Strategies for Prevention of HCC

Molecular Epidemiology

- Identify risk factors and outcome
- Biomarkers
  - Carcinogen-macromolecular adducts
  - Normal DNA sequence variants
  - Mutations in target genes
- Measure in urine, serum or tissue
  - Immunoassays
  - GC/MS, LC/MS
  - Florescence spectometry

HCC Epidemiology

- Annual new cases ~600,000
- ~600,000 annual deaths
  - 80% burden in Asia and sub-saharan Africa
  - 300,000+ cases in People's Republic of China
- High risk areas early age of onset 20's
- Low risk areas early age of onset 50's

HCC Epidemiology

- Main causes in high risk areas
  - HBV infection
  - Aflatoxins in diet
- Synergism leading to increased risk

Impact on HCC incidence

HBV vaccination

aflatoxin exposure

HCC Epidemiology: Aflatoxin Studies

- Taiwan[1]: BsAg+ males with HCC compared to control subjects
  - OR = 2.8 detectable vs. nondetectable aflatoxin metabolites
  - OR = 5.5 high vs. low urinary metabolite levels
- Shanghai[2]: relative risk for HCC with presence aflatoxin metabolites = 3.8

1. Wang LY et al. Int J Cancer. 1996 Sep 4;67(5):620-5.
2. Ross RK et al. Lancet. 1992 Apr 18;339(8799):943-6.

Aflatoxins

- Produced by fungi
  - 1960 outbreak of "Turkey 'X' disease" in UK
  - *Aspergillus flavus*
- Common in corn, peanuts, fermented soy products

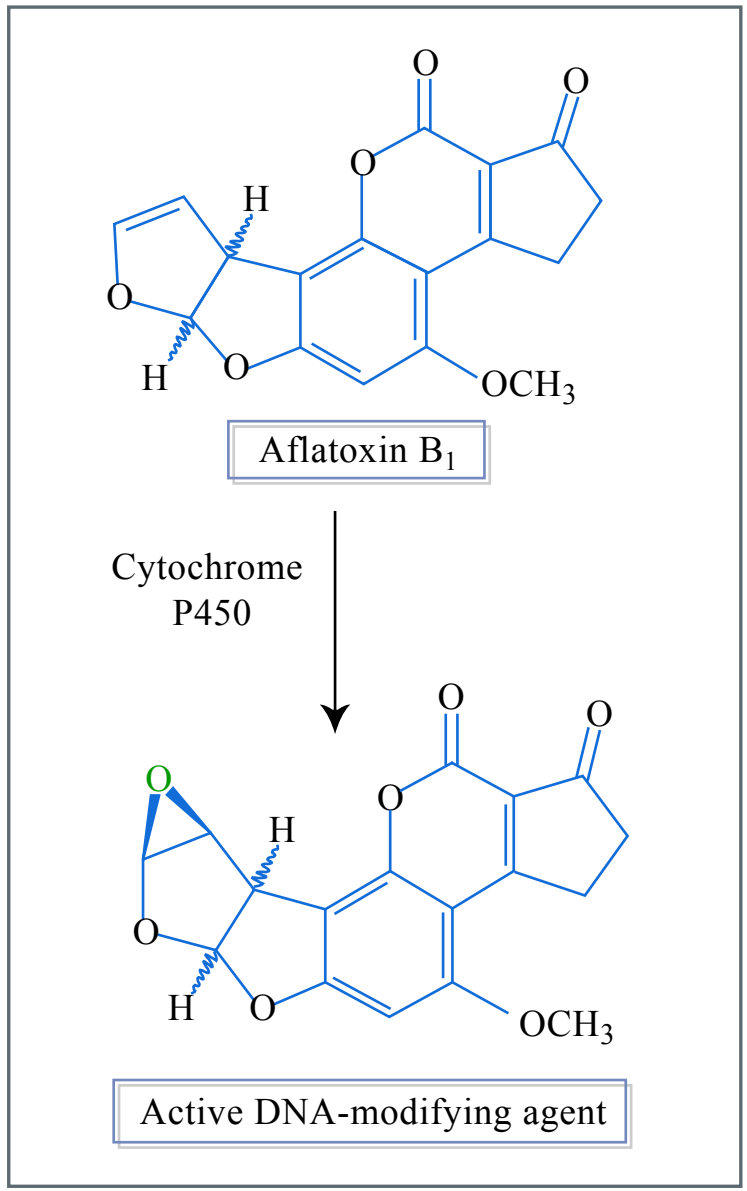


Figure by MIT OCW.

HCC Prevention/Intervention

- Primary
  - Vaccination
  - Reduced contamination
- Secondary
  - Pharmaceuticals
  - Natural products

HCC Prevention/Intervention

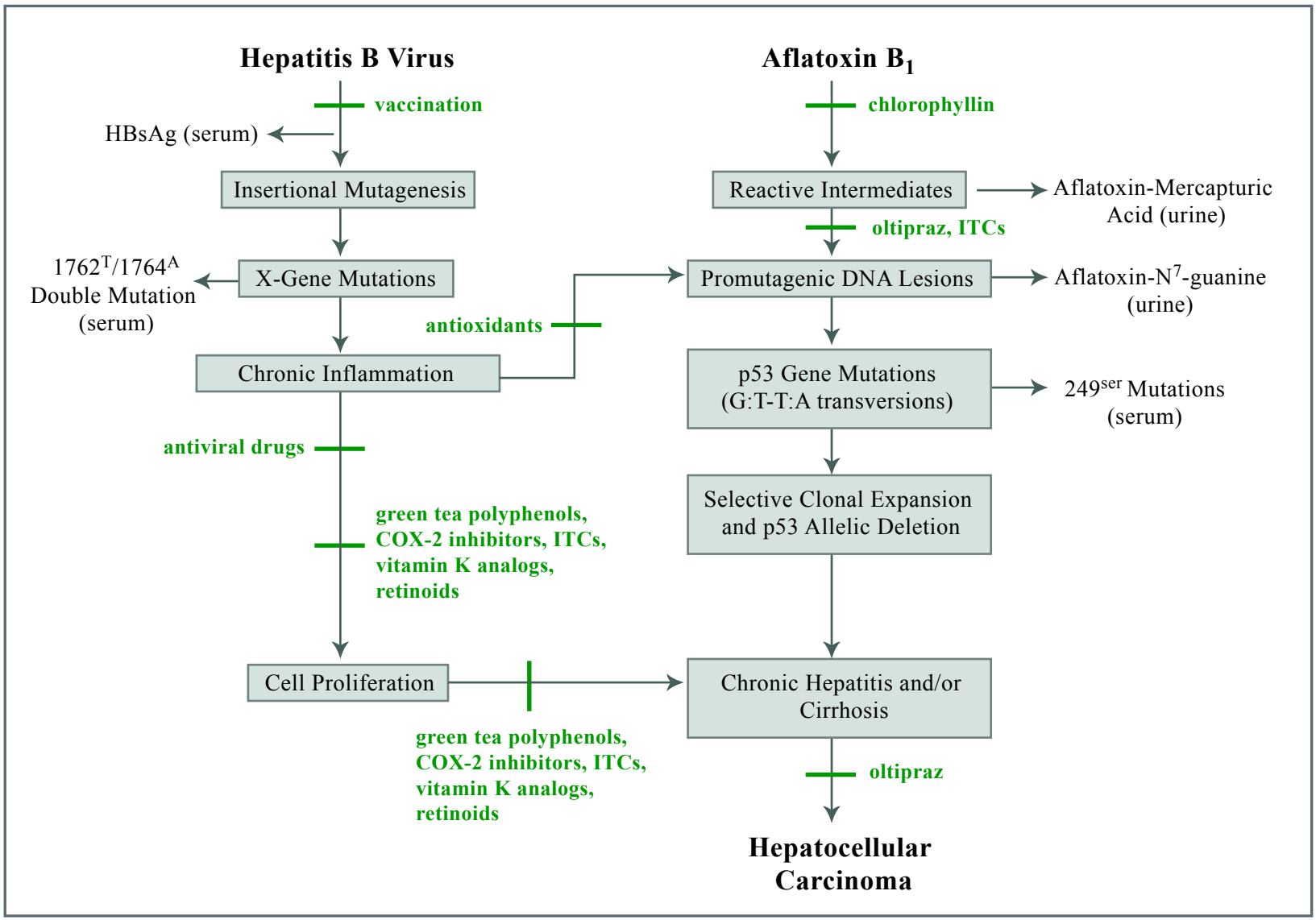


Figure by MIT OCW.

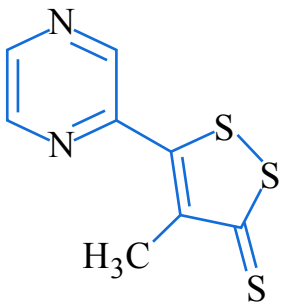
Primary Interventions

- HBV vaccination
  - Taiwan HCC cases in 6-14 year olds
    - Born 1981-1986 = 0.70
    - Born 1986-1990 = 0.57
    - Born 1990-1994 = 0.36
- Reduction of aflatoxins in food

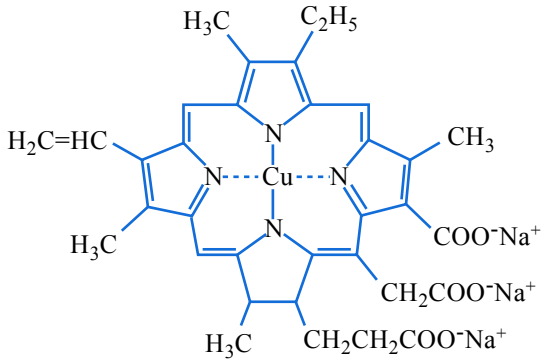
Chang MH et al. N Engl J Med. 1997 Jun 26;336(26):1855-9.

Secondary Intervention

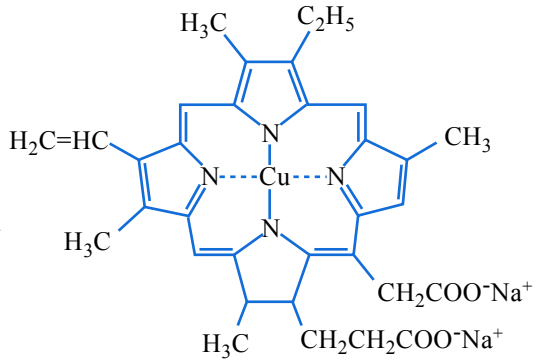
Oltipraz



Chlorophyllin

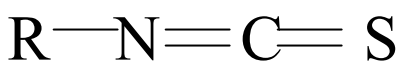


Trisodium Copper Chlorin e_6

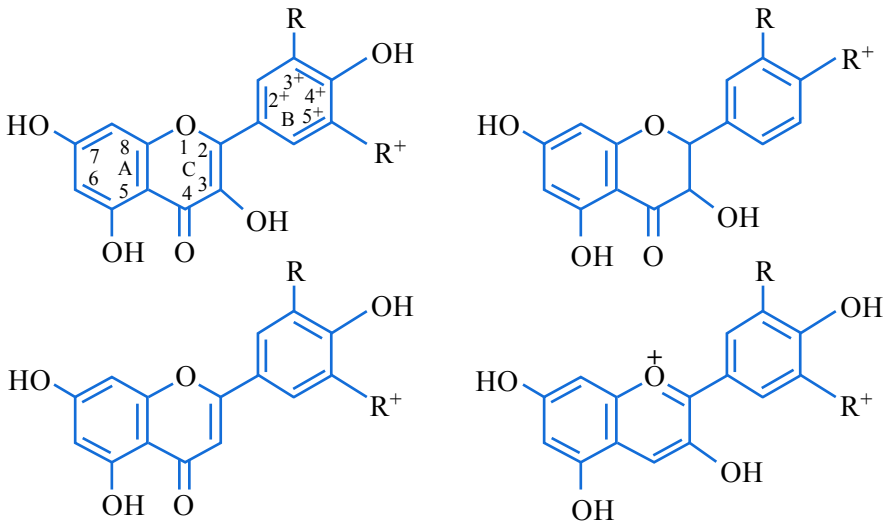


Disodium Copper Chlorin e_4

Isothiocyanates



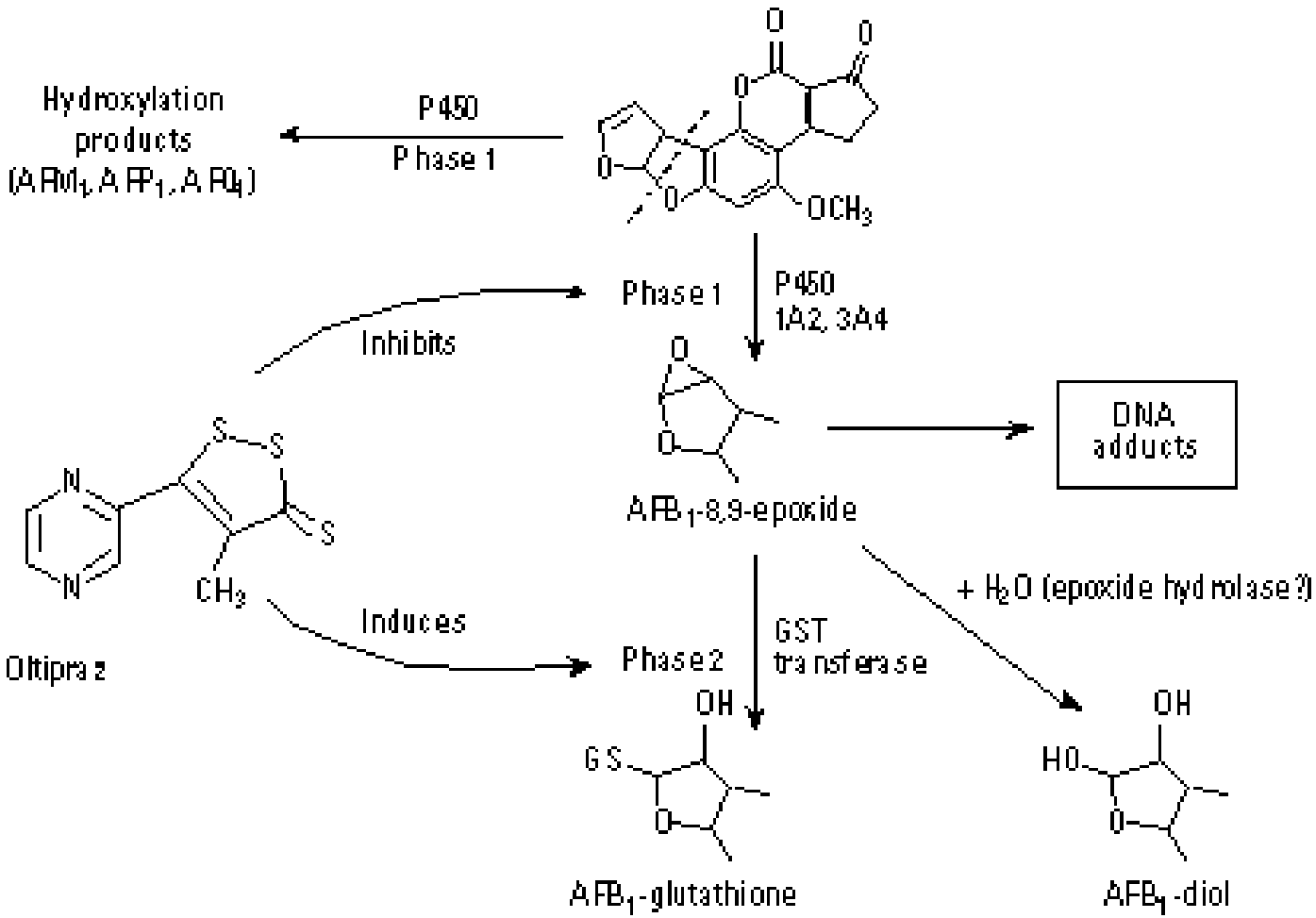
Polyphenols



Secondary Intervention: Oltipraz

- Oltipraz
  - Induces phase 2 enzymes
  - Inhibits phase 1 enzymes
- Higher doses (500mg+) not more effective at induction or inhibition than lower doses (125mg and 250mg)

Mechanism of Oltipraz



Source: Kensler,T. W. "Chemoprevention by inducers of carcinogen detoxication enzymes." *Environmental Health Perspective* 105, Supplement 4 (1997): 965-970. Reproduced with permission from Environmental Health Perspectives.

Secondary Intervention: Oltipraz

- Phase IIa intervention trial
  - Feasibility of biomarker measurements
  - Dose response
  - Tolerance/effectiveness longer term exposure
  - Chronic toxicity

Source: Kensler, T. W., et al. "Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas." *Gastroenterology* 127, no. 5, Supplement 1 (2004): S310-318.

Secondary Intervention: Oltipraz

Location: Dazin Township, Qidong, People's Republic of China

- Randomized, placebo-controlled, double blind
- 240 adults without history of chronic disease
- Detectable serum aflatoxin-albumin adducts
- 3 intervention groups
  1) Placebo
  2) 125mg once daily
  3) 500mg once weekly

Source: Kensler, T. W., et al. "Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas." *Gastroenterology* 127, no. 5, Supplement 1 (2004): S310-318.

Secondary Intervention: Oltipraz

- 500mg weekly after 1 month
  - 51% decrease median levels aflatoxin M_1 excretion
  - No effect on aflatoxin-mercapturic acid
  - Inhibits activation
- 250mg daily after 1 month
  - 2.6-fold increase in median levels of aflatoxin-mercapturic acid
  - Modest effect on aflatoxin M_1 levels
  - Increase phase 2 conjugation

Source: Kensler, T. W., et al. "Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas." *Gastroenterology* 127, no. 5, Supplement 1 (2004): S310-318.

Secondary Intervention: Oltipraz

- Ongoing follow-up phase IIb trial
  - Sustained expression enhancement of aflatoxin detoxification enzymes
  - 250mg versus 500mg once weekly for 1 year
  - Measuring multiple biomarkers for mechanisms of action

Secondary Intervention: Chlorophyllin

- Mixture of sodium-copper salts of chlorophyll
- OTC drug
  - Wound healing accelerant
  - Controls body, fecal and urinary odor
- *In vitro* and *in vivo* antimutagen in short-term genotoxicity assays

Secondary Intervention: Chlorophyllin

- Complexes with aflatoxin B1
- Reduction in bioavailability
- Needs molar excesses to carcinogen for efficacy
- *In vitro* inhibitor of cytochrome P450 enzymes
- Antioxidant-reduction in lipid peroxidation

Secondary Intervention: Chlorophyllin

- Chemoprevention study in Qidong
  - 180 healthy adults
  - 100mg chlorophyllin or placebo 3-times daily for 4 months
  - Endpoint of modulated aflatoxin-*N*7-guanine adducts in urine after 3 months
- Resulted in 55% decrease in median urinary adduct levels

Source: Kensler, T. W., et al. "Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas." *Gastroenterology* 127, no. 5, Supplement 1 (2004): S310-318.

Secondary Intervention: Isothiocynates

Source: Family Cruciferae (mustards), Genus *Brassica* (cauliflower, Brussels sprouts, broccoli, cabbage)

- Lower cancer rates in individuals consuming high levels of yellow and green vegetables
  - Isothiocyanates
  - Particularly glucosinolate precursors
  - Sulforaphane induces phase 2 enzymes in rats (glucoraphanin is precursor)

Secondary Intervention: Polyphenols

Source: Green tea

- Inverse association of consumption versus risk and development of cancer
- Green tea-derived polyphenols (ongoing study)
  - Reduce aflatoxin M_2 excretion
  - Increase aflatoxin-mercapturic acid excretion
  - Reduced 8-oxo-deoxyguanosine

Outlook: Primary Interventions

- HBV vaccination
  - Only benefits younger generations
  - Vertical transmission not prevented
- Reduced food contamination
  - Requires infrastructure for production, processing and distribution
  - Monitoring mycotoxins $$
  - Not feasible in developing countries

Outlook: Pharmaceutical Chemoprevention

- Not practical for populations at highest risk
  - SE Asia, China, Africa
- First-generation (oltipraz) expensive
- 2nd and 3rd generation dithiolethiones
  - Cheaper
  - 10-fold increase in potency over oltipraz
  - Ongoing safety evaluations
- Long-term costs potentially high, chronic treatment

Outlook: Natural Products

- Practical for populations at highest risk
  - SE Asia, China, Africa
- Inexpensive, diet-based
- Long-term compliance better
- Immediate impact

Potential Impact

- Reduction of aflatoxin-N7-guanine
  - Reduced risk HCC in animals
  - Increased latency period
- Decreased aflatoxin exposure in Bejing correlated with later onset of HCC

Image removed due to copyright reasons.

Source: Kensler, T.W., et al. "Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas." *Gastroenterology Review* 127, no. 5, Supplement 1 (2004): S310-318.

Questions?