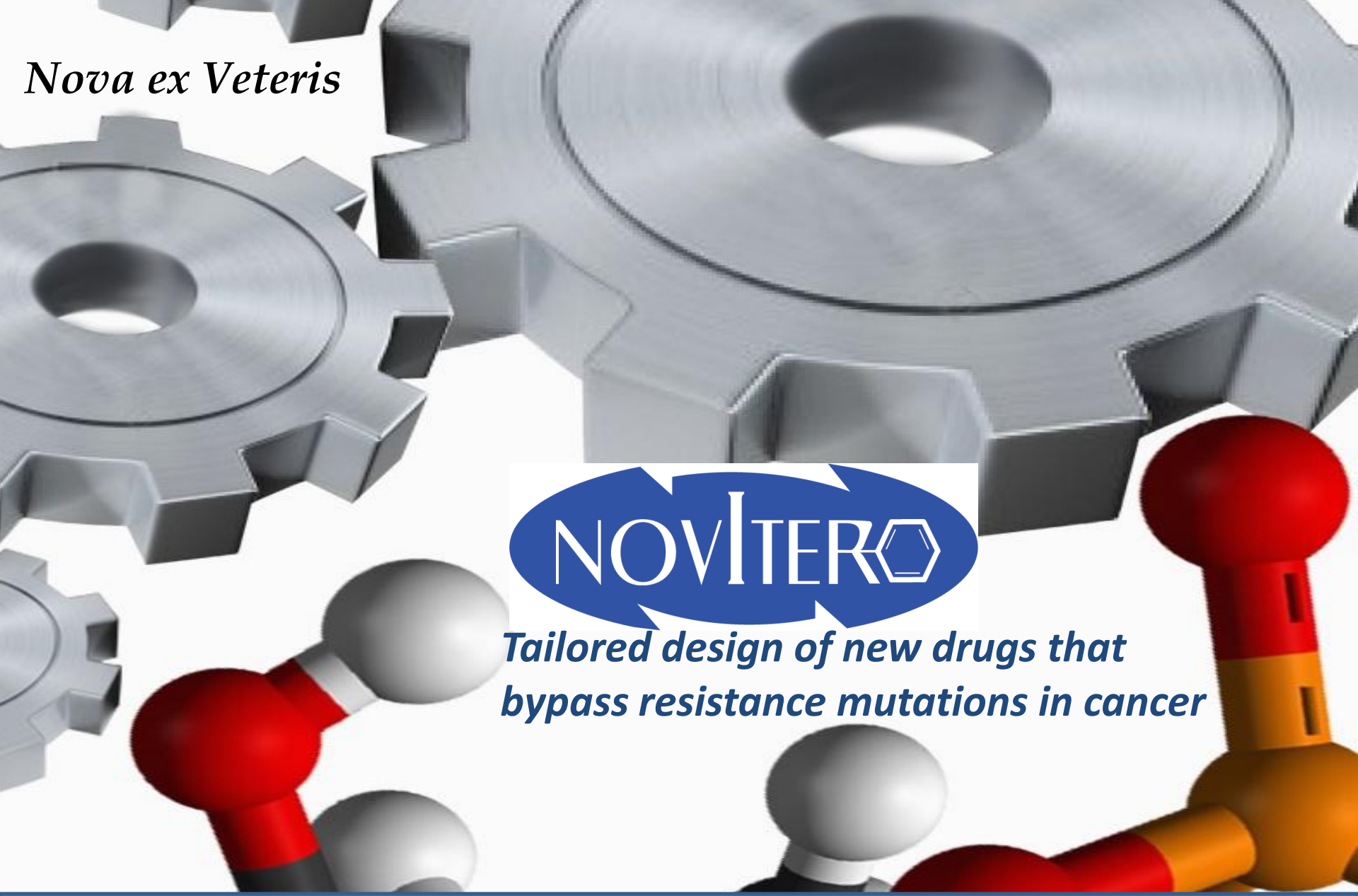
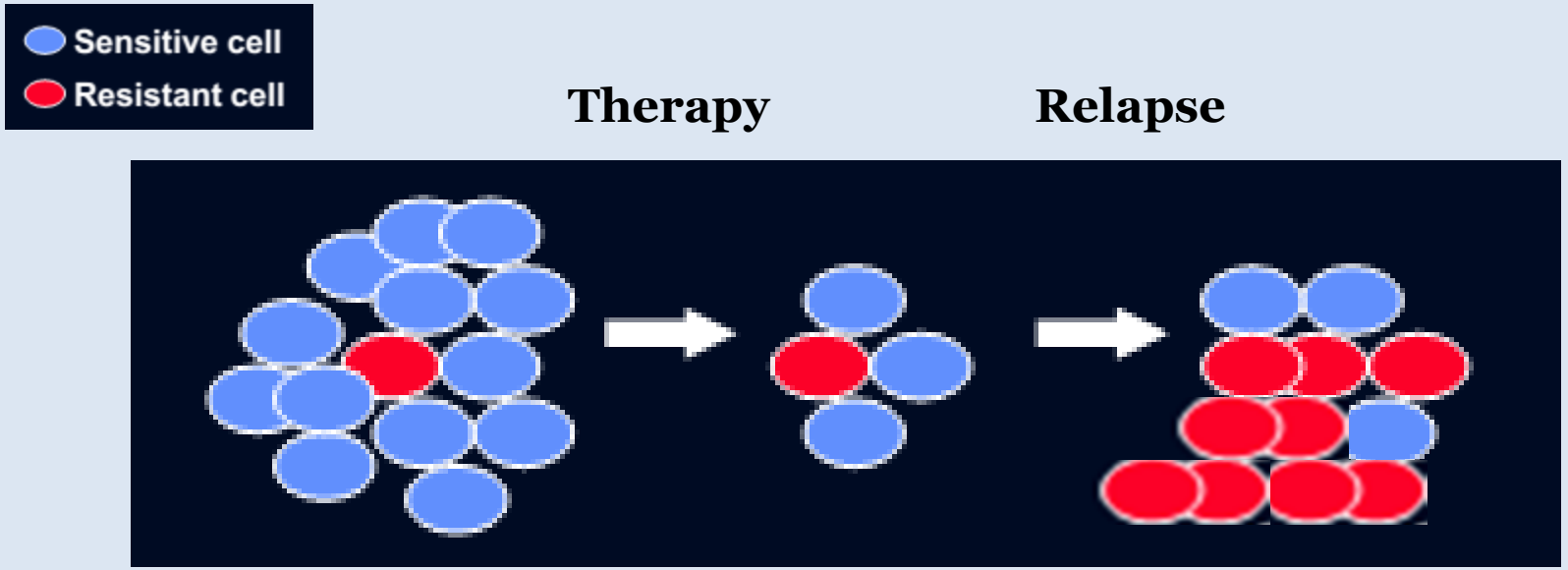
Nova ex Veteris



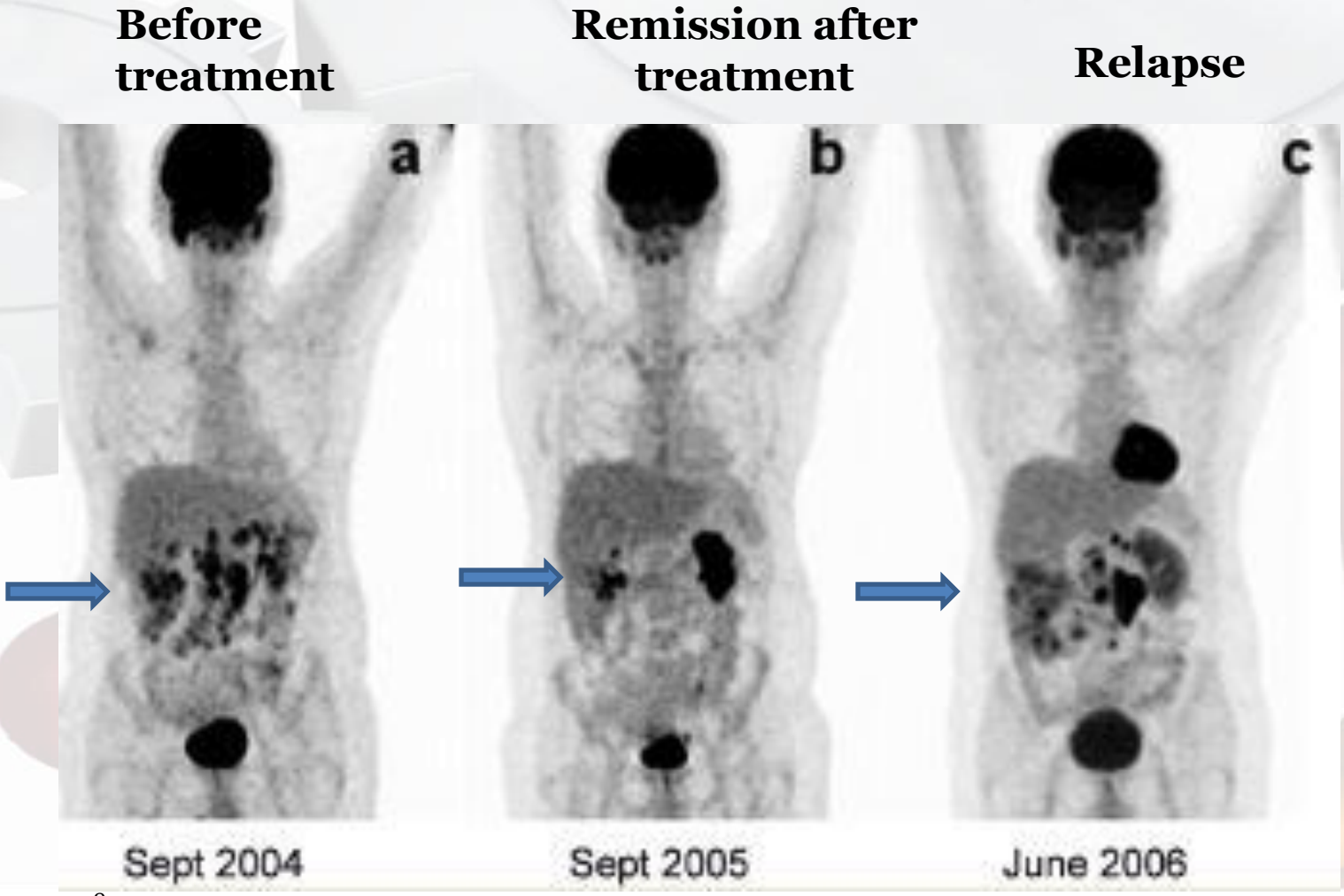
NOVITERO

Tailored design of new drugs that bypass resistance mutations in cancer

Resistance to therapies is the main cause of cancer treatment relapse



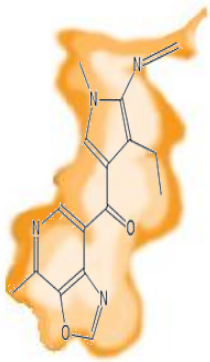
People still die from cancer mainly due to the development of resistance to therapies

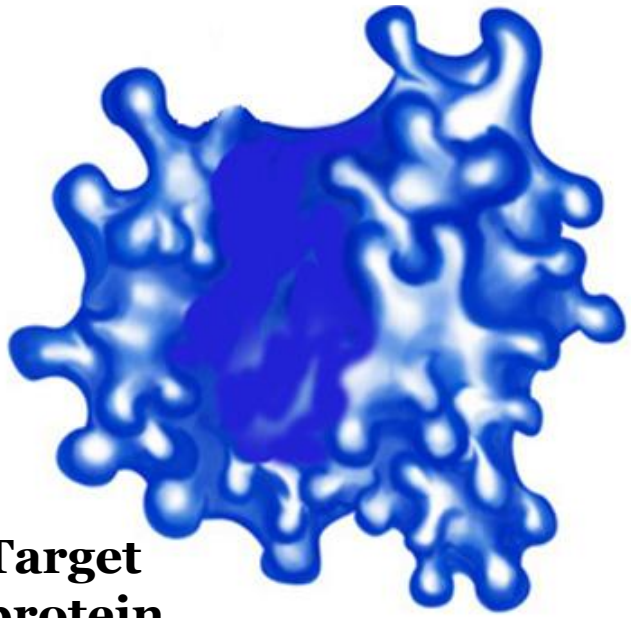


Whole-body ^{18}F-FDG PET-CT images in 43-year old patient with DSRCT.
From Ben-Sellem et al., Rare Tumors (2009)

To exert its therapeutic activity a drug needs to fit its target

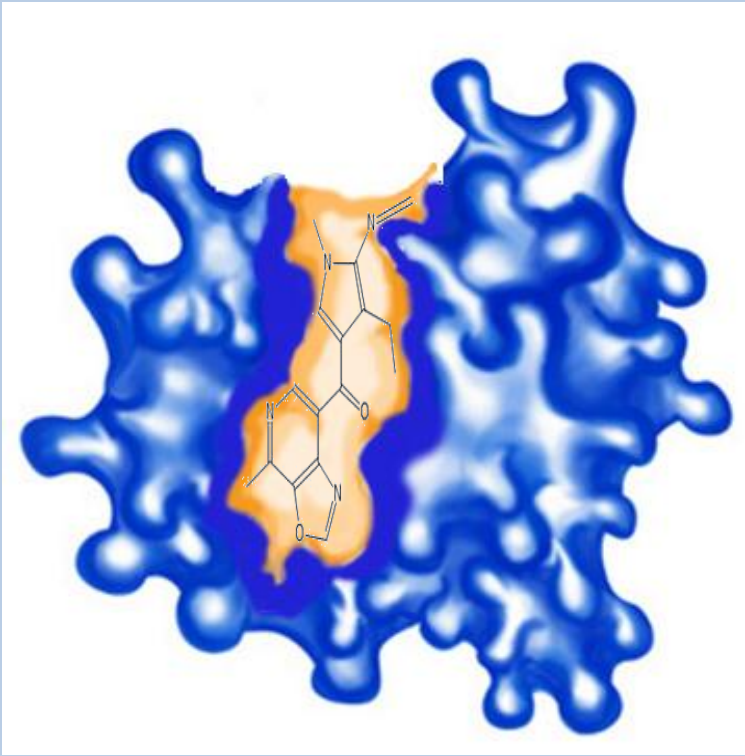
Marketed drug





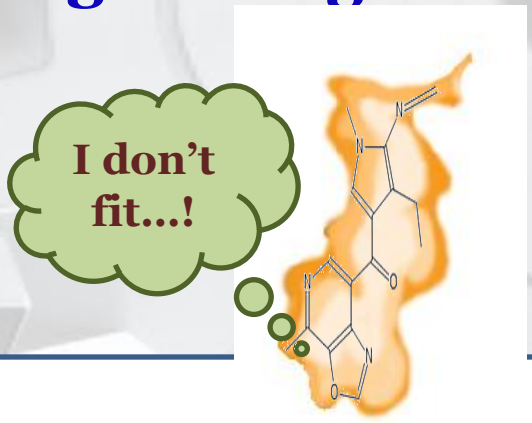
Target protein

Drug fit to target



The better the fit, the higher the affinity and activity

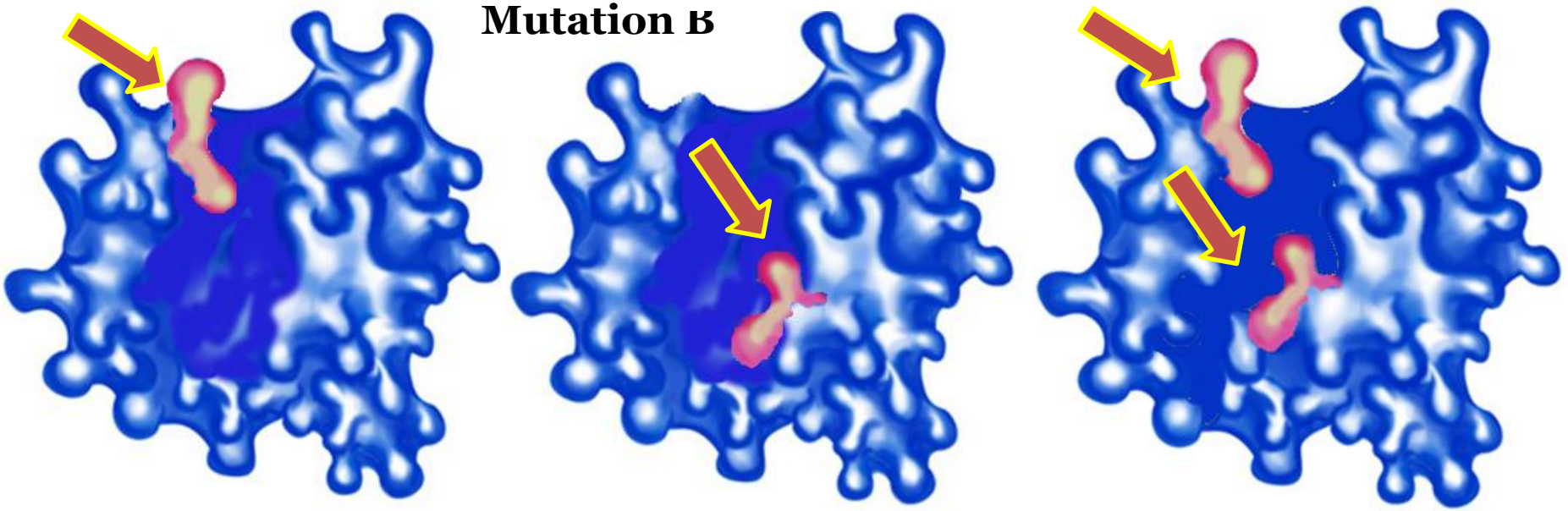
Structural changes (mutations) at the target recognition site cause resistance



Mutation A

Mutation B

Compound Mutations (A+B)

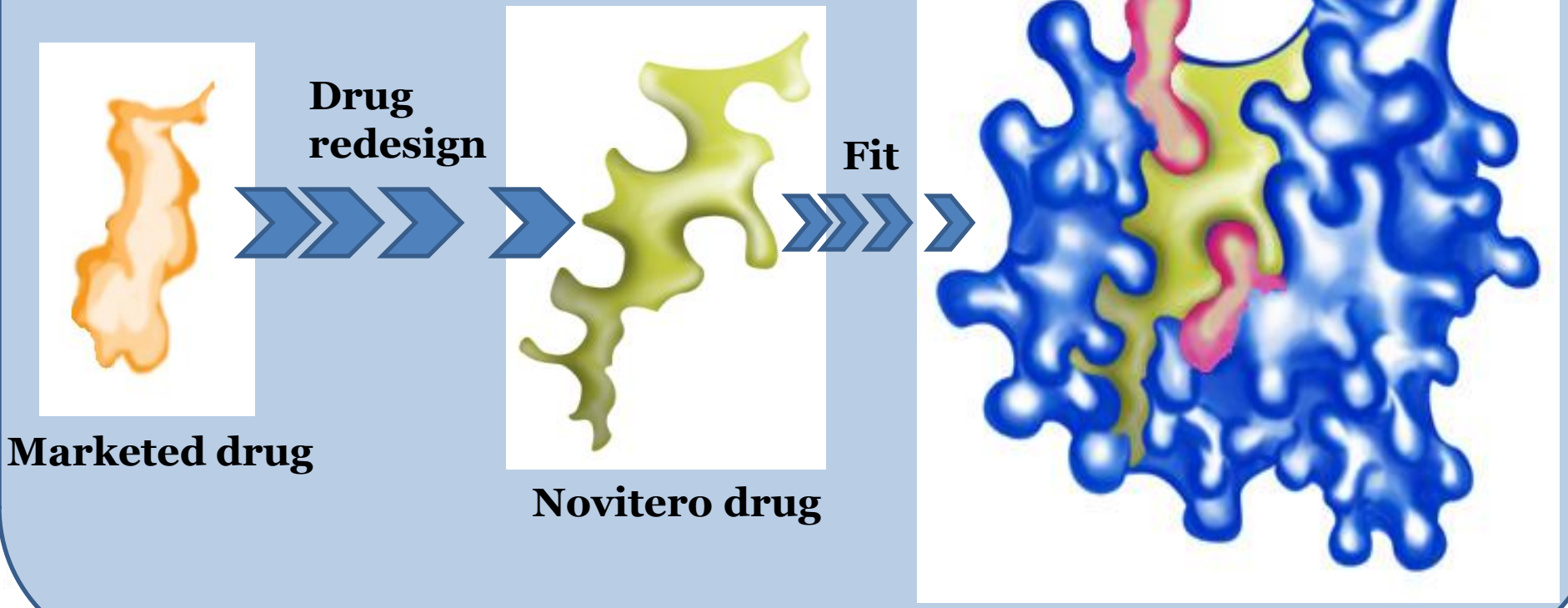


Mutations reduce the fit of the drug to the target, rendering the drugs ineffective

Novitero overcomes resistance through tailor-made drugs that better fit mutated targets

Novitero redesigns marketed drugs to better fit to proteins with multiple and compound mutations

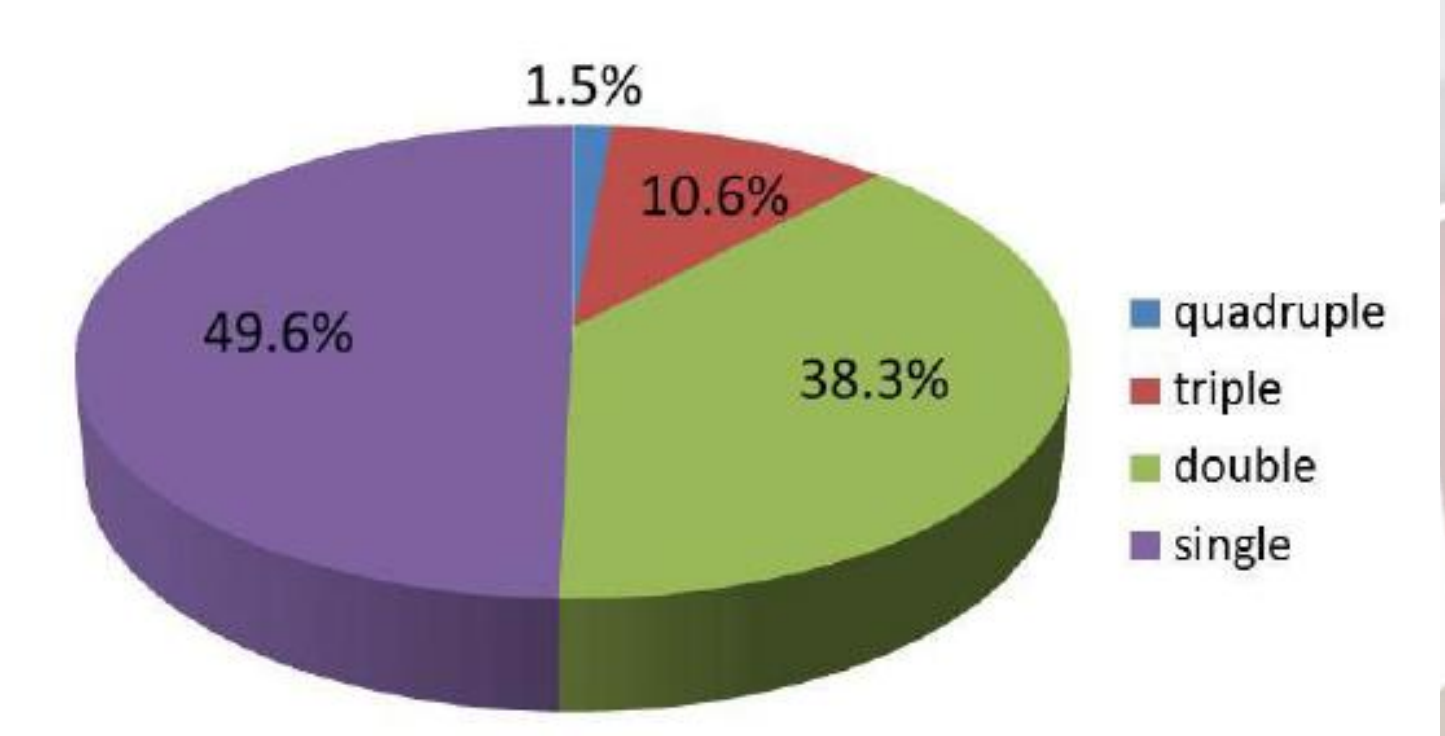
Modified drug has a perfect fit to mutated target proteins



Emerging importance of multiple mutations

- Resistance to targeted cancer therapy and the subsequent disease propagation, treatment failure and relapse, are often caused by mutations in the target recognition site that alter the response to drugs.
- Recently, it became nonetheless evident that multiple mutations often occur, and abrogate the inhibitory action of novel third generation drugs, designed to inhibit the most frequently expressed single known mutation, to induce resistance in these targets.
- Compound mutations, defined as two or more mutations of the drug target in the same clone, may lead to enhanced resistance against the most selective inhibitors.
- The common use of sequential target-selective drugs has outlined the importance of multiple- and compound-mutations in the development of subsequent resistance to therapy
- Using ultra-deep sequencing of the BCR-ABL1 kinase domain in resistant populations, it was recently demonstrated that the frequency of multiple- and compound-mutations is much higher than previously thought.
- The need to develop drugs that will be effective against multiple- and compound-mutations is becoming evident, as the evolution of resistance to therapies persists, and the populations harboring these mutations increases.

Multiple mutations occur more frequently than previously thought

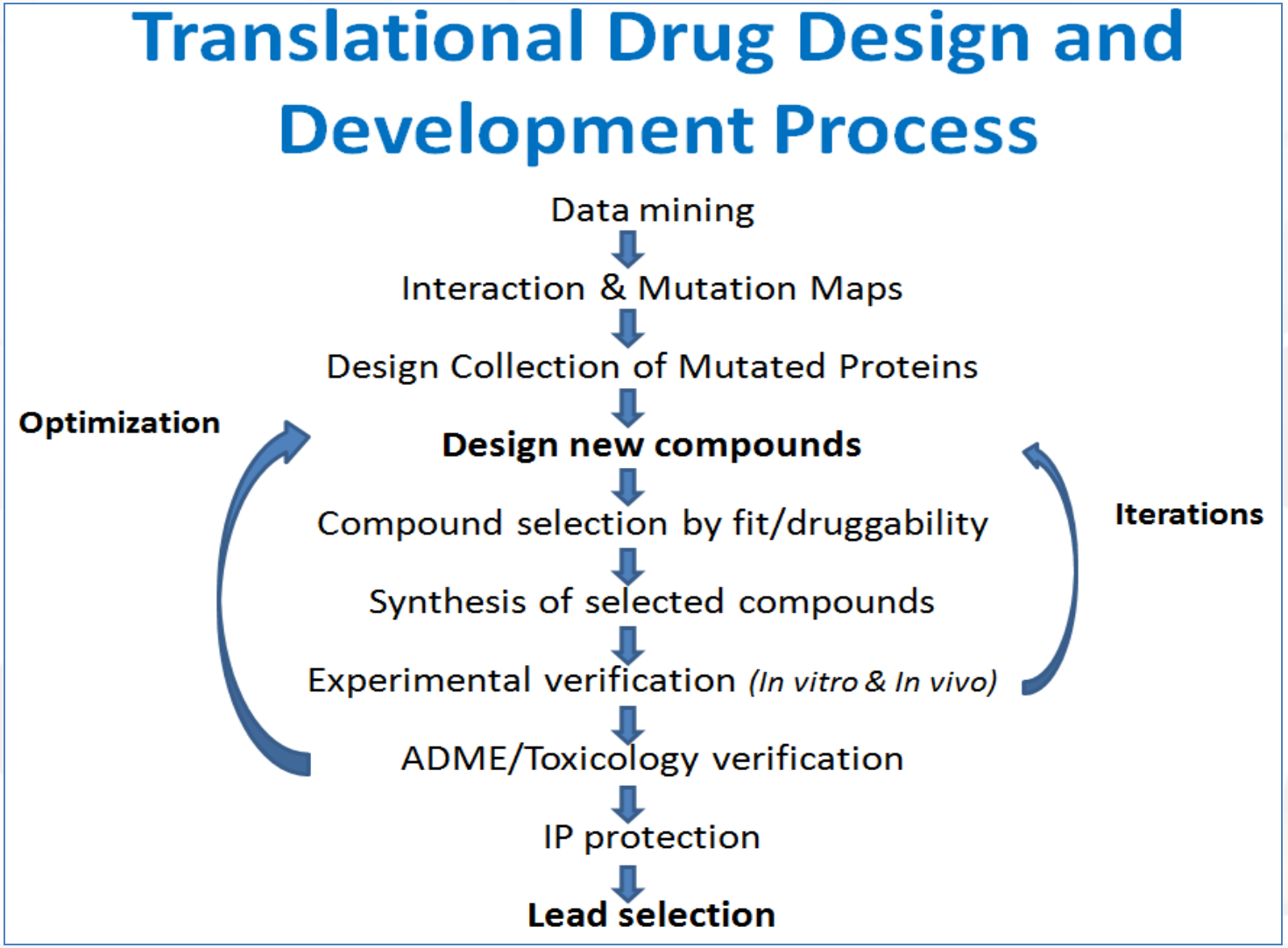


Relative frequency of single as against compound mutants of BCR-Abl. From Soverini et al, Blood, 2013.

Novitero's process

- Based on computational chemistry and proprietary algorithms and processes we
  - Predict and design mutated proteins
  - Evaluate the impact of multiple and compound target-mutations on drug resistance
- Design, test and develop mutation-bypassing tailored drugs
  - Broad spectrum: bypass multiple and compound mutations
  - New Patented structures

Our Process


Translational Drug Design and Development Process
Data mining
Interaction & Mutation Maps
Design Collection of Mutated Proteins
Optimization
Design new compounds
Compound selection by fit/druggability
Iterations
Synthesis of selected compounds
Experimental verification (In vitro & In vivo)
ADME/Toxicology verification
IP protection
Lead selection

Founder and CEO

Dr. Itzchak Angel

- **Experienced executive** in **pharmaceutical industry**
- Over **30 years experience** in guiding **drug discovery and development teams** in both large and emerging companies
- Was previously **Head of Pharmacology at Sanofi** (Formerly Synthelabo, Paris, France) and brought **several drugs to market** (Ambien, Xatral, Migpriv and Mizollen)
- Formerly been VP R&D at **Proteologics Ltd, D-Pharm** (Rehovot, Israel)
- Head of **Angel Pharmaceutical Consulting & Technologies (APCT) Ltd**
- Confirmed experience and network in **business development and pharmaceutical deals**
- Co-inventor and co-author of over **100 patents and publications**

Scientific Advisory Board

Prof Aaron Ciechanover, M.D, D.Sc.

2004 Nobel Prize Laureate

in Chemistry

Distinguished professor at the Tumor and Vascular Biology Research Center at The Rappaport Faculty of Medicine and Research Institute - Technion-Israel Institute of Technology

Prof. Arieh Warshel, Ph.D.

2013 Nobel Prize Laureate

in Chemistry

Distinguished Professor of Chemistry and Biochemistry, Dana and David Dornsife Chair in Chemistry, Member of the Norris cancer center, University of Southern California

Targeted cancer therapy is a multi Billion $ Market.

Market size*:

- Top 20 biggest-selling cancer drugs generated combined sales of $53 billion in 2013.
- Top selling small molecule targeted therapy represents a market of approximately $ 23 Billion.
- The estimated 2018 market for these drugs amounts to $ 41 Billion.

Competition:

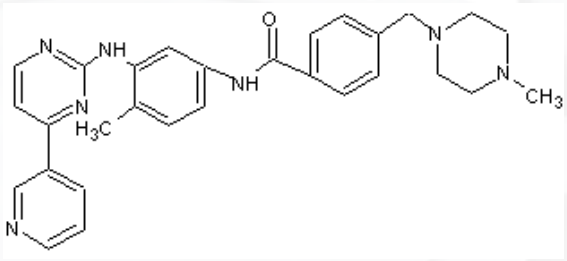
- Several drugs addressing single known mutations are under development
- The majority of the efforts of other companies in this field are currently dedicated to the families of Iressa/Tarceva and Gleevec treatment-emergent mutations.
- Current approaches do not address combined and/or multiple mutations

* From FirstWord Pharma, March 2014 best selling cancer drug review

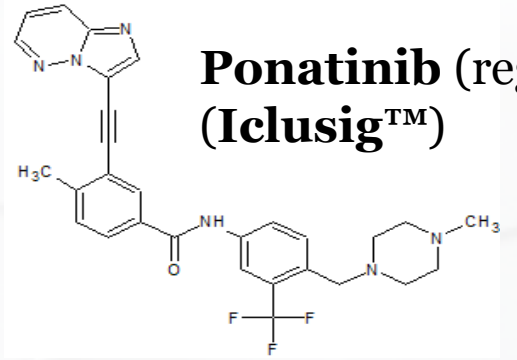
Novitero can select from a large number of Targeted Therapies

Major Drug	Trade name™	Company	Market year (FDA)	Target protein	Major Cancer types	Major Acquired Resistance Mutations
Imatinib Dasatinib Nilotinib Ponatinib	Gleevec Sprycel Tasigna Iclusig	Novartis BMS Novartis Ariad	2001 2006 2007 2013	BCR-ABL	GIST Leukemia NSCLC	T315I,E225K/V, Y253H, L248R, F317V
Gefitinib Erlotinib	Iressa Tarceva	AZ/Teva Genentech	2003 2005	EGFR	NSCLC	T790M, T854A
Sunitinib	Sutent	Pfizer	2006	RTK, KIT	GIST, RCC	D816H/V
Vemurafinib Dabrafenib	Zelboraf Tafinlar	Genentech GSK	2011 2013	BRAF	Melanoma	L505H
Vismodegib	Erivedge	Genentech	2012	SMO	BCC	D473H
Enzelutamide	Xtandi	Medivation	2012	AR	Prostate	F876L,W741C,T877A
Tofacitinib	Xeljanz	Pfizer	2012	JAK	B-ALL	E864K,G935R,Y931C
Ibrutinib	Imbruvica	J&J	2013	BTK	BCL, Myeloma	C481S
Trametinib	Mekinist	GSK	2013	MEK	Melanoma	Q60P
Crizotinib Ceritinib	Xalkori Zykadia	Pfizer Novartis	2013 2014	ALK	NSCLC	L1196M, G1269A, I1171T,G1202R, F1174C

Novel targeted inhibitors are effective against targets with only a single Mutations

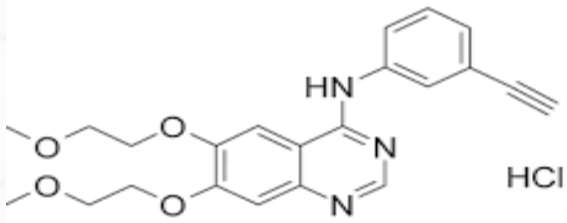


Imatinib (registered 2001)
(**Gleevec™**, estimated 2013 sales US $ 4.7$5B)



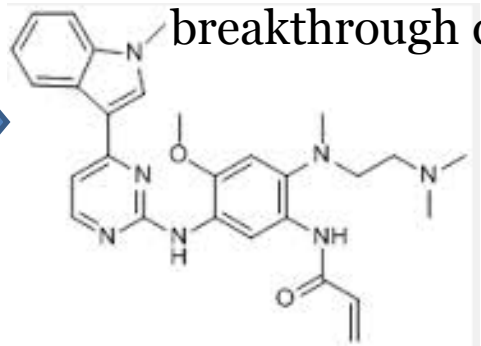
Ponatinib (registered 2013)
(**Iclusig™**)

Effective against T315I mutation of BCR-ABL protein



Erlotinib (registered 2005)
(**Tarceva™**, estimated 2013 sales US $1.5B)

AZD 9291 (in development, FDA breakthrough designation)

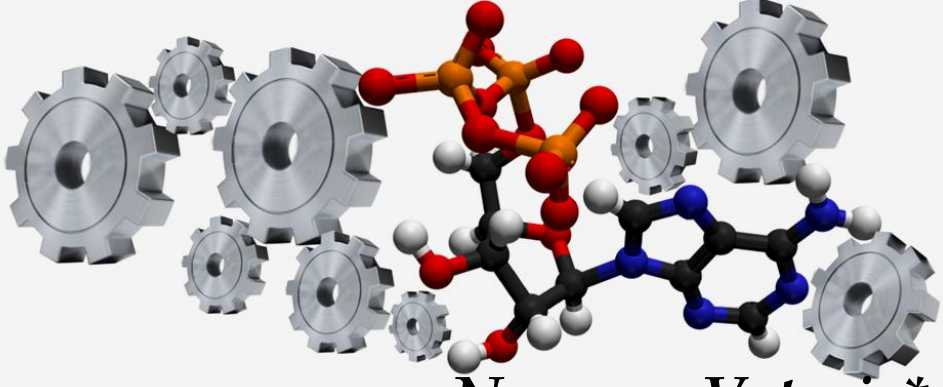


Effective against T790M mutation of EGFR protein

Our Business model

- Drugs are designed, tested, validated and developed **for out-licensing**
- Each year we design and develop several drugs
  - Acting on several distinct targets
  - Interfering with different cancer types
- These drugs are attractive to Pharmaceutical companies as they:
  - Act on validated targets
  - Are validated experimentally
  - Their structure and interactions are based on marketed and clinically proven drugs
  - Have recent patents
- Their targeted and personalized design enables
  - Simplified regulatory approval
  - More rapid clinical development
  - Well defined clinical populations and validated outcome measures

Tailored for mutations



*Nova ex Veteris**

Thank you

** Nova ex Veteris – From Latin, "The new is created from the old"*