

第27回 日本頭頸部外科学会 特別企画  
「私の手術修練とキャリアパス」

「広く見て、先を読み、前を向いて、  
人を治す手伝いをする」  
～嚥下障害診療を通して～

上羽 瑠美

東京大学 耳鼻咽喉科・聴覚音声外科

# 私の略歴

- 2003年 5月 医師国家試験合格
  - 2003年 5月 研修医（東京大学 耳鼻咽喉科）
- 

- 2005年 4月 NTT東日本関東病院 耳鼻咽喉科
- 2007年 4月 東京都立神経病院 神経耳科
- 2008年 4月 亀田総合病院 耳鼻咽喉科

結婚

- 2010年 9月 東京大学 耳鼻咽喉科 特任臨床医
- 

- 2012年 5月 Visiting researcher  
(Department of Pathology, University of Michigan)
- 

- 2012年 12月 東京大学 耳鼻咽喉科 助教
- 2017年 1月 学位取得



# 私の略歴

- 2003年 5月 医師国家試験合格
- 2003年 5月 研修医 (東京大学 耳鼻咽喉科)
- 2005年 4月 NTT東日
- 2007年 4月 東京
- 2008年 4月 亀田
- 2010年 9月 東京大
- 2012年 5月 Visiting researcher  
(Department of Pathology, University of Michigan)
- 2012年 12月 東京大学 耳鼻咽喉科 助教

**医者は、人を治すのではない。**

**人を治す手伝いをするだけだ。**

**治すのは、本人の気力なんだ。**

# 私の略歴

- 2003年 5月 医師国家試験合格
- 2003年 5月 研修医（東京大学 耳鼻咽喉科）

気道疾患と嚥下診療に興味を持つ ⇒ 専門を決定：**喉頭・気管・嚥下・音声**

- 2005年 4月 NTT東日本関東病院 耳鼻咽喉科

• 200

• 200

• 201

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• 201



- 2005年 4月(3-4年目) NTT東日本関東病院 耳鼻咽喉科
  - 3年目: 喉頭微細手術(4月に一人きりで), 気管切開術(助手は神経内科医)
  - 喉頭全摘術
  - 4年目: 咽喉頭食道摘出術
  - 喉頭気管分離術(Separation)

和文論文初投稿

脳卒中センター嚥下チームを作る ⇒ 嚥下機能評価(1人で300症例/年)

- 2007年 4月(5年目) 東京都立神経病院 神経耳科
  - 5年目: 困難症例の気管切開術(重症心身障害児・障害者:50症例以上/年)
  - 喉頭気管分離術(Diversion) + 気管食道吻合術
  - 両側声帯麻痺症例のファイバー下気管挿管
  - 多系統萎縮症のセルシン負荷試験による気道狭窄評価

初の国際学会発表

ALS, Parkinson D, MSAの舌背筋電図検査による診断記録調査

- 2008年 4月(6-8年目)
  - 6年目: 食道バルーン拡張術
  - 粘膜下喉頭形成術
  - 7年目: 披裂軟骨内挿管
  - 喉頭形成術(外傷)
  - 局麻下声門閉鎖術

人を治す手伝いをするには、  
本人のだけでなく  
医者の気力も必要だ!!!

取得

腕頭動脈瘻, 座位での気管切開, 輪状甲状間膜切開も経験

物)

腹が空いては戦ができぬ！！！！

人を治す手伝いをするには、  
医者の体力も必要だ！！！！



私にとっても、嚥下機能維持はとても重要・・・

# 上羽家の家事事情

	私	夫
掃除機	3	7
お風呂掃除	0	10
トイレ掃除	10	
	5	

人を治す手伝いをするには、  
**体力回復も必要**よね



理解ある夫に  
本当に感謝！！

• 2010年 9月 東京大学 耳鼻咽喉科 特任臨床医

• 8年目以降

披裂軟骨内転術・甲状軟骨形成術(局麻)

輪状咽頭筋切除術(全麻)・喉頭挙上術

新生児舌根鼻咽手術

口咽

ゼー)

英文論文初投稿

喉頭関連の手術は  
自分の判断で執刀できるようになっ  
た…

上部消化



Ope室内全員女性

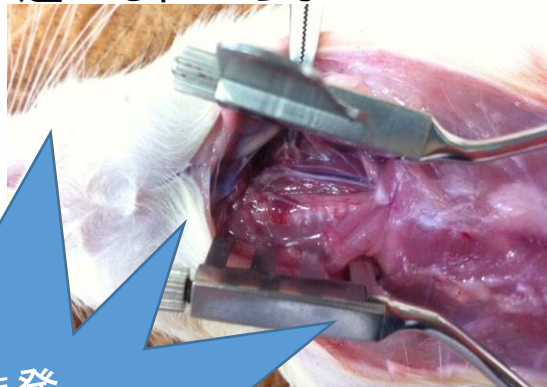


男性医師も一緒に



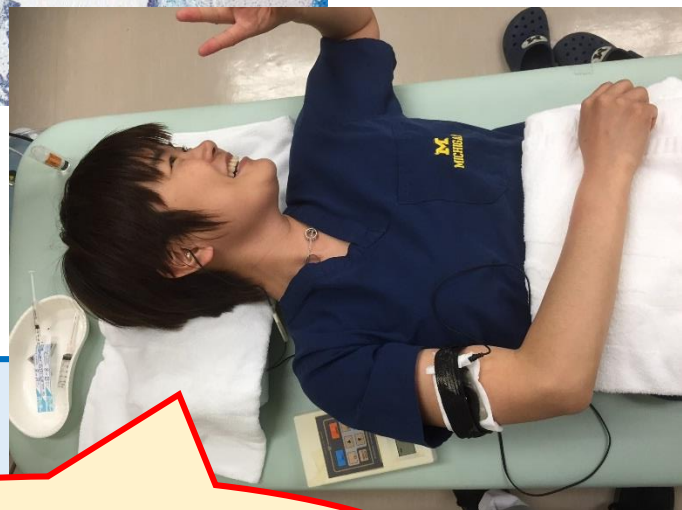
# 大学には, , , 研究という悪夢も待っていた...

初めての動物実験  
ラットとマウスの違いもわからない



突発性難聴発症  
耳鳴りに苦しむ  
(笑っているが...)

前に進むしかない！！



人を治す手伝いをするには、  
医者のリフレッシュも大切だ！！

- 2012年 5月 Visiting researcher  
(Department of Pathology, University of Michigan)



十分リフレッシュできたので、  
臨床も研究も頑張れる！！



## Viral Disruption of Olfactory Progenitors is Exacerbated in Allergic mice

R. Ueha MD<sup>1,2</sup>, S. Mukherjee PhD<sup>1</sup>, S. Ueha PhD<sup>1,3</sup>,  
K. Kondo MD, PhD<sup>2</sup>, T. Yamasoba MD, PhD<sup>2</sup>,  
N.W. Lukacs PhD<sup>1</sup> and S.L. Kunkel PhD<sup>1</sup>

<sup>1</sup>Department of Pathology, University of Michigan

<sup>2</sup>Department of Otolaryngology, University of Tokyo

<sup>3</sup>Department of Molecular Preventive Medicine, University of Tokyo



## Acknowledgement

- This work was supported in part by NIH grant 00000

### Dept Patho Med, Univ Michigan

Denise E de Almeida Nagata  
Judith Connett  
Takehiko Shibata  
Sihyug Jang

Matthew Scaller  
William F Carson  
Lisa Riggs  
Ron Allen

### Dept Otolaryngo Med, Univ Tokyo

Takashi Sakamoto  
Keigo Suzukawa  
Shu Kikuta  
Koich Tsunoda

指導医取得

• 2012年12月 東京大学 耳鼻咽喉科 助教

• 10年目以降

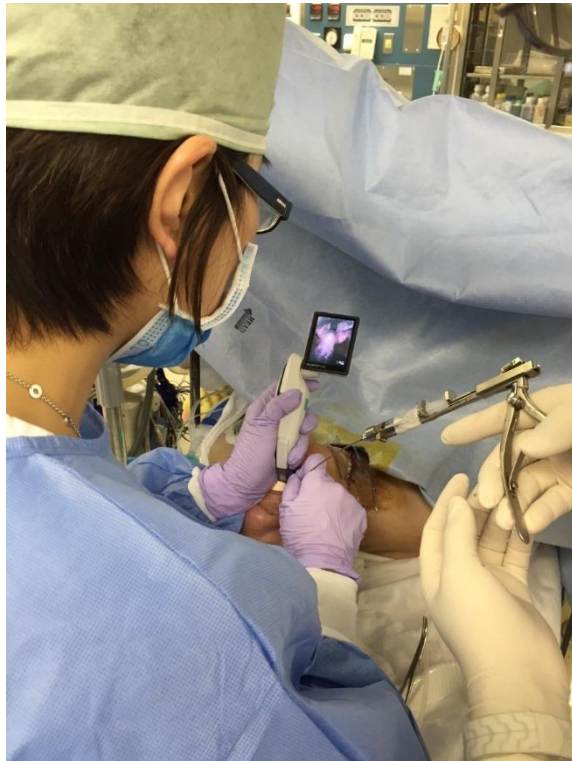
TOVS(舌根腫瘍:FK-WOリトラクター, 咽頭喉頭粘膜下腫瘍,  
輪状咽頭筋切除術, 披裂軟骨切除術, Ejunell法 など)

声帯内注入術(マックグラス下, 経皮的)

先天性喉頭奇形手術

咽頭弁形成術

など



# Transoral videolaryngoscopic surgery



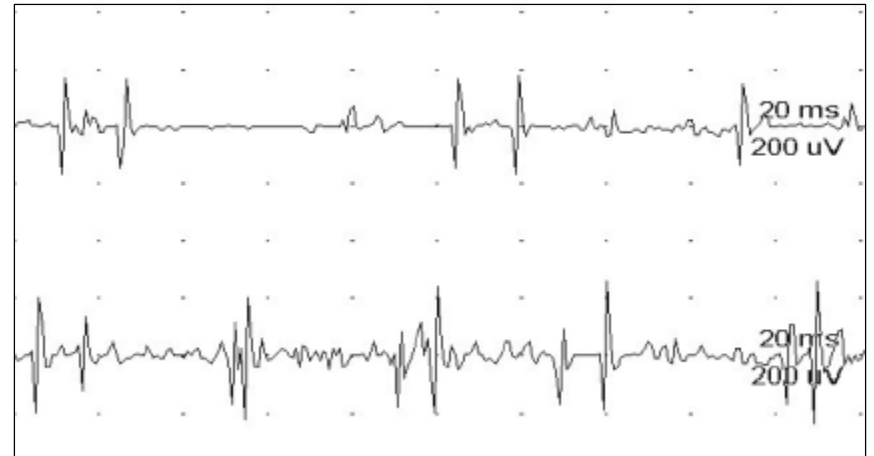
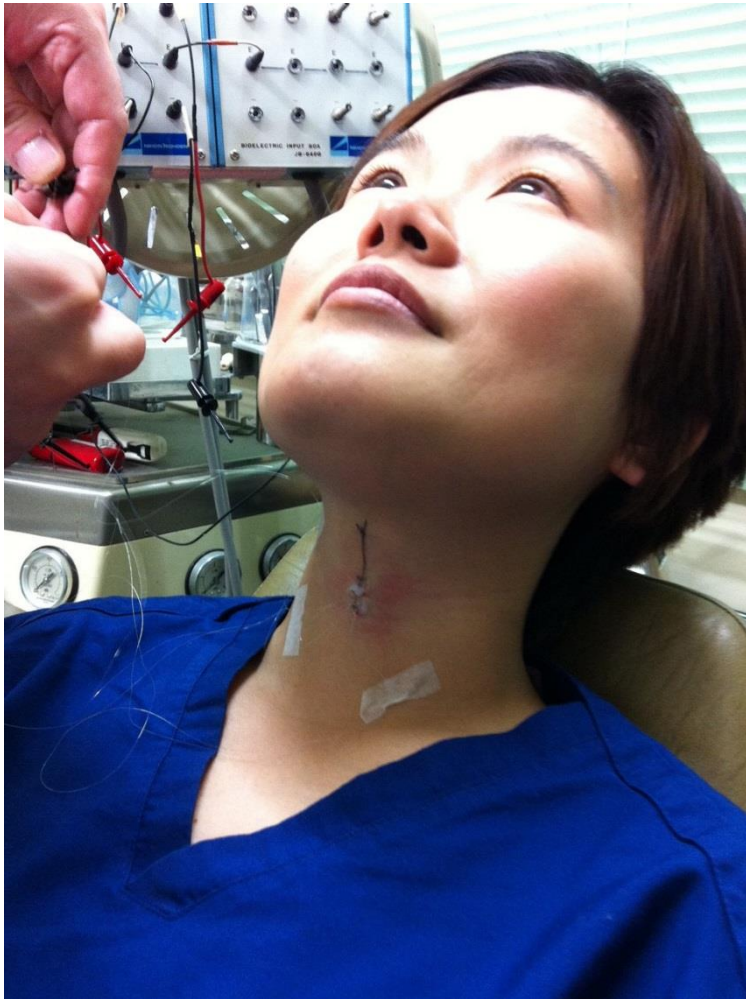
**前に進む！！**

**患者にあった治療法選択のためには、  
患者それぞれの的確な評価を！！**

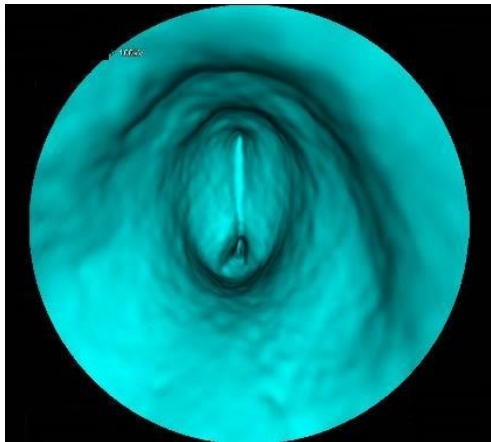
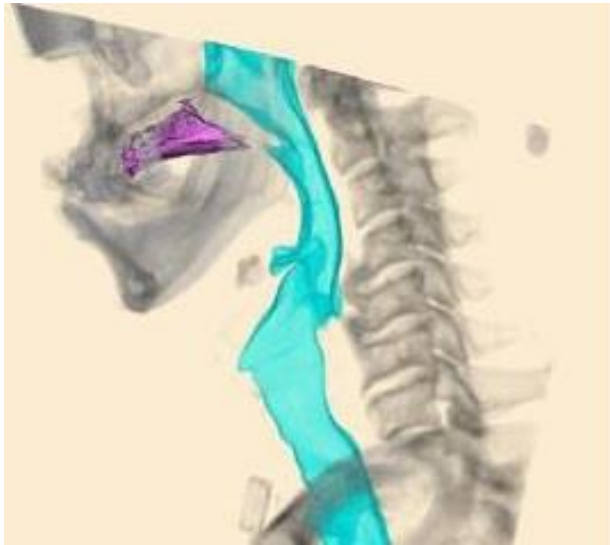
**臨床応用できる検査は、  
できるだけ自ら実践し、  
侵襲度を体感する！！**

**臨床応用につながりうる研究を  
自分のペースで考えてみよう！！**

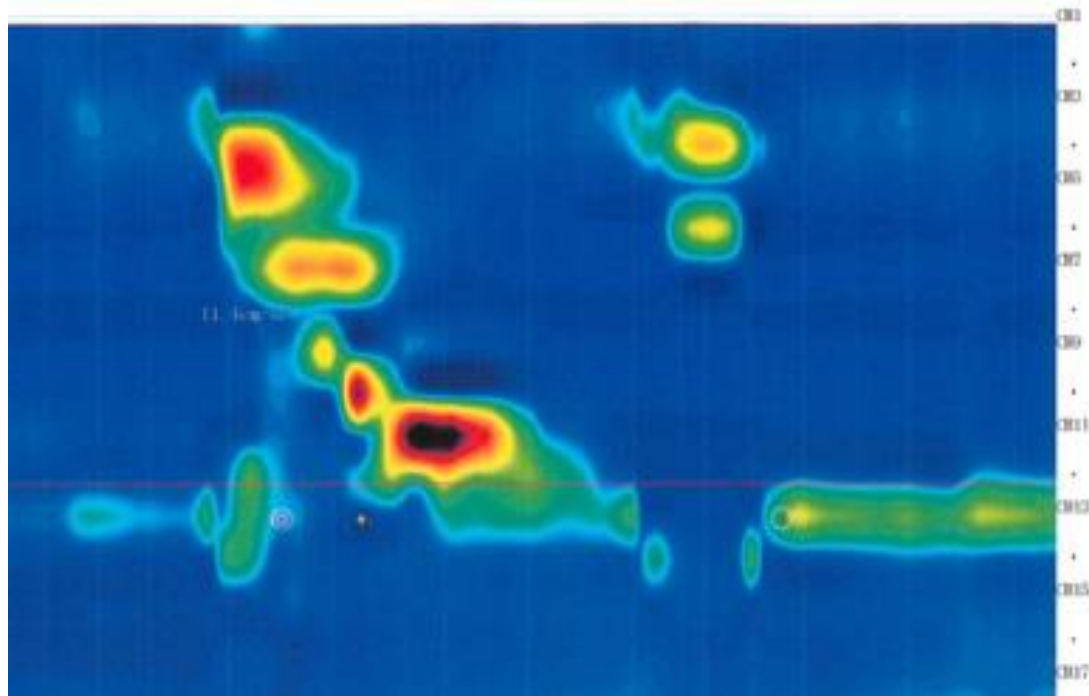
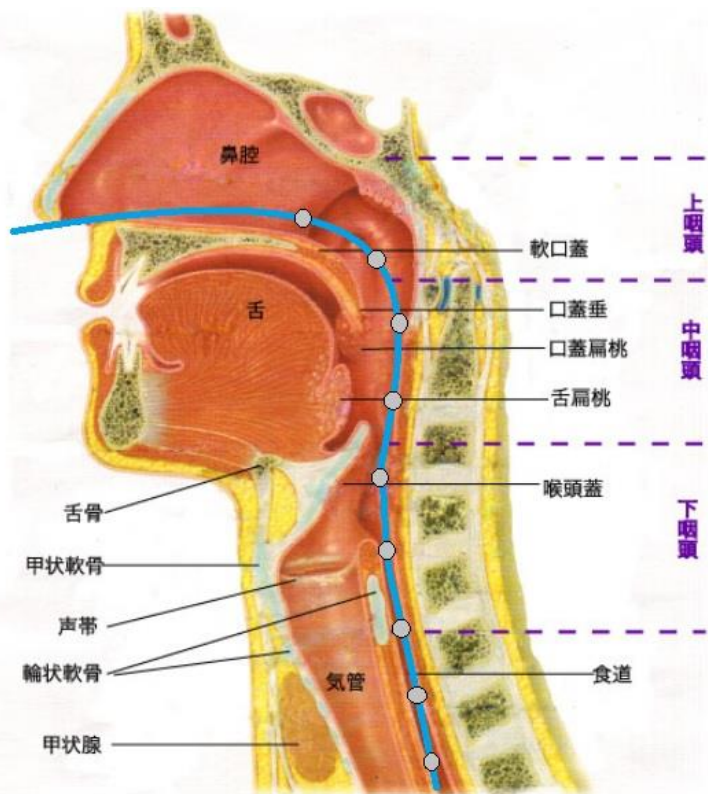
# 喉頭筋電図



# 4次元 嚥下CT

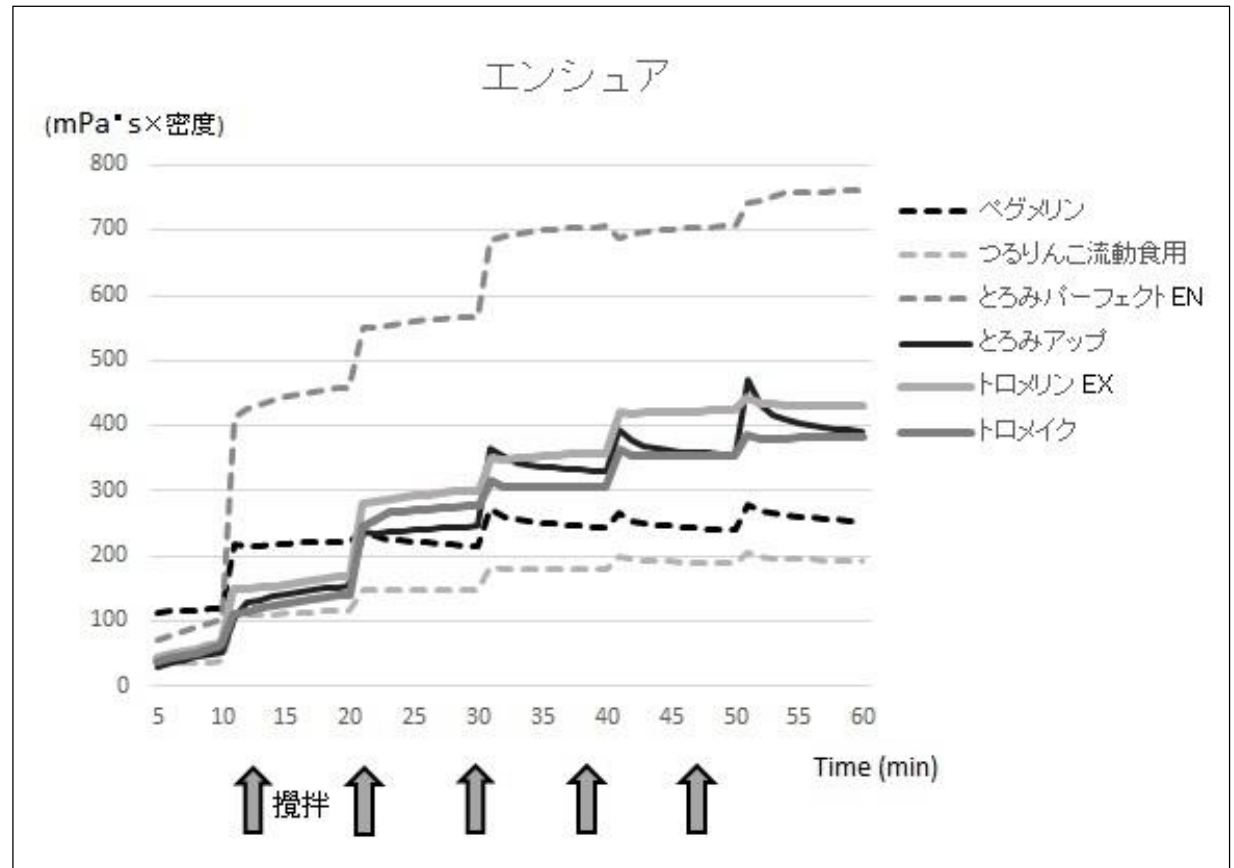


# 多チャンネル咽頭食道内圧計





# 食品テクスチャーの検証



# とろみ・ゼリーおたく



# 基礎研究

現在、喉頭領域と嗅覚の基礎研究進行中。  
うましくないことばかりでも、楽しくやる。

## Cigarette smoking and smoking cessation restores laryngeal mucus secretory homeostasis in rats

Bumi Ueha<sup>1</sup>, Satoshi Ueha<sup>1</sup>, Takaharu Nito<sup>1</sup>, Kenji Kondo<sup>1</sup>, Yoko Fujimaki<sup>1</sup>, Hironobu Nishijima<sup>1</sup>, Koichi Tsunoda<sup>1</sup>, Francis Shand<sup>2</sup>, Kouji Matsumura<sup>1</sup> and Tatsuya Yamashita<sup>1</sup>

<sup>1</sup> Department of Otolaryngology, University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo, Japan  
<sup>2</sup> Department of Molecular Preventive Medicine, Graduate School of Medicine, University of Tokyo  
<sup>3</sup> Department of Artificial Organs and Otolaryngology, National Institute of Sensory Organs, Tokyo



### Objectives

Cigarette smoking (CS) induces mucus hypersecretion and coughing. Coughing after smoking cessation (SC) is also common. However, the mechanisms that underlie the effects of CS and SC on laryngeal mucus secretion remain elusive.

In this study, we hypothesized that CS and SC cause laryngeal hypersecretion due to an increase of pro-inflammatory mediators, resulting in coughing. To test this hypothesis, we explored the effects of smoking, short-term (four weeks) SC, and long-term (three months) SC on laryngeal secretion and pro-inflammatory responses using rat models of smoking that involved administration of a cigarette smoke solution (CSS).

In addition, we investigated the effects of short-term administration on laryngeal secretion and inflammatory responses.

### Methods

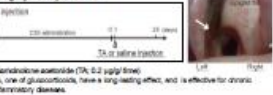
#### I. Rat model of smoking



#### II. Enzyme-linked immunosorbent assay (ELISA) of Cotinine

To confirm the absorption and metabolism of Nicotine after CSS administration

#### III. Drug injection procedure



#### IV. Histological analyses

H&E staining: Evaluation of whole tissue structure  
Alcian blue staining: Observation of the mucus and goblet cells.  
To compare the amount of mucus, the cross-sectional area of Alcian blue-positive mucus and goblet cells over the perichondrium of thyroid and cricoid cartilage (boxed areas) were measured using Image analysis (area pixel count × 10<sup>-6</sup> mm<sup>2</sup>/pixel).

#### V. Quantitative real-time polymerase chain reaction (qPCR)

Pro-inflammatory cytokines: TNF- $\alpha$ , IL-1 $\beta$ , IL-6, Muc5b, MUC5AC

### Results

#### I. CSS exposure temporarily increases the serum Cotinine level

CS rats on day 1 showed significantly higher cotinine serum levels as compared to those in the untreated group and CSS group on day 7.



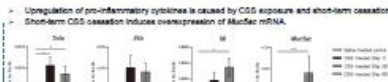
#### II. CSS exposure induces laryngeal mucus hypersecretion and short-term smoking cessation causes further hypersecretion

Untreated, Administered control, CSS-treated, Day post final CSS dose, Day 7, Day 28



#### III. Triamcinolone acetonide suppresses CSS-induced laryngeal mucus hypersecretion, pro-inflammatory cytokine production, and upregulation of Muc5b mRNA

Untreated, CSS, CSS+TA, Day post final CSS dose, Day 7, Day 28



### Discussion

#### CSS-induced mucus hypersecretion and Muc5b upregulation are considered to be due to direct effects on transcriptional regulation of epithelial growth factor receptor (EGFR)-mediated signaling pathway.

CS-induced effects through inflammatory reactions

Nicotine, a major constituent of cigarette smoke, has immunosuppressive effects, and the decrease of nicotine concentration due to SC possibly reverses nicotine-induced expression of the inflammation in the larynx.

TA inhibits all stages of the inflammatory response, and reduces airway mucus production and the proliferation of epithelial goblet cells. In addition, TA induces repression of NF- $\kappa$ B activation caused by CS, and directly regulate EGFR.

TA might be effective to suppress laryngeal mucus hypersecretion by directly regulating EGFR-mediated signaling pathway and by downregulating inflammatory cytokines, IL-6, and TNF- $\alpha$ .

#### Conclusion

We have demonstrated that CSS induces laryngeal hypersecretion, besides short-term SC causes further hypersecretion and upregulation of pro-inflammatory cytokines and Muc5b mRNA.

The inflammatory responses and mucus hypersecretion that occur during smoke exposure and after SC represent promising targets for the treatment of cigarette smoke-associated prolonged cough after SC.

TA may reduce expression of pro-inflammatory cytokines in the larynx and might be useful for the treatment of CSS-induced mucus hypersecretion, which may cause prolonged cough after SC.

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## Damage to olfactory progenitor cells is involved in cigarette smoke-induced olfactory dysfunction in mice

Bumi Ueha<sup>1</sup>, Satoshi Ueha<sup>1</sup>, Takaharu Nito<sup>1</sup>, Kenji Kondo<sup>1</sup>, Yoko Fujimaki<sup>1</sup>, Hironobu Nishijima<sup>1</sup>, Koichi Tsunoda<sup>1</sup>, Francis Shand<sup>2</sup>, Kouji Matsumura<sup>1</sup> and Tatsuya Yamashita<sup>1</sup>

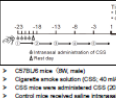
<sup>1</sup> Department of Otolaryngology, University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo, Japan  
<sup>2</sup> Department of Molecular Preventive Medicine, Graduate School of Medicine, University of Tokyo  
<sup>3</sup> Department of Artificial Organs and Otolaryngology, National Institute of Sensory Organs, Tokyo

### Abstract

Objective: Exposure to cigarette smoke is a major cause of olfactory dysfunction. However, the underlying mechanism by which cigarette smoke interferes with the highly regenerative olfactory nerve system remains unclear. We investigated whether cigarette smoke induces olfactory dysfunction by disrupting cell proliferation and cell survival in the olfactory epithelium (OE). We developed a mouse model of smoke that involved intranasal administration of a cigarette smoke solution (CSS). Methods: Firstly, we explored the effects of CS on olfactory progenitor and olfactory neurogenesis using histological analysis and behavioral testing with mice. Secondly, we investigated the effects of CS on pro-inflammatory responses using histological analysis and quantitative real-time PCR analysis. Results: Immunohistological analysis and behavioral testing showed that CS administration over a period of 28 days reduced the number of olfactory marker protein-positive mature olfactory neurons (ORNs) in the OE and induced olfactory dysfunction. These changes coincided with a reduction in the number of SOX2<sup>+</sup> progenitors and NS2<sup>+</sup> proliferating cells in the basal layer of the OE, an increase in the number of caspase-3<sup>+</sup> apoptotic cells, and an increase in the expression of mRNA for the inflammatory cytokines IL-6 and IL-1 $\beta$ . Notably, the pro-ORN progenitor population recovered following cessation of treatment with CSS, resulting in the subsequent restoration of mature ORN numbers and olfaction. Conclusion: These results suggest that SOX2<sup>+</sup> ORN progenitors are targets of CS-induced impairment of the OE, and that by damaging the ORN progenitor population and increasing ORN death, CS appears eventually to compromise the regenerative capacity of the epithelium, resulting in reduced numbers of mature ORNs and olfactory dysfunction.

### Methods

#### I. Mouse model of smoking



#### II. Histological analyses

H&E staining: Evaluation of whole tissue structure  
Immunohistochemical staining: Evaluation of olfactory epithelium (OE) structure  
Immunohistochemical staining: Evaluation of olfactory epithelium (OE) structure  
Immunohistochemical staining: Evaluation of olfactory epithelium (OE) structure

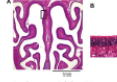
#### III. Behavioral testing to evaluate olfactory function

paper with substrate essential oil  
1 address  
2 address  
3 address

### Results

#### I. CSS exposure impairs olfactory receptor neurons

Immunohistochemical staining of OMP<sup>+</sup> cells in the olfactory epithelium



#### II. CSS exposure induces olfactory dysfunction

In saline-treated mice, the duration of investigative behavior on the fourth exposure was significantly longer than that on the first two, supporting that the mice were capable of smelling the odorant.

In CSS-treated mice, there was no significant difference in the duration of investigative behavior between the first and fourth trials on day 1 or day 7 after the final CSS administration, suggesting a decrease in olfactory sensitivity.

The loss of olfactory sensitivity was most on severe on day 7 after the final CSS administration, but recovered by day 14.

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### Discussion

In this study, we demonstrate for the first time that long-term CSS administration damages not only OMP<sup>+</sup> mature ORNs but also SOX2<sup>+</sup> ORN progenitors in the OE.

The numbers of SOX2<sup>+</sup> ORN progenitors and NS2<sup>+</sup> proliferating cells increased transiently around 7 days after final CSS administration, preceding recovery of the OMP<sup>+</sup> mature ORN population.

Increased apoptosis is unlikely to be solely responsible for the reduction in ORN numbers.

The reduction in mature ORN numbers was associated with olfactory dysfunction.

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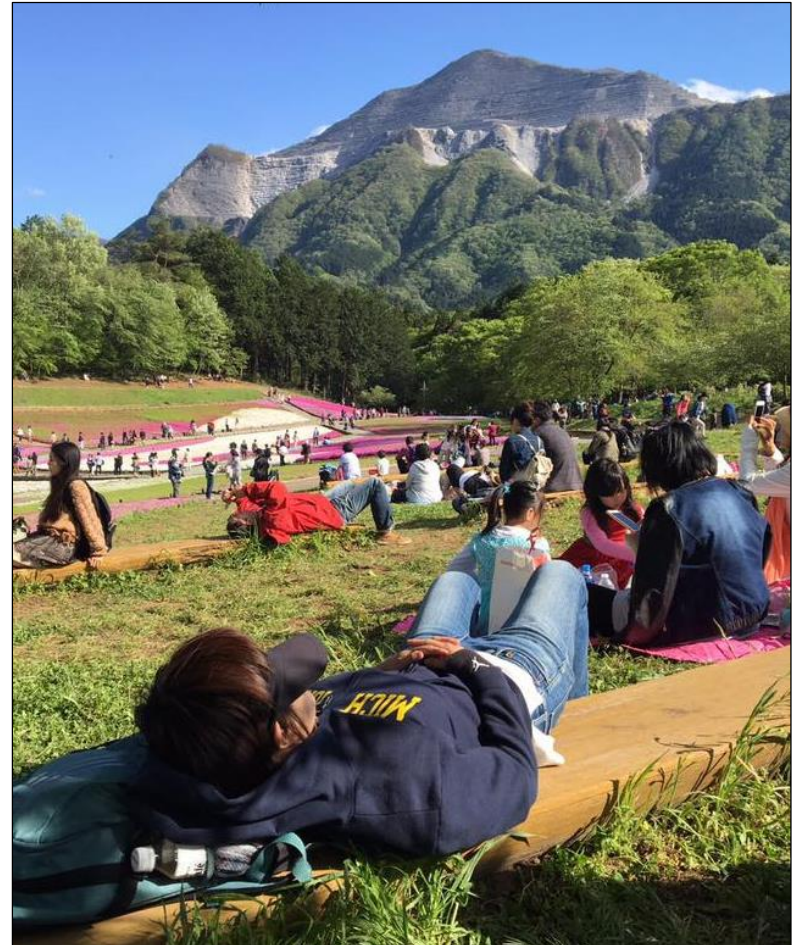
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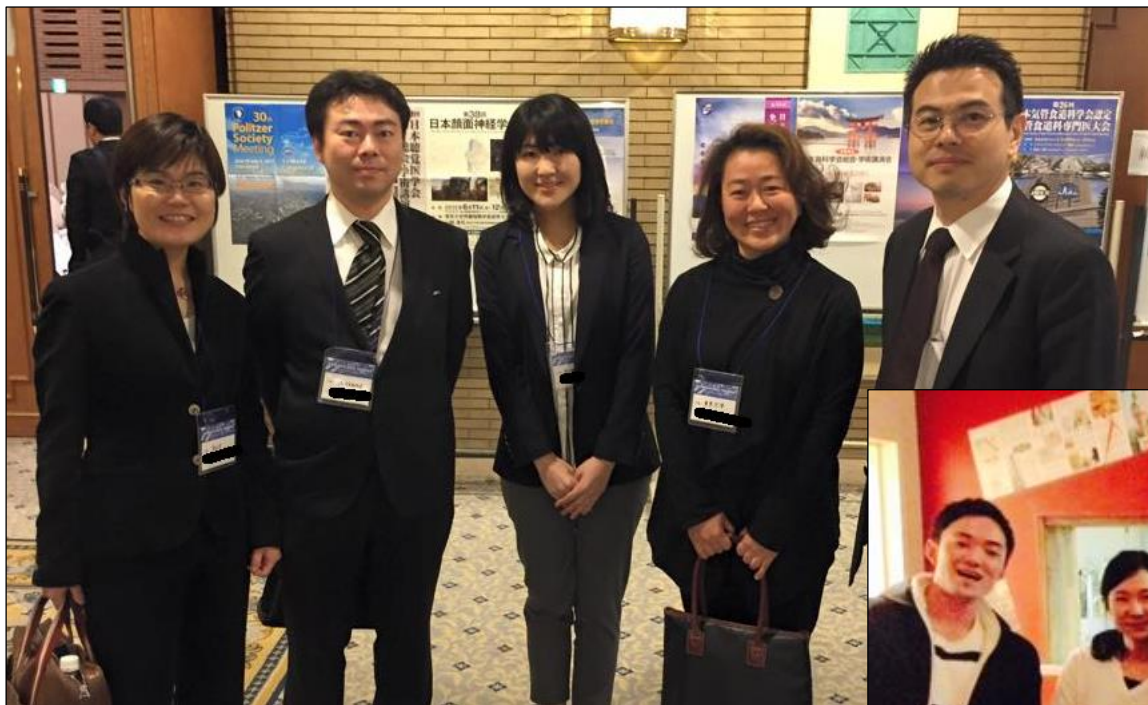
The reduction in mature ORN numbers was associated with olfactory dysfunction.

The reduction in mature

# 家族とリフレッシュ



# 職場環境・仲間の協力！



医者は、人を治すのではない。

人を治す手伝いをするだけだ。

でも、サポートする医者にも、

気力と体力、休息が必要だ。

個人事情に応じた勤務環境への

理解・協力・感謝を

お互いに・・・

## Take home message ??

- 「医師」として、患者さんに関わる時間を、人生を通して継続.
- 仕事へのアプローチはいろいろ. 個人個人で多様であって当然.
- 悩み・もがき・相談し、「努力から楽しく」に変えられたらHappy.
- 気力・体力・リフレッシュ！！
- 自分がやってきたやり方・背中を、後輩に見せつつ、押し付けない.
- 現在に至るまで・・・我が人生に悔いなし・・・??



東京大学  
THE UNIVERSITY OF TOKYO

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