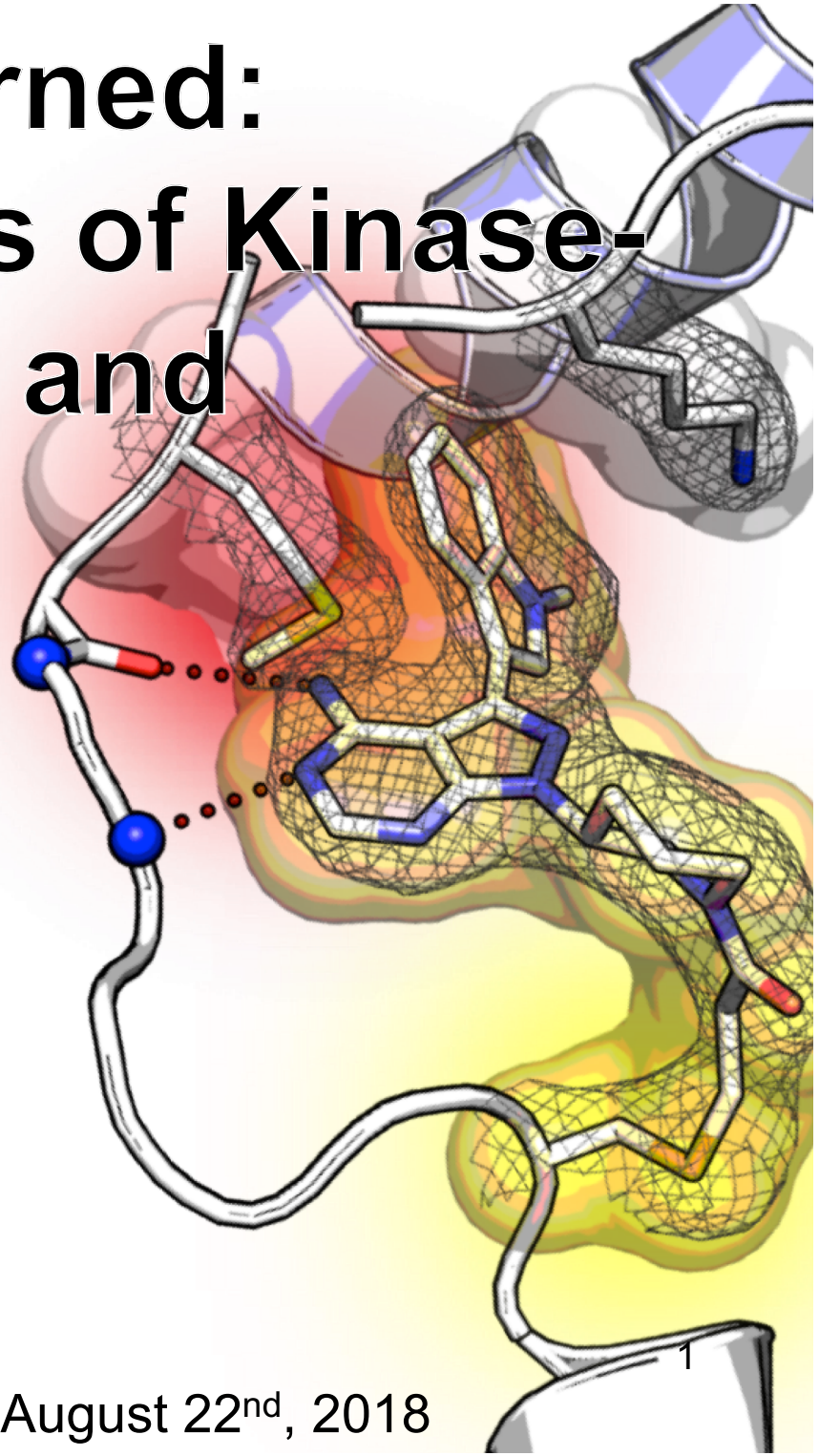
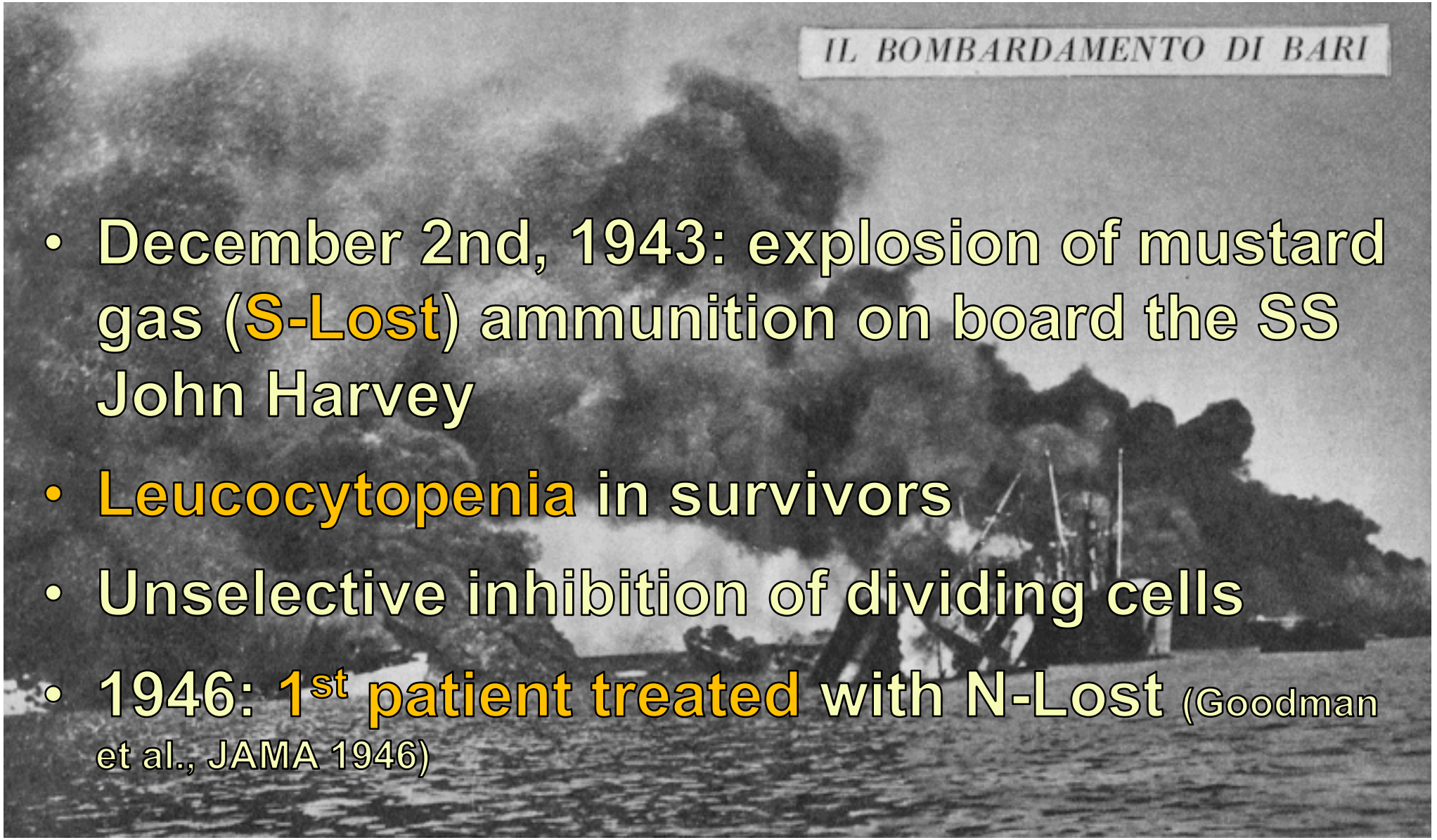
Lessons To Be Learned: The Molecular Basis of Kinase-Targeted Therapies and Drug Resistance in NSC Lung Cancer



Daniel Rauh
TU Dortmund University
Dortmund, Germany

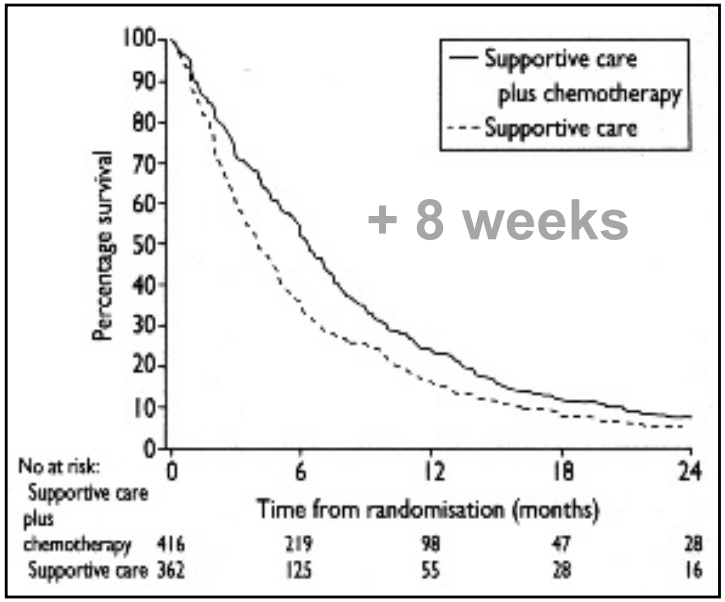
daniel.rauh@tu-dortmund.de

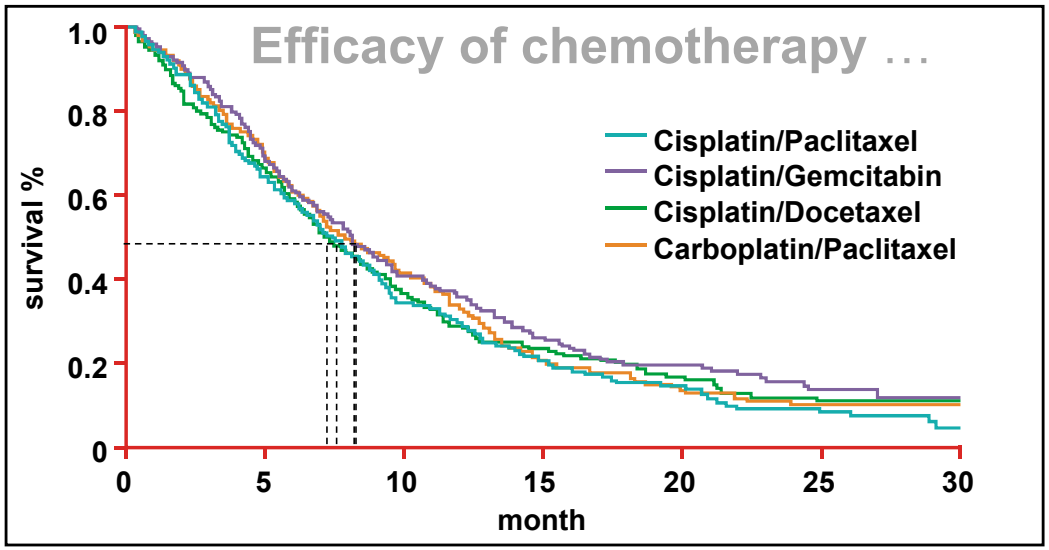
11th Swiss Pharma Science Day 2018, Bern, August 22nd, 2018



- December 2nd, 1943: explosion of mustard gas (S-Lost) ammunition on board the SS John Harvey
- Leucocytopenia in survivors
- Unselective inhibition of dividing cells
- 1946: 1st patient treated with N-Lost (Goodman et al., JAMA 1946)

Progress in the treatment of lung cancer?



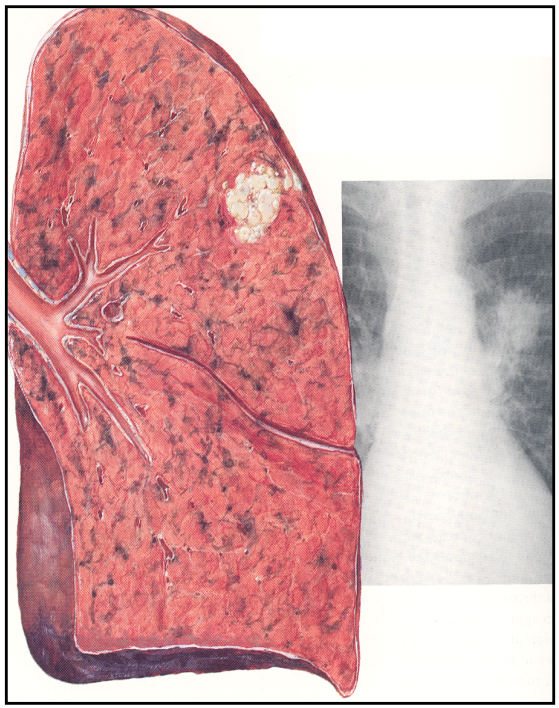


NSCLC Collaborative Group & MRC UK (Cullen **1997**)

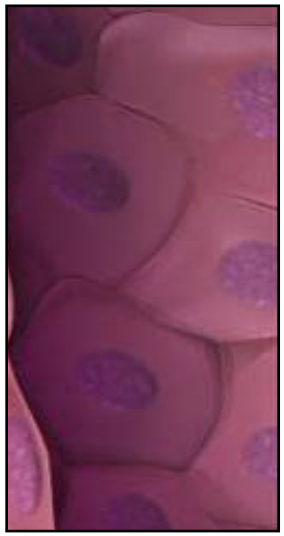
J. Schiller, *N Engl J Med.* **2002**, *346*, 92-8.

Understanding tumor biology – molecular biology revolution

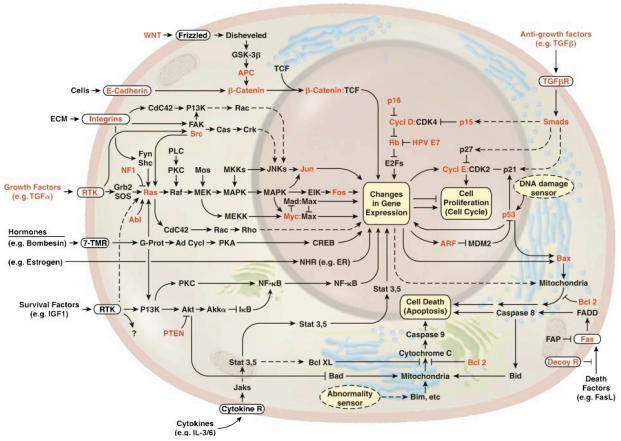
organ



tissue



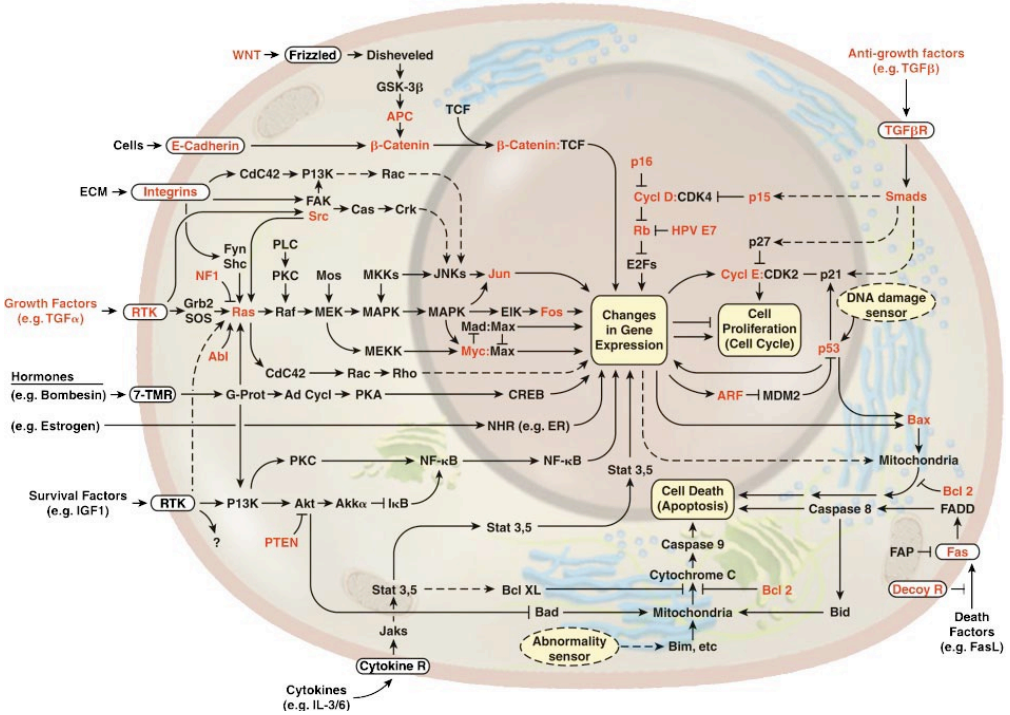
cell



Precision medicine

Last decade: revolutionary epoch of cancer science & cancer medicine

- Molecular, atomic **understanding** of cancer
- **Knowledge** about genes; why cancer; how it manifests and spreads …



R.A. Weinberg, et al., *Cell* **2000**, *100*
"The Hallmarks of Cancer"; R.A. Weinberg, et al., *Cell* **2011**, *144,* "Hallmarks of Cancer: The Next Generation"

Precision medicine

Cancer is a disease of the genome!

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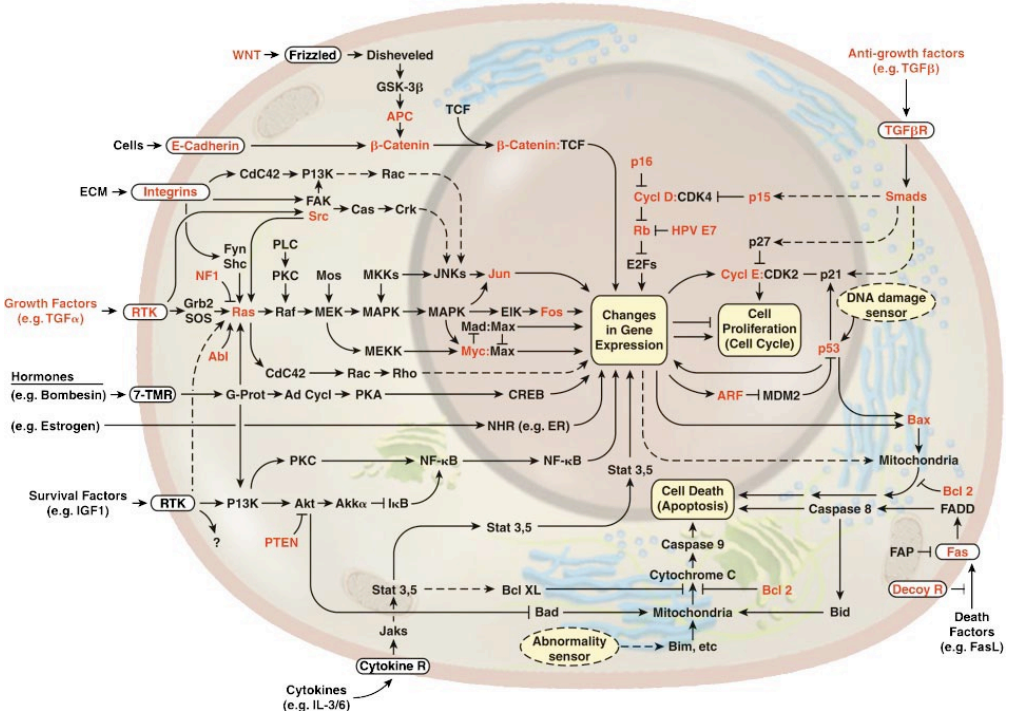

R.A. Weinberg, et al., *Cell* **2000**, *100*
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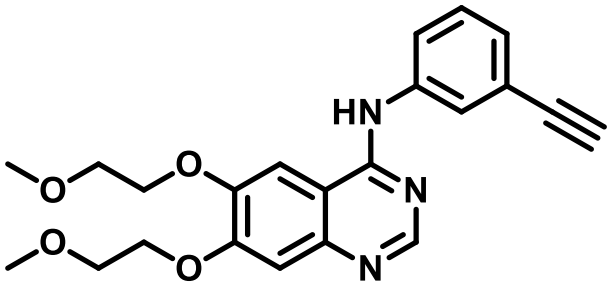
Precision medicine

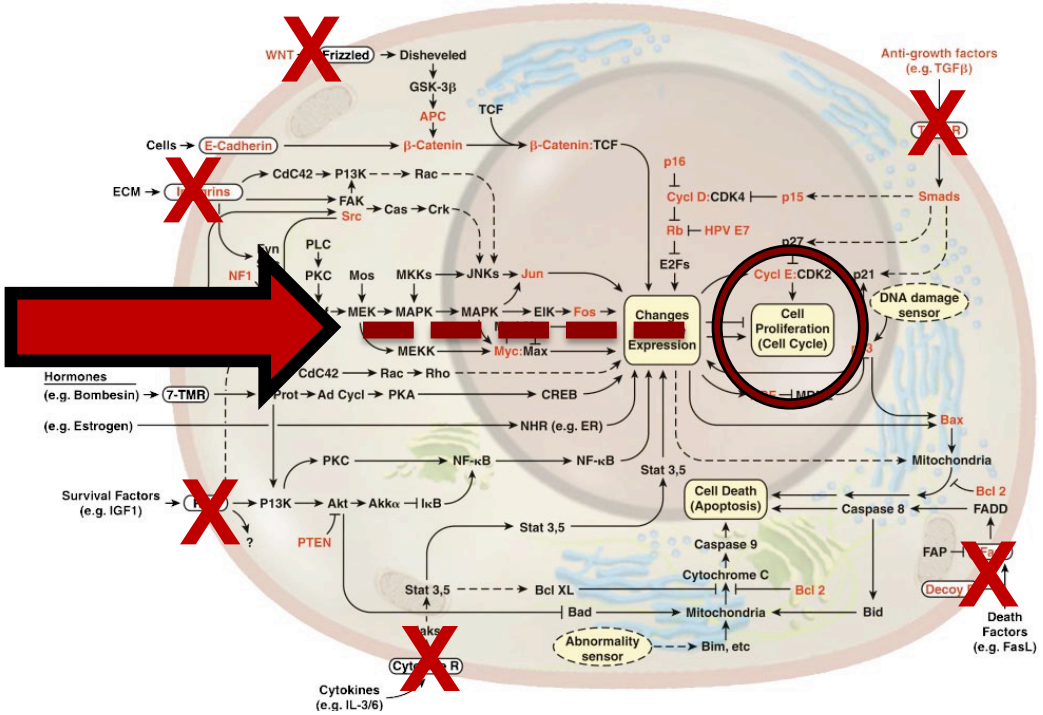
Cancer is a disease of the genome!

Hour of birth of Precision medicine

- cancer arises and persists because of **mutations**
- **attacking** the **weaknesses**



Erlotinib, approved by the FDA 2005



R.A. Weinberg, et al., *Cell* **2000**, *100*
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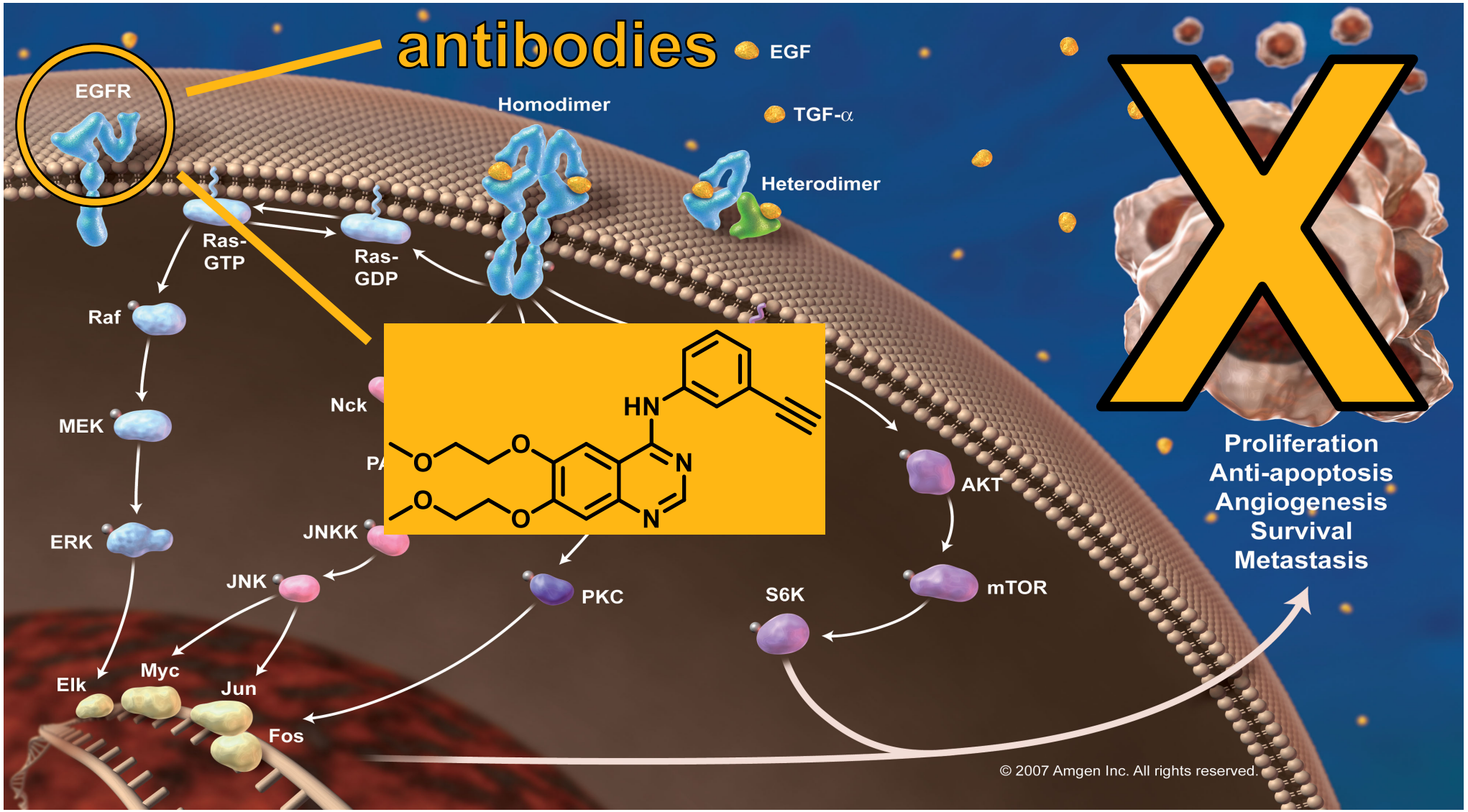
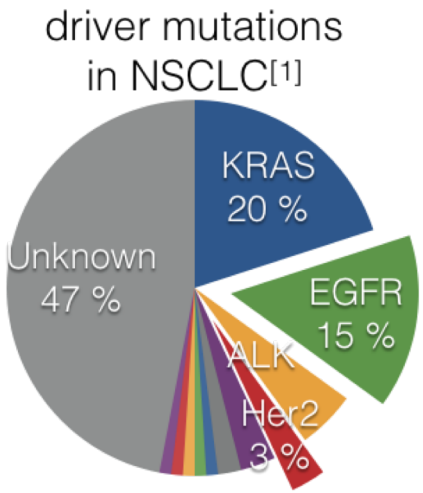
technische universität
dortmund

EGFR: molecular signaling switch of tumor cells



What are these weaknesses?



- **amplifications**
- **mutations**
- **deletions**
- **insertions**
- **oncogene addiction**
- **oncogenic shock**
- **predictive for resp.**

[1] M.E. Arcila, et al., *Clinical cancer research* **2012**, *18*, 4910-4918.
[2] W. Pao, et al., *Nature medicine* **2012**, *18*, 349-351.
[3] H.A. Yu, et al., *Clin Cancer Res* **2013**, *19*, 8, 2240-2247.
[4] G. R. Oxnard, et al., *in 16th World Conference on Lung Cancer* (*Denver, Colorado,* **2015**).
[5] M.E. Arcila, et al., *Mol Cancer Ther* **2013**, *12*, 2, 220-229.

What are these weaknesses?

ications

ons

ons

ons

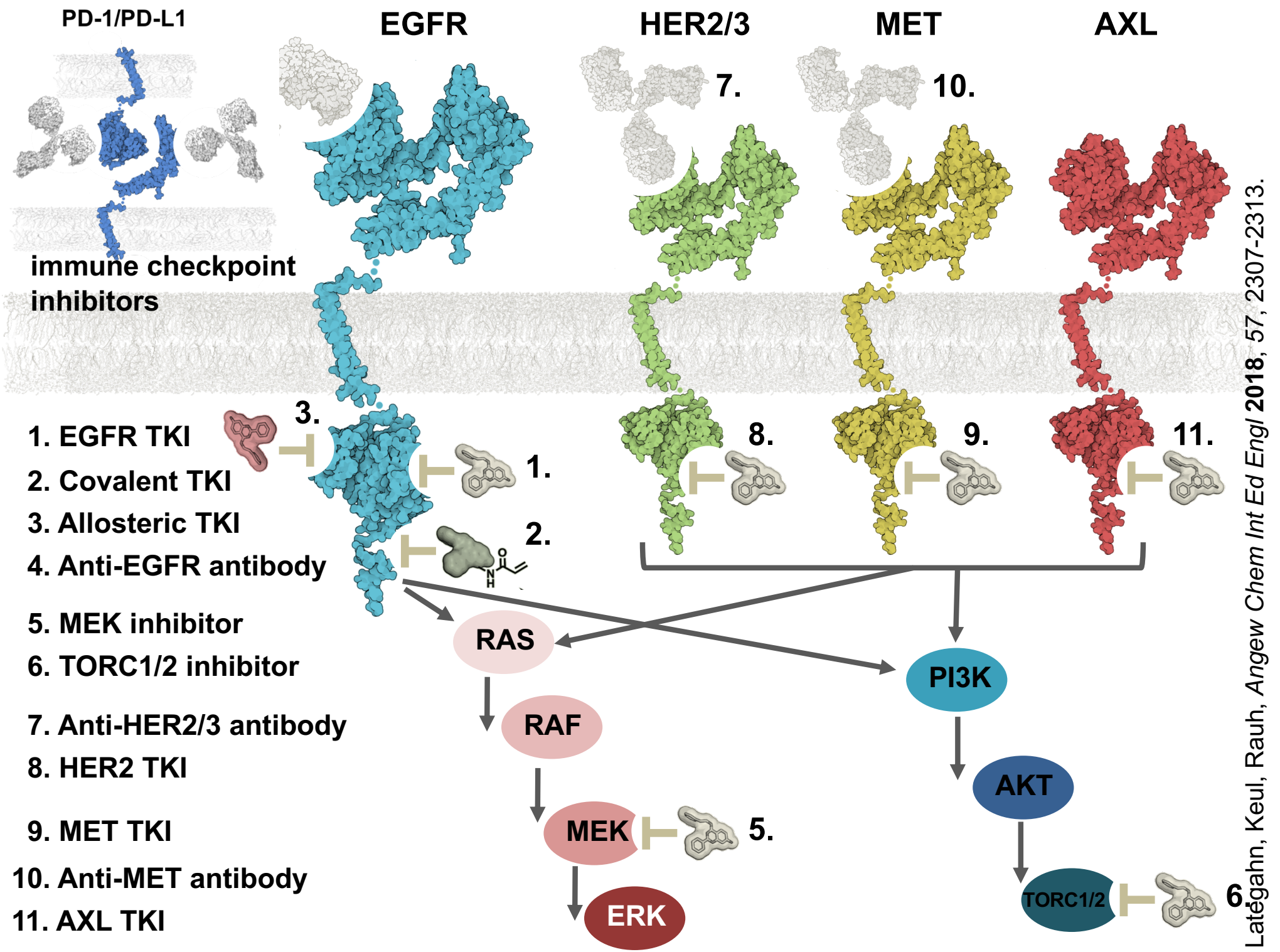
ene addiction

enic shock

- predictive for resp.

Seeing the “dragon”, its weaknesses

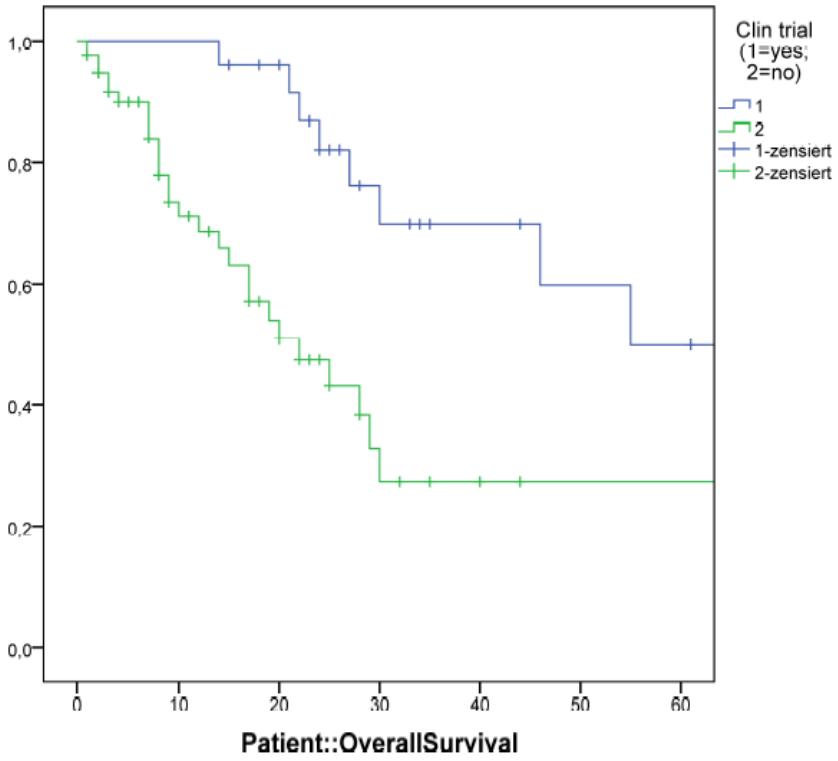
Knowing how to attack …


PD-1/PD-L1
EGFR
HER2/3
MET
AXL
immune checkpoint inhibitors
1. EGFR TKI
2. Covalent TKI
3. Allosteric TKI
4. Anti-EGFR antibody
5. MEK inhibitor
6. TORC1/2 inhibitor
7. Anti-HER2/3 antibody
8. HER2 TKI
9. MET TKI
10. Anti-MET antibody
11. AXL TKI
RAS
RAF
MEK
ERK
PI3K
AKT
TORC1/2
Latégahn, Keul, Rauh, *Angew Chem Int Ed Engl* **2018**, 57, 2307-2313.

NGM-Evaluation II: Nächstgenerations-Inhibitoren verlängern das Überleben signifikant

Netzwerk Genomische Medizin Lungenkrebs

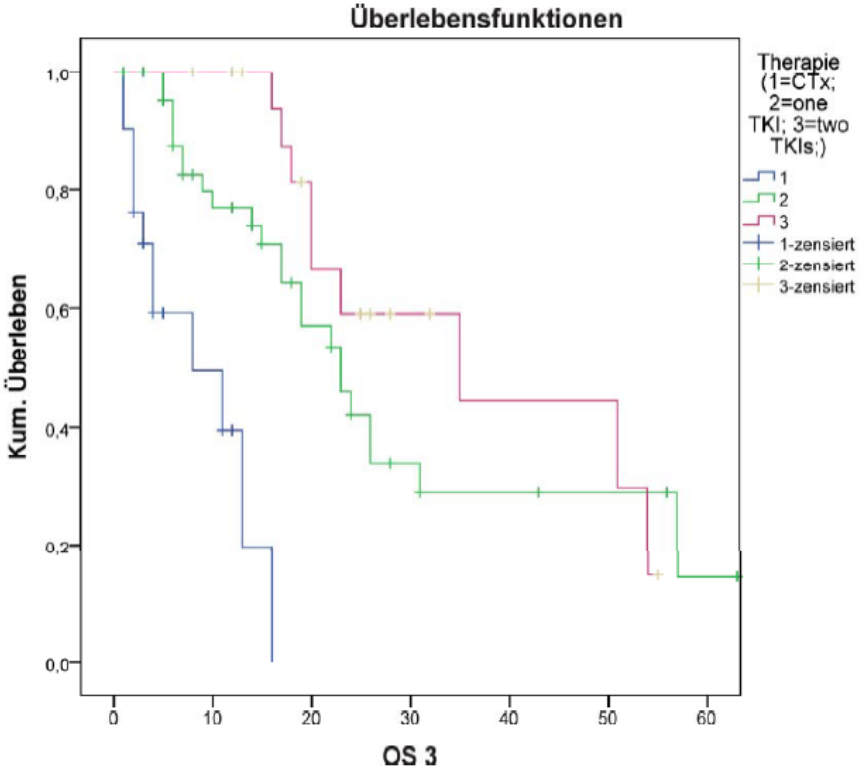
EGFR Mutation



	No. of pts	mOS
1 = clin trial	25	55
2 = no trial	83	22
Total	108	29
P = 0,002 (log-rank test)		

Einsatz von Dritt.gen.EGFR-Inh.

ALK Fusion



1: Chemo: 21 pts - mOS 8
2: 1 ALKi. 45 pts - mOS 22
3: 2 ALKi. 19 pts - mOS 35

P < 0,0001

Kostenko et al, ASCO 2017

Curtesy Jürgen Wolf, Köln

What are these weaknesses?

Seeing the “dragon”, its weaknesses

but …

rare alterations, 04/18 28 drugs, resistance …

Chemical Oncology

converging cancer genetics, structural biology and medicinal chemistry …

Roman Thomas, Köln

Martin Sos, Köln

Reinhard Büttner, Köln

Sebastian Bauer, Essen

Martin Schuler, Essen

Jens Siveke, Essen

NOVARTIS

Bundesministerium für Bildung und Forschung

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

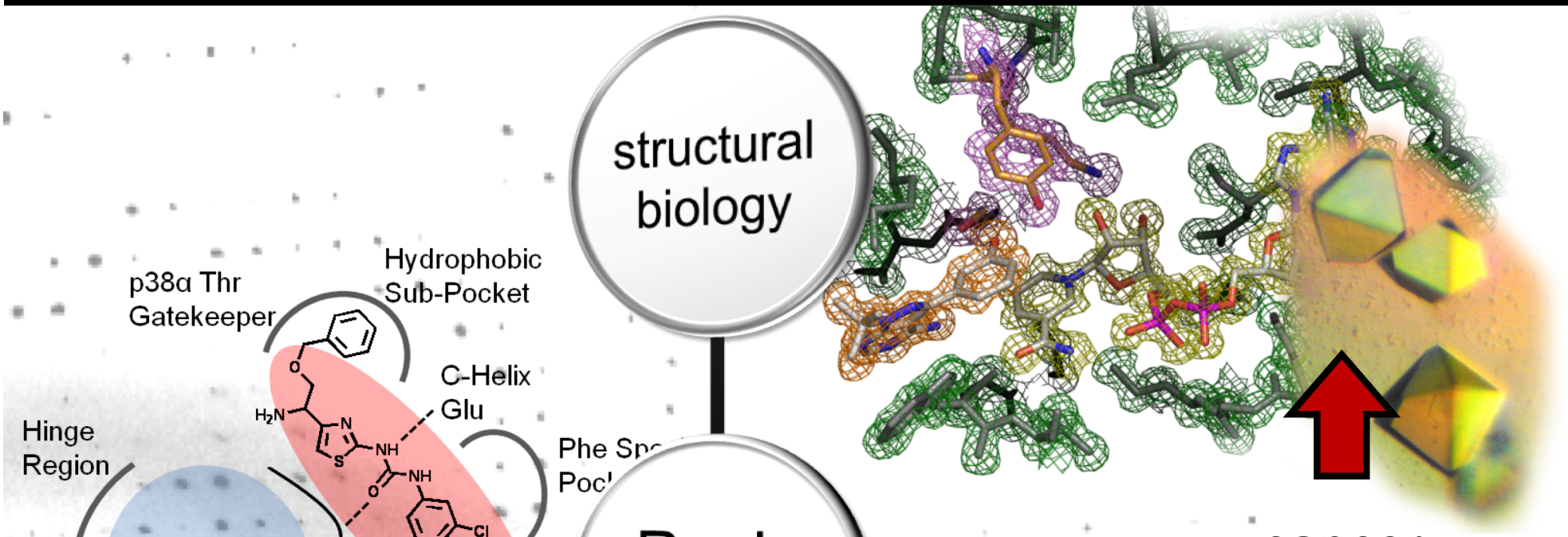
Lead Discovery Center LDC

technische universität dortmund

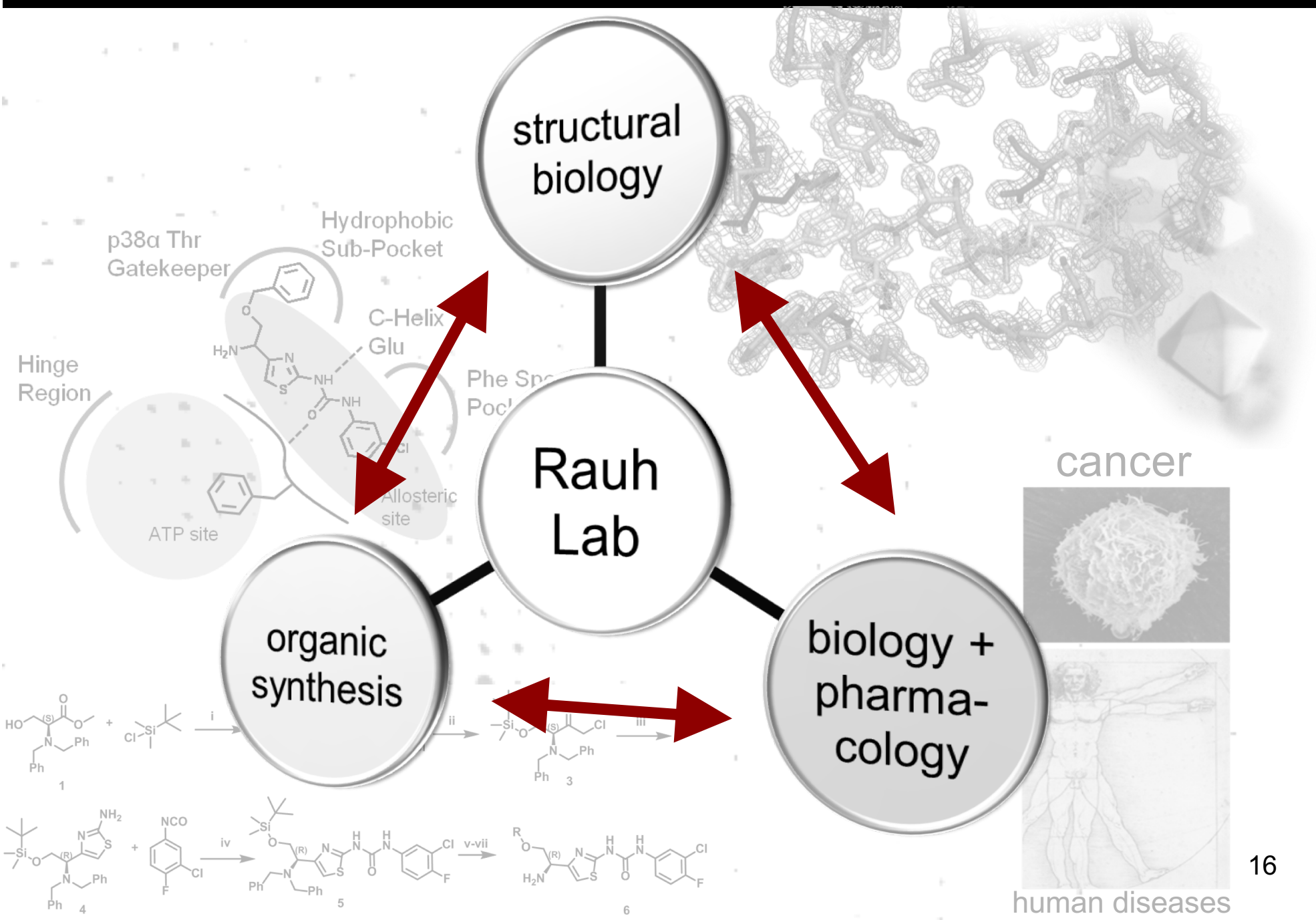
TAROS

Deutsche Forschungsgemeinschaft DFG

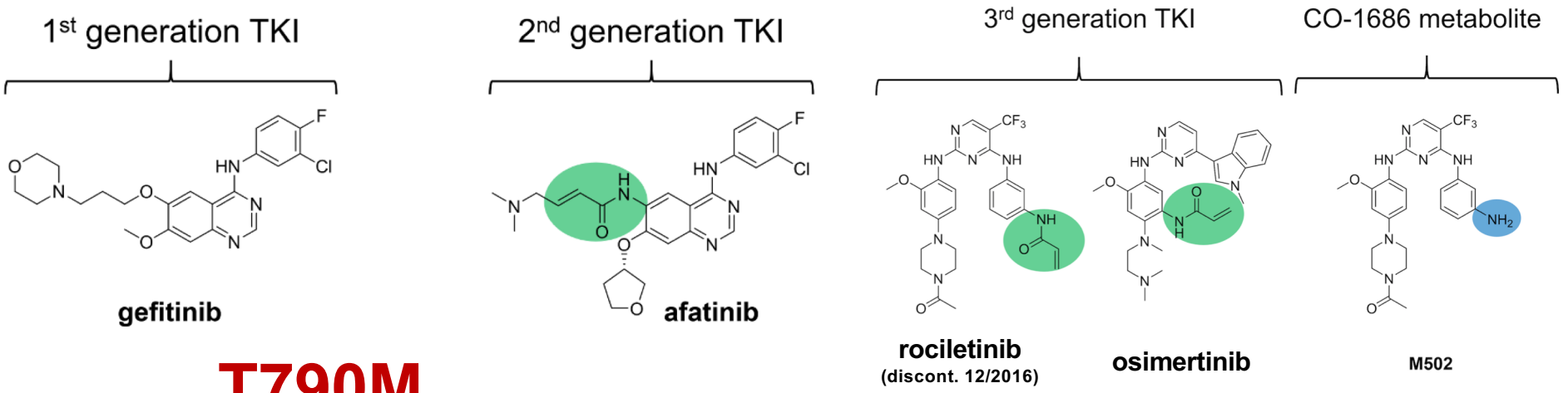
Small Molecules for Dissecting Protein Function

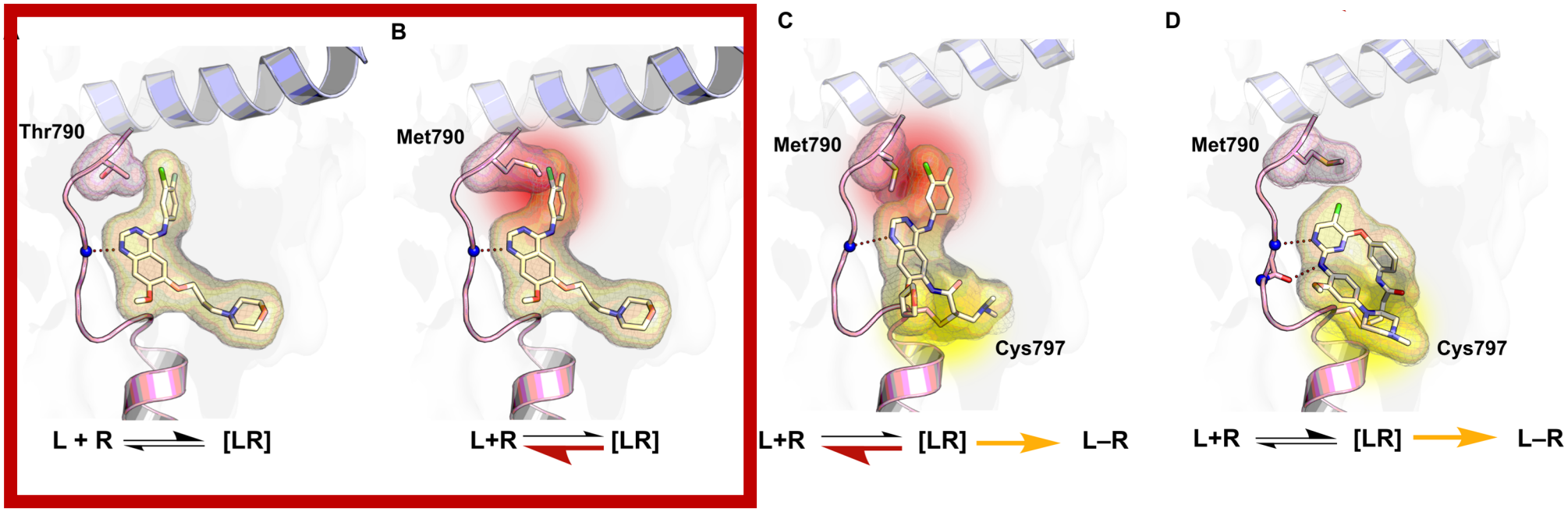


Small Molecules for Dissecting Protein Function



Hope and Disappointment: Covalent Inhibitors to Overcome Drug Resistance in Non-Small Cell Lung Cancer





Engel, Lategahn, Rauh, *ACS Med Chem Lett,* **2016**, *7(1):2-5.*

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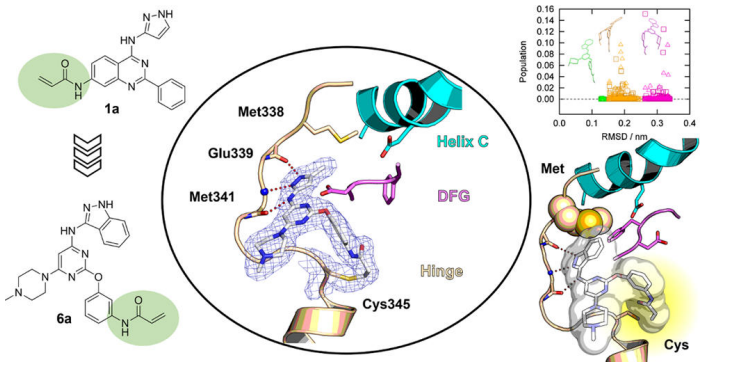
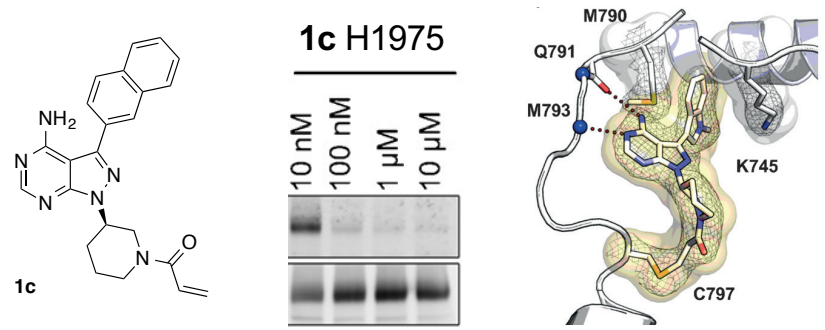
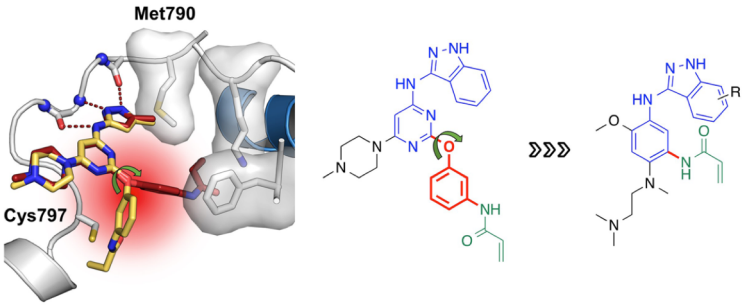


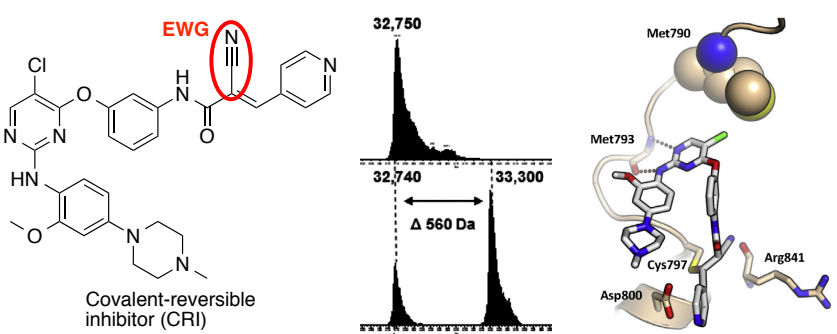
Engel, et al. *J Med Chem* **2015,** *58*, 6844-63.



Engel, Becker, et al. *Angew. Chem. Int. Ed.* **2016**.
Engel, Smith, et al., *J Med Chem* **2017,** *60*, 7725-7744.



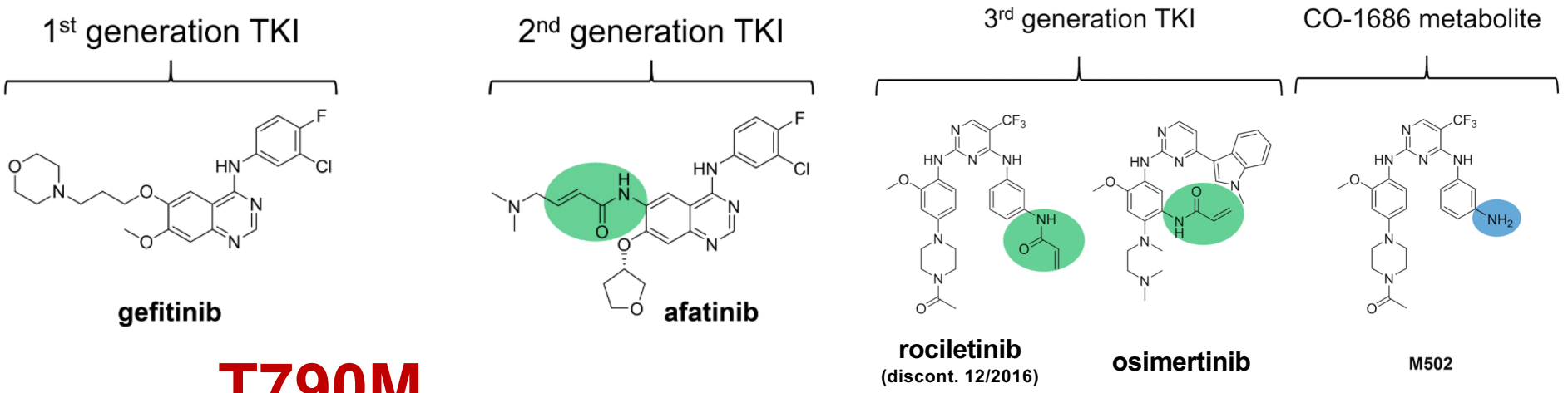
Tomassi, Lategahn, et al.
J Med Chem **2017,** *60*, 2361-2372.



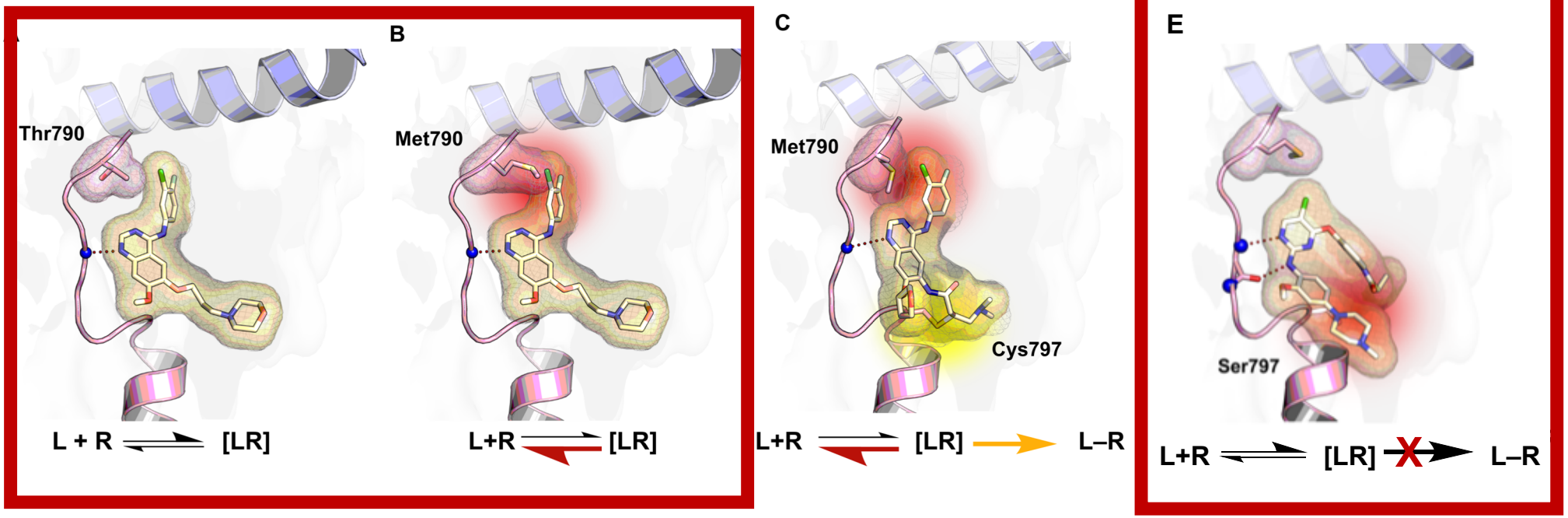
Basu, et al. *Bioorg Med Chem* **2015,** *23*, 2767-80.
Smith, et al. *ACS Omega* **2017,** *2*, 1563-1575.

Engel, Lategahn, Rauh, *ACS Med Chem Lett,* **2016**, *7(1):2-5.*

Hope and Disappointment: Covalent Inhibitors to Overcome Drug Resistance in Non-Small Cell Lung Cancer



T790M

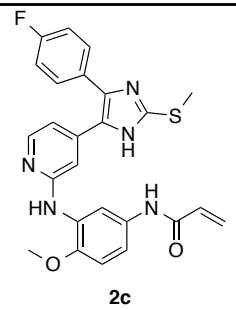


C797S

Engel, Lategahn, Rauh, *ACS Med Chem Lett,* **2016**, *7(1):2-5.*

- Thress, et al. *Nat Med* **2015,** *21*, 560-2.
  Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M.
- Niederst, et al. *Clin Cancer Res* **2015,** *21*, 3924-33.
  The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies.
- Oxnard, et al. *J Thorac Oncol* **2015,** *10 (suppl 2): ORAL17.07.*
  Mechanisms of Acquired Resistance to AZD9291 in EGFR T790M Positive Lung Cancer.
- Ercan, et al. *Clin Cancer Res* **2015,** *21*, 3913-23.
  EGFR Mutations and Resistance to Irreversible Pyrimidine-Based EGFR Inhibitors.

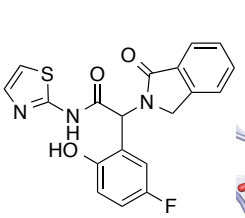
Need for 4th generation TKIs!



2c

	IC_{50} [nM] against EGFR L858R/T790M/C797S
1a	21
1b	336
2c	90
2d	167
Staurosporine	1
WZ4002	7294

Günther, et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 1-6.



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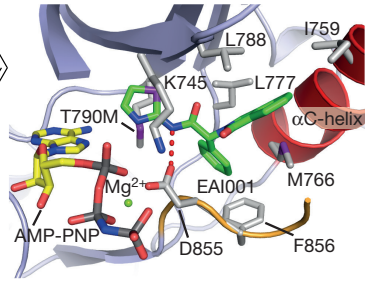
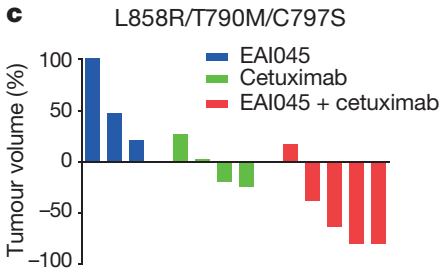
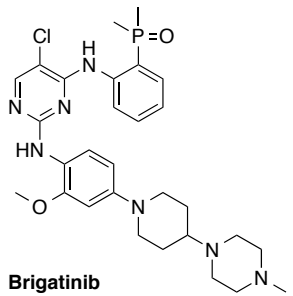
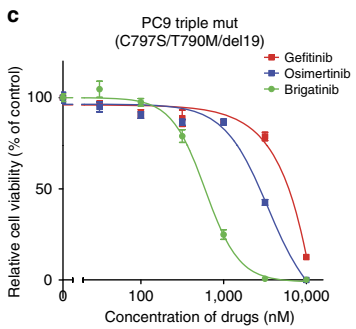




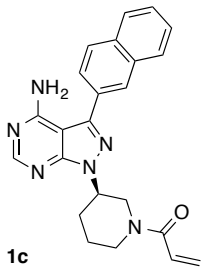
Jia, et al. *Nature* **2016,** *534*, 129-32.



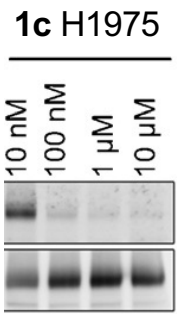
Brigatinib

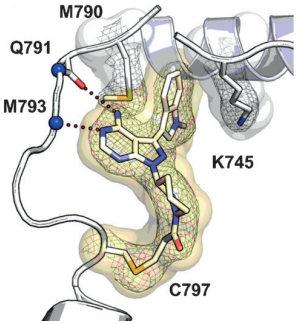


Uchibori, et al. *Nat Commun* **2017,** *8*, 14768.



1c





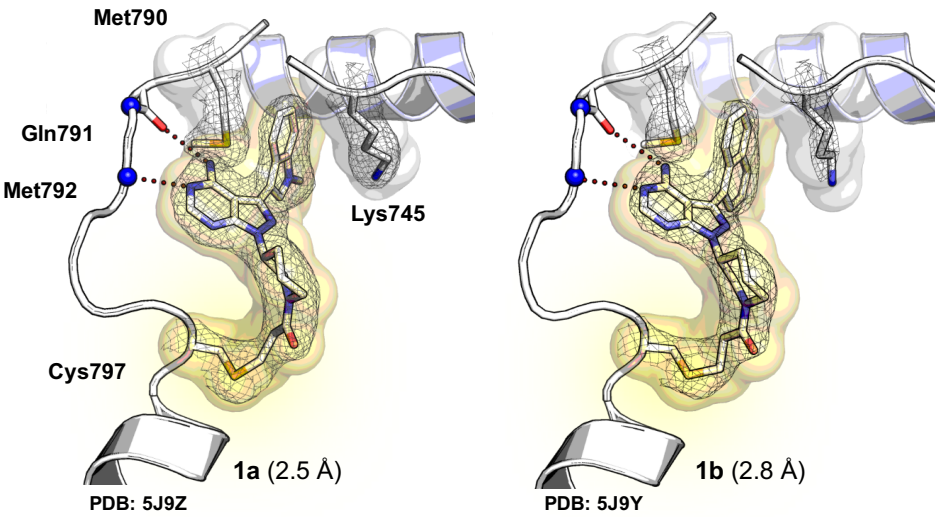
Engel, Becker, et al.
Angew. Chem. Int. Ed. **2016**, *55*, 10909-12.

Grabe, Lategahn, Rauh, *ACS Med Chem Lett,* **2018***, 9, 779-782.*

in vitro Evaluation

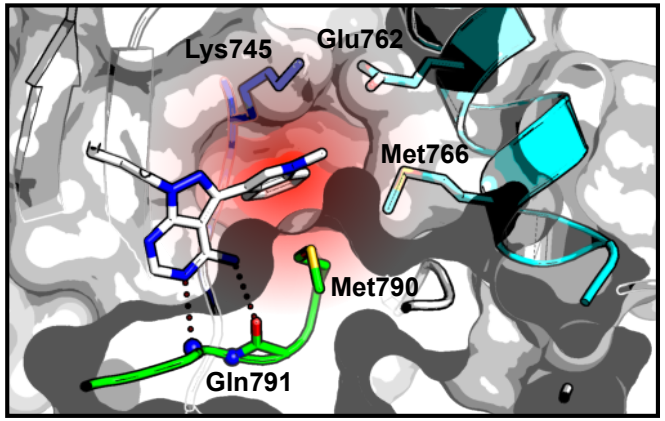
can we target both drug-resistant mutants (T790M & T790M/C797S) with one and the same drug?

in drug-resistant H1975 cells



covalent bond formation with Cys797
lipophilic interaction (Met790&Lys745)

dose-dependent effect on EGFR phosphorylation and its downstream signaling



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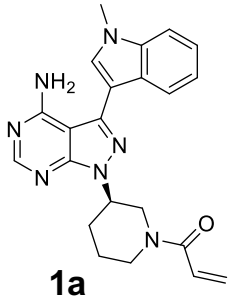
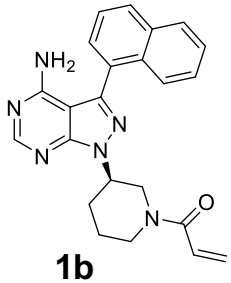
Engel, Becker et al., *Angew Chem Int Ed Engl* **2016**, *55*, 10909-12.
Tomassi, Lategahn et al., *J Med Chem*, **2017,** *60*, 2361-2372.

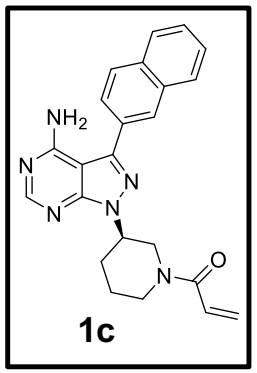
Acquired Drug Resistance – C797S Mutation



1a



1b

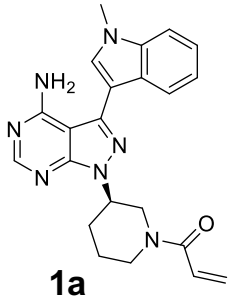


1c

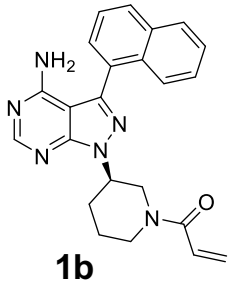
Compound	EGFR	IC_{50} [nM]
1a	L858R/T790M	2.5
	L858R/T790M/C797S	838
1b	L858R/T790M	1.9
	L858R/T790M/C797S	7900
1c	L858R/T790M	<1
	L858R/T790M/C797S	88
AZD9291	L858R/T790M	<1
	L858R/T790M/C797S	77

Engel, Becker et al., *Angew Chem Int Ed Engl* **2016**, *55*, 10909-12.

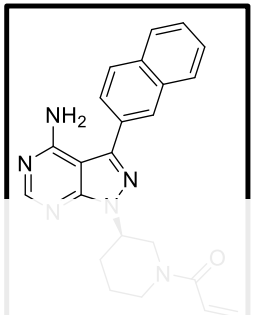
Acquired Drug Resistance – C797S Mutation



1a



1b



1c

Compound	EGFR	IC_{50} [nM]	K_i [nM]	k_{inact} [min^{-1}]
1a	L858R/T790M	2.5	16	0.29
	L858R/T790M/C797S	838	1008	-
1b	L858R/T790M	1.9	58	0.31
	L858R/T790M/C797S	7900	1068	-
1c	L858R/T790M	<1	1.5	0.17
	L858R/T790M/C797S	88	49	-
AZD9291	L858R/T790M	<1	1.5	0.33
	L858R/T790M/C797S	77	25	-

high affinity towards

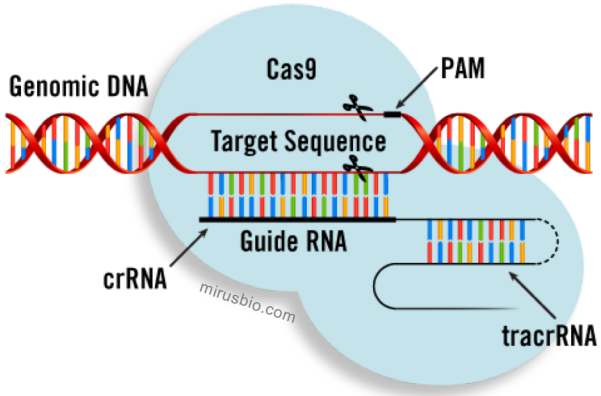
the gatekeeper (Met790) is key for

targeting T790M/C797S resistance!

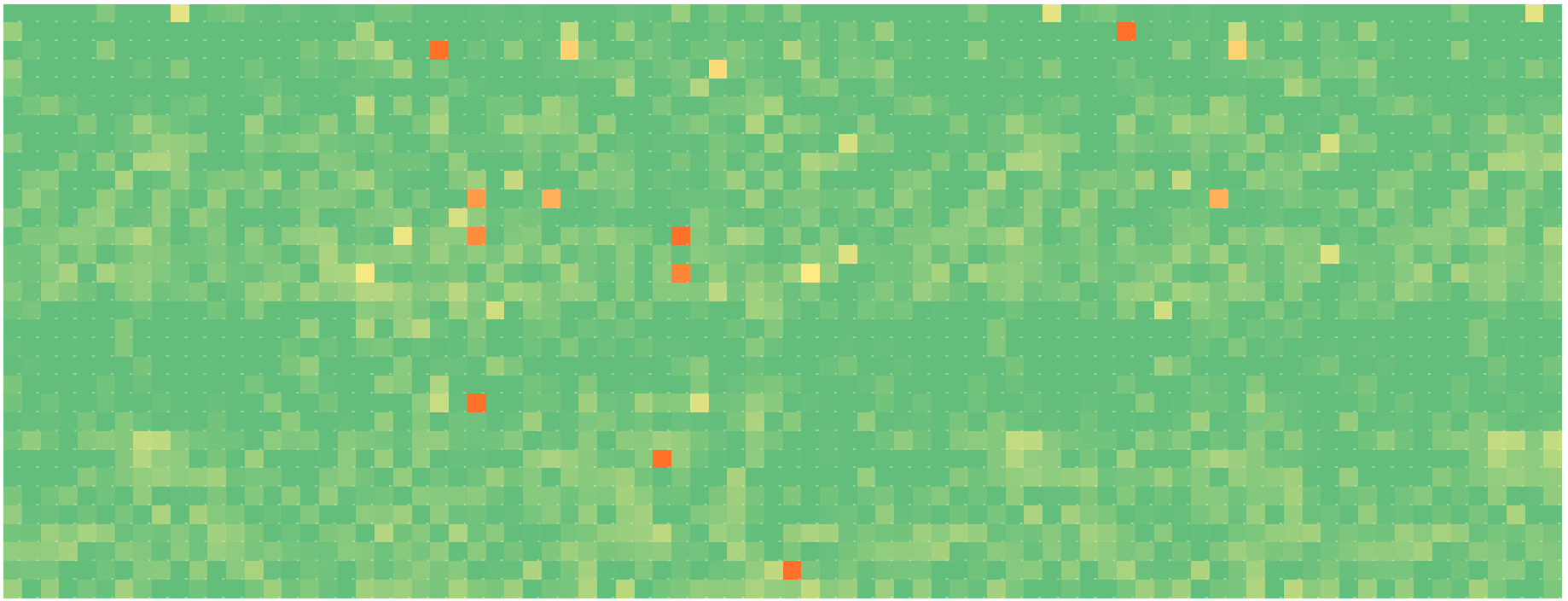
Engel, Becker et al., *Angew Chem Int Ed Engl* **2016**, *55*, 10909-12.

Acquired C797S mutation - screening for novel chemical entities

cell-based screens



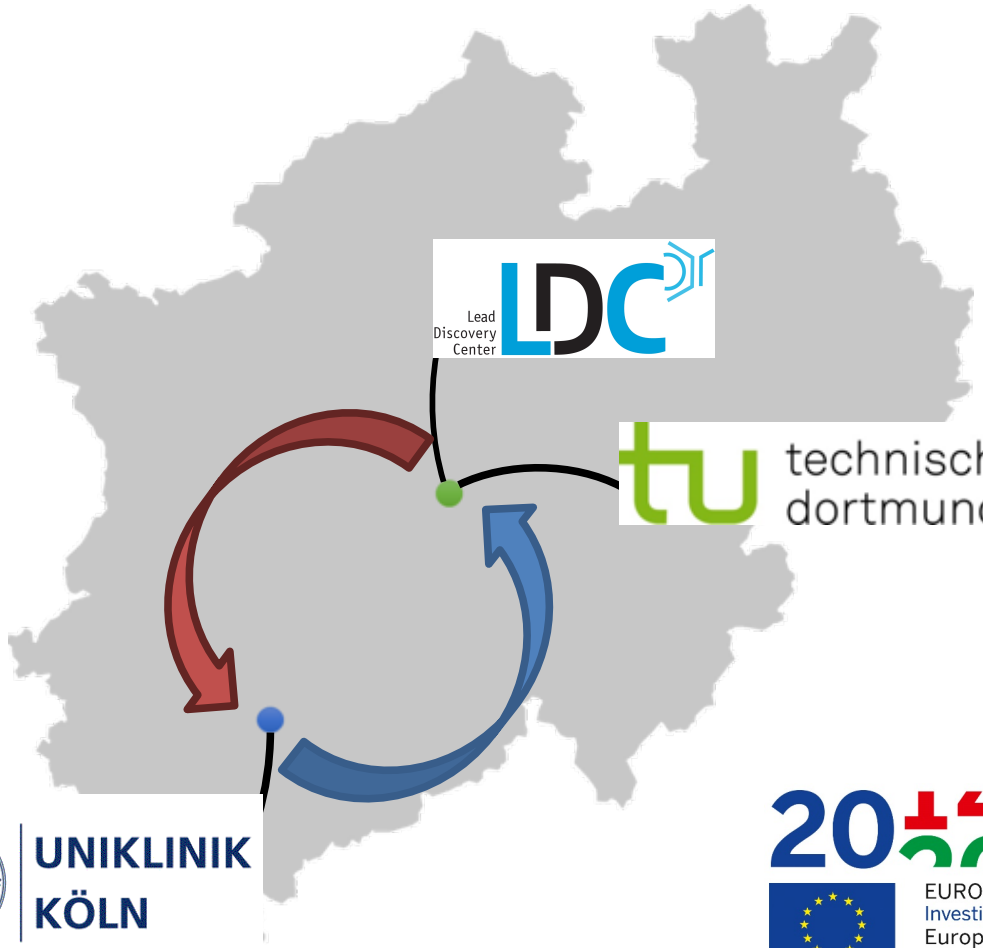
CRISPR/Cas9 engineered lung cancer cell line with T790M/C797S mutation



Marina Keul, Hannah L. Tumbrink, Jonas Lategahn & AG Martin Sos, *unpublished*

Complex regulation of EGFR

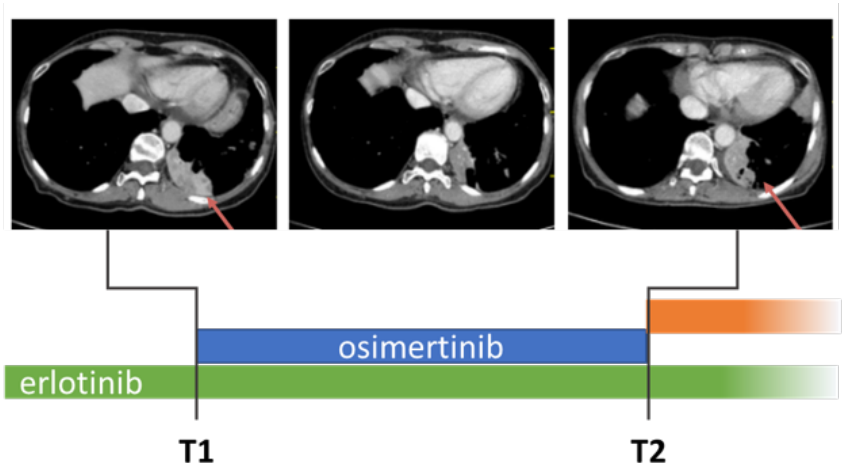
EGFR G724S-mediated **osimertinib** resistance



EFRE.NRW
Investitionen in Wachstum
und Beschäftigung
EUROPÄISCHE UNION
Investition in unsere Zukunft
Europäischer Fonds
für regionale Entwicklung

Complex regulation of EGFR

EGFR G724S-mediated **osimertinib** resistance



green – ex19del

blue – T790M

orange – G724S

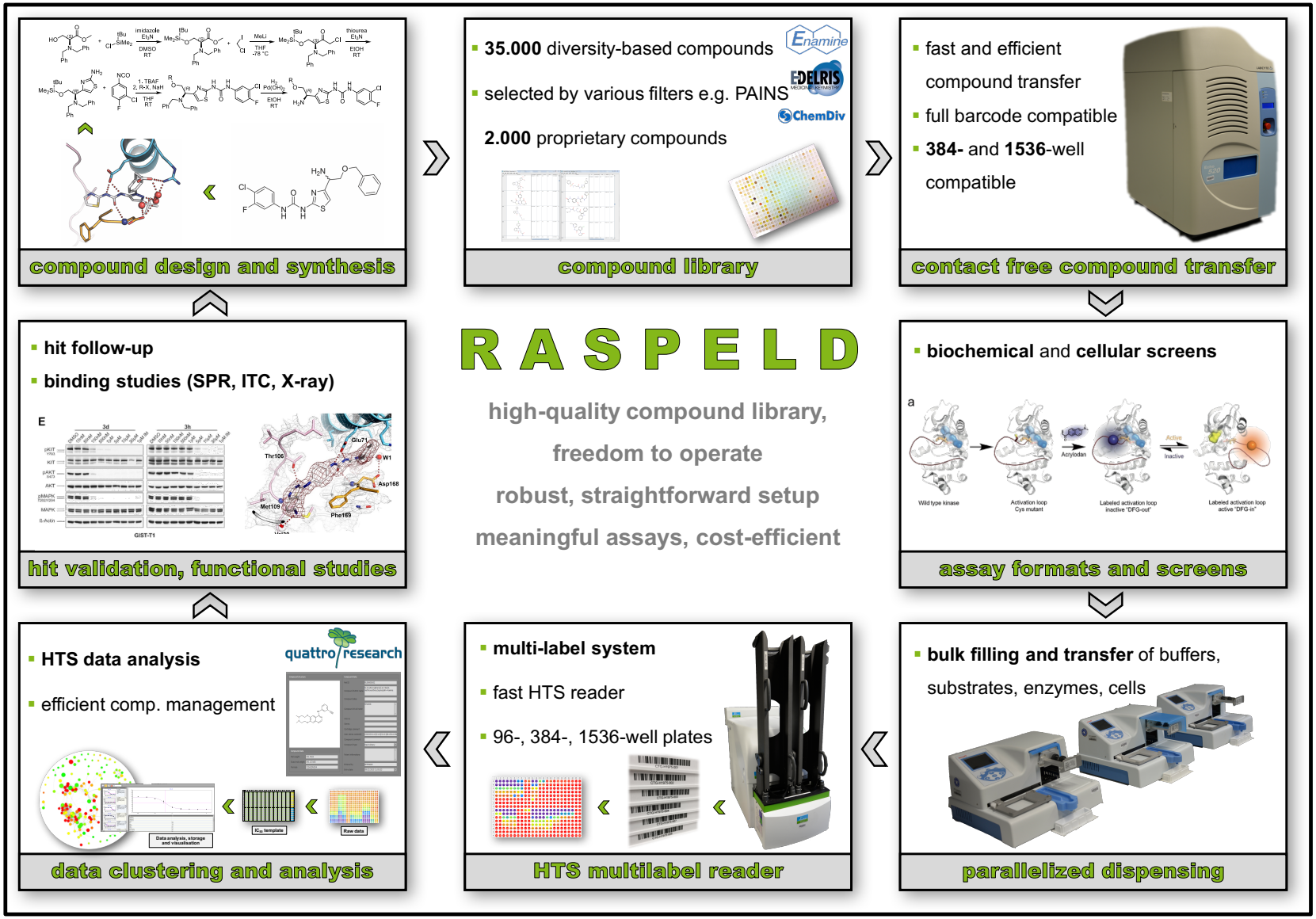
G724S mutation found in NSCLC patients after the treatment with osimertinib

validation!

J. Fassunke, F. Müller, M. Keul, S. Michels, M. Dammert *et al*., **2018**, *revised*.

Complex regulation of EGFR

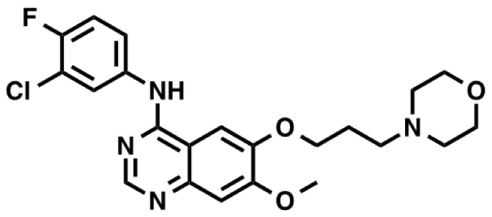
EGFR G724S-mediated osimertinib resistance



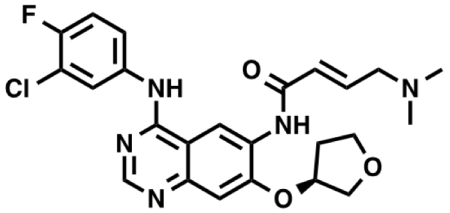
J. Fassunke, F. Müller, M. Keul, S. Michels, M. Dammert *et al.*, **2018**, *revised*.

Complex regulation of EGFR

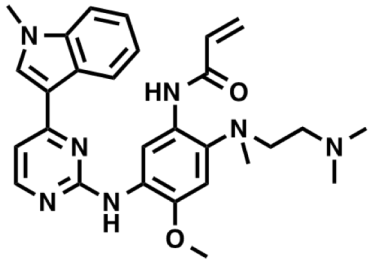
EGFR G724S-mediated osimertinib resistance



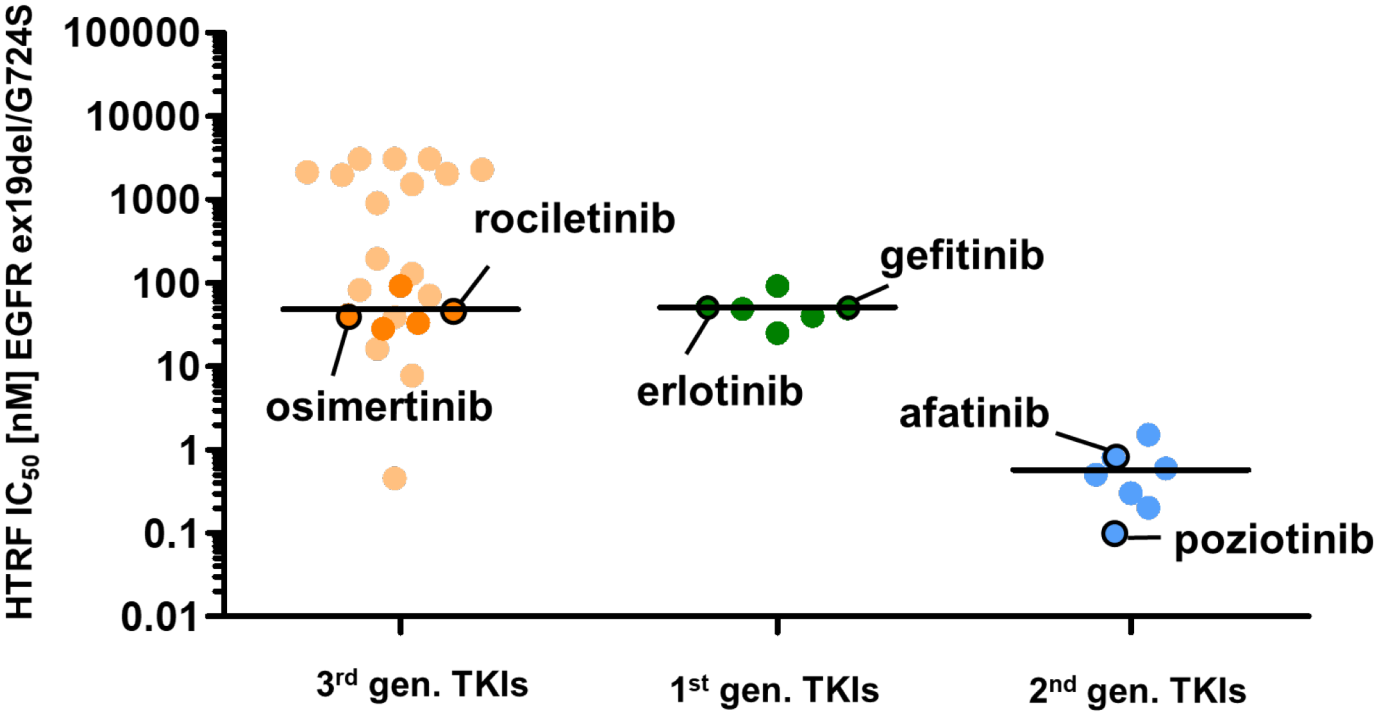
1st gen. TKIs
gefitinib



2nd gen. TKIs
afatinib



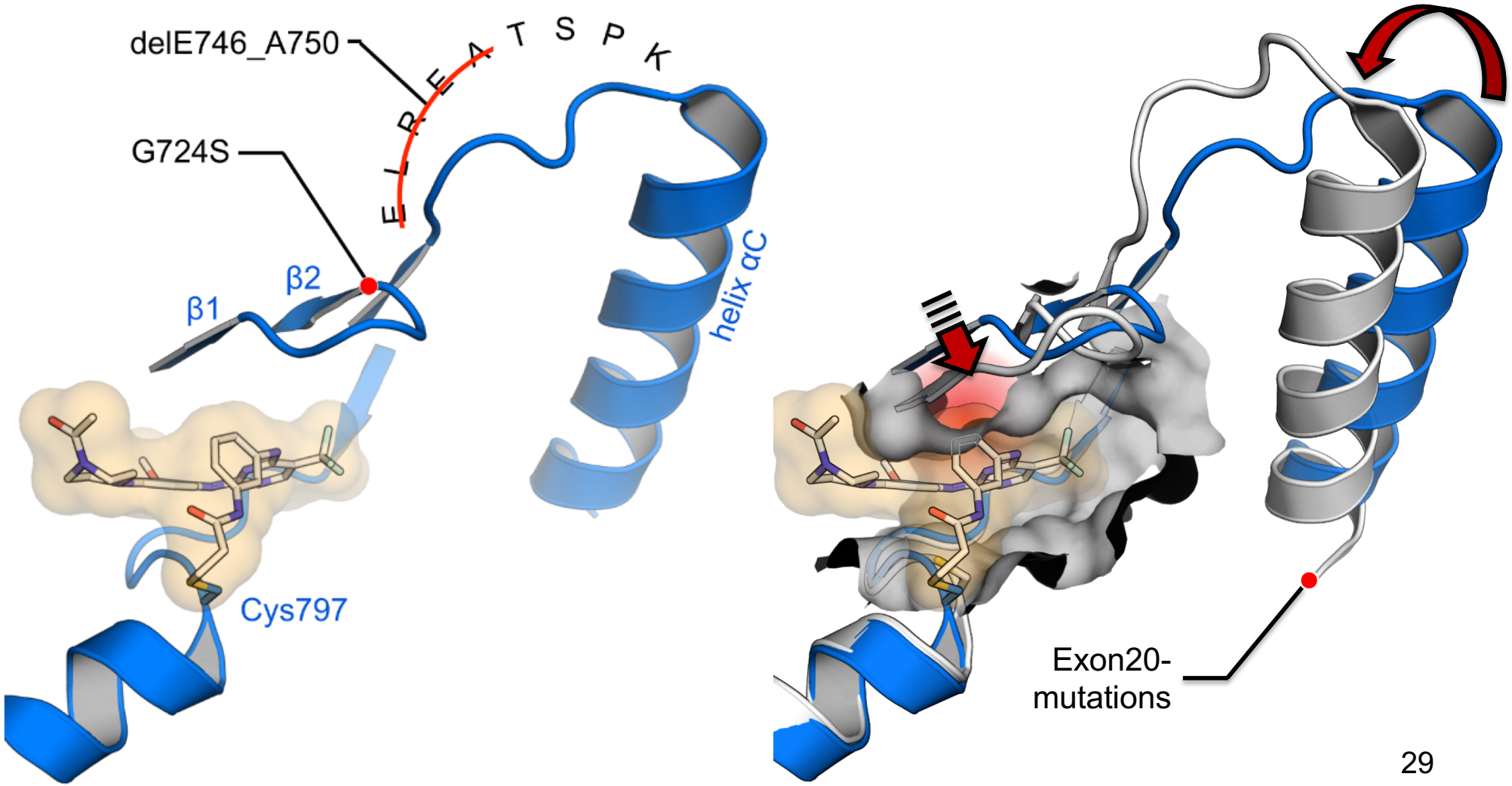
3rd gen. TKIs
osimertinib



J. Fassunke, F. Müller, M. Keul, S. Michels, M. Dammert *et al*., **2018**, *revised*.

Complex regulation of EGFR

EGFR G724S-mediated osimertinib resistance

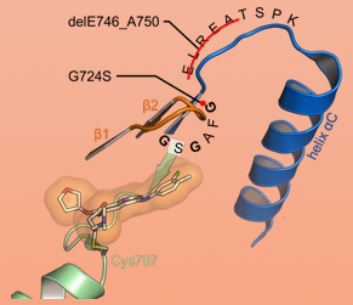


J. Fassunke, F. Müller, M. Keul, S. Michels, M. Dammert *et al*., **2018**, *revised*.

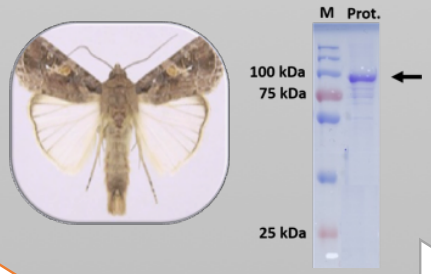
Complex regulation of EGFR

EGFR G724S-mediated osimertinib resistance

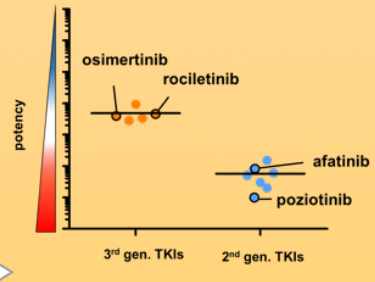
Identification of novel drug resistance mutation



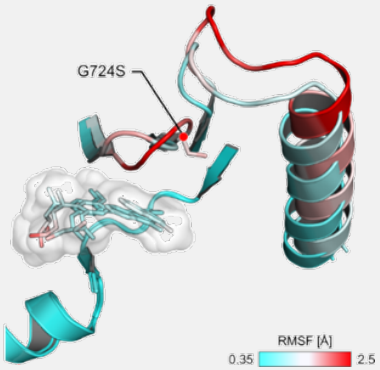
Successful expression of active target proteins



Biochemical and kinetic evaluation



MD-Simulations and structural analysis

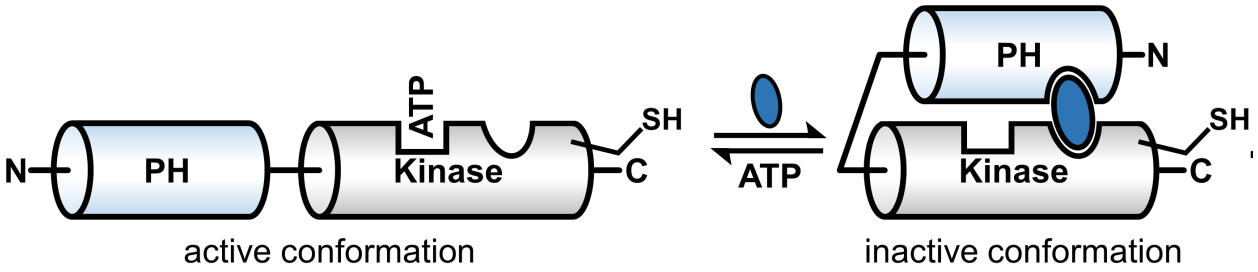


Cellular and mouse studies confirm activity of 2nd gen. TKIs!

Translation of already approved 2nd gen TKIs into the clinical setting of EGFR$^{ex19del/G724S}$

J. Fassunke, F. Müller, M. Keul, S. Michels, M. Dammert *et al*., **2018**, *revised*.

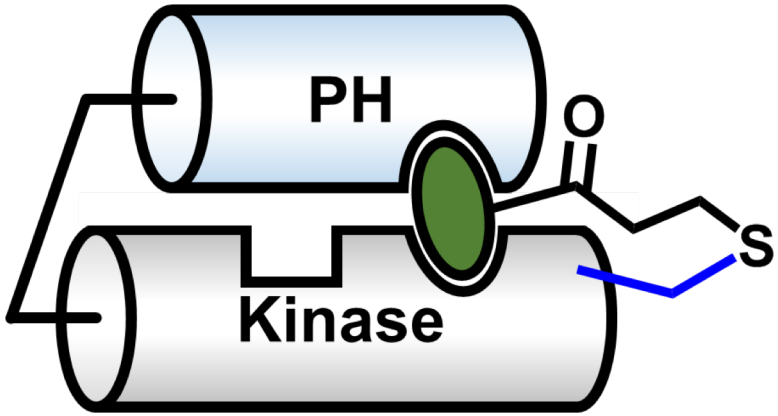
Stabilizing inactive kinase conformations



allosteric

access to conform. space

highly selective



covalent

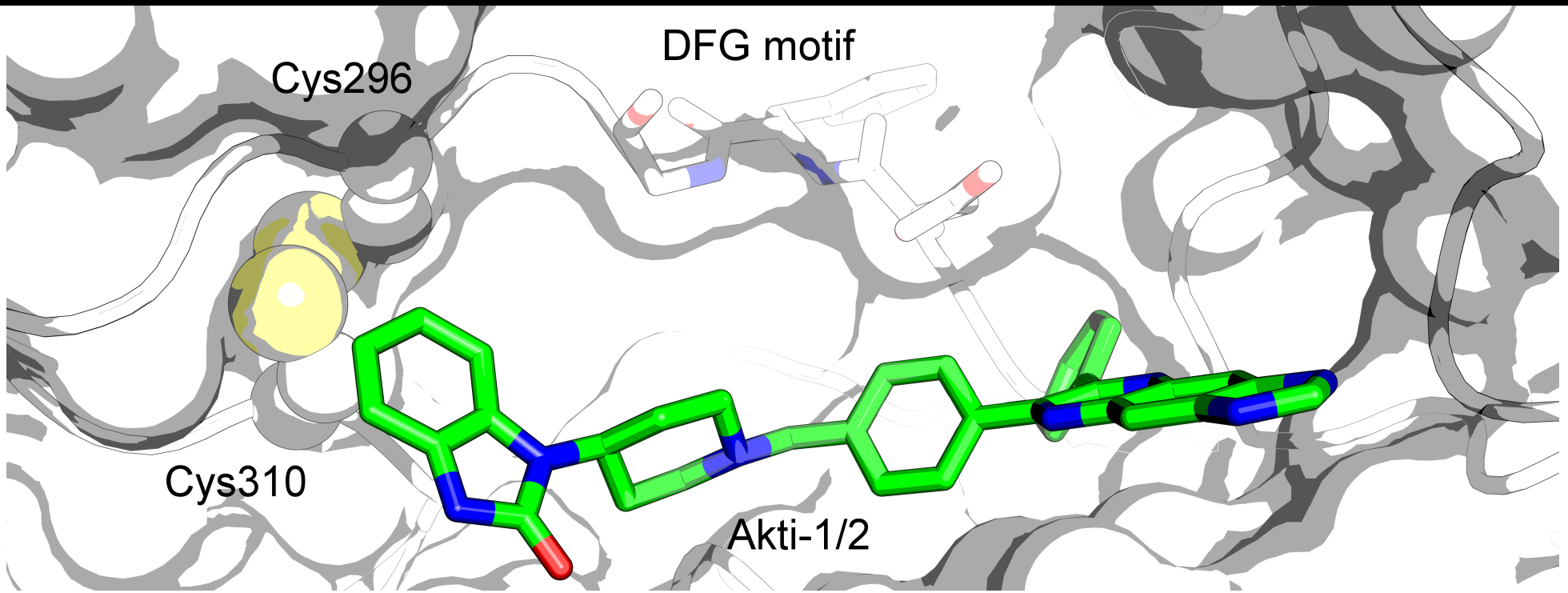
binds irreversibly

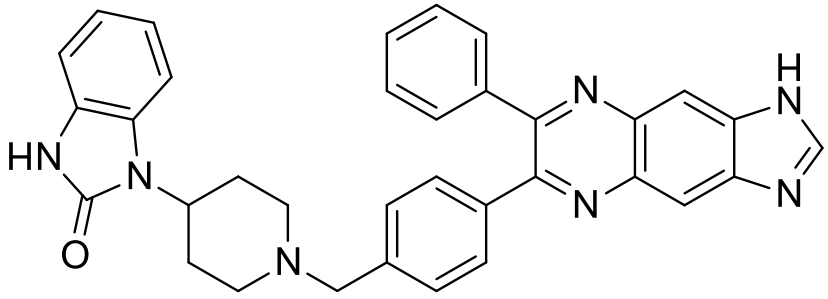
highly potent

drug-target residence time

covalent-allosteric inhibitors to irreversibly stabilize inactive conformations!

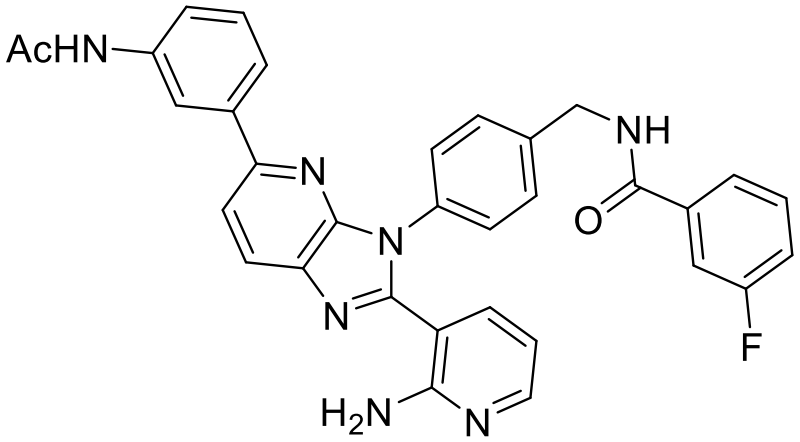
Stabilizing inactive kinase conformations





Akti-1/2

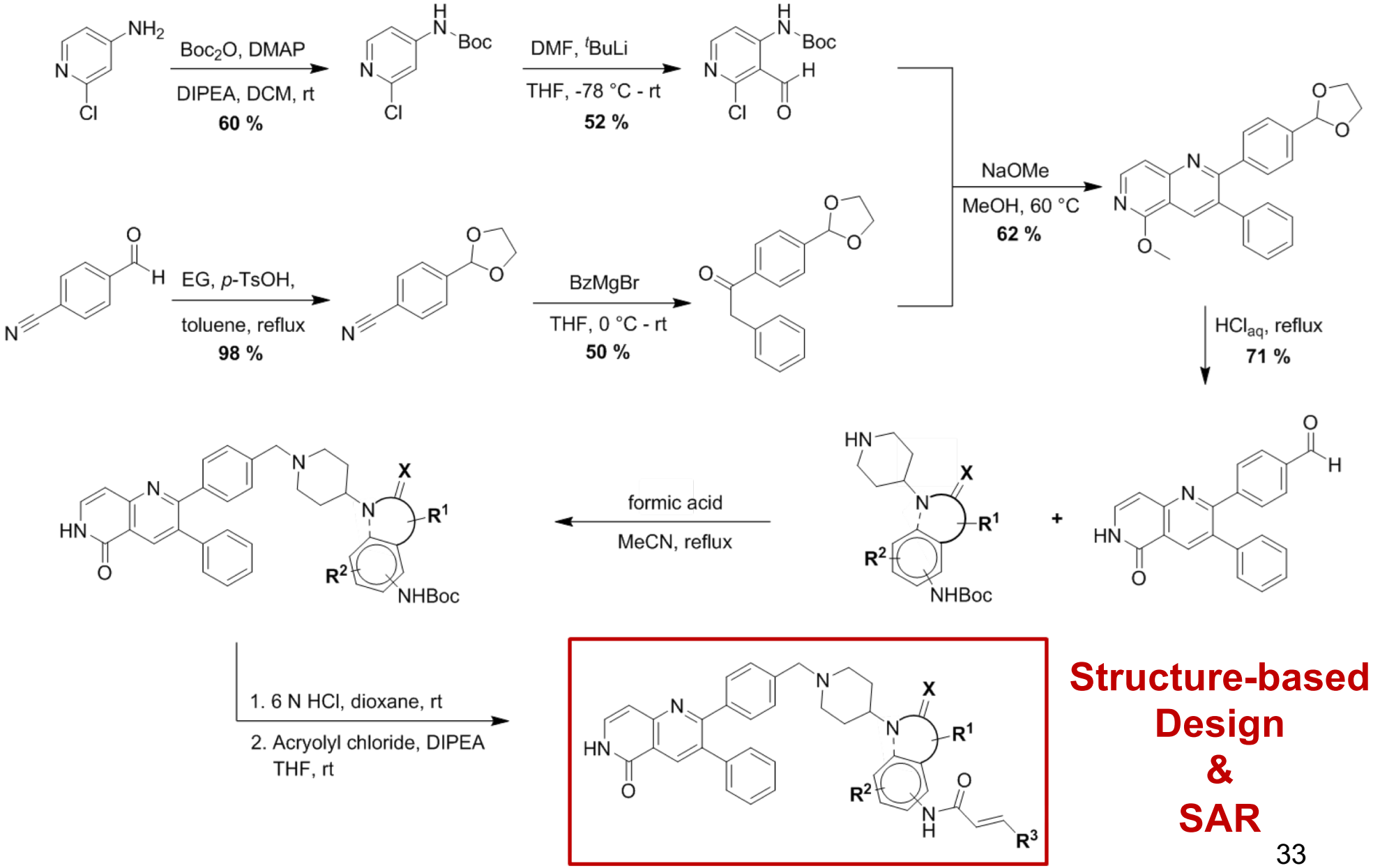
(PDB code: 3O96)



12j

(PDB code: 4EJN)

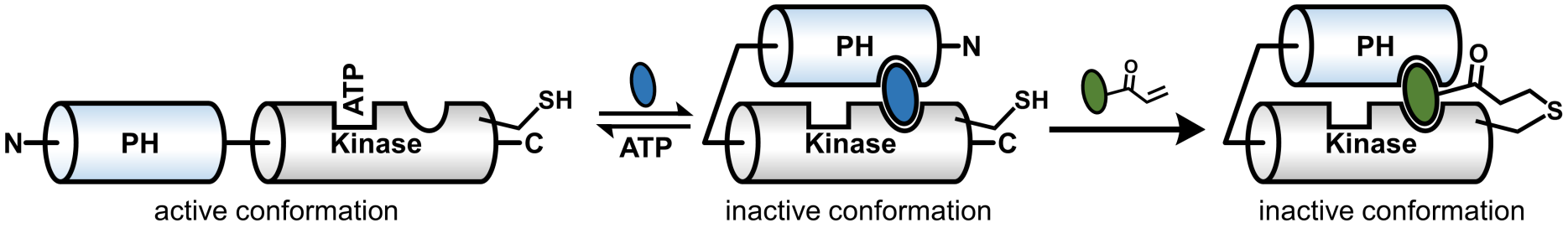
Stabilizing inactive kinase conformations



Structure-based Design & SAR

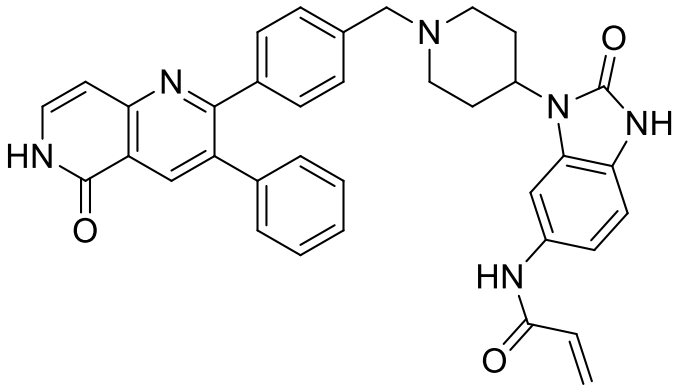
Niklas Uhlenbrock, Steven Smith, Rajesh Gontla, Marius Lindemann, Lena Quambusch

Irreversibly stabilizing inactive kinase conformations



active conformation | inactive conformation | inactive conformation

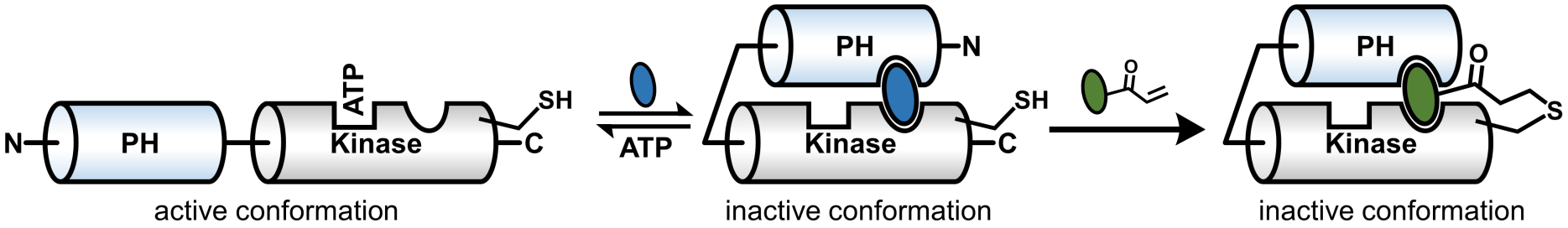
	IC_{50} / nM	
Compound	**Akt1_wt**	**Akt1_E17K**
GSK690693	2.2 ± 0.7	1.3 ± 0.5
MK-2206	10 ± 2.1	4038.2 ± 783.2
RL1782	3.6 ± 0.8	839.7 ± 225.5
Borussertib	0.8 ± 0.3	115.1 ± 24.1
RL1969	1.2 ± 0.3	171.8 ± 75.7
RL2231	14 ± 6.1	990.8 ± 352.3
RL2232	10.8 ± 2.5	676.7 ± 259.4
RL2283	7.1 ± 1.5	942.7 ± 325.1
RL2284	1.9 ± 0.4	72.4 ± 33.3
RL2321	3.7 ± 0.7	582.5 ± 149.8



Borussertib / RL1784

Weisner, Gontla, et al., *Angew Chem Int Ed Engl.* **2015**, 54, 10313-6.
adapted from: Schirmeister, et al., *J Am Chem Soc*. **2016**, 138, 8332-5.

Irreversibly stabilizing inactive kinase conformations



	IC_{50} / nM	
Compound	**Akt1_wt**	**Akt1_E17K**
GSK690693	2.2 ± 0.7	1.3 ± 0.5
MK-2206	10 ± 2.1	4038.2 ± 783.2
RL1782	3.6 ± 0.8	839.7 ± 225.5
Borussertib	0.8 ± 0.3	115.1 ± 24.1
RL1969	1.2 ± 0.3	171.8 ± 75.7
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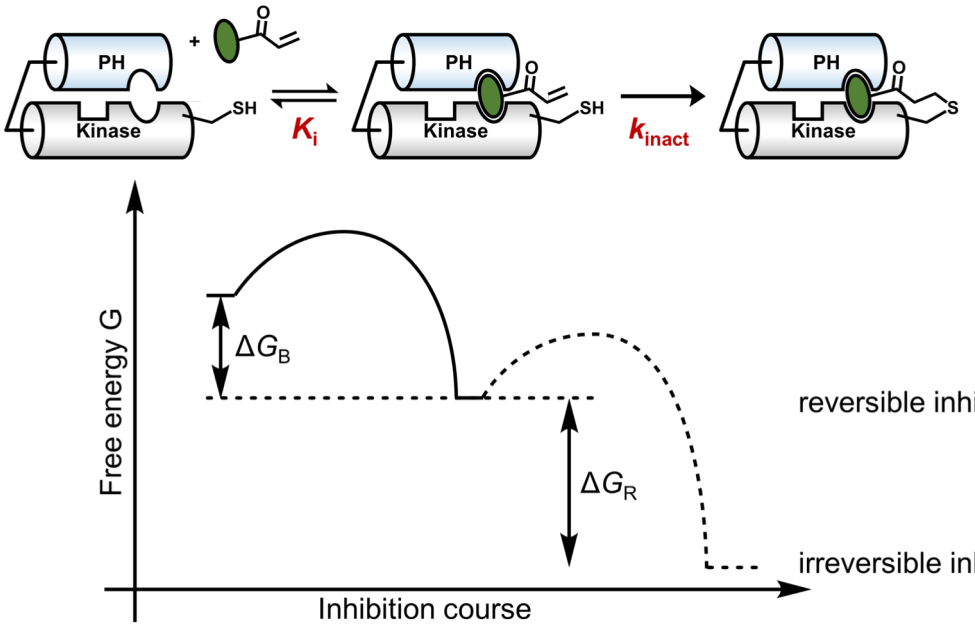

adapted from: Schirmeister, et al., *J Am Chem Soc*. **2016**, 138, 8332-5.

Weisner, Gontla, et al., *Angew Chem Int Ed Engl.* **2015**, 54, 10313-6.
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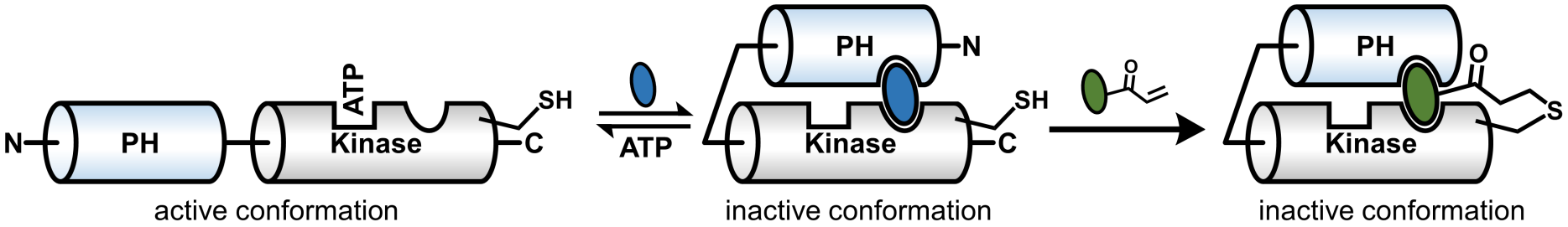
Irreversibly stabilizing inactive kinase conformations



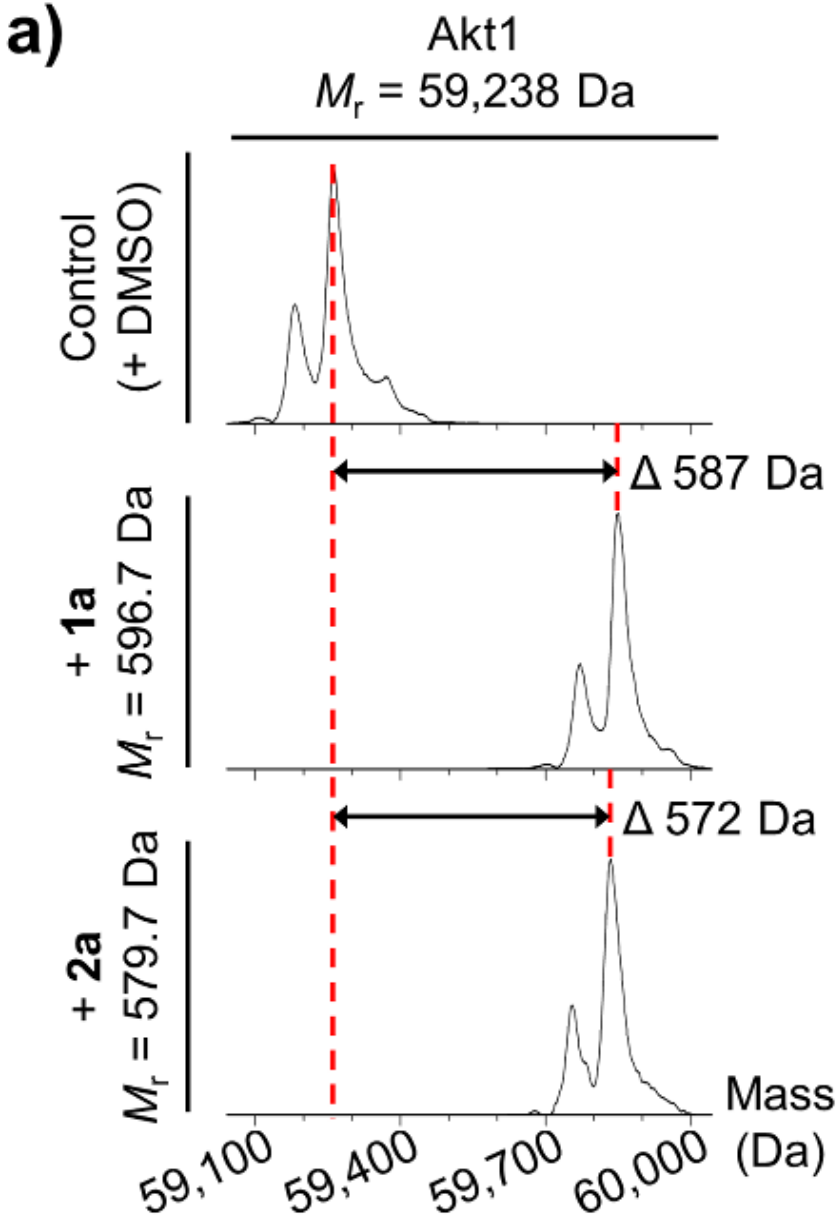
active conformation | inactive conformation | inactive conformation

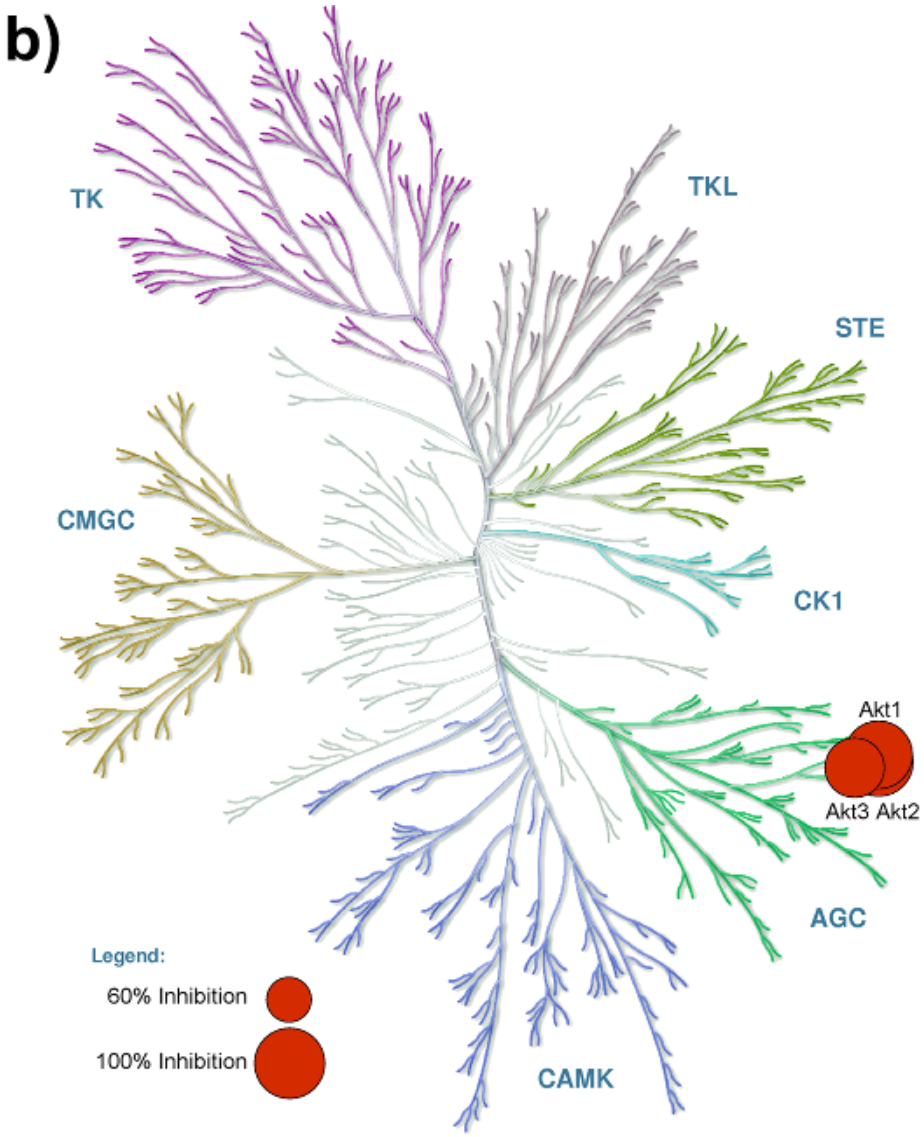
	Akt1_wt		
Compound	**K_i / nM**	**k_{inact} / min^{-1}**	**k_{inact}/K_i / µm^{-1} s^{-1}**
RL1782	6.8 ± 0.3	0.083 ± 0.016	0.202 ± 0.035
Borussertib	2.2 ± 0.3	0.113 ± 0.020	0.853 ± 0.038
RL1969	4.1 ± 0.7	0.110 ± 0.023	0.447 ± 0.074
RL2231	39.3 ± 6.6	0.088 ± 0.010	0.038 ± 0.007
RL2232	27.2 ± 4.2	0.138 ± 0.031	0.085 ± 0.018
RL2283	5.6 ± 0.8	0.032 ± 0.004	0.095 ± 0.013
RL2284	2.6 ± 0.4	0.055 ± 0.006	0.331 ± 0.026
RL2321	7.6 ± 1.1	0.078 ± 0.022	0.168 ± 0.025

- **affinity-driven loss of potency (WT vs. E17K)**
- **covalent bond formation rescues enzyme inhibition**

Weisner, Gontla, et al., *Angew Chem Int Ed Engl.* **2015**, 54, 10313-6.

Stabilizing inactive kinase conformations

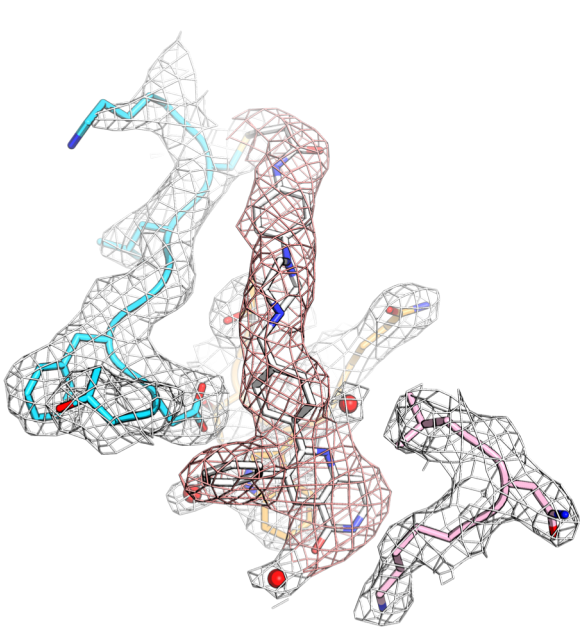


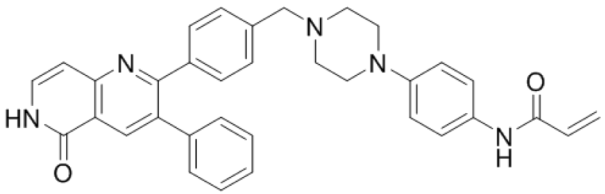


Weisner, Gontla, et al., *Angew Chem Int Ed Engl.* **2015**, 54, 10313-6.

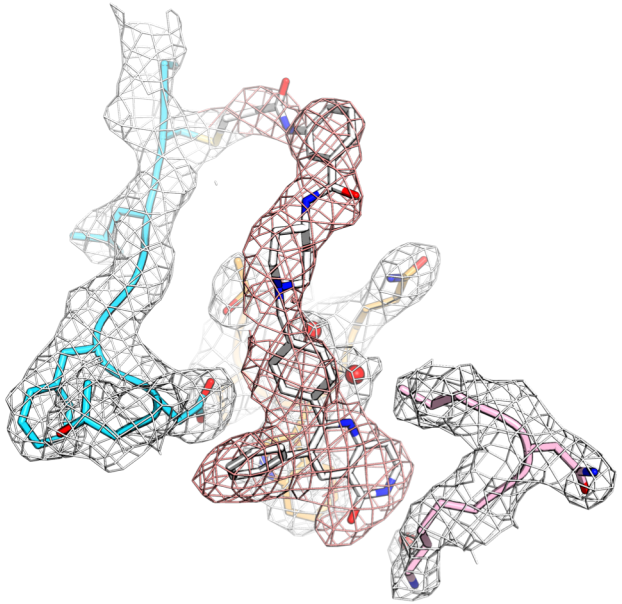
Stabilizing inactive kinase conformations

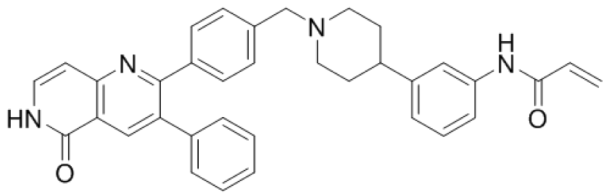
CAAIs in complex with full-length Akt



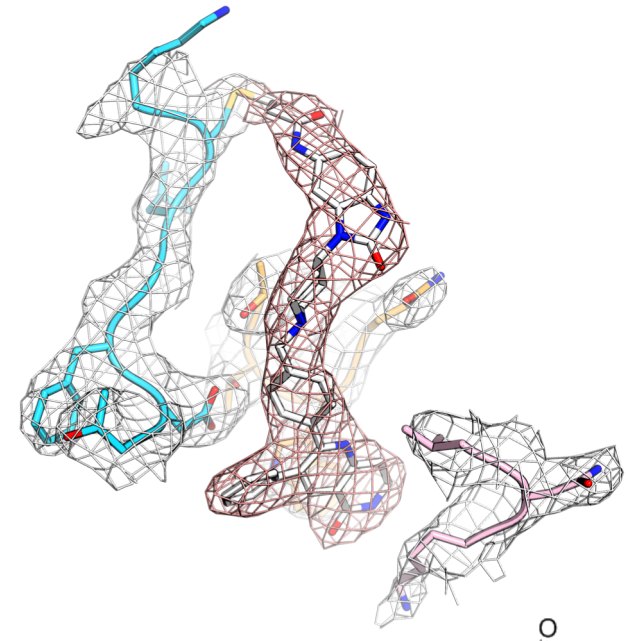


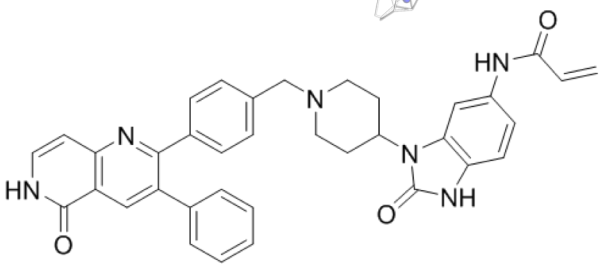
RL1781





RL1782

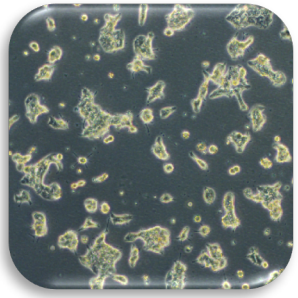




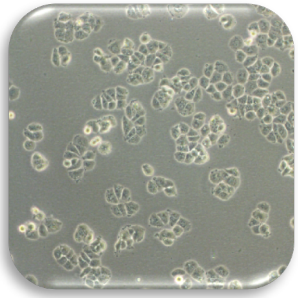
Borussertib / RL1784

Rebekka Scheinpflug, Patrik Wolle, Jörn Weisner, Ina Landel, *unpublished*

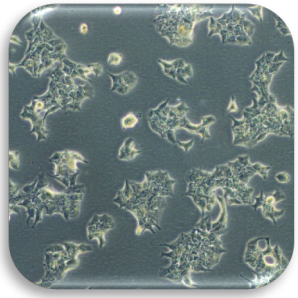
Stabilizing inactive kinase conformations



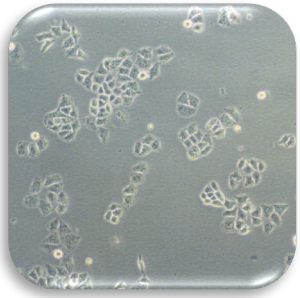
ZR-75-1
(breast)
PTEN^{L108R}



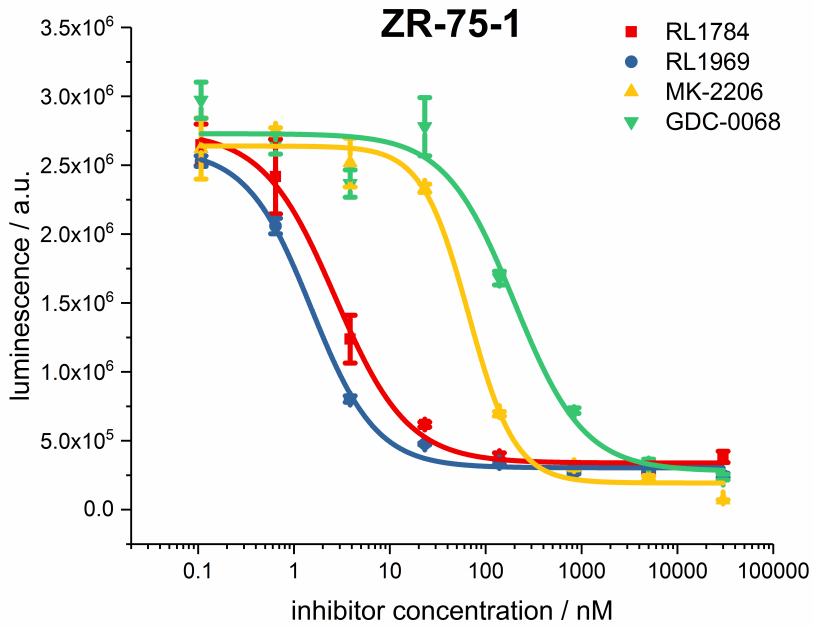
T-47D
(breast)
PIK3CA^{H1047R}
TP53^{L194F}



BT-474
(breast)
PIK3CA^{K111N}
TP53^{E285K}



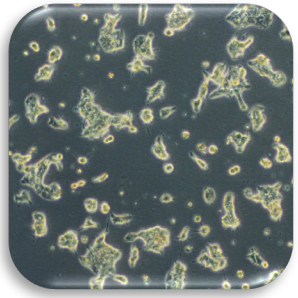
AN3-CA
(endometrium)
PIK3R1$^{R557_K561>Q}$
PTEN^{R130fs}
TP53^{R213Q}



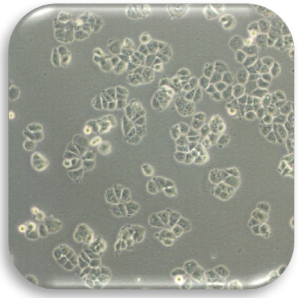
Compound	CTG EC_{50} / nM ZR-75-1	T-47D	BT-474	AN3CA
GDC-0068	219 ± 83	447 ± 2	2371 ± 745	925 ± 457
MK-2206	63 ± 21	411 ± 23	1682 ± 316	972 ± 322
RL1782	11 ± 3	95 ± 20	464 ± 31	382 ± 31
RL1784	5 ± 1	48 ± 15	373 ± 54	191 ± 90
RL1969	2 ± 0	25 ± 7	259 ± 68	159 ± 70
RL2231	33 ± 9	370 ± 195	1104 ± 212	879 ± 223
RL2232	22 ± 7	255 ± 86	2268 ± 700	1328 ± 60
RL2283	424 ± 253	5503 ± 2520	17191 ± 5466	27089 ± 2338
RL2284	19 ± 4	194 ± 67	1202 ± 447	957 ± 302
RL2321	10 ± 3	119 ± 36	621 ± 85	568 ± 106

Jörn Weisner, Ina Landel, Stephan Hahn, Jens Siveke, *unpublished*

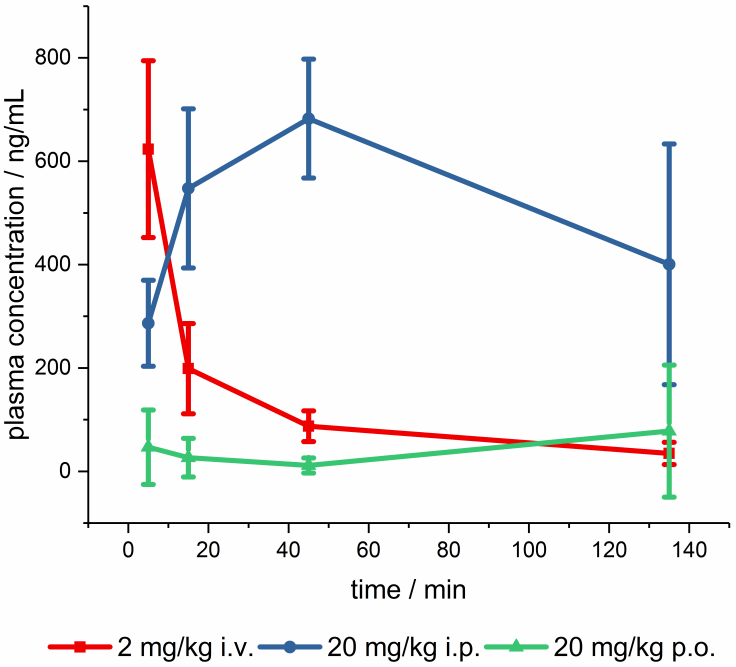
Stabilizing inactive kinase conformations

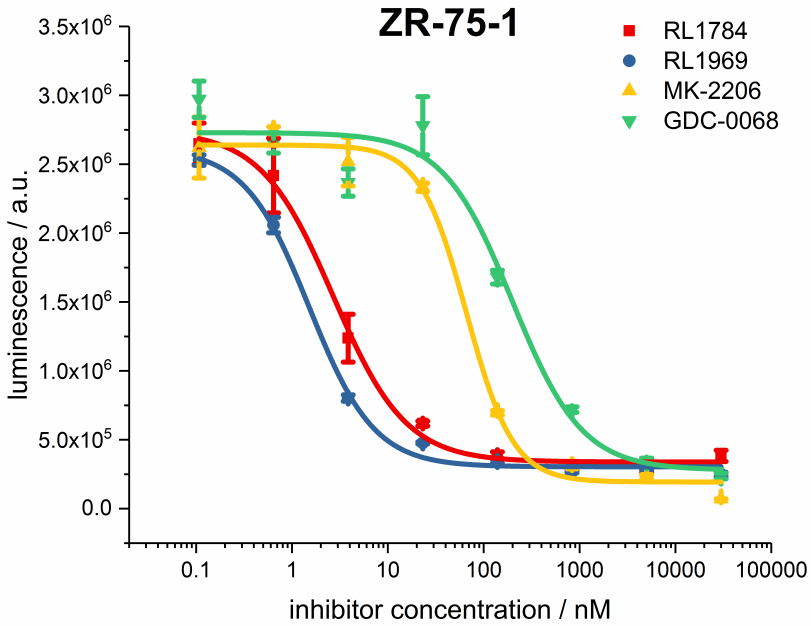


ZR-75-1
(breast)
$PTEN^{L108R}$



T-47D
(breast)
$PIK3CA^{H1047R}$
$TP53^{L194F}$



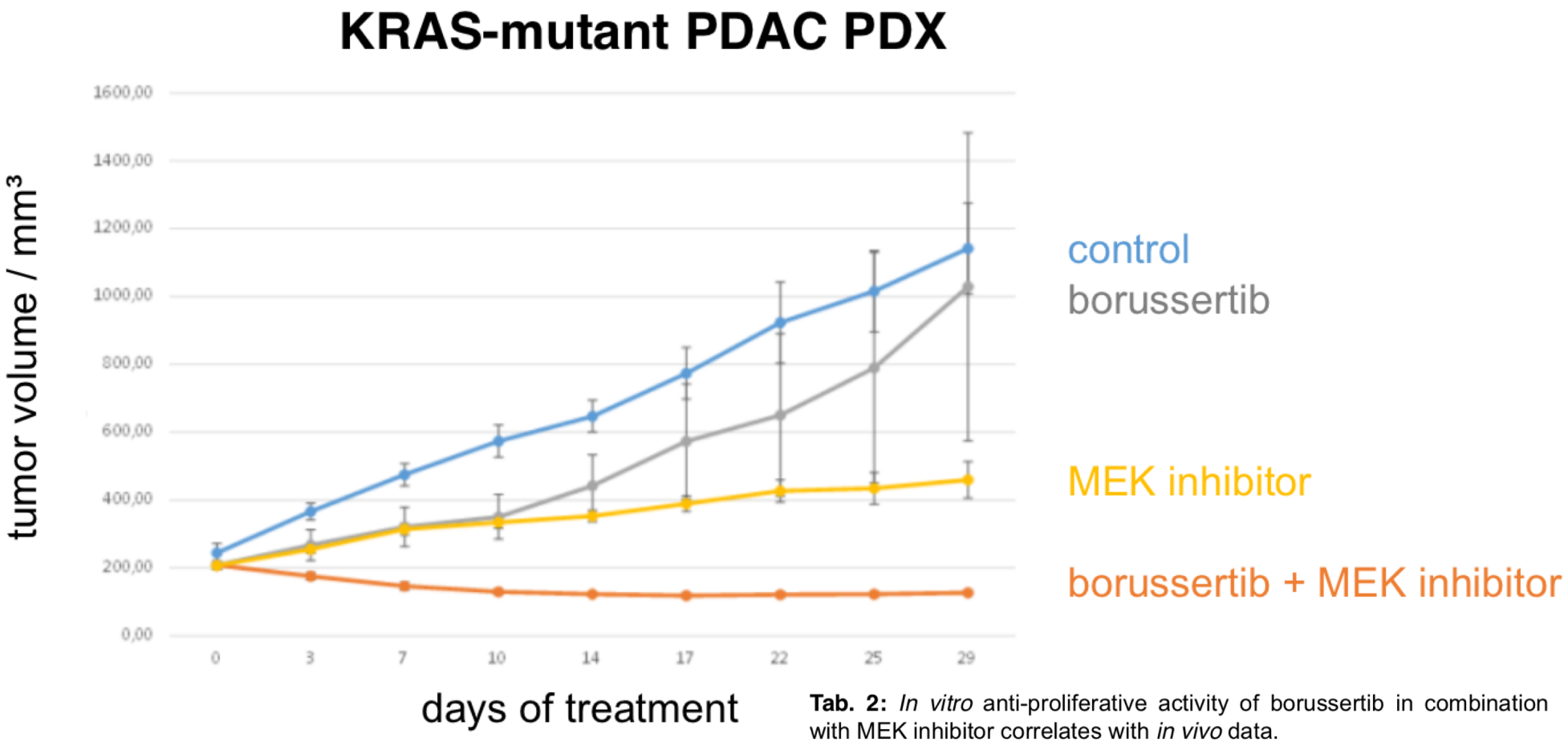


Parameter	2 mg/kg i.v.	20 mg/kg i.p.	20 mg/kg p.o.	
c_{max}	623.37 1.04	682.53 1.14	77.92 0.13	ng/mL µM
$t_{1/2}$	0.85	0.75	2.25	h
AUC 0-t	303.65	1201.25	84.57	h*ng/mL
CL_{obs}	5.77	-	-	l/h/kg
Vss_{obs}	4.94	-	-	l/kg
F		47.7%	3.4%	

Mouse MTD and PK, **good bioavailability**

Jörn Weisner, Ina Landel, Stephan Hahn, Jens Siveke, *unpublished*

Stabilizing inactive kinase conformations

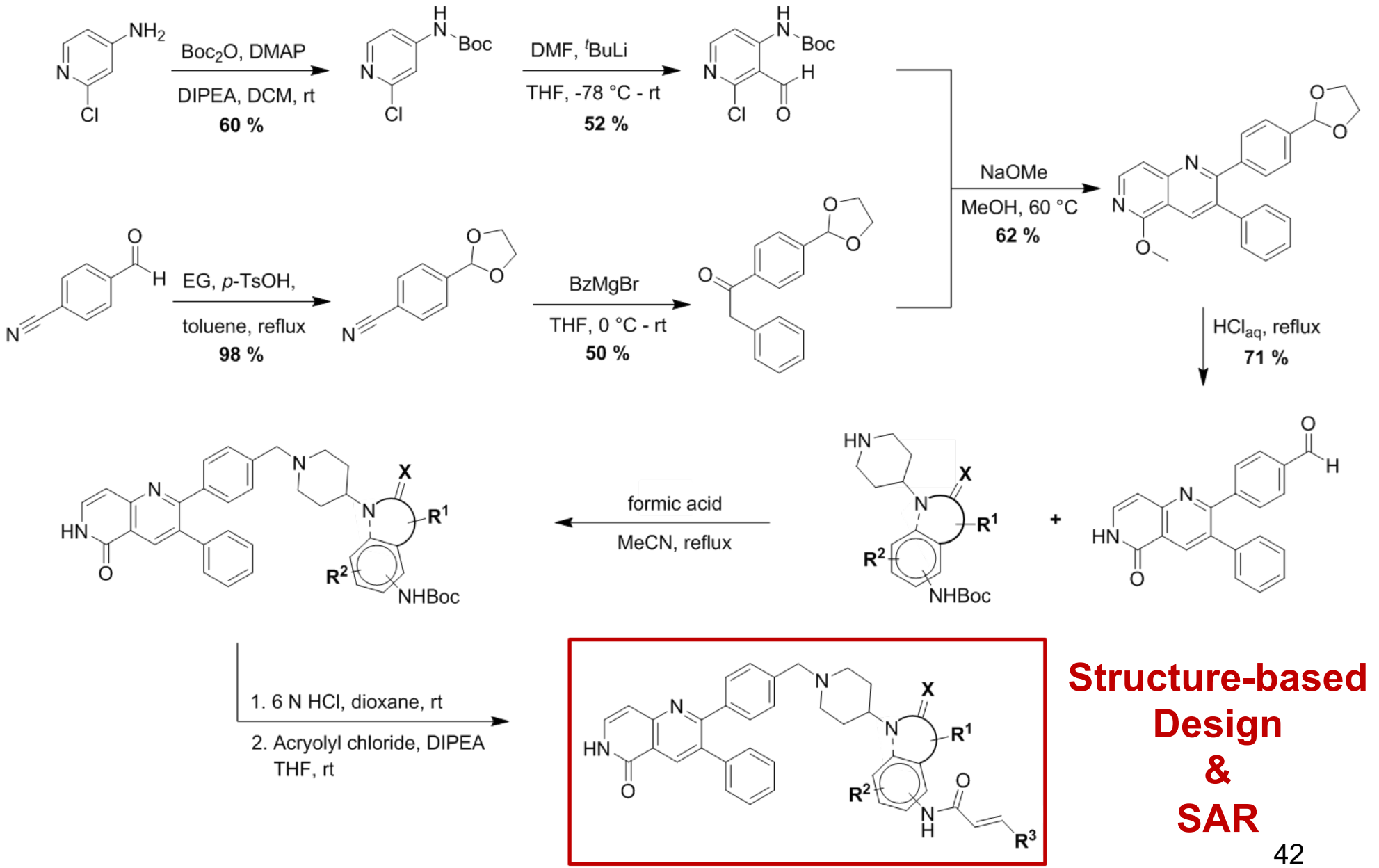


Tab. 2: *In vitro* anti-proliferative activity of borussertib in combination with MEK inhibitor correlates with *in vivo* data.

Compound	CTG EC_{50} / nM
borussertib	1486 ± 584
MEK inhibitor	177 ± 136
borussertib + MEK inhibitor	15 ± 3

Jörn Weisner, Ina Landel, Stephan Hahn, Jens Siveke, *unpublished*

Stabilizing inactive kinase conformations

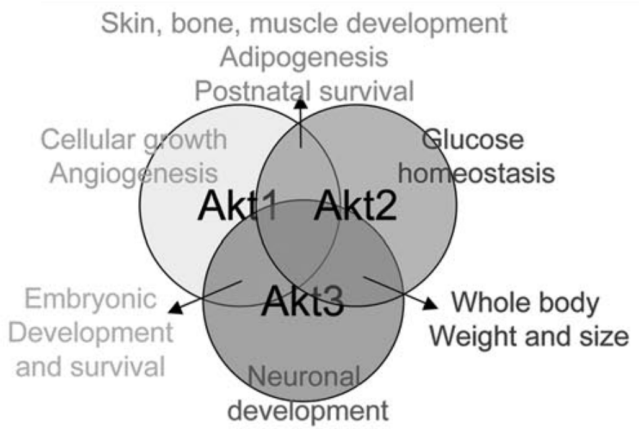


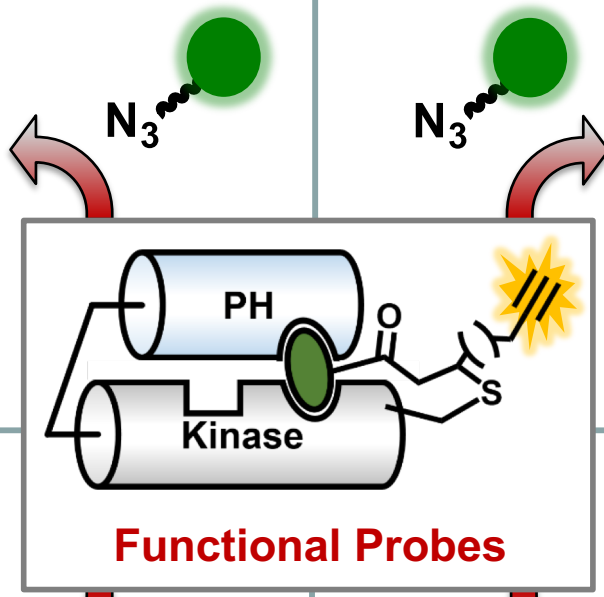
Structure-based Design & SAR

Niklas Uhlenbrock, Steven Smith, Rajesh Gontla, Marius Lindemann, Lena Quambusch

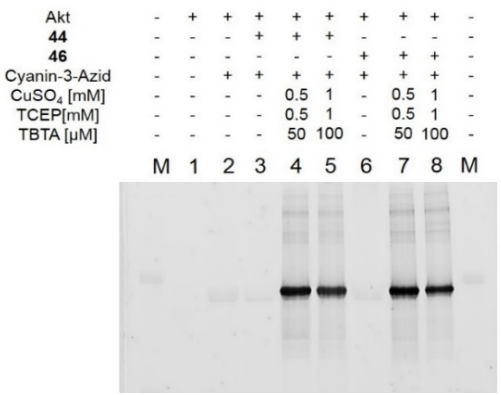
Stabilizing inactive kinase conformations

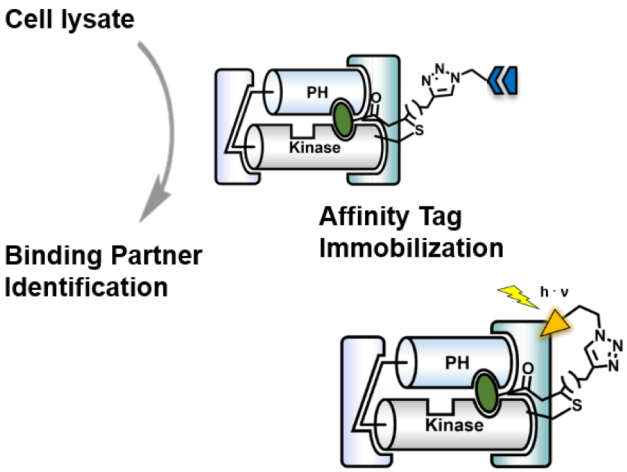
Design of Isoform-selective functional Probes

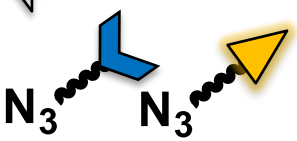




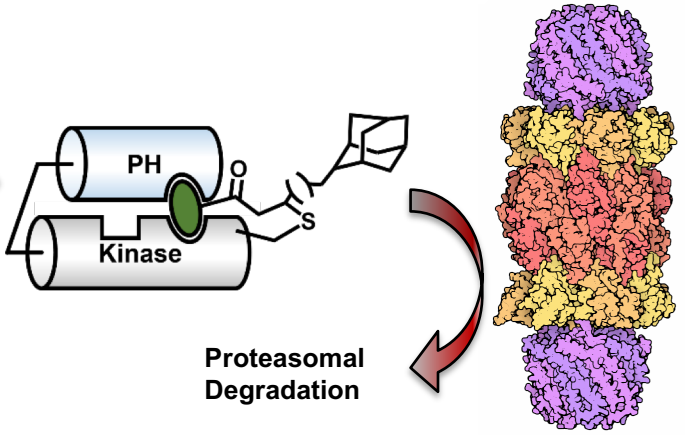
Identify Interaction Partners by Fluorescent Probe Labeling





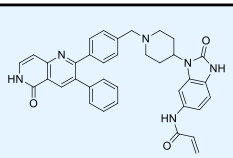


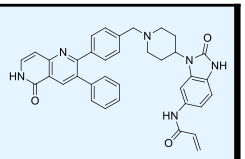
Pull-down Assays and Photo-induced Crosslinking

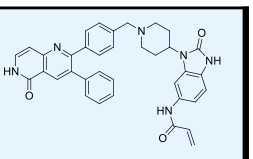


Small molecule-induced proteasomal Degradation

Stabilizing inactive kinase conformations

Activity	
	Borussertib
Her2 INSERT Her2 wt EGFR T790ML858R EGFR wt Lance IC_{50} [nM]	>10000 - >10000 >10000
Her2 INS EGFR INS BaF3 CTG [nM]	885 9226
A431 A2780 H1975 HCC1937 CTG IC_{50} [nM]	1629 100 8285 2576

ADME	
	Borussertib
Sol [uM]	14
Clint [uL/min/mg] mouse / human	36 / 7
Microsomal Stability Phase II [% Remain] mouse / human	-
Plasma Stability [% Remain] mouse / human	100 / 99
PPB [%] mouse / human	98.65 / 99.90
PAMPA [%]	<5
Caco-2 P_{app} [10^{-6}cm/s] A=>B B=>A	0.04 4.03

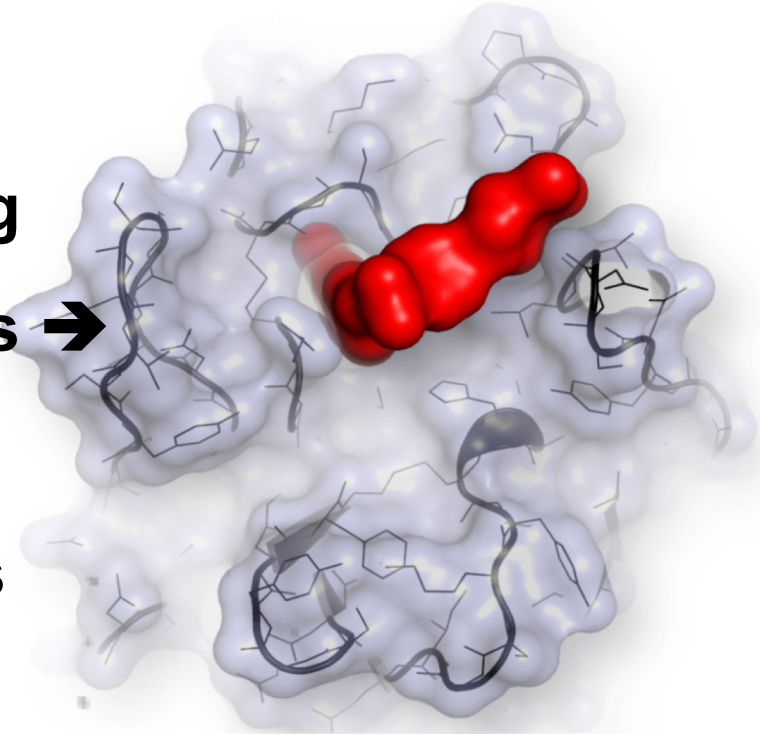
Tox	
	Borussertib
hPBMCs CTG IC_{50} [nM]	6470
HepTox HepG2 IC_{50} [nM]	>30000
MitoTox Glu IC_{50} [nM]	>30000
MitoTox Gal IC_{50} [nM]	>30000
hERG Predictor Assay IC_{50} [nM]	880
hERG Patch Clamp @ Cyprotex IC_{50} [nM]	-

In need, compound optimization ...

Thanks to LDC GmbH, Dortmund

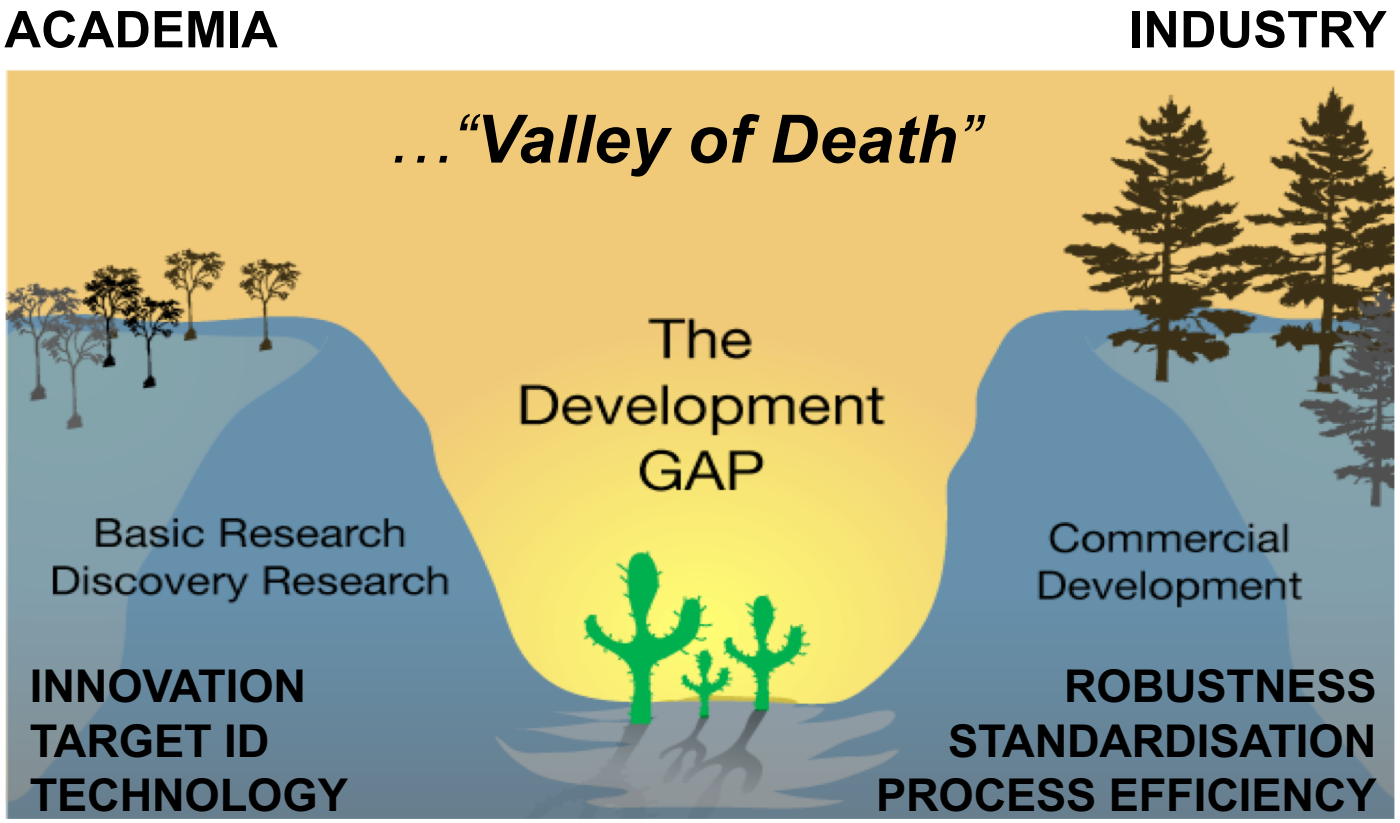
summary

- Cancer is a disease of the genome
- Genetics lesions across key signaling pathways (EGFR) drive tumorigenesis ➔ historic impact
- Revolution of DNA sequencing drives development ...



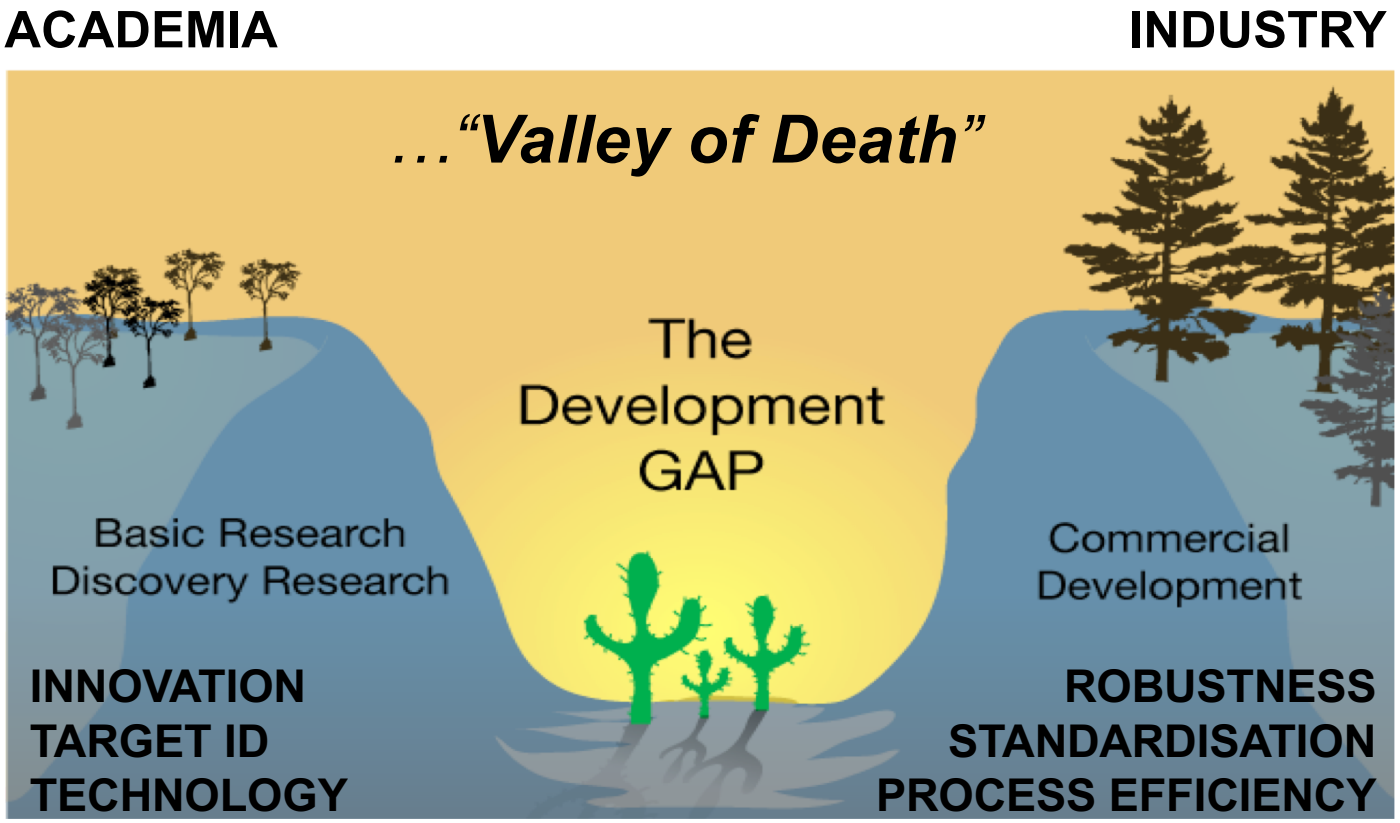
- Additional key discoveries in the translation – bench-to-beside-to-bench ...
- In need: new technologies/ approaches, novel collaborative models, dialog for a better medicine ...

The Academia-Industry Innovation Gap



Adapted from Larry Steranka, CRT; BIO 2007

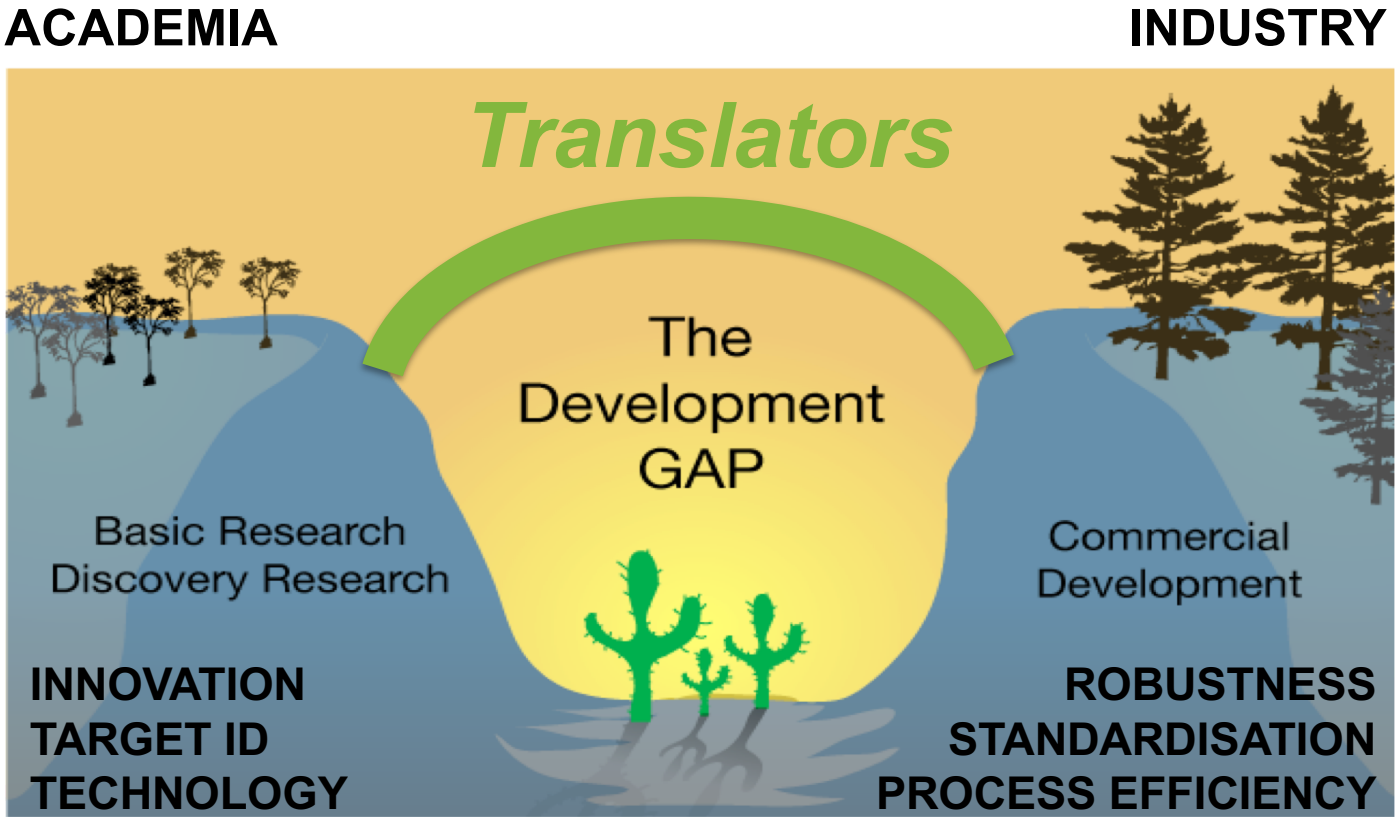
The Academia-Industry Innovation Gap



Adapted from Larry Steranka, CRT; BIO 2007

Profound **structural problem** in Germany –
lost opportunities!

The Academia-Industry Innovation Gap



Adapted from Larry Steranka, CRT; BIO 2007

Profound **structural problem** in Germany –

lost opportunities!

Efficient mechanisms are needed

drug discovery hub dortmund

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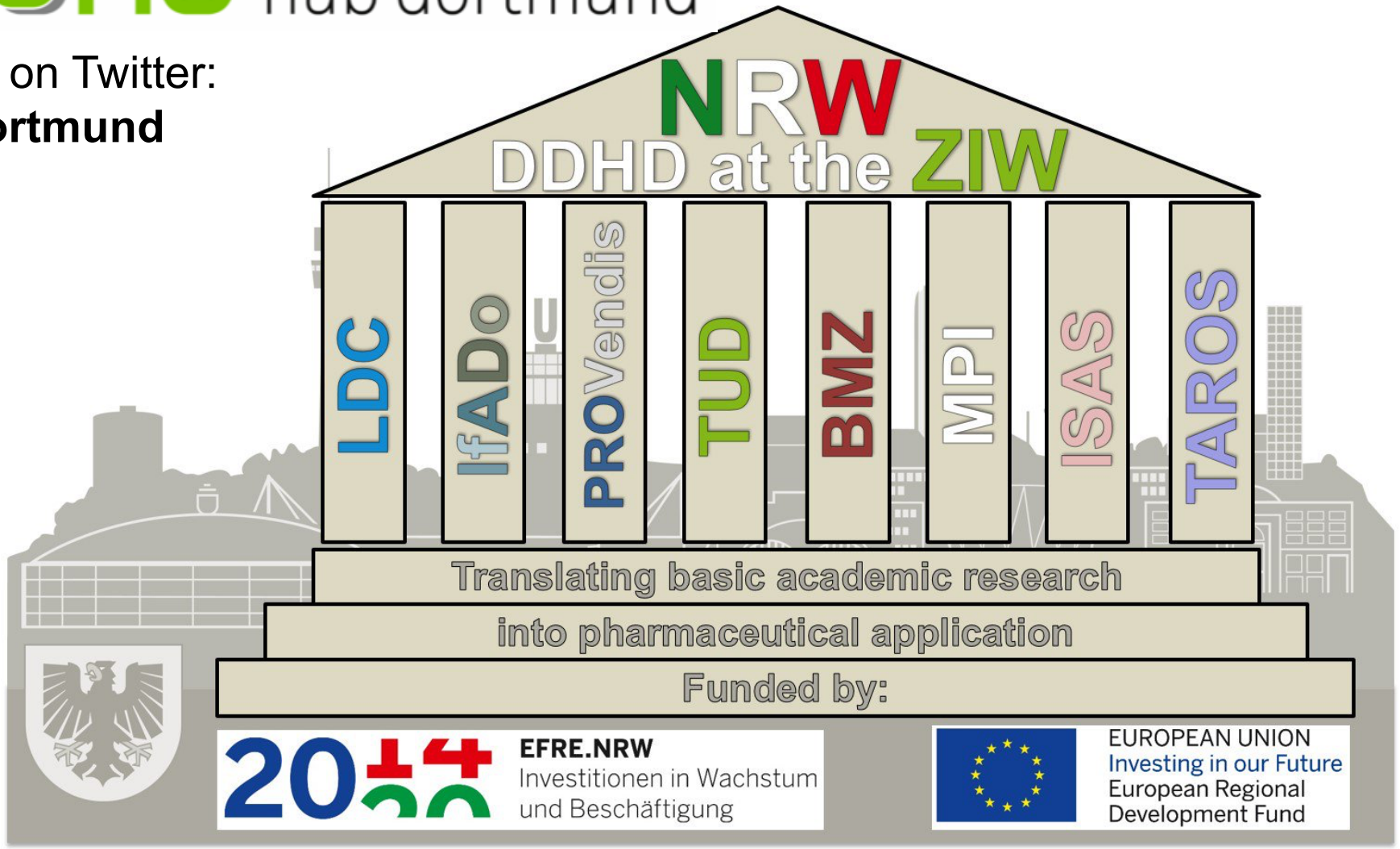

Operational since April 1st, 2018; funds for three years (infrastructure – PoC – education/ entrepreneurship)

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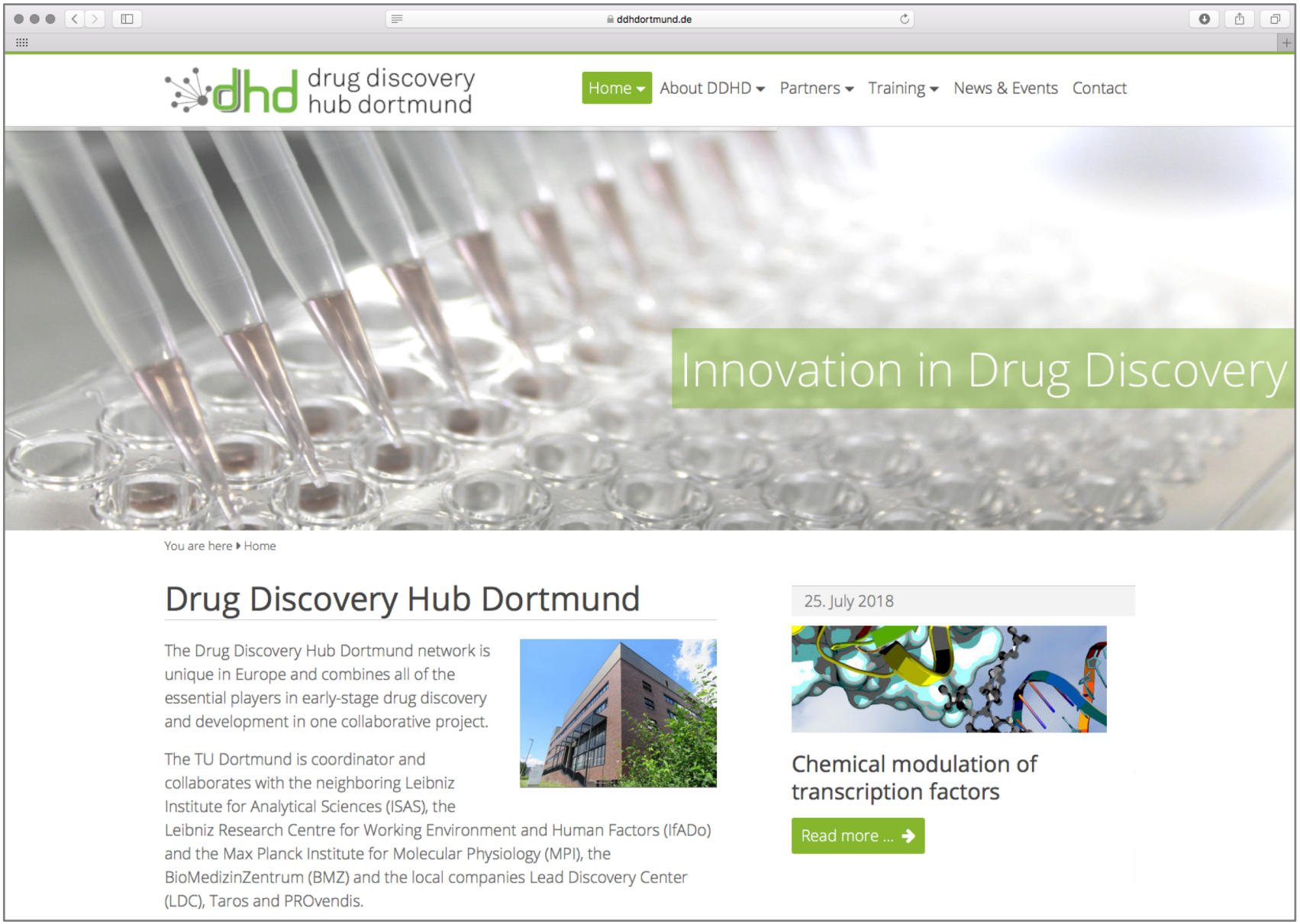
funds for three
ucation/



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