

This symposium will appeal to all grades of clinicians and scientists in the dental and head & neck specialties. All are welcome.

Keynote Speaker:

Dr Jay Boyle

Memorial Sloan Kettering
Cancer Centre,
Manhattan, NY, USA



Jay is a clinician scientist who has been at the forefront of the chemoprevention field in head & neck cancer for many years. He has an appointment as an attending in head and neck surgery at MSKCC & also at Cornell University. He has led many chemoprevention trials and has published dozens of high impact papers in translational aspects of HNSCC. Jay contributes to the editorial panel of 13 oncology and H&N journals and has delivered innumerable distinguished lectures. He has contributed to many of the standard texts that define the H&N surgery field and currently is programme director of H&N fellowship training at Memorial Sloan Kettering.

Speakers:

We will give a platform to the most experienced clinicians and most innovative researchers in this field. We have a balance between clinical research, biomarkers and clinical trials. Full programme will be available shortly on www.lctu.org.uk/lecmc



In association with:



LECmc

Liverpool Experimental Cancer Medicines Centre

One Day Translational Symposium in Head & Neck Oncology: New perspectives in Head & Neck Premalignant Lesions

Friday 27th February 2009

MERSEYSIDE
MARITIME
MUSEUM







National Veterans Affairs Datasets - VA Cancer Registry

Inclusion

1. Diagnosis of one or more: bipolar, PTSD, epilepsy, migraine
2. Known smoking status
3. Follow up > 1 year
4. Age > 40

(7%) 27000 NaV >1 year, 413000 had not

Long-Term Use of Valproic Acid in US Veterans Is Associated With a Reduced Risk of Smoking-Related Cases of Head and Neck Cancer

Hyunseok Kang, MD, MPH¹; Theresa W. Gillespie, PhD^{2,3,4}; Michael Goodman, MD, MPH⁵; Seth A. Brodie, PhD^{2,3,6}; Mina Brandes, MD⁷; Maria Ribeiro, MD^{2,3,6}; Suresh S. Ramalingam, MD^{3,6}; Dong M. Shin, MD^{3,6}; Fadlo R. Khuri, MD^{3,6}; and Johann Christoph Brandes, MD, PhD^{2,3,6}

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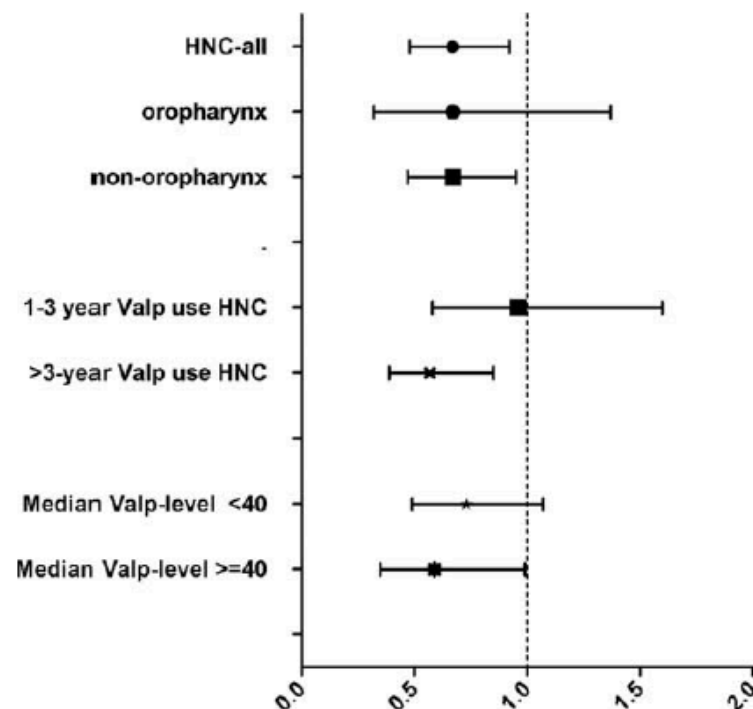
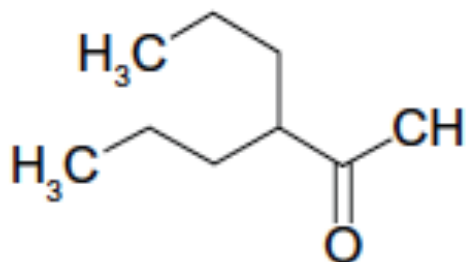
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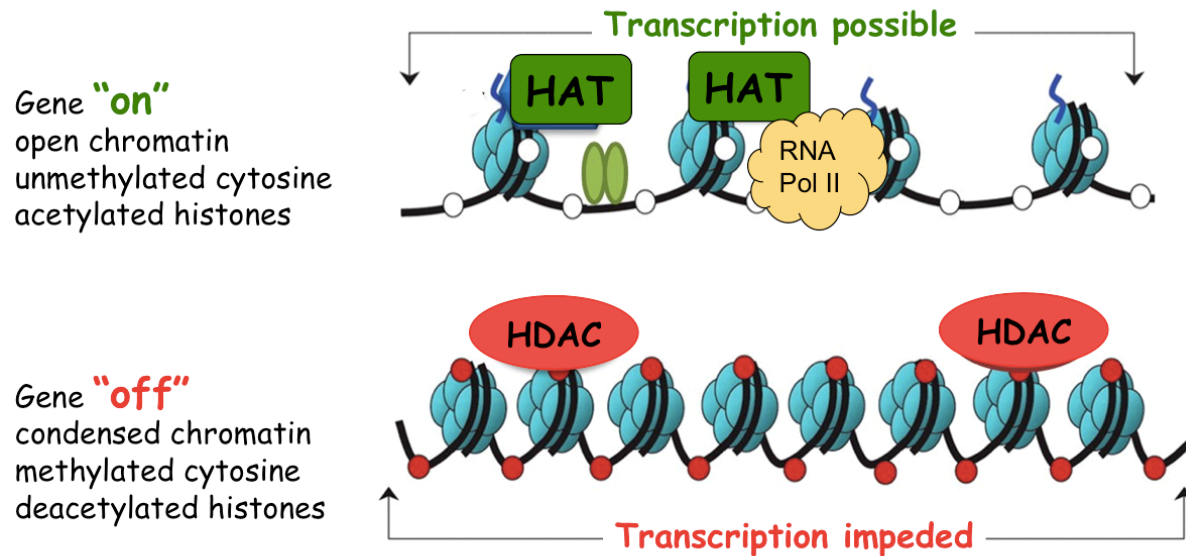
Hazard Ratio for developing HNSCC: 0.66

i.e. a third of the HNSCC were missing in those on VPA



Kang study:

- NaV is a class 1 HDAC inhibitor and cancer prevention is through epigenetic means
- Further investigation as a single agent chemoprevention is justified

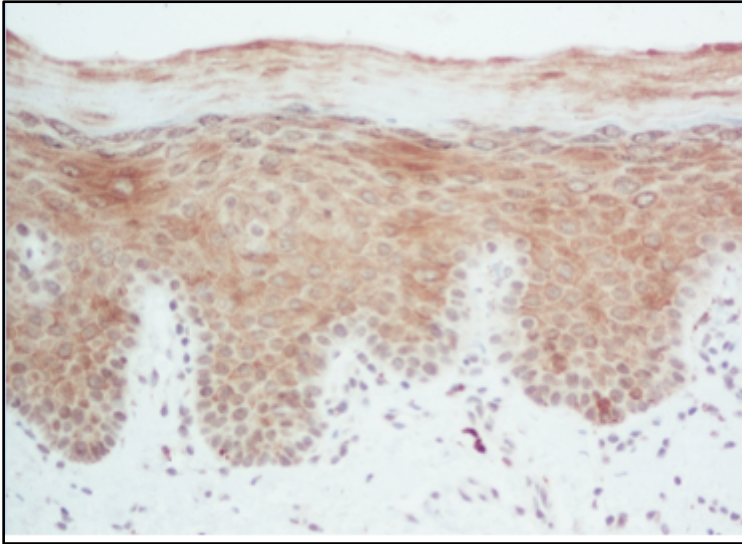




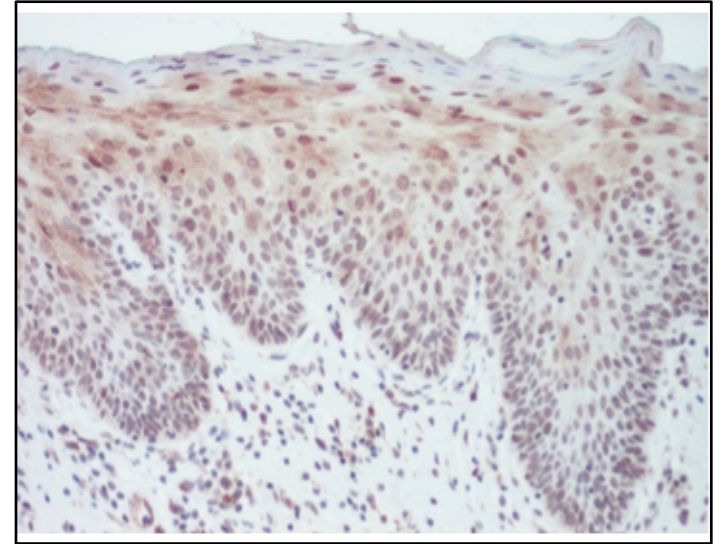
Michael Ho et al.

Defects in the DNA damage sensing-signalling-repair cascade → malignant transformation in OED

Fanc D2
IHC



Non-Transforming OED



OED Undergoing
malignant transformation

Mechanism of loss of FancD2, FancG, Chk1, ATR
in non-smokers who undergo malignant transformation?

.... epigenetic?.... & reversible??...

VPA a HDAC inhibitor?

- VPA binds to the catalytic centre of HDAC, → hyperacetylation of histones → differentiation in malignant cells → reducing tumour growth & metastasis (Gottlicher M 2001 EMBOJ 17;20(24):6969-78.
- Preclinical data in HNSCC cell lines: VPA → dose-dependent increase in histone H3 acetylation (Erlich Cancer Chemother Pharmacol (2009) 63:381-389).
- HDAC1 mediates smoking-induced stabilization of DNMT1 (Brodie et al Cancer Prev Res 2014 7(3):351-61.) → carcinogen induced DNA methylation in lung cancer cell lines.
- VPA inhibits self-renewal in HNSCC stem cells & decreases the expression of stem cell markers (Oct4, Sox2, CD44) (Lee SH Oncol Rep. 2015 Oct;34(4):2065-71)

SAVER Trial

Sodium Valporate in Epigenetic Reprogramming of Oral Epithelial Dysplasia

- Phase 2
- Randomised
- Placebo controlled
- Double blinded

..... trial of Sodium Valproate maintenance
monotherapy in chemoprevention of high risk oral
epithelial dysplasia.

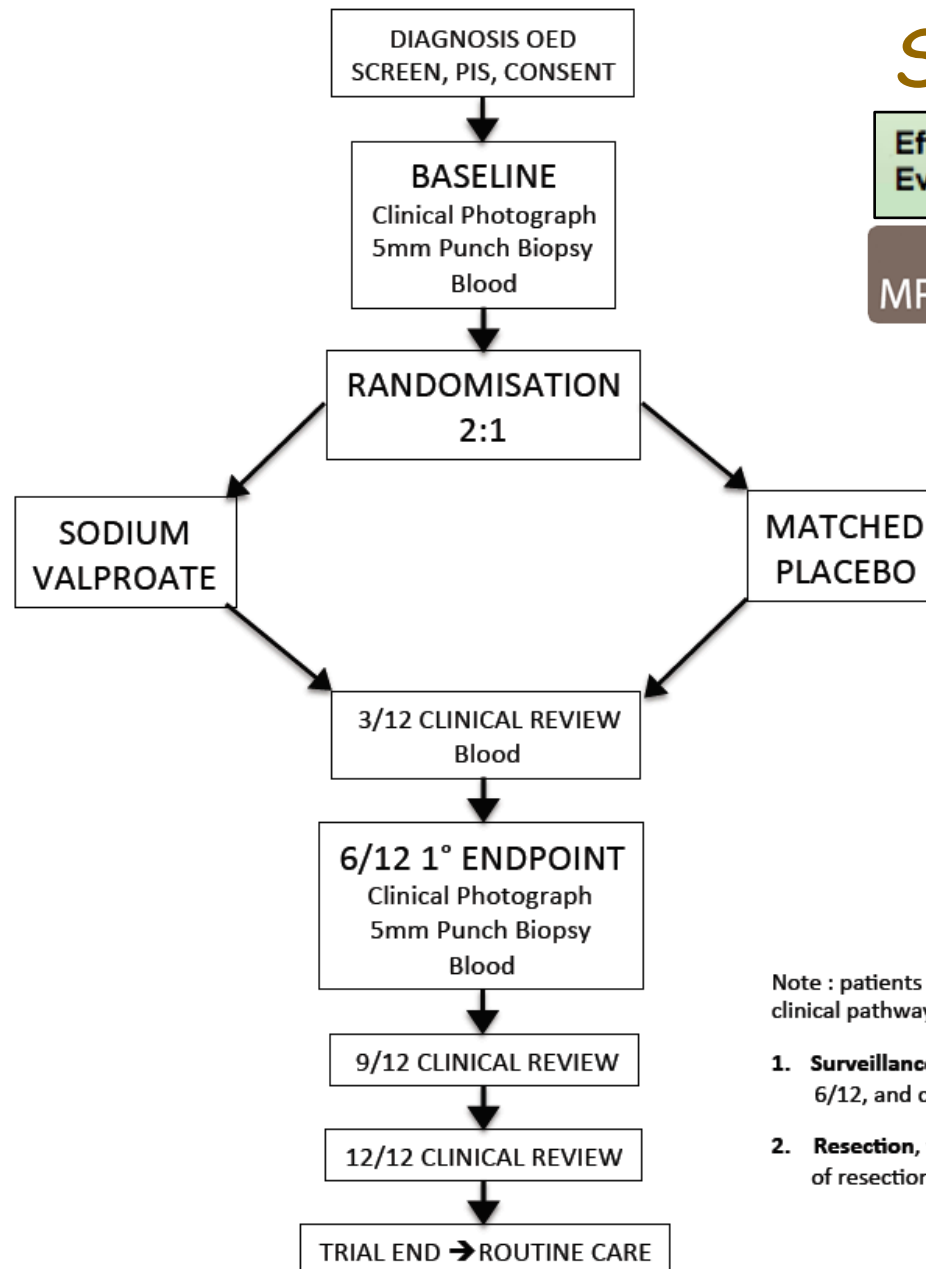
SAVER Trial

Efficacy and Mechanism
Evaluation (EME) Programme



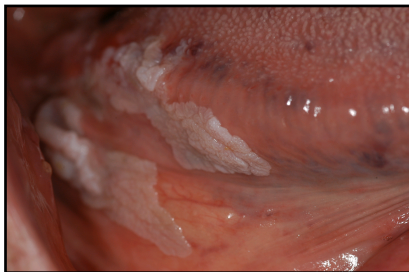
NHS
National Institute for
Health Research

Stefano Fedele
Joe Sacco
Saman Warnakasuria
Richard Jackson
Michael Ho
John Field
Bridget Young
Max Robinson
Caroline McCarthy
Margaret Daunt
Lakis Liloglou
Christiane Hertz-Fowler
Stephen Porter



Note : patients may be included on either of two clinical pathways:

1. **Surveillance**, (as shown) with 1° endpoint at 6/12, and clinical review 3, 9 & 12/12
2. **Resection**, with 1° endpoint at 3/12, at time of resection, and clinical review 6, 9 & 12/12



Clinical endpoints: EFFICACY

For follow on phase III trial:

- Overall survival
- Malignant progression free survival
- Health economics

For phase Iib

Composite of surrogates* (MDAnderson):

1. Size of lesion (photography)
2. Grade of OED (histology)
3. Genomic biomarkers (LOH 3p & 9p)

*Mallery SR et al, Clin Can Res 2014;20(7):1910-24

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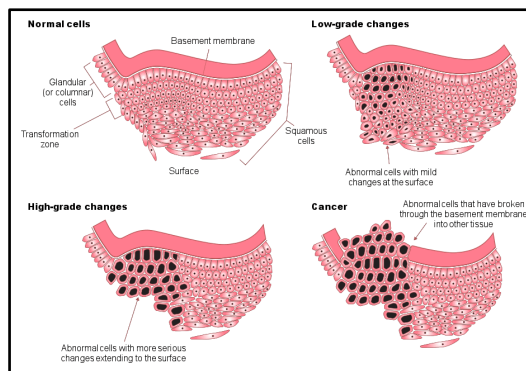
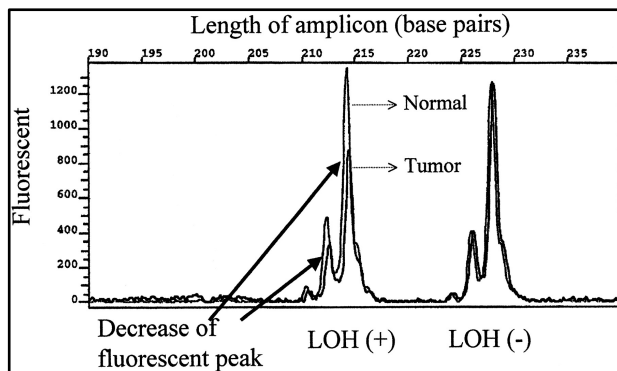
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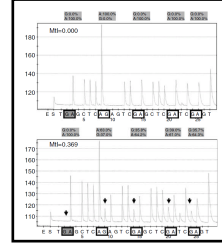
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Stephen Porter



Biological endpoints: MECHANISM

Changes between punch biopsy randomisation / endpoint:



SAVER Trial

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MRC Medical
Research
Council

NHS
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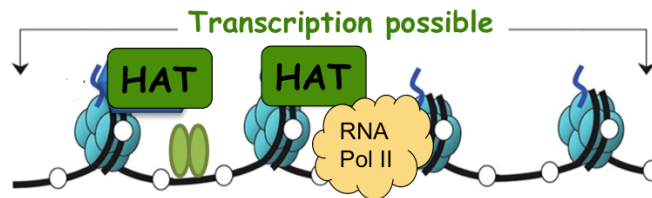
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Epigenetic: DNA methylation, Histone acetylation

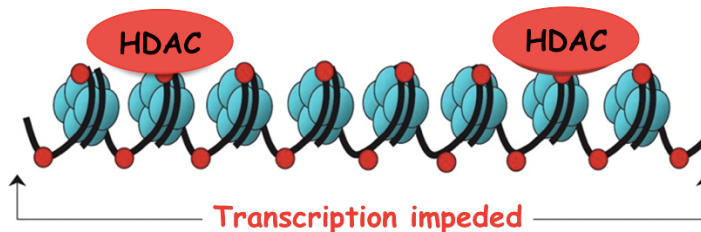
Gene expression: mRNA in senescence / apoptosis / cell cycle

IHC for proliferation, apoptosis & senescence

Gene **"on"**
open chromatin
unmethylated cytosine
acetylated histones



Gene **"off"**
condensed chromatin
methylated cytosine
deacetylated histones



MHNORG

Basic / translational science

HPV +/- / biomarkers /
Novel agents
Microenvironment /
Premalignancy

Clinical Trials

Early / Late phase /
Core outcomes /
NCRN roles /
Methodology

NWSTC
North West Surgical Trials Centre



Clinical

Surgery / Survival
/ QoL / Voice /
Reconstruction /
Laser Surgery
/ Swallowing