AAPM 2017

Provocative Questions from a *Clinical* Perspective

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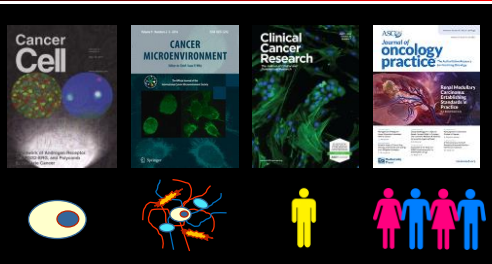
General Provocative Questions

- If anything is possible, what is important?
  - *Need to prioritize*
- What would you do if you knew you could not fail?
  - *No reward without risk of failure*
- Is it worse to fail or never attempt it in the first place?
  - *Learning from our mistakes*

Units of consideration in cancer research



Why are these units important?

- Mechanistic discovery and understanding of underlying biologic processes in cancer (new targets)
- Effects of microenvironment on tumor formation, progression, and treatment (new approaches)
- Develop new drugs (better therapies)
- Reduce burden of cancer for patients, families and the community (prevent, control, eliminate)

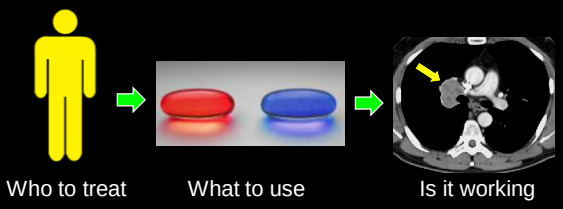
NCI Provocative Questions initiative

- How do cancer-specific subcellular pathognomonic structures develop, what is their function, and can they be a source of novel therapeutic targets?
- What are the predictive biomarkers for the onset of immune-related adverse events associated with check-point inhibition, and are they related to markers for efficacy?
- Can we develop bifunctional small molecules that will couple oncoproteins or other cancer causing molecules of interest to inactivating processes such as degradation and achieve tissue-specific loss of function?
- How do microbiota affect response to cancer therapies?
- Through what mechanisms do diet and nutritional interventions affect the response to cancer treatment?
- What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?

NCI Provocative Questions initiative

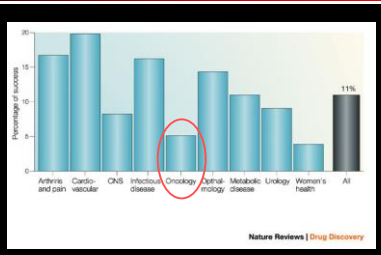
- What molecular mechanism influence disease penetrance in individuals who inherit a cancer susceptibility gene?
- How do variations in immune function caused by comorbidities or observed among different populations affect response to cancer therapy?
- Do genetic interactions between germline variations and somatic mutations contribute to differences in tumor evolution or response to therapy?
- Can we develop tools to directly change the expression or function of multiple chosen genes simultaneously and use these tools to study range of changes important for human cancer?
- How can mitochondrial heterogeneity influence tumorigenesis or progression?
- How do circadian processes affect tumor development, progression, and response to therapy?

What is important to a clinical oncologist?



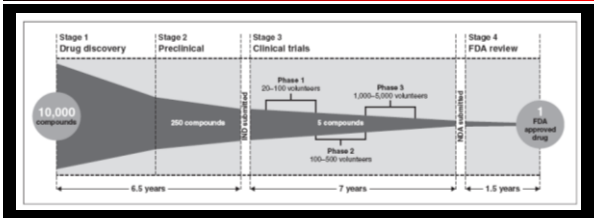
Who to treat | What to use | Is it working

Success Rate in Drug Development



Kola and Landis, 2004

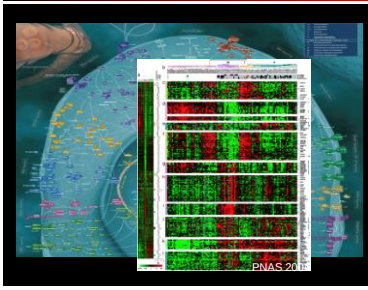
Drug Development

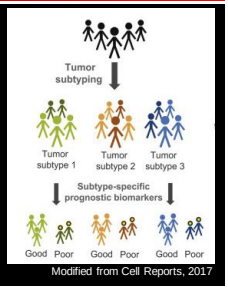


IOM Report

- *…many products and programs in development*, but high costs, long timelines, and *excessive failure rates* result in relatively few investigational drugs progressing to marketing approval
- …high attrition rate suggests that *initial candidate selection processes are not optimal*
- Advances in molecular biology and patient *molecular profiling* that may facilitate targeted therapies…hope and enthusiasm for better clinical outcomes.
- Targeted therapy represents a transition from broader-acting cytotoxic agents… and hence *therapeutic benefit for a well-defined group of patients* with a particular molecular biological profile
- A vision of the future would be for newly diagnosed patients to have a *comprehensive molecular profile performed* and then be *matched* to participate in the right trial based on that profile
- Leveraging 'intelligent biomarker selection' of patients to participate in early phase clinical trials has potential to make *more efficient go/no-go decisions* on product candidates at the earliest possible stage.

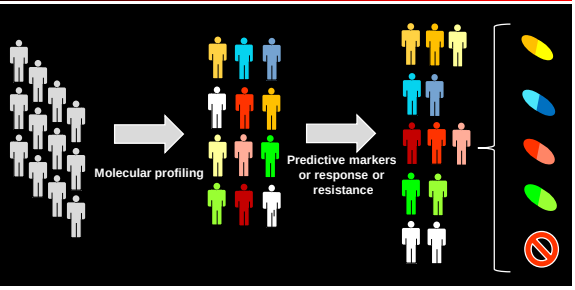
Who to treat



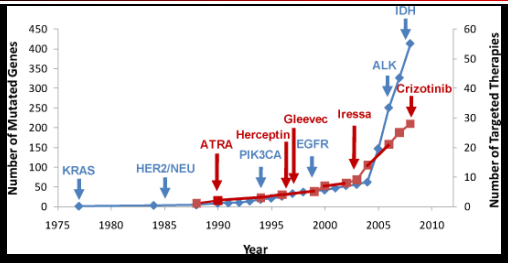


Modified from Cell Reports, 2017

What to use (Precision Medicine)

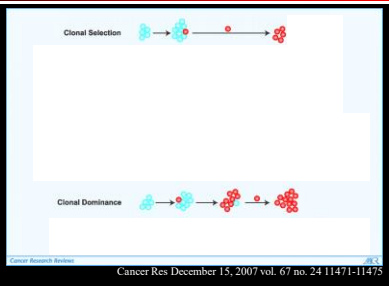


Drug Development



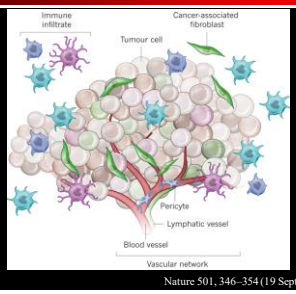
McDermott et al. NEJM 364(4):340-50, 2011

Tumor Heterogeneity



Cancer Res December 15, 2007 vol. 67 no. 24 11471-11475

Tumor microenvironment affects treatment response

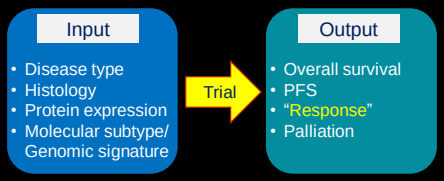


Nature 501, 346–354 (19 September 2013)

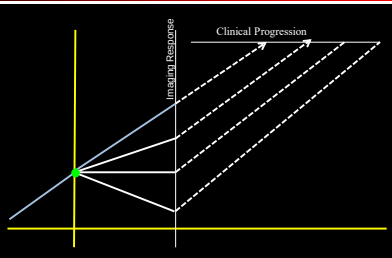
Central Rationale

- **Patient**: individual receiving treatment for disease
- **Disease**: abnormal condition that affects the body of a host
  - Not all disease affect individuals the same
- **Genotype**: genetic make-up of a cell/tumor
  - Not all cells/tumor with same genotype look/behave the same
- **Phenotype**: cell/tumor's observable characteristics (e.g. behavior) resulting from expression of genes, as well as influence of environmental factors, and the interaction between the two
  - Phenotype can vary at different sites within the same host (*plasticity*)

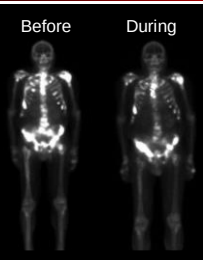
Is it working?



Clinical Imaging

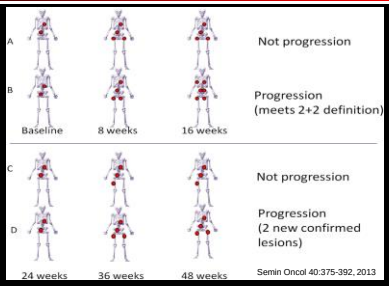


Response or progression?

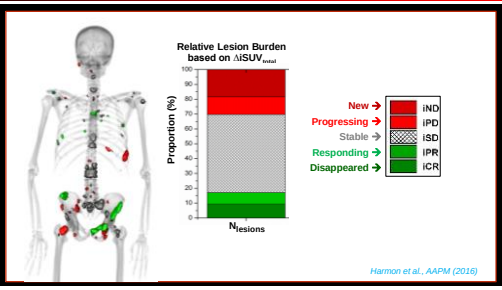


- Pain?
- Are they tolerating treatment?
- Risks to continue/stop therapy?
- Do I have other options?

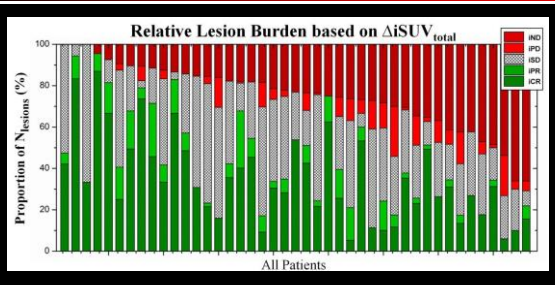
PCWG2 Definition of Progressive Disease



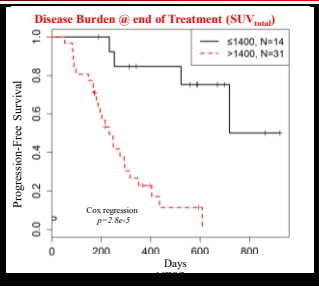
Interlesional disease response heterogeneity



Interpatient disease response heterogeneity

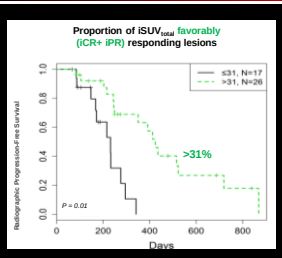


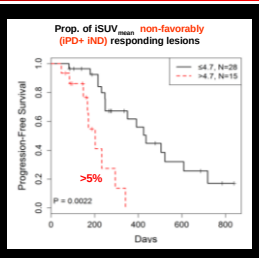
Total functional burden and PFS



Harmon et al., AAPM (2016)

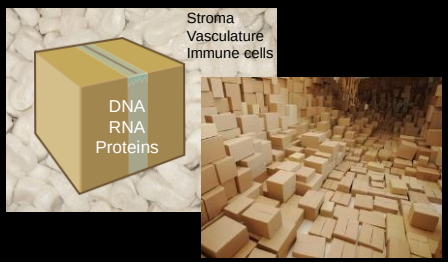
Interlesional response





Harmon et al., AAPM (2016)

"Box" Analogy



Drug Development vs Therapy Development

- Drug development
  - Goal: regulatory approval
  - *Risk adverse, incremental gains, financial incentives*
- Therapy Development
  - Goal: most effective therapeutic strategy
  - *Higher risk, more meaningful gains, societal incentives*