The ABCs of Chemoprevention

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Division of Cancer Prevention, CADRG, NCI, NIH, DHHS
Overview of Chemoprevention in DCP

I. Cancer chemoprevention
   - Cancer
   - Carcinogenesis process
   - Drugs and the carcinogenesis process
   - Biomarkers
   - How biomarkers relate to clinical endpoints

II. Chemoprevention clinical trial design
   - Phases of clinical chemoprevention trials
   - Our NCI / DCP Phase I/II Consortium trials
Chemoprevention clinical trial design

Agents

Endpoints: Clinical Biomarkers

Cohorts
I. Cancer Chemoprevention

Agents
I. Cancer Chemoprevention

Definition(s)

cancer chemoprevention =
---the use of **Agents** to inhibit, delay or reverse carcinogenesis

---a new **pharmacological** approach to the prevention of cancer, especially during the period of ...**premalignancy/precancer**...

---the use of **natural, synthetic or biological chemical agents** to reverse, suppress or prevent either the **initial phase of carcinogenesis** or the progression of neoplastic cells to cancer
Cancer Chemoprevention

Definition

cancer chemoprevention

--- the use of agents to inhibit, delay or reverse carcinogenesis

--- a new pharmacological approach to the prevention of cancer, especially during the period of premalignancy/precancer...

--- the use of natural, synthetic or biological chemical agents to reverse, suppress or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer

Distinguish pharmacological from other approaches, e.g. stop bad things like tobacco, asbestos; eat a better diet, etc.

Kelloff 1999
Sporn 1976, Kelloff 2006
William, Lippman 2009

Agents
Cancer Chemoprevention Definition

cancer chemoprevention =

---the use of agents to inhibit, delay or reverse carcinogenesis

---a new pharmacological approach to the prevention of cancer, especially during the period of ... premalignancy/precancer...

---the use of natural, synthetic or biological chemical agents to reverse, suppress or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer

Kelloff 1999
Sporn 1976, Kelloff 2006
William, Lippman 2009
Carcinogenesis

What is cancer?
What is carcinogenesis?

Why does carcinogenesis make chemoprevention possible?
gene = piece of DNA, inherited

The DNA Double Helix

How does DNA fit into the picture?

What is cancer?
What is carcinogenesis?
“cancer is a ‘genetic’ disease”

“normal” DNA sequence

Adenine (A) Cytosine (C)
Thymine (T) Guanine (G)
What is cancer?
What is carcinogenesis?
“cancer is a ‘genetic’ disease”

How does DNA fit into the picture?

*gene* = piece of DNA, inherited

The DNA Double Helix

“non-normal” DNA sequence
↓
“mutation”

- Adenine (A)
- Cytosine (C)
- Thymine (T)
- Guanine (G)
What is Cancer?
Cancer Arises From Somatic Mutations in Genes

Non-inherited mutations

\textit{somatic genetics} = \textit{passed on cell to cell}

- In only one cell or organ
- \textbf{Not} in eggs or sperm
- \textbf{Not} inherited from parent to child
2 types of genetics

- Somatic tissue
  - Mutant sector
  - Normal progeny

- Germinal tissue
  - Mutant sector
  - Normal progeny
  - Mutant progeny

Cancer

Somatic

Germline

W. H. Freeman
What is Carcinogenesis?

Premalignant Progression to Cancer

<table>
<thead>
<tr>
<th>Normal</th>
<th>Initiated</th>
<th>Precancer/Premalignancy</th>
<th>Cancer</th>
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</table>

- Breast
  - Atypical Hyperplasia: 14 - 18 yrs
- Cervix
  - CIN I: 9 - 13 yrs
- Colon
  - Adenoma: 5 - 15 yrs
- Prostate
  - PIN: ≥10 yrs

Genetic changes cumulative
Why does carcinogenesis make chemoprevention possible?

- The process of malignant transformation can take years

<table>
<thead>
<tr>
<th>Premalignant Progression to Cancer: Definitions of Types of Biomarkers</th>
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<tr>
<td>Normal</td>
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<tr>
<td>Premalignancy</td>
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</tbody>
</table>
Drugs and the Carcinogenesis Process: Chemoprevention

- Chemoprevention uses pharmacological agents to delay, arrest or reverse carcinogenesis at its earliest stages:
  - the initial phase of carcinogenesis or
  - the progression of neoplastic cells to cancer


Neoplasm is an abnormal growth of tissue, and, when it also forms a mass, is commonly referred to as a tumor.
What is Carcinogenesis?

Premalignant Progression to Cancer

Breast
- Atypical Hyperplasia (14-18 yrs)
- DCIS (6-10 yrs)

Cervix
- CIN I (9-13 yrs)
- CIN III/CIS (10-20 yrs)

Colon
- Adenoma (5-15 yrs)
- Latent Carc. (3-15 yrs)

Prostate
- PIN (≥10 yrs)
- Clin. Carc.

Genetic changes cumulative

Baseline membrane/boundary
Drugs and the Carcinogenesis Process: Chemoprevention

Chemoprevention uses pharmacological agents to delay, arrest or reverse carcinogenesis at its earliest stages:

- the initial phase of carcinogenesis
- the progression of neoplastic cells to cancer


Neoplasm is an abnormal growth of tissue, and, when it also forms a mass, is commonly referred to as a tumor.
Drugs and the Carcinogenesis Process

Premalignant Progression to Cancer

Agents

Chemo-prevention Agent

Normal
Initiated
Precancer/Premalignancy
Cancer

Breast
Cervix
Colon
Prostate

Atypical Hyperplasia
CIN I
CIN III/CIS
Adenoma
PIN
DCIS
Latent Carc.
Clin. Carc.

Genetic changes cumulative

Atypical Hyperplasia
14 - 18 yrs
Moderate
Severe
CIS

CIN I
9 - 13 yrs

Adenoma

PIN
≥10 yrs

DCIS
6 - 10 yrs

CIN III/CIS
10 - 20 yrs

Latent Carc.
3 - 5 yrs

Clin. Carc.

5 - 20 yrs

20 yrs
Premalignant Progression to Cancer

Atypical Hyperplasia
14 - 18 yrs

DCIS
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CIN I
9 - 13 yrs

CIN III/CIS
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Adenoma
5 - 15 yrs

≥10 yrs

Latent Carc.
3 - 5 yrs

Clin. Carc.

Agents

Halt or obliterate

Genetic changes cumulative
Drugs and the Carcinogenesis Process

Premalignant Progression to Cancer

intervention

slow down!

Genetic changes cumulative

Agents

Breast
Cervix
Colon
Prostate

Normal
Initiated
Precancer
Cancer

Atypical Hyperplasia
CIN I
CIN III/CIS
Adenoma
PIN

14 - 18 yrs
9 - 13 yrs
6 - 10 yrs
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≥10 yrs
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Latent Carc.
Clin. Carc.

5 - 20 yrs
20 yrs

Drug and the Carcinogenesis Process Agents

Genetic changes cumulative
Drugs and the Carcinogenesis Process

Premalignant Progression to Cancer

Agents

Genetic changes cumulative

Breast
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Prostate
- PIN
- Clin. Carc.
- ≥10 yrs

 intervened

介入
Carcinogenesis: A Double-Edge Sword

- **Bad news:**
  transformation of normal cells to invasive cancer

- **Good news:**
  slow transformation process allows for the possibility of intervention
II. Chemoprevention clinical trial design

Agents

Endpoints: Clinical Biomarkers

Cohorts
II. Chemoprevention clinical trial design

Endpoints:
- Clinical
- Biomarkers
Biomarkers: Definition

Biomarkers =

physical entities or images or manifestations of these entities that can be

- measured and
- used to indicate a biological process, disease process, or drug response
- (that reflect a “characteristic” of a tissue)

Endpoints: Clinical Biomarkers
Biomarkers and How Biomarkers Relate to Clinical Endpoints

Biomarkers = physical entities or images of these entities that are derived from the carcinogenesis pathway.
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Allows intervention to prevent invasive cancer

Sets up stages for obtaining biomarkers

Endpoints: Clinical Biomarkers
Biomarkers: Applications in Cancer Prevention

Biomarkers of Risk of Cancer
Biomarkers for
Detection of Pre-malignant lesions
Early Detection (invasive cancer)
Diagnosis
Prognosis
Prediction of Response to Treatment

Surrogate Endpoint Biomarkers
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Endpoints:
- **Biomarkers**
- **Clinical**

Genetic changes cumulative

**Breast**
- Atypical Hyperplasia
  - 14-18 yrs
  - DCIS
  - 6-10 yrs

**Cervix**
- CIN I
  - 9-13 yrs
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**Colon**
- Adenoma
  - ≥ 10 yrs
  - Latent Carcinoma
  - 3 yrs

**Prostate**
- PIN
  - ≥ 10 yrs
  - Latent Carcinoma
  - 3 yrs

**Normal**

**Initiated**

**Mild**

**Moderate**

**Severe**

**CIS**

**Cancer**
How Biomarkers Relate to Clinical Endpoints

Different Physical Types of Biomarkers: Genetic/Epigenetic Changes vs Histologic Changes

Prostate
- AR, SRD5A2, CYP17, GSTP1 Polymorphisms
- Genetic Susceptibility to Infection
- Histologic biomarkers

Colon
- APC, BCL-2, c-MYC
- Histologic biomarkers

Breast
- E2 Metabolism, Cyt P450, ER, PR, DNA Repair
- DNA Adducts, Genomic Instability, Thrombospondin

Lung
- 3p, 9p, 13q, 15p, 18p
- Histologic biomarkers

Head & Neck
- 3p, 9p, 1p53, FHIT, p16, p19
- Histologic biomarkers

Esophagus
- p16, p53, IDNA Content
- Histologic biomarkers

Liver
- HBV, HCV, Carcinogen/DNA Adducts
- Histologic biomarkers

Molecular biomarkers

Histologic biomarkers

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Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Endpoints:
- Biomarkers

Any biomarker prior to transformation to actual cancer can be used as a “Risk Biomarker” => Risk of transforming into cancer
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Endpoints: Clinical Biomarkers

Early detection of cancer Biomarker- Screening (mammography -image)
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Normal → Initiated → Mild → Moderate → Severe → CIS → Cancer

Risk biomarker

“Early detection” of pre-cancer Biomarkers - screening (mammography - DCIS)

Endpoints: Clinical Biomarkers
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Normal → Initiated → Mild → Moderate → Severe → CIS → Cancer

Risk biomarker

“Early detection” of pre-cancer biomarker

Biopsy:
- Surrogate Endpoint Biomarker

Endpoints: Clinical Biomarkers
Premalignant Progression to Cancer

Baseline Biopsy: Surrogate Endpoint Biomarker

Post-treatment biopsy: OBLITERATE pre-malignant lesion or REVERSE/ MODULATE it to earlier stage

“Early detection” of pre-cancer biomarker

Endpoints: Clinical Biomarkers

Agents

Risk biomarker

Chemo-prevention Agent

Mild

Moderate

Severe

CIS

Cancer
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Normal Initiated
Mild
Moderate
Severe
CIS
Cancer

Baseline Biopsy: Surrogate Endpoint Biomarker
Intermediate Endpoint Biomarker

Premalignant Progression to Cancer

Risk biomarker
Chemo-prevention Agent
Risk biomarker

Early detection of cancer biomarker

post-treatment biopsy: OBLITERATE pre-malignant lesion or REVERSE/ MODULATE it to earlier stage
All kinds of Biomarkers based on the Carcinogenesis pathway

Endpoints:
- Biomarkers
- Clinical Biomarkers

Risk Biomarker

"Early detection" of Pre-cancer Biomarker

Early detection of Cancer Biomarker

Biopsy:
Surrogate Endpoint Biomarker (SEB)

Post-treatment:
Obliterate pre-malignant lesion or Modulate SEB: back toward earlier lesion

Diagnostic Biomarker (follow-up symptoms); Prognostic and Predictive Biomarker

Dunn 2010 Sem Onc
Biomarkers: Applications in Cancer Prevention

Biomarkers of Risk

Biomarkers for Detection of Pre-malignant lesions
Early Detection (invasive cancer)
Diagnosis
Prognosis
Prediction of Response to Treatment

Surrogate Endpoint Biomarkers
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Biomarkers: Applications in Cancer Prevention

Biomarkers of Risk
Biomarkers for
- Detection of Pre-malignant lesions
- Early Detection (invasive cancer)
- Diagnosis
- Prognosis
- Prediction of Response to Treatment

Surrogate Endpoint Biomarkers (SEBs):

SEBs are “surrogates” for the real thing:
Clinical Endpoints =

We hope that the chemopreventive agent modulates the SEBs in the same direction as the clinical endpoint (usually cancer occurrence/ incidence)
Surrogate Endpoint Biomarkers

How biomarkers relate to clinical endpoints

Clinical endpoint: Reduction in cancer

post-treatment biopsy: OBLITERATE pre-malignant lesion or REVERSE/ MODULATE it to earlier stage

Baseline Biopsy: Surrogate Endpoint Biomarker

Early detection of cancer biomarker

Endpoints: Clinical Biomarkers
Surrogate Endpoint Biomarkers are critical to “early phase” (phase I, II) chemoprevention trial design......

...like the Consortium trials
## Chemoprevention Clinical Trial Design

### Clinical trial phases

#### chemoprevention vs. chemotherapy

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<th>Chemoprevention</th>
<th>Chemotherapy</th>
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<td><strong>Phase I</strong></td>
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<tr>
<td>Healthy volunteer cohort</td>
<td>End stage disease cohort</td>
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<tr>
<td>Dose finding</td>
<td>Dose finding</td>
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<tr>
<td>Safety and toxicity</td>
<td>Safety and toxicity</td>
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<tr>
<td><strong>Phase II</strong></td>
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<tr>
<td>High risk/pre-surg cohort</td>
<td>Disease specific cohort</td>
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<tr>
<td>Agent v. placebo or standard of care</td>
<td>Agent v placebo or standard of care</td>
</tr>
<tr>
<td>Biomarker modulation</td>
<td>Efficacy and toxicity</td>
</tr>
<tr>
<td>Efficacy: 1-arm, multi-arm</td>
<td><strong>Phase III</strong></td>
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<tr>
<td><strong>Phase III</strong></td>
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<td>High risk cohort</td>
<td>Disease specific cohort</td>
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<tr>
<td>Definitive efficacy</td>
<td>Definitive efficacy</td>
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<tr>
<td>Cancer incidence endpoint</td>
<td>Cancer regression, control, palliation endpoint</td>
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<tr>
<td>Randomized controlled trials (RCTs)</td>
<td>RCTs</td>
</tr>
<tr>
<td>Clinical trial phases</td>
<td>Chemoprevention</td>
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<tr>
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</table>
| **Phase I**           | Healthy volunteer cohort  
  - Dose finding  
  - Safety and toxicity |
| **Phase II**          | High risk/pre-surg cohort  
  - Agent vs. placebo or standard of care  
  - Biomarker modulation  
  - Efficacy and toxicity |
| **Phase III**         | High risk cohort  
  - Definitive efficacy  
  - Cancer incidence endpoint  
  - Randomized controlled trials (RCTs) |
| **Phase I**           | End stage disease cohort  
  - Dose finding  
  - Safety and toxicity |
| **Phase II**          | Disease specific cohort  
  - Agent vs placebo or standard of care  
  - Efficacy and toxicity |
| **Phase III**         | Disease specific cohort  
  - Definitive efficacy  
  - Cancer regression, control, palliation endpoint  
  - RCTs |
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<th>Cohort</th>
<th>Chemoprevention</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>Healthy volunteer</td>
<td>Healthy volunteer</td>
<td>Cancer patient</td>
</tr>
<tr>
<td>High-risk</td>
<td>High-risk</td>
<td>Clinical endpoint</td>
</tr>
<tr>
<td>Pre-surgical - localized cancer</td>
<td>Pre-surgical - localized cancer</td>
<td>Cancer regression</td>
</tr>
<tr>
<td>Premalignant lesion</td>
<td>Premalignant lesion</td>
<td>Cancer control/palliate</td>
</tr>
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<th>End-Point (Biomarkers)</th>
<th>Chemoprevention</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>Biomarker modulation</td>
<td>Biomarker modulation</td>
<td>Moderate toxicity</td>
</tr>
<tr>
<td>- Apoptosis</td>
<td>- Apoptosis</td>
<td>- Relatively short term</td>
</tr>
<tr>
<td>- Angiogenesis</td>
<td>- Angiogenesis</td>
<td>- Oral or topical</td>
</tr>
<tr>
<td>- Proliferation</td>
<td>- Proliferation</td>
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<tr>
<td>- Tumor supressor genes</td>
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<tr>
<td>- Cancer incidence (phase 3)</td>
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<tr>
<th>Agent</th>
<th>Chemoprevention</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>Minimal toxicity</td>
<td>Minimal toxicity</td>
<td>Oral or topical</td>
</tr>
<tr>
<td>Potentially long term</td>
<td>Potentially long term</td>
<td>Topical</td>
</tr>
<tr>
<td>Oral or topical</td>
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Chemoprevention clinical trial design

Agents

Endpoints: Clinical Biomarker

Cohorts
Agents for prevention

Where do the ideas come from?

- Epidemiologic evidence
- Pre-clinical evidence
  - Cell culture experiments
  - Animal models
- Mechanistic evidence
- Known, approved drugs - toxicity is already known...(repurposing)
Toxicity

--- a perennial issue in chemoprevention trials!
Therapeutic Index

Benifit vs Risk

efficacy vs toxicity
Example: Nonsteroidal Anti-inflammatory Drugs (NSAI Ds-aspirin, naproxen, celecoxib)

Scientific evidence and drug development

- **Rationale for NSAI Ds in cancer prevention:**
  - NSAI Ds target inflammation
  - association between inflammation and cancer
  - epidemiology studies suggest lower incidence of certain cancers with use of NSAI Ds
  - animal data support use of NSAI Ds
  - **Cardiovascular side effects in all NSAI Ds (esp. COX2 inhibitors)**
ABCs of Chemoprevention Clinical Trial Design

Cohorts
Endpoints:

- Clinical
  - cancer incidence
  - mortality
  - morbidity
- Biomarker

ABCs of Chemoprevention Clinical Trial Design
Cohorts at Risk for Cancer

- **Exogenous exposures**
  - Lifestyle choices

- **Endogenous susceptibility**
  - Family history/ age/ race
  - Genetic predisposition
  - Personal history of cancer
  - Personal history of pre-cancer
  - Physiologic features
    - Early menarche
    - Late menopause
    - nulliparity
  - Risk biomarker (ADH, DCI S)

- Tobacco
- Diet
- Physical activity
- Occupational exposures
- Estrogen exposure (HRT) in breast cancer

- BRCA1/2, HNPCC, FAP mutation
- Estrogen exposure in breast cancer
Biomarkers: How Biomarkers Relate to Clinical Endpoints

Premalignant Progression to Cancer

Any biomarker prior to transformation to actual cancer can be used as a “Risk Biomarker”
II. Chemoprevention Clinical Trial Design
Clinical Trial Design: Window-of-Opportunity Trial/Window Trial

Examples: breast cancer, prostate cancer

**Biopsy** (prompted by screening: imaging-mammo; lab test-PSA) → **Biopsy-based: Diagnosis** → **Definitive surgical resection of “diagnosed” cancer or pre-cancer**

*This is the “window-of-opportunity” to give Chemoprevention Agent (~neoadjuvant therapy in treatment context)*

_surgery planned few weeks-months_
Clinical Trial Design: Window-of-Opportunity Trial/Window Trial

Examples: breast cancer, prostate cancer

Biopsy (prompted by screening: imaging-mammo; lab test-PSA) → Biopsy-based: Diagnosis → Definitive surgical resection of “diagnosed” cancer or pre-cancer

Endpoints:
- Biomarkers
- Clinical Biomarkers
- OBLITERATE pre-malignant lesion or REVERSE/MODULATE it to earlier stage

Baseline Biopsy: Surrogate Endpoint Biomarker ~ Intermediate Endpoint Biomarker

Post-treatment Biopsy: Chemoprevention Agent
Example: Metformin trial in prostate cancer prevention
Scientific evidence and drug development

“repurposing” metformin – ~based on epidemiologic evidence
Cancer Prevention Clinical Window-of-Opportunity Trial/
Window Trial Design: ABCs

Cohort: Organ confined PCa scheduled for prostate resection (RP)

TIME
Cohort: Organ confined PCa scheduled for RP

Pre-Surgical Model
- Participants have cancer
- Short duration of drug exposure
- Access to tissue for analysis
- Specimen comparison before/after treatment
- Specimen comparison participant to participant

Cohorts

Agents

Cancer Prevention Clinical Window-of-Opportunity Trial/Window Trial Design: ABCs
Cohort: Organ confined PCa scheduled for RP

Informed consent elements:
- Research purpose/ duration
- Participant expectations
- Potential risks/ benefits
- Alternatives to participation
- Confidentiality of records
Cohort: Organ confined PCa scheduled for RP

Informed Consent

Baseline Data & Specimens

Prostate biopsy

Endpoints: Clinical Biomarkers

Cancer Prevention Clinical Window-of-Opportunity Trial/Window Trial Design: ABCs
Cohort: Organ confined PCa scheduled for RP

Baseline Data & Specimens

Lab Analysis: Ki-67, CD34, p-AMPK, etc.

Endpoints: Clinical Biomarkers

Prostate biopsy

Informed Consent

Cancer Prevention Clinical Window-of-Opportunity Trial/Window Trial Design: ABCs
Cohort: Organ confined PCa scheduled for RP

Informed Consent
Baseline Data & Specimens

Prostate biopsy

Cohorts

Phase II trial
Metformin v placebo

Intervention
Agents

Endpoints: Clinical Biomarkers

Lab Analysis: Ki-67, CD34, p-AMPK, etc.
Cohort: Organ confined PCa scheduled for RP

Informed Consent
Baseline Data & Specimens

Lab Analysis: Ki-67, CD34, p-AMPK, etc.

Intervention

4-12 weeks

Metformin v placebo

Agents

Cohorts

Prostate biopsy

Cohort: Organ confined PCa scheduled for RP

Radical prostatectomy

Closeout Data & RP Specimen

Endpoints: Clinical Biomarkers

Endpoints: Clinical Biomarkers

Lab Analysis: Ki-67, CD34, p-AMPK, etc.

Cohorts

Cohorts

Cohorts

Cohorts
Cohort: Organ confined PCa scheduled for RP

Baseline Data & Specimens

Lab Analysis: Ki-67, CD34, p-AMPK, etc.

Statistical analysis

Intervention

Agents

Compare Before v After

Surrogate endpoint biomarkers: indicators of drug effect

Endpoints: Clinical Biomarkers

Closeout Data & Specimens

Informed Consent
Cohort: Organ confined PCa scheduled for RP

Informed Consent

Baseline Data & Specimens

Intervention

Surrogate endpoint biomarkers: indicators of drug effect

Compare

Lab Analysis: Ki-67, CD34, p-AMPK, etc.

Closeout Data & Specimens

BIOMARKER of risk

Phase 2 Trial: this is the primary endpoint

Cancer Prevention Clinical Window-of-Opportunity Trial/Window Trial Design: ABCs
Cancer Prevention Clinical Window-of-Opportunity Trial/Window Trial Design: ABCs

This is what we publish: (often change in Ki-67) change in a Surrogate Endpoint Biomarker

Phase 2 Trial: this is the primary endpoint

Intervention

Surrogate endpoint biomarkers: indicators of drug effect

Compare

Lab Analysis: Ki-67, CD34, p-AMPK, etc.

Closeout Data & Specimens
Chemoprevention Clinical Trial Design

- The hope/expectation is that a validated Surrogate Endpoint Biomarker - one that really reflects what is going on in the tissue regarding cancer - will be modulated in the right direction and suggest that the Agent is truly chemopreventive.

- This would lead us to a phase III trial with that Agent.
FIN