THE NEW FACE OF ORAL CANCER

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FELLOW ORAL/HEAD AND NECK TUMOR AND MICROVASCULAR SURGERY

Disclosure Statement

The following potential conflict of interest relationships are germane to my presentation.

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Enter Device or Drug Name or state: NA

HEAD AND NECK SQUAMOUS CELL CARCINOMA

- Head and Neck Cancers are the sixth most common cancers globally
- It accounts for about 4% of all cancers in the United State
- It is estimated that 65,000 people will develop head and neck cancer in 2018 with an estimated 14,000 death will occur same year*
- Smoking and Alcohol are considered the major risk factors
- Men over 45 usually affected more than female

**Statistics adapted from the American Cancer Society's publication,* Cancer Facts & Figures 2018, *and the National Cancer Institute.*

HEAD AND NECK SQUAMOUS CELL CARCINOMA

- New risk factors associated with SCC

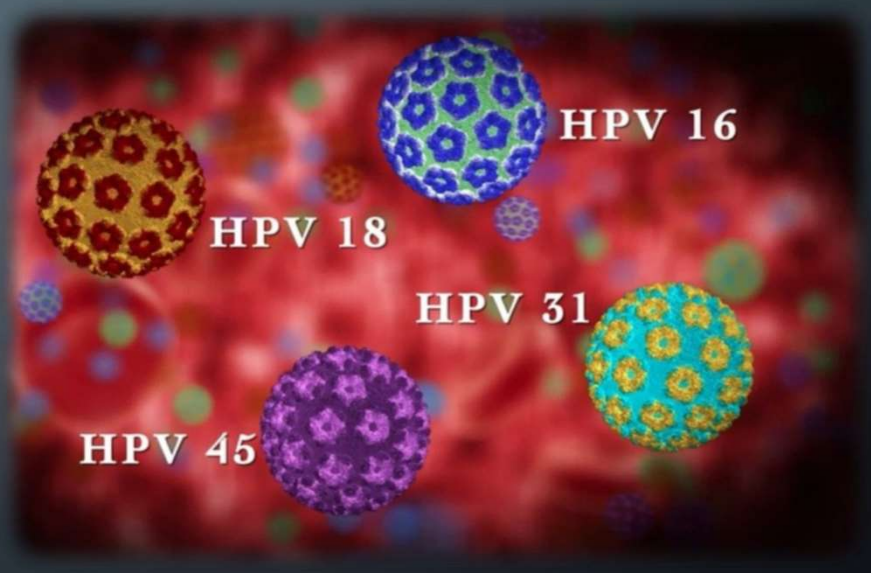
    1- Viruses:

        - HPV

        - HSV

        - EBV

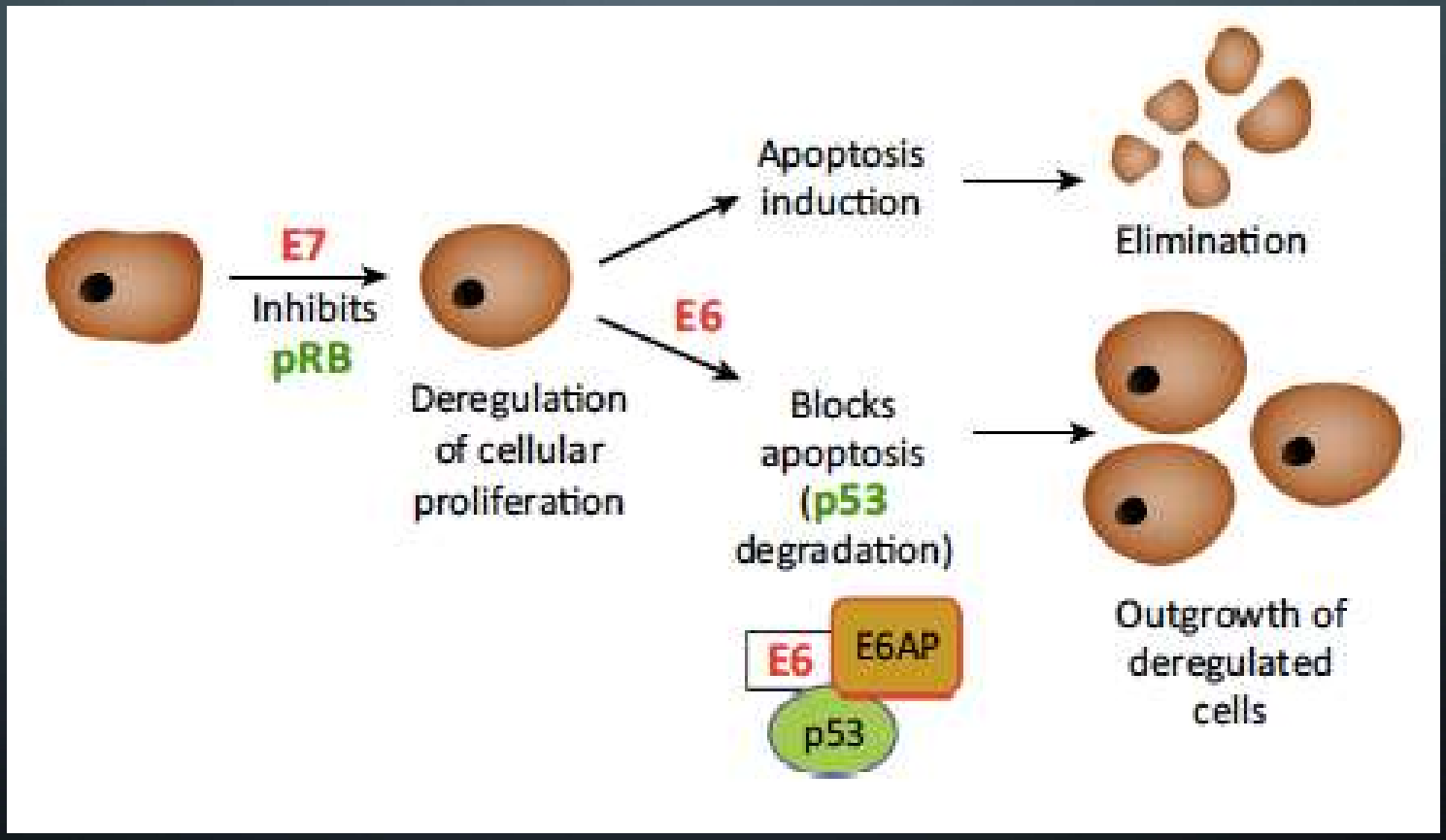
    2- Genetic Abnormalities



1- HUMAN PAPILLOMA VIRUS (HPV)

- There are nearly 200 different HPV genotype
- HPV infection plays a significant role in the pathogenesis of virtually all cases of cervical carcinoma as well as many head and neck cancers.
- Approximately, 30% of all head and neck SCC are now thought to be HPV initiated
- HPV 16 is the most common type identified in Oral SCC

HOW DOES HPV INDUCE CARCINOGENESIS?



2- GENETICS

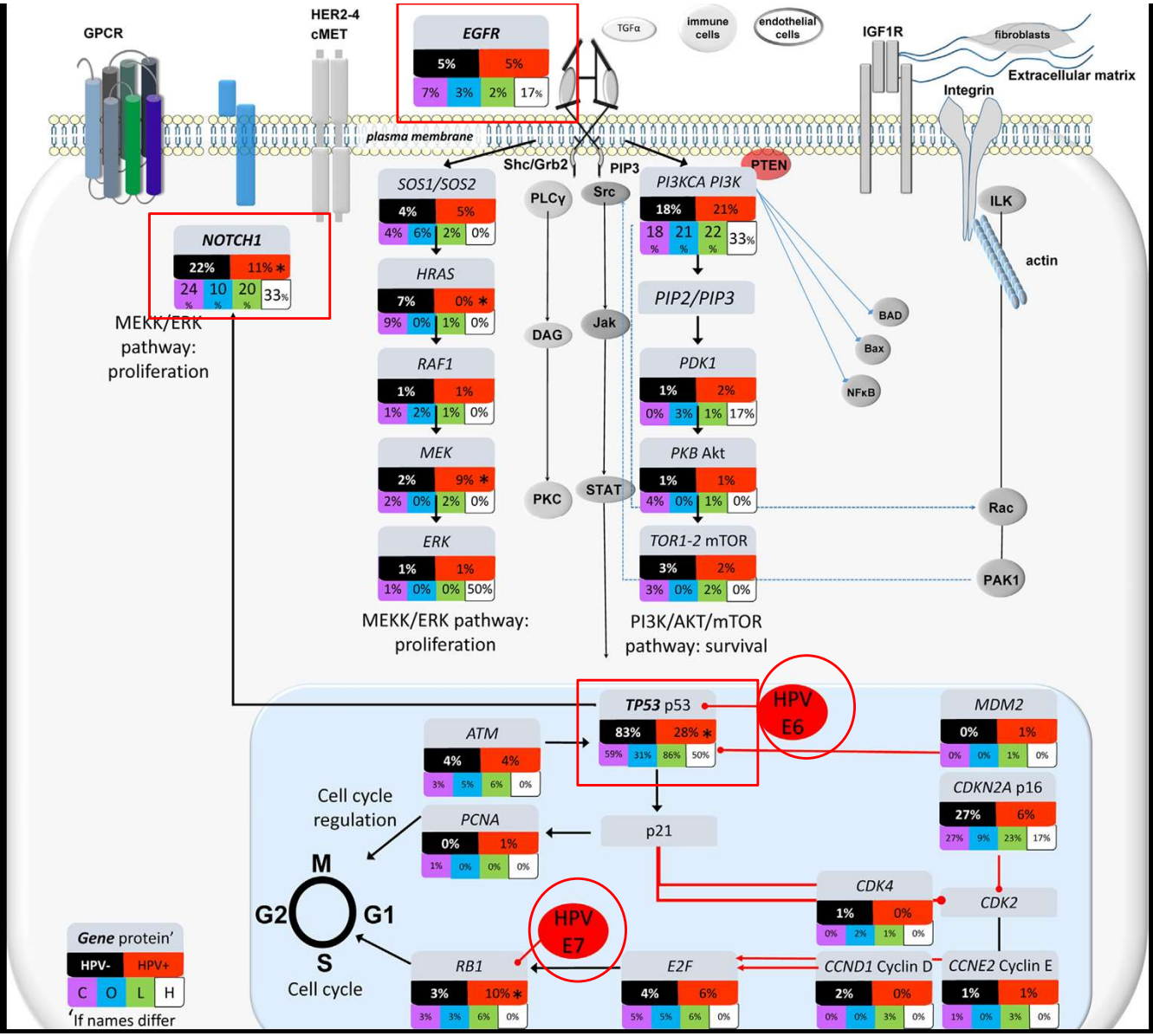
- HNSCC is known to be heterogenous at both histopathologic and molecular level
- HNSCC is characterized by genetic variability and multiple mutations
- The most common genetic mutations in HNSCC are P53 and NOTCH 1
- The ultimate goal of these genetic investigations is to provide a new targeted therapies and personalized medicine

EGFR Inhibitors:

- Failed to show a consistent and predictable response

NOTCH/P53:

- Two most common mutations in H&N SCCa in Smoker and Drinker



E6 Protein will inhbit the action of P53

E7 Protein will induce mutation in Rb gene only in 10%

MUTATIONAL PROFILES IN HNSCC

- Three different mutational profiles arise from genomic sequencing of HNSCC:

  1- Smoker and Alcohol: P53 and NOTCH 1

  2- HPV+ Cancer: RB1

  3- HPV- and non smoker: No identified mutation

THE NEW FACE OF ORAL CANCER

OUR DATA ANALYSIS

- From 1975-2005: n= 2817 biopsy proven oral SCC

-Smokers	= 2262	(80.3%)
-Non-smokers	= 554	(19.7%)
-Smokeless tobacco	= 0	(0%)
-Pipe	= 2	(0.07%)
-Cigars	= 4	(0.14%)
-Quit smoking > 10 years	= 928	(41%)

OUR DATA ANALYSIS

- From 2005-2017: n= 1012 biopsy proven oral SCC
  - Smokers = 577 (57.0%)
  - Never smokers= 369(42.1%)
  - Pipe = 2 (0.20%)
  - Smokeless tobacco = 0 (0%)

THE NEW FACE OF ORAL CANCER

- Rising trends of oral cancer have been reported among young and middle aged individuals under the age of 45 years, particularly female who never been exposed to etiological factors

VOLUME 29 · NUMBER 11 · APRIL 10 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Increasing Incidence of Oral Tongue Squamous Cell Carcinoma in Young White Women, Age 18 to 44 Years

Sagar C. Patel, William R. Carpenter, Seth Tyree, Marion Everett Couch, Mark Weissler, Trevor Hackman, D. Neil Hayes, Carol Shores, and Bhishamjit S. Chera

From the School of Public Health and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; and Warren Alpert Medical School, Brown University, Providence, RI.

A B S T R A C T

Purpose
To evaluate the incidence of oral cavity squamous cell carcinoma (OCSCC) and oral tongue squamous cell carcinoma (OTSCC) in young white women, age 18 to 44 years.

Clin Otolaryngol. 2010 Aug;35(4):307-12. doi: 10.1111/j.1749-4486.2010.02164.x.

Squamous cell carcinoma of the oral tongue in patients younger than 30 years: clinicopathologic features and outcome.

Soudry E[1], Preis M, Hod R, Hamzany Y, Hadar T, Bahar G, Strenov Y, Shpitzer T.

⊕ **Author information**

Abstract

OBJECTIVE: To assess the possible effect of young age on clinical behaviour and survival outcome of squamous cell carcinoma of the oral tongue.

DESIGN: Retrospective, case control study.

SETTING: A major tertiary referral centre.

PARTICIPANTS: Eighty-five patients with oral tongue squamous cell carcinoma with at least 2 years of follow-up.

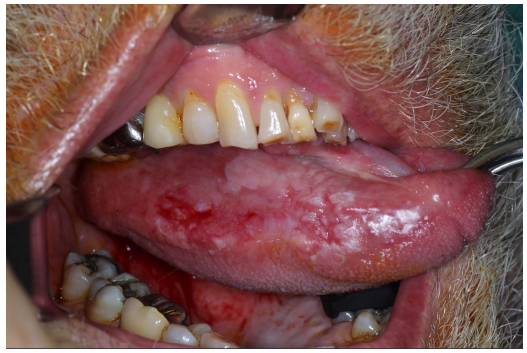
MAIN OUTCOME MEASUREMENTS: Clinical and histopathological staging, disease-free survival, disease-specific survival and overall survival.

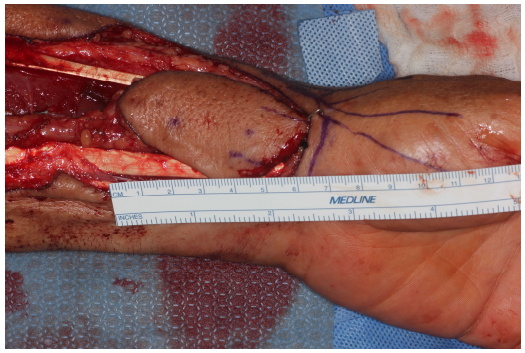
RESULTS: Eleven patients (13%) were younger than 30 years. Compared to the older patients, they had a significantly worse N stage (P = 0.041), more perineural invasion (P = 0.012), and higher rates, though not significant, of treatment failure (46%, including 60% with distant metastases, versus 35%, nearly all locoregional) and mortality (100% of treatment failures versus 73%). There were no significant between-group differences in 5-year disease-free, disease-specific, and overall survival.

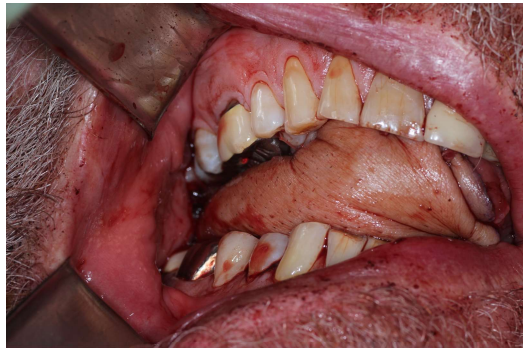
CONCLUSION: In this study, patients younger than 30 years of age presented with advanced tumour stages and with a different failure pattern compared to the older age group. This may be attributable to age-related biologic behaviour or delayed cancer diagnosis. Differences in disease free survival and overall survival could not be established.

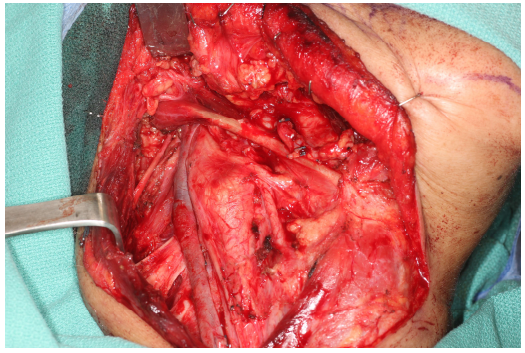
WHAT HAS CHANGED?

- Increases in never smokers and non drinker (now 42%)
- More women (41%)
- No direct correlation to HPV (2%)
- Increase in tongue cancer
- Increase in five year survivals 50% to 65%
- Reduced morbidity of surgery
- Functional reconstruction

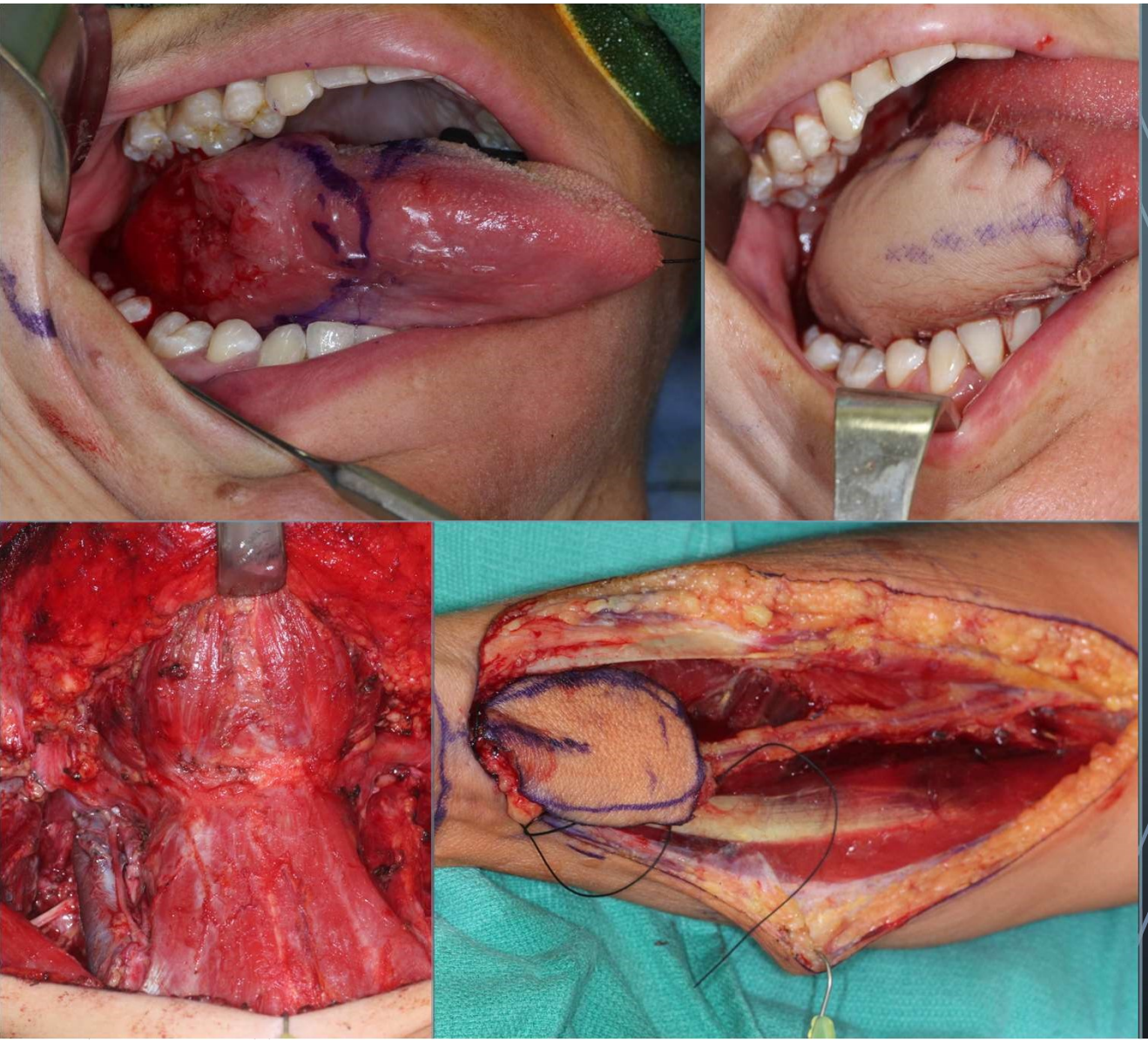








48 YEAR OLD MALE
NO RISK FACTORS
HPV NEGATIVE
STAGE II ORAL TONGUE SCC



43 YEAR OLD
FEMALE
NO RISK FACTORS
HPV NEGATIVE
STAGE IV ORAL
TONGUE SCC

WHAT IS THE DRIVING FORCE IN THIS POPULATION?

- Is there a specific genetic mutation associated with oral SCC in young patients with no identifiable risk factor?

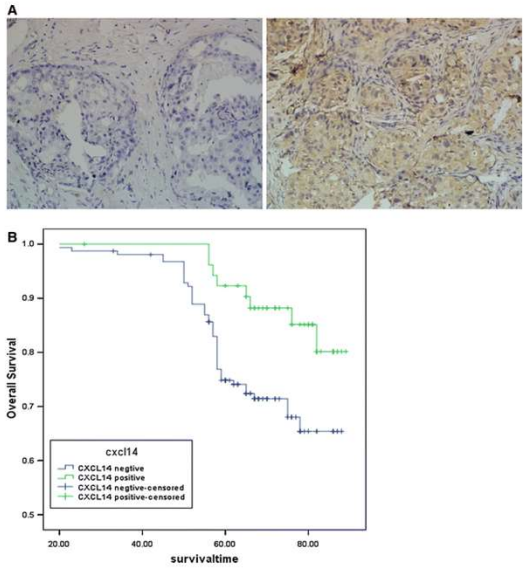
- Does certain cytokines in TME play a role?

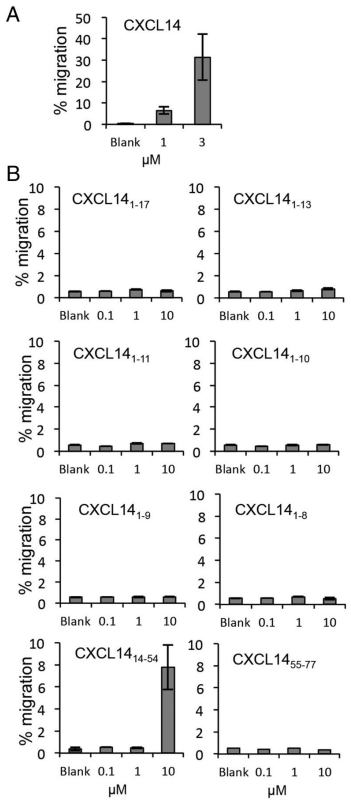
THE TUMOR MICROENVIRONMENT (TME)

- The TME consists of variable combination of tumor cells, stromal cells, macrophages, endothelial cells, tumor infiltrating lymphocyte (TIL) , and dendritic cells
- Tumors influence their microenvironment through secreting growth factors, immune suppressive molecules and cytokines
- All these cells and cytokines will determine the progression and behavior of the cancer

THE TUMOR MICROENVIRONMENT (TME) IN HPV INDUCED CANCER

- Many pro-inflammatory cytokines increase their expression in cervical cancer
- These chemokines play an important roles in how the epithelial cells differentiate into cancer
- The Question is, do they do the same in HNSCC?

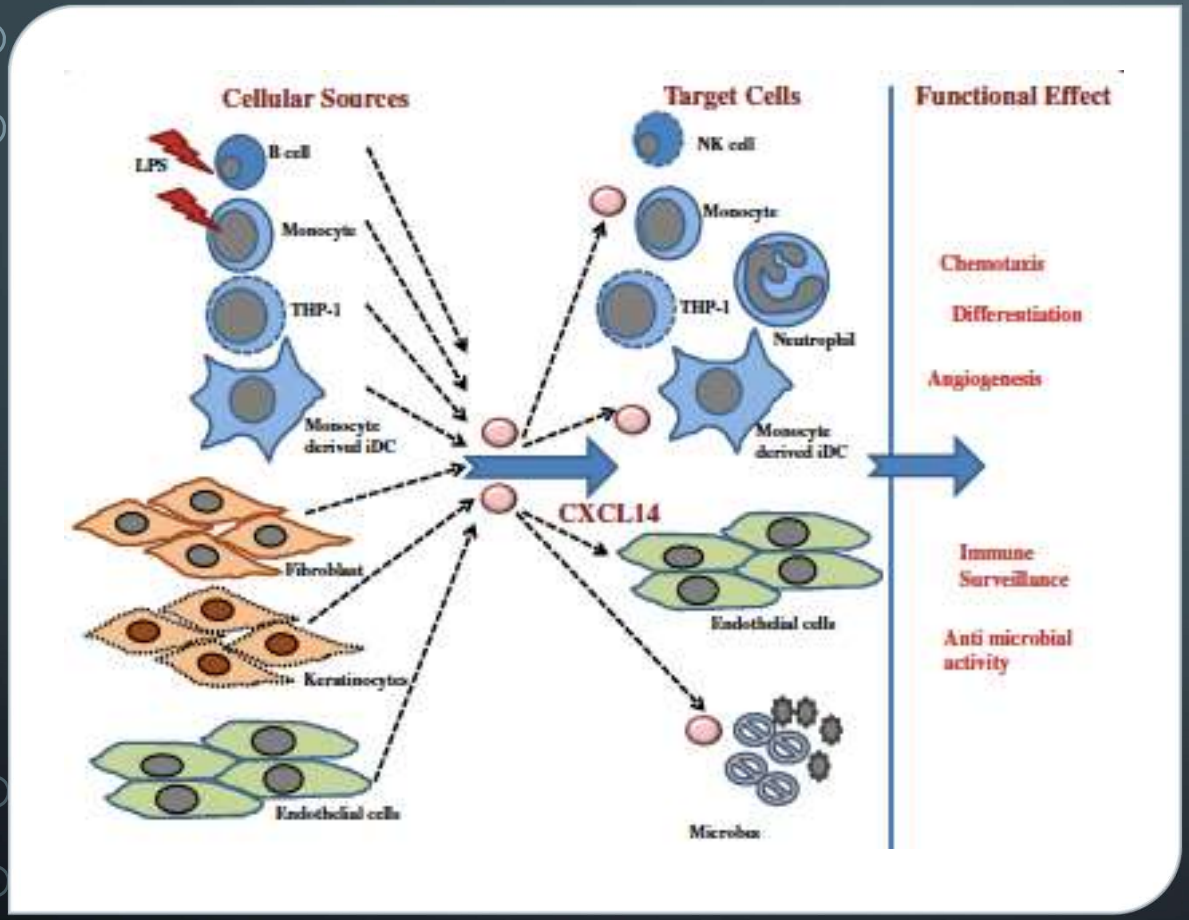




- In vitro studies have shown that most of the proinflammatory chemokines are overexpressed in head and neck cancer except CXCL 14

References:
1- Cicchini L, Westrich JA, et al. Suppression of Antitumor Immune Responses by Human Papilloma Virus through Epigenetic Downregulation of CXCL14.mBio 7(3):e00270-16

2- T Kondo,S Ozawa, et al.
Expression of the chemokine CXCL14 and cetuximab-dependent tumor suppression in head and neck squamous cell carcinoma. Oncogenesis (2016) 5, e240; doi:10.1038/oncsis.2016.43



WHAT IS CXCL14?

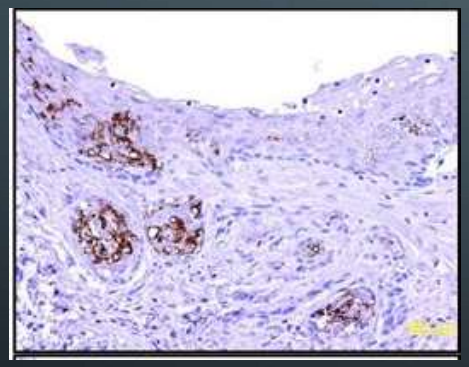
- CXCL 14 is a chemokine and is expressed by a variety of immune and non-immune cells, particularly epithelial tissues
- It functions mainly as an angiogenesis inhibitor, antimicrobial and chemotactic factor for monocyte and NK cells

Armed with the previous knowledge about the TME and the CXCL 14, we have preliminary investigated the expression of CXCL 14 in human sample of Oral SCC

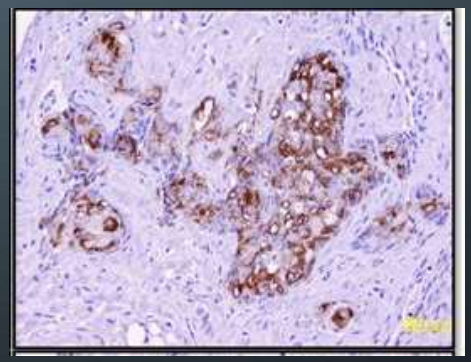
20 specimen sent:	
- 18/20 were P16/HPV Negative	- 2/20 were P16/HPV Positive

RESULTS

- All 20 specimen process with PCR to confirm the HPV status
- 6/18 were PCR positive for HPV 16
- All 20 specimen had a significantly downregulated level of CXCL-14



Expression of CXCL 14
in Tumor cells



Expression of CXCL 14 in
normal control

FINDING OF THE PRELIMINARY RESULT

- The chemokine CXCL 14 appears to be downregulated to a greater extent in HPV positive Oral SCC

FUTURE STUDIES

- Given these findings it will be important to be able to reverse the downregulation of CXCL 14 in order to restore antitumor immune response

- Fasudil, ROCK pathway inhibitor, has shown promises in overexpressing the BRAK gene and hence upregulate the CXCL 14

Biomedical Research (Tokyo) 35 (6) 381-388, 2014

Fasudil, a Rho kinase inhibitor, suppresses tumor growth by inducing CXCL14/BRAK in head and neck squamous cell carcinoma

Chihiro Miyamoto[1, 2*], Yojiro Maehata[1, 2*] Kazuhiko Motohashi[1*], Shigeyuki Ozawa[2, 3], Takeharu Ikoma[2, 3], Kouki Hidaka[4], Satoko Wada-Takahashi[1], Shun-Suke Takahashi[1], Fumihiko Yoshino[1], Ayaka Yoshida[1], Eiro Kubota[2, 3], Ryu-Ichiro Hata[1, 2], and Masaichi-Chang-il Lee[5]

[1] Department of Oral Science, Graduate School, Kanagawa Dental University, Japan; [2] Oral Health Science Research Center, Graduate School, Kanagawa Dental University, Japan; [3] Department of Oral Surgery, Graduate School, Kanagawa Dental University, Japan; [4] Department of Periodontal Regeneration, Kanagawa Dental University, Japan; and [5] Yokosuka-Shonan Disaster Health Emergency Research Center, Graduate School, Kanagawa Dental University, Japan

(Received 18 August 2014; and accepted 3 October 2014)

CONCLUSION

- Newer risk factors, adjoining smoking and HPV, may contribute to the pathogenesis of oral SCC
- Understanding of the complex interaction between oral SCC and the immune system has led to the introduction of numerous immunotherapeutic strategies
- Downregulation of the CXCL 14 in oral SCC, particularly HPV positive, may offer novel insights to develop therapeutic medications for restoring antitumor immune response