Approvals of 2016 (Listed in order of approval date).

Drug Name	Active Ingredient	Approval Date	What it is used for
Zepatier	elbasvir; grazoprevir	01/28/2016	To treat patients with chronic hepatitis C virus (HCV) genotypes 1 and 4 infections in adult patients.
Briviact	brivaracetam	02/18/2016	To treat partial onset seizures in patients age 16 years and older with epilepsy.
Anthim	obiltoxaximab	03/18/2016	To treat inhalational anthrax in combination with appropriate antibacterial drugs.
Taltz	ixekizumab	03/22/2016	To treat adults with moderate-to-severe plaque psoriasis.
Cinqair	reslizumab	03/23/2016	To treat severe asthma
Defitelio	defibrotide sodium	03/30/2016	To treat adults and children who develop hepatic veno-occlusive disease with additional kidney or lung abnormalities after they receive a stem cell transplant from blood or bone marrow called hematopoietic stem cell transplantation
Venclexta	venetoclax	04/11/2016	For chronic lymphocytic leukemia in patients with a specific chromosomal abnormality
Nuplazid	pimavanserin	04/29/2016	To treat hallucinations and delusions associated with psychosis experienced by some people with Parkinson's disease
Tecentriq	atezolizumab	05/18/2016	To treat urothelial carcinoma, the most common type of bladder cancer
Axumin	fluciclovine F-18	05/27/2016	A new diagnostic imaging agent to detect recurrent prostate cancer
Ocaliva	obeticholic acid	05/27/2016	To treat rare, chronic liver disease known as primary biliary cirrhosis
Zinbryta	daclizumab	05/27/2016	To treat multiple sclerosis
Netspot	gallium Ga 68 dotatate	06/01/2016	A diagnostic imaging agent to detect rare neuroendocrine tumors

Drug Name	Active Ingredient	Approval Date	What it is used for
Epclusa	sofosbuvir; velpatasvir	06/28/2016	To treat all six major forms of hepatitis C virus
Xiidra	lifitegrast	07/11/2016	To treat the signs and symptoms of dry eye disease
Adlyxin	lixisenatide	07/27/2016	To improve glycemic control (blood sugar levels)
Exondys 51	eteplirsen	09/19/2016	To treat patients with Duchenne muscular dystrophy
Lartruvo	olaratumab	10/19/2016	To treat adults with certain types of soft tissue sarcoma
Zinplava	bezlotoxumab	10/21/2016	To reduce the recurrence of Clostridium difficile infection in patients aged 18 years or older
Eucrisa	crisaborole	12/14/2016	To treat mild to moderate eczema (atopic dermatitis) in patients two years of age and older
Rubraca	rucaparib	12/19/2016	To treat women with a certain type of ovarian cancer
Spinraza	nusinersen	12/23/2016	To treat children and adults with spinal muscular atrophy (SMA)

Second fragment-based drug approved 11/04/2016

The story of venetoclax (VENCLEXTA)



venetoclax=ABT-199

- Drug discovered at AbbVie and Genentech; Initial work done at Abbott
- Two decades from initial 3D structure to approval!

- Second generation drug for the treatment of chronic lymphocytic leukemia (CLL)
- Targets Bcl-2, a protein regulator of apoptosis
- Orphan drug for the thousands of patients with relapsed CLL who have 17p deletion
- In the registration trial, 80% of patients showed a partial or complete remission

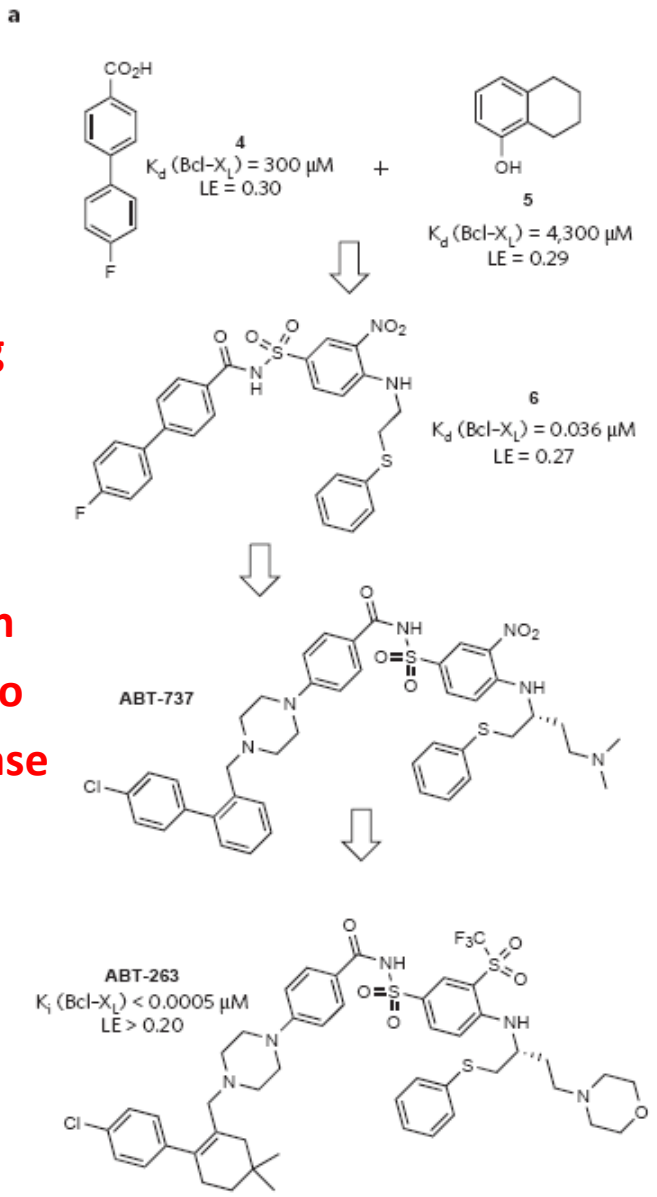
Compound evolution until ABT-263

Fragments

Fragment-linking + optimization

Lead optimization remove binding to albumin and increase affinity to Bcl-2

Improvement oral pharmacokinetics



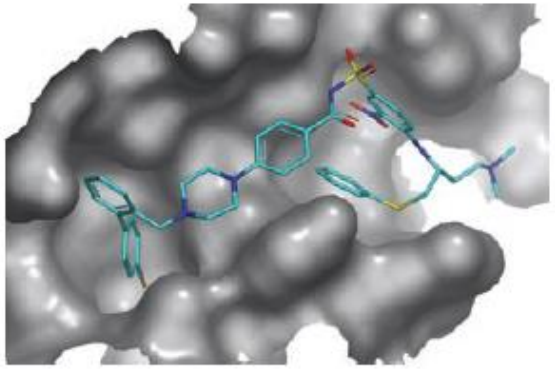
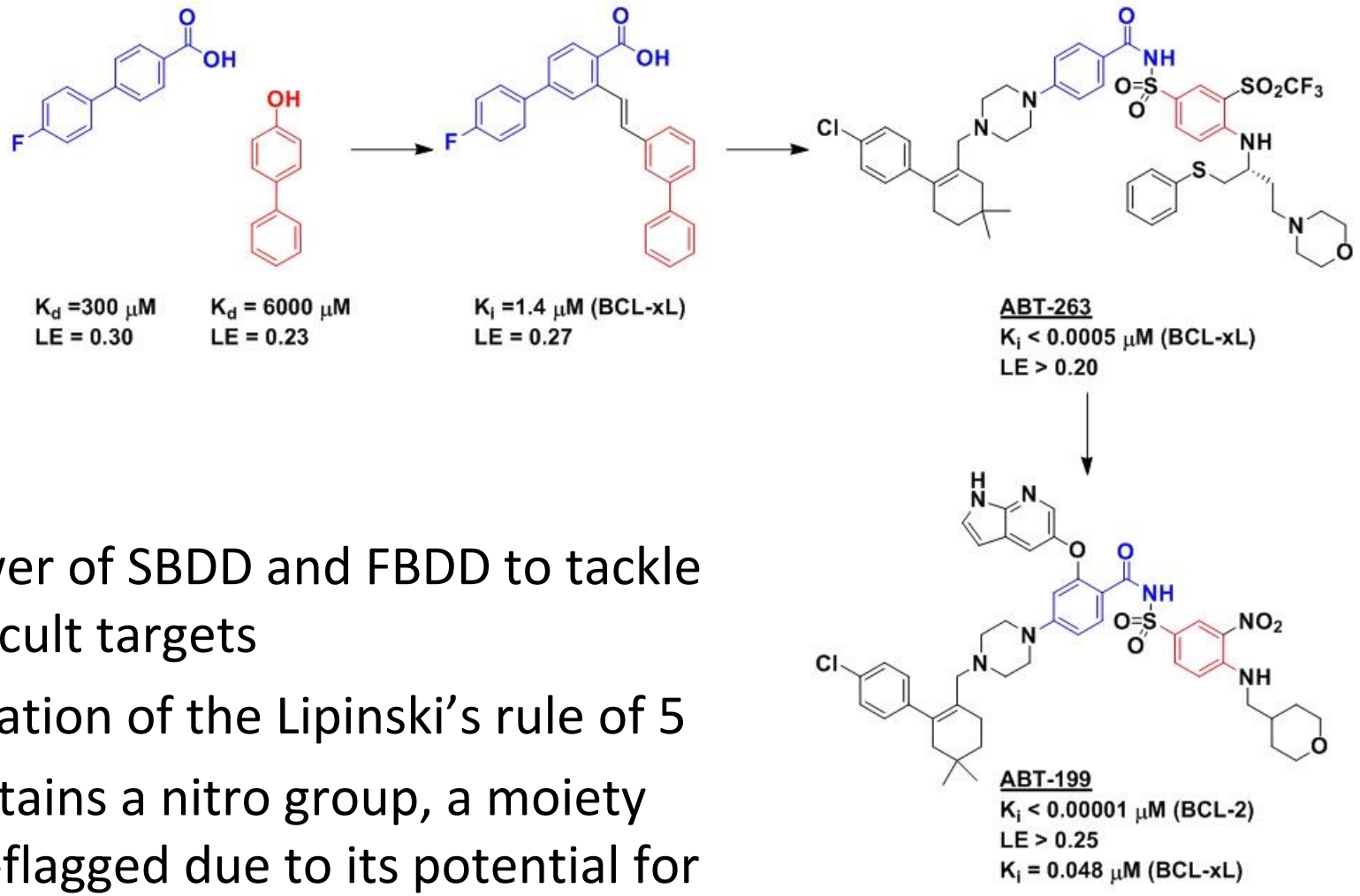


Figure 2 | The discovery of ABT-263, an inhibitor of protein–protein interactions involving Bcl-2 family proteins. a, A 10,000-member fragment library was screened using 2D-NMR leading to the identification of fragment hits **4** and **5**. Subsequent structure determination by NMR spectroscopy showed the compounds bound in proximal pockets and was used in linking the fragments; further elaboration[46,47] led to compound **6**. An early candidate, **ABT-737**, was identified following substantial lead optimization aimed at removing binding to human serum albumin and increasing binding to other Bcl family members[48,49]. The final candidate, **ABT-263**, was discovered following additional iterations of medicinal chemistry focused on improved oral pharmacokinetics[50]. **b**, The experimental binding mode for **ABT-737** on the relatively flat surface of Bcl-X_L.

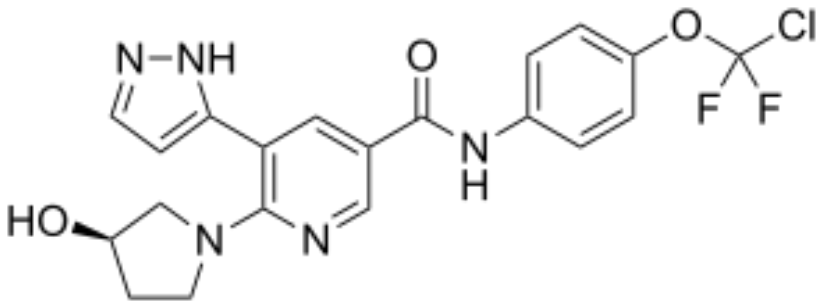
Murray & Rees (2009) The rise of fragment-based drug discovery. Nature Chem. 1: 187-192

Compound evolution until drug



- Power of SBDD and FBDD to tackle difficult targets
- Violation of the Lipinski's rule of 5
- Contains a nitro group, a moiety red-flagged due to its potential for forming toxic metabolites

The story of Asciminib (Scemblix)



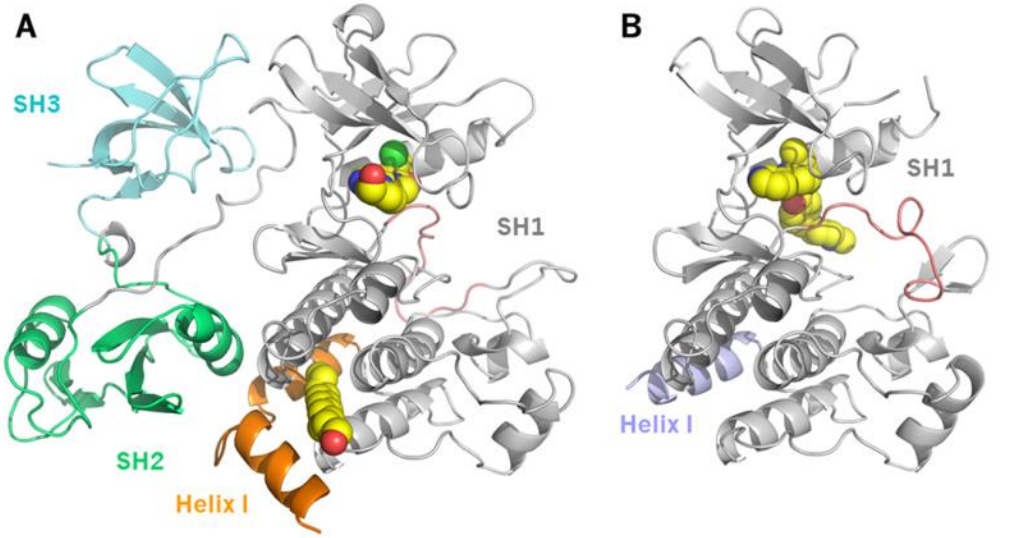
Asciminib=ABL001

- Drug discovered at Novartis
- First allosteric inhibitor of a protein kinase
- Targets myristoylation site

- Treatment of Chronic myelogenous leukemia (CML)
- Targets BCR-ABL1 T315I, a protein tyrosine-kinase
- Asciminib binds to the myristate pocket of BCR-ABL1 and maintains activity against TKI-resistant ATP-site mutations

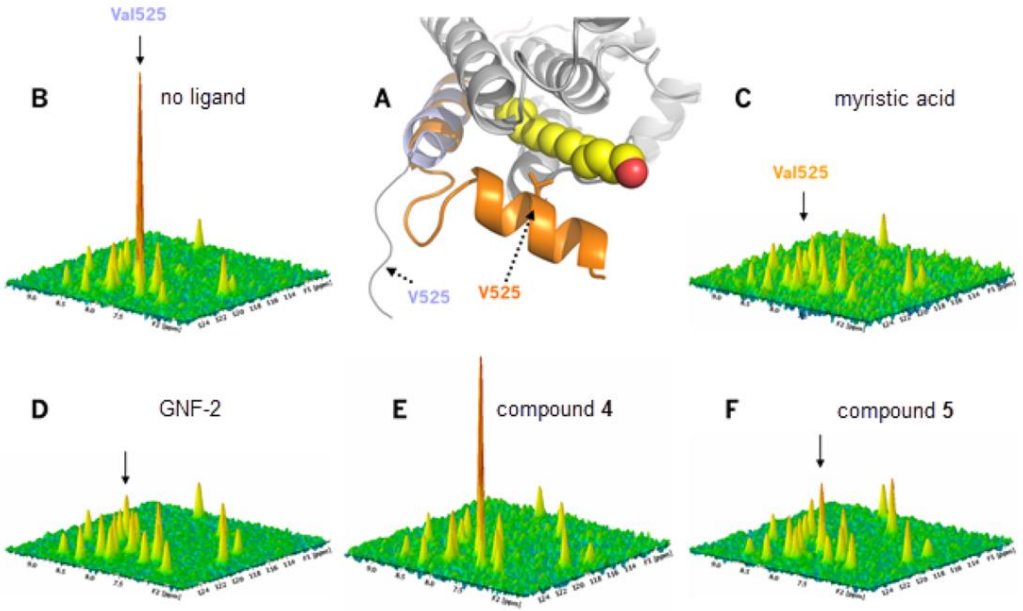
Selecting compounds that inhibit the kinase

innactive



active

Figure 2. (A) Assembled inactive state of ABL1 kinase as seen in the minimal autoinhibitory construct, comprising the SH3, SH2, and SH1 domains, bound to PD166326 (Figure 1; a type-I tyrosine kinase inhibitor) and myristic acid (1opl).[14] (B) Structure of the ABL1 SH1 domain in complex with imatinib (2hyy).[28] Note the two different conformations of helix-I, which is bent in the assembled inactive state (panel A, orange) but linear and partially disordered in the absence of autoinhibition (panel B, light blue).

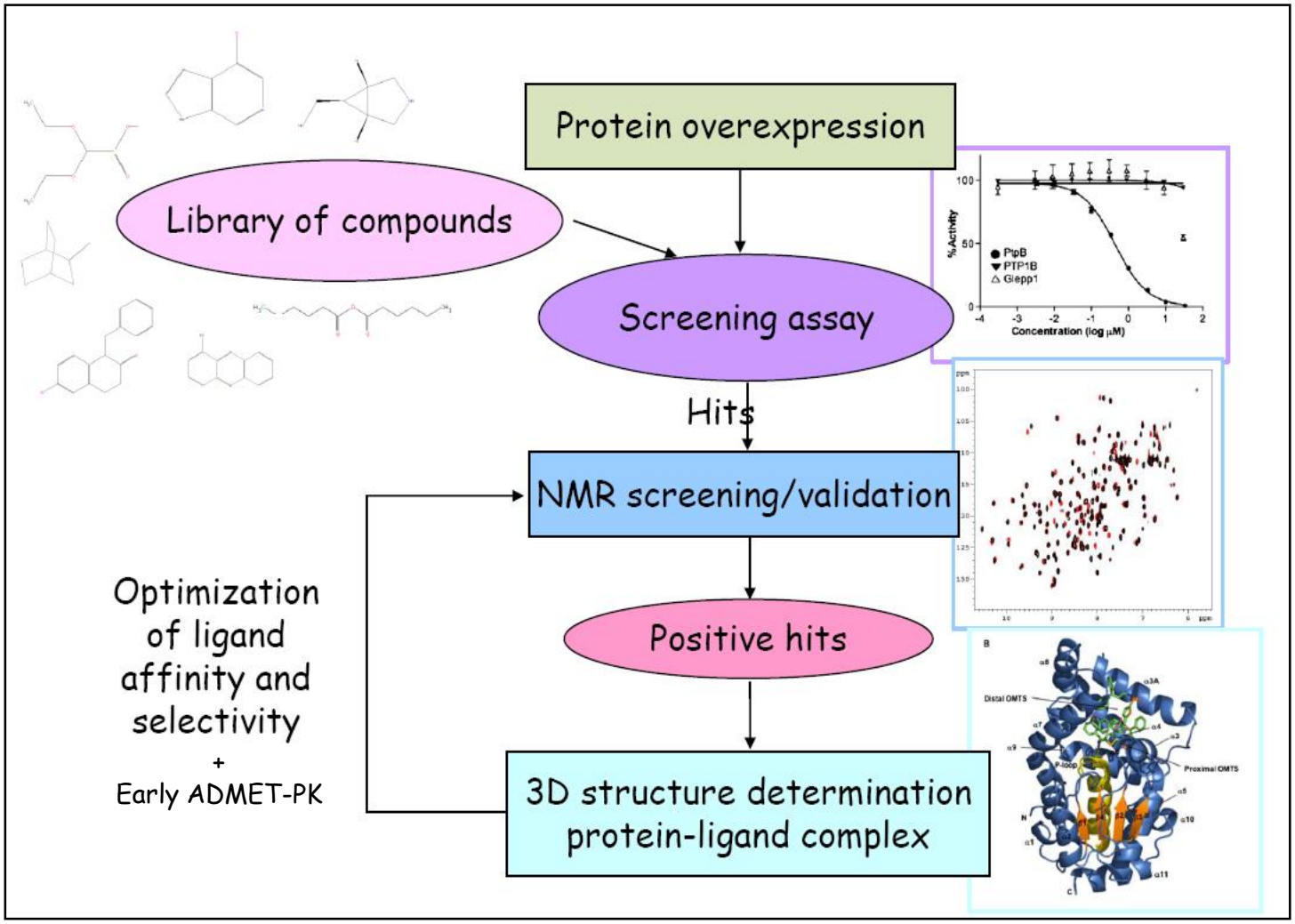


Schoepfer, J et al J. Med. Chem. 2018, 61, 18, 8120

Food for thought: SBDD in the XXI century

- Current world threats:
  - chemical pollution
  - non-degradable drugs affecting ecosystems (wild-life)
  - reduce animal testing
  - limited resources
  - climate change
- What can be done to reduce current problems?
  - Better planning of projects including environmental impact studies
  - Use of computational tools to reduce animal testing and save resources
  - Can we learn from nature about drug design? Degradable molecules – reduce halogens
  - Improve chemical synthesis

Summary



- SBDD is a powerful method for delivering new drugs
- Strategy for screening, hit validation and optimization – lead compound
- Expertise at STB- HMGU (Protein production, NMR spectroscopy, X-ray crystallography, CryoEM, SBDD, Chemistry, Machine learning, Chemoinformatics)