MASARYK UNIVERSITY

Vývoj nových organických sloučenin s cílenou biologickou aktivitou

Kamil Paruch

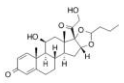
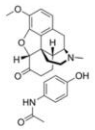
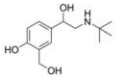
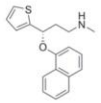
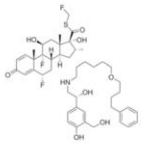
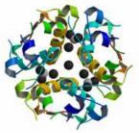
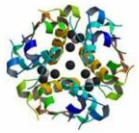
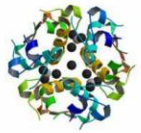
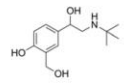
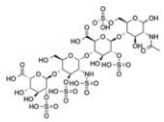
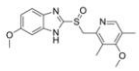
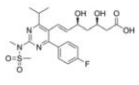
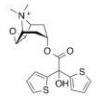
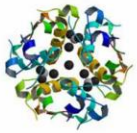
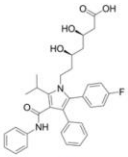
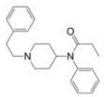
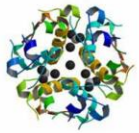
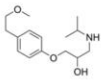
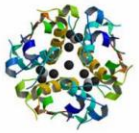
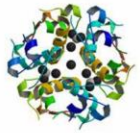
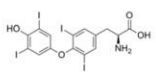
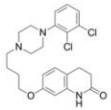
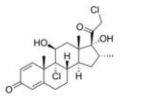
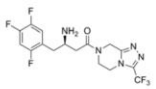
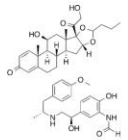
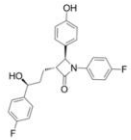
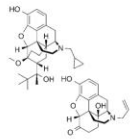
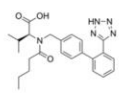
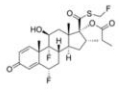
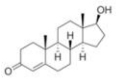
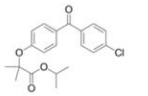
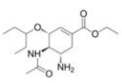
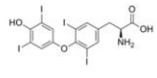
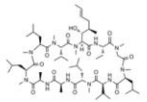
1990-1995: Mgr. organická chemie; PřF MU, Brno

1996-2000: PhD. organická chemie; Columbia University, New York, USA

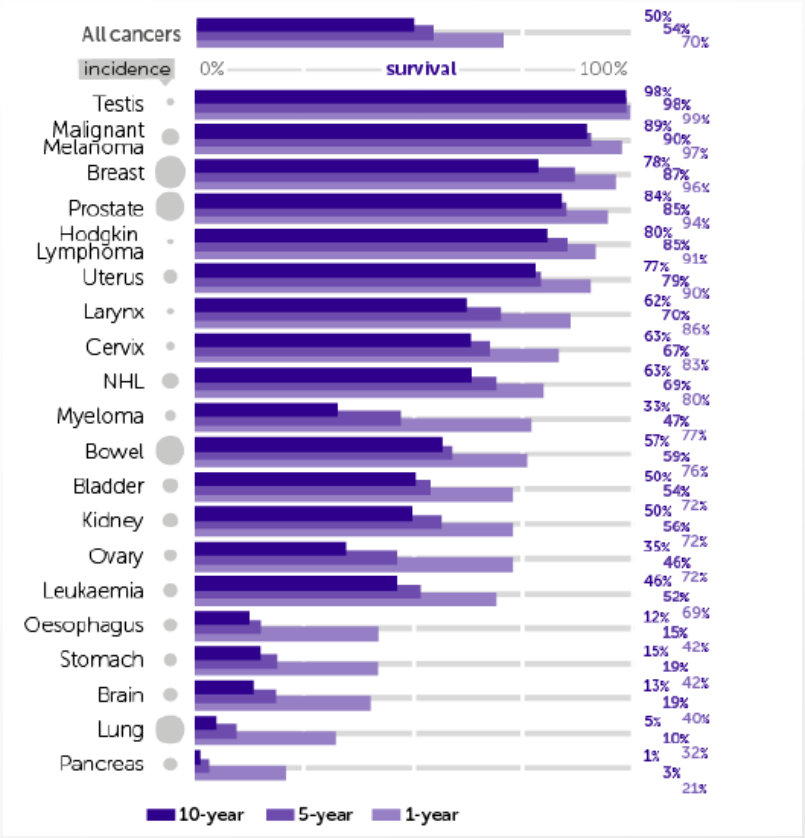
2001-2008: drug discovery, Schering-Plough, New Jersey, USA

2009-nyní: Ústav chemie PřF MU & FNUSA-ICRC, Brno

orgsyn.sci.muni.cz

1 **Budesonide** (Budesonide)  ALM DER RES Approved 1997	2 **Hydrocodone/APAP** (Hydrocodone & Acetaminophen)  Nervous System Approved 1982	3 **Proair HFA** (Salbutamol)  Respiratory System Approved 2004	4 **Cymbalta** (Duloxetine)  Nervous System Approved 2004	5 **Nexium** (Esomeprazole)  Alimentary Tract & Metabolism Approved 2001	6 **Advair Diskus** (Fluticasone Propionate & Salmeterol)  Respiratory System Approved 2000	7 **Lantus** (Insulin Glargine)  Endocrine System Approved 2000	8 **Lantus SoloSTAR** (Insulin Glargine)  Endocrine System Approved 2000	9 **OneTouch** (Insulin Glargine)  Endocrine System Approved 2006	10 **Ventolin HFA** (Salbutamol)  Respiratory System Approved 2001
11 **Enoxaparin** (Enoxaparin)  BBO MSK Approved 1993	12 **Omeprazole** (Omeprazole)  Alimentary Tract & Metabolism Approved 1989	13 **Crestor** (Rosuvastatin)  BBO CAR Approved 2003	14 **Spiriva** (Tiotropium)  Respiratory System Approved 2004	15 **Levemir** (Insulin Detemir)  Endocrine System Approved 2005	16 **Atorvastatin** (Atorvastatin)  BBO CAR Approved 1996	17 **Fentanyl** (Fentanyl)  NER ONC Approved 1968	18 **NovoLog FlexPen** (Insulin Aspart)  Endocrine System Approved 2000	19 **Metoprolol** (Metoprolol)  Cardiovascular System Approved 1978	20 **NovoLog** (Insulin Aspart)  Endocrine System Approved 2000
21 **Humalog** (Insulin Lispro)  Endocrine System Approved 1996	22 **Synthroid** (Levothyroxine)  Endocrine System Approved 2002	23 **Abilify** (Aripiprazole)  Nervous System Approved 2002	24 **Nasonex** (Mometasone)  Respiratory System Approved 1997	25 **Januvia** (Sitagliptin)  Endocrine System Approved 2006	26 **Symbicort** (Budesonide & Formoterol)  Respiratory System Approved 2006	27 **Lyrica** (Pregabalin)  MSK NER Approved 2004	28 **Zetia** (Ezetimibe)  BBO CAR Approved 2002	29 **Namenda** (Memantine)  Nervous System Approved 2003	30 **Suboxone** (Buprenorphine & Naloxone)  Nervous System Approved 2002
31 **Diovan** (Valsartan)  CAR END Approved 1996	32 **Flovent HFA** (Fluticasone Propionate)  Respiratory System Approved 1996	33 **AndroGel** (Testosterone)  Genito-Urinary & Sex Hormone Approved 2000	34 **Fenofibrate** (Fenofibrate)  BBO CAR END Approved 1993	35 **Remicade** (Infliximab)  END MSK Approved 1998	36 **OneTouch Ultra**  Endocrine System Marketed 2006*	37 **Tamiflu** (Oseltamivir)  Anti-Infective Approved 1999	38 **Levothyroxine** (Levothyroxine)  Endocrine System Approved 2000	39 **Restasis** (Cyclosporine)  Sensory Organ Approved 2002	40 **Lovaza** (Omega 3-Acid Ethyl Esters)  Cardiovascular System Approved 2004
41 **Dexilant** (Dexlansoprazole) Alimentary Tract & Metabolism Approved 2009	42 **Benicar** (Olmesartan) CAR END Approved 2002	43 **Lidoderm** (Lidocaine) CAR DER NER RES SEN Approved 1948	44 **Humalog KwikPen** (Insulin Lispro) Endocrine System Approved 1996	45 **Oxycontin** (Oxycodone) END MSK Approved 2010	46 **VESIcare** (Solifenacin) Genito-Urinary & Sex Hormone Approved 2004	47 **Celebrex** (Celecoxib) MSK ONC Approved 1998	48 **Vytorin** (Ezetimibe & Simvastatin) BBO CAR Approved 2004	49 **Enbrel** (Etanercept) Musculo-Skeletal System Approved 1998	50 **Janumet** (Metformin & Sitagliptin) Alimentary Tract & Metabolism Approved 2007

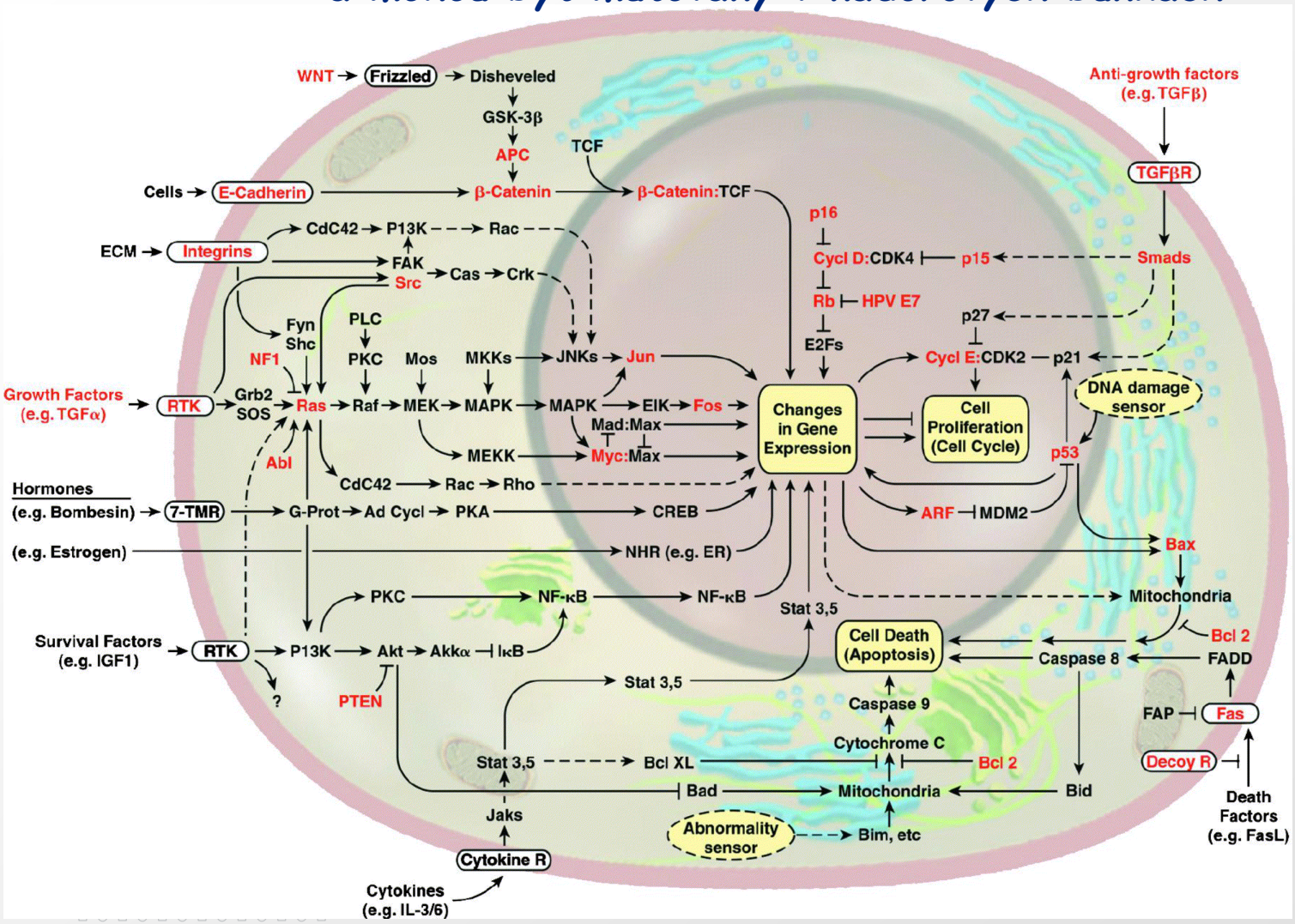
Onkologie: nové přístupy



www.cancerresearchuk.org

- relativně nízká úspěšnost léčby některých nádorových onemocnění
- které procesy potřebujeme ovlivnit, aby byla možná selektivní eliminace nádorových buněk?

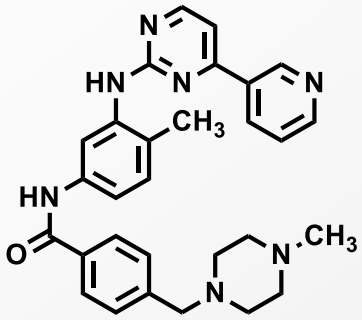
Příklady signálních drah, které regulují buněčnou proliferaci a mohou být mutovány v nádorových buňkách

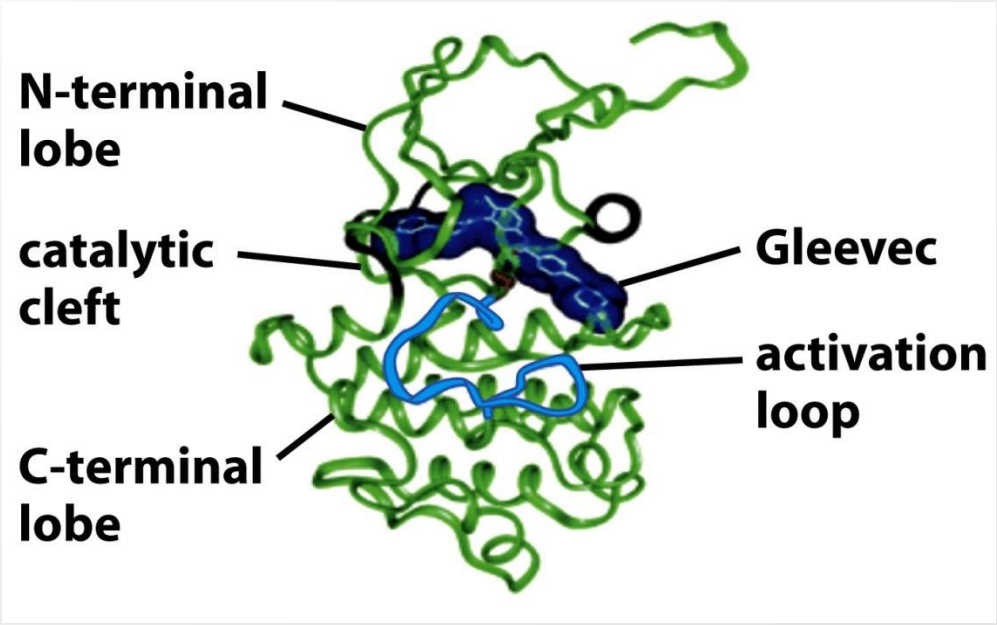


Hanahan, D; Weinberg, R. A. *Cell* **2000**,*100*, 57.

Imatinib: přelom v oblasti kinázových inhibitorů

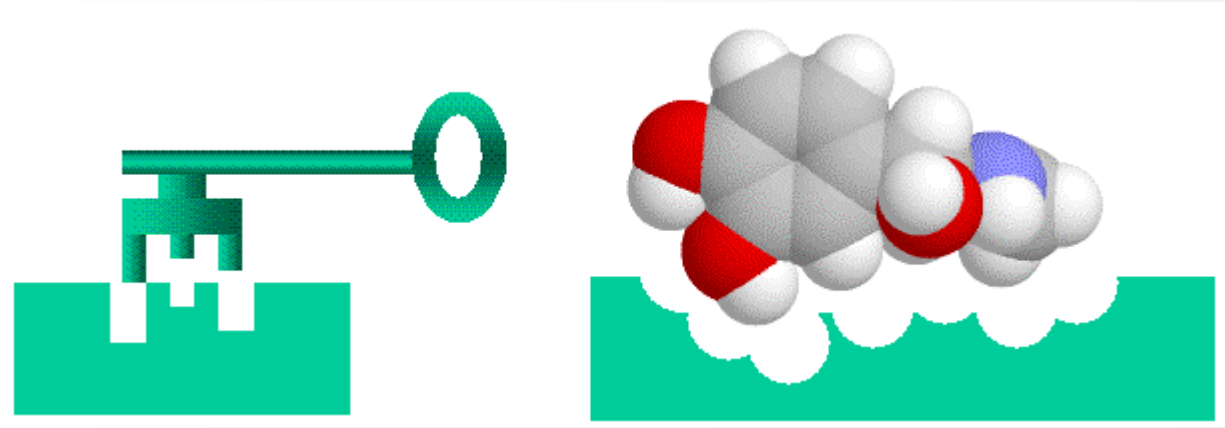
imatinib (Gleevec)



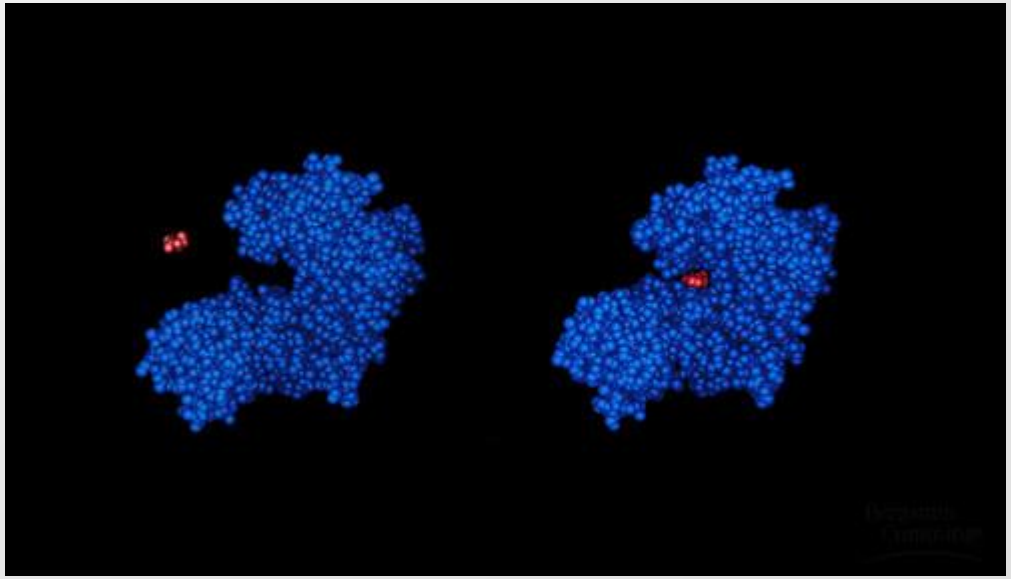


- 2001: revoluce v léčbě chronické myeloidní leukemie
- velká část pacientů prakticky vyléčena
- 90% pacientů: doba dožití >5 let
  - ➢ intenzivní výzkum inhibitorů proteinových kináz

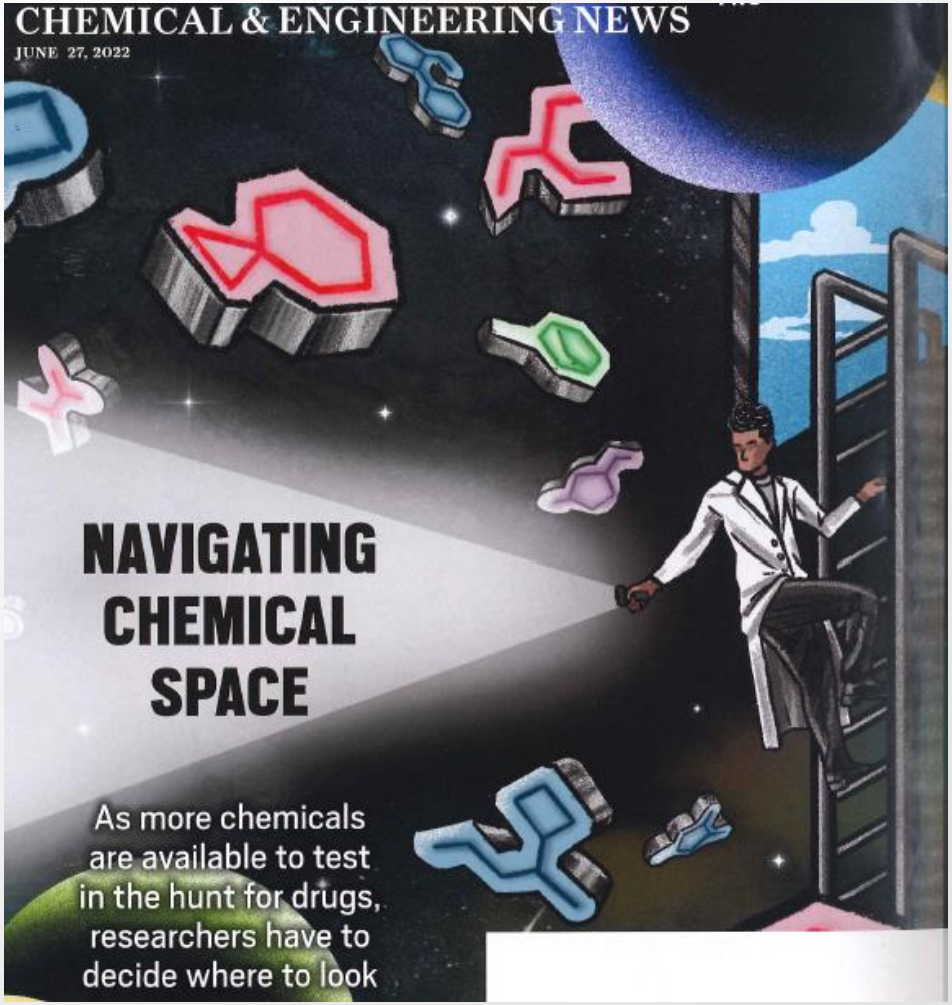
Můžeme najít dostatečně selektivní modulátor?



- poměrně malý „klíč" (M < 500 g/mol)
- tisíce různých „zámků"
- „zámky" mohou pozměnit tvar

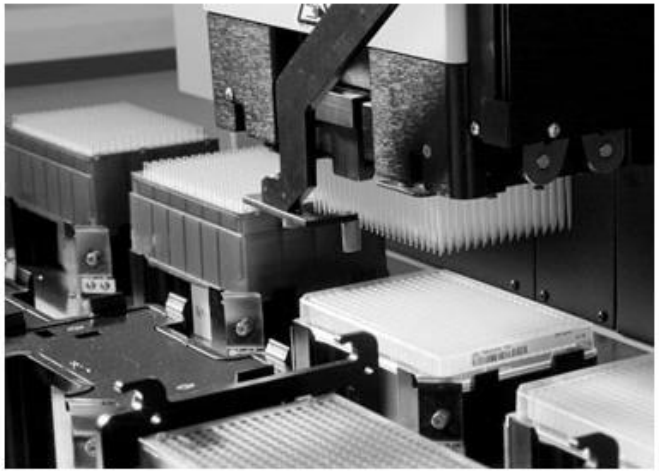


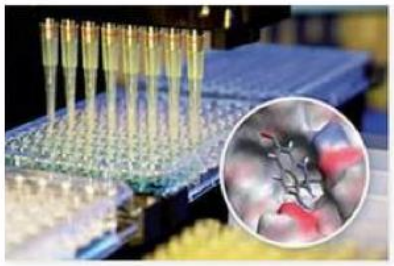
K dispozici je nesmírně rozsáhlý „chemický prostor“

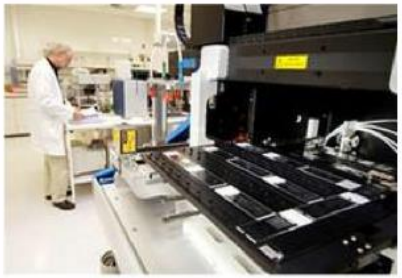


Identifikace výchozí („lead“) sloučeniny

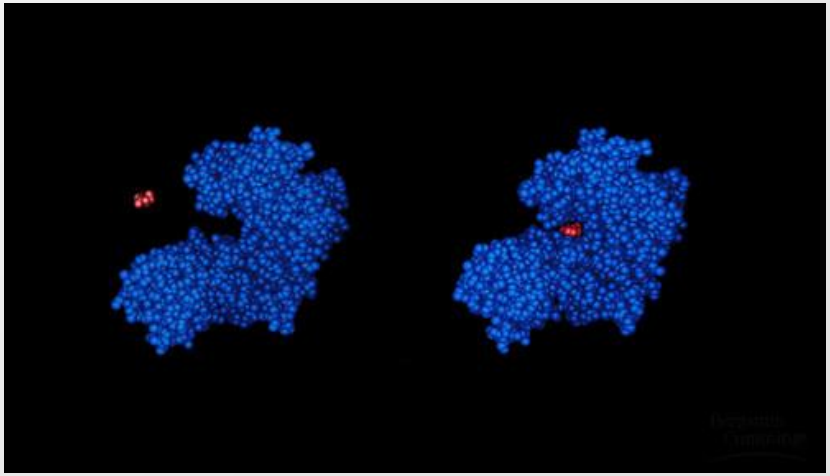
vysokokapacitní (high-throughput) screening





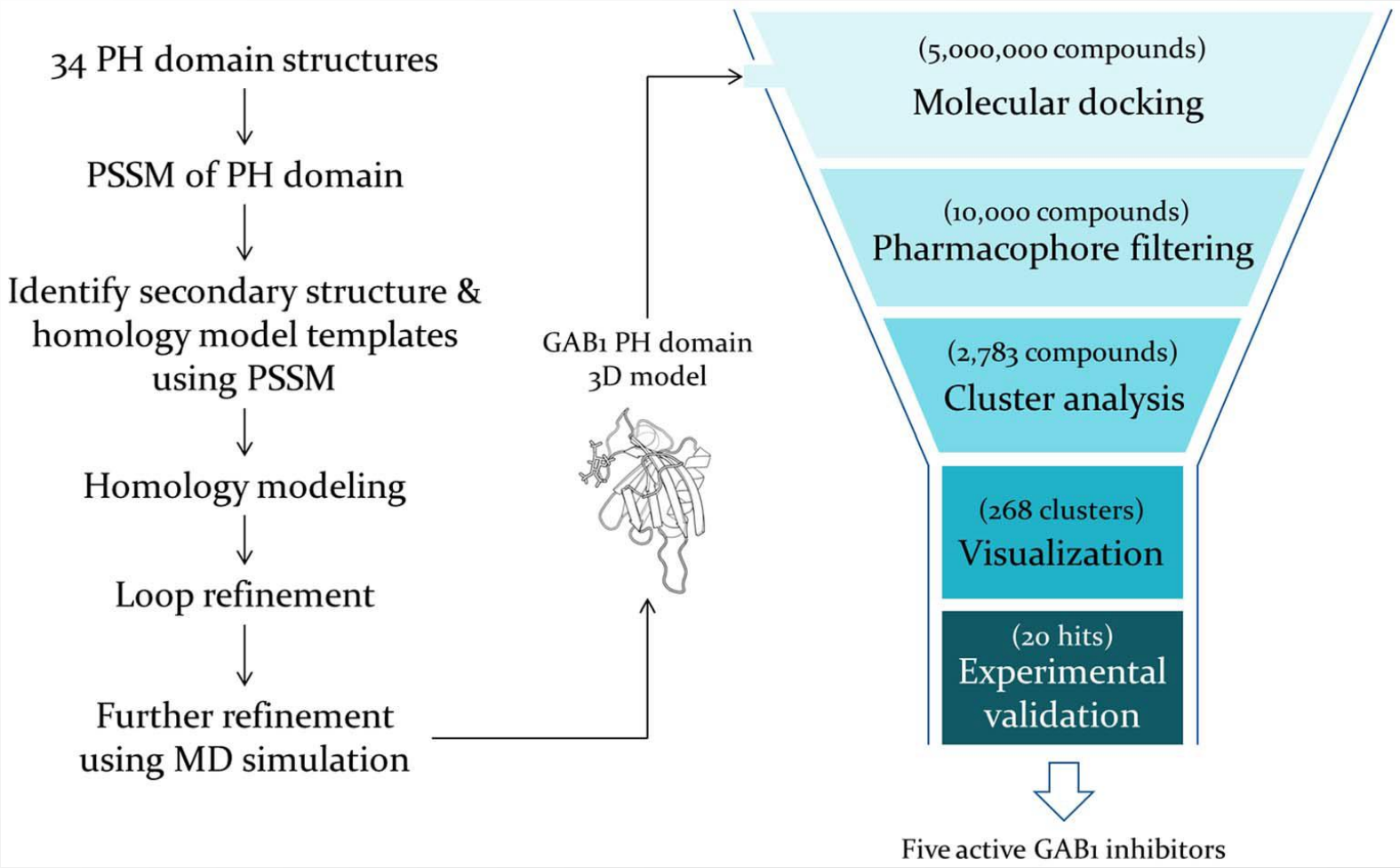


molekulové modelování & intuice

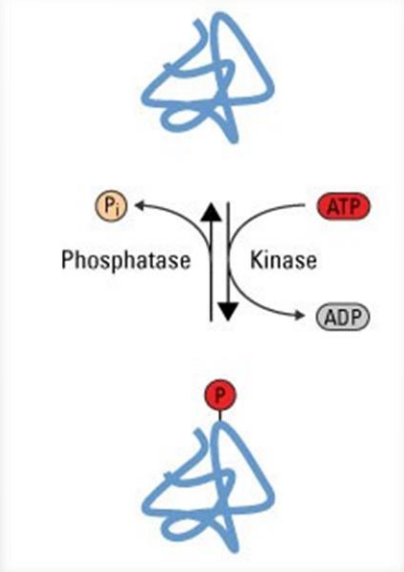


známá aktivní sloučenina

„in silico" přístup

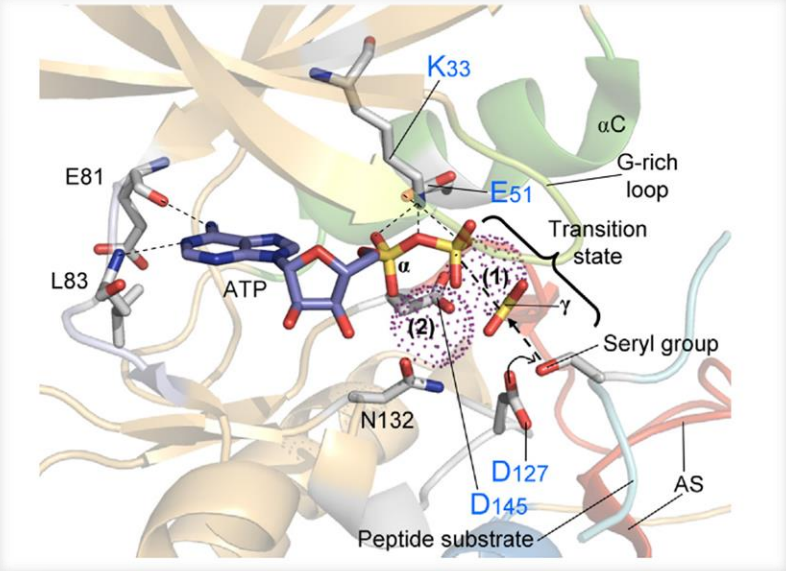


Proteinové kinázy



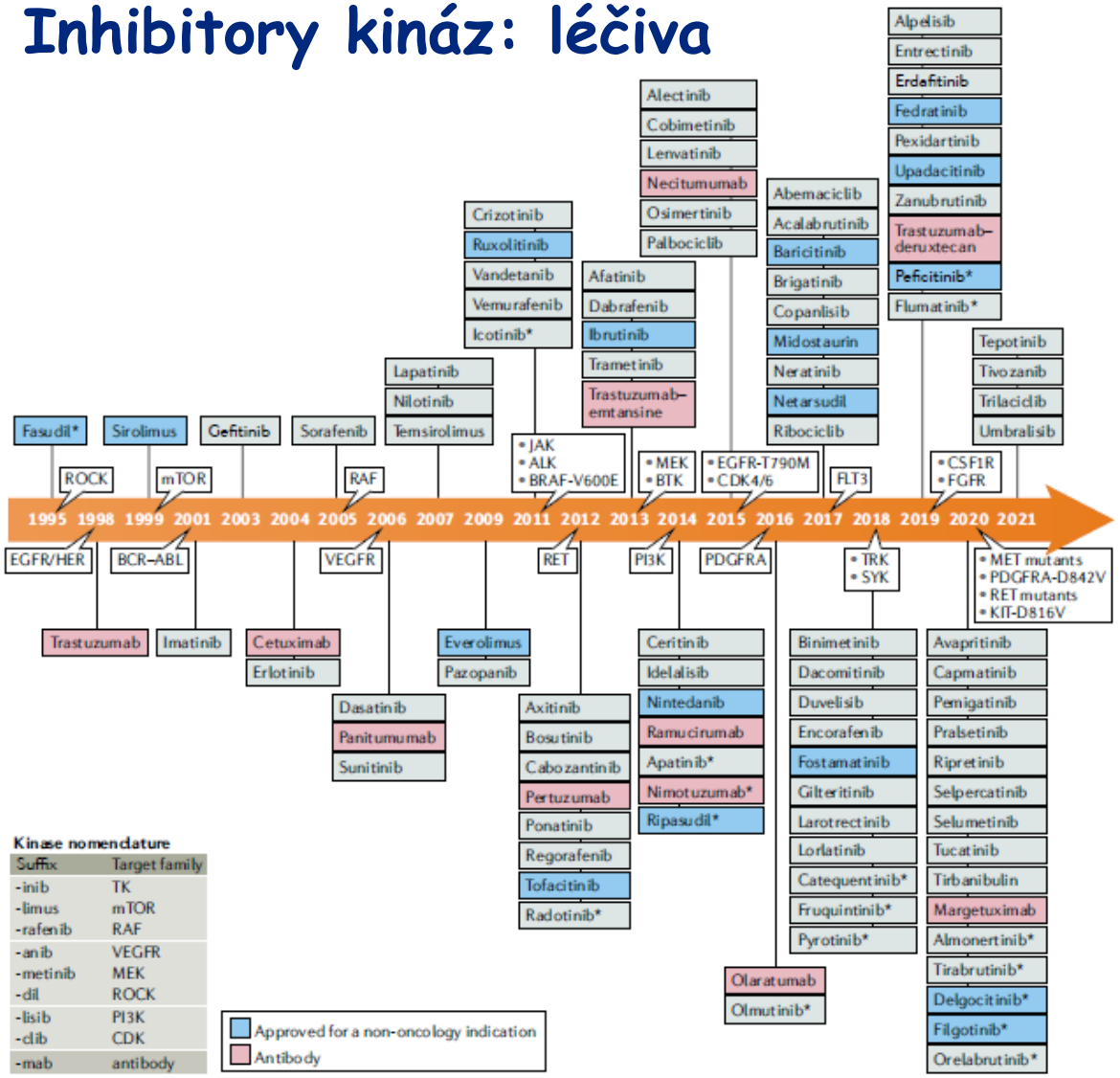
- >500 enzymů (ca. 1.7% lidského genomu)
- ATP fosfotransferázy
  - katalyzují reverzibilní fosforylaci
    - důležitý signální mechanismus
    - regulace mnoha procesů v buňce

- inhibitory proteinových kináz – „hot topic"
  v současném (farma) výzkumu
  (>70 substancí schváleno pro klinické použití)



Roskoski, J. *Pharmacol. Res.* **2016**, *107*, 249.

Inhibitory kináz: léčiva

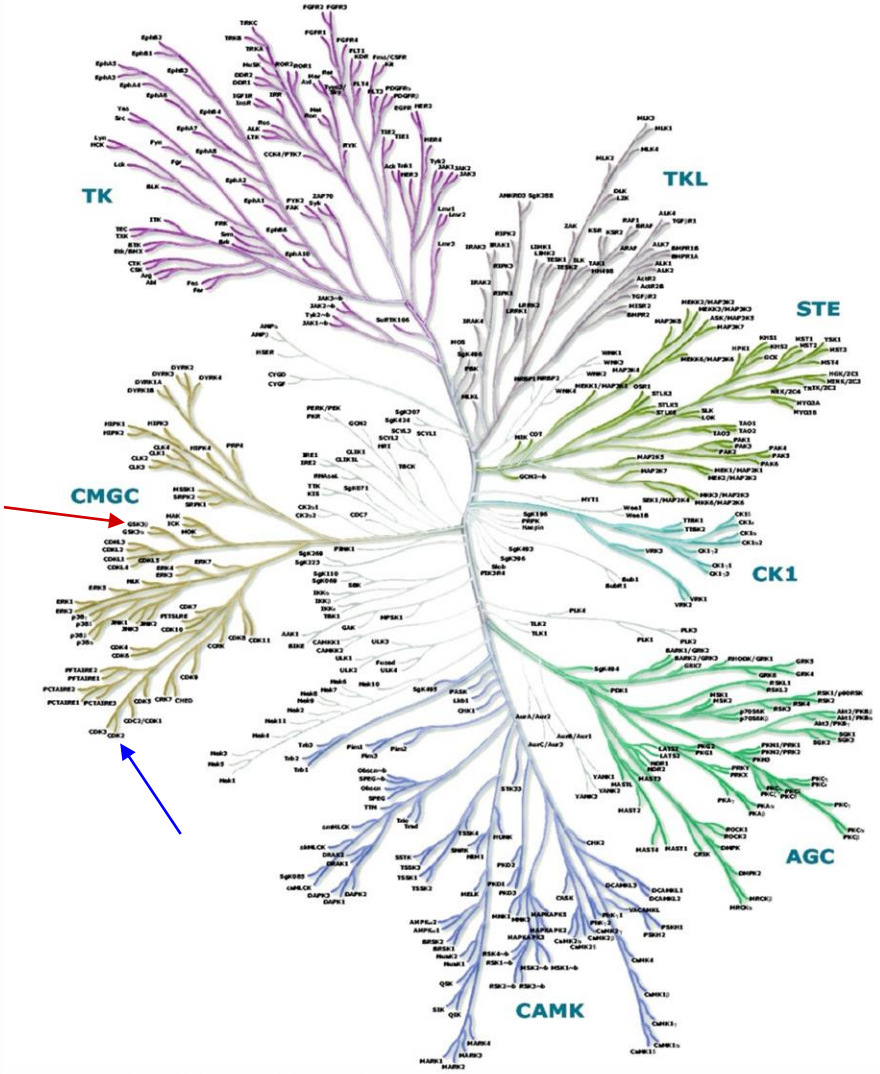


Nat. Rev. Drug Disc. **2021**, *20*, 839.

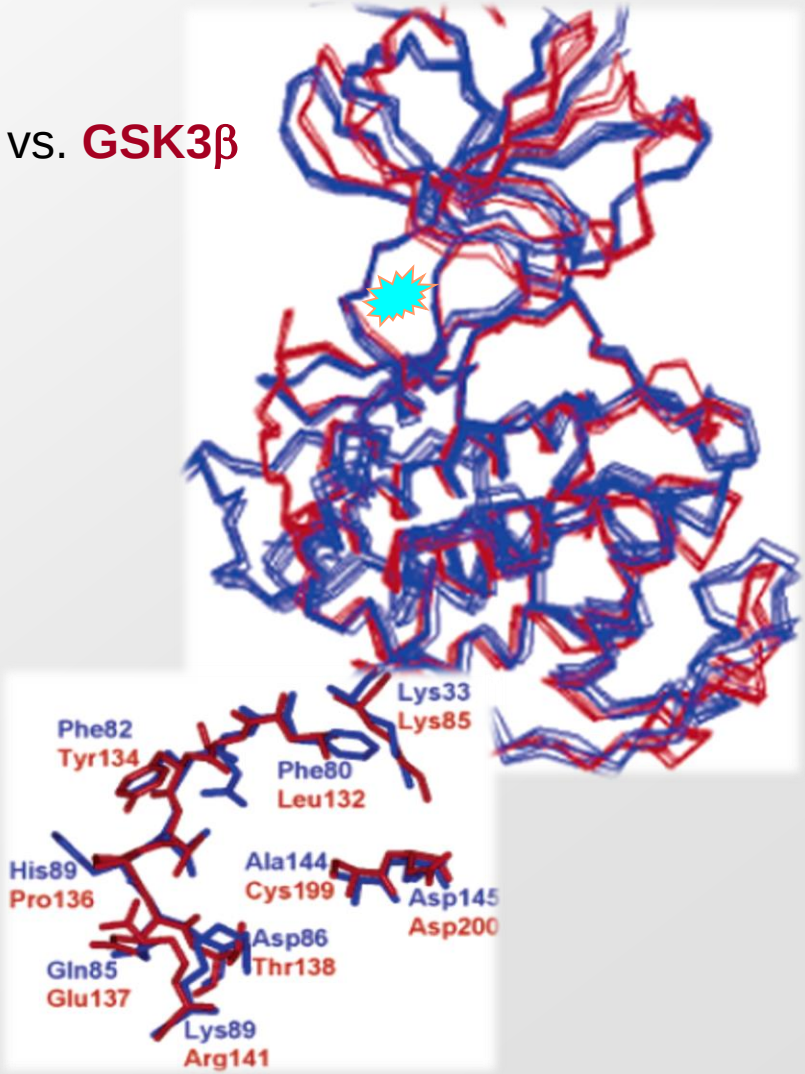
Podobnost proteinových kináz

human kinome: >500 kináz

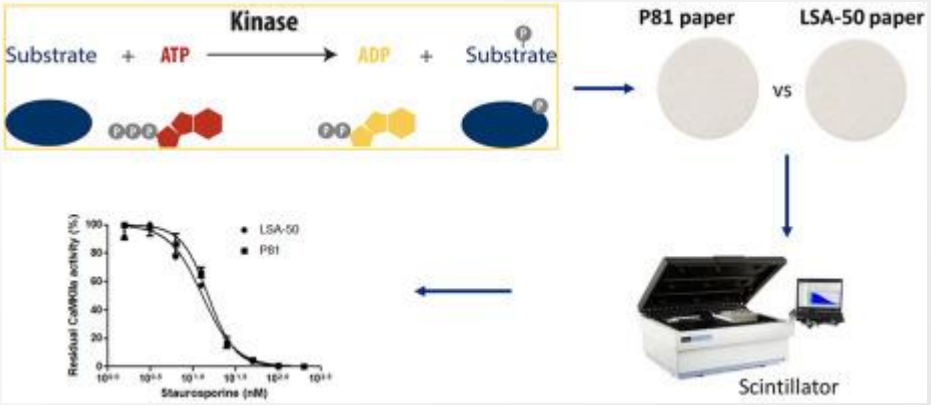
Manning, G. et al. *Science* **2002**, *298*, 1912.



CDK2 vs. **GSK3β**



Proteinové kinázy: testování inhibitorů

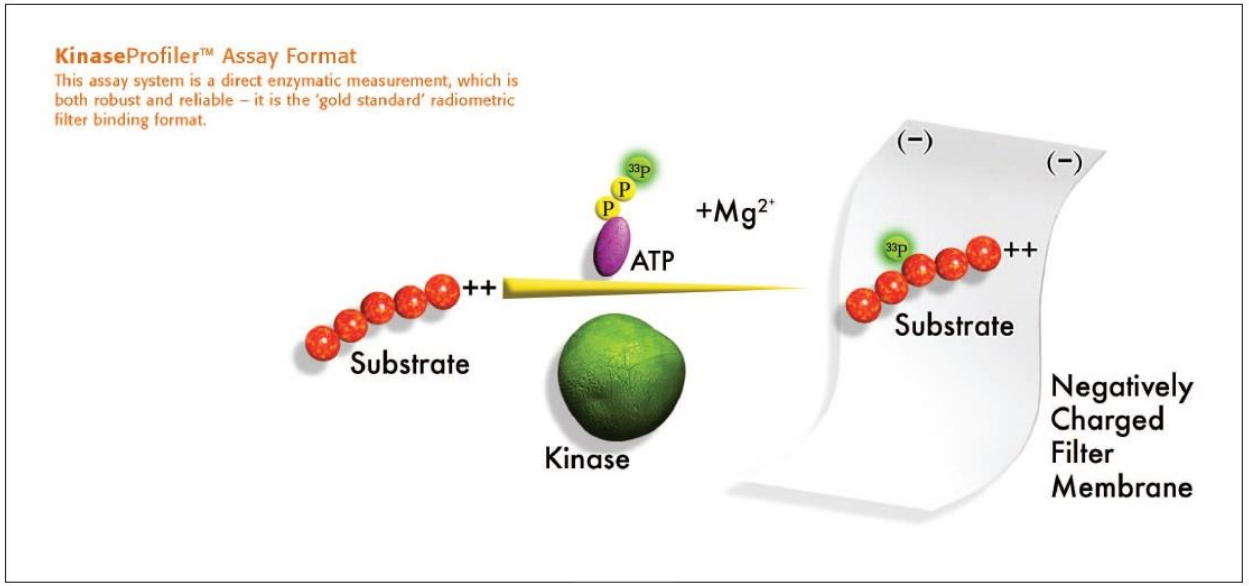


M = 500 g/mol

IC_{50} = 10 nmol/l (10 nM)

= 0.000005 g/l

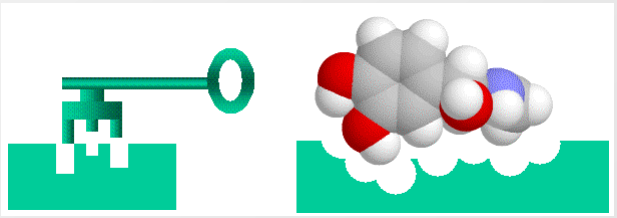
= 5 μg/l



Selektivní vs. neselektivní inhibitory

(léčivo vs. selektivní „sonda" pro molekulární biologii)

- hledání selektivního „klíče" = inhibitoru pro pouze jeden z více než 500 velmi podobných „zámků" - kináz

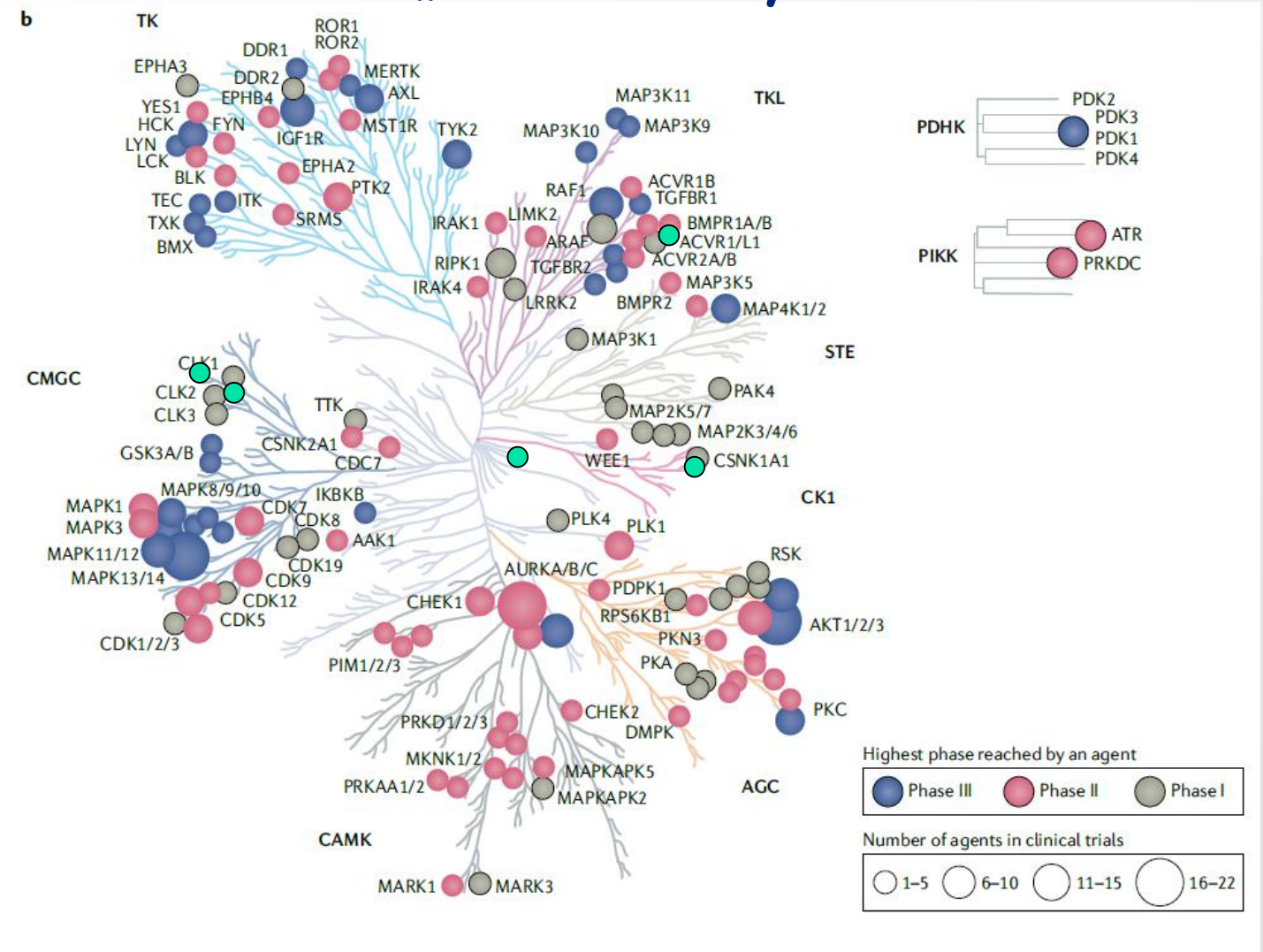


neselektivní inhibitor

selektivní inhibitor

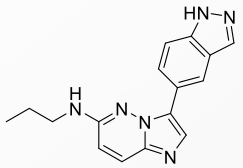
vysoce selektivní inhibitor

„Nové" kinázy



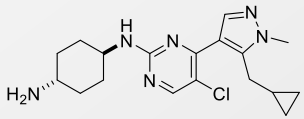
Nat. Rev. Drug Disc. **2021**, *20*, 839.

Typické inhibitory „nových" kináz



Oncogene **2012**, *31*, 1408.

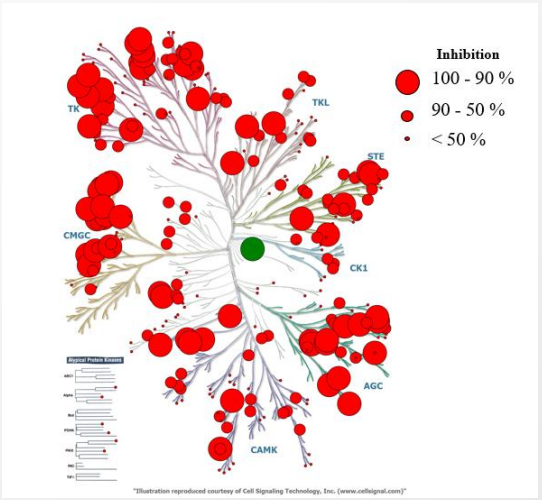
CHR6494
IC_{50} (Haspin) = 6 nM

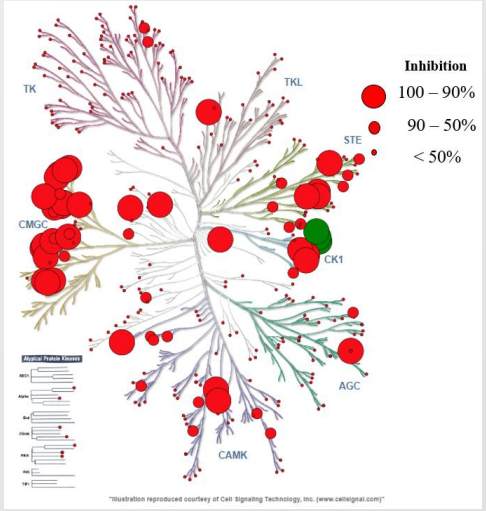


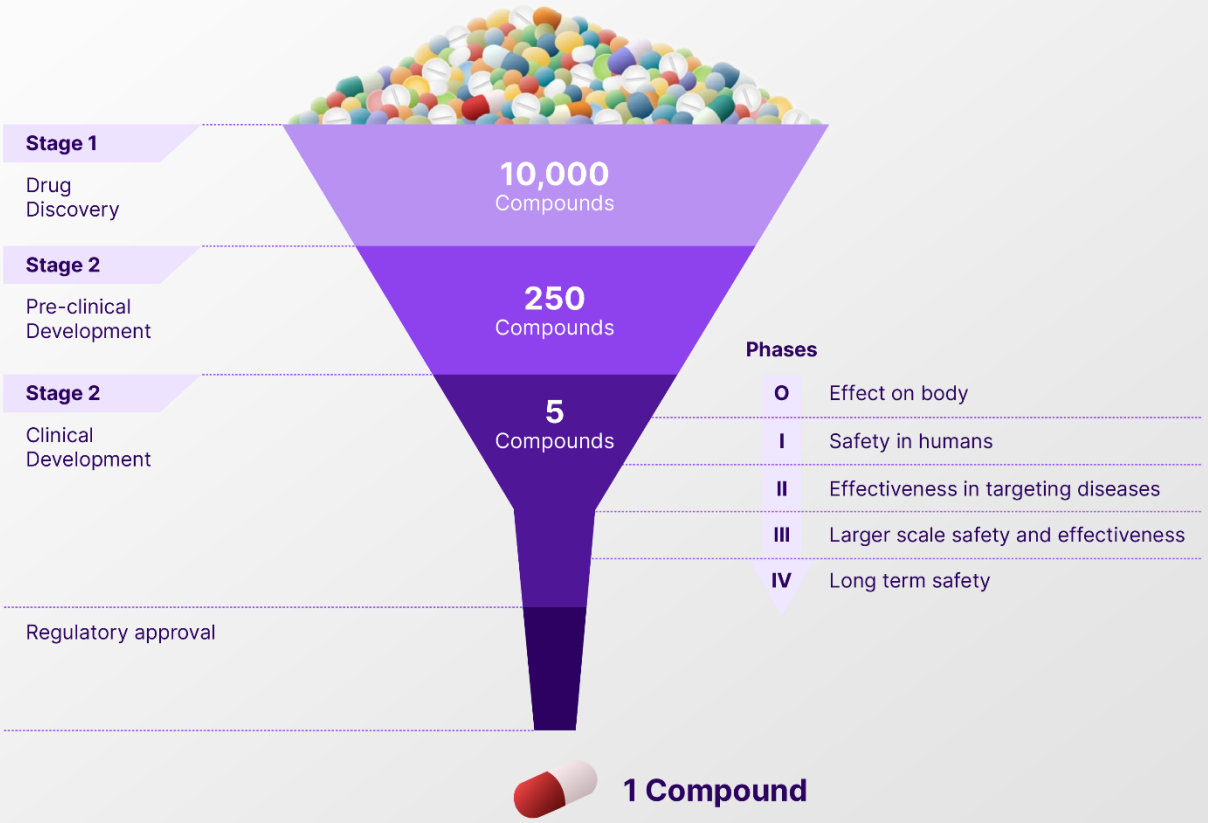
Cell **2018**, *175*, 171.

BTX-A51
IC_{50} (CK1α) = 34 nM
IC_{50} (CK1δ) = 6 nM
IC_{50} (CK1ε) = 21 nM

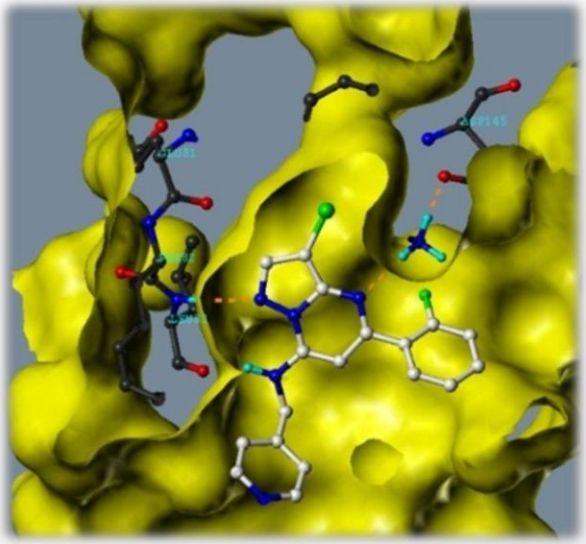
412 human kinases @ 1 μM (Eurofins)

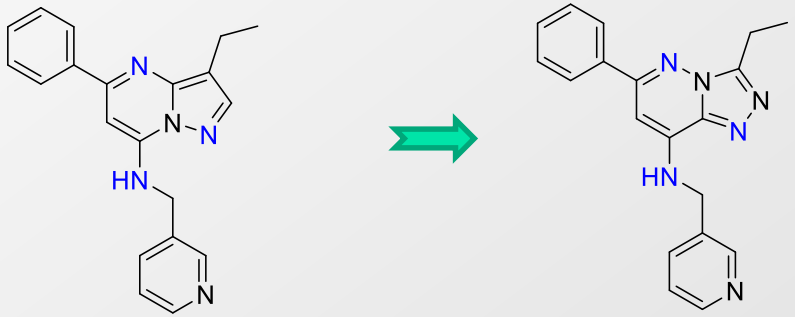





Stage 1
Drug Discovery
10,000 Compounds
Stage 2
Pre-clinical Development
250 Compounds
Stage 2
Clinical Development
5 Compounds
Regulatory approval
1 Compound
Phases
0 Effect on body
I Safety in humans
II Effectiveness in targeting diseases
III Larger scale safety and effectiveness
IV Long term safety

Podobné molekuly mohou mít (velmi) rozdílnou biologickou aktivitu

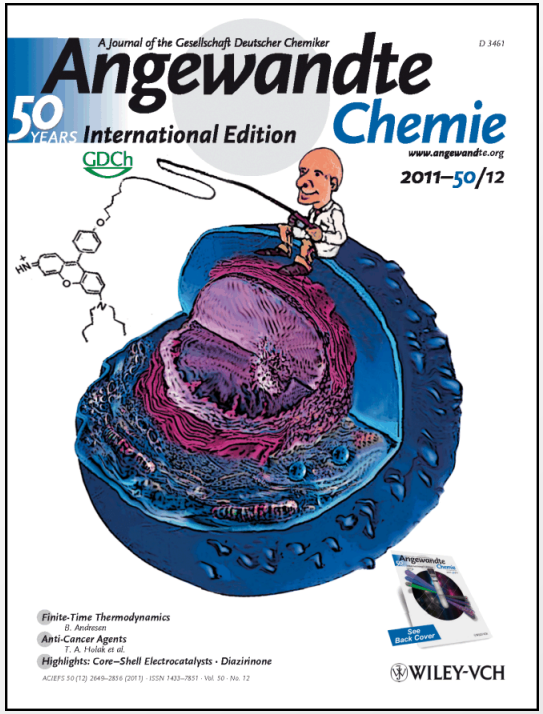




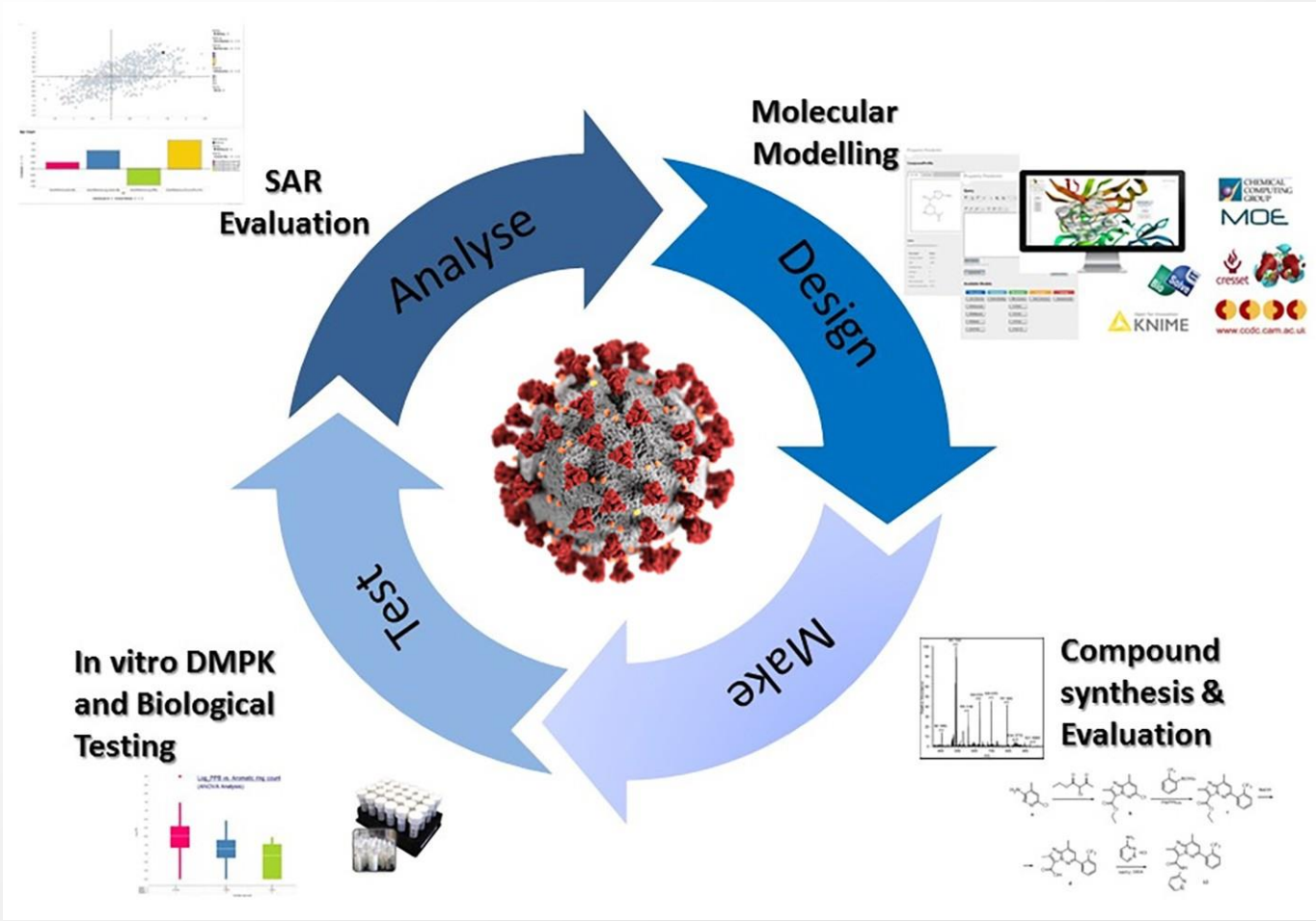
CDK2 IC_{50} = 8 nM

CDK2 IC_{50} > 50 000 nM

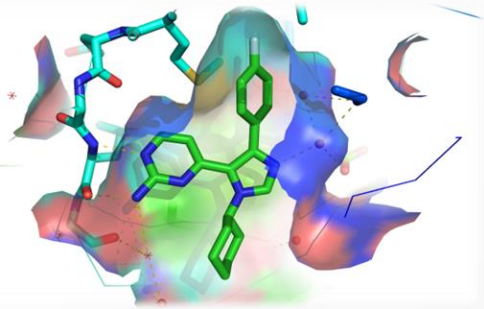
Identifikace biologicky aktivních sloučenin je (stále) značně empirický proces

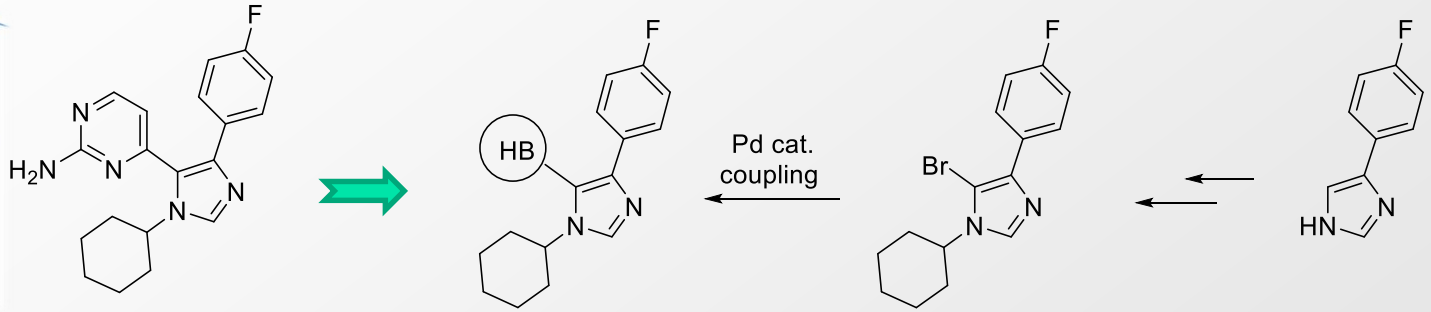


organická chemie: účinné postupy k přípravě nových sloučenin „molecular Lego“


SAR
Evaluation
Analyse
Molecular
Modelling
Design
MOE
KNIME
Make
Compound
synthesis &
Evaluation
Test
In vitro DMPK
and Biological
Testing

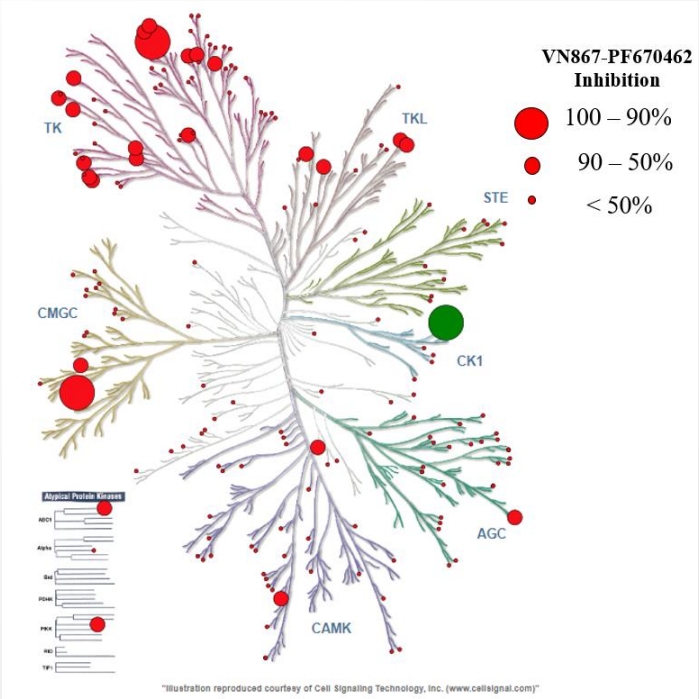
Inhibitory kinázy CK1

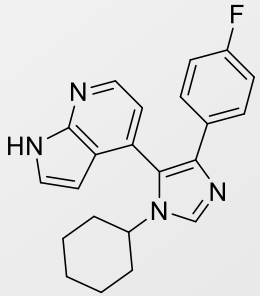




PF-670462

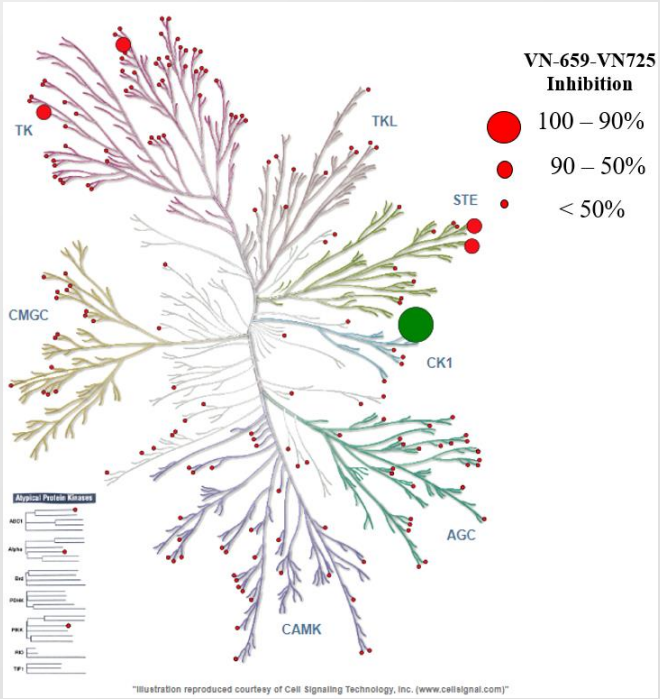
15 potenciálních „hinge binders" nainstalováno



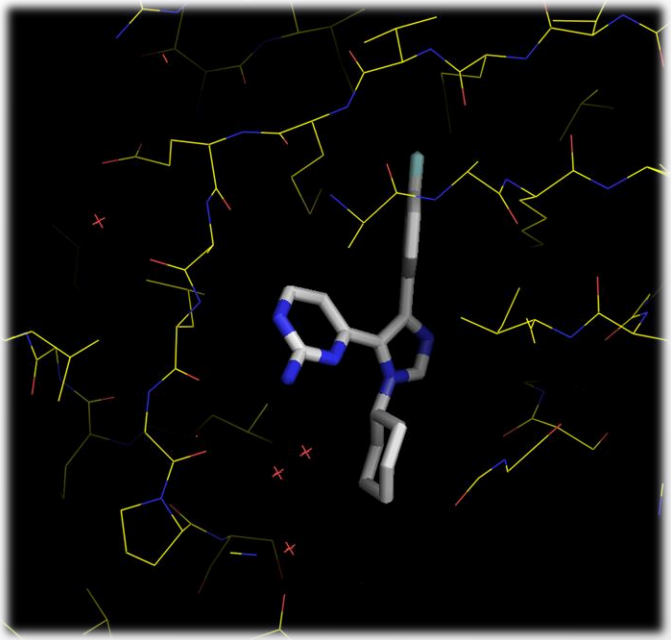


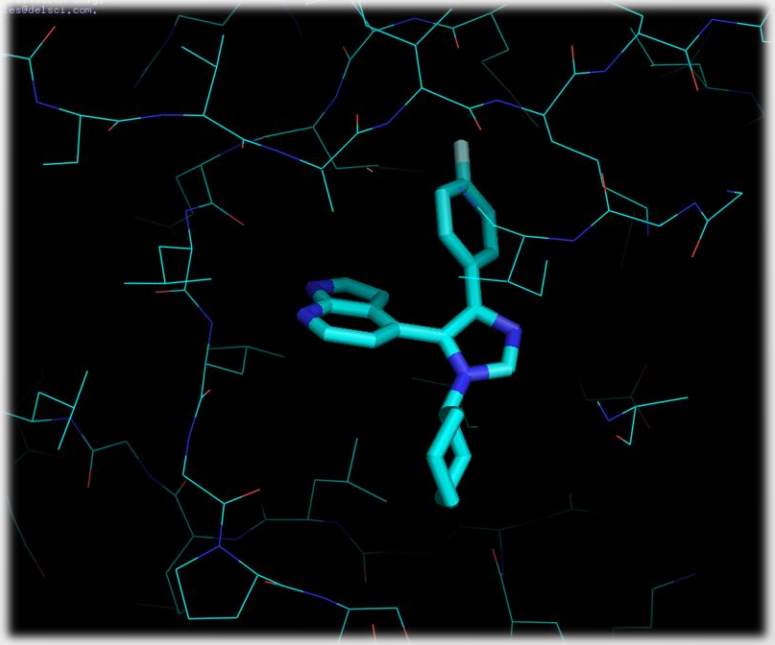
205 human kinases

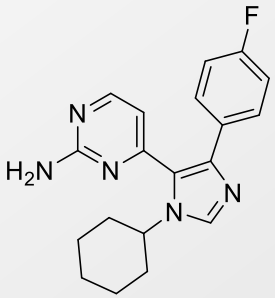
(1 μM, Eurofins KinaseProfiler)

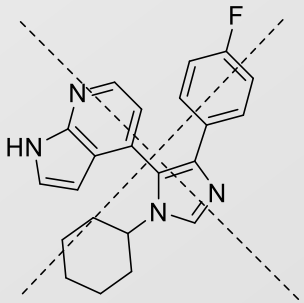


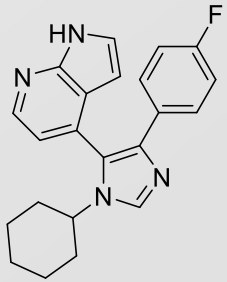
CK1 inhibitory: překvapivě rozdílné vazebné módy



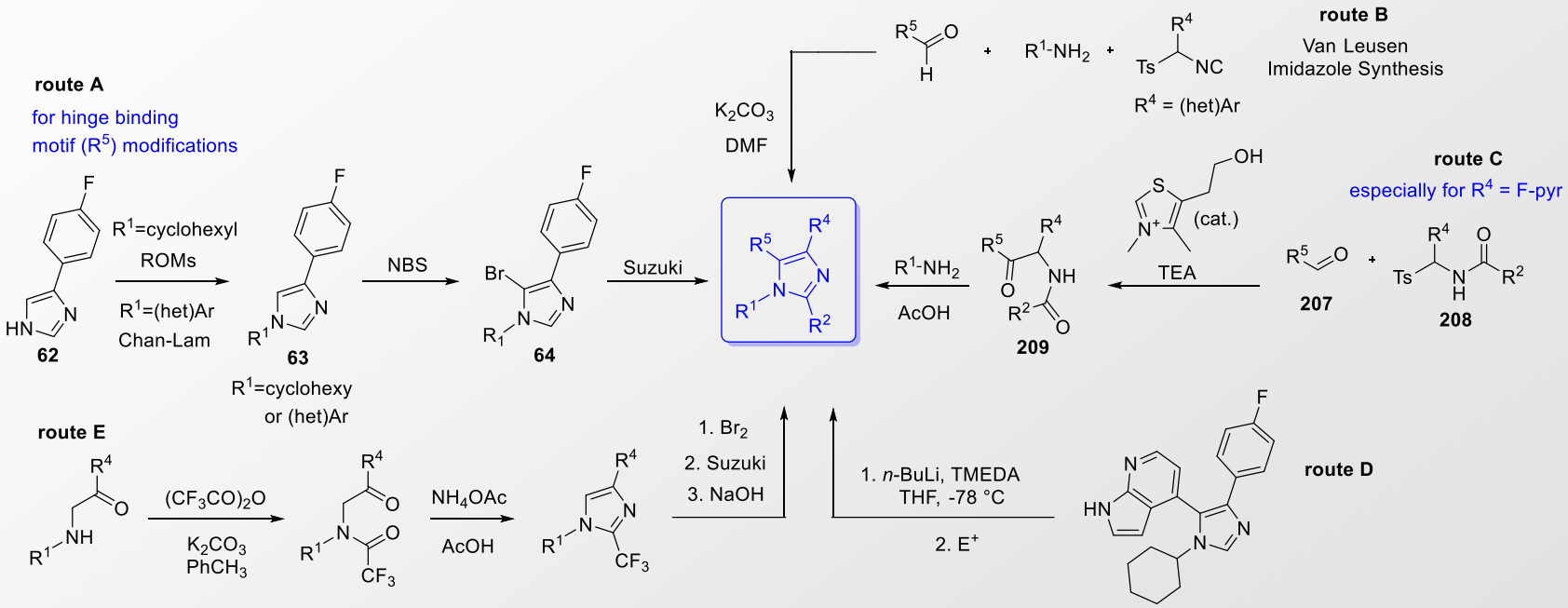


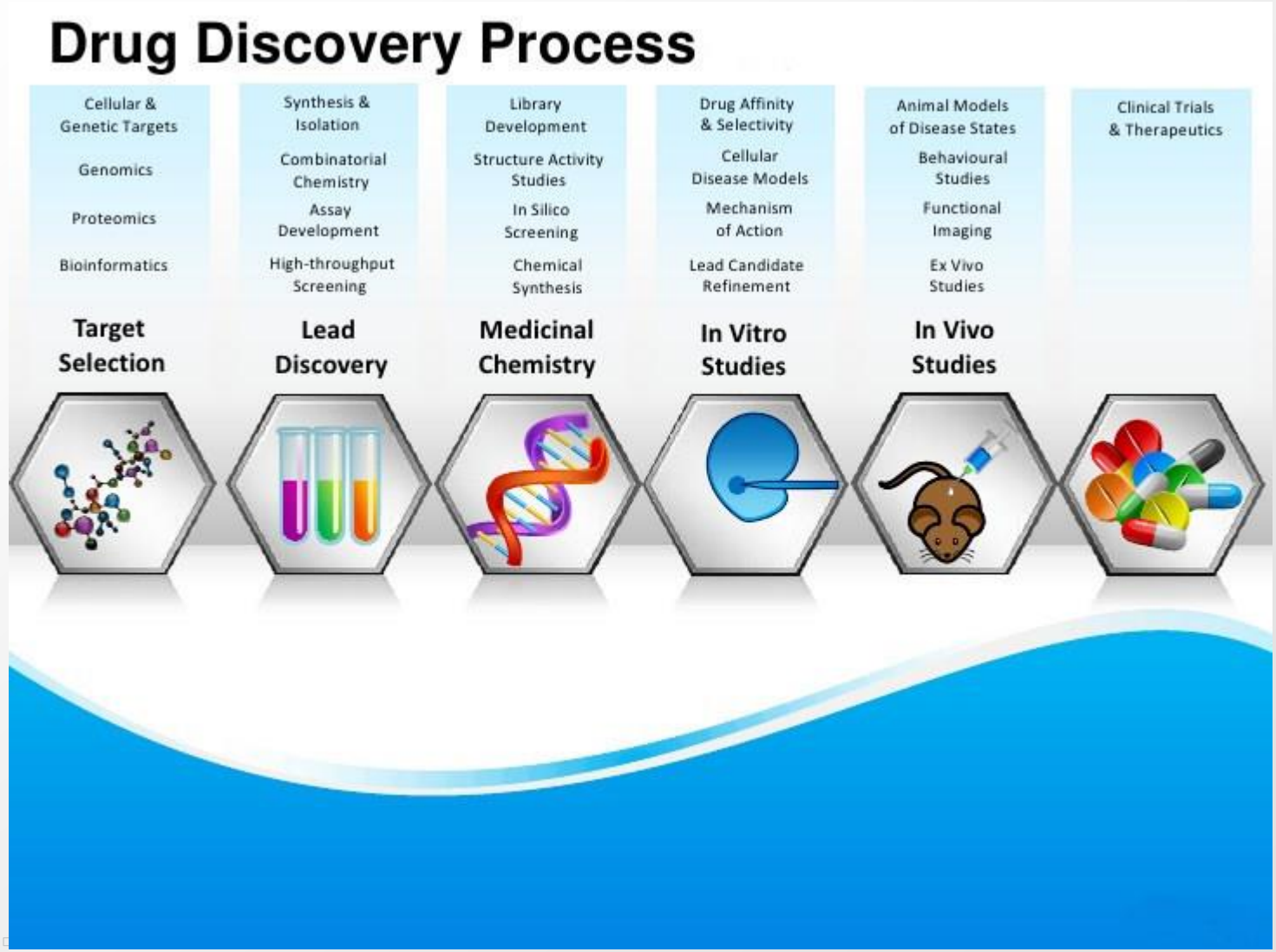






Různé cesty přípravy inhibitorů kinázy CK1



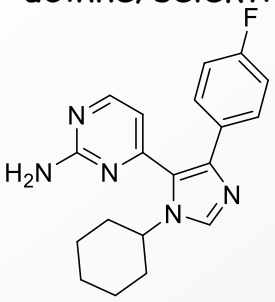

Drug Discovery Process
Cellular & Genetic Targets
Genomics
Proteomics
Bioinformatics
Target Selection
Synthesis & Isolation
Combinatorial Chemistry
Assay Development
High-throughput Screening
Lead Discovery
Library Development
Structure Activity Studies
In Silico Screening
Chemical Synthesis
Medicinal Chemistry
Drug Affinity & Selectivity
Cellular Disease Models
Mechanism of Action
Lead Candidate Refinement
In Vitro Studies
Animal Models of Disease States
Behavioural Studies
Functional Imaging
Ex Vivo Studies
In Vivo Studies
Clinical Trials & Therapeutics

Inhibitory kinázy CK1

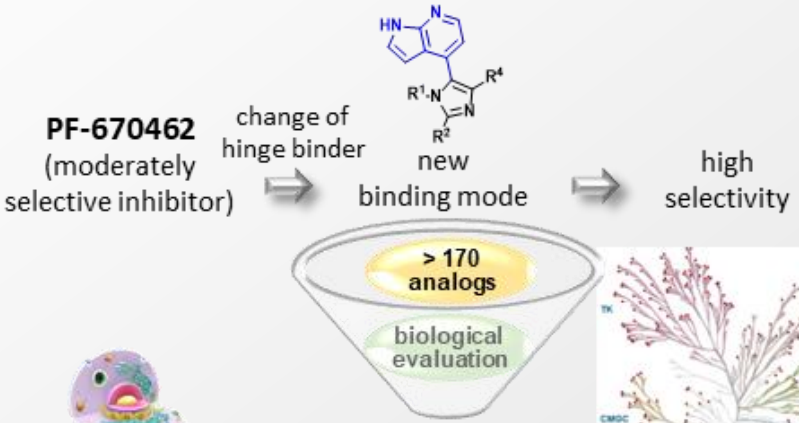
- inhibice CK1α : nová možnost léčby leukemie AML

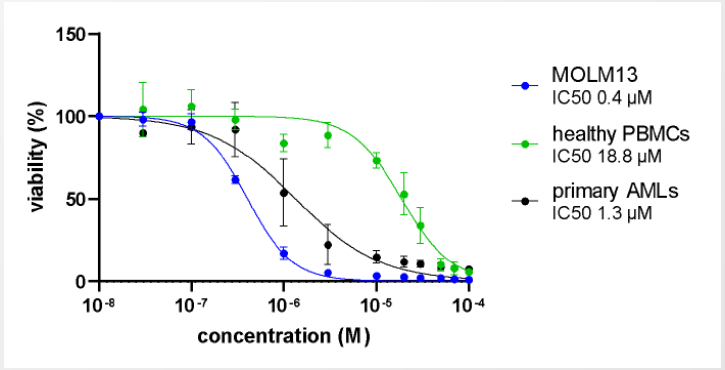
  Cell **2018**, *175*, 171.; *N. Engl. J. Med.* **2018**, *379*, 1873.

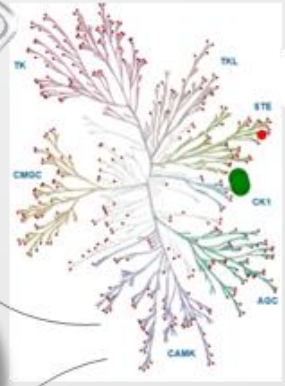
- účinné/selektivní CK1α inhibitory dosud nejsou známy



PF-670462
IC_{50} (CK1α) > 100 nM

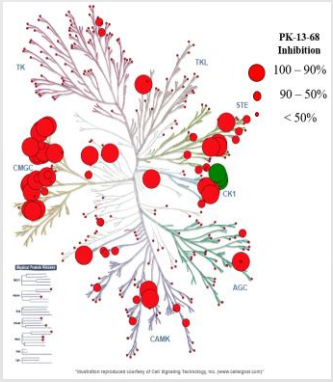






MU1742
IC_{50} (CK1α) = 7 nM
IC_{50} (CK1δ) = 6 nM
IC_{50} (CK1ε) = 27 nM

vs.



BTX-A51
IC_{50} (CK1α) = 34 nM
IC_{50} (CK1δ) = 6 nM
IC_{50} (CK1ε) = 21 nM

Cell **2018**, *175*, 171.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

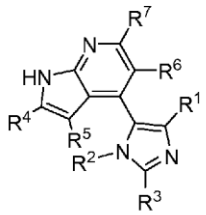
(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 October 2019 (03.10.2019)

WIPO | PCT

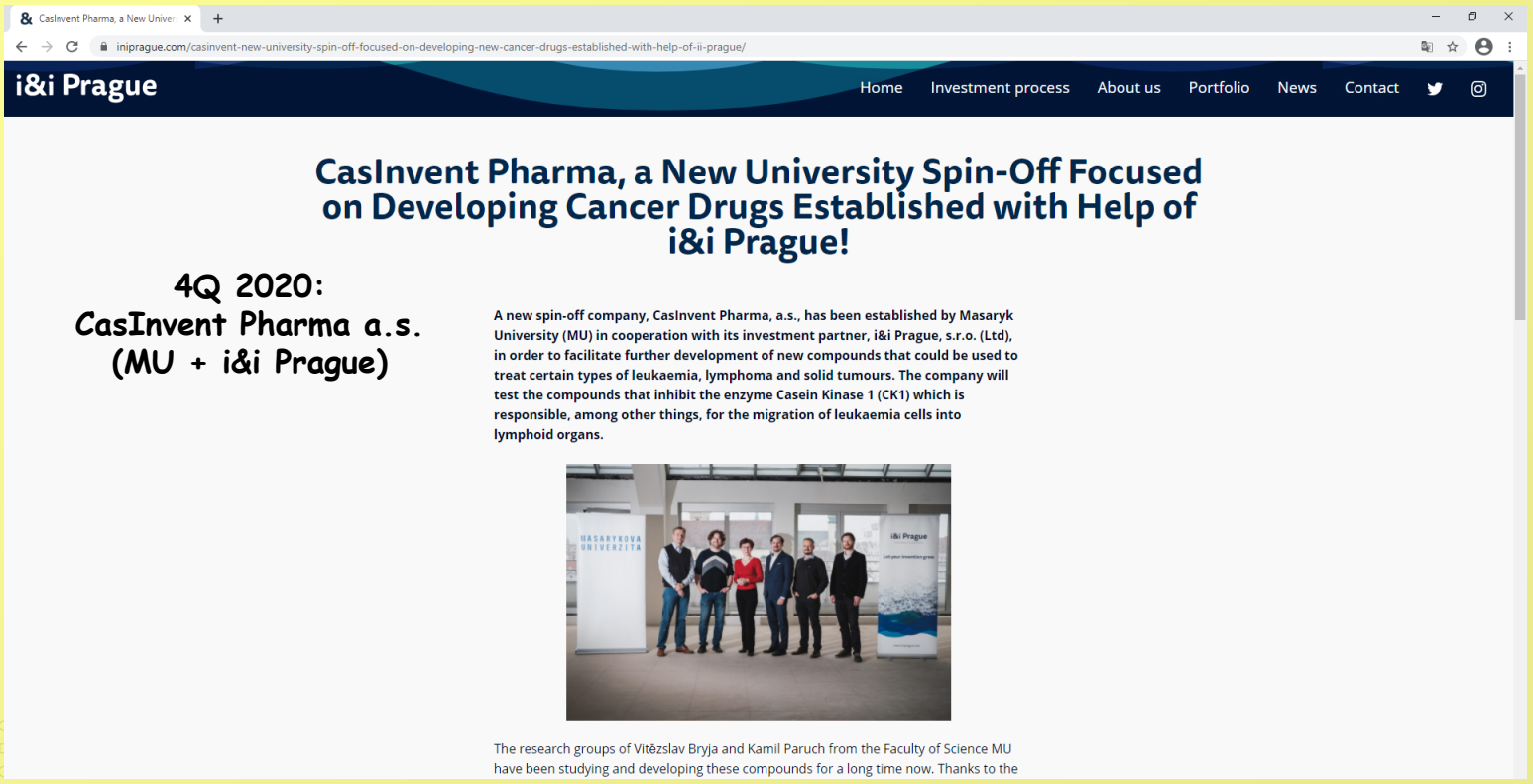
(10) International Publication Number
WO 2019/185631 A1

(54) Title: 4—(1H— IMIDAZOL— 5— YL) -1H-PYRROLO [2, 3-B] PYRIDINES FOR USE IN THE TREATMENT OF LEUKAEMIAS, LYMPHOMAS AND SOLID TUMORS

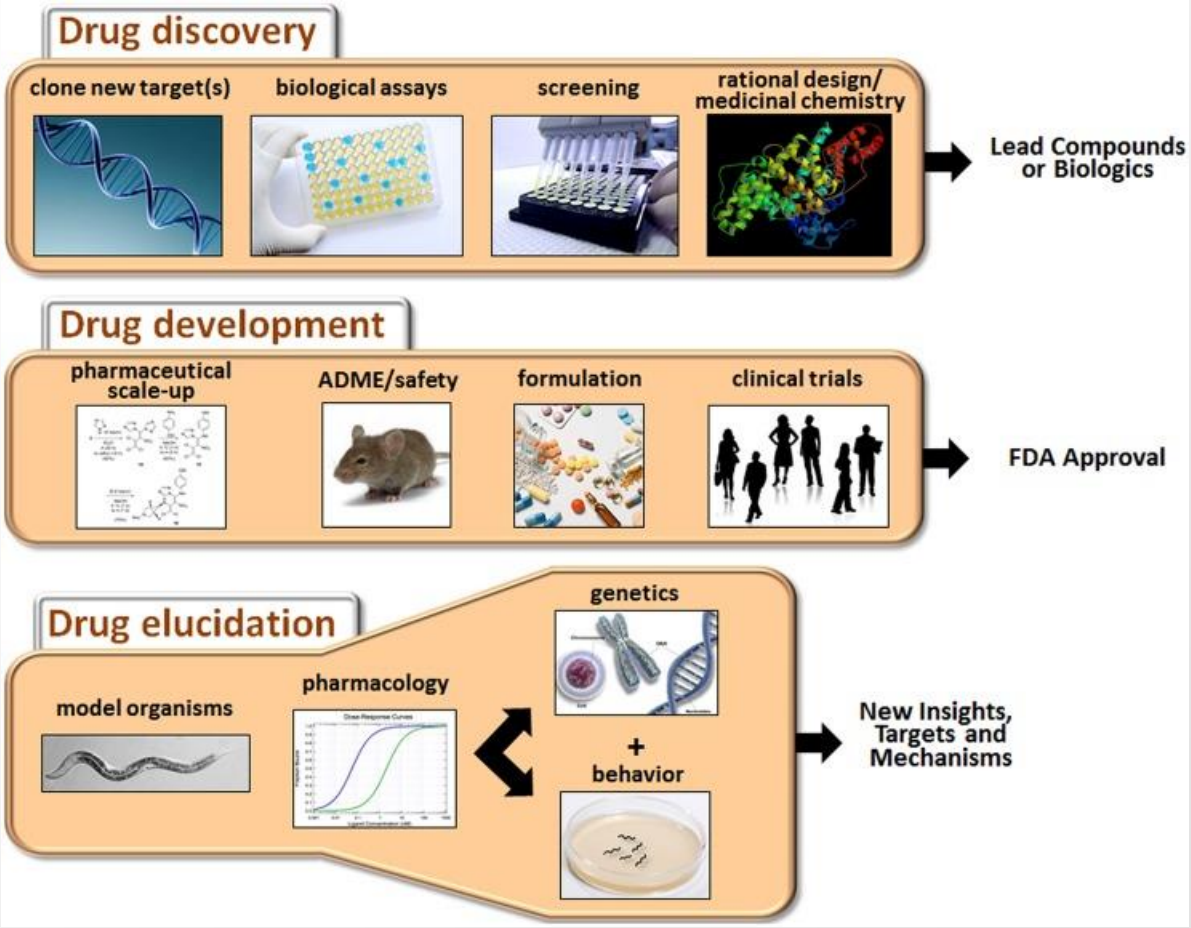


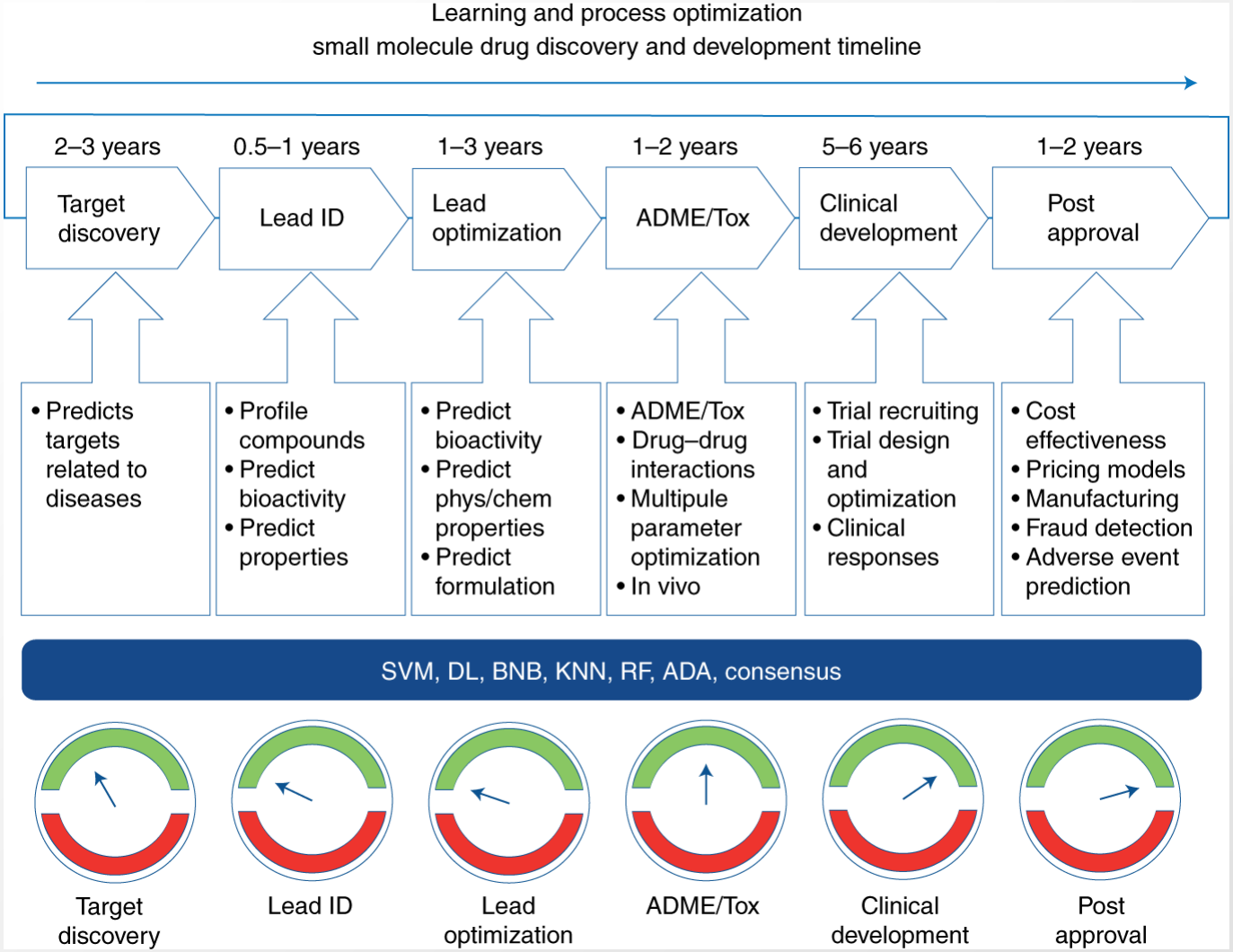
(57) Abstract: The present invention relates to novel 4-(1*H*-imidazol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine compounds which are useful in the treatment of lymphomas, leukaemias, and solid tumors.

CASINVENT

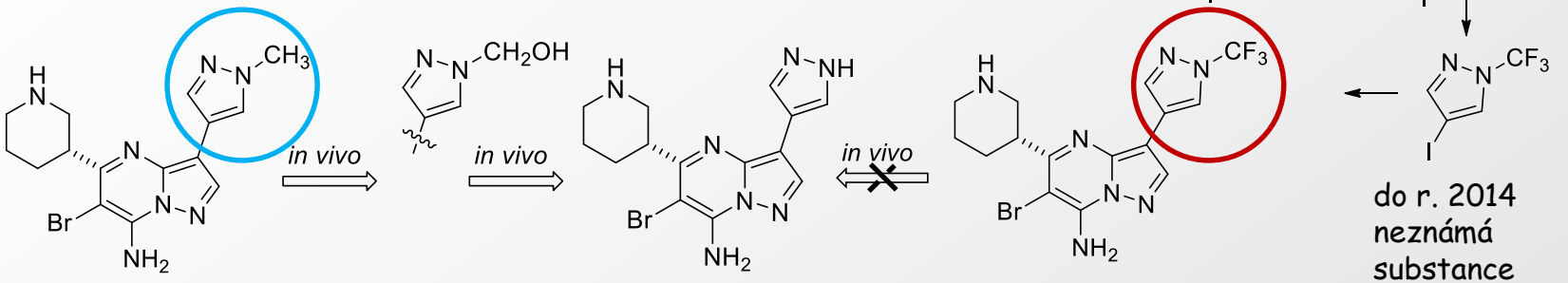


4Q 2020:
CasInvent Pharma a.s.
(MU + i&i Prague)


Drug discovery
clone new target(s)
biological assays
screening
rational design/ medicinal chemistry
Lead Compounds or Biologics
Drug development
pharmaceutical scale-up
ADME/safety
formulation
clinical trials
FDA Approval
Drug elucidation
model organisms
pharmacology
genetics
+
behavior
New Insights, Targets and Mechanisms


Learning and process optimization
small molecule drug discovery and development timeline
2–3 years
0.5–1 years
1–3 years
1–2 years
5–6 years
1–2 years
Target discovery
Lead ID
Lead optimization
ADME/Tox
Clinical development
Post approval
• Predicts targets related to diseases
• Profile compounds
• Predict bioactivity
• Predict properties
• Predict bioactivity
• Predict phys/chem properties
• Predict formulation
• ADME/Tox
• Drug–drug interactions
• Multipule parameter optimization
• In vivo
• Trial recruiting
• Trial design and optimization
• Clinical responses
• Cost effectiveness
• Pricing models
• Manufacturing
• Fraud detection
• Adverse event prediction
SVM, DL, BNB, KNN, RF, ADA, consensus
Target discovery
Lead ID
Lead optimization
ADME/Tox
Clinical development
Post approval

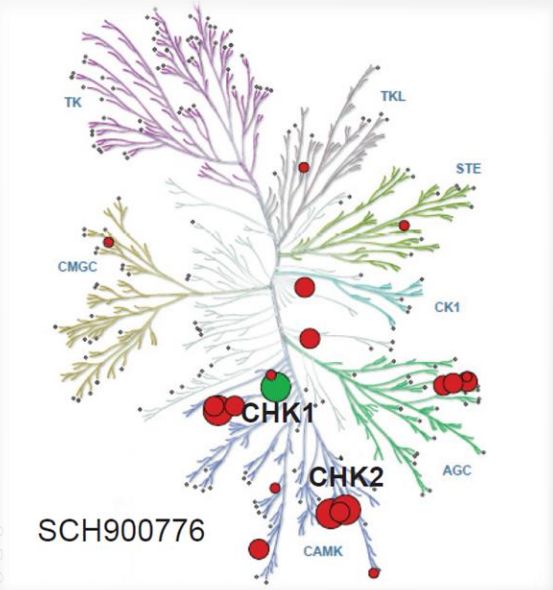
Inhibitory kinázy CHK1



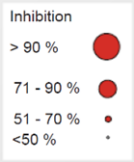
SCH 900776
CHK1 IC_{50} = 5 nM
fáze II klinického testování
(AML, kombinace s cytarabinem)

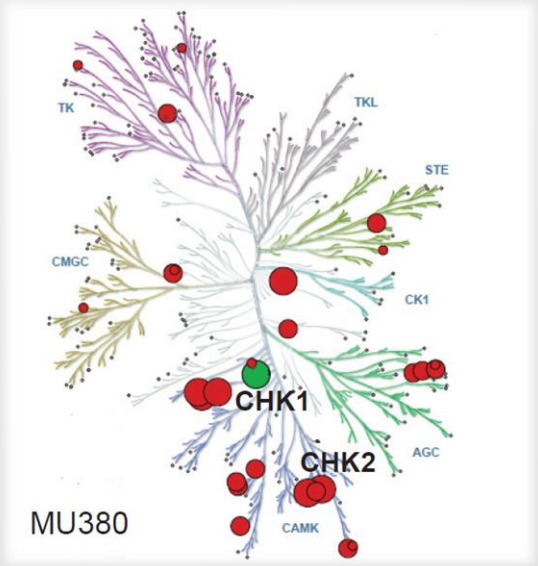
MU379
(metabolit)
výrazně méně selektivní
➢ „off-target" efekty

MU380
CHK1 IC_{50} = 2 nM
- účinnější *in vitro*
- výrazně účinnější v nádorových buňkách

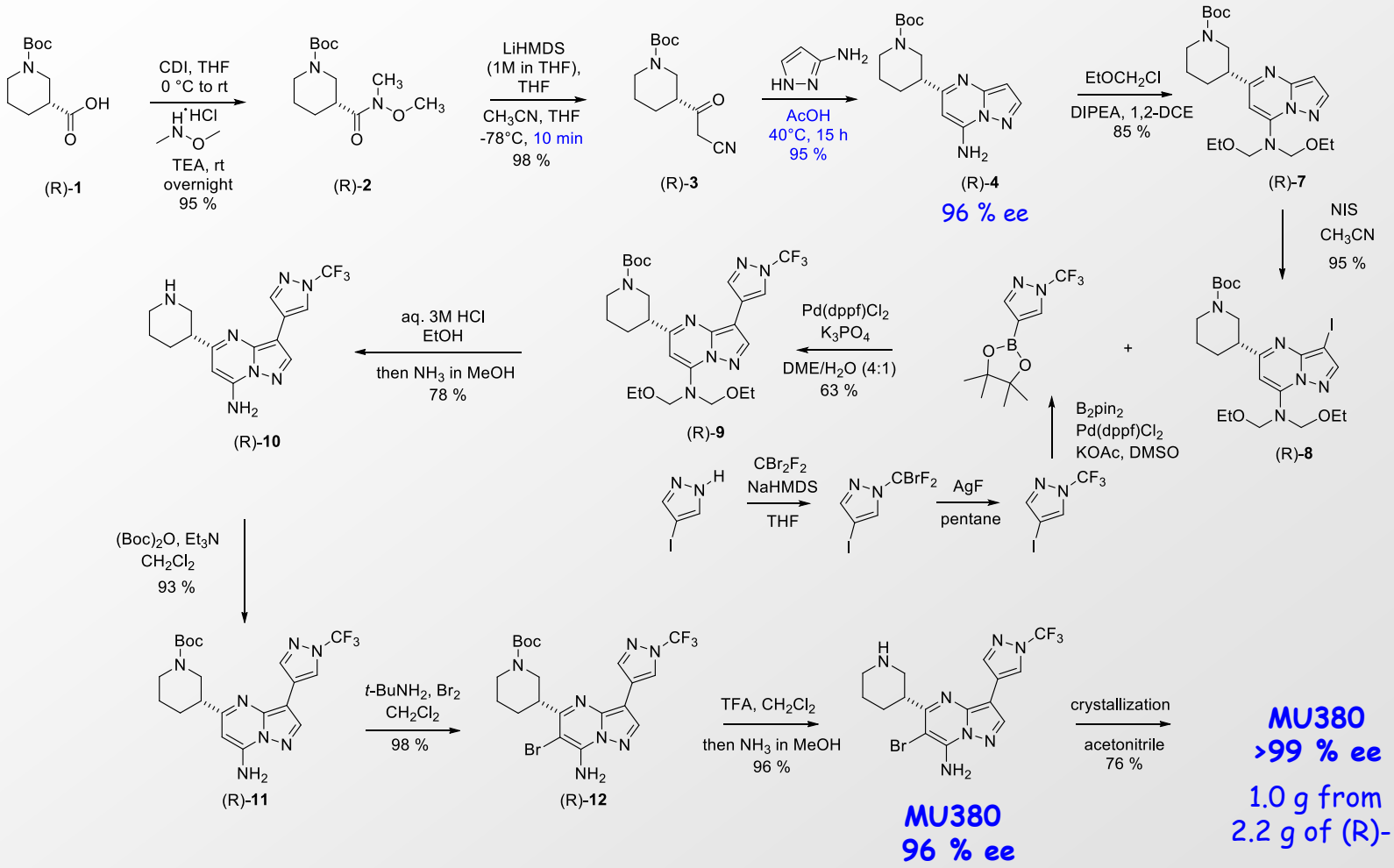


- srovnatelná selektivita 206 kináz @ 1 μM (Merck Milipore)



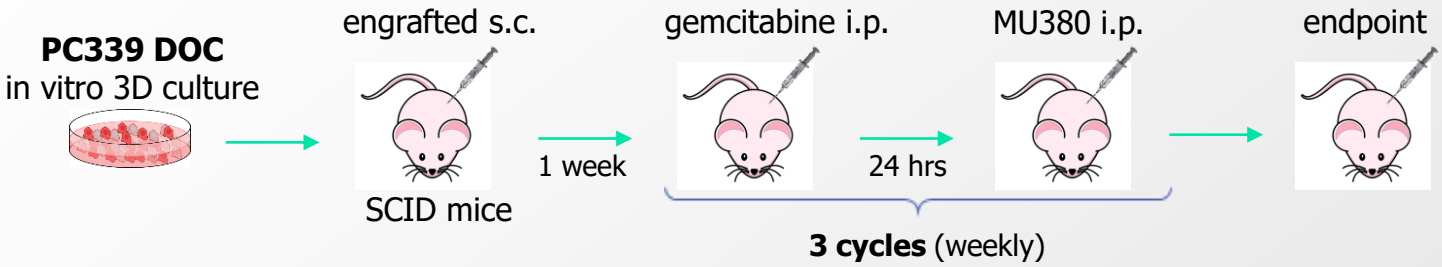


Enantioselektivní syntéza MU380

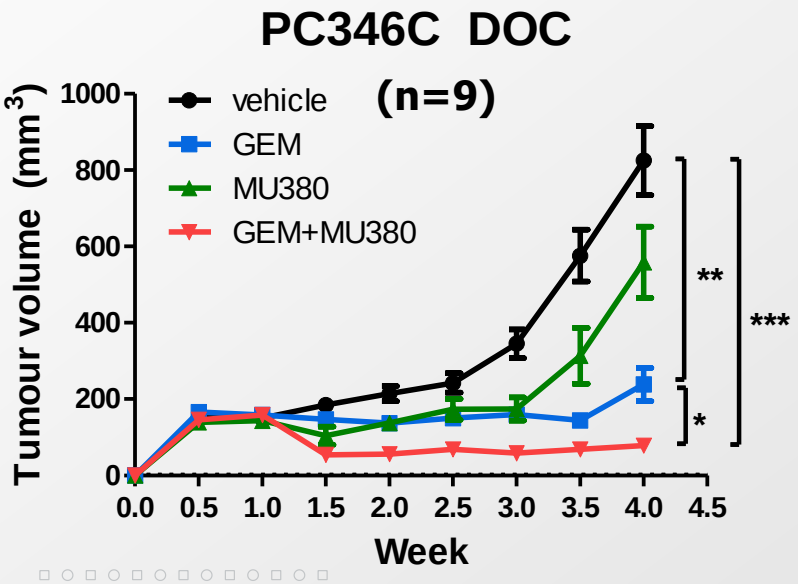


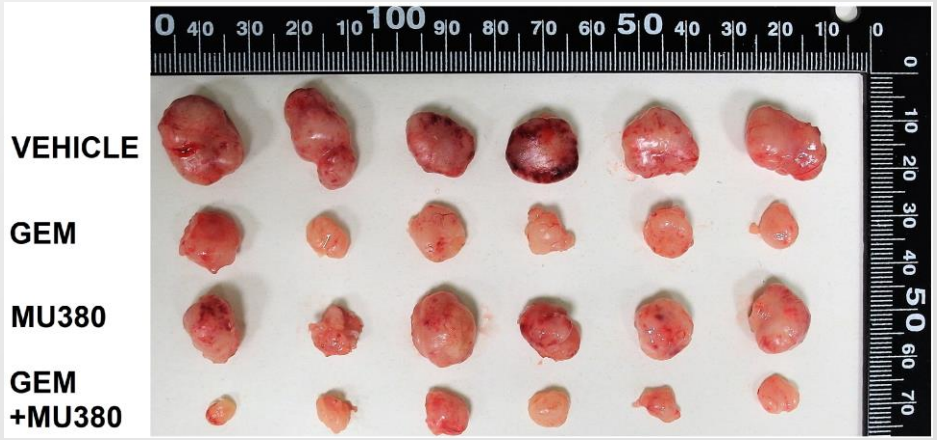
MU380 *in vivo*

- **docetaxel-resistant prostate cancer**



P. Sammader et al. *Mol. Cancer Ther.* **2017**, *16*, 1831.

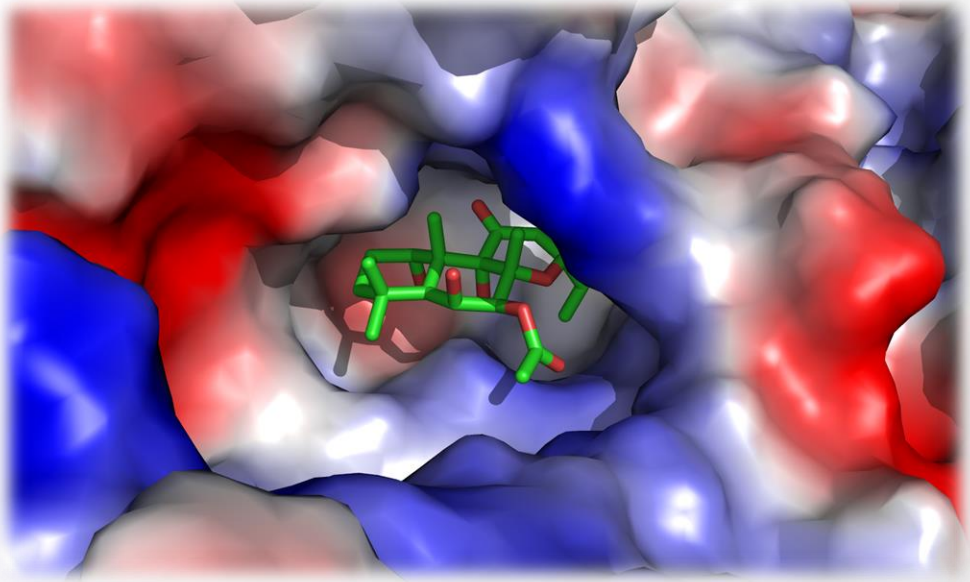


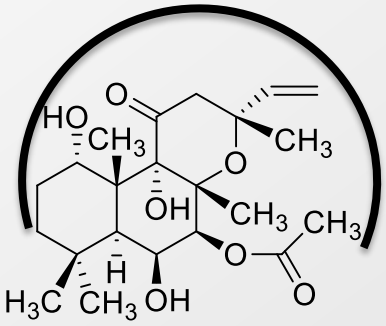


S. Drápela et al. *Mol. Oncol.* **2020**, *14*, 2487.

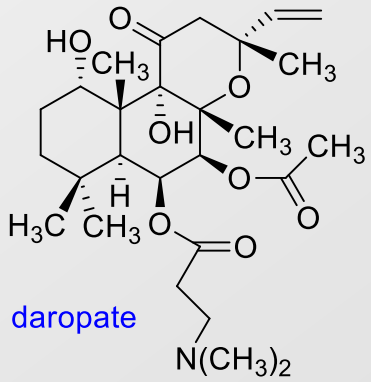
Forskolin a jeho analogy

- adenylátcyklázy (*ACs*) jsou atraktivní cíle (Pierre, S. et al. *Nat. Drug Disc.* **2009**, *8*, 321.)



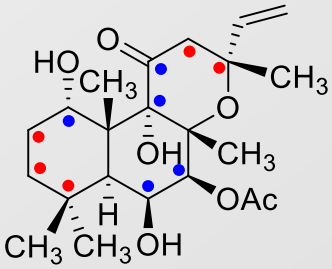


Forskolin



Colforsin daropate

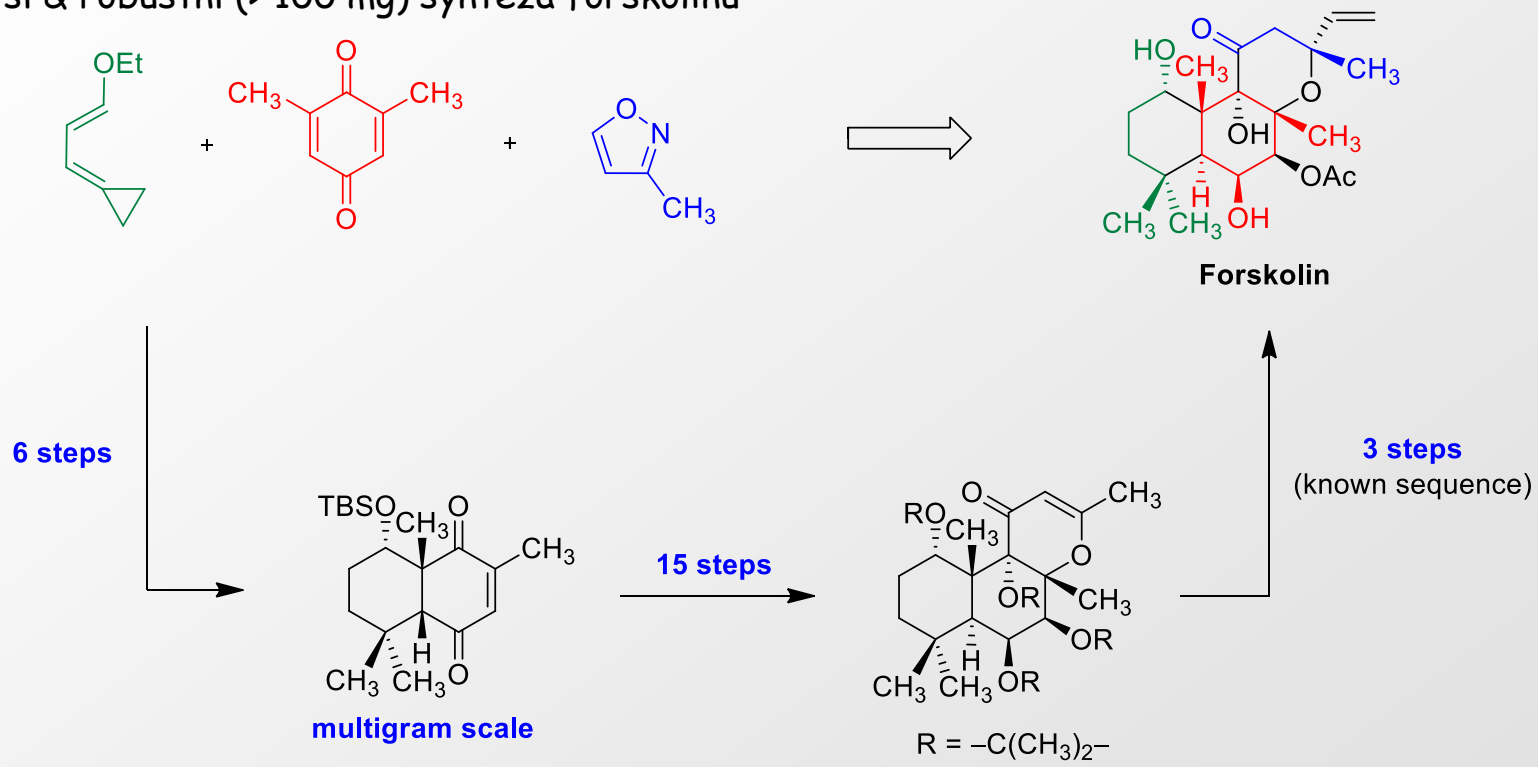
- deriváty forskolinu
  - selektivní aktivita vůči jednotlivým *ACs*



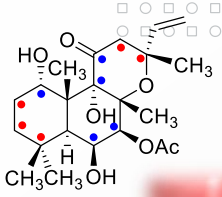
- pozice modifikovatelné semisynteticky
- pozice modifikovatelné synteticky

Naše syntéza forskolinu a jeho analogů

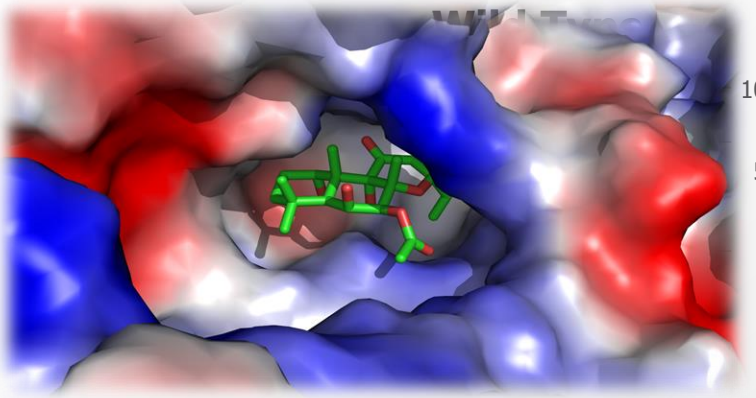
- nejkratší & robustní (> 100 mg) syntéza forskolinu

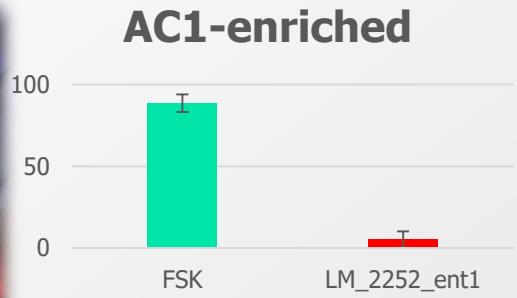


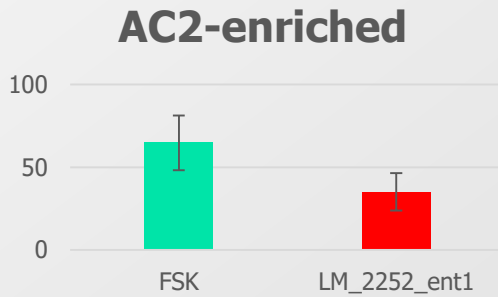
O. Hylse et al. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 12586.

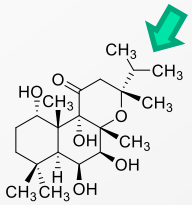


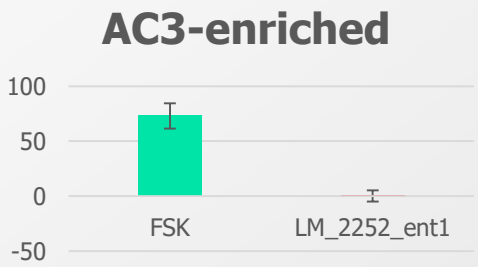
Biologická aktivita analogů forskolinu

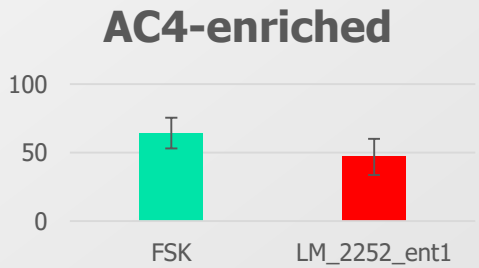


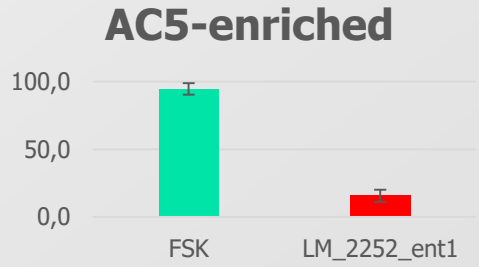


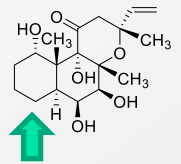


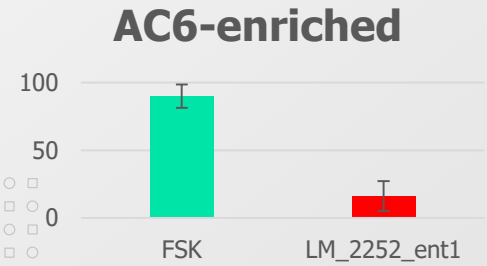


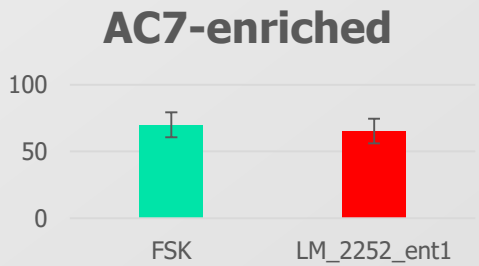


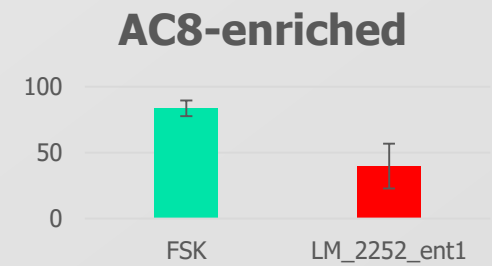












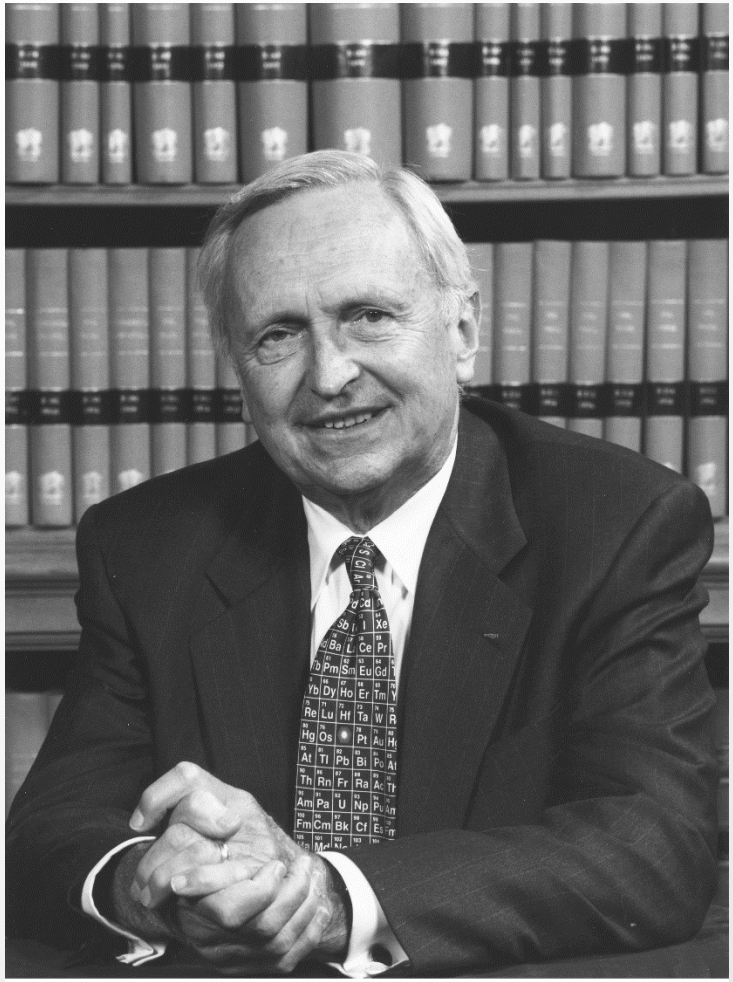
Laboratories of Organic Synthesis and Medicinal Chemistry
orgsyn.sci.muni.cz

- personnel
  - Dr. Kamil Paruch (Ph.D. Columbia University)
  - Dr. Jakub Švenda (Ph.D. Harvard University)
  - 6 postdocs,
  - 5 doctoral students,
  - 10 BS/MS/high school students,
  - 3 technicians

- modern laboratories in new campus

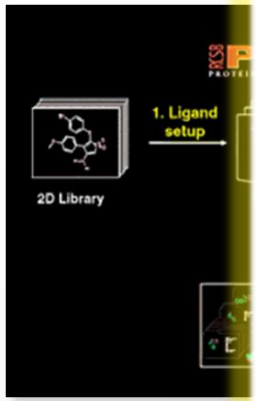
- state-of-the-art instrumentation
(e.g. in-house 500 MHz NMR, MS-TOF, autopurification LC/MS, semi-prep. chiral HPLC etc.)

The End



„Lidem, kteří se na nic neptají, nemá cenu cokoliv vykládat.“

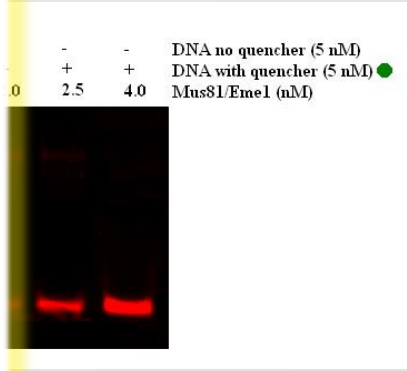
Inhibitory nukleáz



high-t

reening

- identifikovány inhibit
- žádné nízkomolekulár
- progrese „leads" (bio
  - Mus81: IC_{50} ~ 1
    - PCT I
  - Mre11: IC_{50} < 0.2
  - ***spolupráce s fir***



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20. 2. 2019 Artios exercises option to in-license potential first-in-class nuclease development programme - Artios

artios
DNA DAMAGE RESPONSE

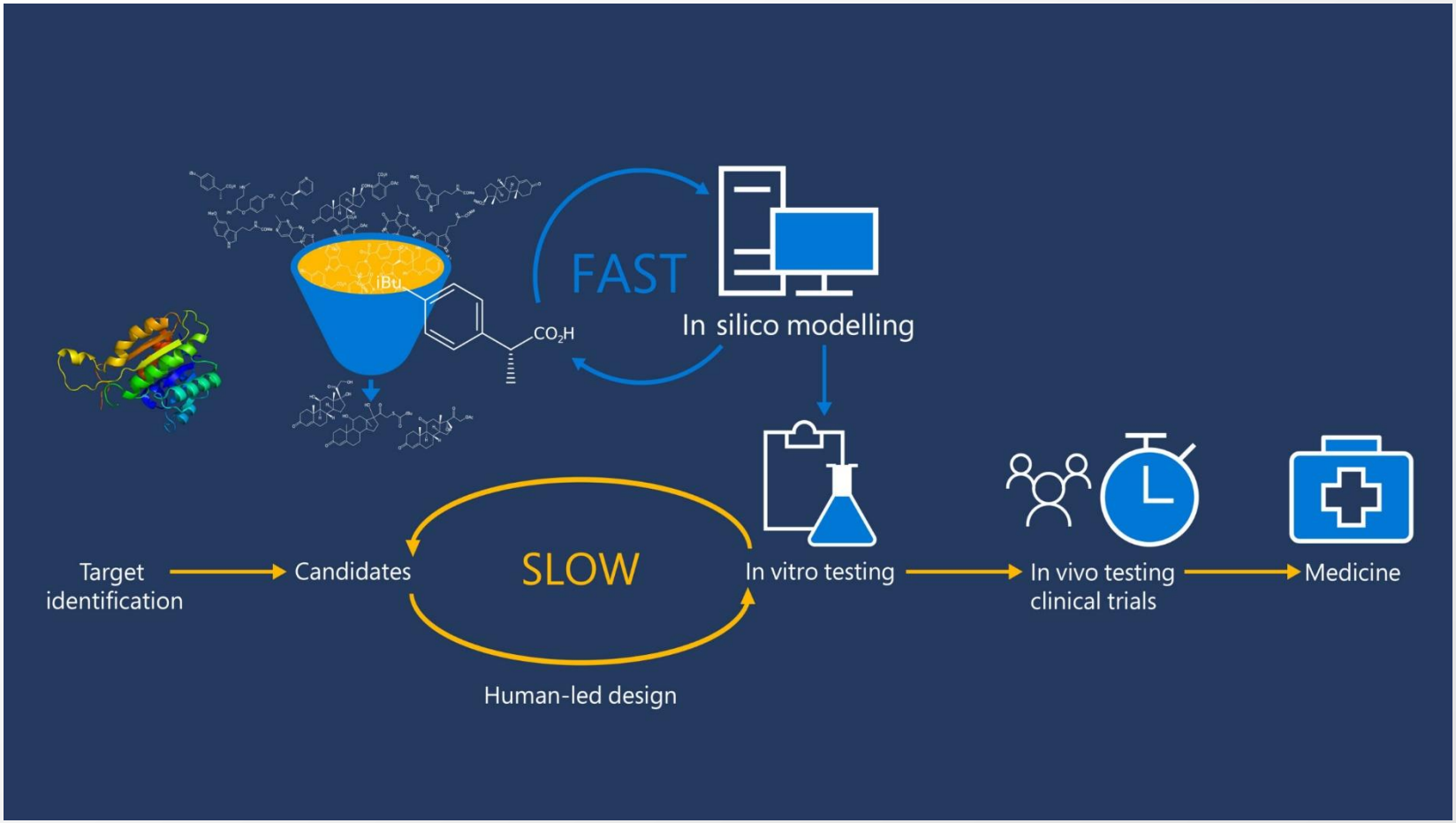
News and Events

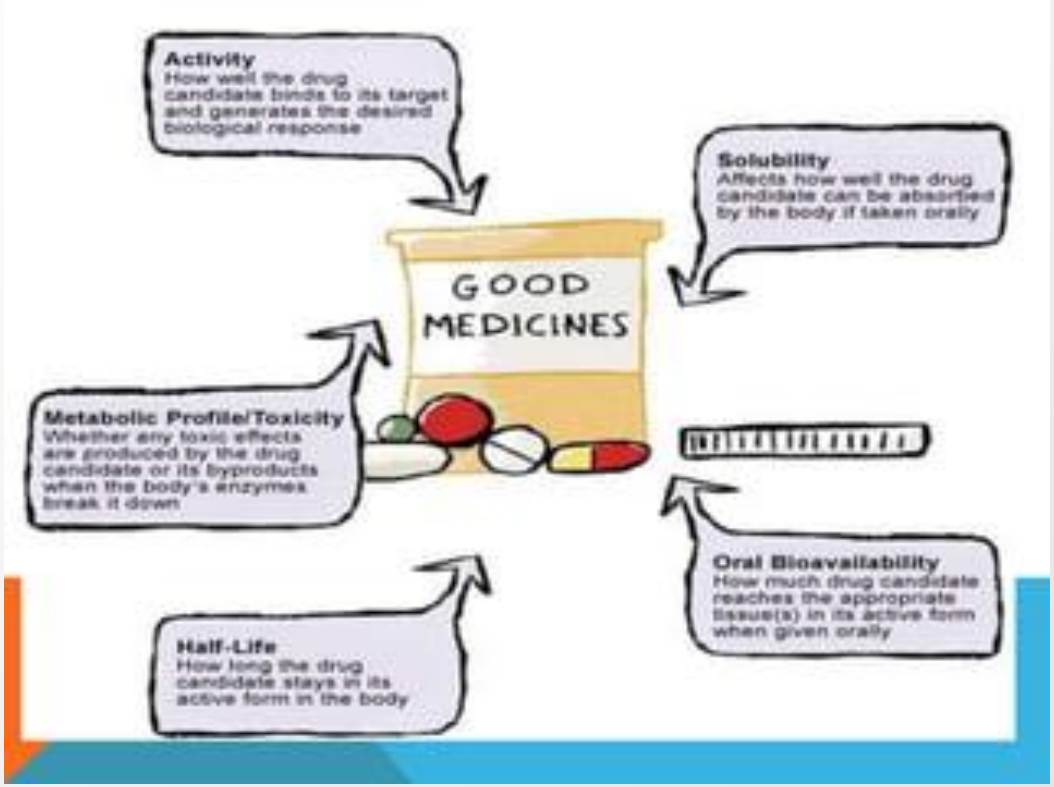
Follow our progress

Artios exercises option to in-license potential first-in-class nuclease development programme

Cambridge, UK, 5 March 2018. Artios Pharma, a leading DNA Damage Response (DDR) company developing innovative new treatments for cancer, today announces that it has exercised its option to in-license the first nuclease drug development programme under its research collaboration and option agreement with Masaryk University in the Czech Republic. The collaboration was formed in June 2017 to discover and develop novel cancer treatments by targeting DNA nucleases involved in the DDR.

Commenting on today's announcement, Niall Martin, Chief Executive Officer at Artios Pharma, said: "We are delighted to announce the in-licensing of our first nuclease programme from Masaryk University. This reflects the strong progress that has been made under our research and development collaboration with Drs Krejci and Paruch at Masaryk University on DDR nucleases. The in-licensed programme has the potential to become a novel, first-in-class DDR targeted treatment for cancer, which complements our current development pipeline and further supports our position as a leader in the DDR field."


FAST
In silico modelling
iBu
CO_2H
Target identification
Candidates
SLOW
In vitro testing
In vivo testing clinical trials
Medicine
Human-led design


Activity
How well the drug candidate binds to its target and generates the desired biological response
Solubility
Affects how well the drug candidate can be absorbed by the body if taken orally
GOOD MEDICINES
Metabolic Profile/Toxicity
Whether any toxic effects are produced by the drug candidate or its byproducts when the body's enzymes break it down
Oral Bioavailability
How much drug candidate reaches the appropriate tissue(s) in its active form when given orally
Half-Life
How long the drug candidate stays in its active form in the body