Emerging Drugs to Treat HNSCC: Sensitization of HNSCC to Cisplatin Through the Use of a Novel Curcumin Analog

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Presenter Disclaimer:

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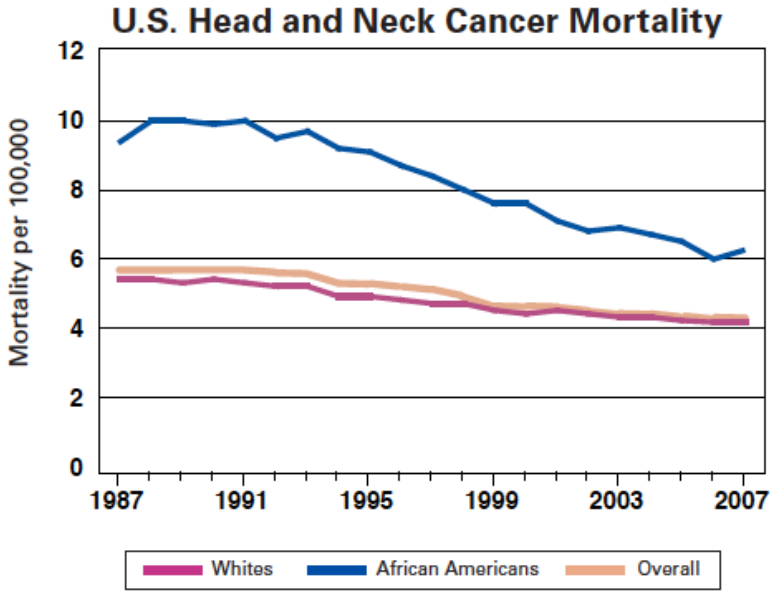
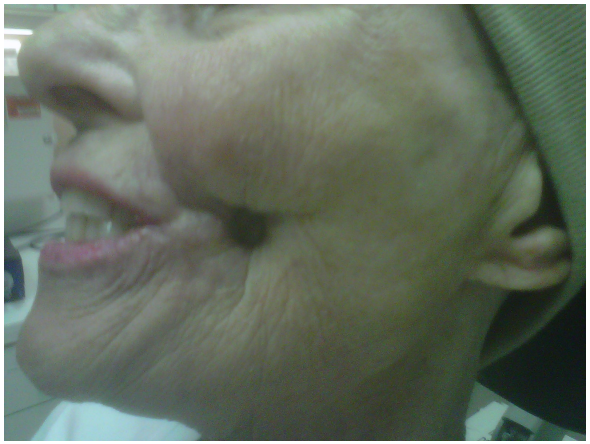
Introduction:
Squamous Cell Carcinoma (SCC)

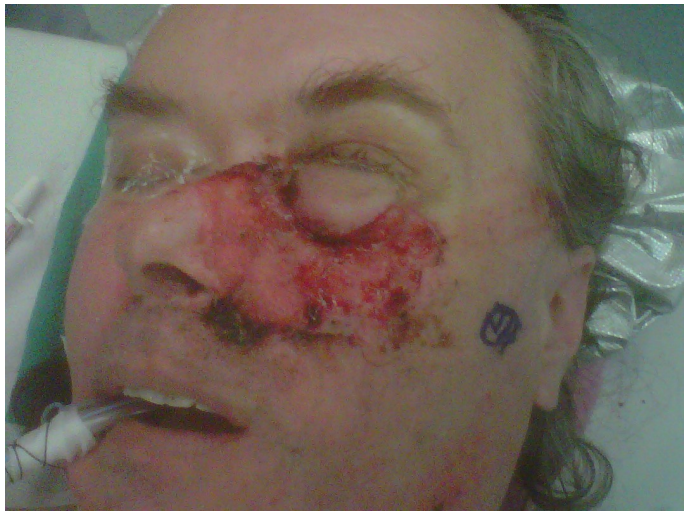
- HNSCC is the 8th leading cause of deaths worldwide, 11000 US deaths
- Despite advances in surgery and chem/XRT→ no improvement in survival in last 4 decades
- Current surgery and chemo/ xrt→ very morbid
- Stagnant overall survival had driven the search for novel therapeutic agents

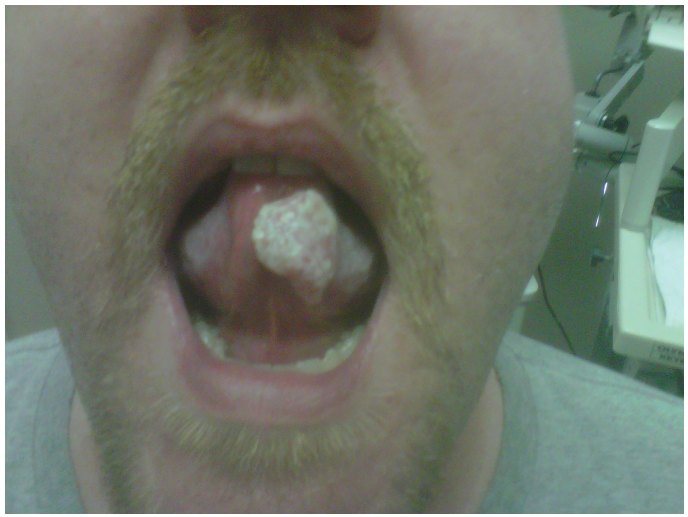




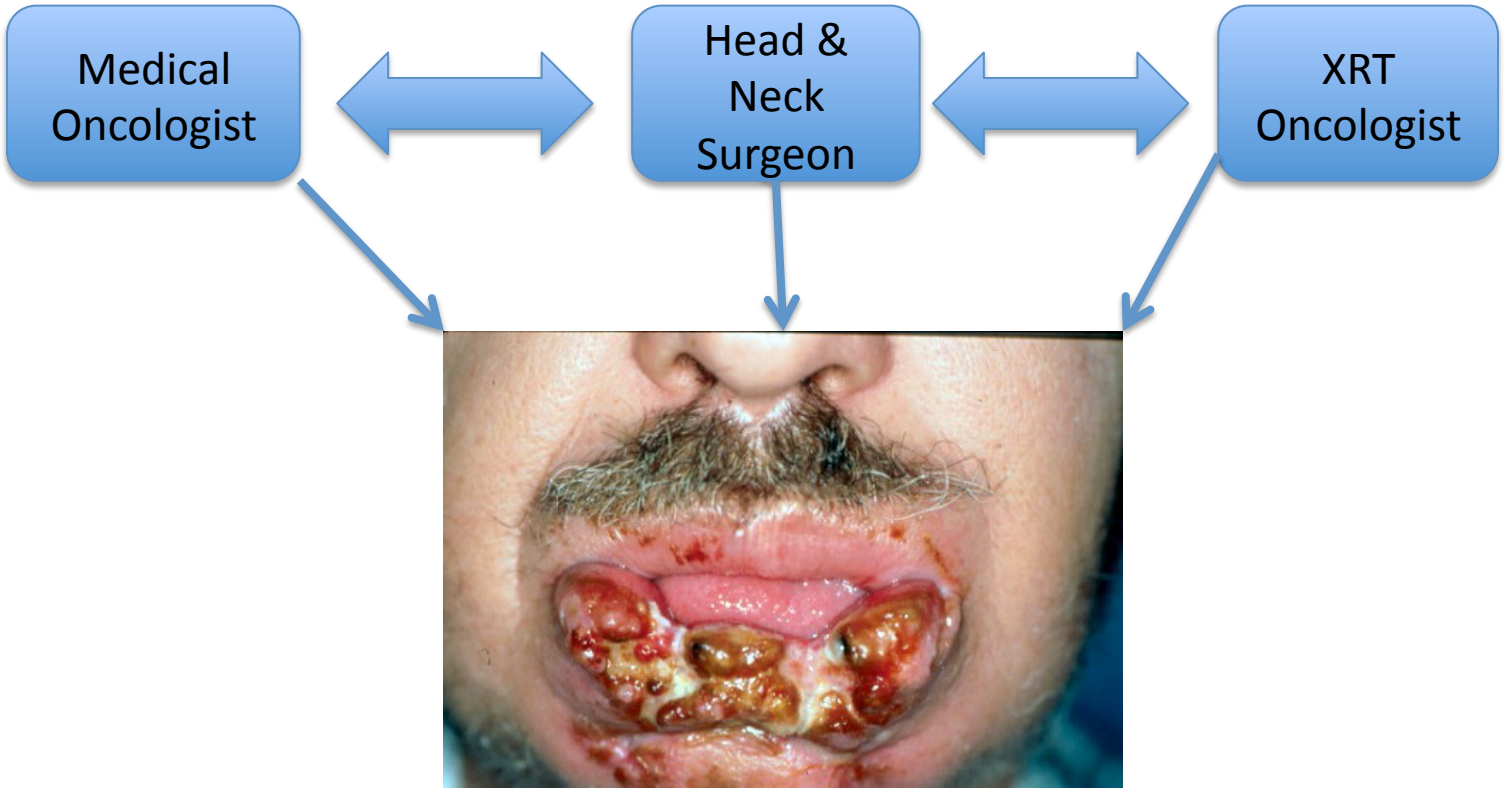
SCC: Two Flavors

- Cutaneous SCC:
  - Sun exposure, immunocompromised, fair skin, red hair, blue eyes
- Upper aerodigestive SCC:
  - Mucosal lining from lips to below vocal cords
  - Tobacco, EtOH, HPV, 5^{th}-6^{th} decade of life

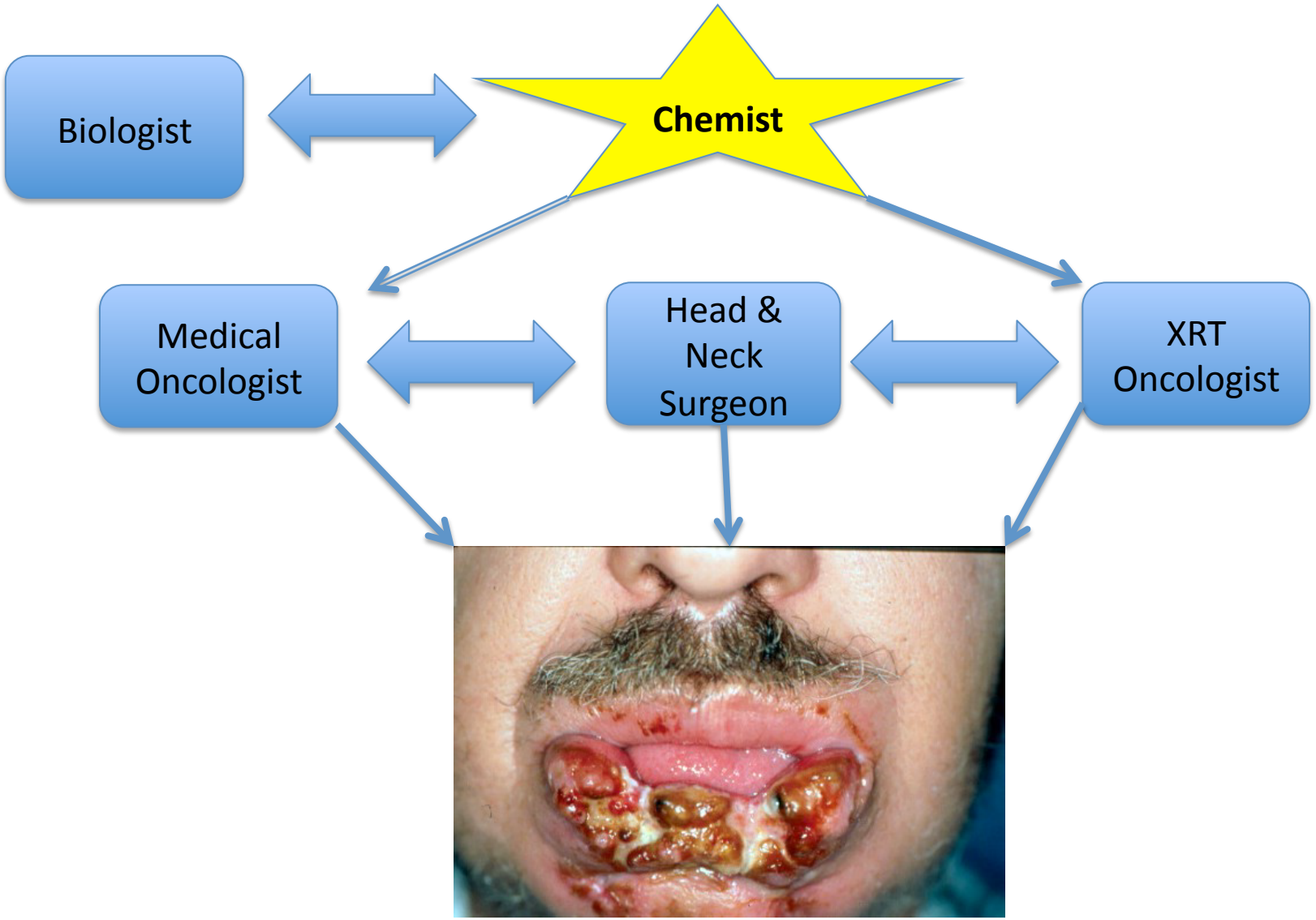




HNSCC Treatment: Multidisciplinary Approach



HNSCC Treatment:
New Multidisciplinary Approach

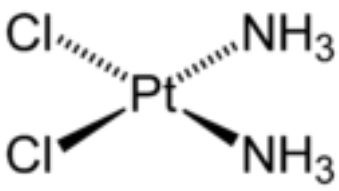


HNSCC: Role of Chemotherapy

- Chemotherapy: adjuvant therapy with XRT, i.e. not a cure
  - Advanced disease, high risk features, i.e multiple positive lymph nodes, ECS, perineural invasion
- Advantages: simultaneous therapies may synergistically maximize therapeutic effect
  - Chemo sensitizes cells to xrt and can kill micrometastatic disease→distant disease (lungs)
  - Postulated mechanisms:
    - chemo inhibits repair of cells that may recover from XRT before next cycle of XRT
    - Concomitant therapy damage cells in different ways that may otherwise be resistant
- Disadvantages:
  - Increased side effects from concurrent therapy
  - Partial response→30% of HNSCC only respond

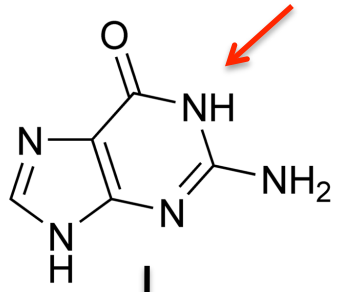
HNSCC Chemotherapy Agents: Alkylating Agents

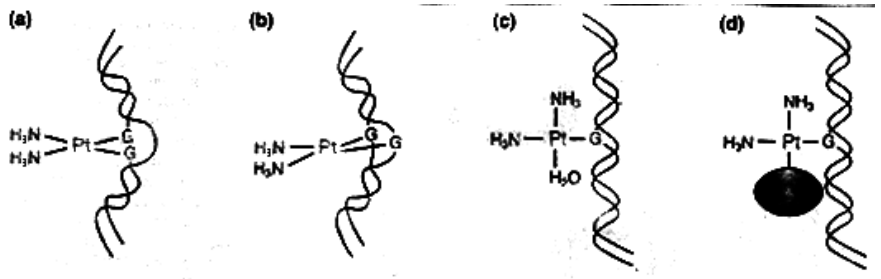
- Cisplatin
  - Mechanism: intracellular binding→bifunctional covalent links that interfere with normal DNA
  - Side effects: nephrotoxicity, ototoxicity (SNHL, oscillopsia)
  - 15-30% respond
- Carboplatin
  - Analogue of cisplatin
  - Less overall toxicity



$[PtCl(H_2O)(NH_3)_2]^+$

Cisplatin: 1978



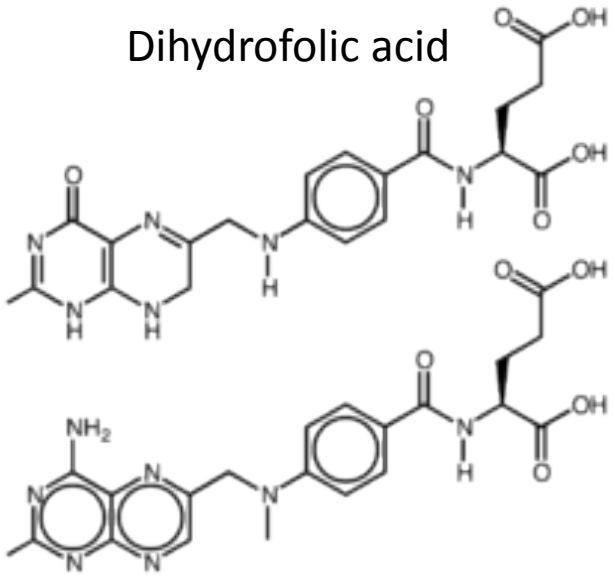


DNA crosslinking = cell death

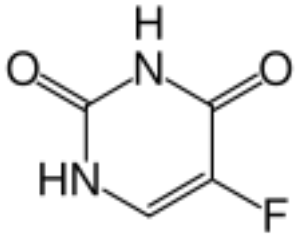
HNSCC Chemotherapy Agents: Antimetabolites

- Methotrexate (MTX)
  - Mechanism: inhibits dihyrdofolate reductase to form folic acid→*de novo* synthesis of thymidine
  - Side effects: immunosuppression, hepatic fibrosis
- 5-Flurouracil
  - Mechanism: blocks conversion of uridine into thymidine and synthesis of proteins
  - Side effects: similar to MTX

Dihydrofolic acid



Methotrexate: 1950s

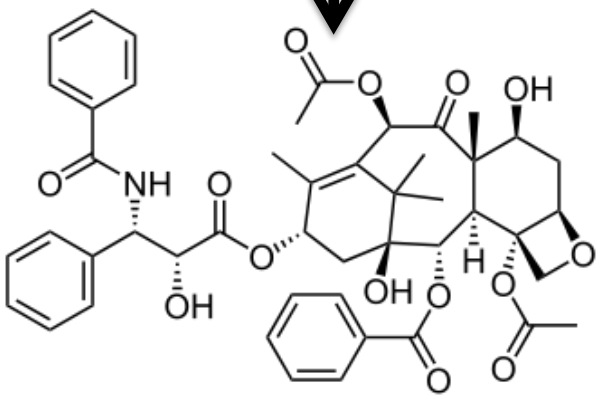


5-FU: 1957

HNSCC Chemotherapy Agents: Microtubule Stabilizers

- Paclitaxel
  - Awesome history→NCI, Holton, BMS = $$$$
  - Mechanism: stabilizes tubulin and prevent cell division in mitosis
  - Recently approved for HNSCC
  - Side effects: hair loss, bone pain, immunosuppression, etc

Pacific Yew Tree

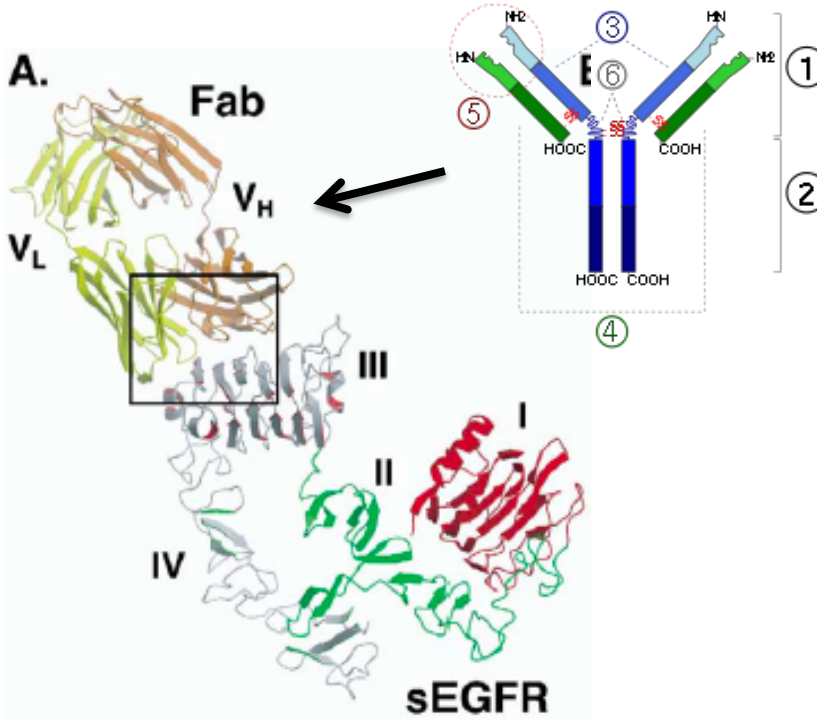


Taxol: 1984

HNSCC Chemotherapy Agents: Epidermal Growth Factor Receptor (EGFR)Inhibitor

- Cetuximab: monoclonal antibody
  - 2006, first FDA molecular targeted therapy for HNSCC
  - Inhibits EGFR: transmembrane glycoprotein, overexpressed in HNSCC
    - Phosphorylation of tyrosine kinase→cell signaling for survival and proliferation
  - Cetuximab + XRT sustained survival of 9% (5-yr OS, 45 vs 36%)

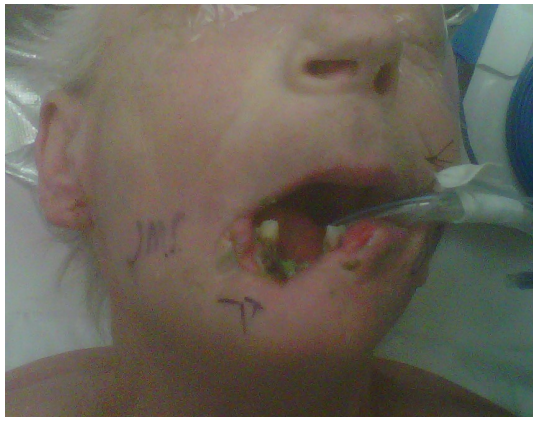
Generic antibody

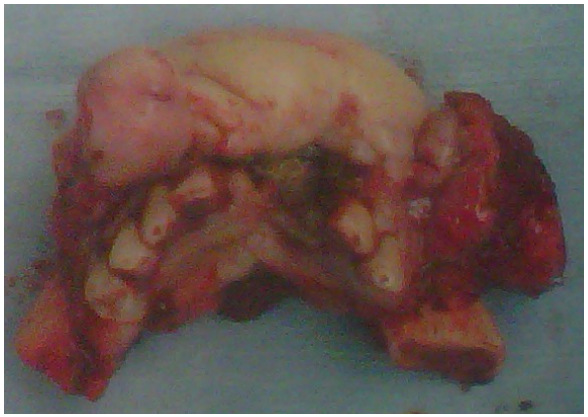


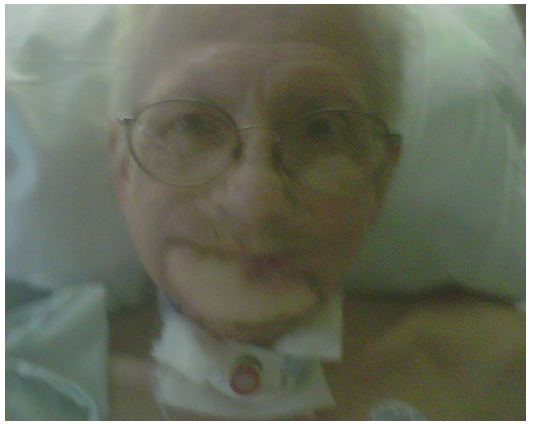
Cetuximab binding to EGFR

Why Do We Need New Chemotherapy Agents?

- The development of new agents with greater efficacy and tolerability is needed
- Overall survival has been stagnant
- Surgery is morbid (fun for me but not for the patient!)
- Chemotherapy (cisplatin) saved this patient's life!

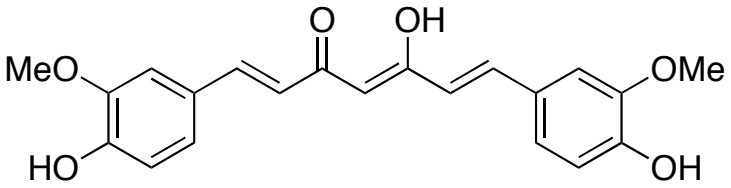




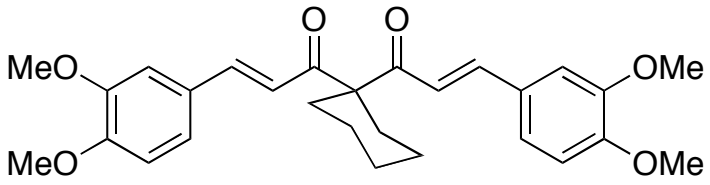


Sensitization of HNSCC to Cisplatin Through the use of a Novel Curcumin Analog

- Objective: To determine if curcumin analog, FLLL 32 (inhibitor of STAT3?), would induce cytotoxic effects in STAT3-dependent HNSCC and would sensitize tumors to cisplatin



Curcumin: Indian spice tumeric



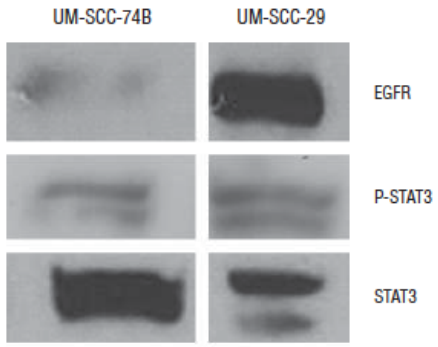
FLLL 32: non-enolizable

Signal Transducer and Activator of Trascription Factor 3 (STAT3)

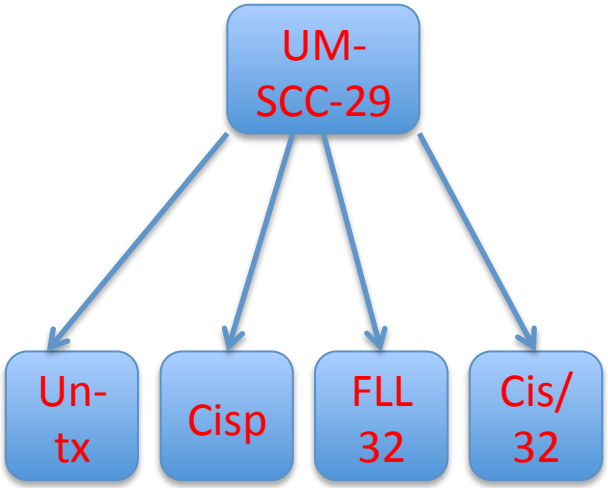
- STAT3: member of a family of transcription factors→regulates expression of many critical genes in tumor growth and survival
- Overexpressed in various cancer cells: leukemia, lymphoma, breast, pancreas, RCC, HCC, prostate, lung etc
- Oncogene: phosphorylated via IL-6 and EGFR
- HNSCC models→overexpression of pSTAT3 plays a role in cell growth, migration and inhibiting apoptosis
  - May contribute to tumorigenesis and treatment resistance
  - STAT3 expression correlated with cisplatin resistance

Study Design

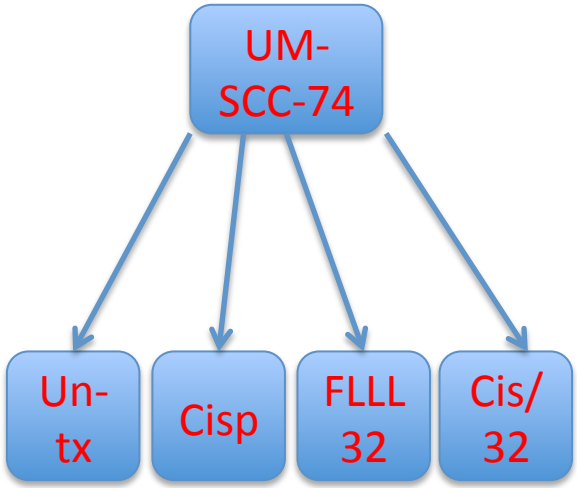
- Two HNSCC cell lines
  - Cells susceptible to cisplatin (UM-SCC-74B) and cells not (UM-SCC-29)
  - Both cells lines express pSTAT3
- Three arms with 4 concentrations of therapy = 12 groups x 2 cell lines = 24 assays
- One arm: Untreated



Cisplatin-resistant



Cisplatin-sensitive

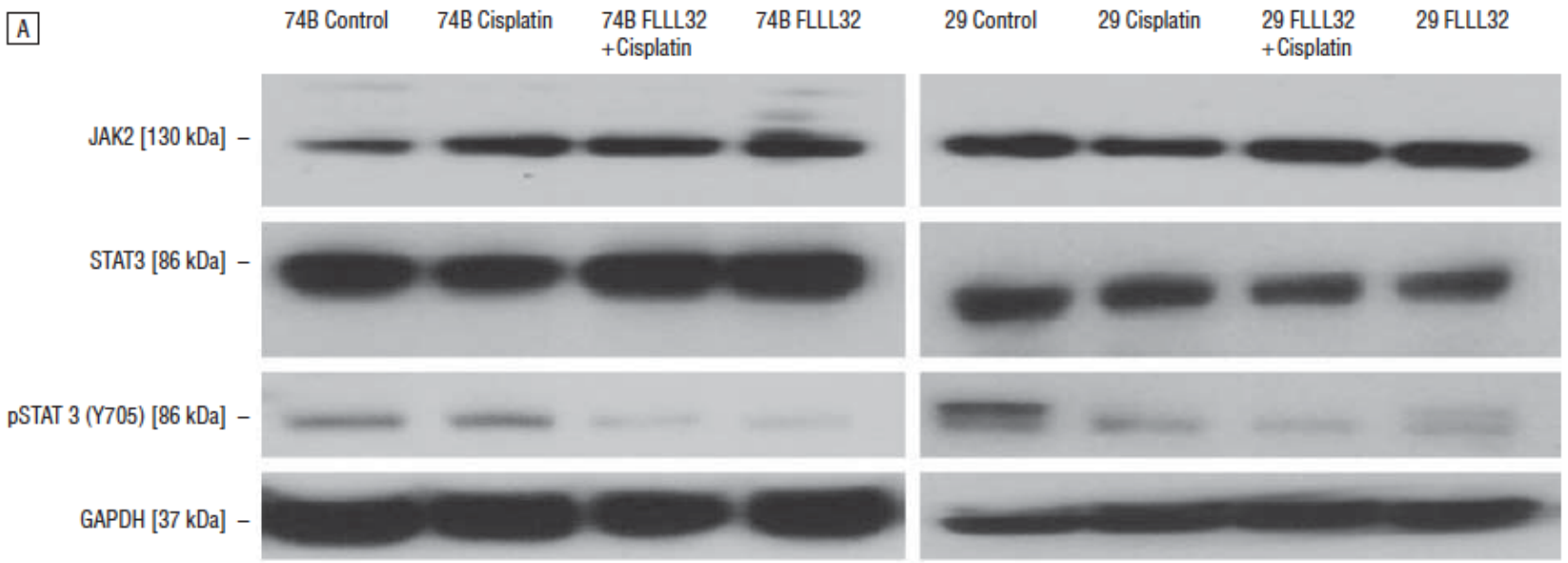


Outcomes Measured

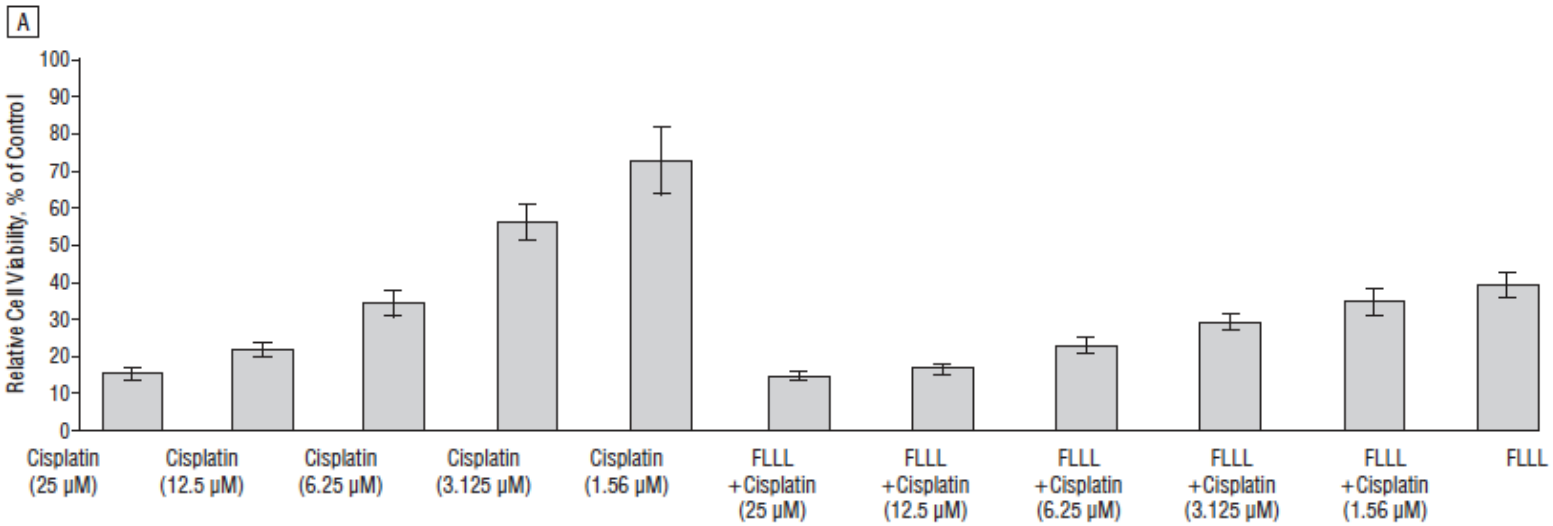
- Primary outcomes:
  - The proportion of of apoptotic cells after cisplatin, FLLL 32, and combination therapy
- Secondary outcomes:
  - FLLL 32 treatment on the expression of pSTAT3 and other key proteins in cell apoptosis

Results: pSTAT3 expression

- Western blot analysis:
  - densitometry analysis demonstrated significant down regulation of pSTAT3 protein w cells treated with FLLL 32 vs. untreated and cisplatin alone (P< 0.05).
  - Did not affect total STAT3 or JAK2 (activates STAT3)

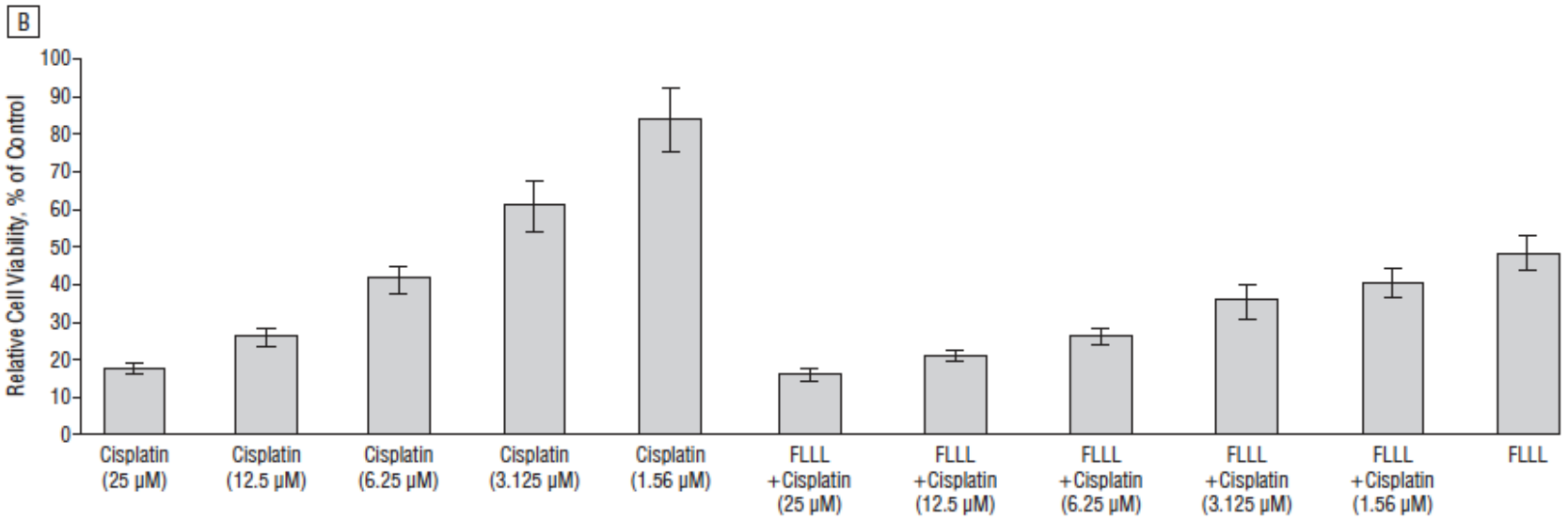


Results: Therapy Cytotoxic Effects on Cisplatin Sensitive HNSCC



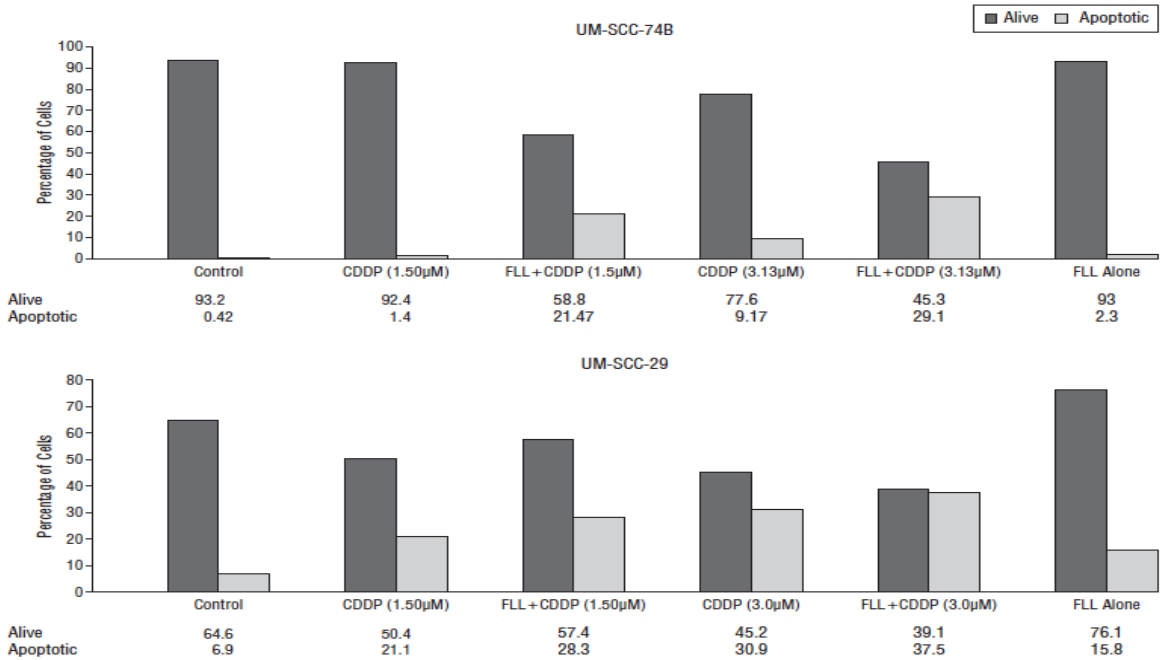
- Cell survival assays
  - In UM-SCC-74B (cisplatin sens), FLLL 32 potentiates the effects of cisplatin
  - FLLL 32 with cisplatin (1.56 µM) induced tumor cytotoxic effects = cisplatin @ 6.25 µm (4x)

Results: Therapy Cytotoxic Effects on Cisplatin Resistant HNSCC



- Cell survival assays
  - In UM-SCC-29 (cisplatin res.), FLLL 32 again potentiates the effects of cisplatin
  - FLLL 32 with cisplatin had a suppressive effect (proliferation) and synergistic cytotoxic effect

Results: FLLL 32 Potentiates Apoptosis in HNSCC



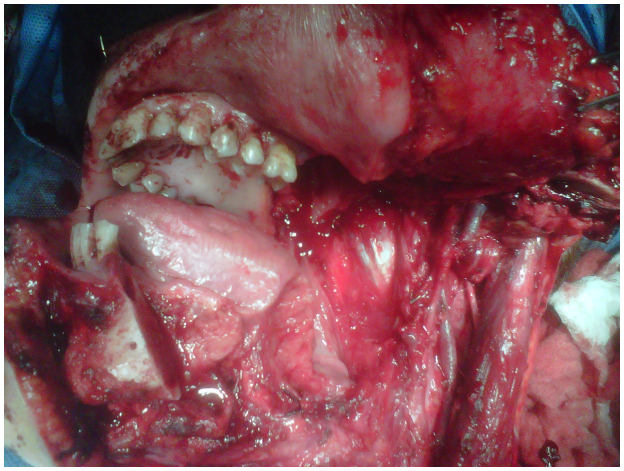
- Apoptosis assays
  - FLLL 32 alone induced an increase in apoptosis in both cells lines
  - Combination therapy induces greater apoptosis than monotherapy alone (do not report stat. sig)

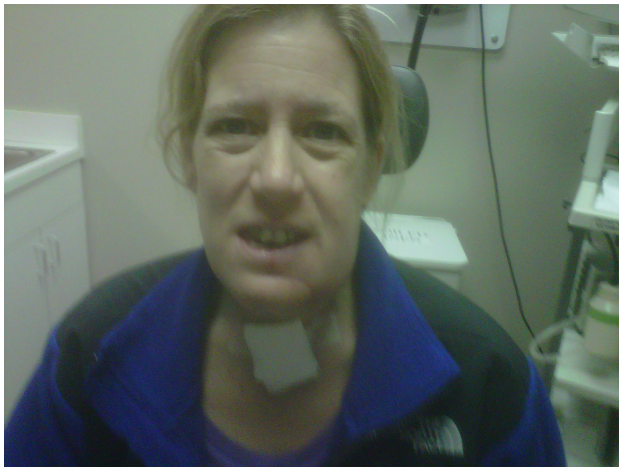
Discussion

- Platinum-based compounds are often used as first-line agents in HNSCC→toxic, not selective
  - Patients relapse with cisplatin-resistant disease
  - Efflux of drug, increased detoxification of drug
- HNSCC has multiple mutations so one therapy does not work for all (caveat: HPV SCC)
- Disruption of STAT3 through FLLL 32 has been shown *in vitro* to be very effective

Conclusion

- Head and neck cancer drug market is rapidly evolving.
- Coordination between drug and biomarker development efforts may soon yield targeted therapies that can achieve the promise of better personalized cancer medicine





THANK YOU!

Chemists Rule!