Translational Strategies for Personalized Medicine

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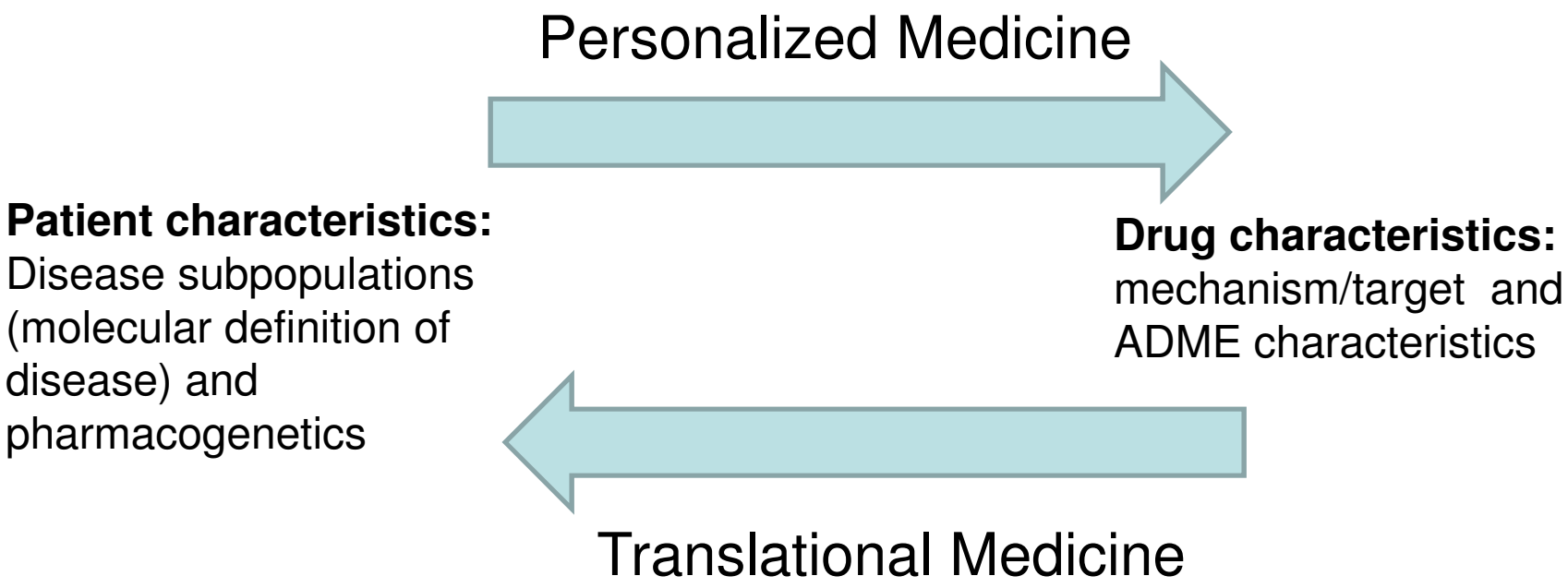
Personalized medicine strategies are translational…

- **TM and PM share the same strategies**
- **The disease**
  - Disease phenotype Vs. molecular definition of disease
  - Biomarkers and pathways
- **TM: the molecular target and the POC study**
  - RA TNFα targeted NCE
- **PM: the patient's disease biology and the drugs**
  - Biomarkers identify most important pathways
  - Therapeutic options Vs. most relevant targets
  - Pharmacogenetics and ADME
  - Oncology is leading the way
  - Molecular definition of chronic diseases
  - RA DMARDs: Create and test PM hypotheses
- **It's time to put knowledge to practice**

Translational and personalized medicine strategies…

- TM- validate novel targets in humans and reduce late phase attrition
  - Select human populations that optimize efficacy and safety signals in early studies
    - Disease subpopulations with abnormal expression/activity of drug target/pathway
    - ADME characteristics dictate population and dose to achieve adequate exposure to test the target
- PM- optimize efficacy and safety for each individual patient
  - Select therapeutics based on individual characteristics:
    - Disease biomarkers help select appropriate targeted drug
    - Dose and regimen based on pharmacogenetics, etc.

The starting point is the difference…



Disease phenotype Vs. molecular definition…

- Disease phenotypes: traditional disease definitions
  - Clinical description, e.g. lung cancer
  - Pathologic description, e.g. non-small cell
- Molecular definitions: related to pathogenesis of disease
  - Oncogene mutations, e.g. K-ras
  - Gene expression, e.g. HER-2
  - Biomarkers, e.g. estrogen receptor positive

Biomarkers and pathways…

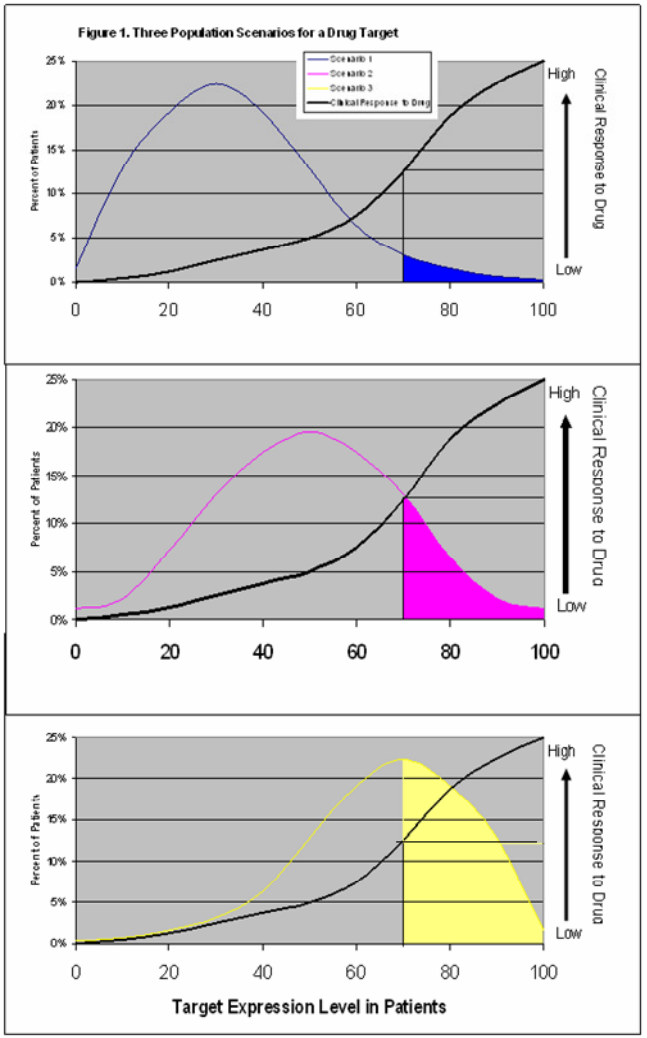
- Identification of abnormally expressed genes, proteins and pathways critical to the expression of a disease phenotype
  - Translational medicine: select “molecularly correct” population to achieve POC for drug target and drug molecule
  - Personalized medicine: select the best therapeutics for an individual patient

TM: the molecular target and the POC study…

The proportion of patients with abnormal pathway expression for three different targets.

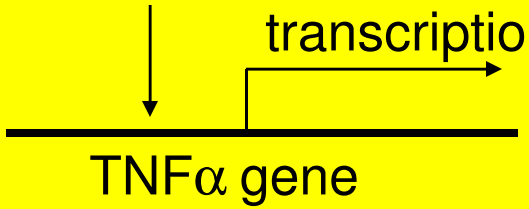
Drug target: Select the population of patients whose disease expression is most dependent on the targeted pathway.

Study endpoint: Select patients to minimize variability of the primary endpoint (biomarker linked to outcome or standard endpoint).



RA: a TNFα targeted NCE…

Molecularly correct population- TNFα

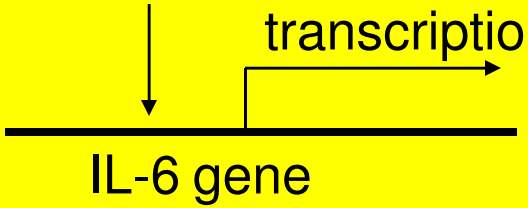


G allele frequency reported to be 0.77, about 60% of population G/G

A allele results in larger TNF response to stimuli and lower chance of good clinical response to TNF blockers in RA patients (DAS 28 score improvement >1.2):

- 42% of A/A and A/G group
- 82% of G/G group

Reduce endpoint variability (CRP and IL-6)

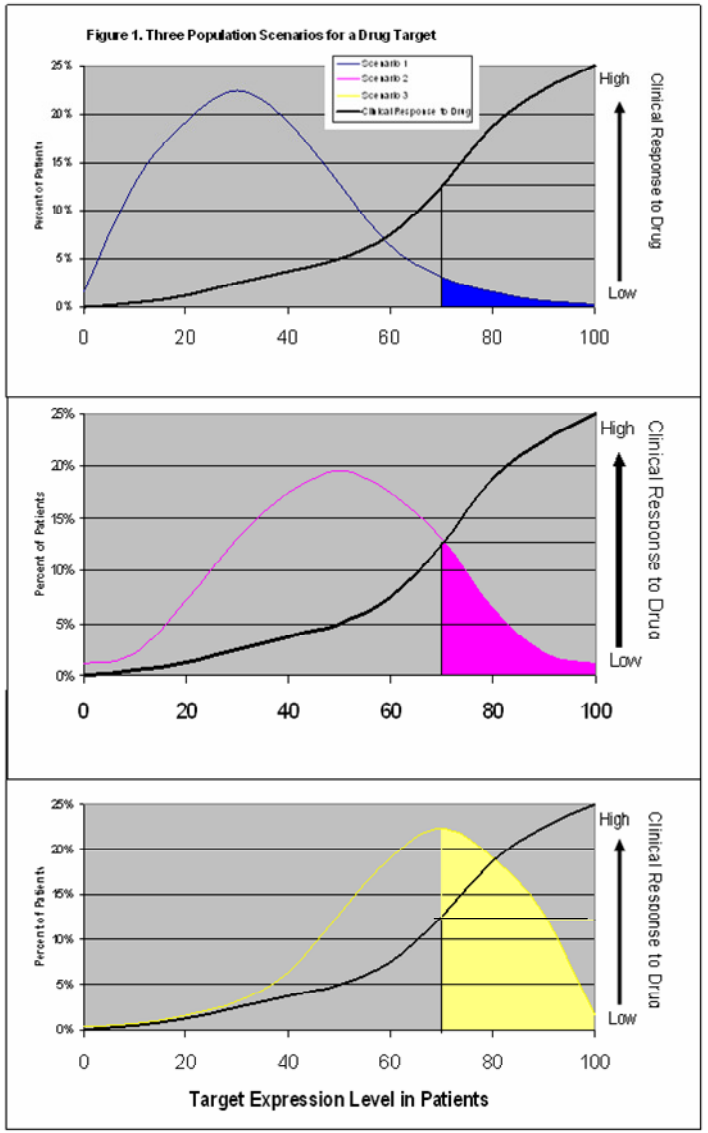


C allele frequency reported to be 0.4, about 16% of population C/C

C allele results in lower IL-6 response to IL-1 and LPS. IL-6 also drives CRP production by the liver. If IL-6 and CRP reduction are the efficacy signal, greatly reduce variability by excluding RA patients with C/C genotype.

Personalized medicine…

- A single drug mechanism is not equally safe and efficacious
- Biomarkers identify the most important pathways in the patient
- Select most appropriate therapeutic



Therapeutic options Vs. most relevant targets…

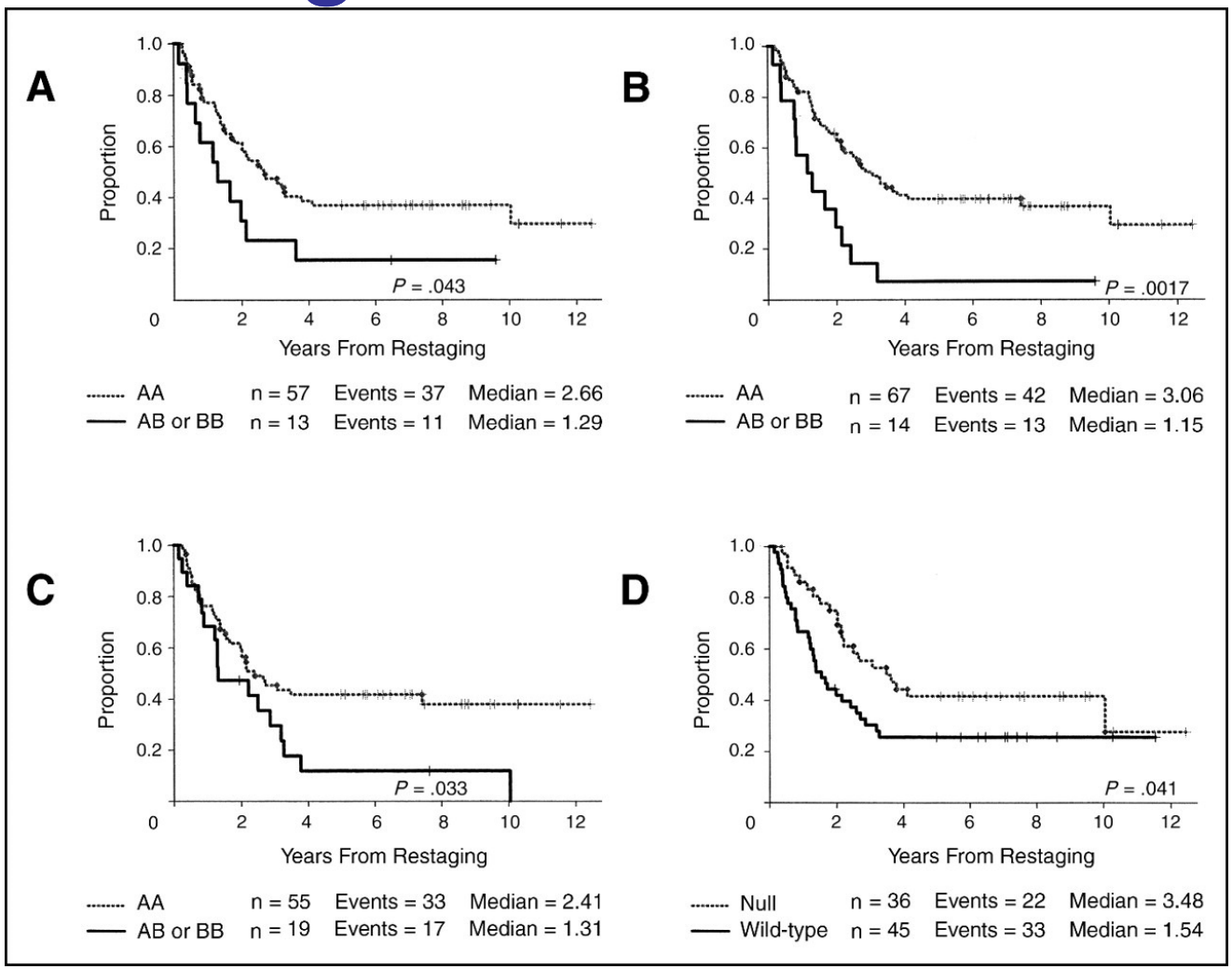
- Personalized therapies are becoming standard in oncology because “molecular definition of disease” started there and many drugs have a narrow therapeutic index
- Oncogene mutations are biomarkers
  - Her2 over-expression for Herceptin
  - K-ras WT genotype for anti-EGFR antibodies
  - EGFR mutations and resistance to EGFR TK inhibitors (Tarceva And Iressa)

Pharmacogenetics and ADME…

- TM: Choose the subjects, dose and regimen based on ADME characteristics of the drug to ensure exposure sufficient to test the validity of the drug target
- PM: Choose the dose and regimen to optimize exposure and improve outcomes for individuals
  - Most critical for drugs with a narrow therapeutic index to achieve good efficacy and safety, e.g. *UGT1A1* polymorphisms and individualized dosing of irinotecan

Breast cancer survival and pharmacogenetics…

Kaplan-Meier analyses of overall survival following standard dose chemotherapy and high dose cyclophosphamide, cisplatin and carmustine. Patients segregated based on the presence of genetic polymorphisms in (A) CYP 3A4*1B, (B) CYP3A5*1, (C) MET1F G-7T, (D) glutathoine-S-transferase M1



Petros, W. P. et al. J Clin Oncol; 23:6117-6125 2005

Molecular definition of chronic diseases…

- Most chronic diseases are clinical descriptions (common phenotypes) each with underlying pathway abnormalities due to different molecular and environmental causes
  - Current therapies are indicated for the “average” patient and usually do not work well in 30-60% of patients with the disease
    - Approved drugs have a defined mechanism of action that may not target the most important pathway abnormities in a given patient
  - Molecular understanding of disease and biomarkers lead to “personalized medicine hypotheses”

Rheumatoid Arthritis DMARDs: PM opportunities…

- Early treatment helps to delay or prevent joint damage and leads to better long-term outcomes
- Issues with current therapeutic strategy: safety (e.g. TB, lymphoma), high cost for biological DMARDs (~$10,000/year) and unpredictable treatment responses
  - 46% of RA patients achieve an ACR20 response with low dose MTX (most common initial DMARD)
  - 29-54% of patients do not achieve a satisfactory clinical (ACR20) response to TNFα-targeted biologics
  - Other approved and soon to be approved biologics have similar issues: anakinra (IL-1RA), abatacept (CTLA4-Ig), rituximab (anti-CD20) and tocilizumab (anti-IL6R)
  - Current strategy: “try it and see”

Personalized medicine hypotheses for RA…

- RA is really a heterogeneous phenotype associated with multiple molecular differences and inflammatory pathway abnormalities
  - At least 19 specific genes are significantly associated with RA susceptibility, disease severity or response to therapy (OMIM)
    - Influence T-lymphocyte activation, macrophage function, specific cytokine and inflammatory signaling pathways and/or inflammatory pathway dysregulation
  - PM hypothesis: biomarkers and drug mechanisms

PM hypothesis for TNFα targeted agents…

- Selection of patients and dose selection
  - About 40% of patients do not achieve an ACR20 response
    - A -308 promoter G to A SNP in the TNFα gene has functional significance
      - Allele frequencies are reported as 0.77 for allele G and 0.23 for allele A
      - Clinical response to infliximab: DAS28 improvement of 1.2 occurred in 81% of G/G patients and in only 42% in A/A and A/G patients
        - » The clinical improvement based on DAS28 score was about twice as good in the G/G patients compared to the A/A and A/G patients
      - Therefore 84% of responders would be G/G, 4% would be A/A and 12% would be A/G
    - A/A and A/G patients may be far better off trying a different type of DMARD first or they may require a different dose

PM hypothesis for tocilizumab…

- Selection of patients most likely to respond to tocilizumab (anti-IL-6R)
  - Phase II and III trials: one-third of patients did not achieve an ACR20 clinical responses
  - Promoter SNP at position -174 of the IL-6 gene significantly influences the amount of IL-6 produced in response to IL-1 and other inflammatory stimuli
    - C/C cell constructs do not increase IL6 production in response to IL-1 stimulation compared to a 3.6 fold increase for G/G cell constructs
  - The 30-40% of RA patients without a good clinical response to tocilizumab may not be so dependent on this pathway (e.g. C/C genotype) or may produce large amounts of IL-6 (e.g. G/G genotype) and require higher doses

PM hypothesis for abatacept…

- Selection of patients most likely to respond to abatacept (CTLA4-Ig)
  - Blocks interaction between CD28 and CD80/86 (B7-1 and B7-2) mimicking natural CTLA4-mediated down-regulation of T-lymphocyte immune responses
    - 60% of patients achieved an ACR20 response with MTX background therapy compared to about 30% on MTX alone
  - PTPN22 is a lymphoid-specific phosphatase that down-regulates T-cell activation mediated by TCR and CD28 co-stimulation
    - SNP in ~17% of the general population and ~28% of RA patients (1858C-T transition) results in an arg620-to-trp amino acid change that alters the protein's function as a negative regulator of T cell activation
  - The T-lymphocyte co-stimulation pathway may be more active in patients with a PTPN22 gene that has reduced phosphatase function and perhaps 1858C-T positive patients should receive abatacept as a first line DMARD

It's time to put knowledge into practice…

- Translational Medicine strategies can be applied to clinical practice decisions today
  - Oncology is leading but the same principles apply to all therapeutic areas
- Testable "personalized medicine hypotheses"
  - Rely on translational biomarkers, molecular definition of disease and pharmacogenetics
  - May provide opportunities for personalized medicine resulting in improved efficacy and safety for individual patients