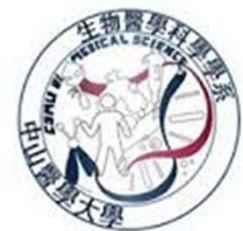




# 口腔黏膜下纖維化症之致病機轉及治療新策略

中山醫學大學

口腔醫學院      牙醫系/口腔科學研究所  
醫學科技學院    生物醫學科學系



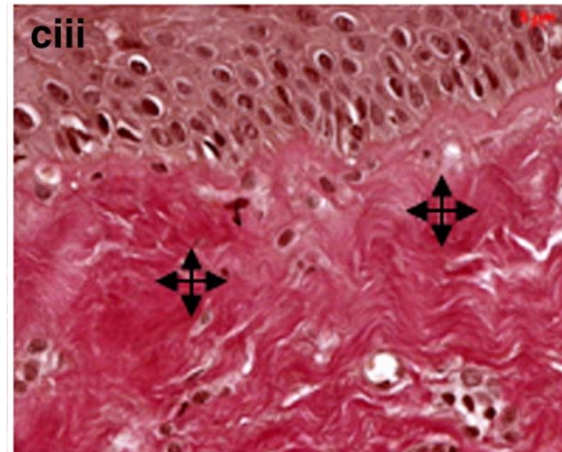
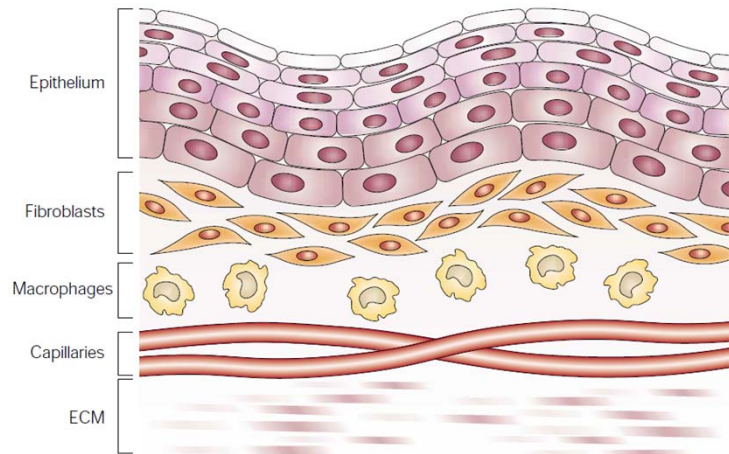
# Oral submucous fibrosis

- Oral submucous fibrosis (OSF) is a chronic progressive scarring disease and as a precancerous lesion (8% for transformation into oral cancer within 10 years)
- An inflammatory fibrotic disease that mainly occurs in Southeast Asian people.
- Major caused by areca quid chewing habit.
- Major symptoms:
  - Blanching of the oral mucosa
  - Trismus
  - Stomatopyrosis



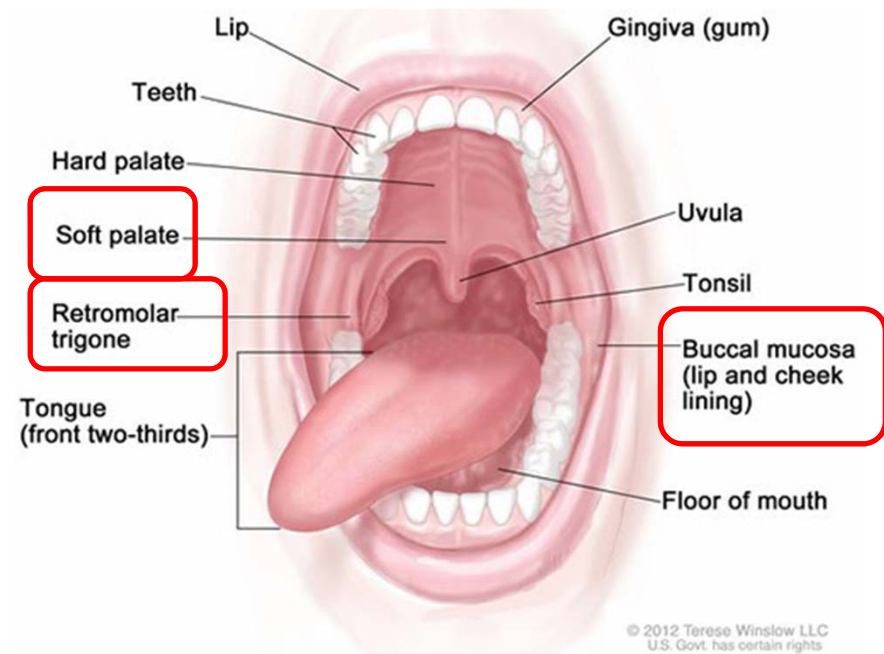
# Oral submucous fibrosis

- Histopathologically :
  - Epithelial atrophy
  - **Chronic inflammation**
  - Juxtaepithelial hyalinization
  - **Excessive extracellular matrix (ECM) deposition** leading to fibrosis of submucosal tissue.



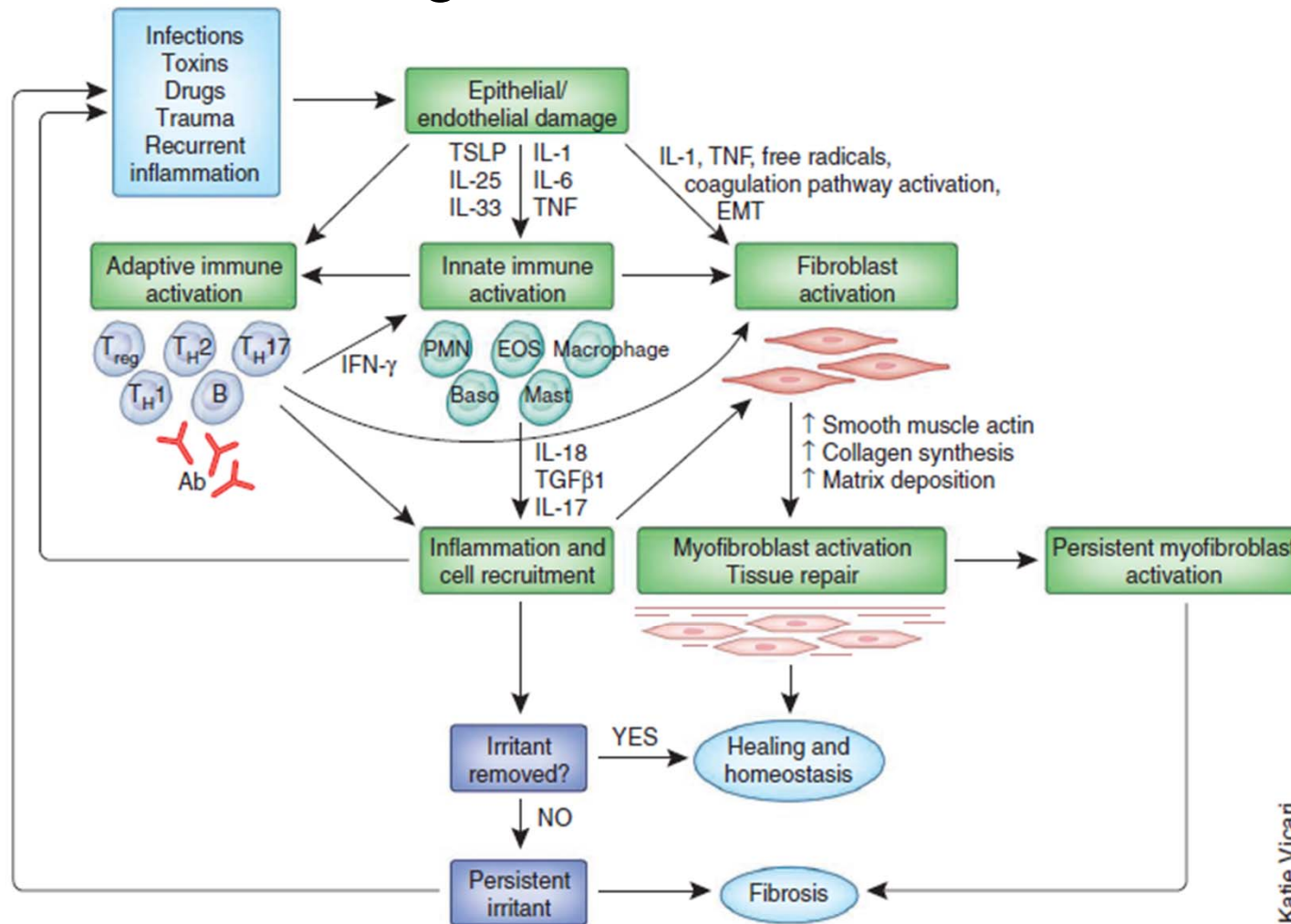
# Oral submucous fibrosis

- Treatment:
  - Corticosteroids
  - Surgical splitting or excision
  - Injections of interferon-  $\gamma$



# Fibrosis & Myofibroblast

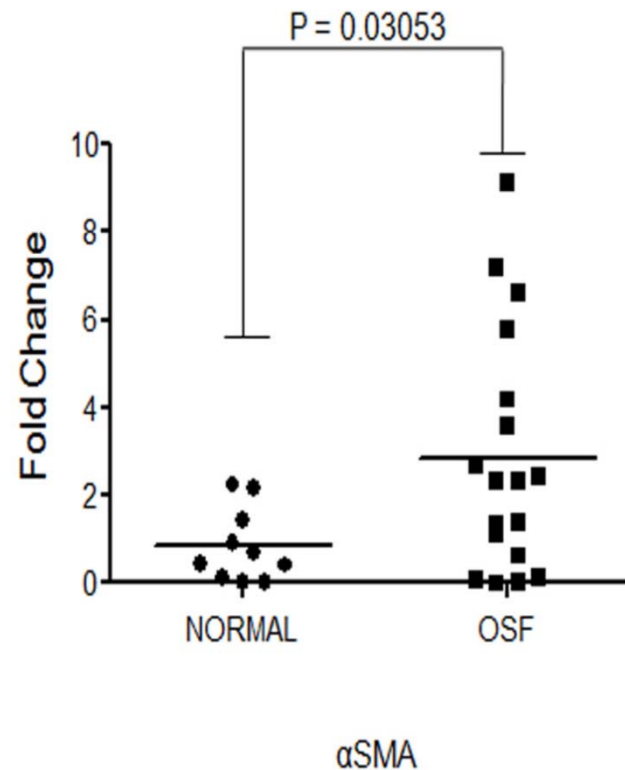
- Myofibroblasts are the key mediators of fibrotic tissue remodeling



Katie Vicari

# Myofibroblast & OSF

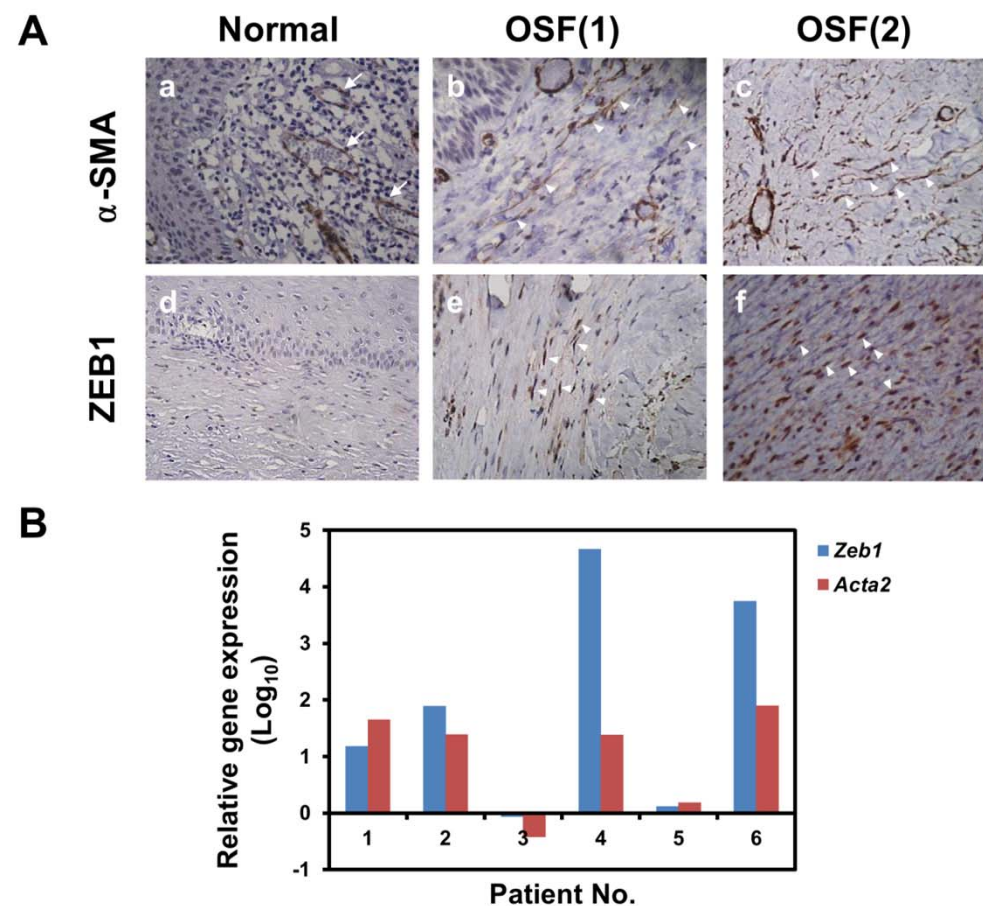
- The myofibroblast activity is positive correlation with disease severity in OSF.



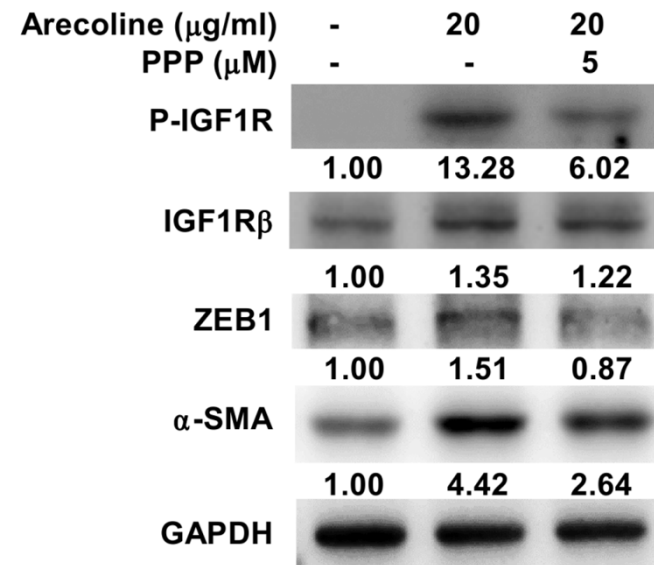
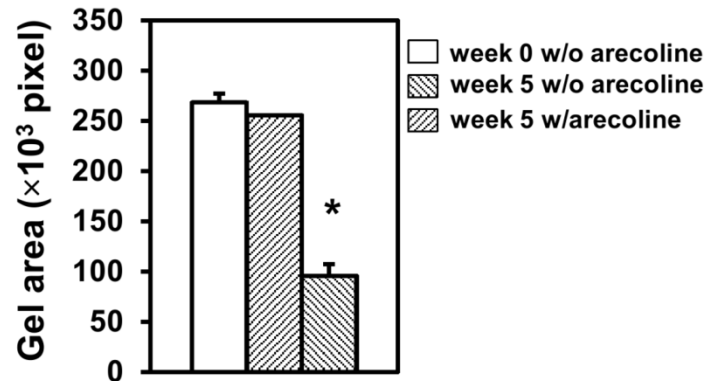
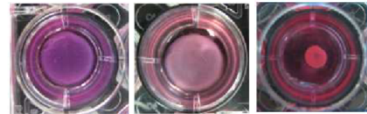
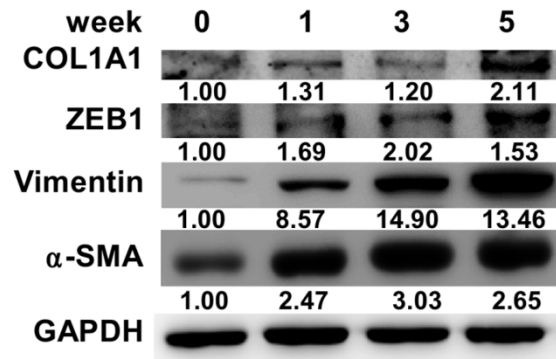


## Arecoline-induced myofibroblast transdifferentiation from human buccal mucosal fibroblasts is mediated by ZEB1

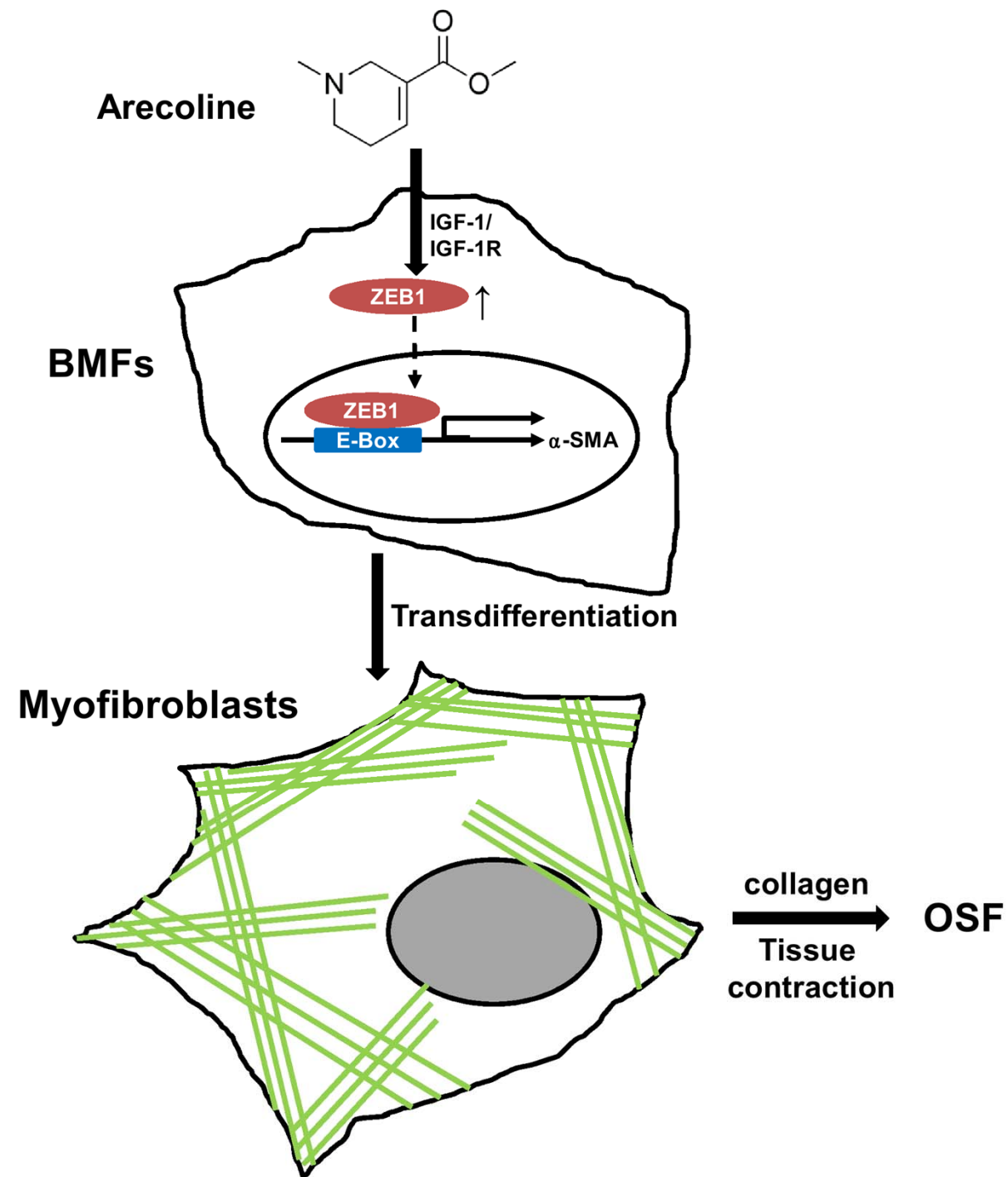
Yu-Chao Chang <sup>a, b</sup>, Chung-Hung Tsai <sup>c, d, #</sup>, You-Liang Lai <sup>e, #</sup>, Cheng-Chia Yu <sup>a, b, f</sup>, Wan-Yu Chi <sup>e</sup>,  
Jung Jung Li <sup>e</sup>, Wen-Wei Chang <sup>e, g, \*</sup>



# Long-term exposure of arecoline induces the expression of fibrogenic genes and is correlated with ZEB1 expression

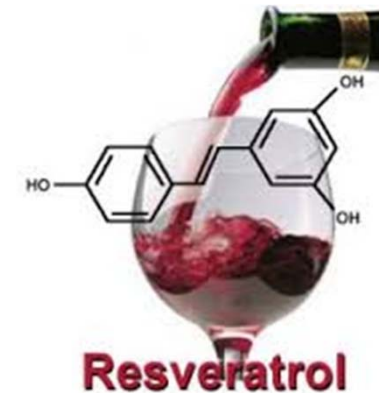






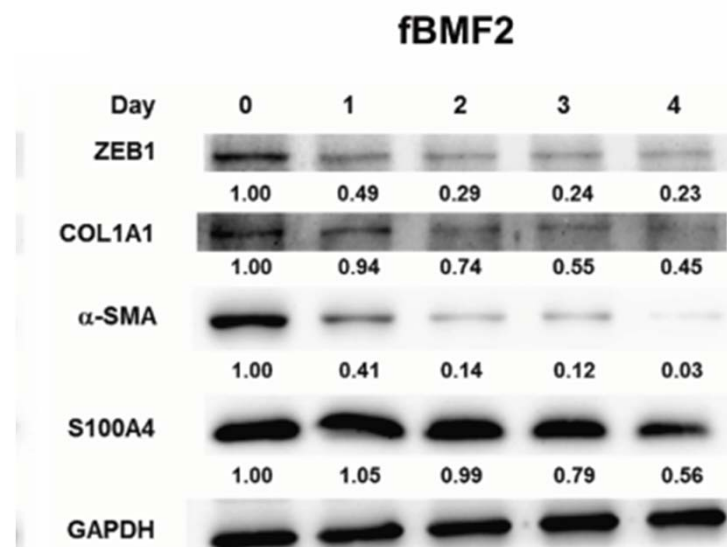
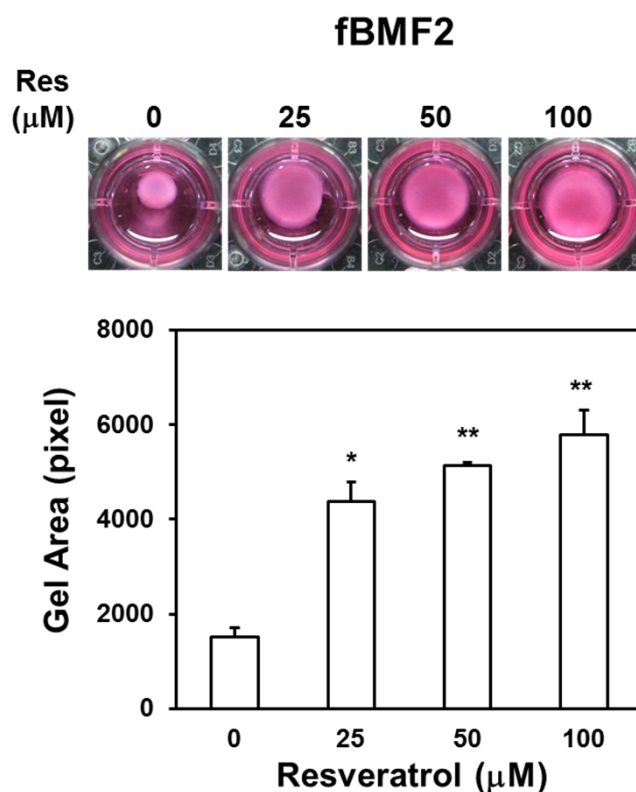
# Resveratrol (白藜蘆醇)

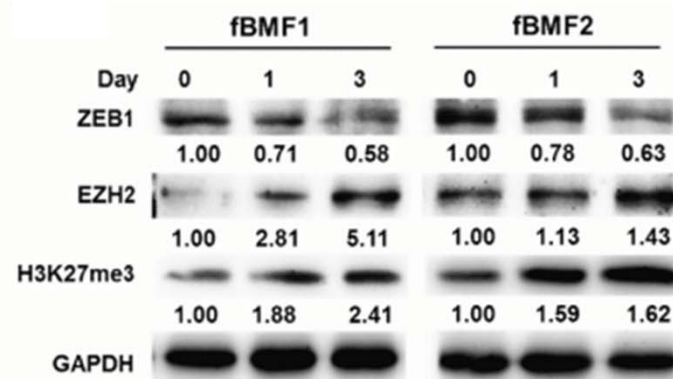
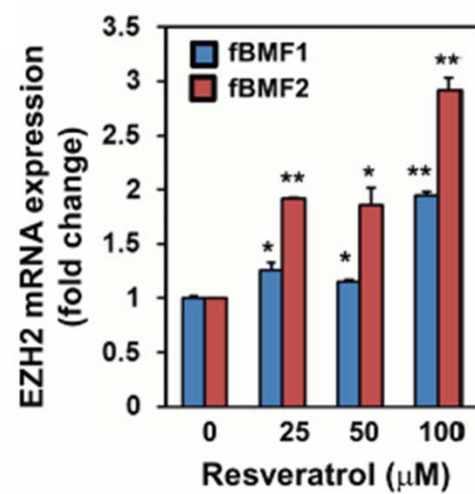
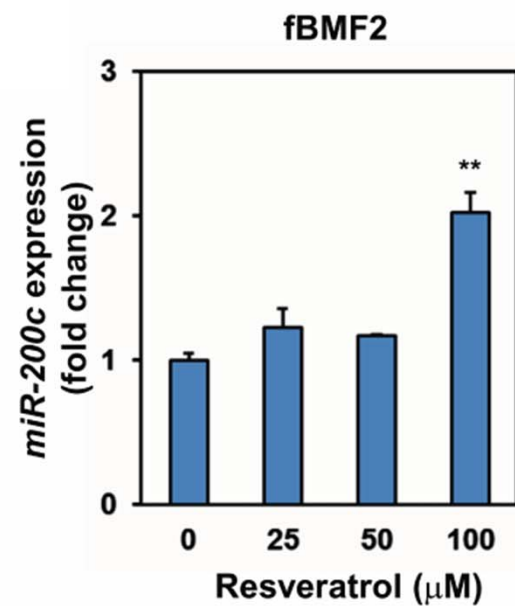
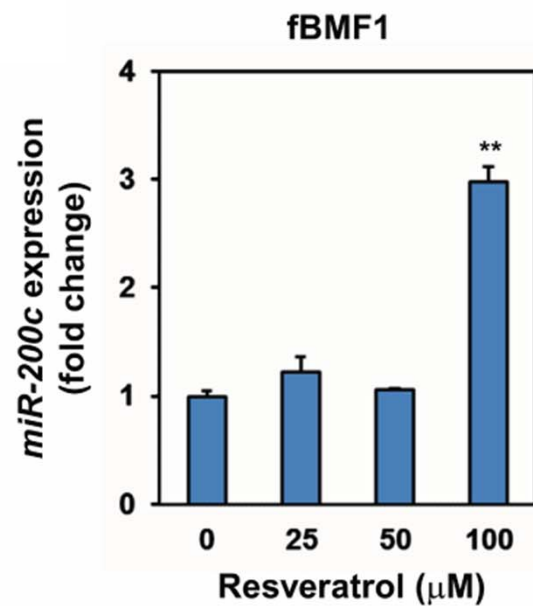
- a natural polyphenolic flavonoid present in red wine.
- antioxidant, anti-inflammation, and anti-aging.
- Resveratrol could downregulate the expression of ZEB1 in head and neck squamous carcinoma cells (余承佳. *Mol Nutr Food Res*. 2012;56:1247–1258.)

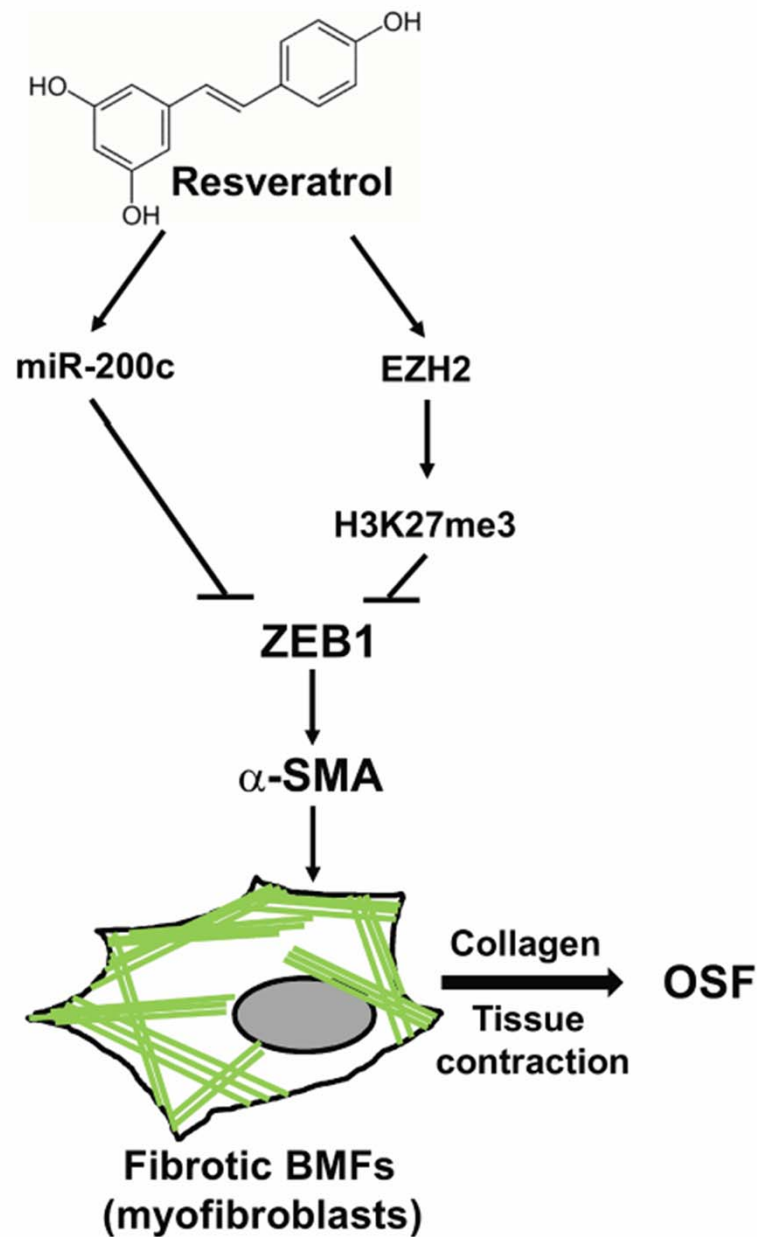
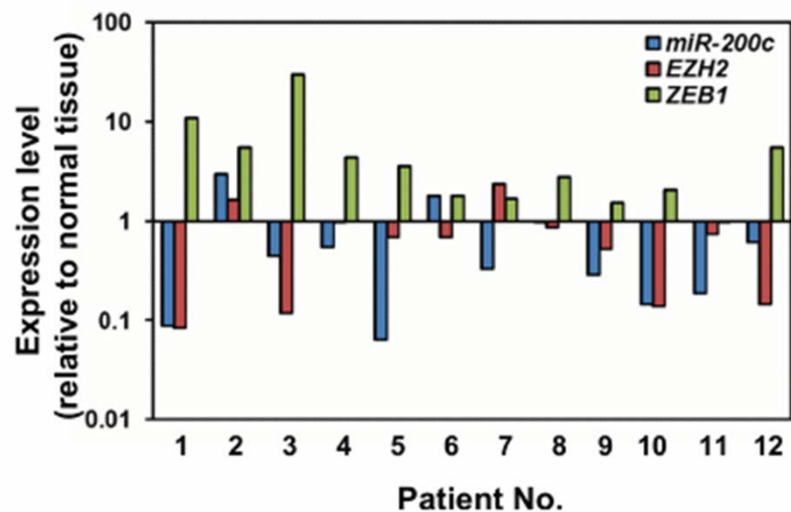
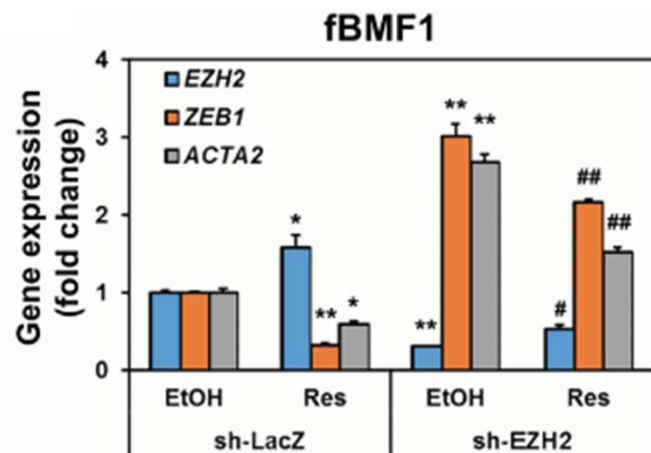


## Resveratrol suppresses myofibroblast activity of human buccal mucosal fibroblasts through the epigenetic inhibition of ZEB1 expression

Yu-Chao Chang<sup>1,2,\*</sup>, Cheng-Wei Lin<sup>3,\*</sup>, Cheng-Chia Yu<sup>1,2,4</sup>, Bing-Yen Wang<sup>5,6,7</sup>, Yu-Hao Huang<sup>3</sup>, Yang-Chih Hsieh<sup>3</sup>, Yu-Liang Kuo<sup>8,9</sup> and Wen-Wei Chang<sup>3,10</sup>







**OPEN**

## **Aberrant SSEA-4 upregulation mediates myofibroblast activity to promote pre-cancerous oral submucous fibrosis**

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**Cheng-Chia Yu<sup>1,2,3</sup>, Chuan-Hang Yu<sup>2,3</sup> & Yu-Chao Chang<sup>2,3</sup>**

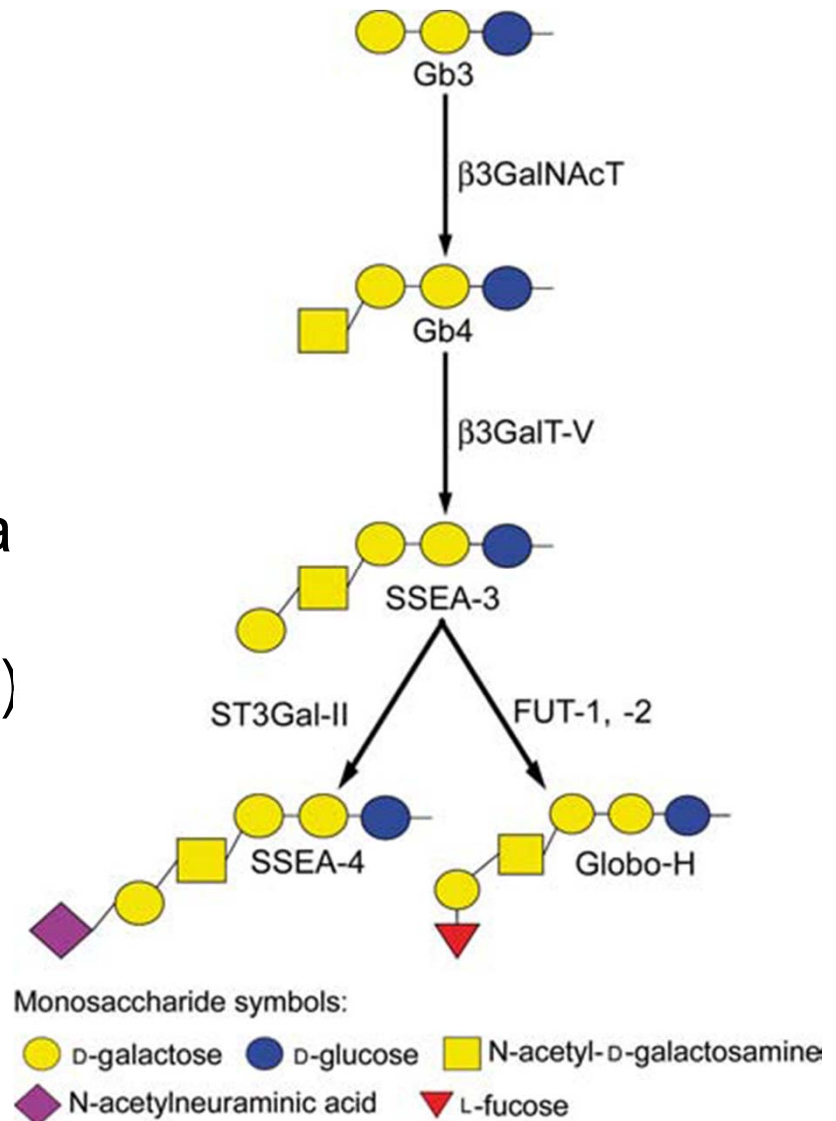


# Stage-specific embryonic antigen-4 (SSEA-4)

- A surface antigen consisting of sialylglycolipid
- A specific and useful marker of pluripotent stem cells
  - Often represents lineage-specific signatures indicating the state of cell differentiation
  - SSEA-3 and SSEA-4 are the most commonly used for identifying pluripotent stem cell-like embryonic stem cells and **highly expressed in human embryonal carcinoma**

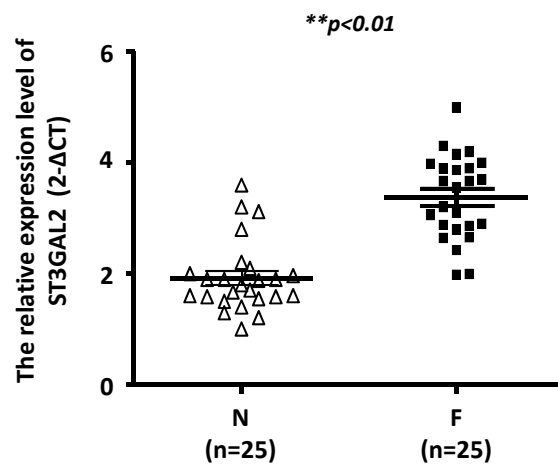
# SSEA4 and ST3GAL2

- SSEA-4 is also important as a cell surface marker for embryonic stem cells and cancer stem cells.
- D2,3-sialyltransferase (ST3Gal II) is a stage-specific embryonic antigen-4 (SSEA-4) synthase.

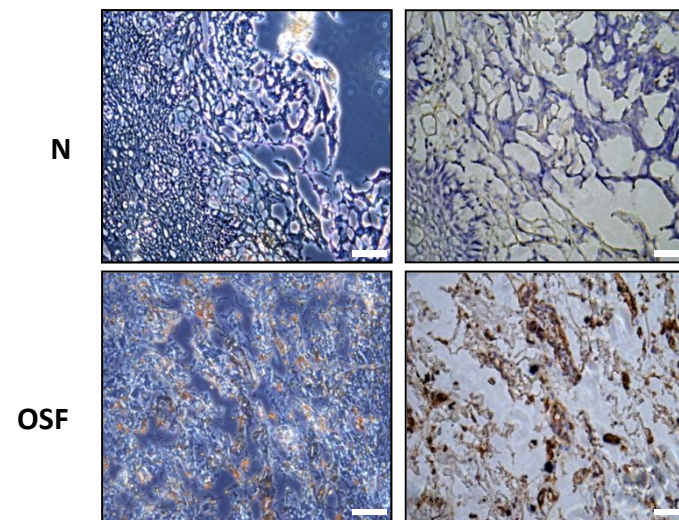


## Elevation of SSEA-4 expression in OSF specimens

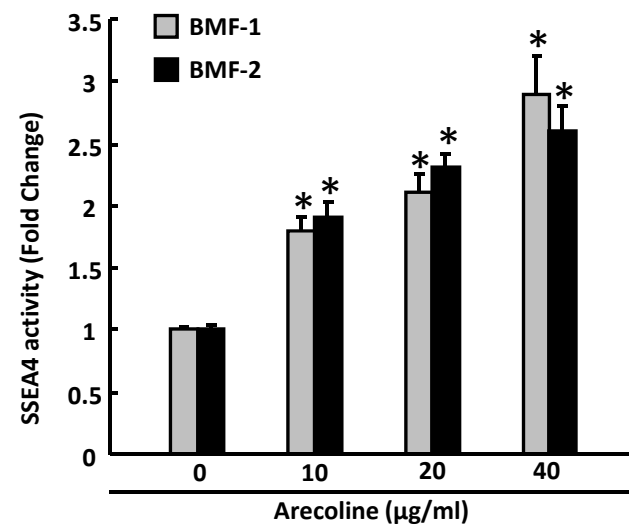
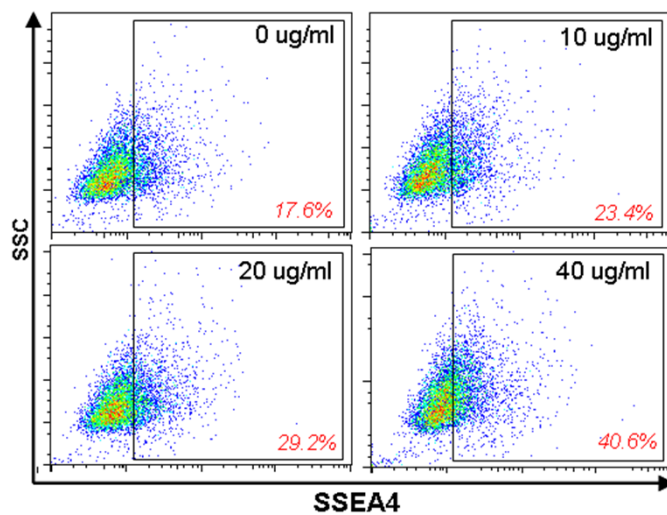
(a)



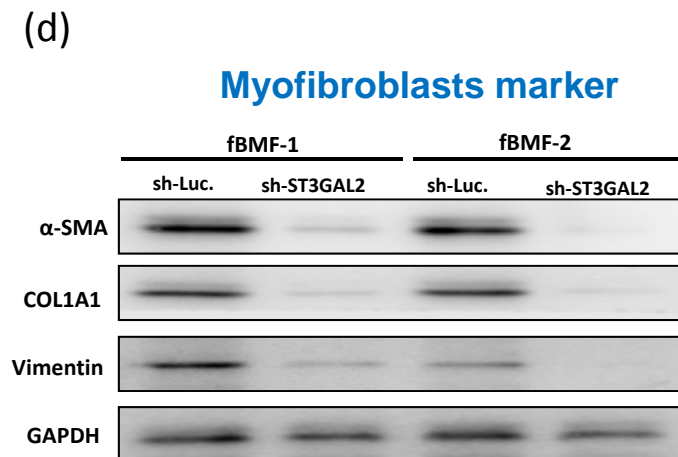
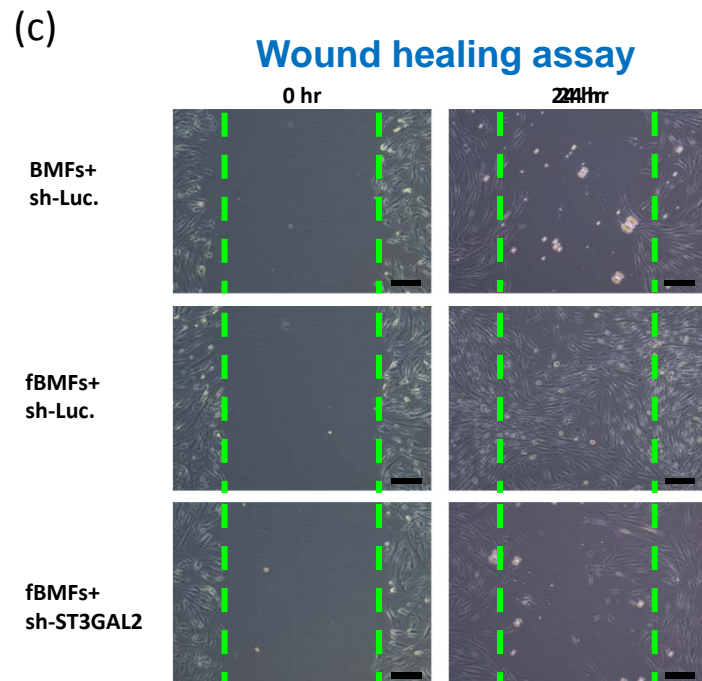
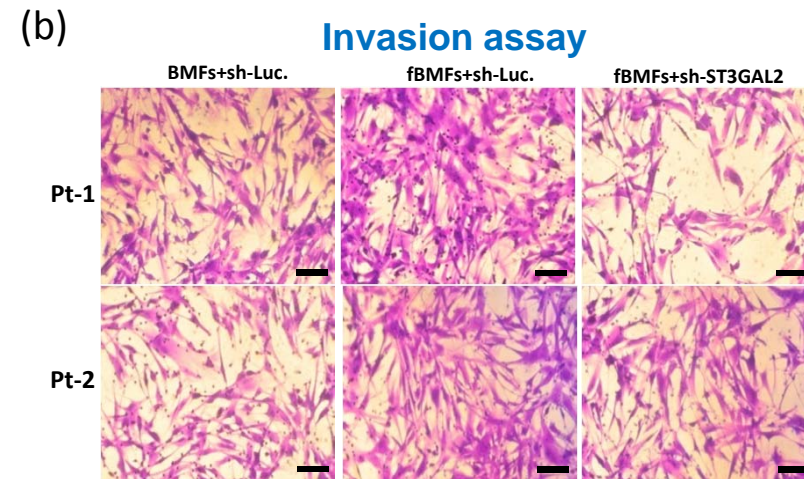
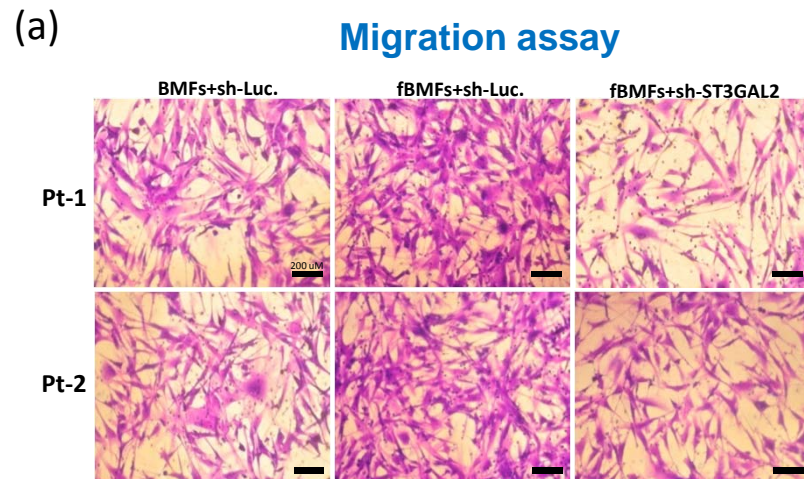
(b)



(c)



# ST3GAL2 down-regulation repressed myofibroblast properties



# Conclusions

- Arecoline in areca nut could induce fibrosis of BMFs.
- The fibrogenic activity of arecoline is mediated by the expression of IGF-1R/ZEB1 and/or ST3GAL2/SSEA4.
- Targeting ZEB1 by resveratrol has a potential in amelioration of OSF.

*中山醫大口腔研究團隊未來將持續致力於口腔相關疾病的研究，並朝向相關保健品或藥物的開發，以期對改善國人口腔健康有所貢獻。*

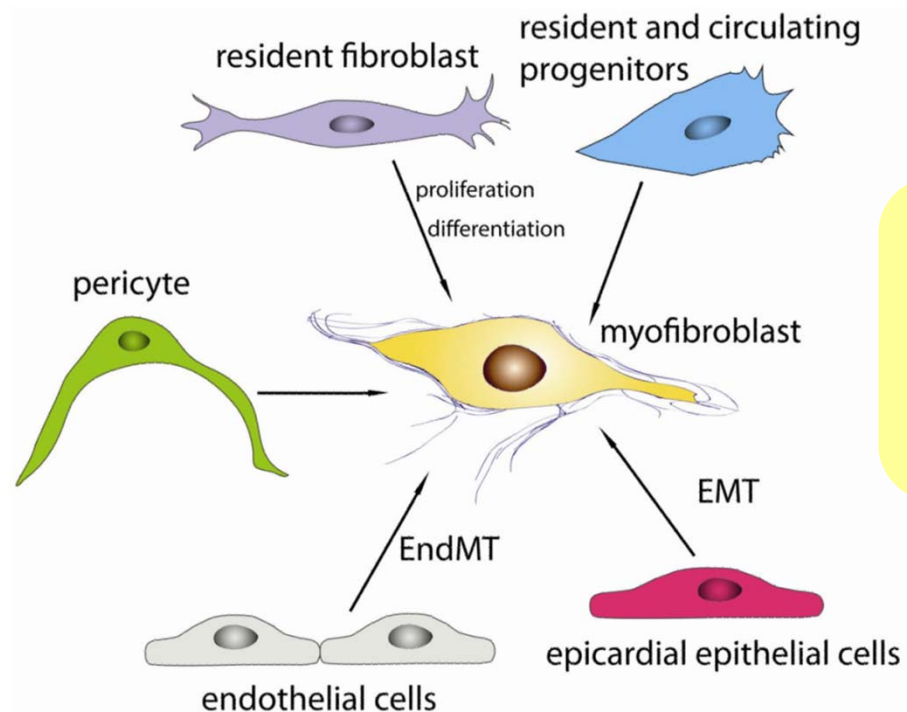
# Fibrosis & Myofibroblast

- Myofibroblasts are the key mediators of fibrotic tissue remodeling
- The major cell type that secretes collagen and reorganizes the extracellular matrix after injury
- Central mediator of fibrogenesis
  - cytokines (transforming growth factor- $\beta$ , TGF- $\beta$ )
  - chemokines (CXCL12)
  - angiogenic factors (VEGF)
  - growth factors (PDGF)



# Myofibroblast

- The contractile cells expressing  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) and collagen I (Coll)
- The myofibroblast precursors-



## Morphology

- Increased mobility
- Invasive
- Increased proliferation (stemness)

## Markers

- vimentin
- $\alpha$ -SMA
- FSP-1
- Laminins
- Fibronectin
- N-cadherin