Biology Based Cancer Interception

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Disclosures

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The most important challenge in the cancer chemoprevention field:

Rational selection of the most effective and safe agents targeting early molecular drivers of cancer
Epithelial Cancer Progression Model

From: Kelloff et al, Clin Cancer Res 2006; 12(12) 3661; June 15,
The Path to Cancer - Three Strikes and You’re Out

New England Journal of Medicine, November 12, 2015
Biology and Signaling Pathways of Cancer

• Identify the “short circuit” unique to cancer cells
• Develop targeted therapy against the problem

Hallmarks of Cancer (2011)

- Sustaining proliferation
- Evading growth suppression
- Resisting cell death
- Achieving immortality
- Inducing angiogenesis
- Invasion & metastasis

Tumor Microenvironment

Signal Transduction Pathways

Hanahan/Weinberg/Hahn
Hypothetical Model of Biology and Signaling Pathways of PreCancer

Hallmarks of PreCancer ???

- Identify the “driving circuit” that transforms cells?
- Develop preventive agents to target major driver pathways?

Hanahan/Weinberg/Hahn
Molecular Heterogeneity

Precancer

Cancer

Easier to target less complex molecular systems

Modified from George Post
Understanding Biology of Precancer Cell is the most crucial for the development of target based Interception strategy.
How we can identify Cancer Drivers that are responsible for malignant progression? And how we can hijack or intercept Cancer Driver?
A Strategy for Identifying Early Intercepting Agent

- Master Molecule affecting all Hallmarks of Cancer cell?
- Selecting Intercepting agent through Reverse Migration?
- Immune Targeting Interception?
Therapeutic Targeting of Hallmarks of Cancer

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 mAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs
- Proapoptotic BH3 mimetics
- Resisting cell death
- Averting immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Genome instability & mutation
- Inducing angiogenesis
- Activating invasion & metastasis
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met
- Deregulating cellular energetics
- Sustaining proliferative signaling
- Evading growth suppressors
- PARP inhibitors

Hanahan D, Weinberg RA. Cell. 2011
Aneustat™ (Master Molecular Switcher ?) inhibiting Multiple Targets in All Hallmarks of Cancer Based on Preclinical studies

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Cancer Interception through Reverse Migration

“Hijacking” Molecular Drivers of Cancer for Prevention

Successful Example: SERMs in Breast Cancer

Cancer Prevention Research Commentary
Blackburn EH, Cancer Prev Res 2011;4:787-792
Reverse Migration of Tamoxifen

**METASTATIC**

- Premenopausal patients
- Metastatic Breast Cancer

- Oophorectomy
- Tamoxifen

**ADJUVANT**

- Buchanana RB et al. J Clin Oncol 1986

**PREVENTION**

- NSABP BCPT P-1 Schema
  - Eligible Participants
  - Stratification
    - Age
    - Relative Risk
    - Race
  - Tamoxifen x 5 years
  - Placebo x 5 years

- Fisher B et al. JNCI 1998
Hypotheses of Reverse Migration Strategy

- Premalignancies share biologic properties with malignancies

- Effective targeted therapy of advanced cancer may be applicable to adjuvant, even prevention setting

- Reverse migration from therapy to prevention is scientifically sound, e.g., tamoxifen in breast cancer
Metastatic potential of a primary tumor can be determined early on in evolution.

- Deregulated early in development of primary tumors
- Actively "drive" metastasis
- Are oncogenic

Lynda Chin
Intercepting agents through Reverse Migration Concept

- SERM in Breast Cancer
- Lenalidomide in Multiple Myeloma
- Hedgehog inhibitor in Basal Cell Carcinoma
- PARP inhibitors in BRCA-mutation carriers
- Androgen inhibitor in Prostate Cancer
- EGFR inhibitor in EGFR mutated NSCLC
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Immunosuppressive Metastatic Microenvironment

**Signal inhibitors**
- TGF-β, IL10, IL6, etc.

**Cancer cell**
- Oncogene activation
  - MAPK (BRAF)
  - STAT3
  - β-catenin

**Immunosuppressive cells**
- Treg
- MDSC
- tDC

**Dendritic cell**
- STAT3
- STAT3, β-catenin

**Anti-tumor T cell**

**Immunosuppressive molecules**
- TGF-β, IL6, IL-10, VEGF, etc.
Targeting the immune system to fight breast cancer was all but dismissed in the 1990s, but the strategy is making a big comeback with the possibility of a breast-cancer vaccine.
MUC1

Cyclin B1

Colon Cancer

Colonic Polyp

Lung Cancer

Lung neoplasia and metaplasia
Malignant Transformation can be blocked and/or Detoured Through Cancer Interception Approach

Premalignant cell
The Biology Behind

Cancer Prevention by Delay


Scott M. Lippman and Waun Ki Hong
Future Cancer Interception Strategy

Integration GWAS and PCGA

Genetic Risk Model as Score Card

Identify Highest Risk Cohort

Identify Target at the Tissue Level

Select Appropriate Intercepting Agent

Novel Clinical Design
Drugs to Deter Some Cancers Are Not Taken

Experts Say Advances Are Largely Ignored

By GINA KOLATA

Many Americans do not think twice about taking medicines to prevent heart disease and stroke. But cancer is different. Much of what Americans do in the name of warding off cancer has not been shown to matter, and some things are actually harmful. Yet the few medicines proved to deter cancer are widely ignored.

Take prostate cancer, the second-most commonly diagnosed cancer in the United States, surpassed only by easily treated skin cancers. More than 192,000 cases of it will be diagnosed this year, and more than 27,000 men will die from it.

And, it turns out, there is a way to prevent many cases of prostate cancer. A large and rigorous study found that a generic drug,

Why has cancer prevention been so challenging, with so few successes in last 10 years?
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Cancer Prevention Strategy for Next 10 Years

PreCancer Genome Atlas (PCGA)

Personalized Targeted Prevention

Identify targets for early interventions

Genetic risk model ("Scorecard")

Identify highest risk cohort

Select agent using reverse migration

Novel clinical trial designs
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Is there Intercepting agent affecting all Hallmarks of Cancer Cell as Multivalent Multitargeted Agent ??
Can we identify Intercepting agent through Reverse Migration Fashion from treatment of advanced cancer?
What about Immune Targeting Interception Strategy?
Vaccines for primary and secondary prevention of non-viral cancers

• Therapeutic vaccines
  – Given after cancer diagnosis
  – After failure of standard therapy
  – In combination with standard therapy
  – To slow cancer progression or prevent recurrence

• Preventive vaccines
  – Not yet widely tested
  – Given in the setting of premalignant disease to prevent progression to cancer
  – Expected to be eventually given to individuals at increased cancer risk