

Breakout 5

Current clinical evidence for targeting inflammation to prevent cancer

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Challenges to Making Cancer Prevention a Clinical Reality

- Who are the people at greatest risk? (cohort selection)
- Appropriate agent selection (target identification)
- What are the best endpoints (phase II vs. phase III)?
- How to incorporate the temporal changes during carcinogenesis and inflammation into clinical trials that are relatively short

Challenges – Part 2

- **Heterogeneity**
 - Cancer - **not one disease** (even in the same target organ)
 - **Cohort heterogeneity** - pharmacogenetics, different stages of carcinogenesis, gene-environment interactions
 - **Heterogeneity of the inflammatory response** (in different cancers, during carcinogenesis, in different cohorts)
- **Incomplete understanding of molecular pathogenesis, including inflammatory response**

**Can cancer chemoprevention
be targeted?**

Aspirin and the Risk of Colorectal Cancer in Relation to the Expression of COX-2

Andrew Chan et al NEJM 2007

Regular use of aspirin appears to reduce the risk of colorectal cancers that over-express COX-2 but not the risk of colorectal cancers with weak or absent expression of COX-2.

Accompanying editorial: **Aspirin and Colon Cancer — Targeting Prevention?** Sanford Markowitz

Can targeting specific groups at risk for cancer facilitate targeted prevention in lung cancer?

Pre-clinical

Clinical

Analysis of pre-invasive lesions

Model early disease
Identify pathways
Analyze mechanisms



Validation of
pathways and
mechanisms

Biomarker discovery

“Filter” proteomic & genomic
changes; develop targets for
endpoints



Validation in human
cancer

Analysis of chemopreventive agents

Test novel agents
Test combinations
Analysis of mechanisms



Clinical trials

Epithelial cells

HBEC controls

-p53

-Kras

-EGFR

-EMT induced

Agents examples

to be tested

PPAR γ ligands

Erlotinib

NSAIDs

Statins

Cannabinoid agonists

Steroids

Resveratrol

Libraries

Outcomes

Phenotype 2D / 3D

Protein profiles

Gene expression

microRNA

Murine models

w the same

mutations

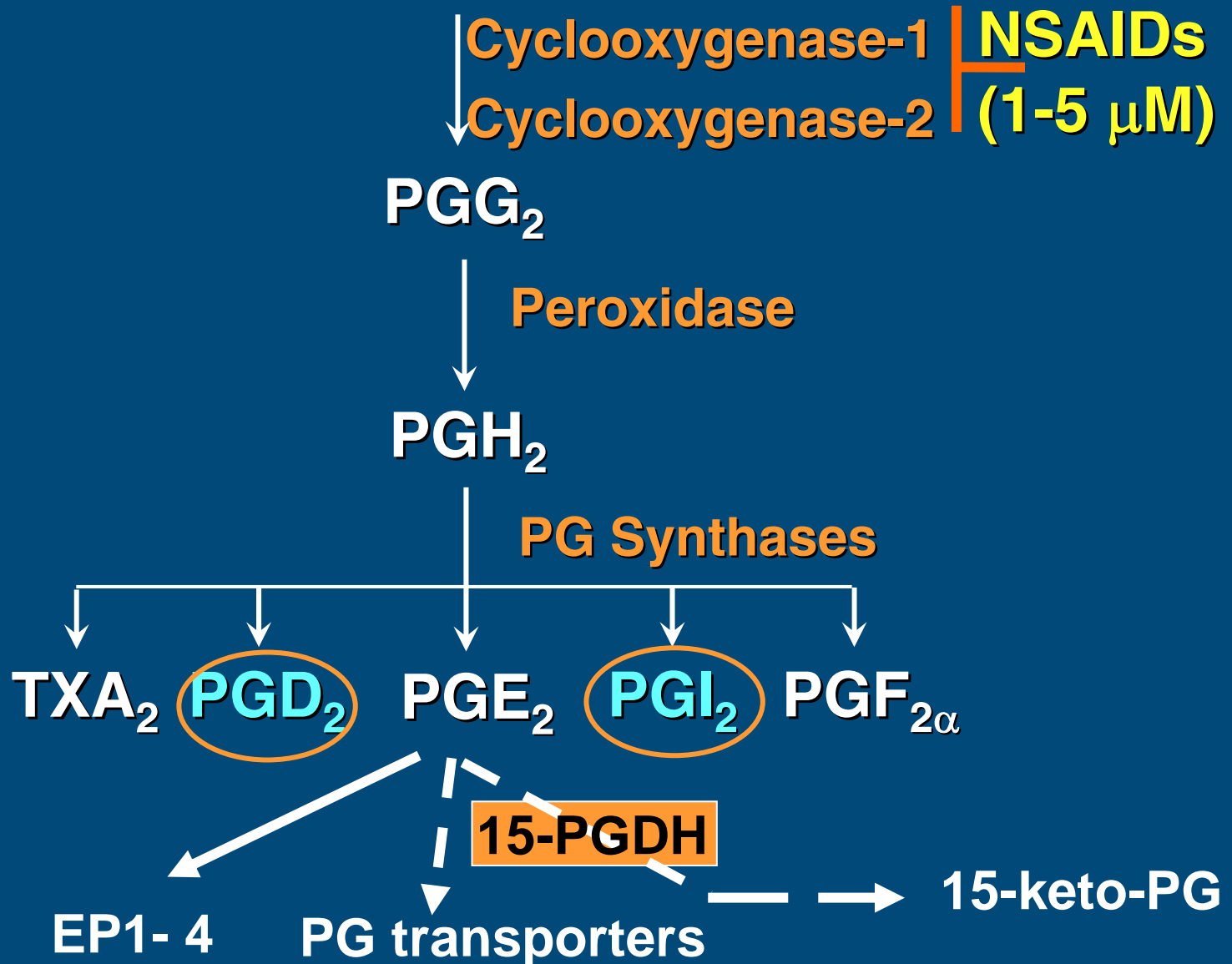
Monitoring
of trials

Clinical trials

Cancer Chemoprevention

- **Trials with a cancer endpoint are long and expensive**
- **Previous trials suffered from inadequate pre-clinical evaluation**
- **Many additional agents are worthy of evaluation**
- **A different strategy is required to:**
 - **Maximize knowledge gained from each trial, including inflammatory endpoints**

Arachidonic Acid



Research Questions

- **Contribution of deregulated inflammation to cancer risk**
- **What are the key inflammatory pathways during early carcinogenesis?**
 - **Balance between pro- and anti-tumorigenic pathways**
- **What is the interplay between epithelial cells and inflammatory pathways?**
- **examples: p53/NFkb and inflammation/EMT**

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