

Wed. 10 - Fri. 12 February 2016

Antwerp, Belgium

**Resistance mechanisms in new drugs and  
how to overcome it:  
the point of view of the **pharmacologist****

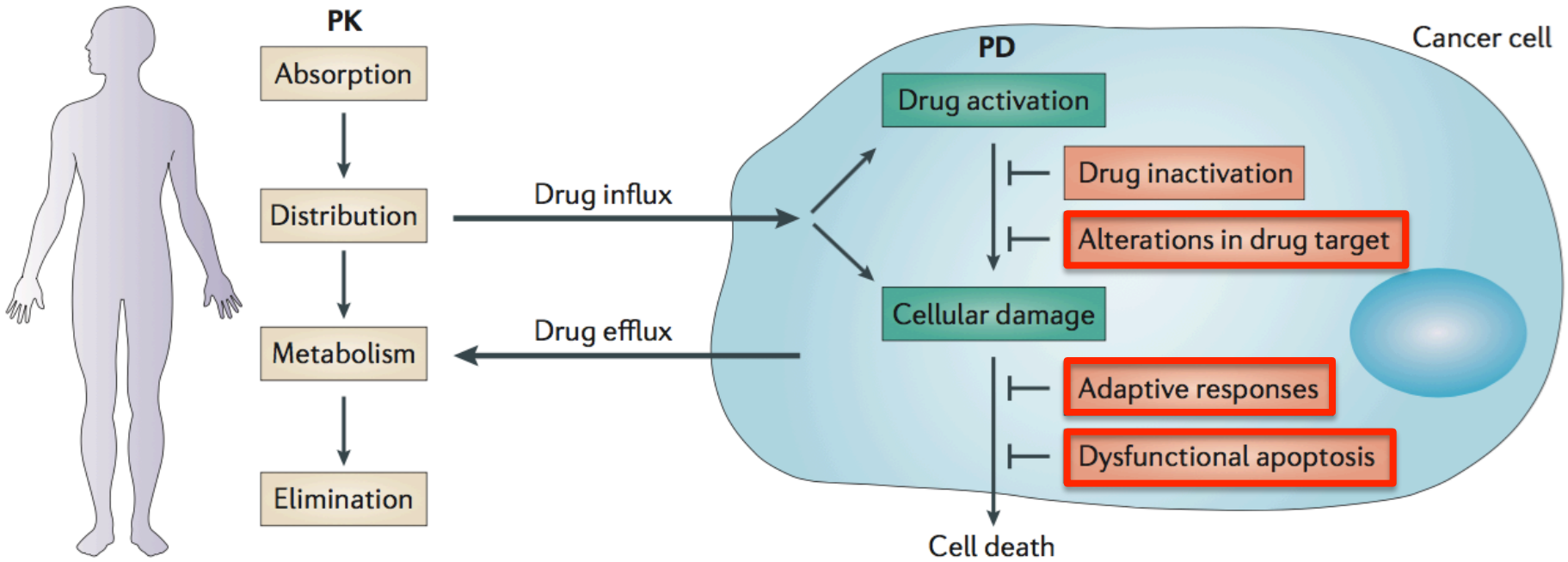
37<sup>th</sup> EORTC-PAMM Winter Meeting

**Elisa Giovannetti**

**Cancer Pharmacology Lab, Pisa University, Italy**

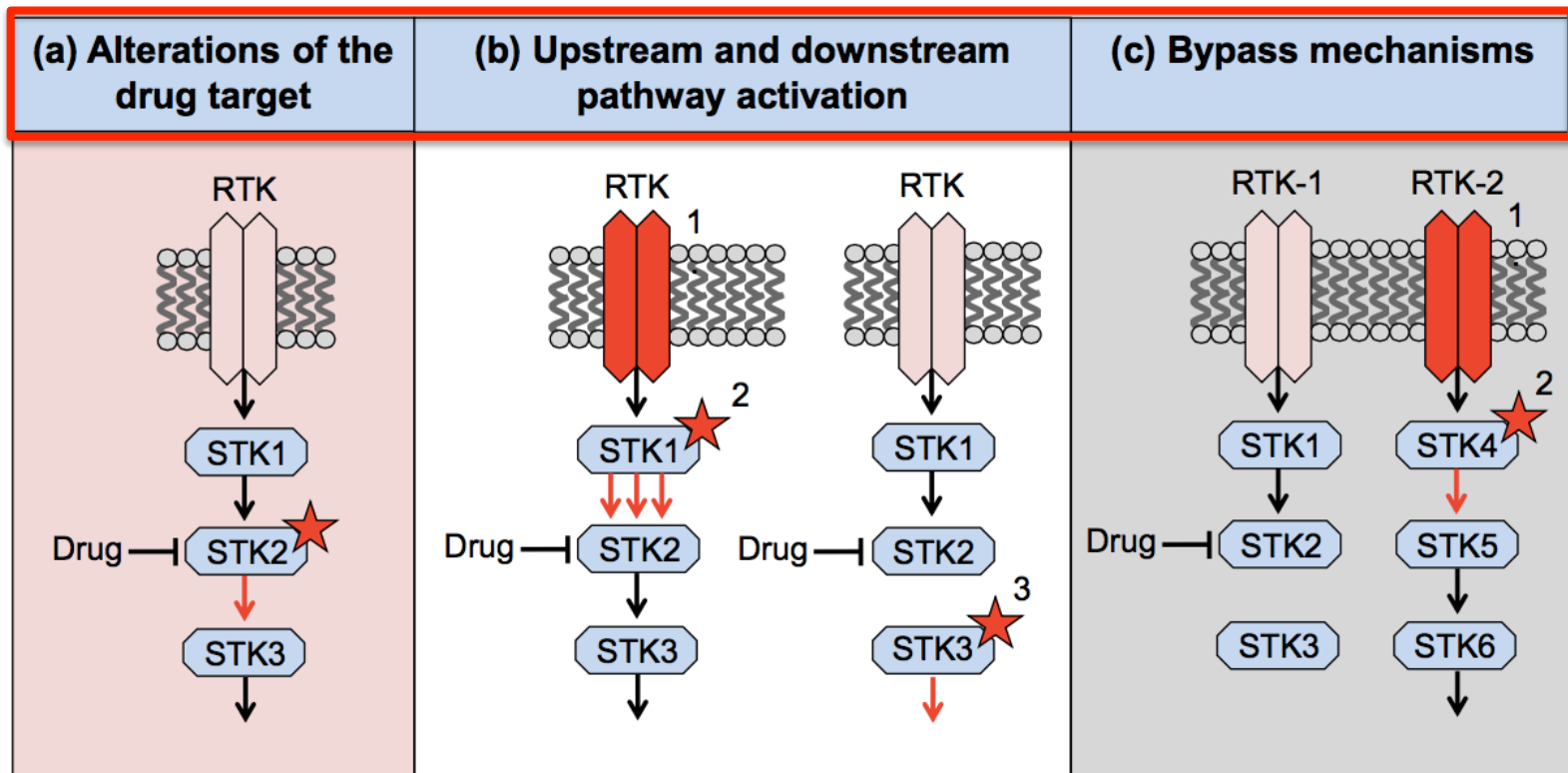
**Lab Medical Oncology, Vumc, Amsterdam, The Netherlands**

# General principles of anticancer drug resistance

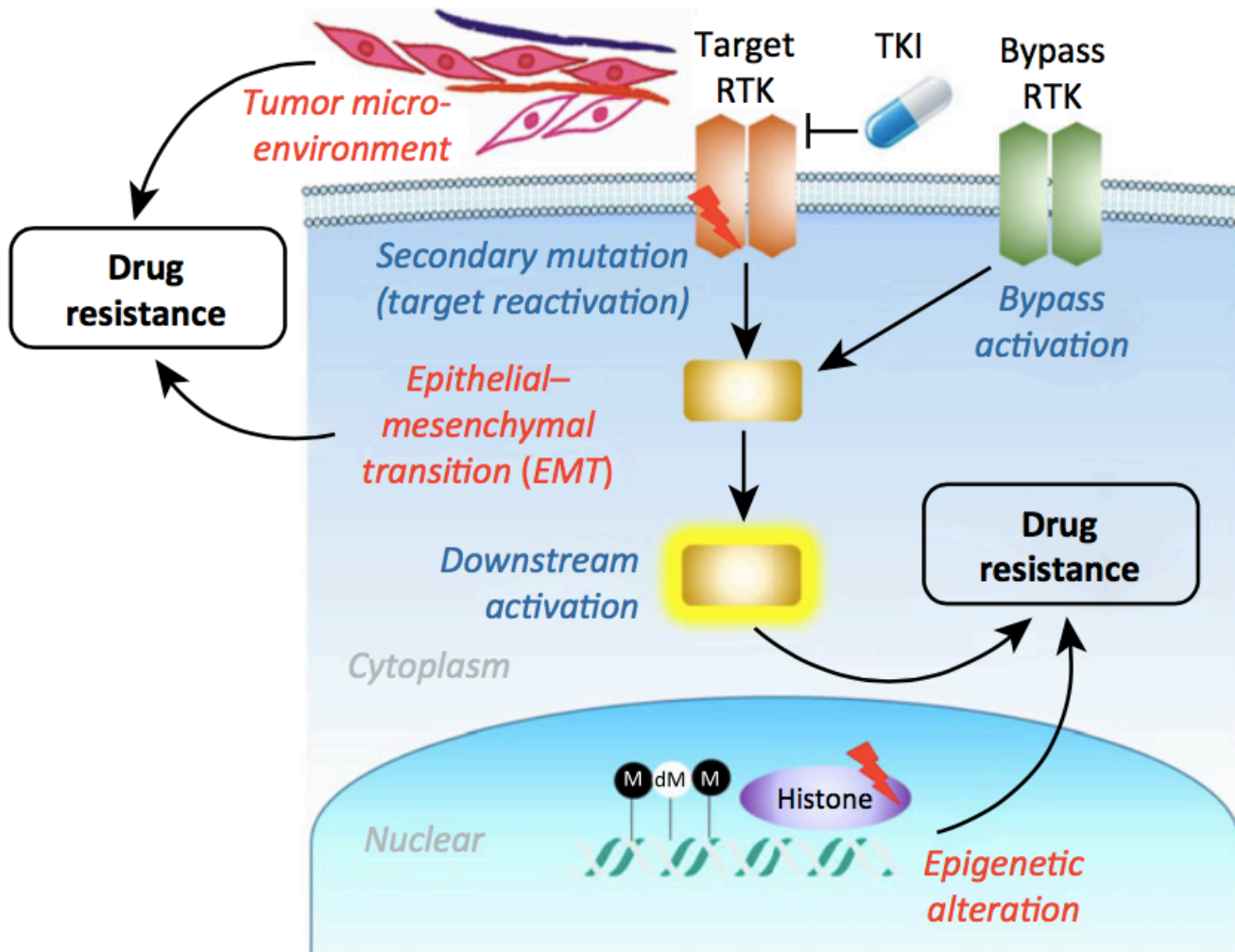


# Resistance to targeted therapies




*the presence of molecular changes that enable a cancer cell to escape the intended effect of targeted agents*



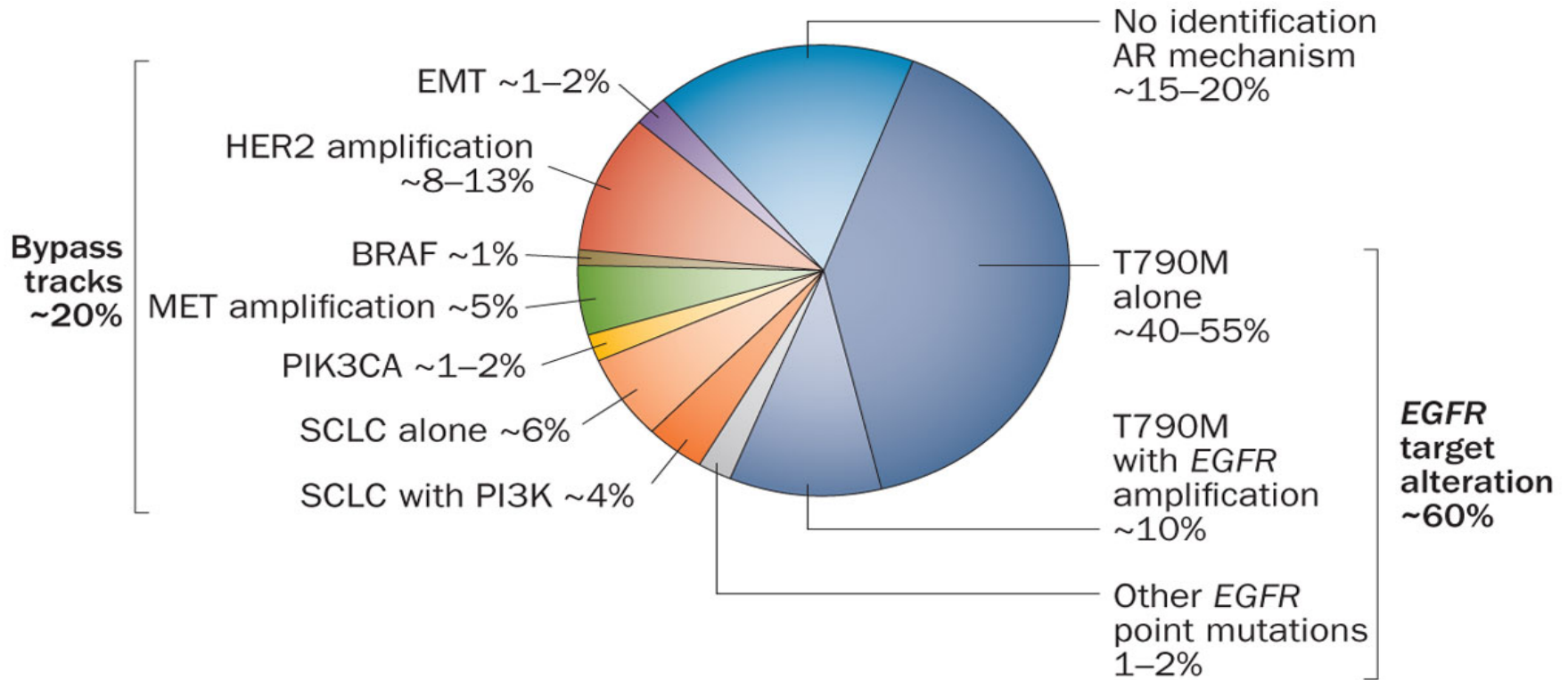
# Examples of resistance to antitargeted anticancer drugs



## Resistance to gefitinib in NSCLC

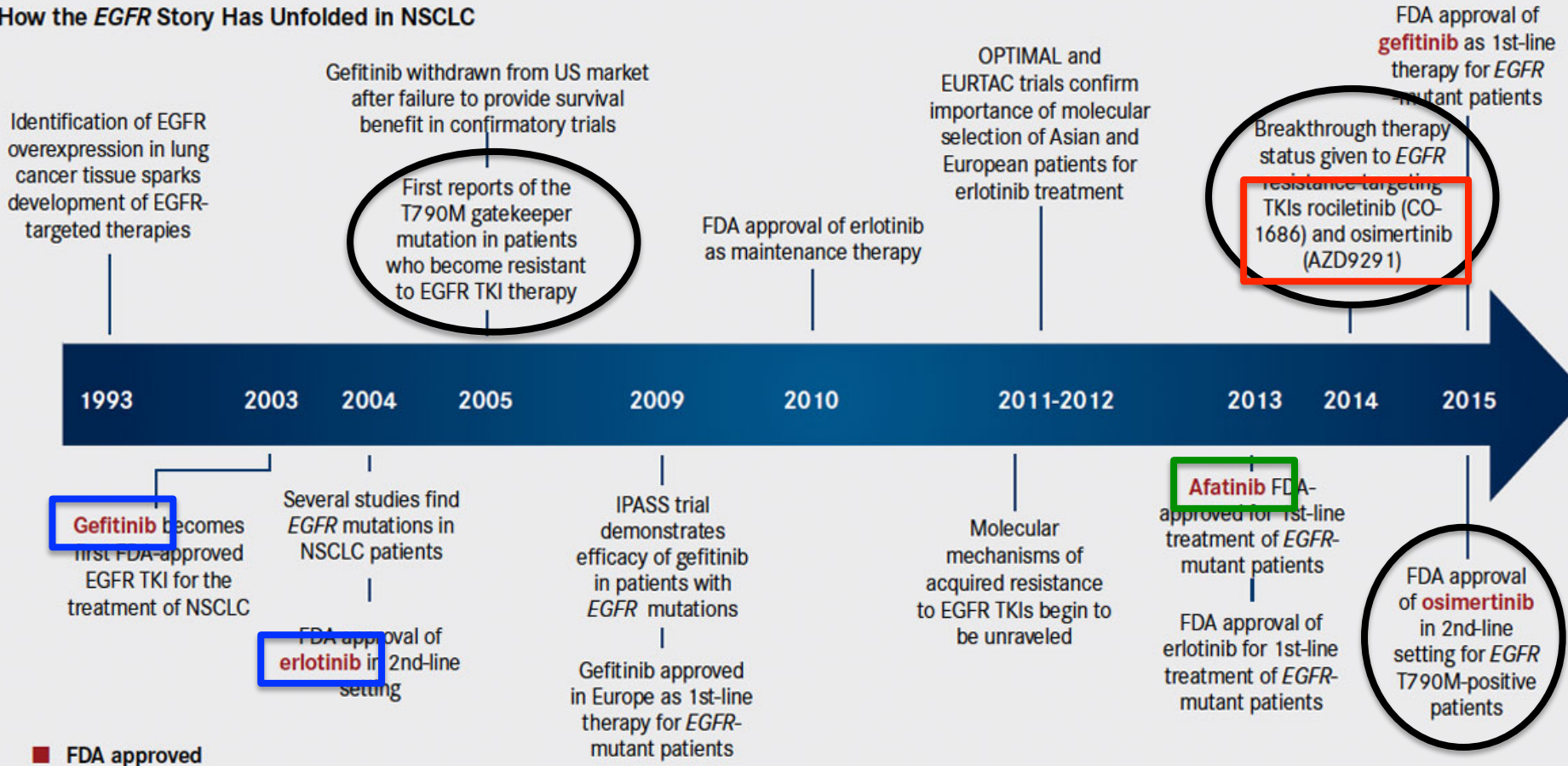
<p>Secondary mutation</p> 	<ol style="list-style-type: none"> <li>1. kinase domain mutations (T790M, exon 20 insertion)</li> </ol>
<p>Downstream activation</p> 	<ol style="list-style-type: none"> <li>1. <i>PIK3CA</i> mutation</li> <li>2. <i>BRAF</i> mutation</li> <li>3. <i>PTEN</i> loss</li> </ol>
<p>Bypass RTK</p> 	<ol style="list-style-type: none"> <li>1. <i>HER2</i> or <i>HER3</i> amplification</li> <li>3. <i>MED12</i> suppression</li> <li>4. NF-<math>\kappa</math>B signaling activation</li> <li>5. <i>FGFR</i> family activation</li> <li>6. <i>Neuregulin-1</i> and <i>P2Y</i> receptors high expression</li> <li>7. <i>MET</i> amplification</li> </ol>

# Role of T790M



# EGFR-TKIs evolution

## How the *EGFR* Story Has Unfolded in NSCLC

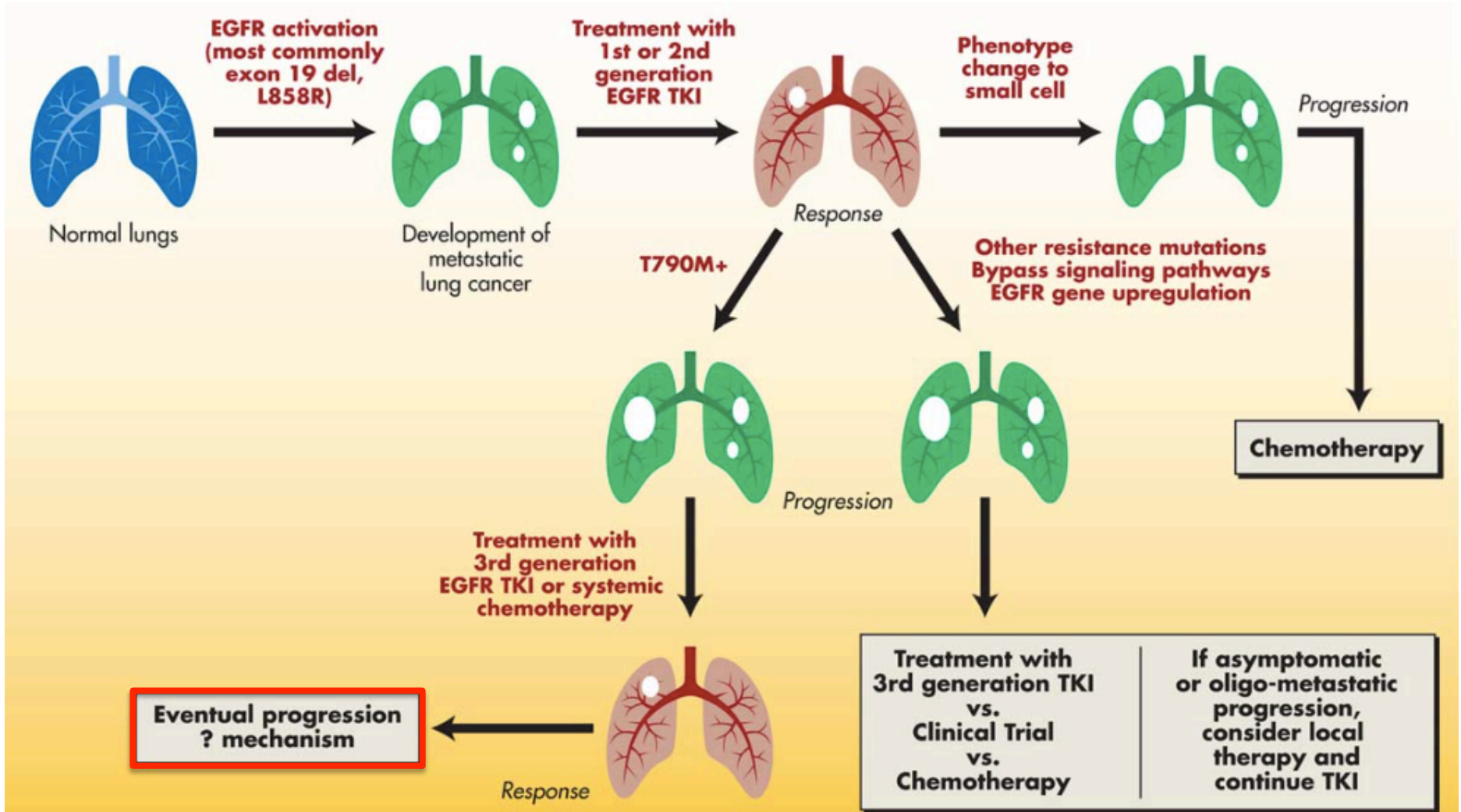


First generation

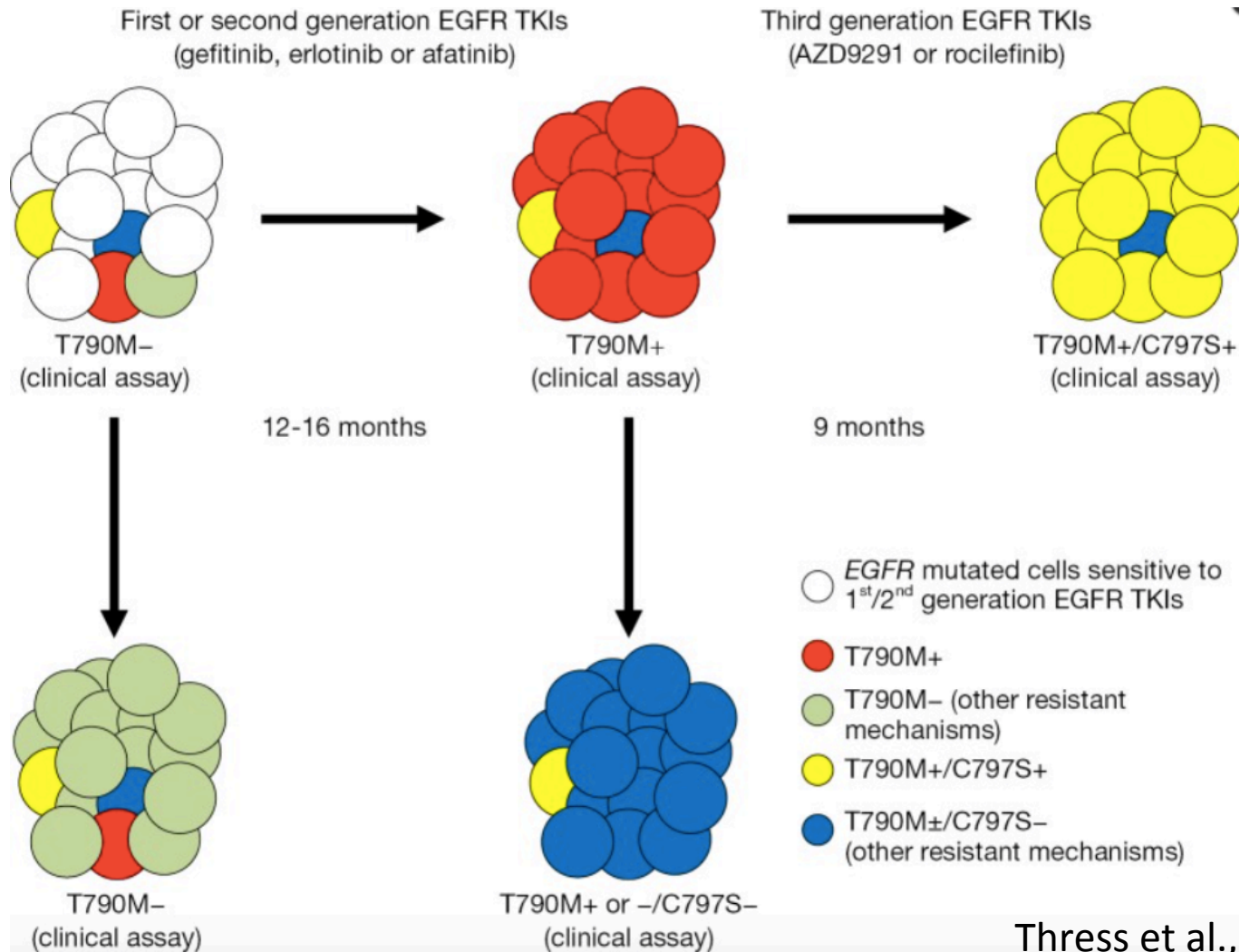
Second generation

Third generation

# Current treatment paradigm for metastatic EGFRm+ NSCLC

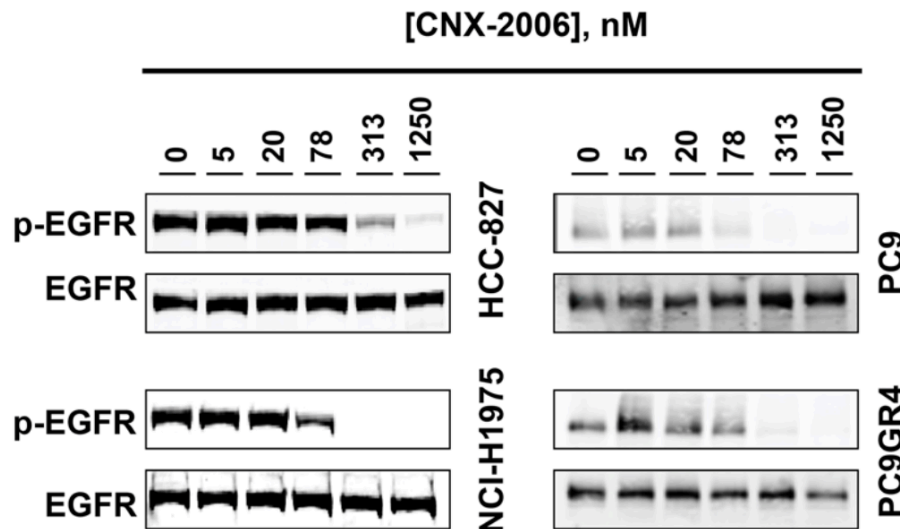
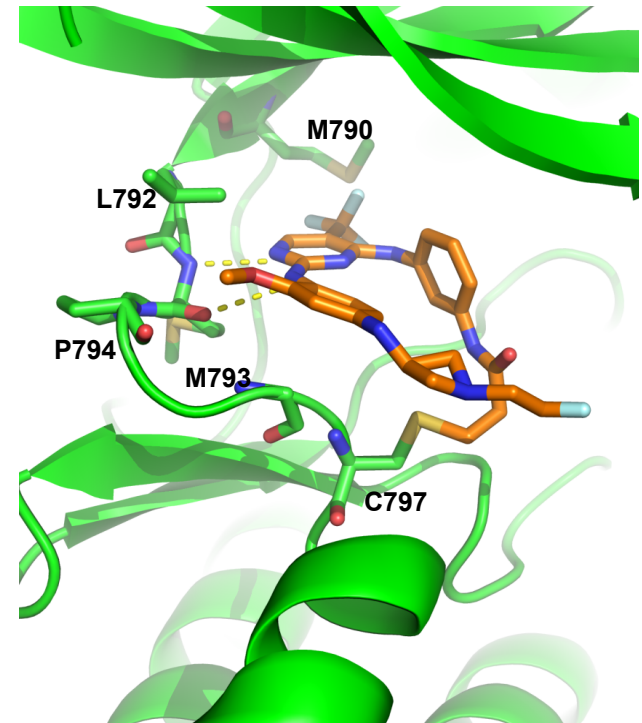
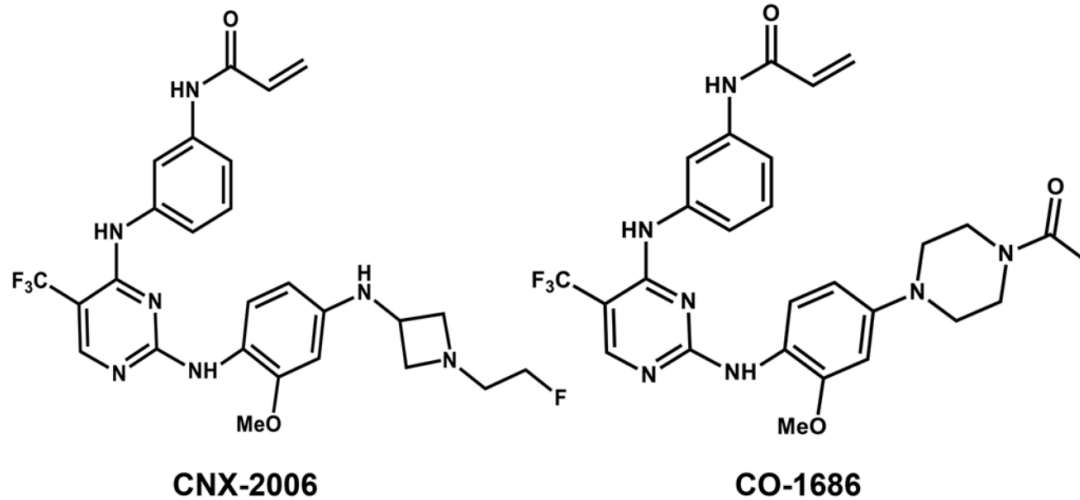


# Looking for mechanisms underlying resistance to 3<sup>rd</sup> generation EGFR-TKIs





# Our study on CNX-2006, an analogue of rociletinib



# Antiproliferative effects

## NSCLC cells

### EGFR WT

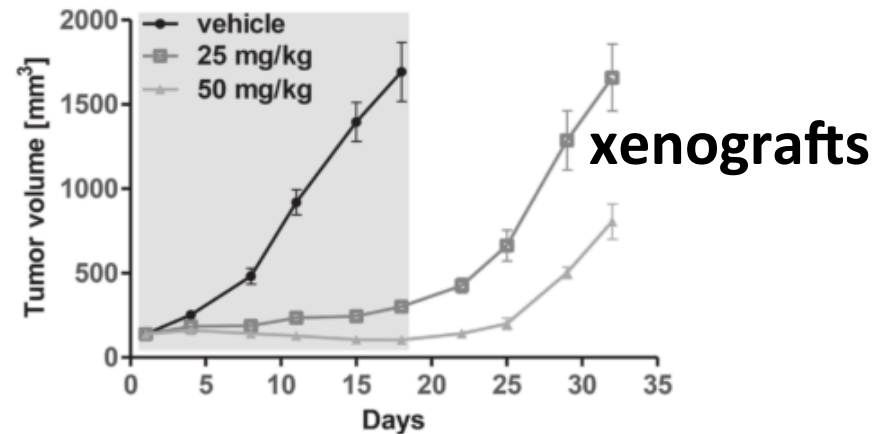
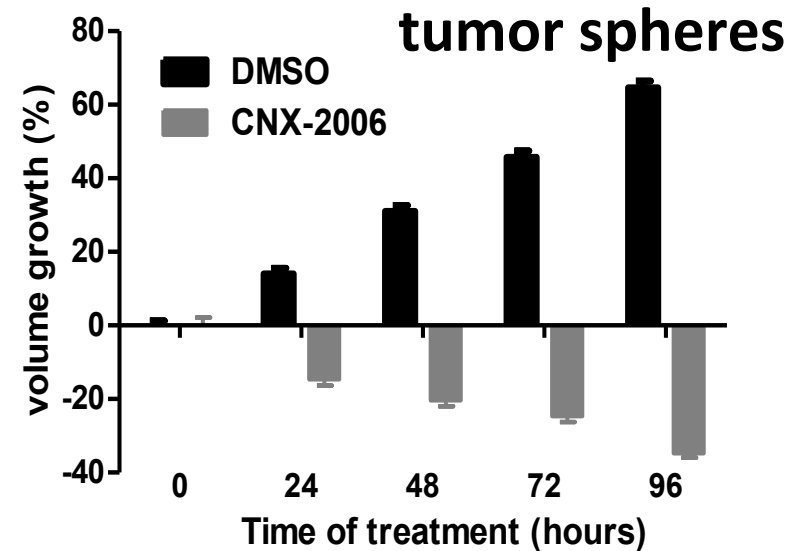
Cell line	Gefitinib IC <sub>50</sub> μM	CNX-2006 IC <sub>50</sub> μM
H23	11.2	2.4
H522	13.7	1.5
H1703	8.2	4.3

### Activating EGFR-mut

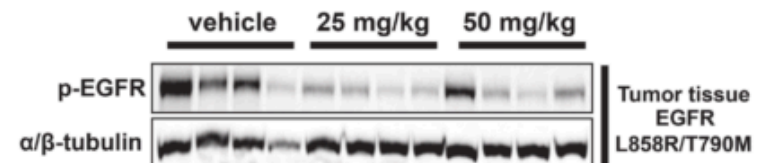
Cell line	Gefitinib IC <sub>50</sub> μM	CNX-2006 IC <sub>50</sub> μM
HCC-827	0.01	0.003
H3255	0.02	0.006
PC9	0.04	0.01

### EGFR-T790M

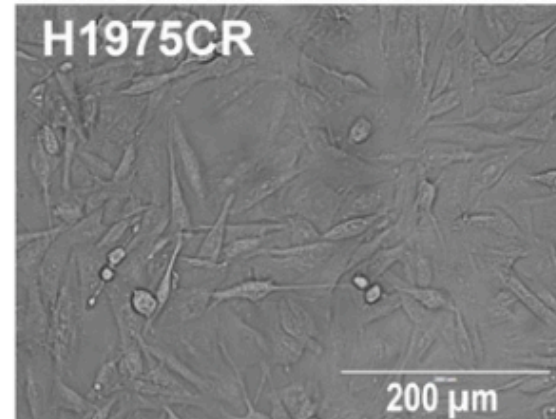
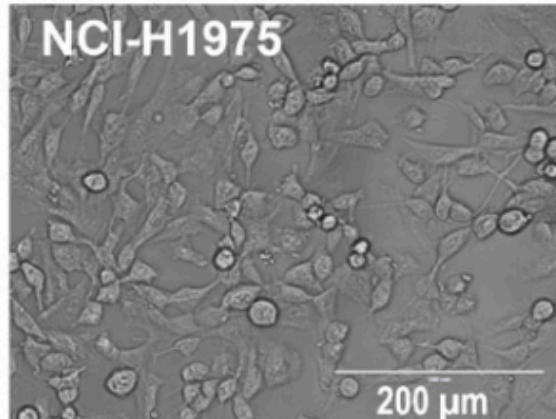
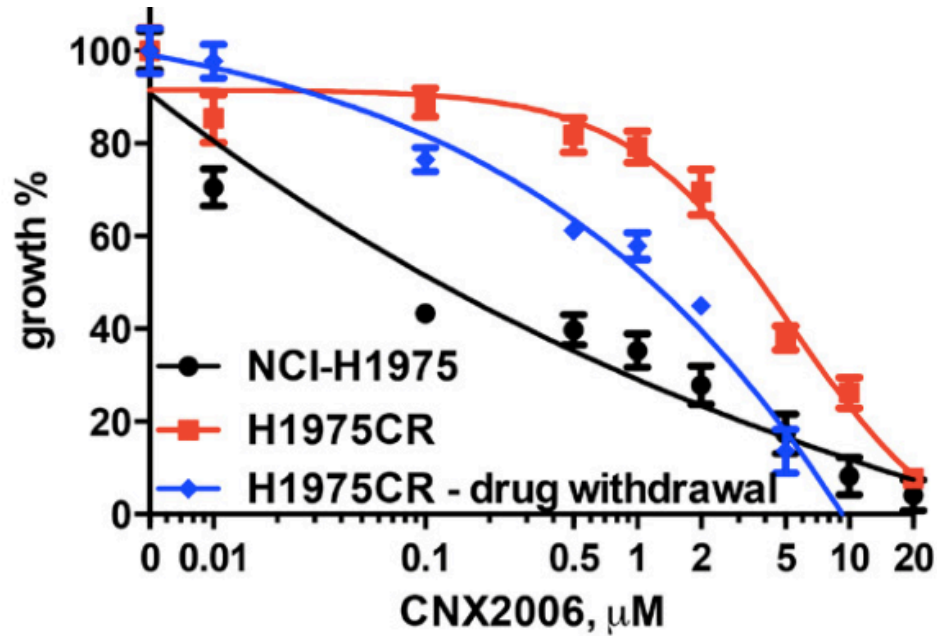
Cell line	Gefitinib IC <sub>50</sub> μM	CNX-2006 IC <sub>50</sub> μM
H1975	10.0	0.07
PC9GR4	2.1	0.008
PC9DR1	7.4	0.006



B

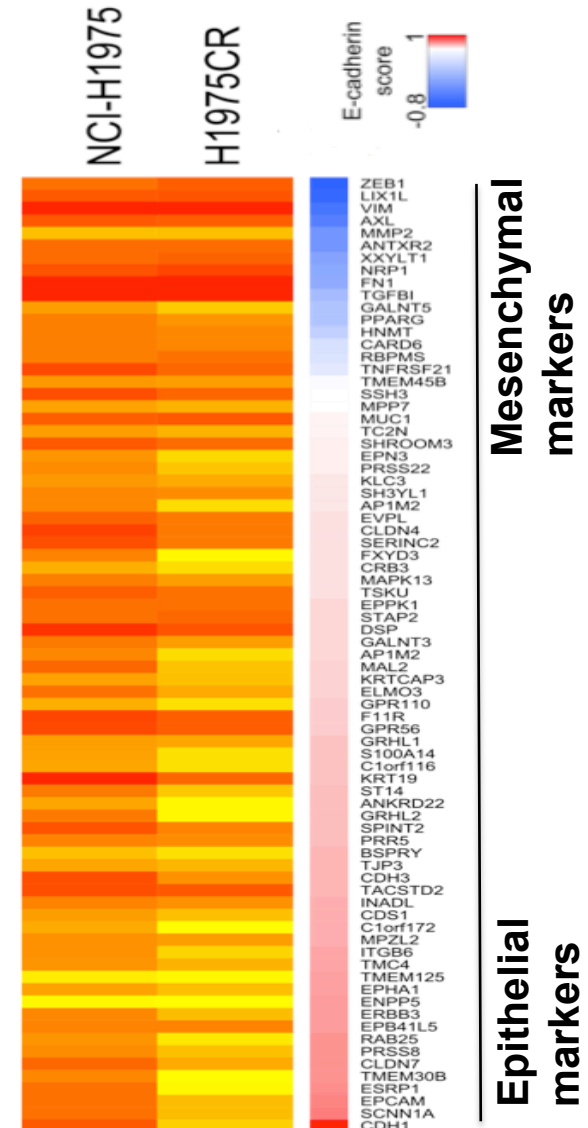
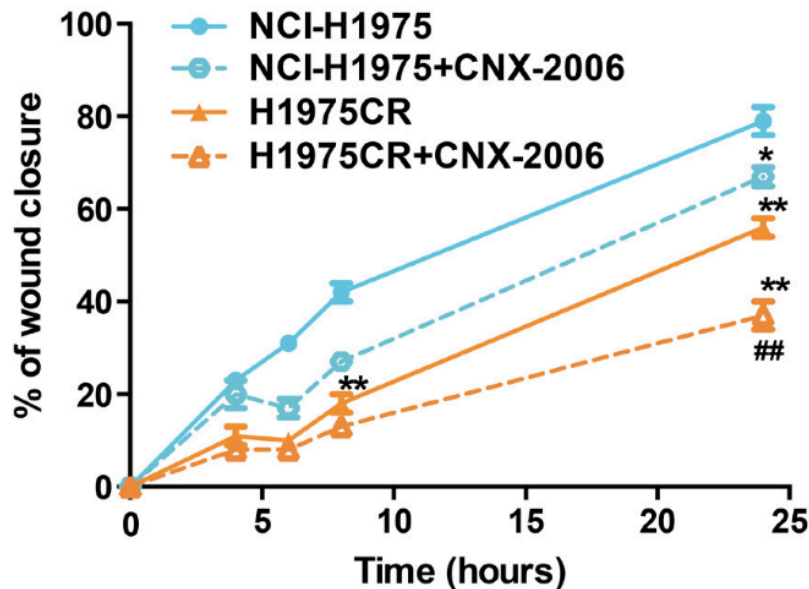
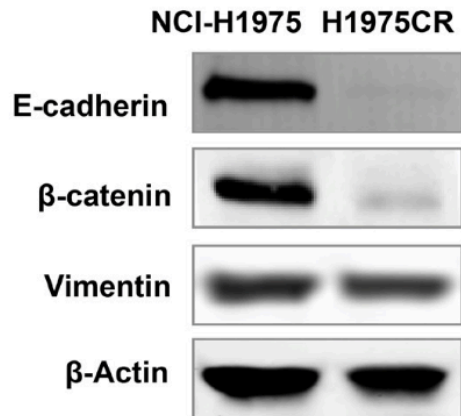


# Creation of a resistant clone to CNX-2006

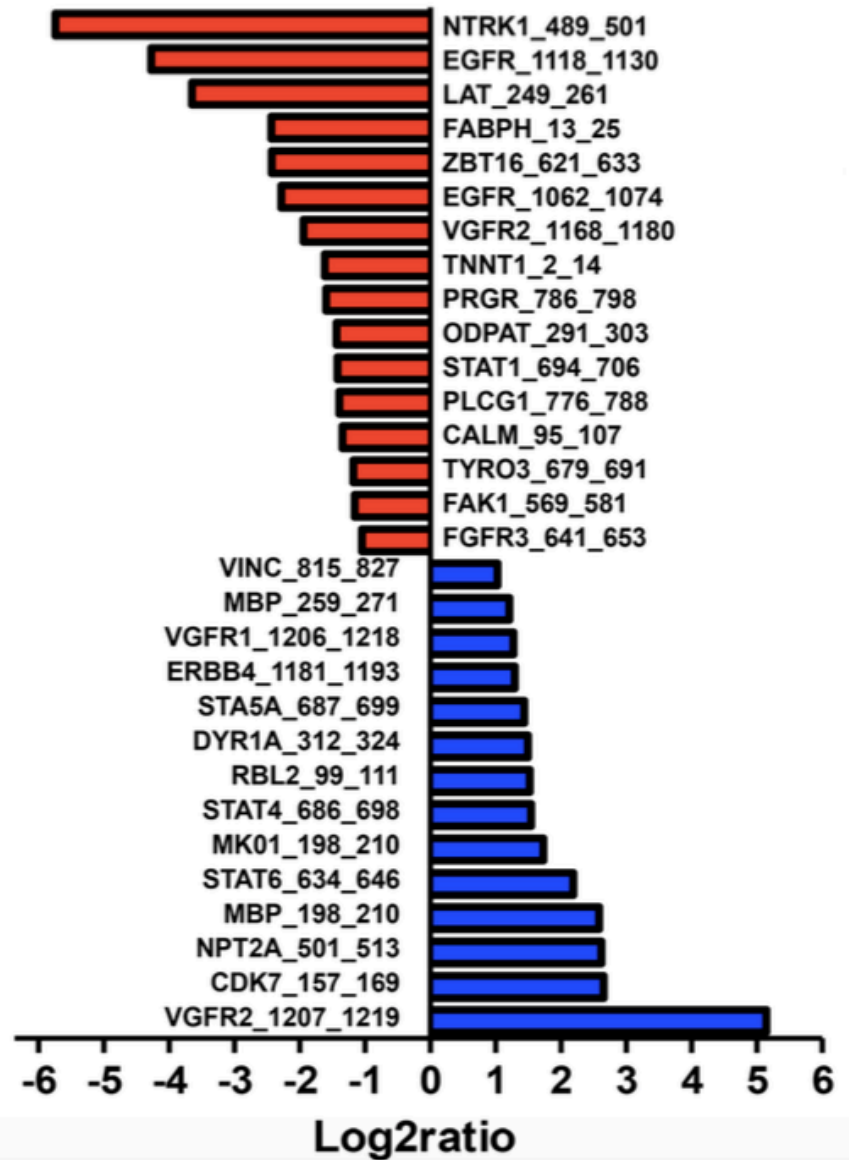
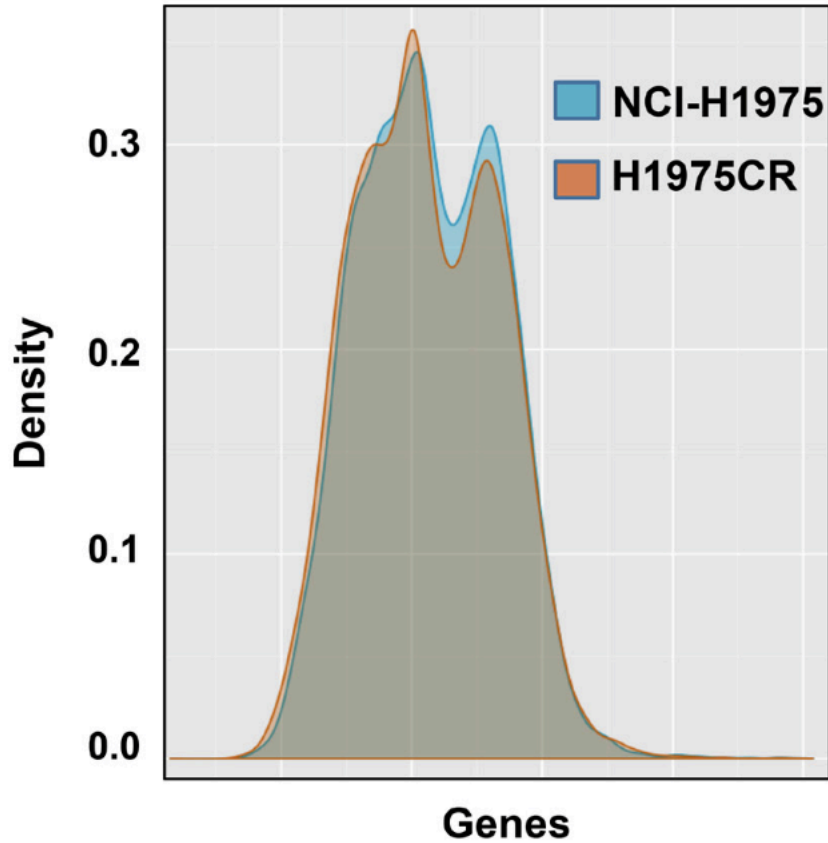


# Controversial role of EMT

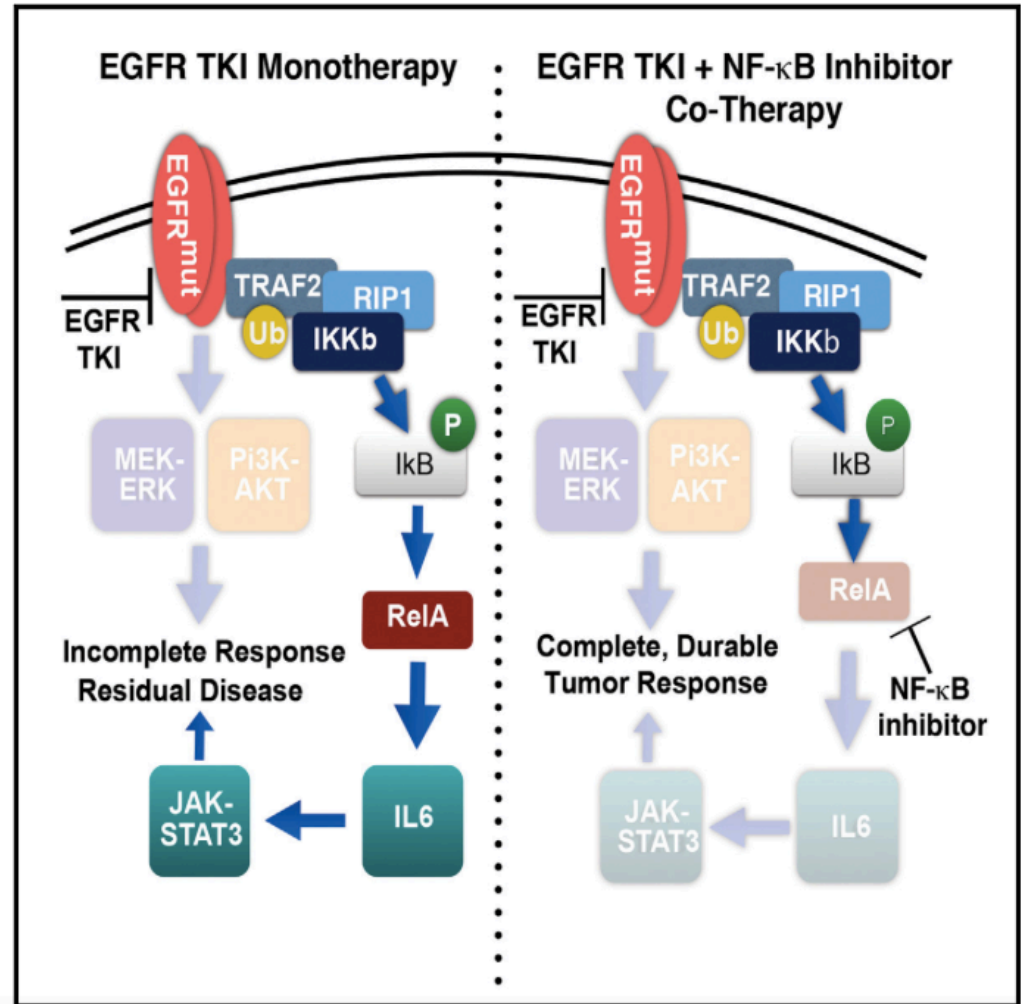
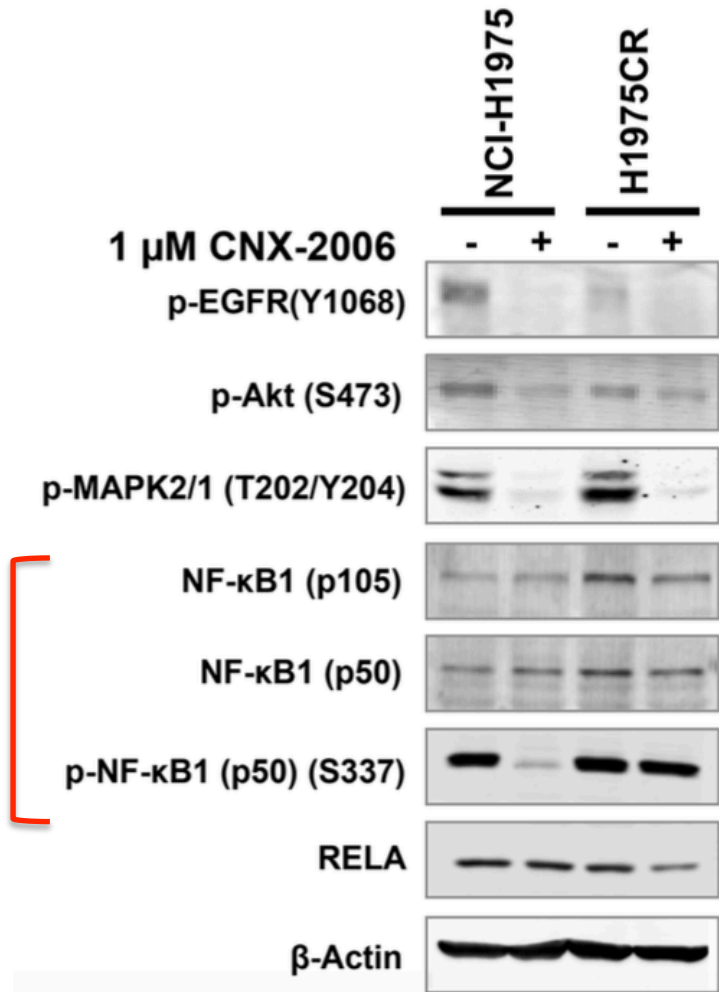
Cells resistant to CO-1686 showed signs of Epithelial-to-Mesenchymal Transition (EMT) (Walter et al., Cancer Discov 2014), but...



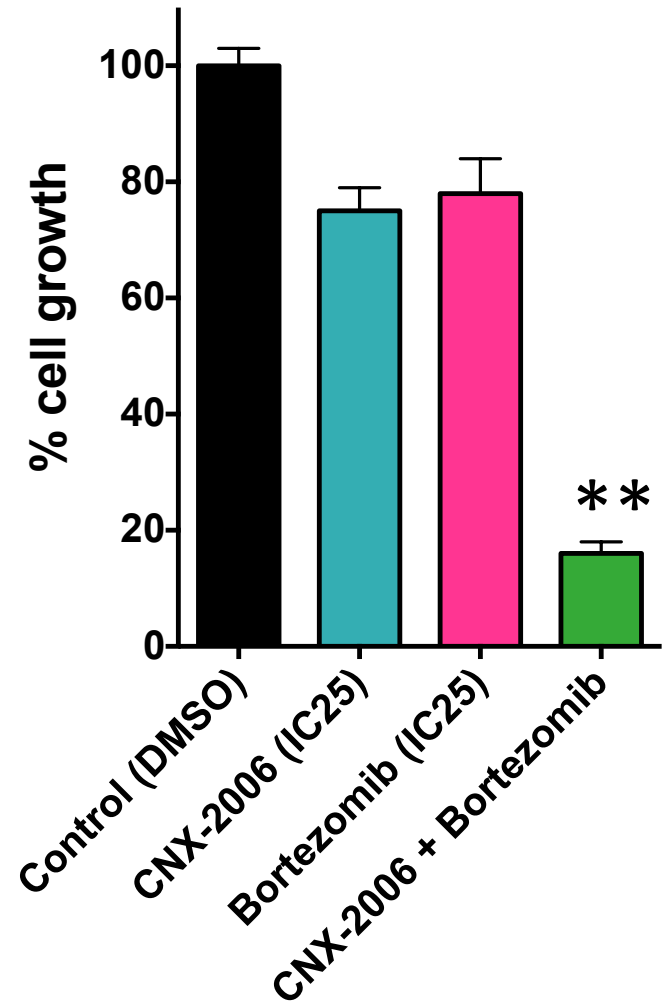
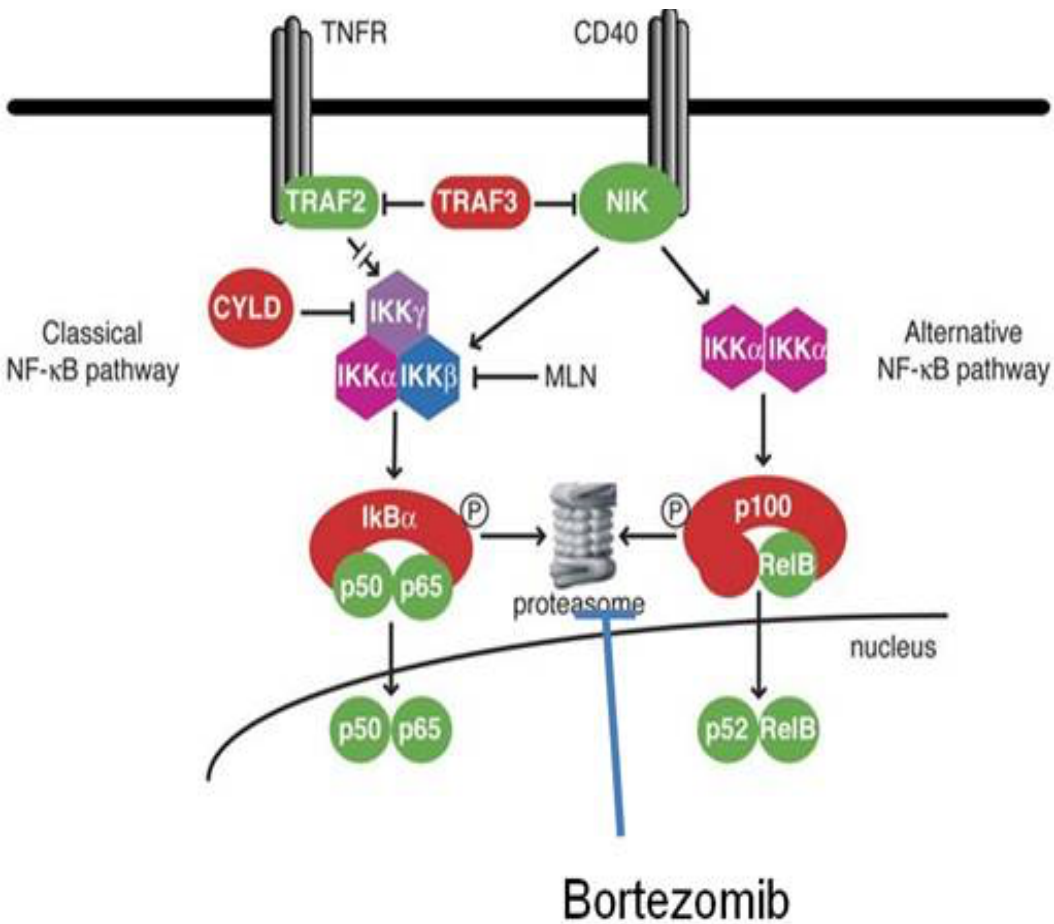
# NGS and kinase array



# Role of NF-κB signaling



# Combination with bortezomib



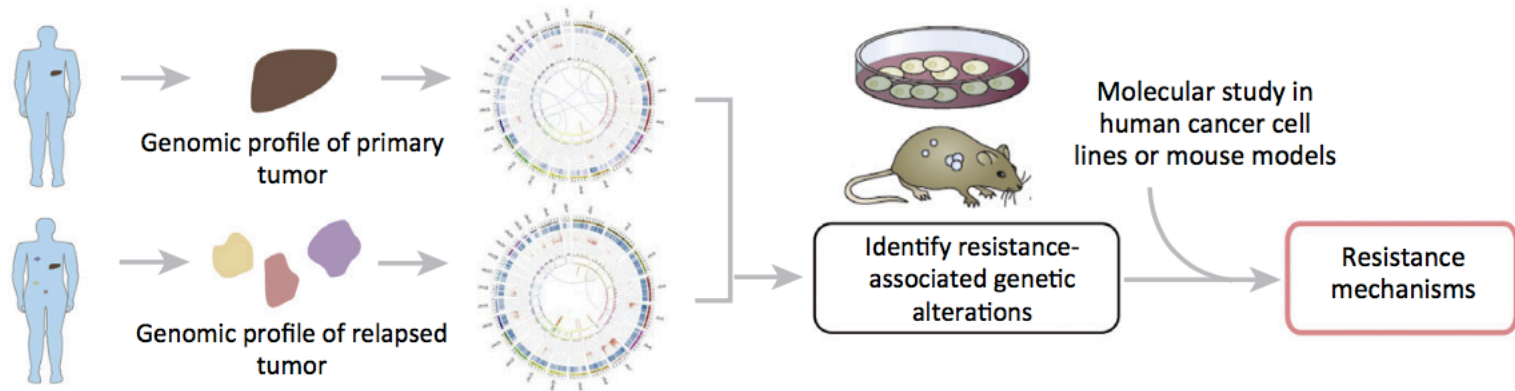
# In conclusion



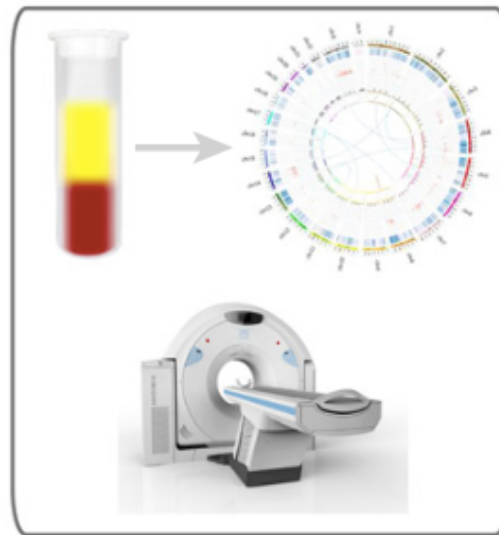
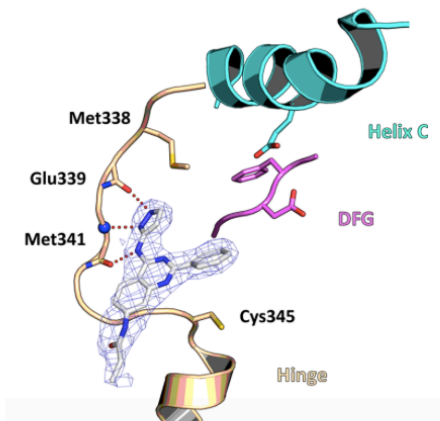


# Future strategies to overcome resistance

1. -OMICS profiling & molecular preclinical studies to identify resistance mechanisms

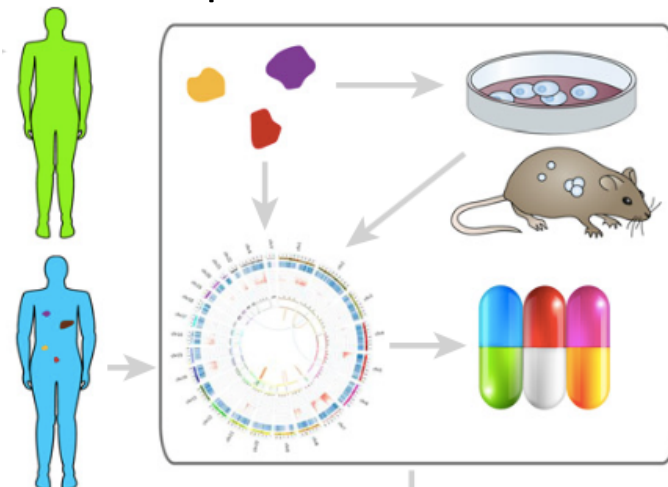


2. Design better & more selective compounds



3. Non-invasive monitoring of relapse

4. Adapt combination therapy on tumor longitudinal profiling and preclinical studies



# Acknowledgments

- **CNX study**

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Dr. I Garajova

- **Studies on bortezomib**

Dr. G Jansen

Dr. J Cloos



MARIE CURIE

