Accelerating drug development from bench to bedside

Young Oncologist Masterclass: Clinical trial protocol development

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Disclosure slide

- I had a consultant/advisory role with Novartis, Janssen Cilag and Amgen.

Accelerating drug development from bench to bedside

- Reasons to believe in a successful strategy
- Examples of everything
- Challenges and unknown subjects
- Bench to Bedside and Bedside to Bench
- Conclusions

Accelerating drug development from bench to bedside

* Reasons to believe in a successful strategy

Chronology of Clinical Research

Phase 3

Prevention

Primary Tumor

Phase 2
Phase 3

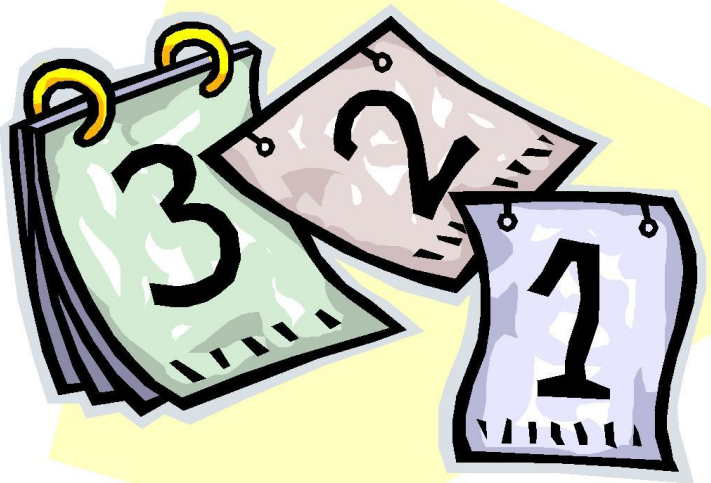
Neo-adjuvant

(Surgery ± Radiotherapy)

Early Cancer

Phase 3

Adjuvant



Palliative

Phase 0
Phase 1
Phase 2;
Phase 3

± 5-7 Years

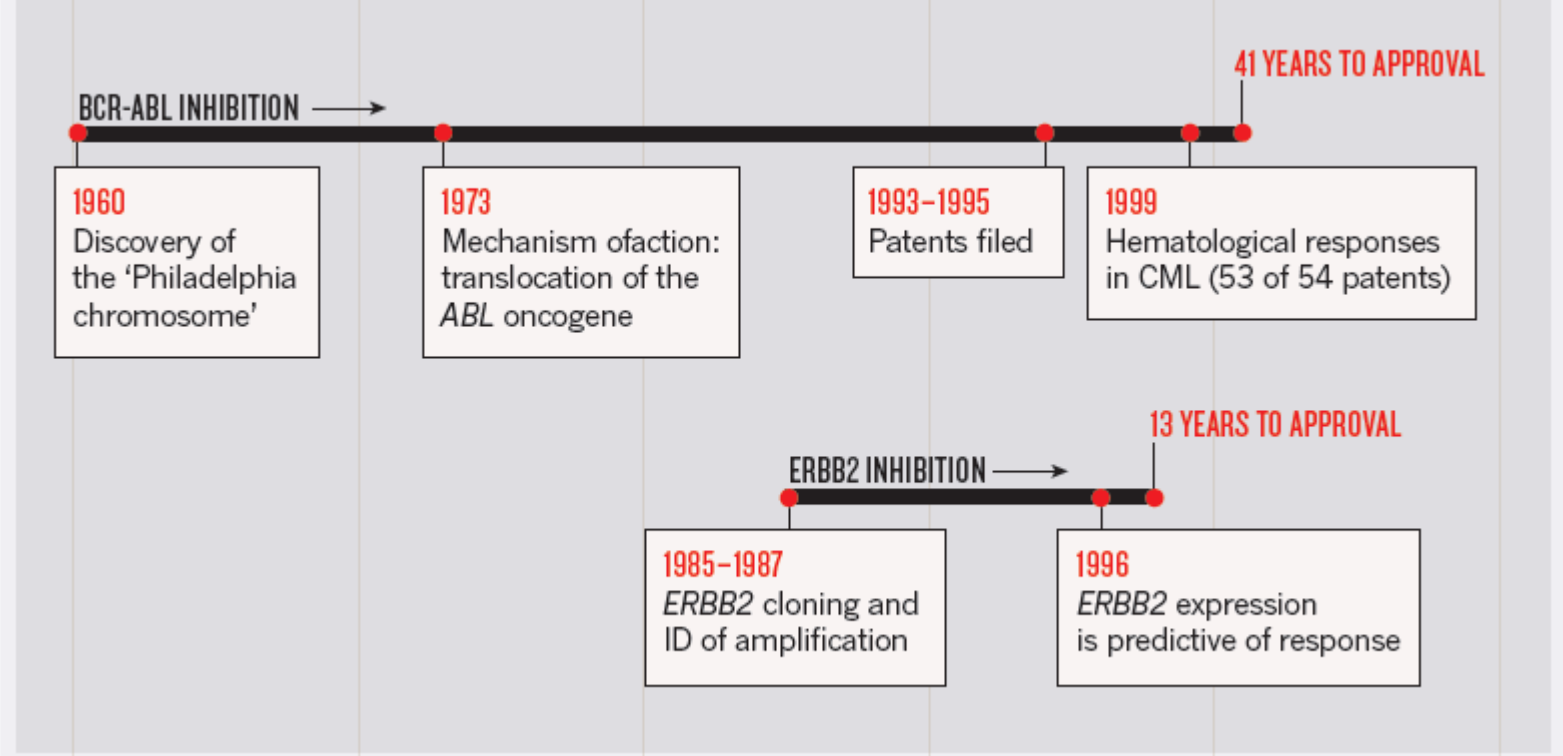
Accelerating drug development from bench to bedside

8% of the tested products entering Phase I trials eventually cleared the hurdle of gaining FDA approval and entered the market.

- ✓Fewer drug and biological submissions
- ✓The development costs of these products reaching unprecedented levels

The Road of Discovery

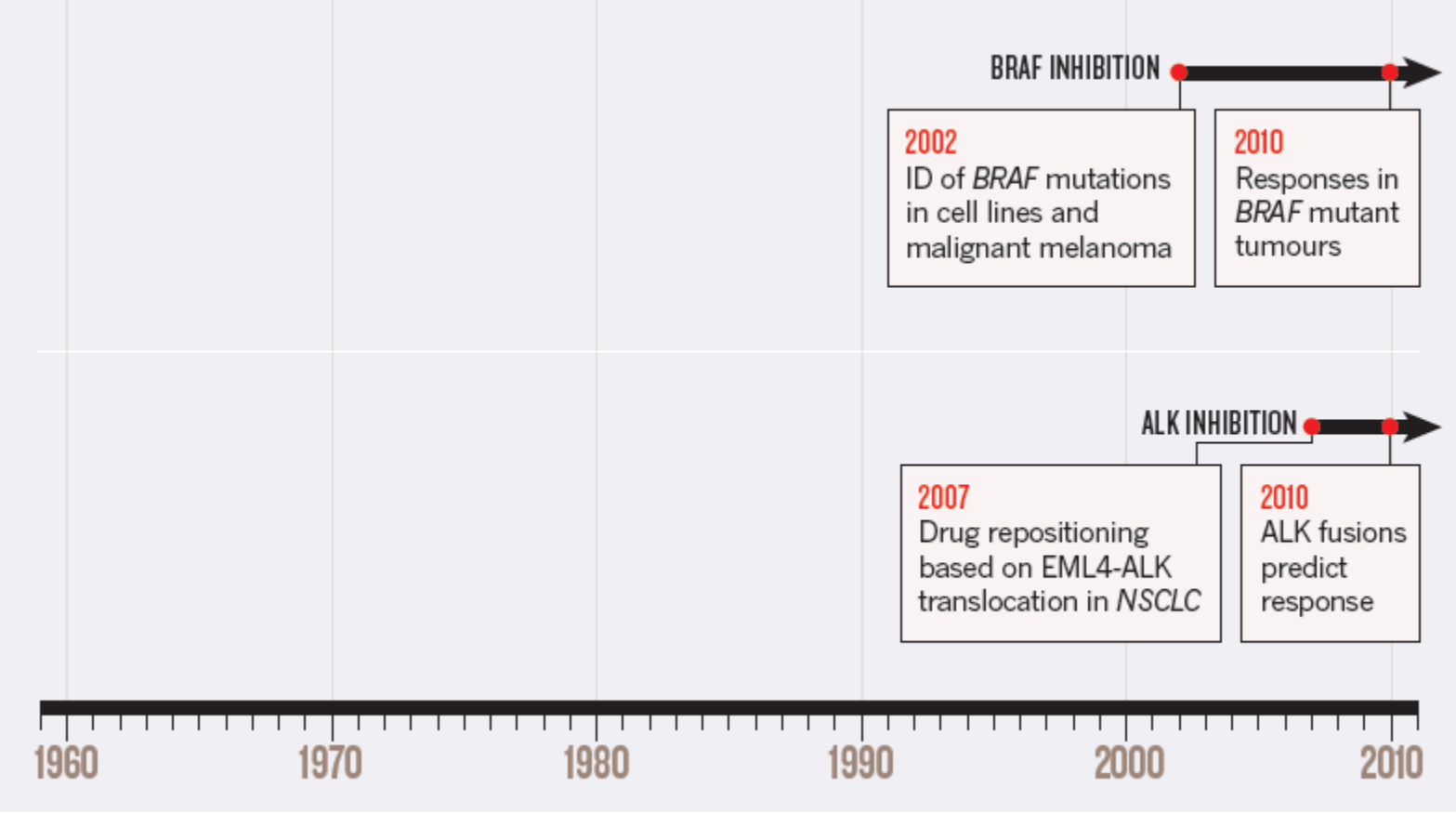
Key stages along the way to FDA approval



Barbara Dunn, Nature (2012)

The Road of Discovery

Key stages along the way to FDA approval



Barbara Dunn, Nature (2012)

Translational Medicine

should be bi-direccional

Industry

Design and produce agents,
prognostic/diagnostic tests

Laboratory

"omics" analysis for target identification,
Pre-clinical models
Clinical samples analysis

Clinic

Disease phenotype,
Clinical Trials
Samples collection

Data Integration

Molecular signatures,
Disease biomarkers,
Drug targets

More effective therapeutic agents
Personalized medicine

The Connectivity Map: a new tool for biomedical research

Justin Lamb (Nature 2007)

connecting a disease with a disease-modifying gene product and a chemical modulator of that protein

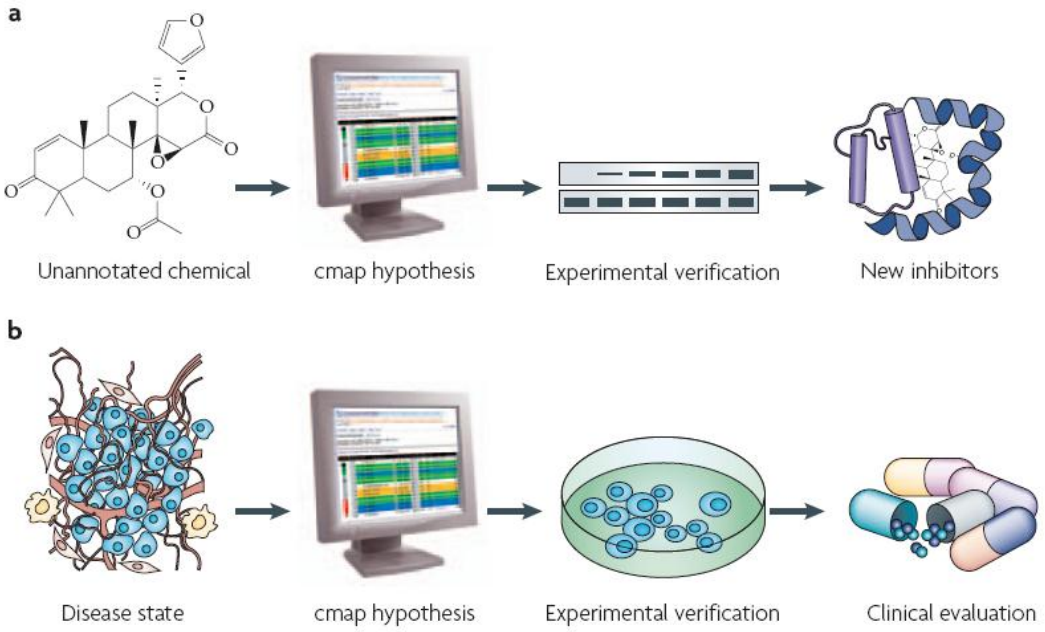


Figure 3 | **The Connectivity Map is a tool for the bench researcher.** The paths to showing that (a) an uncharacterized small molecule is a heat shock protein 90 (HSP90) inhibitor[5] and (b) sirolimus can reverse glucocorticoid resistance in acute lymphoblastic leukaemia[6] (see text for details) illustrate that the Connectivity Map (cmap) resource is best used in the context of a traditional research project. Indeed, its ultimate value relies on detailed experimental validation and follow-up.

Accelerating drug development from bench to bedside

* Examples of everything

Examples of Success

Trastuzumab

Unselected population with metastatic breast cancer → Objective response: 11-26% *

Selected population with metastatic breast cancer (HER2 positive) → Objective response: 34% *

* Hortobagyi, G. N. Trastuzumab in the treatment of breast cancer. *N. Engl. J. Med.* (2005).

Examples of Delay

Genfitinib

Response does not correlate with EGFR levels in the Tumor (IHC)

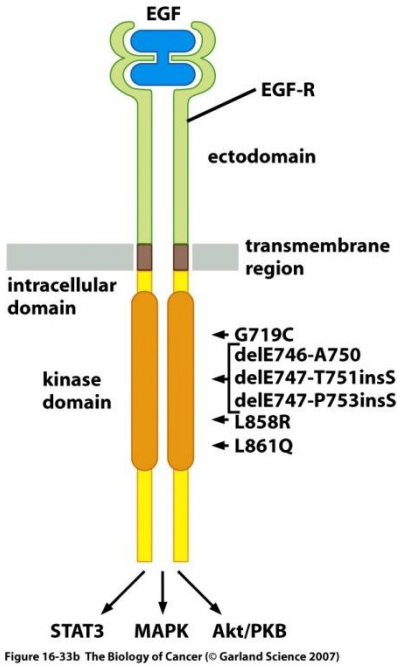


Figure 16-33b The Biology of Cancer (© Garland Science 2007)

Response does correlate with mutations in EGFR[1]

Tumor DNA from patients who responded to Genfitinib had a mutation in EGFR in all responders while only 1 of 61 nonselected patients had such a mutation.

1-Paez JG; et al. *Science* 2004.

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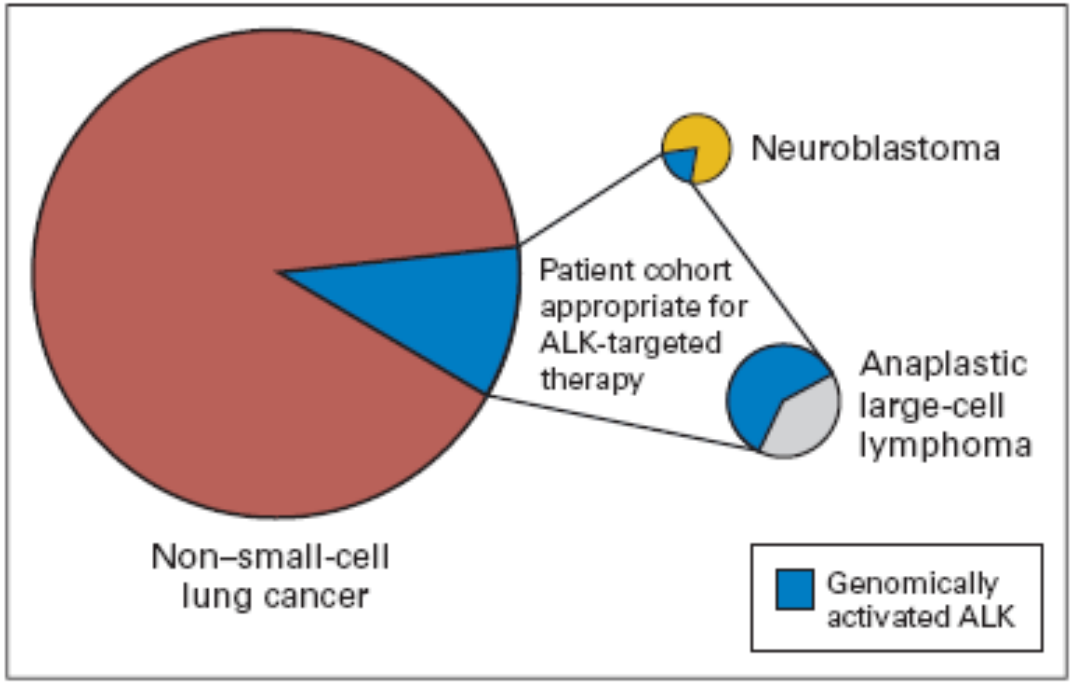
Personalized Cancer Therapy With Selective Kinase Inhibitors: An Emerging Paradigm in Medical Oncology

Ultan McDermott and Jeff Settleman

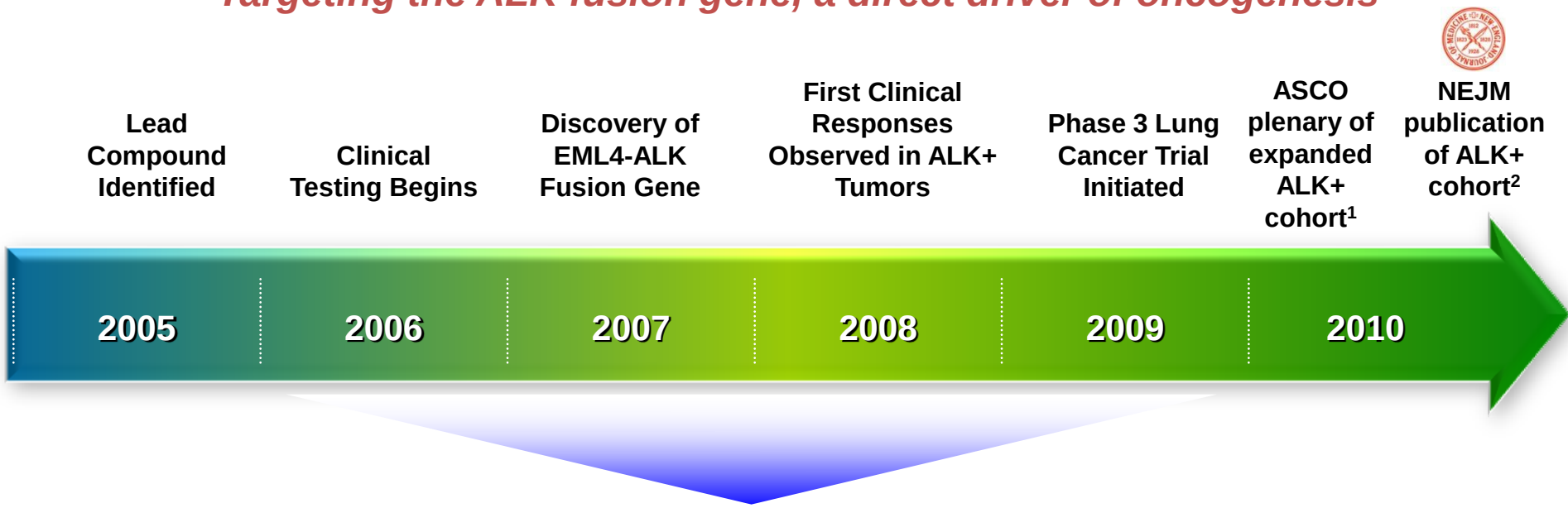


Biology: a transversal approach to different tumor histology

ALK: Anaplastic lynphoma kinase

Crizotinib: Pathway from Compound Identification to Discovery of ALK Target and Clinical Results

Crizotinib (PF-02341066) : Targeting the ALK fusion gene, a direct driver of oncogenesis



Clinical Results to Date

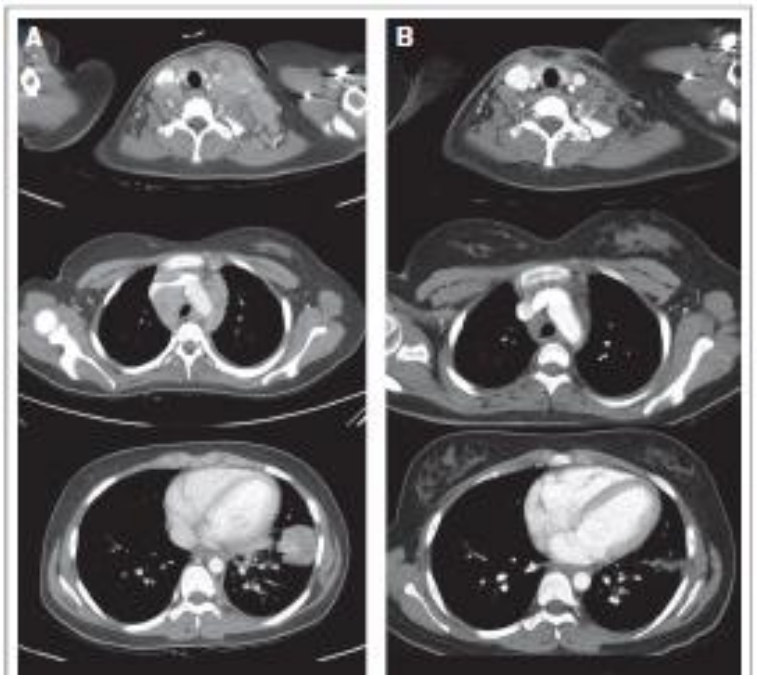
- **Objective response rate = 56%[3]**
- **Disease control rate (CR+PR+SD) = 88%[3]**
- Median duration of response = 36.3 weeks[3]*
- Median PFS = 9.2 months†[3]

*in responding patients
†Fifty-four (47.8%) patients remain in follow-up for PFS

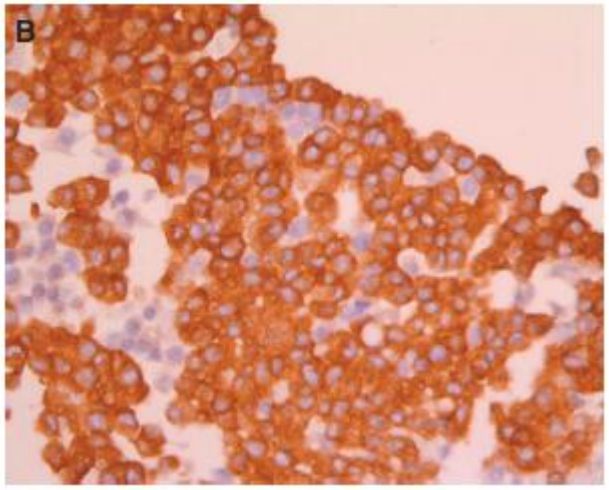
1. Bang JY *et al*. Oral presentation at ASCO, 2010
2. Kwak et al. *New Engl J Med*. 2010;363:1693−03
3. Camidge R et al. Poster 366 presented at the 35th ESMO, 2010

Examples of Success

Tumor response to crizotinib (NSCLC)
JCO; 2012



ALK (IHC)



Crizotinib inhibits ALK; MET; ROS1(?)

Cancer Cell
Minireview

ALK Inhibition for Non-Small Cell Lung Cancer: From Discovery to Therapy in Record Time

David E. Gerber[1,4,*] and John D. Minna[1,2,3,4,*]
[1]Department of Internal Medicine -Division of Hematology-Oncology
[2]Department of Pharmacology
[3]Hamon Center for Therapeutic Oncology Research
[4]Simmons Cancer Center,
University of Texas Southwestern Medical Center, Dallas, Texas 75390
*Correspondence: david.gerber@utsouthwestern.edu (D.E.G.), john.minna@utsouthwestern.edu (J.D.M.)

Table 1. The Shortening Interval between Target Discovery and Effective New Cancer Treatments

Target	Year Target Discovered	Disease(s) and Proportions	Estimated Total # Pts Annually (US)	Drug(s)	Clinical Outcomes	Outcomes from Conventional Chemotherapy	Year Mutation-Targeted Treatment Documented
BCR-ABL	1960	CML (100%)	5,000	Imatinib Dasatinib Nilotinib	RR 90% 5y PFS 80% 5y OS 90%	RR 35% 5y OS 70%	2001
EGFR	1978	*EGFR* mutated NSCLC (10% of NSCLC)	17,000	Erlotinib Gefitinib	RR 75% Median PFS 11 mos Median OS 31 mos	RR 30% Median PFS 5 mos Median OS 24 mos	2004
KIT	1998	GIST	6,000	Imatinib	RR 55% Median PFS 27 mos Median OS 58 mos	RR 5% Median OS 20 mos	2002
BRAF	2002	V600E *BRAF* mutated melanoma (50% of melanoma)	34,000	PLX4032	RR 77% Median PFS 7 mos OS not yet determined	RR 10-20% PFS 1.5 mos OS 8 mos.	2010
ALK	2007	*EML4-ALK* NSCLC (5% of NSCLC)	8,500	Crizotinib	RR 55% 6 month PFS 70% OS not yet determined	RR 25% Median PFS 4-6 mos Median OS 12 mos	2010

ALK, anaplastic lymphoma kinase; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate; mos, months.

Accelerating drug development from bench to bedside

* Challenges and unknown subjects

Limitations of pre-clinical models

Limitations of *in vitro* experiments:
Cells were selected
(ability to growth without stromal support)

Limitations of *in vivo* models (Xenografts tumors):
Human cancer cells interacting with
non-human stromal cells
(immunocompromised mice)

The fundamental bottleneck in drug discovery is not the validation of a target, but the validation of a disease model itself.

Good correlation between the observed model disease phenotype and the human disease condition

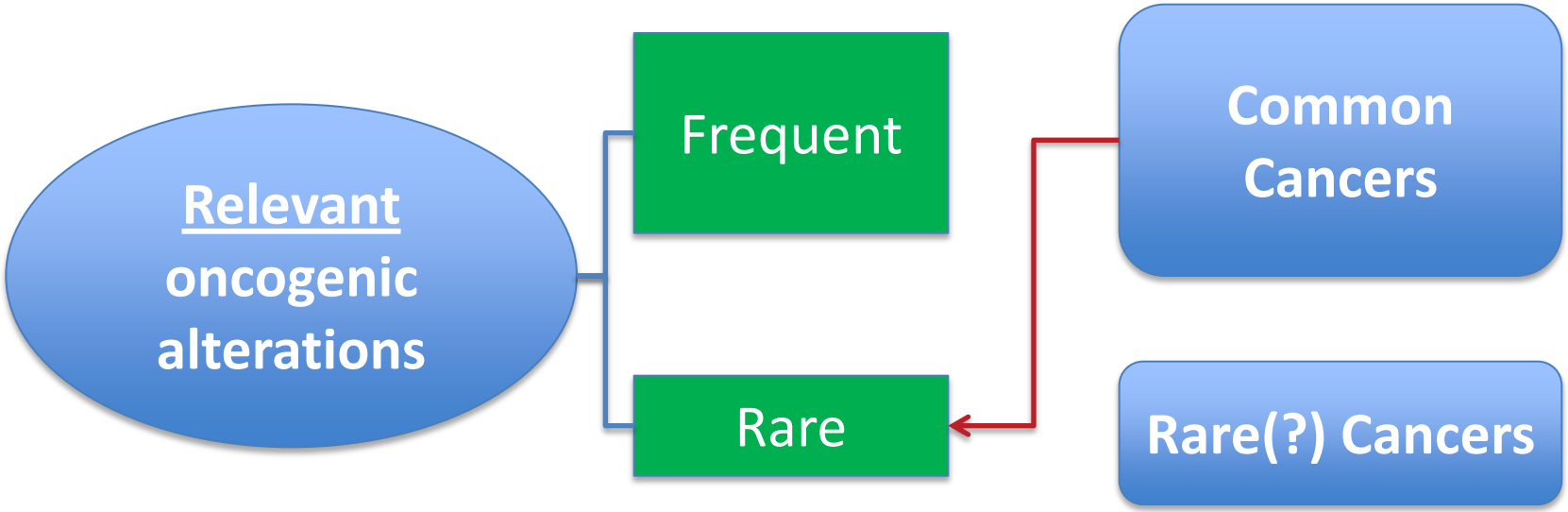
MILESTONE 11

The road less travelled

Congruence between disease models and human disease is ultimately a question of ontology

Signaling Transduction: find what is important

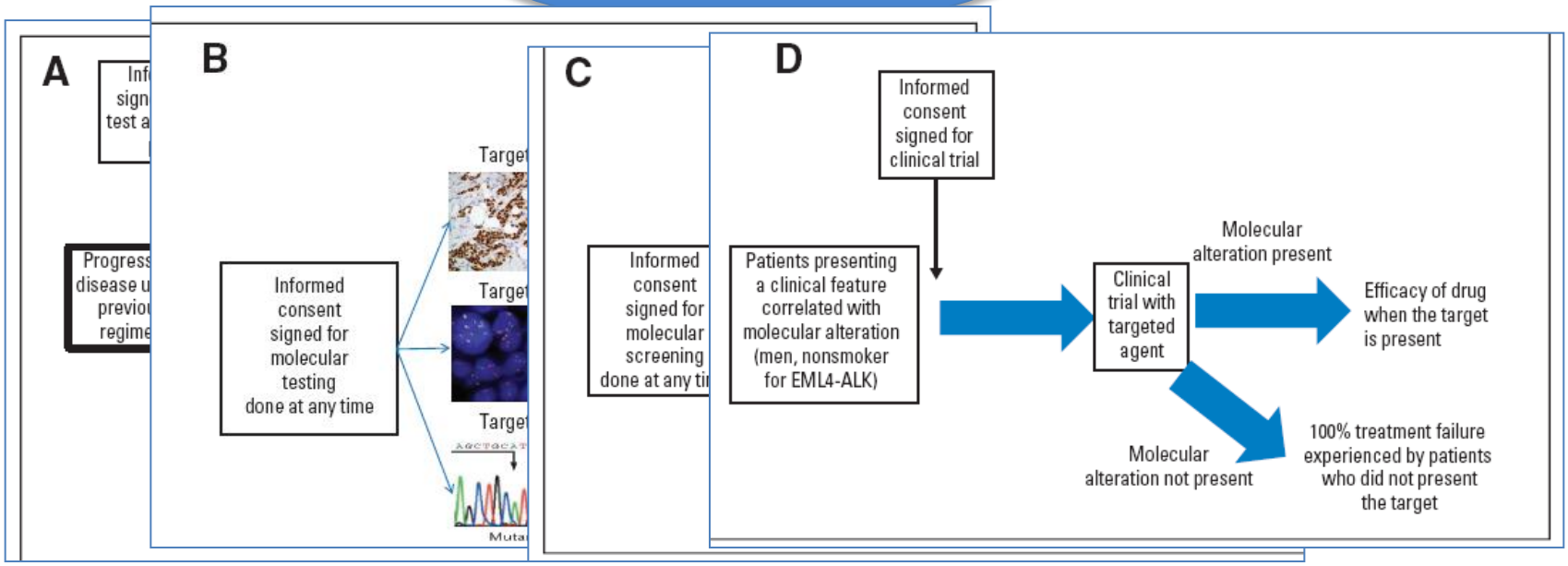
Biology-Driven Clinical Research



"… each frequent cancer type could, in fact, be subdivided into several rare molecular diseases according to relevant oncogenic events." *F. Andre et all JCO (2011)*

biology-driven phase II trials*

Speed drug development



A

Test a Single Biomarker During the Screening Phase of the Phase II Clinical Trial

B

Assess a Limited Number of Relevant Molecular Alterations Outside Phase II Clinical Trials

C

Perform a Molecular Screening Based on High-Throughput Technologies

D

Use Clinical Surrogates for Molecular Testing

proof of mechanism

* F. Andre et all JCO (2011)

biology-driven phase II trials

- ✓large panels of xenograft models for preclinical purposes
- ✓robust bioassay before starting a biology-driven phase II trial
- ✓high throughput-technologies or dedicated bioassay for each molecular alteration
- ✓specific expertise is required for the biologic interpretation of high-throughput technologies
- ✓Easy access (distance) to phase 2 trials

Early phase clinical studies: can we do better?

Phase 0

Proof-of-concept trial: single doses of a new drug; early assessment of whether the molecular target of the drug is beeing inhibited (measuring pharmacodynamics end-points before and after drug administration)

Phase 1

Accelerated Titration Designs: permit within-patient dose escalation and use only one patient per dose level until grade 2 or greater toxicity is seen.

Phase 2

It is often undesirable to restrict entry to phase 2 trials based on what one thinks one knows about the drug target, at least in cases where this knowledge is uncertain…

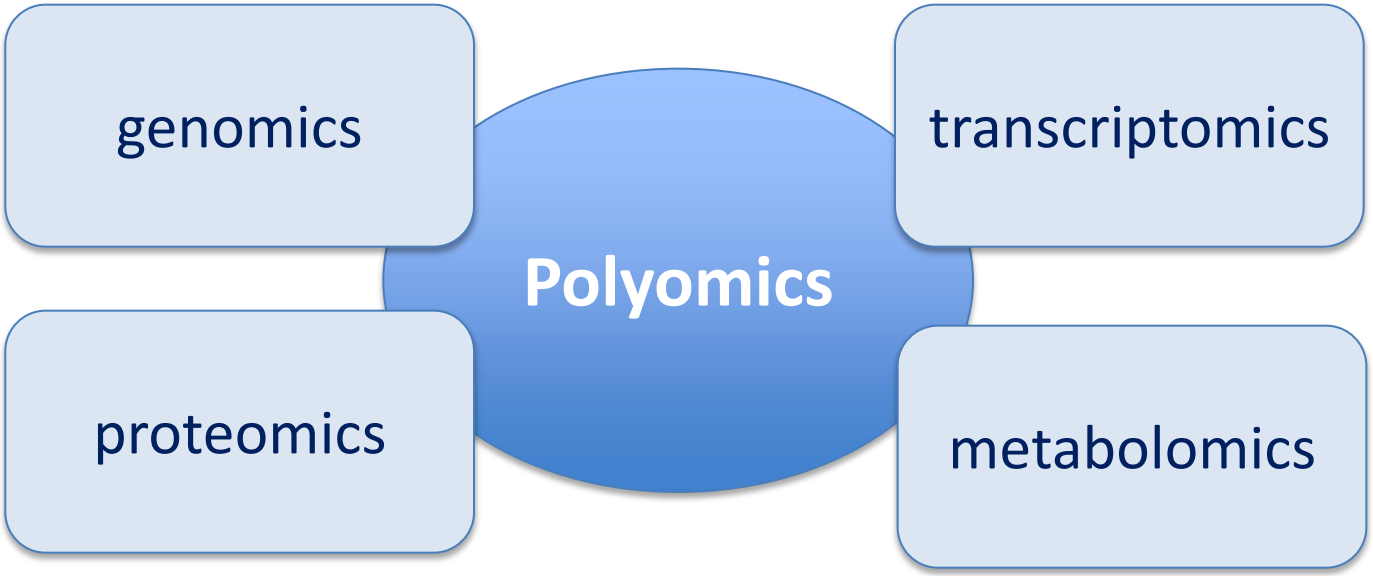
Richard Simon
Cancer Principles & Practice of Oncology; 9th Editon (2011)

Challenges of Tumor Behaviour

Genomic Heterogeneity
Clonal Evolution
Heterotypic Signaling
Metastases Cascade
Minimal Residual Disease
Acquired Resistance
Narrow Therapeutic Margin
…

Host Variability

How to integrate information-rich datasets In the discovery and validation of a disease model ?



Basic Scientist	Clinical Scientist	Mathematician

Accelerating drug development from bench to bedside

* Bench to bedside and Bedside to bench

Translational drug investigators

preclinical and clinical groups

- ✓Discovery biologists,
- ✓Members of preclinical and clinical safety sciences,
- ✓Clinical pharmacologists,
- ✓Experimental medicine experts,
- ✓Biomedical informatician,
- ✓Epidemiologists

Bench to Bedside and Bedside to Bench

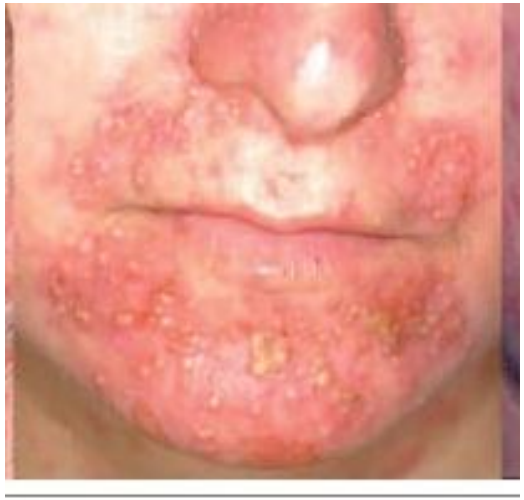
hypotheses derived from complex experimental models often simply do not translate to human pathology.

discovery-driven research should be promoted in the context of translational medicine and should be better referred to as "reality-driven" research

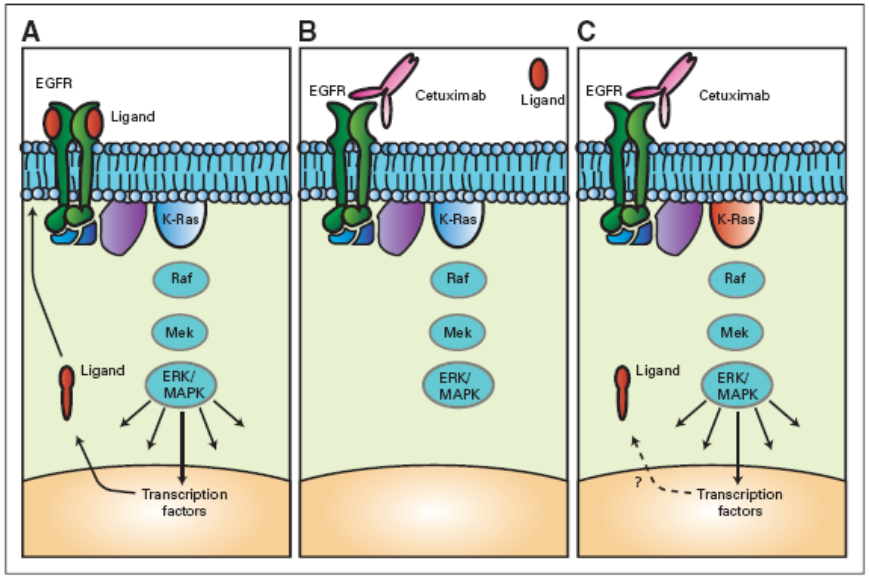
direct human observation may direct to the study of hypotheses relevant to human reality

The Observational Art of Clinical Scientists

Genetic Share: The Tumour and the Host

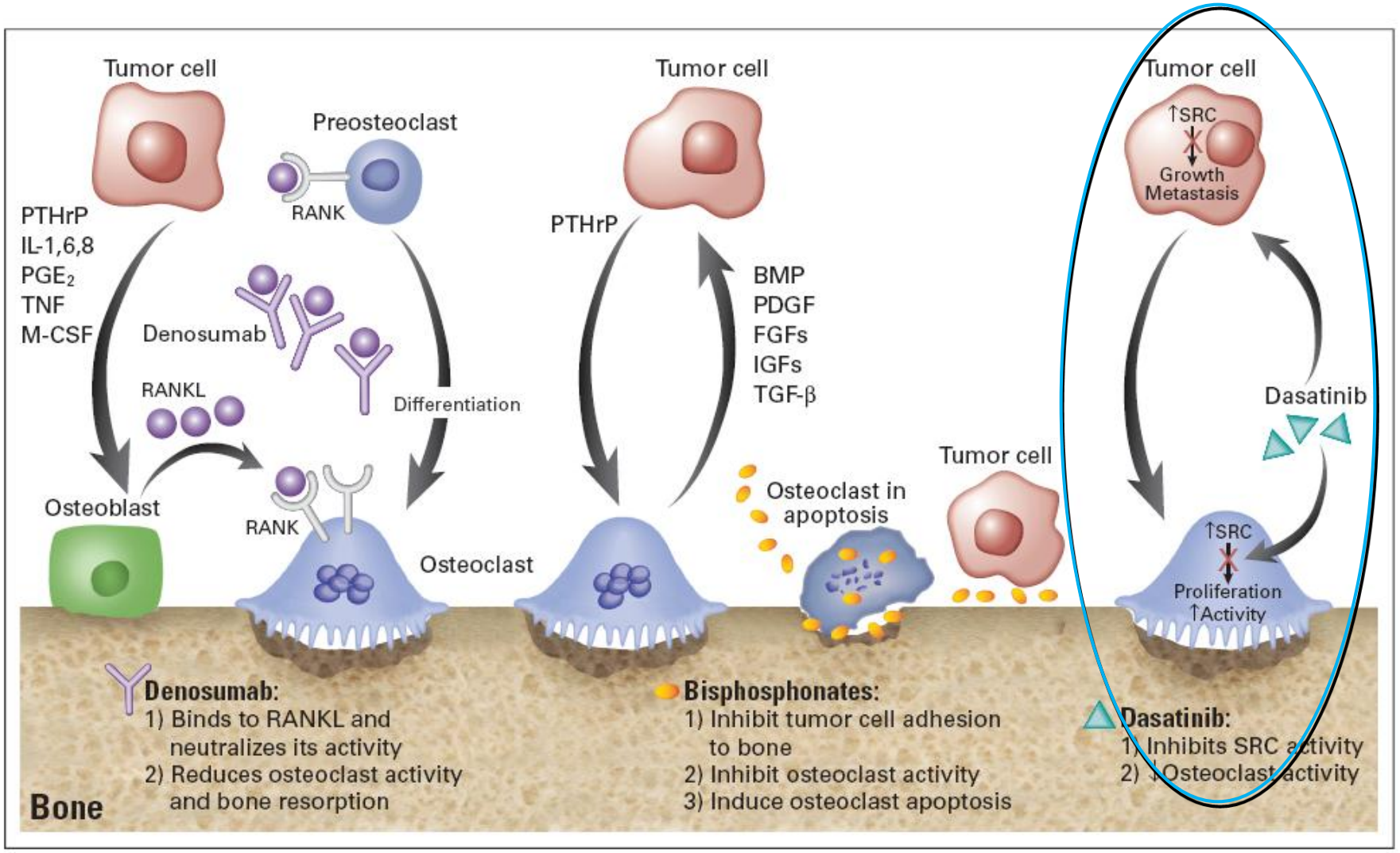


Skin rash with anti-EGFR therapy
Predicts anti-tumor response



What the host tell us about the success of the anti-tumor therapy (tumor biology)?

Bone-Targeted Therapies



Monica Fornier, JCO 2010

Phase II multicentre study to assess saracatinib effects on bone markers in cancer patients with bone metastasis

Patients

- Breast or prostate cancer
- Metastatic bone disease
- No prior exposure to bisphosphonates
- Threshold level of bone resorption (urinary NTx ≥30 nmol BCE/mmol creatinine)

4 weeks

Saracatinib* (175 mg OD) + SoC

Randomization 1:1

Zoledronic acid (4 mg) single iv infusion on day 1 + SoC

Endpoints

- Serum βCTx
- Safety
- Serum: bALP, ICTP, PINP, TRAP5b; Urine: NTx/Cr, aaCTx/Cr
- Saracatinib steady-state PK
- Serum: PTH, tALP, calcium, phosphate, RANKL/OPG
- Pain
- PSA
- PK/PD
- Exploratory biomarkers & DNA

Open label, 4-week treatment period

Stable hormonal therapy allowed; no concomitant chemotherapy

Bone markers assessed at baseline and weeks 1, 2, and 4

SoC, standard of care

*Continuation of therapy beyond 4 weeks if clinical benefit

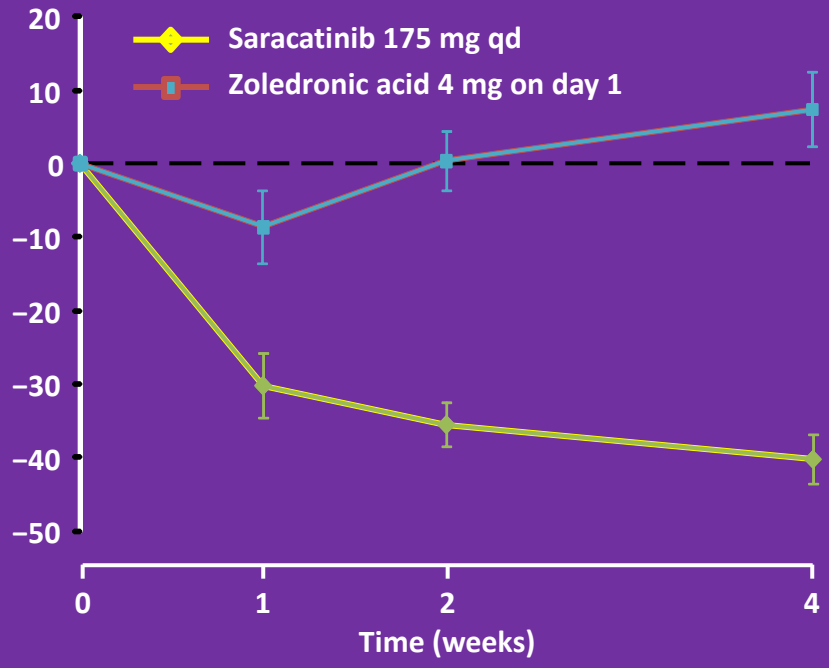
Resorption markers

Mean baseline scaled ratio (%) ± SE

Serum βCTx

At 4 weeks	
Change from baseline* [95% CI] *P*	
Saracatinib	(n=46) −71.1% [−75.9, −65.4] *P* <0.001
ZA	(n=65) −68.4% [−73.0, −63.2] *P* <0.001
Saracatinib vs zoledronic acid *P* = 0.432	

Serum ICTP

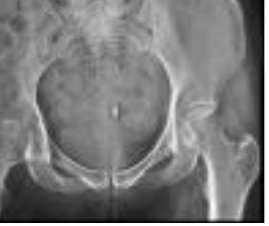
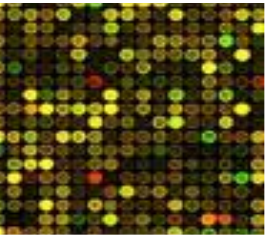
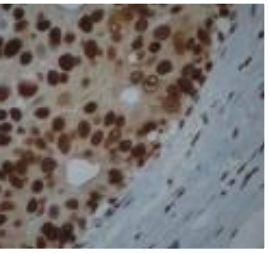


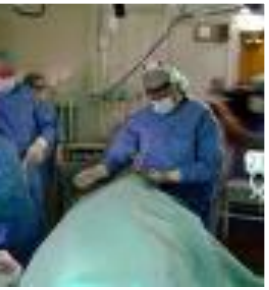
At 4 weeks	
Change from baseline* [95% CI] *P*	
Saracatinib	(n=47) −40.2% [−46.3, −33.4] *P* <0.001
ZA	(n=66) 7.4% [−2.0, 17.7] *P* = 0.126
Saracatinib vs zoledronic acid *P* <0.001	

VIENNA 2012 ESMO congress

www.esmo2012.org

*Derived from the geometric least square estimate of the baseline scale ratio; ZA, zoledronic acid



In vitro evaluation of the anti-tumoral and anti-osteoclastogenic effect of combination schemes of zoledronic acid and saracatinib in breast cancer

Sandra Casimiro, Maria M. Coelho, Irina Alho, Luis Costa

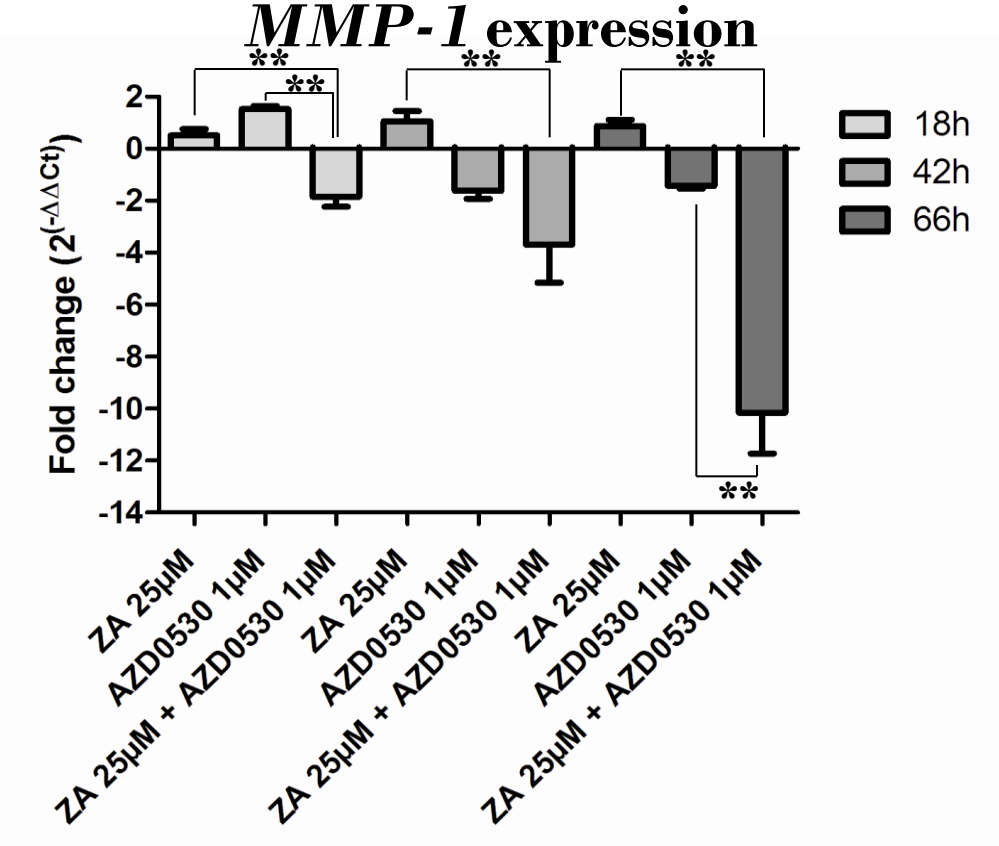
Clinical and Translational Oncology Research Unit

04.07.2012

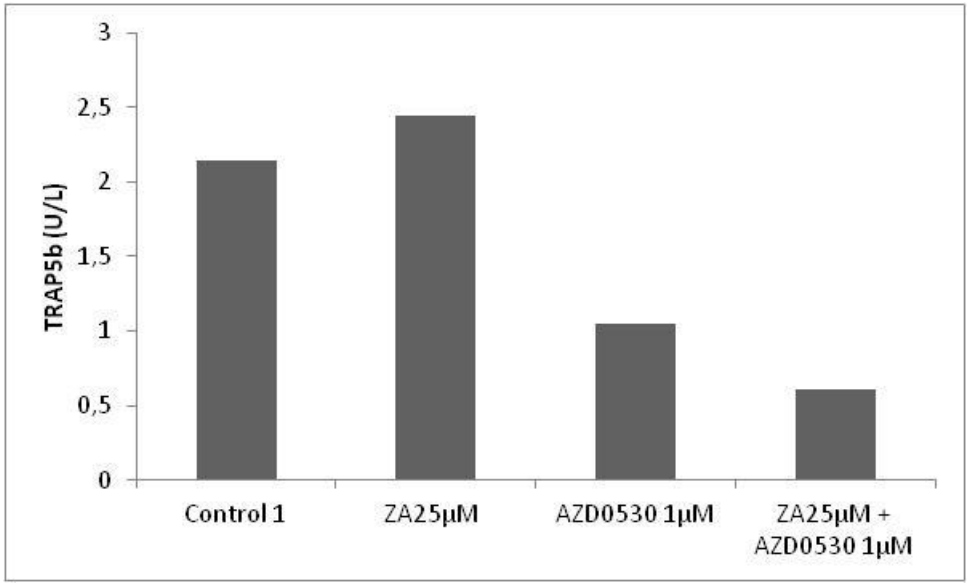
Background

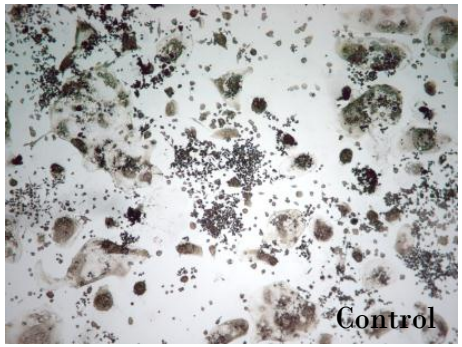
1. **Zoledronic acid (ZA) acts by leading to osteoclast apoptosis**
2. **ZA has anti-tumoral effect *in vitro***
3. **Saracatinib (AZD0530) inhibits Src, an important player in osteoclastogenesis**
4. **ZAD0530 also has anti-tumoral effect *in vitro***
5. **In a phase II trial, AZD0530 decreased ICTP (MMP-1 cleavage of type I collagen), hypothesizing an osteoclast-independent effect**
6. **The combination of ZA with AZD0530 may improve the anti-resorptive therapy and have an increased anti-tumoral effect**

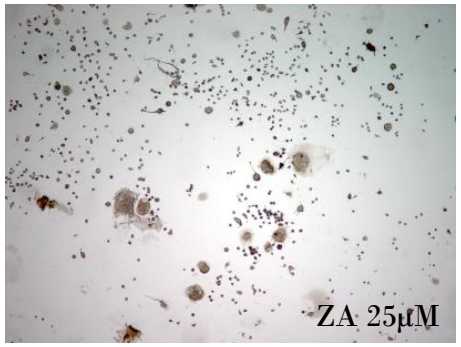
AZD0530 decreases *MMP-1* expression *in vitro* (MDA-MB-231)

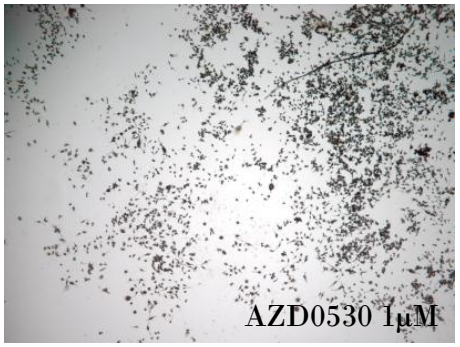


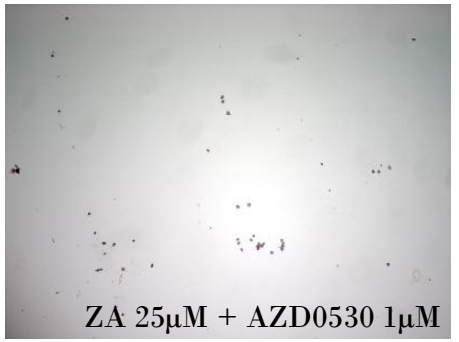
ZA+AZD0530 with increased effect in inhibition of osteoclastogenesis *in vitro* (RAW264.7)











Accelerating drug development from bench to bedside

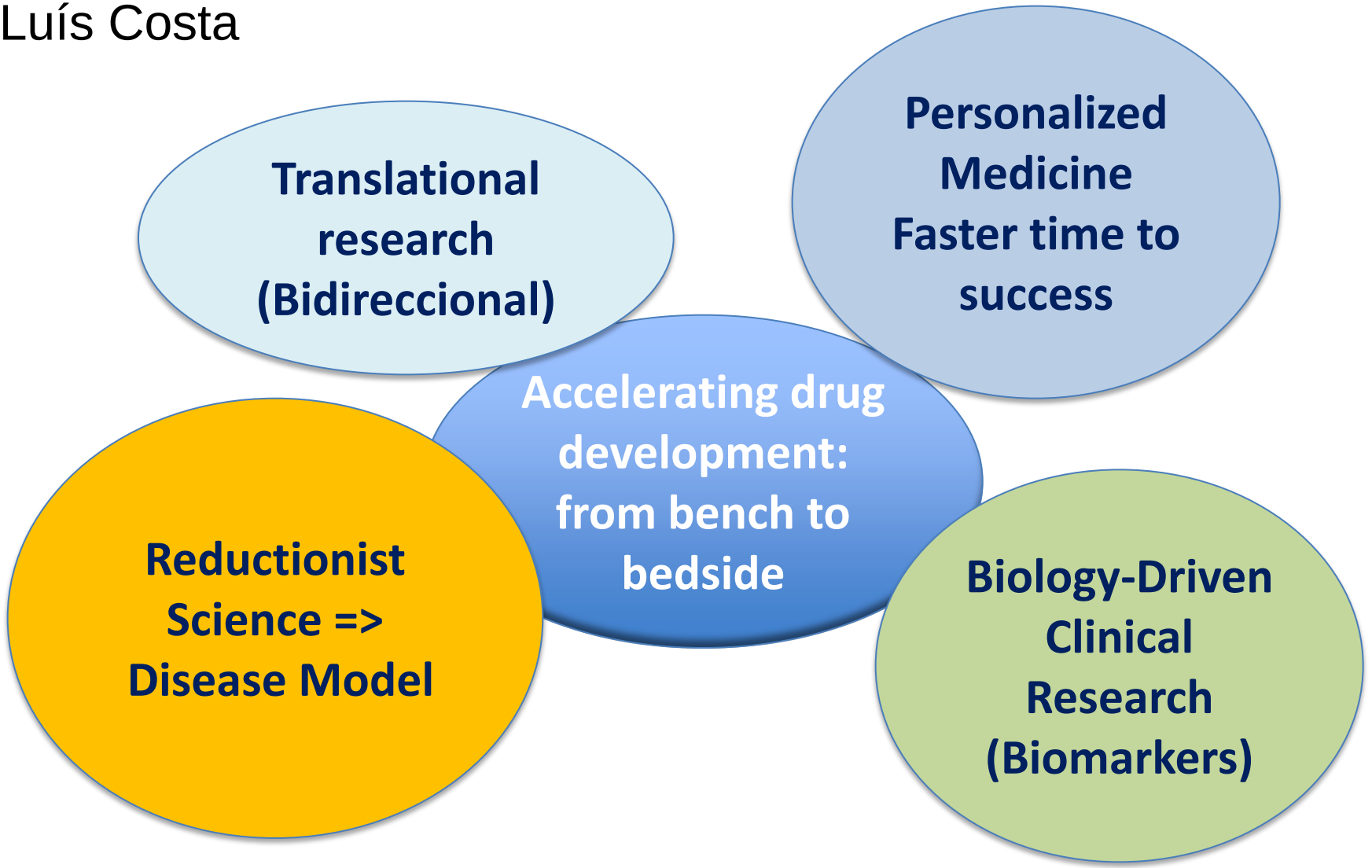
* Conclusions

Accelerating drug development from bench to bedside

"Translational research describes a bi-directional sharing of knowledge and ideas by the scientific and clinical disciplines to develop biomarkers that reliably select the mechanisms that can lead to breakthrough therapeutics"

Damian O'Connell and David Roblin; *Drug Discovery Today* (2006)

Thank you for your attention
Luís Costa



Lisbon Academic Medical Center

Integrate forefront **scientific research**

with **medical teaching**, **medical training** and **patient care**