Reflections on Cancer Moonshots

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Cancer is a disease of mutations
- wrong location (cancer gene)
- wrong cell (stem/progenitor cell)
- wrong timing (too young)

....and bad luck
We know the genomic landscape of cancer

-large scale sequencing projects (TCGA, ICGC) have completed exomes (all coding regions) from ~10,000 cancers
-all common cancer drivers are defined ("common" means present at >5% frequency per tumor type)
The ‘Long Tail’ of Hotspot Mutations Across Cancer

How do we conduct precision medicine studies in these patients?

85% of all hotspot mutations affect <5% of any cancer type in which they are found

‘Basket’ Study Approach – Treating by Mutation not Tumor Location

Lung Cancer

Colorectal Cancer

Breast Cancer

Various Rare Cancers
MSK IMPACT  Next Generation Sequencing
Monthly Case Volume

Growth in Case Volume from ‘14 to ‘15

Current Capacity

2014 (~6,000 total cases) 2015 (~8,400 total cases)
MSK-IMPACT Enables Study Accrual

*Indicates studies in dose escalation (enrollment limited by spots not patients)
What fraction of cancer patients are benefiting?

-2/3 of cancers have known drivers
-1/2 of those with known drivers have therapies, but the other 1/2 are currently undruggable
How do we unravel the unknowns?

- More exome sequencing (to discover all mutations at >1% frequency)
- Whole genome sequencing (to discover mutations in non-coding regions, e.g., enhancers)
How do we address undruggable drivers?

1) new chemistry/pharmacology
   - disrupt protein-protein interaction
   - oncoprotein degradation
2) Generate a comprehensive map of cancer vulnerabilities (synthetic lethal screens, etc)
3) crack the challenge of delivering genetic drugs (siRNA)
   - nanoparticles, etc

Note: druggable ≠ cure (we need rational combinations)
Recommendations

1. Leverage the explosive growth of clinical sequencing
   - comprehensive clinical annotation of all mutations (registries)
   - encourage and support data sharing consortia (GENIE, CancerLinq, ORIEN, etc)

2. Define all cancer vulnerabilities
   - fill in the gaps of existing cell line encyclopedias
   - conduct comprehensive genetic screens (CRISPR/shRNA)

3. Invest in new approaches to drug the undruggable
   - new chemistry, new drug delivery

4. Leverage the huge commercial investment in immuno-oncology
   - support basic cancer immunology (syngeneic models, etc)
Data sharing discussions with the VP

Davos, Jan 19, 2016

Wash DC, Feb 19, 2016

Goal: link genomics with clinical phenotypes
How Does It Work?

Aggregate tumor-only NGS data and limited clinical data from project participants into registry

Clinical question asked

Necessary clinical data Linked to data within the registry

Data made publicly available after defined periods.