Precision Medicine: Present challenges for Future Cures

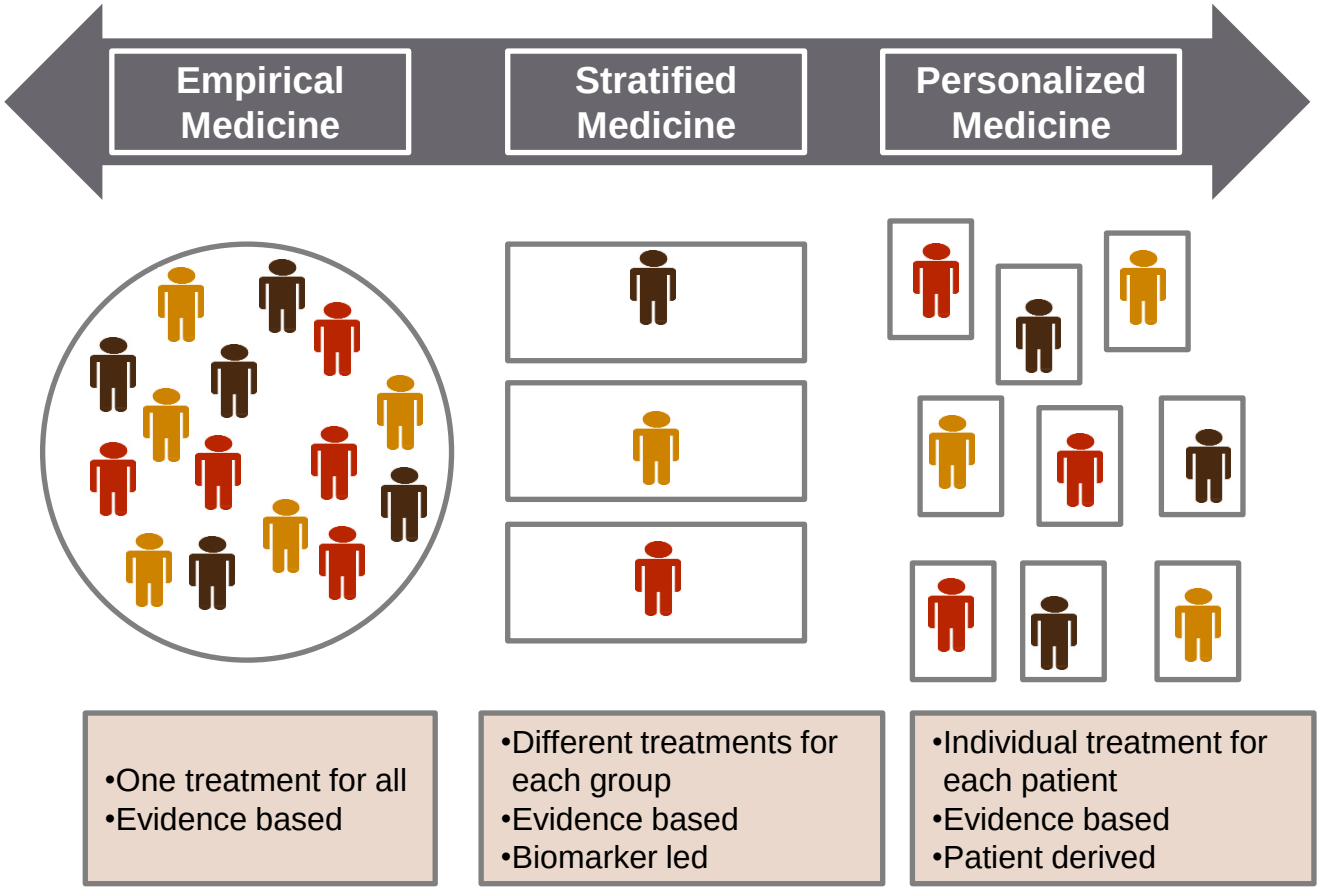
Druggable Future: What it takes and how we can get there

Guido Guidi

Venice - 18 September 2015

Druggable Future: What it takes and how we can get there

Precision Medicine: Where and how to go there?



Source: modification of: Nature Reviews | Immunology – "Immune biomarkers: the promises and pitfalls of personalized medicine". Joanna C.D. Willis and Graham M. Lord. May 2015

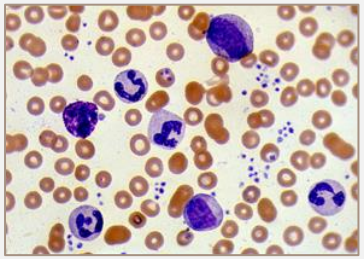
Precision Medicine: Where and how to go there?

Druggable Future: What it takes and how we can get there

Rewriting Medical History 1992

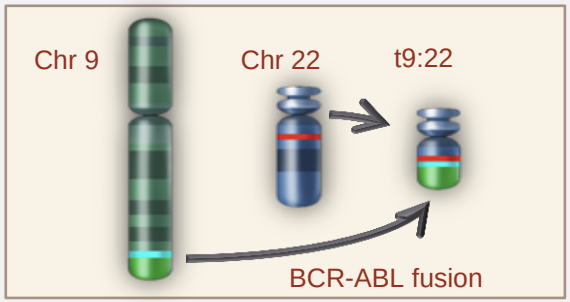
The Paradigm Shift: CML and imatinib

Disease

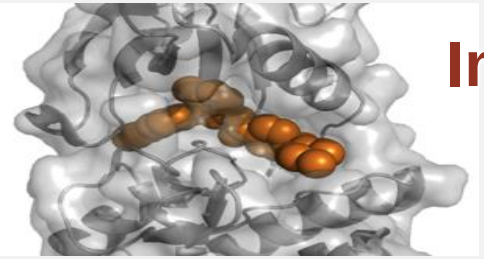


CML

Pathogenesis



Target-based drug discovery



Imatinib

Active compound against Bcr-Abl oncogene

August 1992

A series of compound had passed muster in the biologists' labs on all the requisite tests save one: They were active against the Bcr-Abl oncogene: they were selective. They had even shown activity in vivo (animal testing).

The one thing keeping the compounds from getting a 100 percent stamp approval was the issue of solubility.

Magic Cancer Bullet. How a tiny orange pill is rewriting medical history. Daniela Vasella, M.D.

Some toxicology issues...

May 1996

But then the dogs in the studies began developing blood clots at the point where the catheter tips were placed. It might have been caused by some mechanical problem with the catheters or it could have been caused by the compound itself. Whatever the case, there would be no patient trials until this matter could be resolved.

Magic Cancer Bullet. How a tiny orange pill is rewriting medical history. Daniela Vasella, M.D.

The First 12 patients in the trial

June 1998

By June 1998,...of 12 patients... Using one a month would be enough to sustain him throughout the Phase I trial.

The patient decided to return to Argentina

October 1998

...at the 140- milligram dosage, she clearly responded to the drug though her greatly elevated white cell count did not normalize completely.

...in January 1999, she voluntary took herself off the drug that was arresting her CML and returned to home

...she missed her husband and children in Buenos Aires. She jut wanted out of the routine. "I had an emotional problem. It was very terrible for me," she commented on August 2001.

A magic moment... The cytogenetic response

March 1999

...the lack of a cytogenetic response among any of the patients thus far. Getting such a response, of course, would be the true test of whether the drug could be put in the breakthrough category.

A Magic Moment

The in March 1999 there was some dramatic news.

The investigators got their first indication that the drug might induce a cytogenetic response after all.

Magic Cancer Bullet. How a tiny orange pill is rewriting medical history. Daniela Vasella, M.D.

Industrial Production from Phase I

April 1999

Our task at Novartis was to move to industrial-scale production of Gleevec at once. To contemplate such a step - with data based only on Phase I trials- appeared quite hasty...

Some barriers to access to innovation

2002

UK Health Bodies – NICE restricted the drug for patients in accelerated phase disease due to lack of survival data

Source:The Lancet – Vol 359 – June 8, 2002

CORRESPONDENCE

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Not so NICE for CML

Sir—Imatinib (previously STI571) seems to be a very remarkable contribution to the management of chronic myeloid leukaemia (CML). It is thought to act by inhibiting the kinase activity of the BCR-ABL oncoprotein, which is deemed to cause the chronic phase of CML.

Phase I clinical studies began in 1998 and it became rapidly apparent that the drug reverses symptoms and controls the leucocyte count in most CML patients in the chronic phase.[1,2] Most importantly, it lowers the proportion of Philadelphia-chromosome-positive leukaemia cells in bone marrow to a much greater extent than any other therapeutic agent, and thus raises the possibility that some patients may prove eventually to be cured. It also has activity in the advanced phases of CML. These and other observations led to unusually rapid approval for its use in the USA by the Food and Drug Administration (FDA); the European Medicines Evaluation Agency approved its use in patients with CML in advanced phases and for chronic-phase patients deemed to have failed treatment with interferon-alfa, which was ratified in the UK in November, 2001.

More than 15 000 patients have now been treated with this drug. Haematologists worldwide regard it as a major advance in the management of CML. However, patients have a median survival of 4–7 years, and it is far too early to say whether imatinib prolongs survival compared with other methods of treatment. For this reason the FDA required the manufacturers to undertake a prospective phase III study comparing imatinib with the combination of interferon-alfa and cytarabine in previously untreated CML patients.

Preliminary results of this study were reported at the May meeting of the American Society of Clinical Oncology. Two-thirds of the patients treated with imatinib achieved complete cytogenetic remission. Progression-free survival at 1 year was significantly better in the imatinib group than in the interferon-alfa and cytarabine group (97·2 *vs* 80·3%, p<0·001), although overall survival was similar in the two groups, as would be expected with short follow-up.

Against this background the National Institute for Clinical Excellence (NICE), which advises health authorities in England and Wales on the cost-effectiveness of drugs and techniques used in the National Health Service, has issued a preliminary appraisal consultation document recommending that imatinib should be funded only for patients in accelerated-phase disease and not for those in the chronic phase or in blastic transformation.[3] The NICE Appraisal Committee bases this advice on the current lack of robust survival data and the results of pharmacoeconomic analyses, in which imatinib was not better than other cheaper drugs. By contrast, the Scottish Medicines Consortium (and other European bodies) recommend funding for imatinib in all phases of CML in accordance with the product licence.[4]

We believe that the current NICE recommendations ignore the probability that imatinib will prolong survival for CML patients by a substantial number of years. In recommending that patients await the results of further randomised prospective studies, which, in view of available clinical data, will prove very difficult to design and even more difficult to implement, NICE is in grave danger of denying CML patients the benefit of a potentially invaluable drug. We earnestly hope that the Appraisal Committee will reconsider its preliminary recommendations.

*John Goldman, Jane Apperley, Richard Clark, Tony Green, Tessa Holyoake, Stephen O'Brien, Pat Shepherd

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1 Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; **344:** 1031–37.
2 Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002, **346:** 645–52.
3 NICE Appraisal Consultation Document: imatinib for chronic myeloid leukaemia. http://www.nice.org.uk/article.asp?a=31915 (accessed May 29, 2002).
4 The Scottish Medicines Consortium advises on imatinib mesylate (Glivec). http://www.hhs.co.uk/smc/press/index.asp?did=532 (accessed May 29, 2002).

Science, philosophy, religion, and use of embryonic stem cells

Sir—Riccardo Baschetti (Dec 15, p 2078)[1] dismisses moral objections to stem-cell research that arise solely from religion and philosophy, not science. He argues that religious morality has been superseded by the objective biological ethic, which is aimed at avoiding pain and suffering.

For Baschetti to pretend that his philosophical arguments are scientific is absurd. It is not the nature of science to be able to discover, prove, or invent morality. Scientists do everyone a disservice when they mislabel their philosophies as science.

If the biological ethic of avoiding pain and suffering should be embraced as the chief governing principle, the best way to achieve these aims would be to eliminate all human beings.

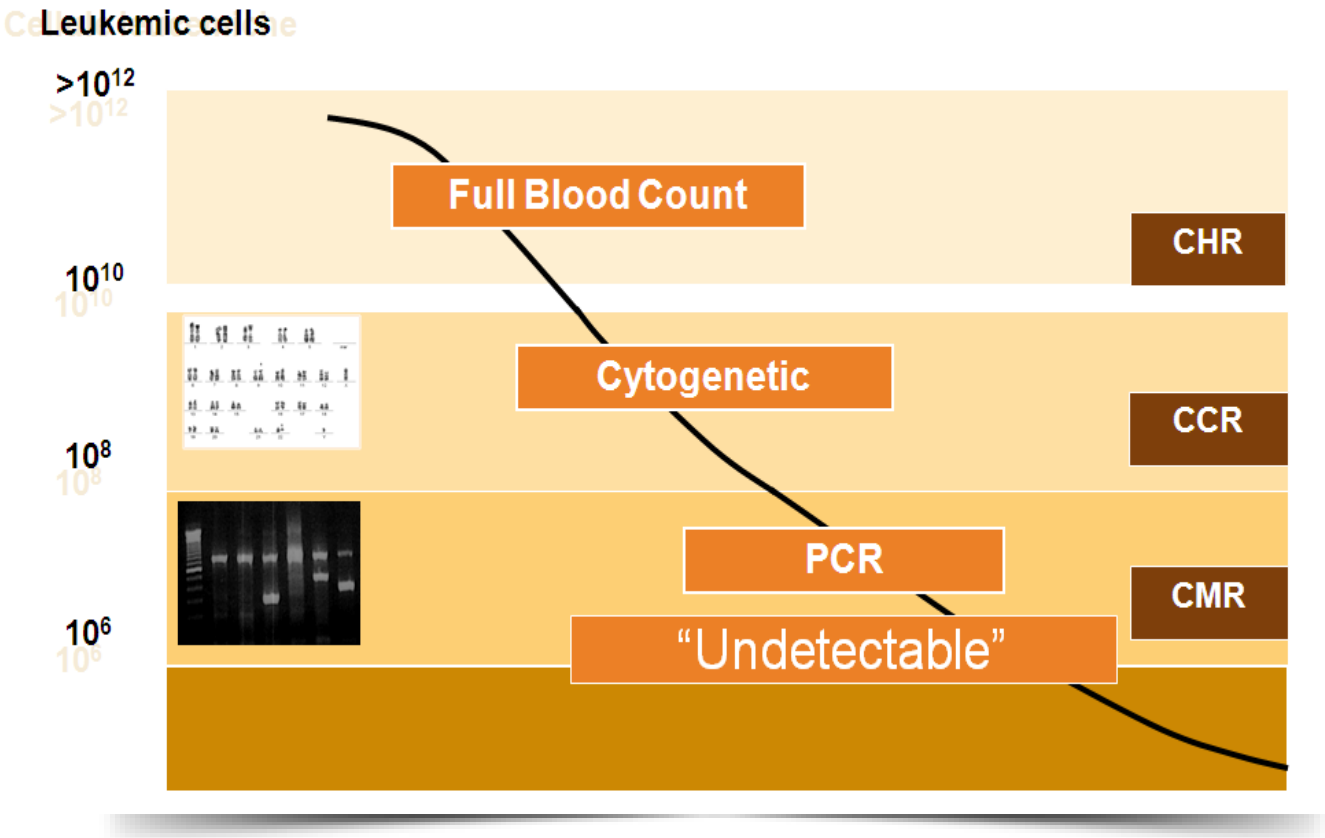
Clearly, Baschetti's ethical rule is simplistic. Other rules and goods must also be considered. One of these, which Baschetti might also call a biological ethic, is the need or desire to reproduce our species and protect our offspring. Those who oppose destructive human embryo research, Baschetti would have to admit, may simply be defending human embryos.

On the most fundamental level, Baschetti's arguments are most flawed by his dismissal of the metaphysical, unseen, or spiritual reality outside the material world observable by scientific methods. Such is the proper and necessary purview of religion and philosophy, disciplines he seems to disdain.

But those who deny any metaphysical reality outside the measure of science have lost all basis on which to argue for anything. In making the argument for materialism,

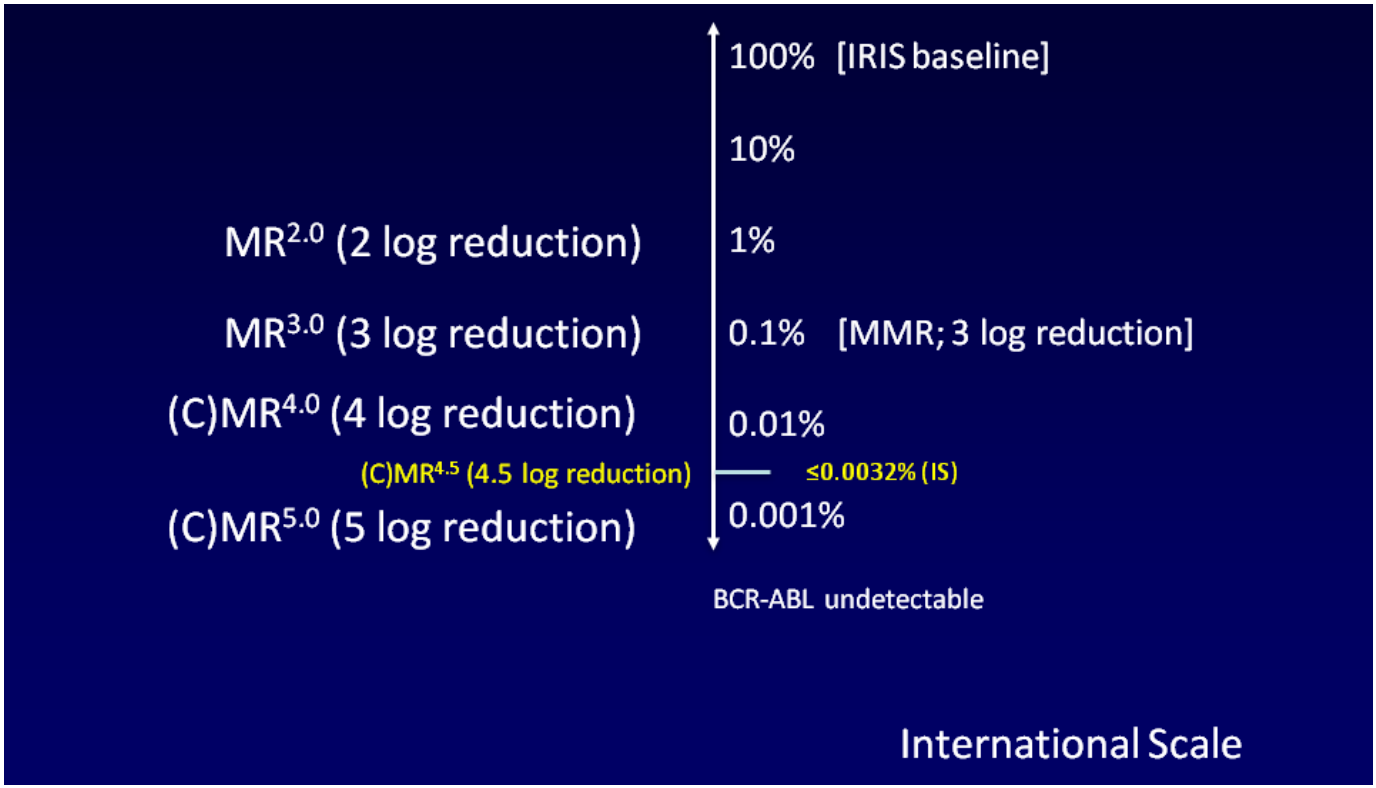
Monitoring CML

Chronic Myeloid Leukemia Monitoring



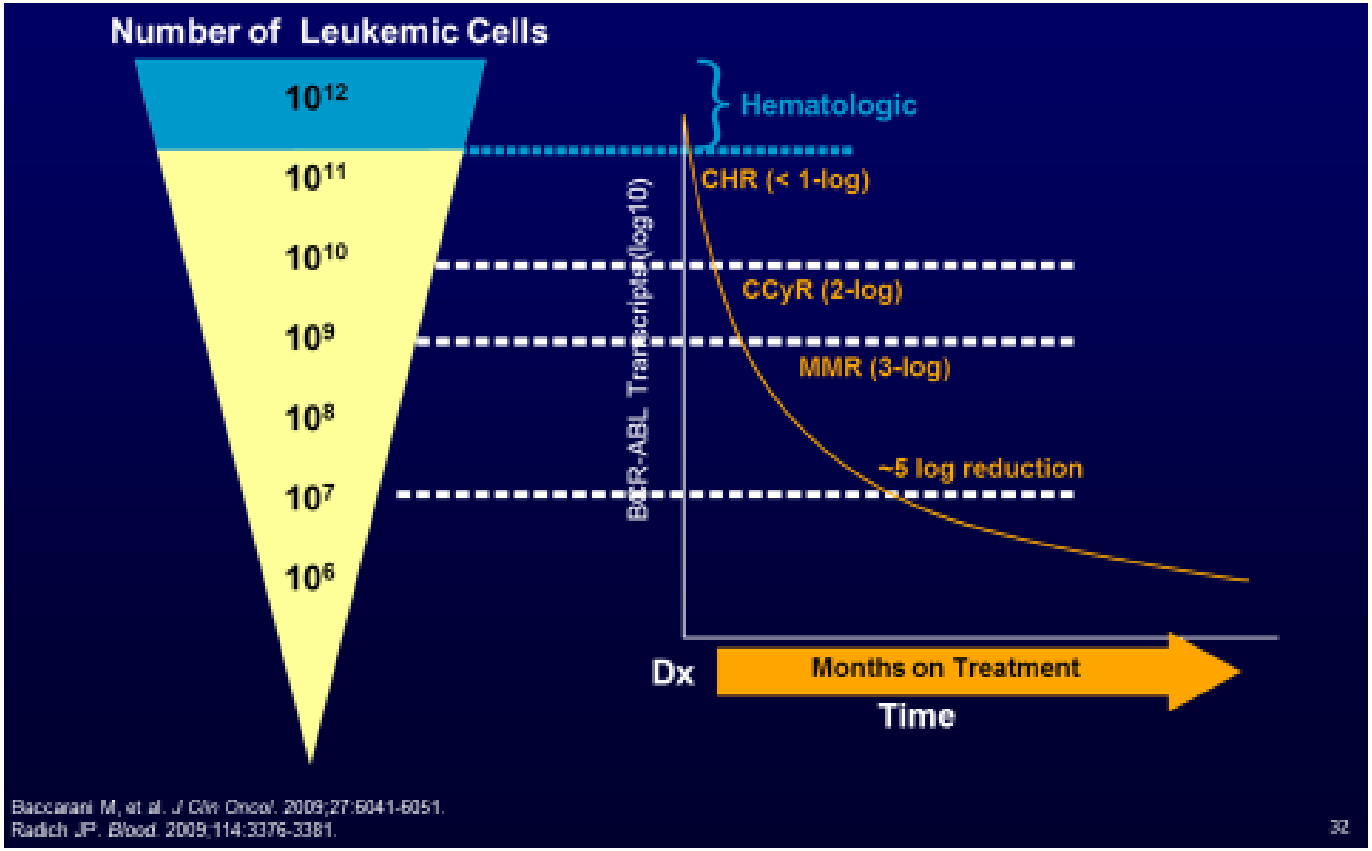
Definition of Response

Definition molecular response: The path to standardization



Definition of Response

Correlation between response and disease burden: Hematological response



2010

Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial

François-Xavier Mahon, Delphine Réa, Joëlle Guilhot, François Guilhot, Françoise Huguet, Franck Nicolini, Laurence Legros, Aude Charbonnier, Agnès Guerci, Bruno Varet, Gabriel Etienne, Josy Reiffers, Philippe Rousselot, on behalf of the Intergroupe Français des Leucémies Myéloïdes Chroniques (FILMC)

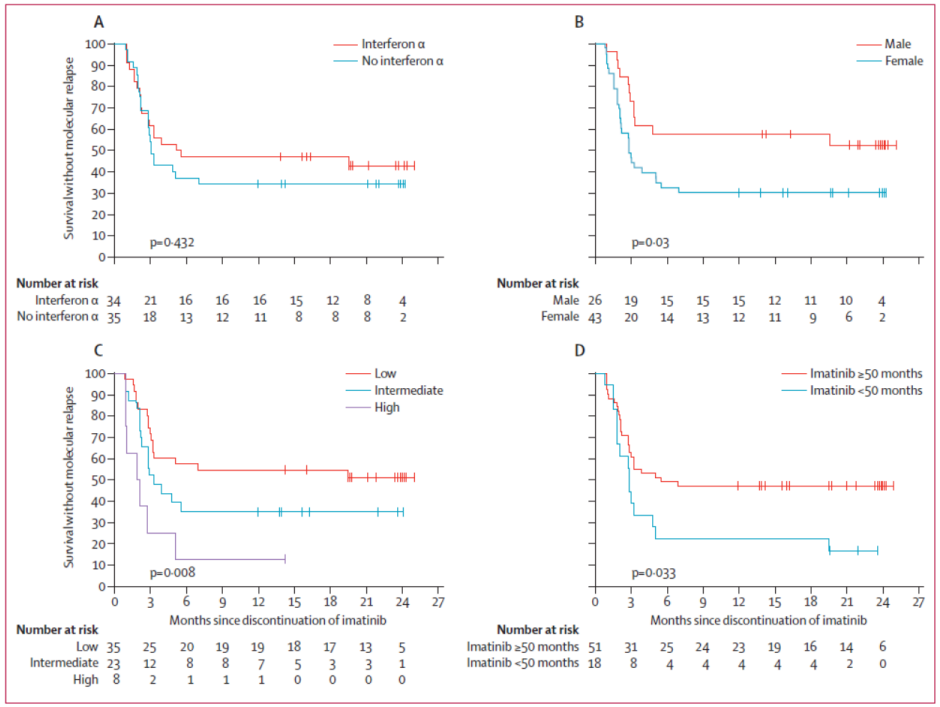


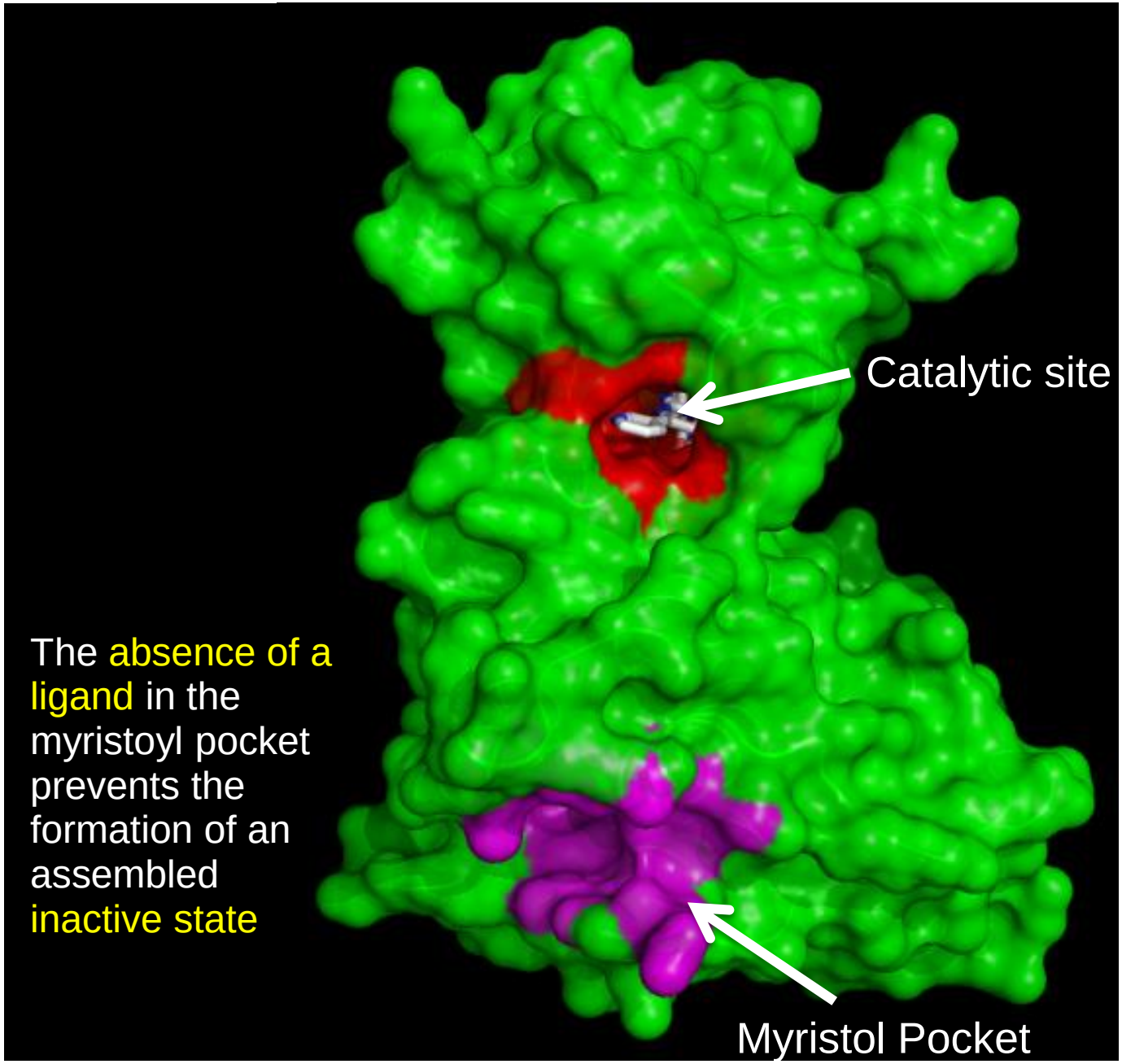
Figure 2: Kaplan-Meier estimates of complete molecular remission after discontinuation of imatinib in 69 patients with chronic myeloid leukaemia, according to factor

Imatinib can be safely discontinued in patients with a CMR of at least 2 years duration

At 12 months, the probability of persistent CMR for these 69 patients was 41% (95% CI 29–52).

Source: The LancetMagic Cancer Bullet. How a tiny orange pill is rewriting medical history. Daniela Vasella, M.D

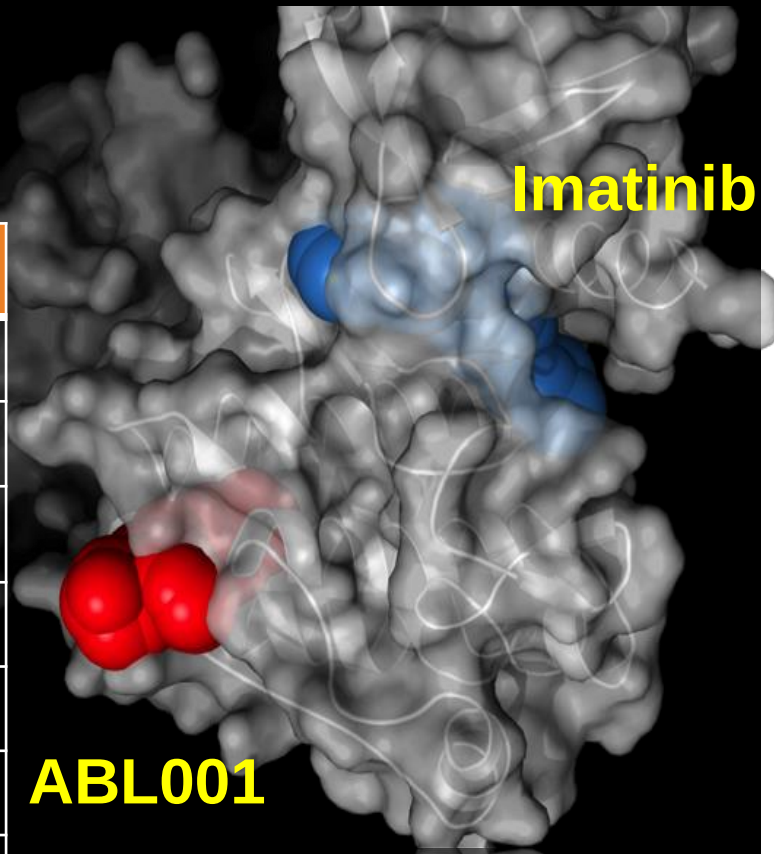
Drugging the myristol pocket of ABL



The absence of a ligand in the myristoyl pocket prevents the formation of an assembled inactive state

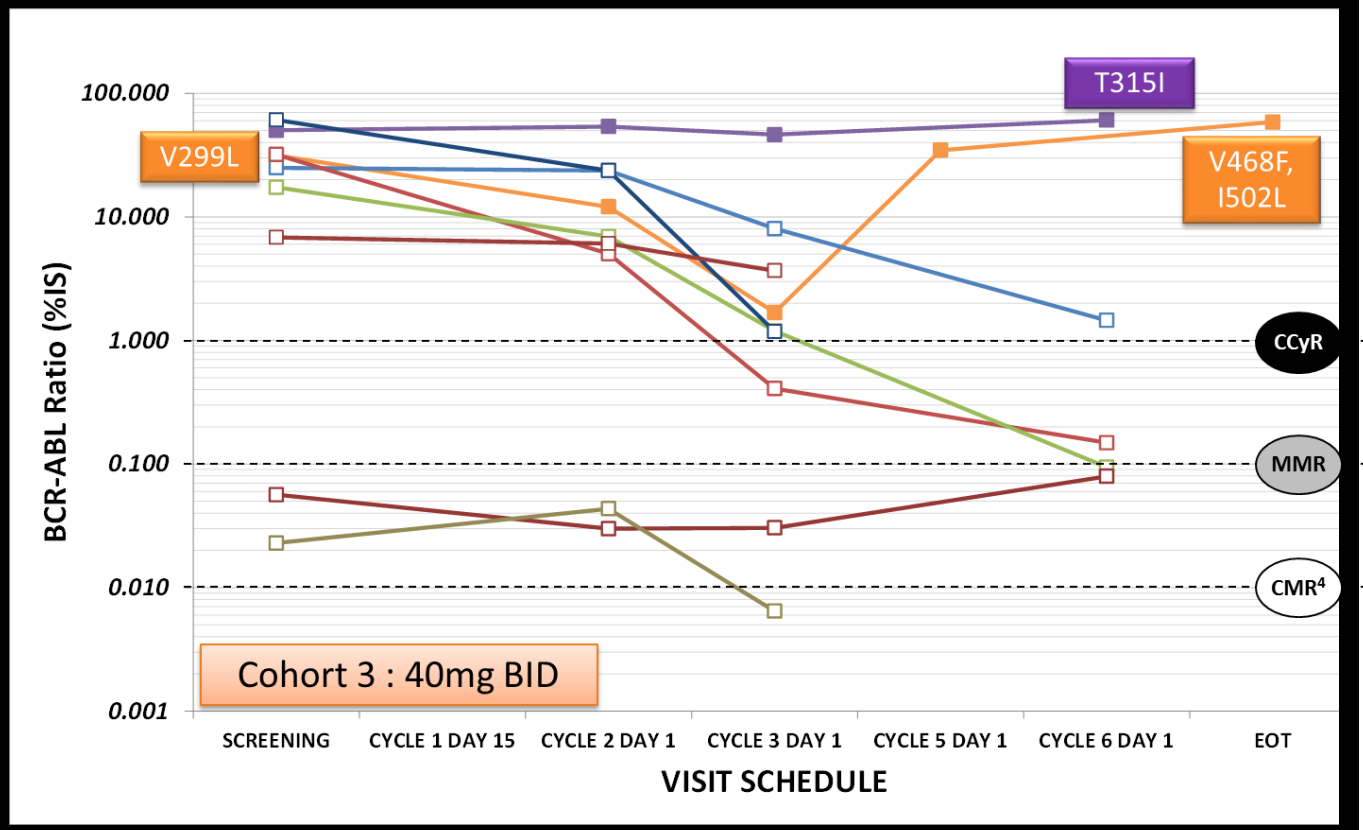
ABL001

Assay	ABL001
Biochemical IC_{50}, ABL^{WT}	1.2 nM
Cellular IC_{50} BCR-ABL^{WT}	1 nM
Cellular IC_{50} BCR-ABL^{T315I}	25 nM
Cellular IC_{50} WT BaF/3	>10 µM
hERG	>30 µM
Qpatch Clamp	26 µM
PAMPA class, F %	36
CYP3A4,2D6,2C9	>20 µM



ABL001 – Potent allosteric inhibitor with good pharmacological properties

ABL001



ABL001 results in early molecular responses in multiple patients failing 2 or more prior TKIs

ABL001

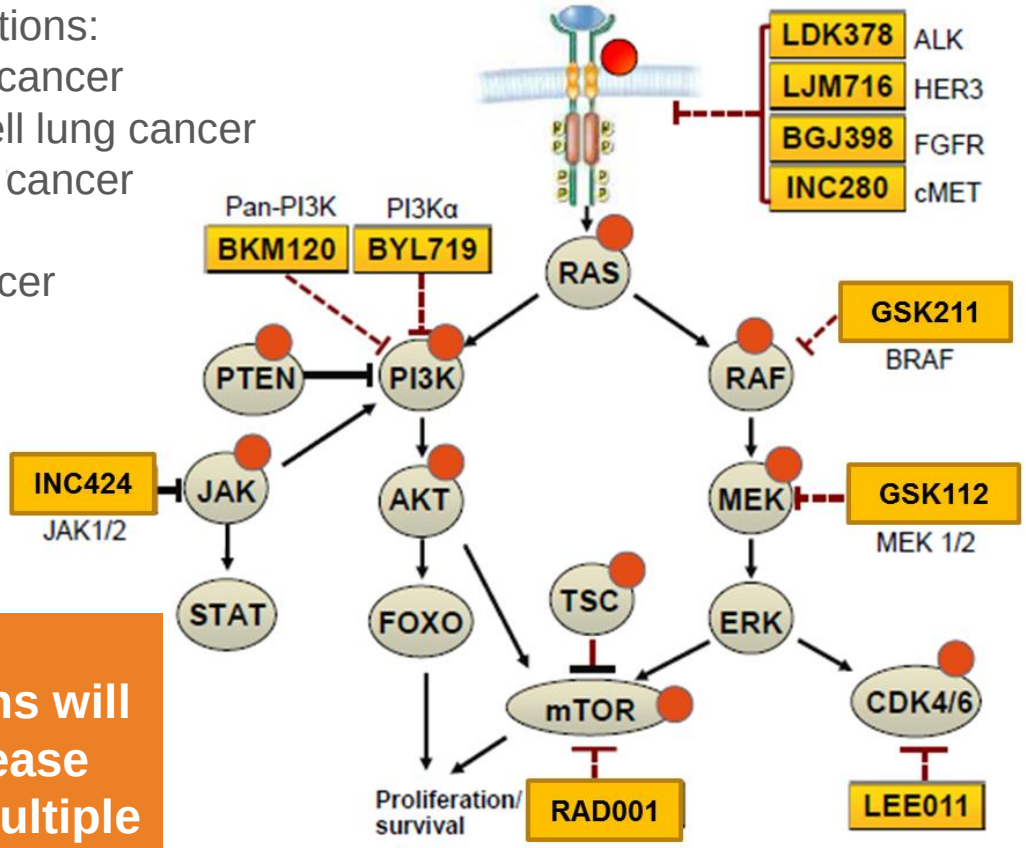
Conclusions

1. ABL001 is a novel potent and selective allosteric inhibitor of BCR-ABL currently in clinical trials.
2. Genetic bar-coding allows the dynamic tracing of clonal evolution during drug treatment in vitro. Studies show that in these settings most resistance emerges from rare pre-existing clones.
3. Non-cross resistant combination regimens may be critical in achieving disease eradication.
4. Clinical testing of combinations of ABL001 and nilotinib will begin shortly.

Druggable Future: What it takes and how we can get there

Combinations are Expected to be the Future of Targeted Therapy

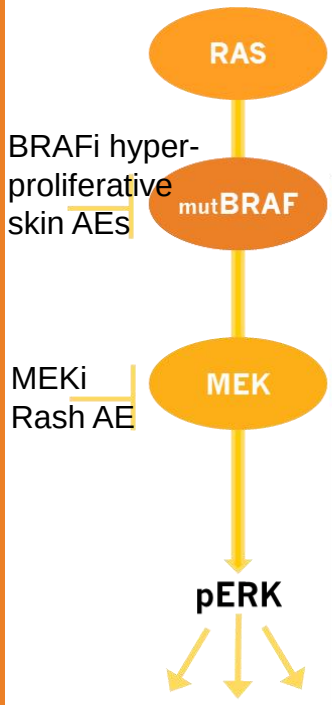
- Frequent pathway activating genetic alterations:
  - Colorectal cancer
  - Non-sall cell lung cancer
  - Pancreatic cancer
  - Melanoma
  - Breast cancer



Combinations will likely increase efficacy in multiple tumor types

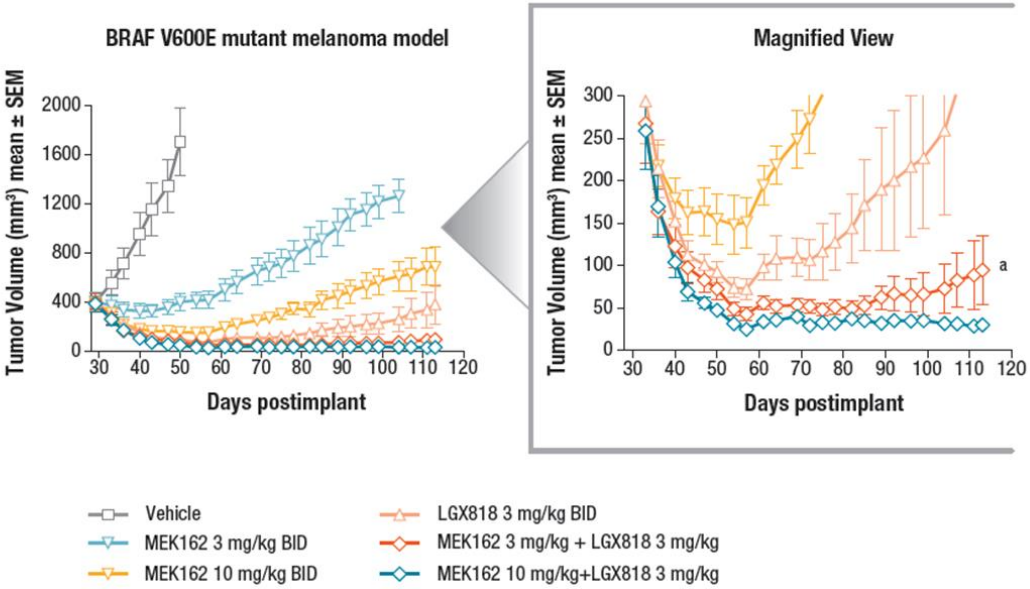
Rationale for Combination of BRAFi + MEKi

Druggable Future: What it takes and how we can get there



Proliferation
Survival
Invasion
Metastasis

Preclinical BRAFi + MEKi
Delays BRAFi resistance
↓ Hyperproliferative skin AE



[a] 12.5% of mice had progressive disease.
BID, twice daily; SEM, standard error of the mean.

Nowak paper describes a model to calculate probability of eradication for combination therapy

Druggable Future: What it takes and how we can get there

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RESEARCH ARTICLE

Evolutionary dynamics of cancer in response to targeted combination therapy

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Abstract In solid tumors, targeted treatments can lead to dramatic regressions, but responses are often short-lived because resistant cancer cells arise. The major strategy proposed for overcoming resistance is combination therapy. We present a mathematical model describing the evolutionary dynamics of lesions in response to treatment. We first studied 20 melanoma patients receiving vemurafenib. We then applied our model to an independent set of pancreatic, colorectal, and melanoma cancer patients with metastatic disease. We find that dual therapy results in long-term disease control for most patients, if there are no single mutations that cause cross-resistance to both drugs; in patients with large disease burden, triple therapy is needed. We also find that simultaneous therapy with two drugs is much more effective than sequential therapy. Our results provide realistic expectations for the efficacy of new drug combinations and inform the design of trials for new cancer therapeutics.
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†These authors contributed equally to this work

Competing interests: The authors declare that no competing interests exist.

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Introduction

The current wave of excitement about targeted cancer therapy (*Sawyers, 2004*; *Sequist et al., 2008*; *Kwak et al., 2010*; *Chapman et al., 2011*; *Gonzalez-Angulo et al., 2011*) was initiated by the success of imatinib in the treatment of chronic myeloid leukemia (CML) (*Druker et al., 2006*; *Gambacorti-Passerini et al., 2011*). Four decades of research passed between the discovery of the Philadelphia chromosome and the first treatment to target an activated oncogene in a human cancer. Targeted therapies against many different types of cancer are now being developed at a fast pace. These include gefitinib and erlotinib for non-small-cell lung cancer patients with EGFR mutations (*Sequist et al., 2008*), panitumumab and cetuximab for metastatic colon cancer (*Amado et al., 2008*), vemurafenib for patients with melanomas harboring BRAF mutations (*Chapman et al., 2011*), and crizotinib for lung cancer patients with EML4-ALK translocations (*Kwak et al., 2010*). At present, dozens of other targeted cancer therapies have either been approved or are being evaluated in clinical trials.

Probability of Eradication

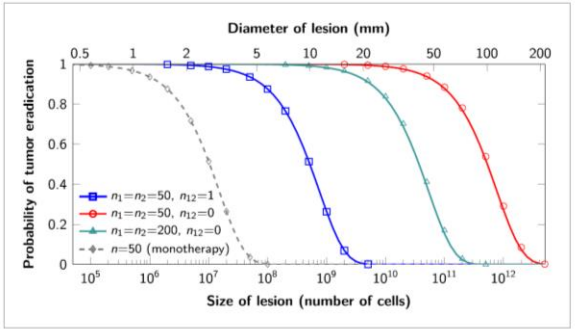


Figure 3. Probability of tumor eradication for two-drug combination therapy. A single mutation conferring cross-resistance to both drugs ($n_{12} = 1$) can prohibit any hope for a successful dual therapy. Solid curves show analytical results for dual therapy and dashed curve shows analytical results for a typical monotherapy, both are calculated using ***equation (1)***. Markers (square, triangle, circle, diamond) indicate simulation results (averages of 10^6 runs). Parameter values: birth rate $b = 0.14$, death rate $d = 0.13$, death rate for sensitive cells during treatment $d' = 0.17$, point mutation rate $u = 10^{-9}$.
DOI: 10.7554/eLife.00747.006

Function of tumor size, mutation rate, growth rate, birth and death rates, **numbers of point mutations that make cell resistant to either or both drugs**

Druggable Future: What it takes and how we can get there

Precision Medicine: Where and how to go there?

Precision Medicine could help to overcome...Some of the obstacles that have already been encountered in "precision oncology": unexplained drug resistance, genomic heterogeneity of tumors, insufficient means for monitoring responses and tumors recurrence , and limited knowledge about the use of drug combinations

Source: A New initiative on Precision Medicine- The New England Journal – Feb 26, 2015

Druggable Future: What it takes and how we can get there

Precision Medicine:
Is the route to a healthy world?

Initiatives such as the French National Cancer Institute's molecular testing network, in which a framework of 28 regional laboratories provide a national service that informs treatment selection, represent a model for this type of approach

Source: Nowak F, Calvo F, Soria JC. Europe does it better: molecular testing across a national health care system-the French example. Am Soc Clin Oncol Educ Book 2013:332-37.

Druggable Future: What it takes and how we can get there

Precision Medicine: Where and how to go there?

Can we afford it?...A particular economic challenge that will need a solution is that of in-year health budgets and budget 'silos'

Source: A New initiative on Precision Medicine- The New England Journal – Feb 26, 2015

Druggable Future: What it takes and how we can get there

Precision Medicine: Conclusions

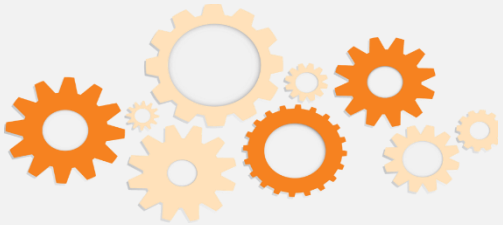
MOVE THE THINKING

from LEFT to RIGHT, to RIGHT to LEFT

Druggable Future: What it takes and how we can get there

Precision Medicine with Precise Organization

- Science and R&D
- Pharma industry
- Health Authorities
- Regulatory Authorities
- Scientific Community
  - Integration of Hospital and Territory healthcare managament
- Patient Associations
- Education and Universities



Together we can make this a reality

Druggable Future: What it takes and how we can get there

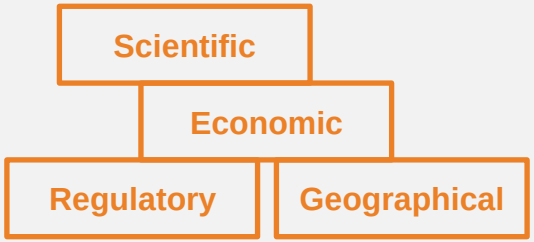
Precision Medicine: Conclusions

- Balancing the Precision: how much precise we need to be and until which extent

- Precision Medicine should consider patients needs

Patients needs and pathology

- Is a difficult and long journey and needs to overcome scientific, economical and regulatory hurdles.



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