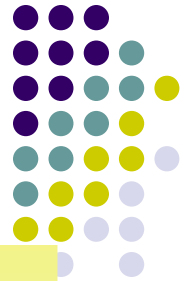


About OMICS Group

OMICS Group is an amalgamation of [Open Access publications](#) and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access [scholarly journals](#) in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 [International conferences](#) annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Regulatory role of microRNAs in severe asthma



J. Chakir, PhD

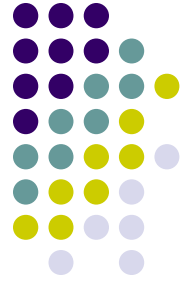
Professor, Faculty of Medicine, IUCPQ
Laval University, Quebec, Canada

3rd International Conference on Integrative Biology
Valencia, Spain, August 04-06 2015



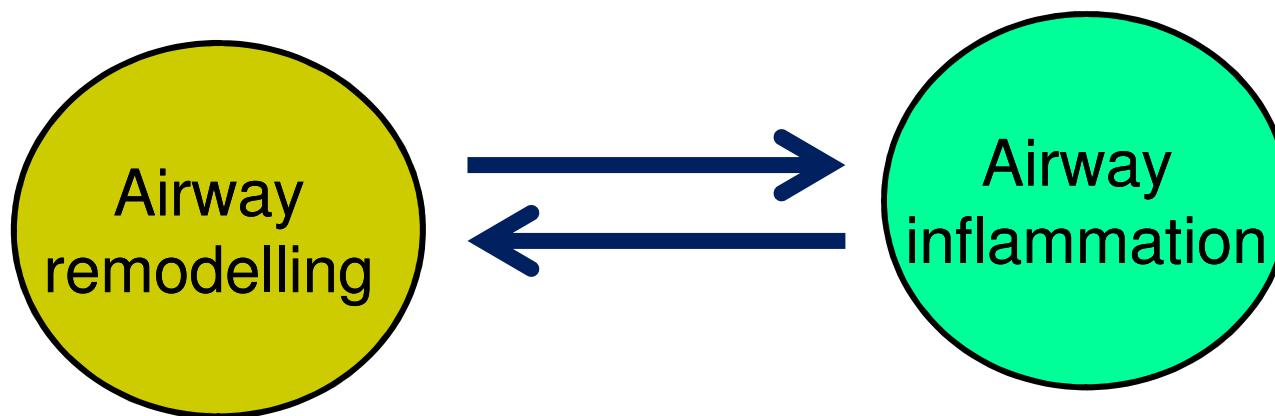
INSTITUT UNIVERSITAIRE
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC

INTRODUCTION



- ❖ Severe asthma is characterized by persistent airway obstruction and frequent exacerbations despite high-dose of corticosteroids.
- ❖ Represents a small proportion of the overall asthmatic population but contributes disproportionately to health care costs.
- ❖ Severe asthma is a complex disease characterized by various clinical, physiological and immunological phenotypes.

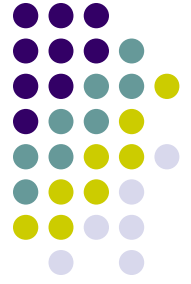
Severe Asthma Pathogenesis



- Increased smooth muscle mass
- Reticular Basement membrane thickening
- Increased angiogenesis
- **Epithelial thickness**

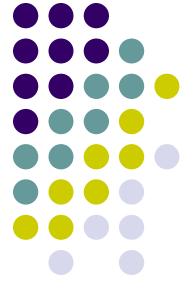
- Th2 high/Low
- Th17
- Eosinophilic/Neutrophilic
- Fibrogenic cytokines

Functional role of airway epithelium



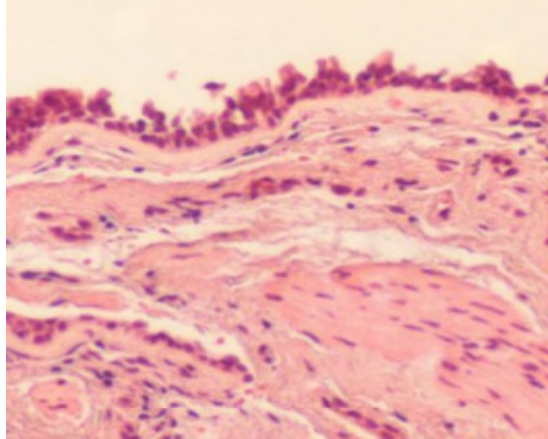
- Bronchial epithelium forms a dynamic barrier that protects the mucosa from inhaled pollutants and infectious agents.
- The airway epithelium protects the internal milieu of the lung by secreting mucus and by signalling and interacting with the innate and adaptive immune systems through the secretion of cytokines and chemokines

Functional and structural alteration of airway epithelium in asthma

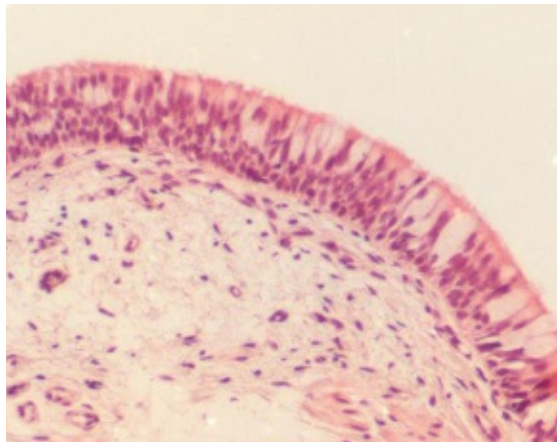


- ❖ Bronchial epithelium activity is disturbed: increased secretion of mucins, increased production of cytokines and growth factors
- ❖ Bronchial epithelium phenotype is altered: high expression of hsp, p21^{waf}, NF-KB
- ❖ Bronchial epithelium has an altered response to injury and has an abnormal repair
- ❖ Structural alteration

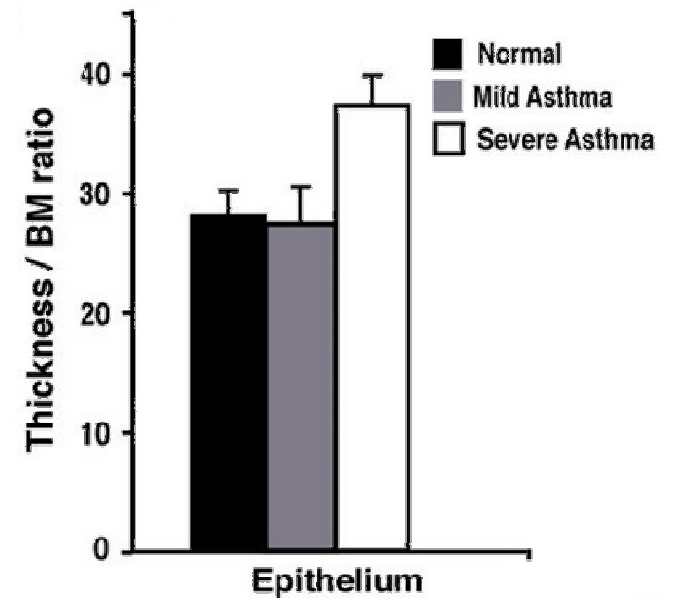
Epithelium thickness in severe asthma



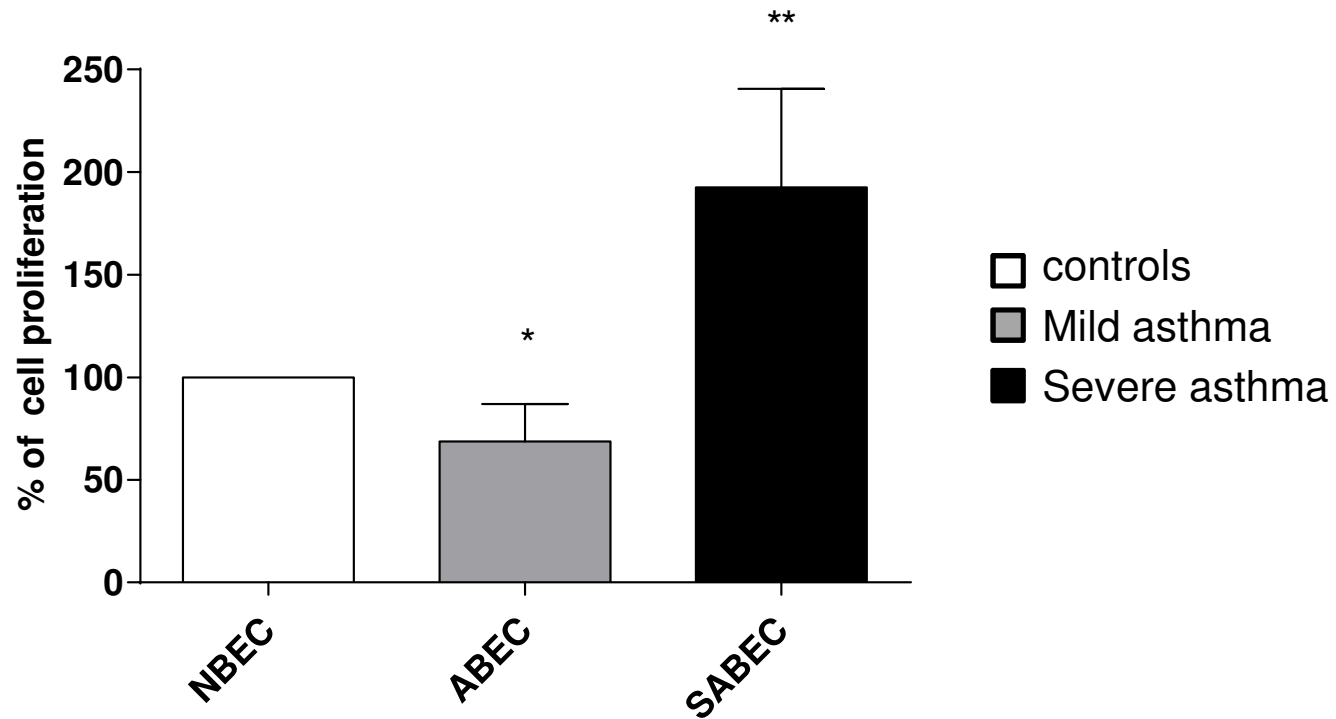
Mild Asthma



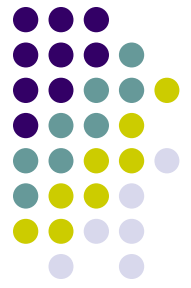
Severe Asthma



Epithelial cell proliferation in severe asthma

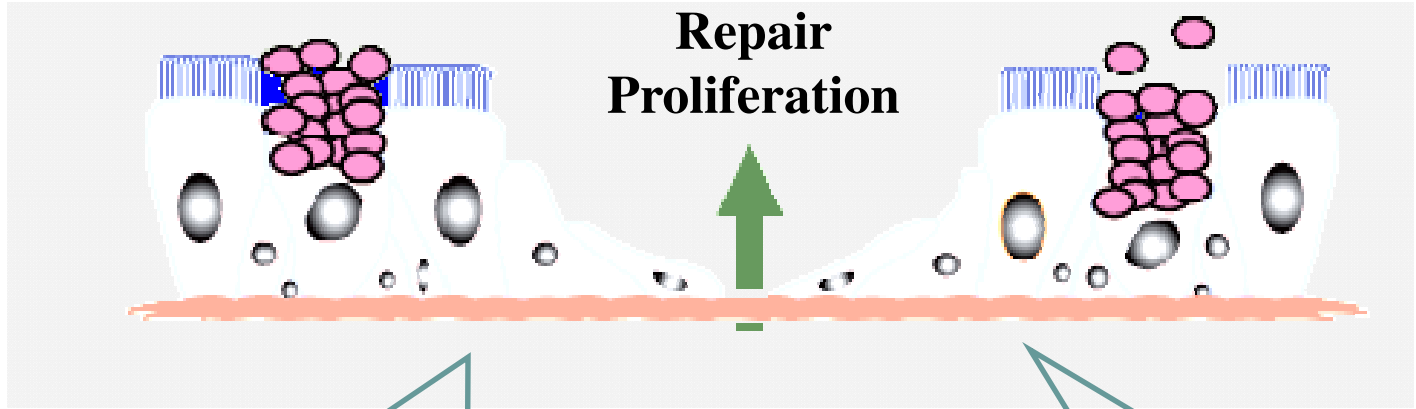


Proliferation in severe asthma



Cytokines

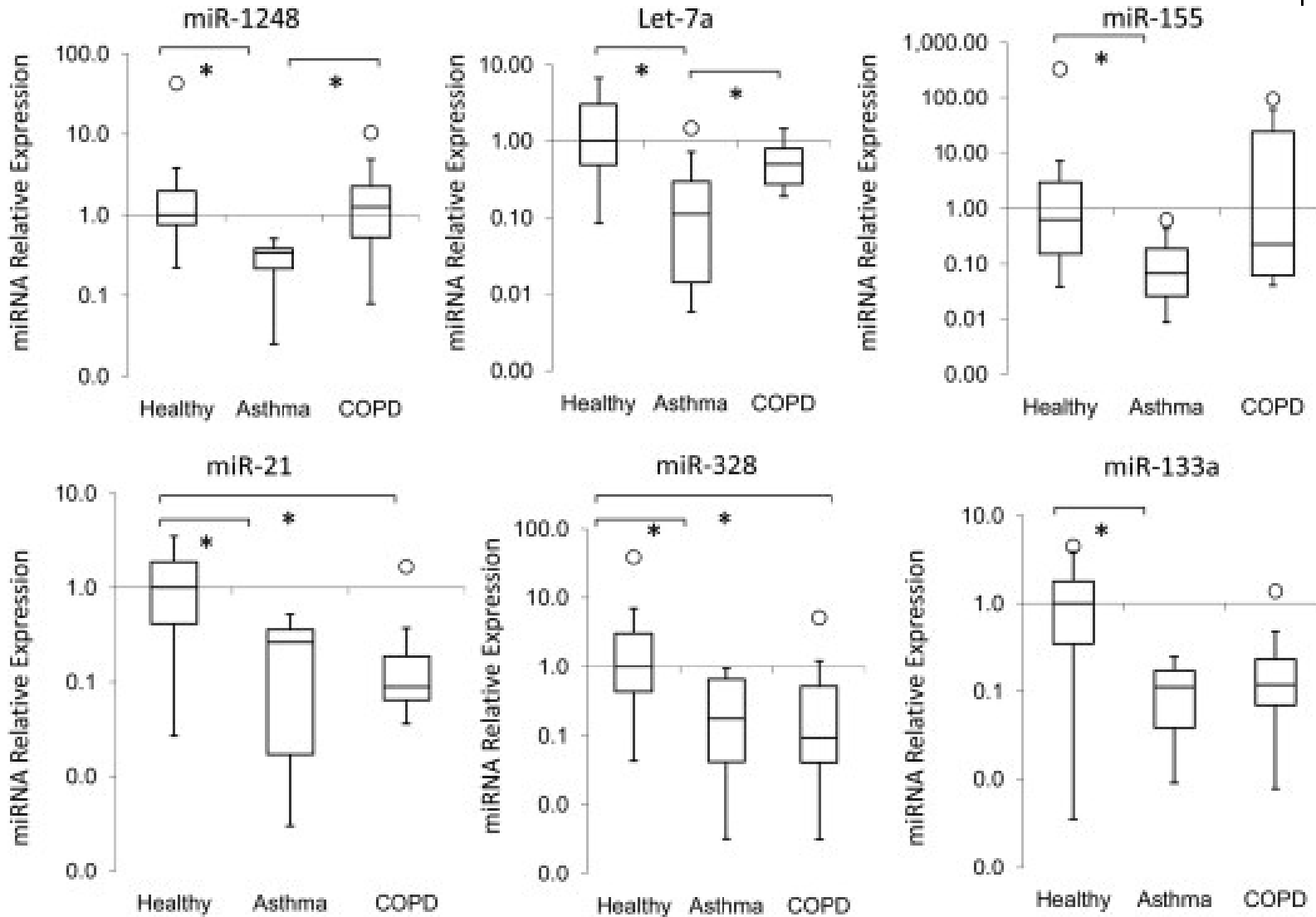
Growth factors



Extracellular matrix

MicroRNAs

MicroRNAs in exhaled breath condensates



miRNAs and airway Epithelium in Asthma

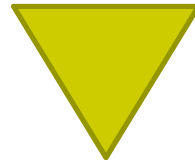


Am J Respir Crit Care Med. 2012 Nov 15;186(10):965-74. doi: 10.1164/rccm.201201-0027OC. Epub 2012 Sep 6.

Airway Epithelial miRNA Expression Is Altered in Asthma

Owen D. Solberg^{1,2*}, Edwin J. Ostrin^{2*}, Michael I. Love¹, Jeffrey C. Peng¹, Nirav R. Bhakta¹, Lydia Hou¹, Christine Nguyen², Margaret Solon¹, Cindy Nguyen¹, Andrea J. Barczak^{1,2}, Lorna T. Zlock³, Denitza P. Blagev^{1,2}, Walter E. Finkbeiner³, K. Mark Ansel⁴, Joseph R. Arron⁵, David J. Erle^{1,2*}, and Prescott G. Woodruff^{1,2*}

¹Cardiovascular Research Institute, ²Division of Pulmonary and Critical Care Medicine, Department of Medicine ³Department of Pathology, and ⁴Department of Microbiology and Immunology, University of California San Francisco, San Francisco, California; and ⁵Genentech, Inc., South San Francisco, California



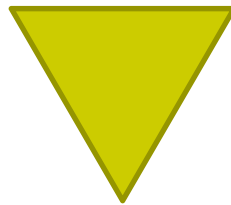
- ❖ **Decreased expression of miR-34/449 family (miR-34c-5p, miR-34c-5p, miR-449a, and miR-449b-5p)**
- ❖ **Repression by IL-13 of miR-34/449 family**
- ❖ **miR-449 inhibits NOTCH1 gene**

Am J Respir Cell Mol Biol. 2012 Oct;47(4):536-42. doi: 10.1165/rcmb.2011-0160OC. Epub 2012 Jun 7.

Distinct MicroRNA Expression in Human Airway Cells of Asthmatic Donors Identifies a Novel Asthma-Associated Gene

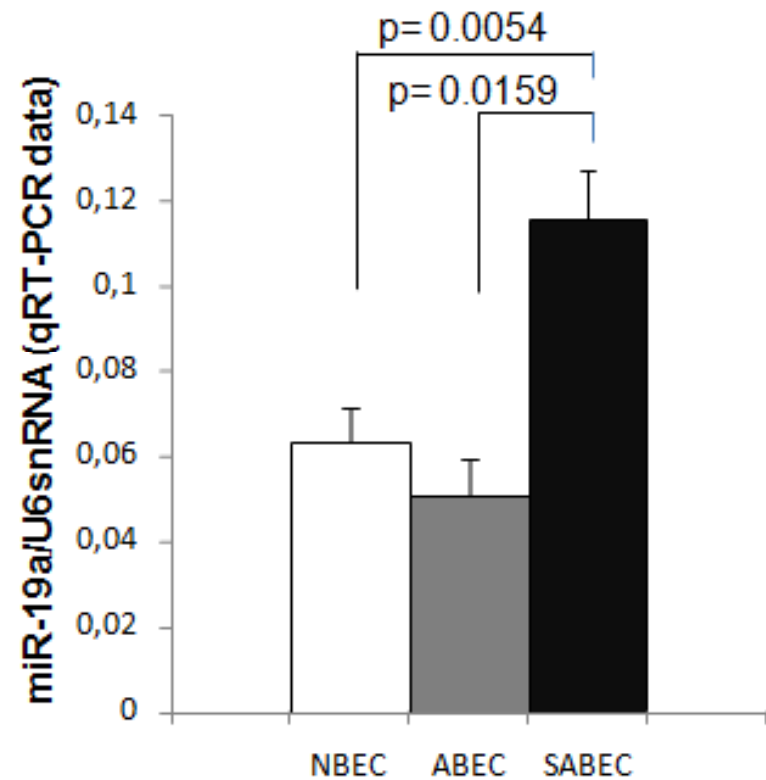
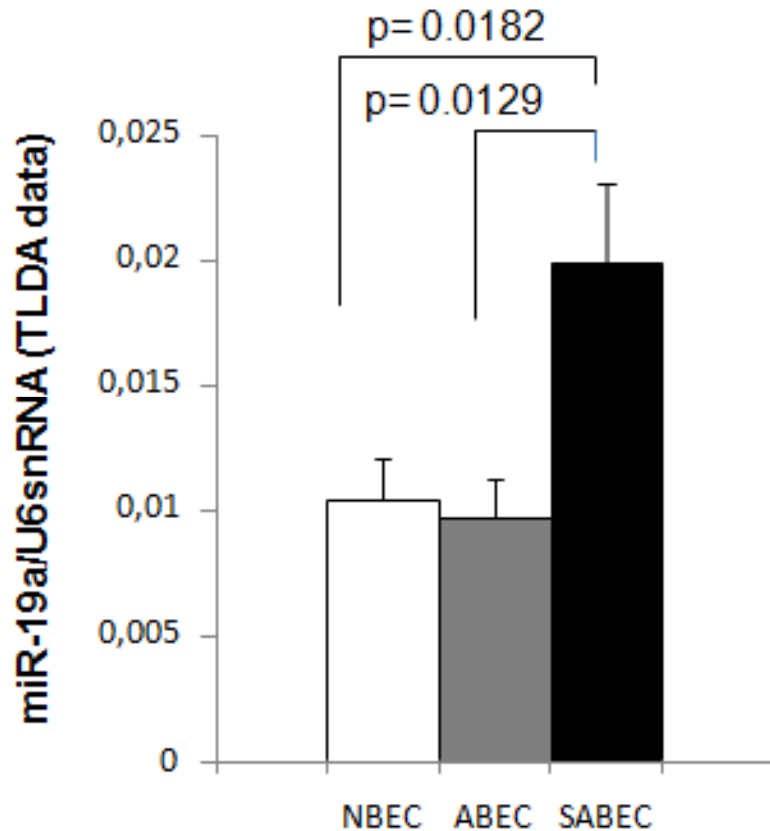
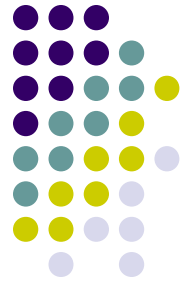
Melanie J. Jardim¹, Lisa Dailey¹, Robert Silbajoris¹, and David Diaz-Sanchez¹

¹National Health and Environmental Effects Research Laboratory, Environmental Public Health Division, United States Environmental Protection Agency, Chapel Hill, North Carolina

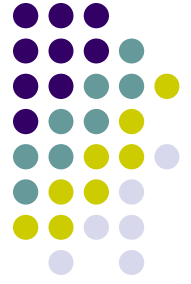


- ❖ **Increased expression of miR-let7f, miR-487b and miR-181c in BEC from mild asthmatic donors**
- ❖ **Increased expression of miR-203 (regulation of *AQP4* transcript)**

hsa-miR-19a differentially expressed in severe asthma



NBEC: Normal controls
ABEC: Mild asthmatics
SABEC: severe asthmatics

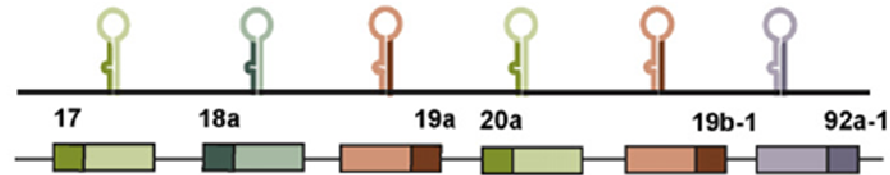


miR-19a

- ❖ MicroARN-19a a member of miR-17~92 cluster



Chr-13 *mir-17-92*

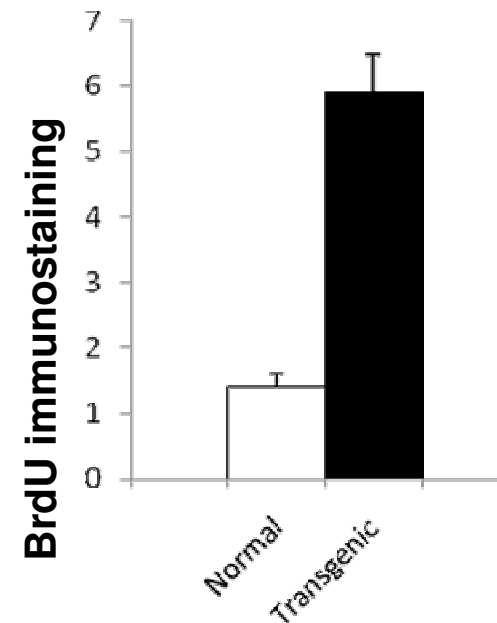
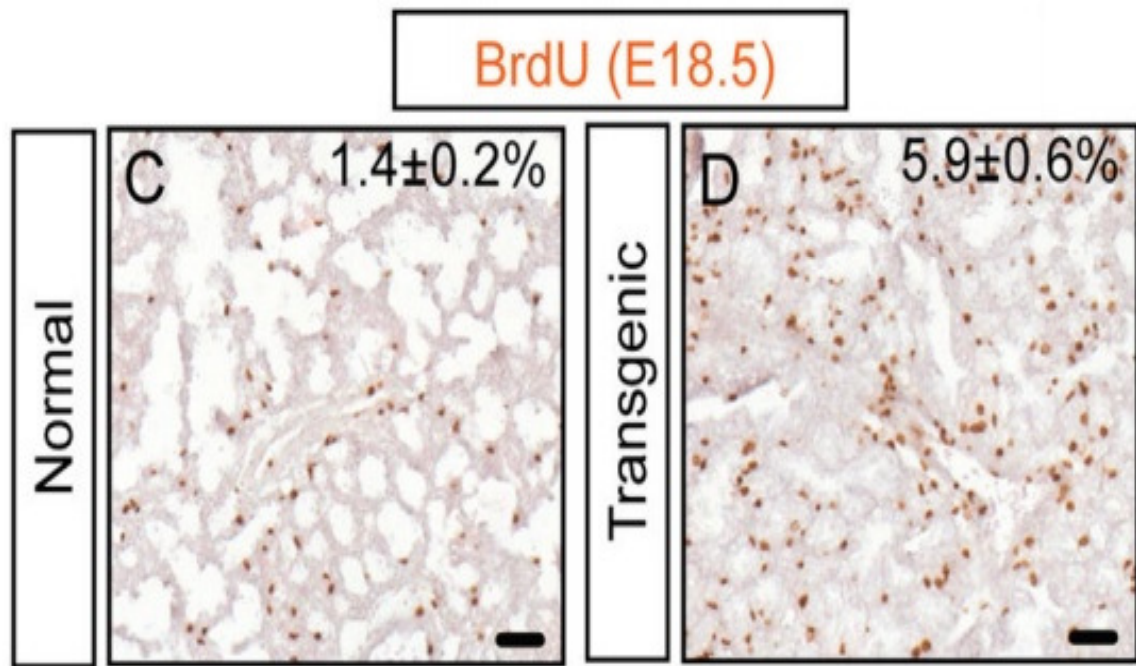
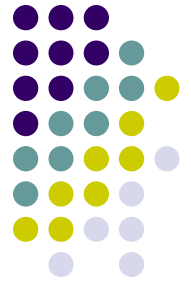


- ❖ MiR-17~92 cluster involved in cell proliferation and differentiation

Dev Biol. 2007 October 15; 310(2): 442–453.

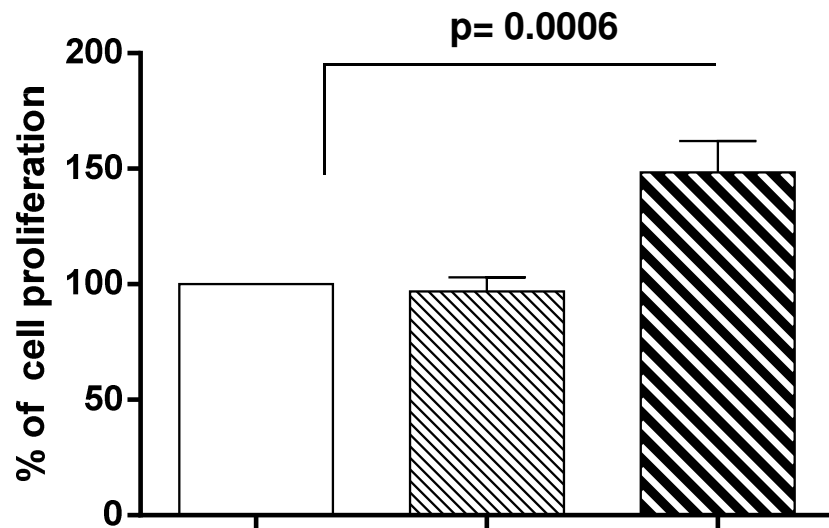
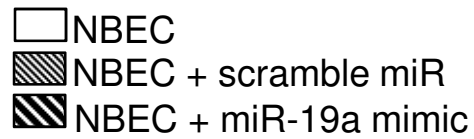
Transgenic over-expression of the microRNA *miR-17-92* cluster promotes proliferation and inhibits differentiation of lung epithelial progenitor cells

Yun Lu¹, J. Michael Thomson², Ho Yuen Frank Wang¹, Scott M. Hammond^{2,3}, and Brigid L.M. Hogan^{1,*}

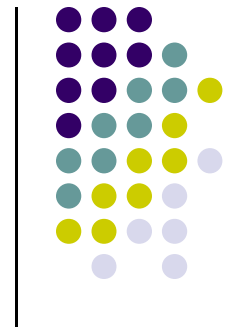
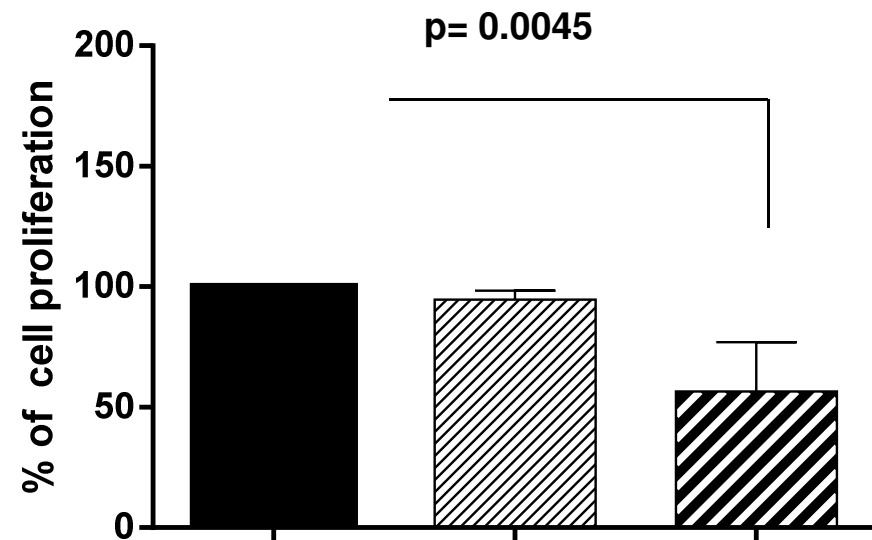
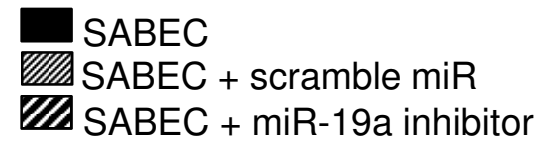


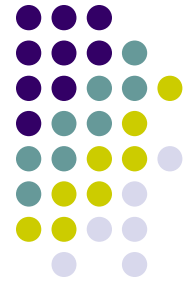
miR-17-92 cluster regulates cell proliferation

Up-regulation with miR 19-a mimic



Down-regulation with miR19a inhibitor





***in silico* search for miR-19a targets
using TargetScan, miRDB, miRTarBase
and MicroCosm databases**

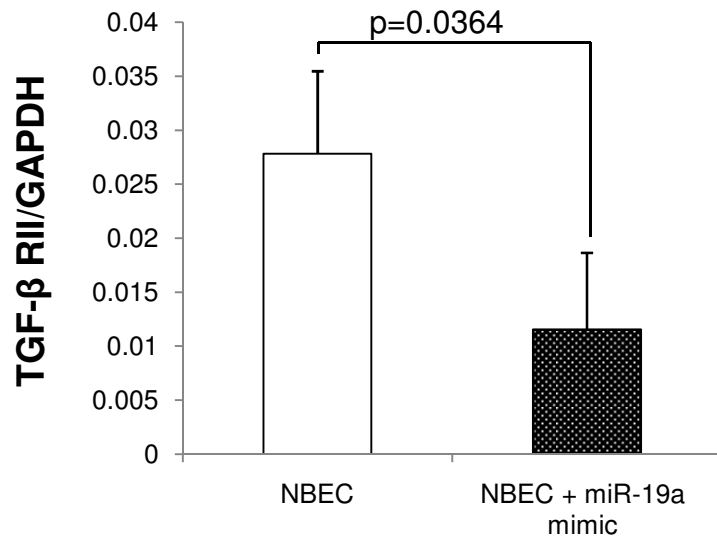


TGF β RII a Potential direct target of miR-19a

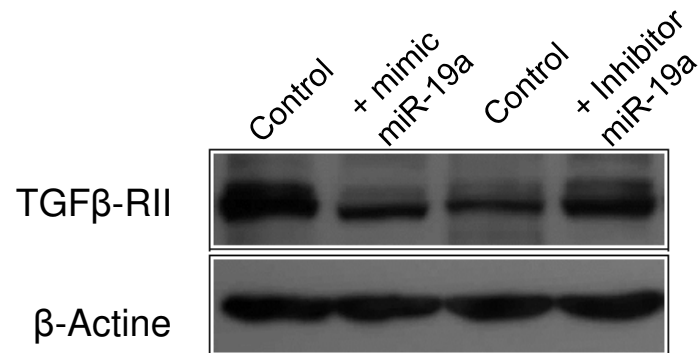
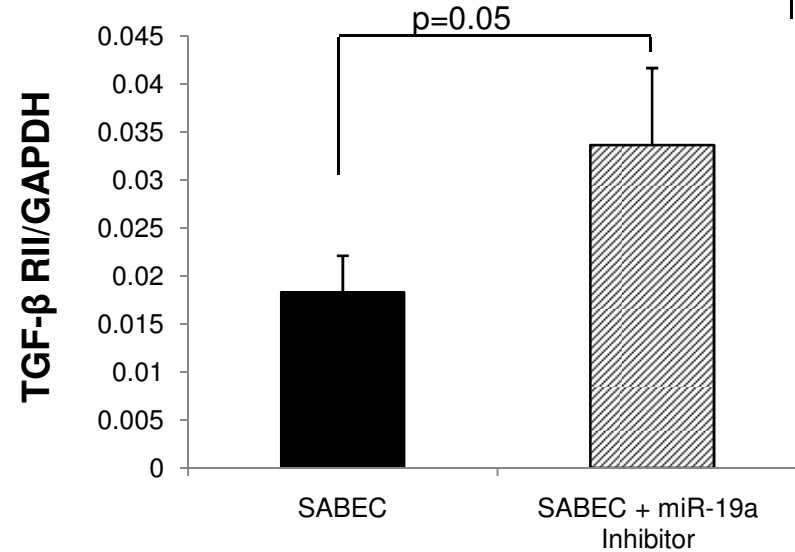
TGF- β RII: Potential target of miR19-a



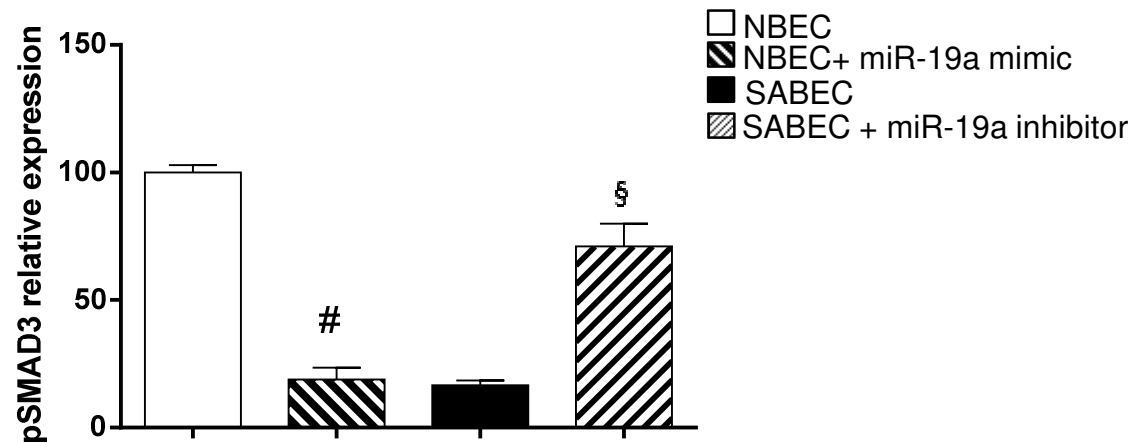
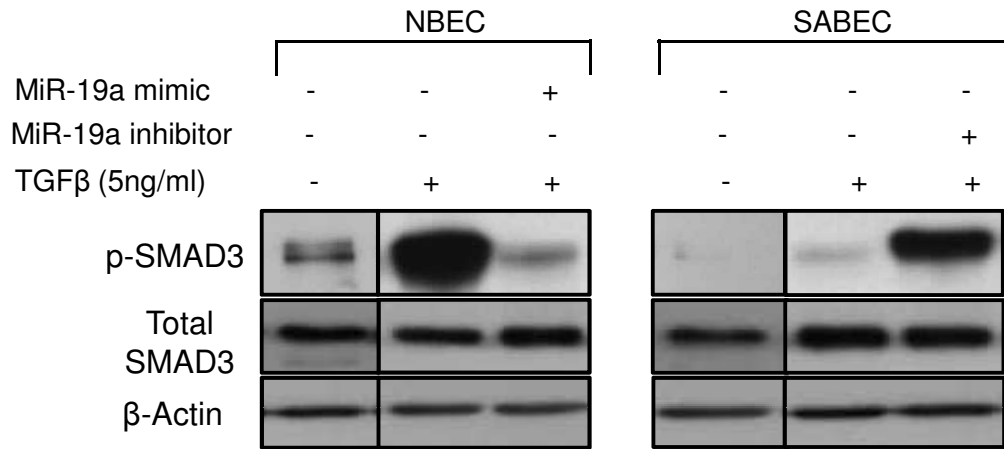
miR-19a Upregulation



miR-19a downregulation



miR19-a regulates TGF- β signalling pathway



TGF- β RII: Potential target of miR19-a



hsa-miR-19a 3' AGUCAAAACG-UAUC-----UAAACGUGU 5'
 IIII I IIII IIIIIIIII

Human	AGGAAAUGAGAUUGAUUUUUUACAAUAGCCAAUAACAUUUGCACUUUAUUAUUGCCU
Chimpanzee	AGGAAAUGAGAUUGAUUUUUUACAAUAGCCAAUAACAUUUGCACUUUAUUAUUGCCU
Gorilla	AGGAAAUGAGAUUGAUUUUUUAAAAUAGCCAAUAACAUUUGCACUUUAUUAUUGCCUGU
Orangutan	AGGAAAUGAGAUUGAUUUUUUACAAUAGCCAAUAACAUUUGCACUUUAUUAUUGCCUGU
Macaque	AGGAAAUGAGAUUAAUUUUUUACAAUAGCCAAUAACAUUUGCACUUUAUUAUUGCCUGU
Marmoset	AGGAAAUGAGAUUGAUUUUUUACAAUAGCCAAUAACAUUUGCACUUUAUUAUUGCCUGU
Mouse	AGGAAAUGAGAUUGAUUUUUUACAAACAGCCAAUAACGUUUGCACUUUAUUAUUGCCUGU

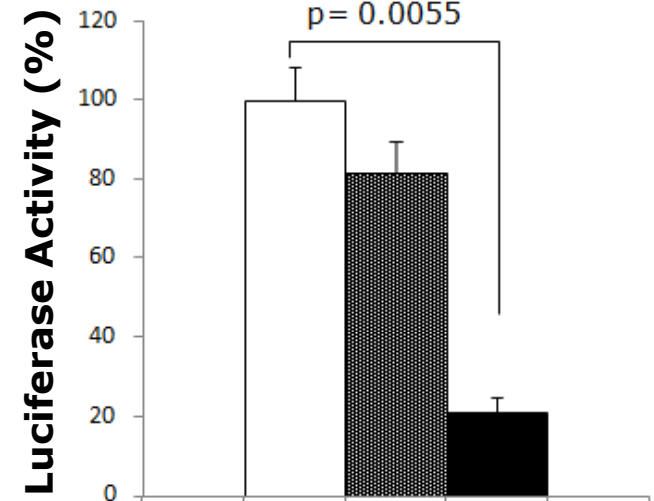
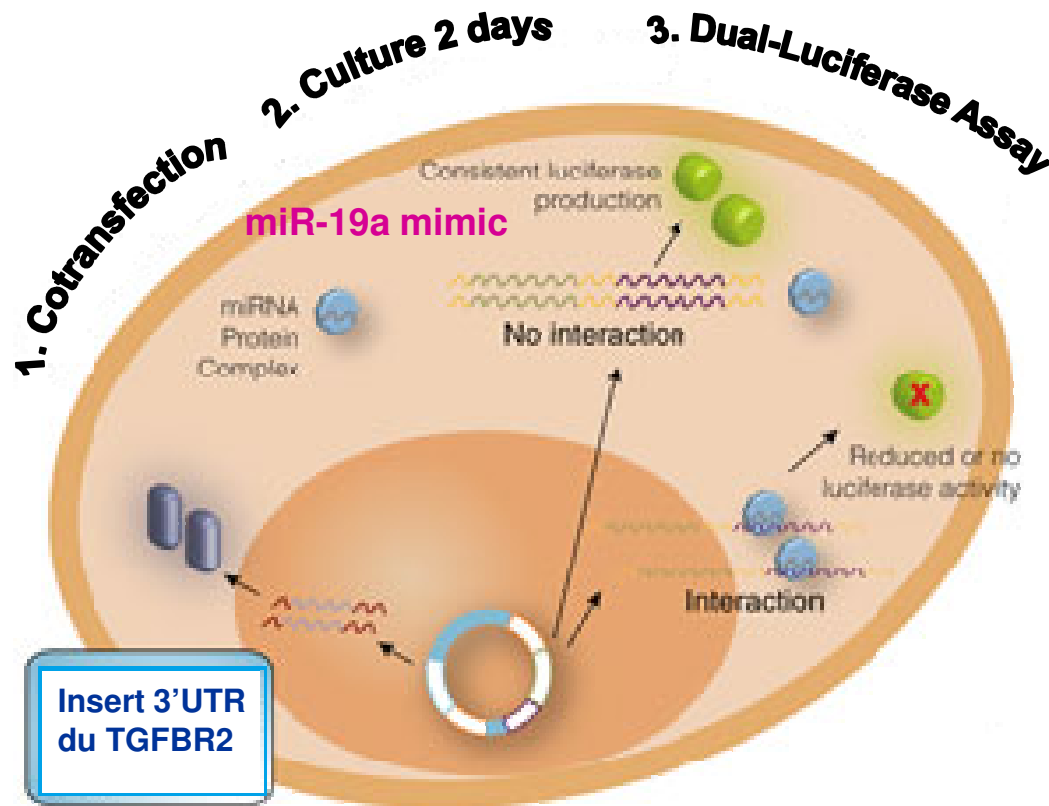
hsa-miR-19a 3' AGUCAAAACGUAUC-UAAACGUGU 5'
 IIIII I IIIII

Human	UCACAGCCAGCUAUGACCACAUUGCACUUGCUUUUGCAAUAUAUCAUUCUCCUGCCUAGCACUU
Chimpanzee	UCACAGCCAGCUAUGACCACAUUGCACUUGCUUUUGCAAUAUAUCAUUCUCCUGCCUAGCACUU
Gorilla	UCACAGCCAGCUAUGACCACAUUGCACUUGCUUUUGCAAUAUAUCAUUCUCCUGCCUAGCACUU
Orangutan	UCACAGCCAGCUAUGACCACAUUGCACUUGCUUUUGCAAUAUAUCAUUCUCCUGCCUAGCACUU
Macaque	UCACAGCCAGCUAUGACCACAUUGCAGUUGCUUUUGCAAUAUAUCAUUCUCCUGCCUAGCAGUU
Marmoset	UCACAGCCAGCUUUGACCACAUUGCACUUGCUUUUGCAAUAUAUCAUUCUCCUGCCUAGGGGUU
Mouse	UUGCAGCCUGCUUUGGCCACAAAACACUUUGUUUUGCA--AUAUAGCCUUCUACAGUAGGGUG

hsa-miR-19a 3' AGUCAAAACUCU-AAACGUGU 5'
 IIII III IIIII

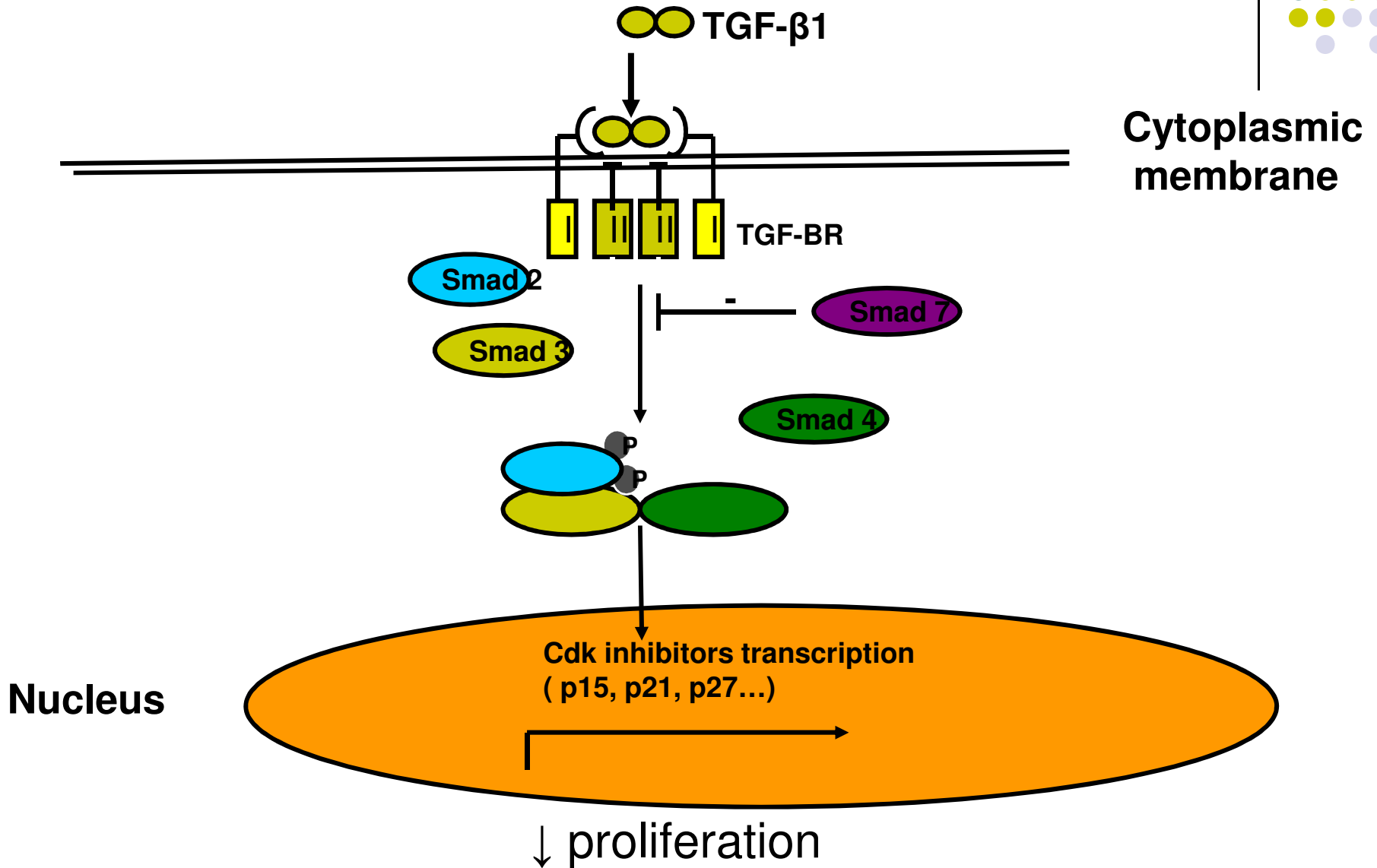
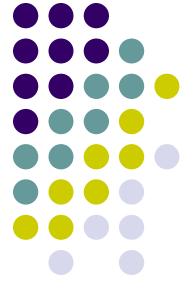
Human	AGUGAAGCCACUUUAUAAAUUUUUGGAGAUUUUGCAGGAAAAUCUGGAUCCCCAGGUAAGGAUAG
Chimpanzee	AGUGAAGCCACUUUAUAAAUUUUUGGAGAUUUUGCAGGAAAAUCUGGAUCCCCAGGUAAGGAUAG
Gorilla	AGUGAAGCCACUUUAUAAAUUUUUGGAGAUUUUGCAGGAAAAUCUGGAUCCCCAGGUAAGGAUAG
Orangutan	AGUGAAGCCACUUUAUAAAUUUUUGGAGAUUUUGCAGGAAAAUCUGGAUCCCCAGGUAAGGAUAG
Macaque	AGUGAAGCCACUUUAUAAAUUACAUUGGAGAUUUUGCAGGAAAAUCUGGAUCCCCAGGUAAGGAGAG
Marmoset	AGCGAAGCCAUUUUAUAAAUUUUUGGAGAUUUUGCAGGAAAAUCUGGAUCCCCAGGUAAGGAUAG
Mouse	AGUUGAGCUUCUUUAGAACUAUUUGG-GAGGUUGCAGAGAAGCUUAGAUUCCCCAAUAAGCAGAG

Interaction of miR19a-TGFβRII 3'UTR

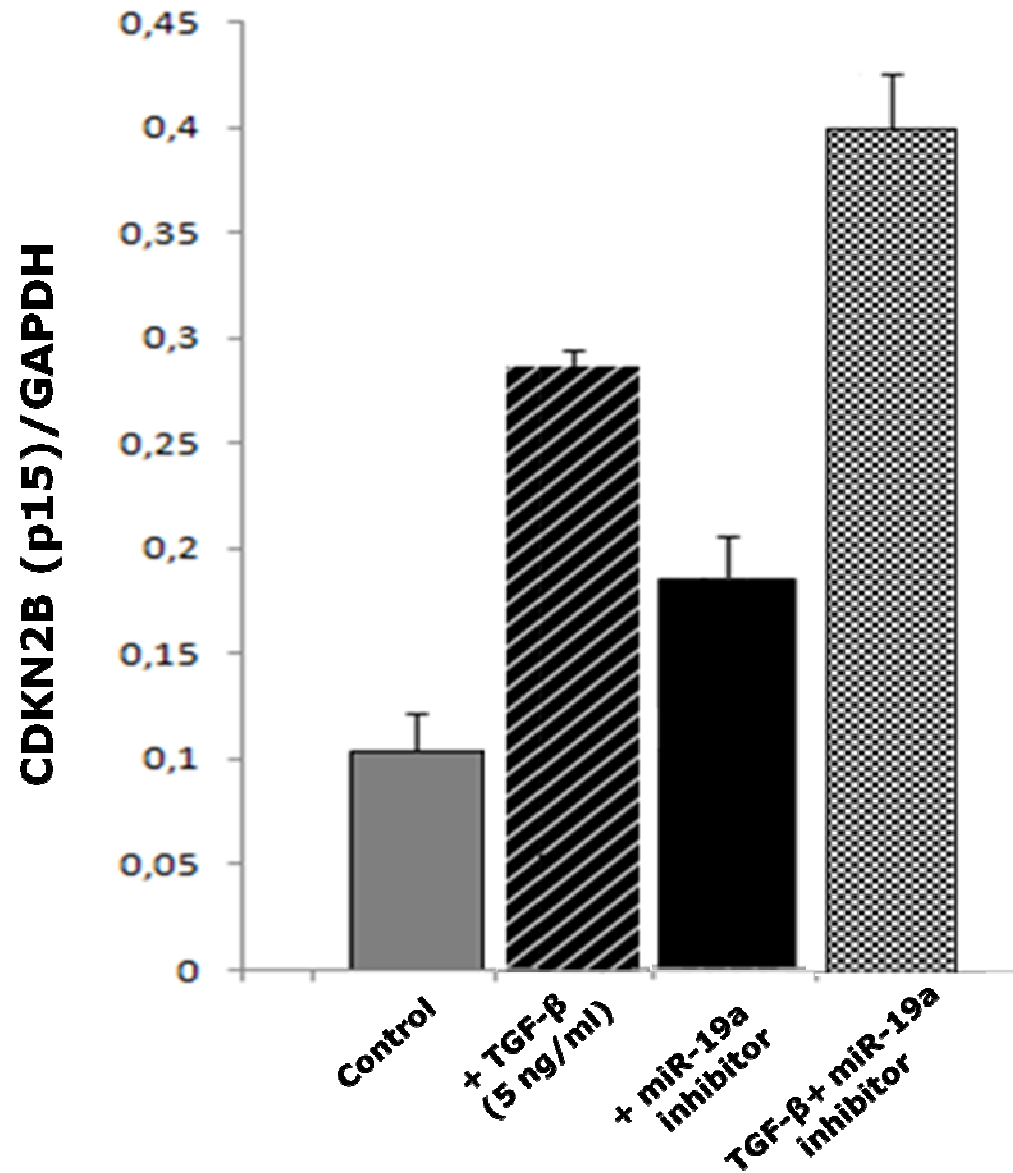


- pMIR-TGFBR2
- ▨ pMIR-TGFBR2 + Scramble miR
- pMIR-TGFBR2 + miR-19a mimic

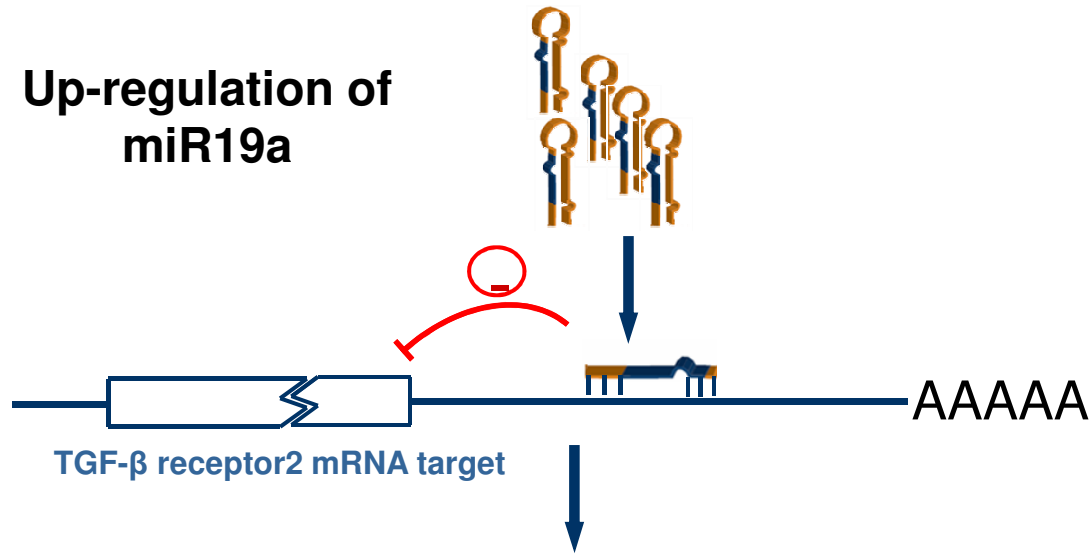
TGF- β 1 effect on proliferation



Up-regulation of *CDKN2B* (p15)



Up-regulation of miR19a



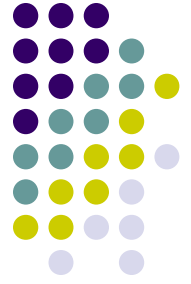
TGF-βRII expression

TGF-β signalling

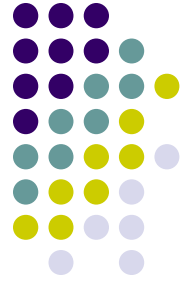
p15
(CDKN2B)

Phase G1----->Phase S

↑ Proliferation

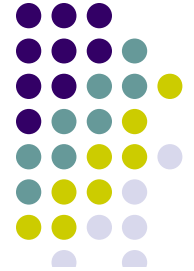


CONCLUSION



- ❖ Mir19-a is a miRNA signature of bronchial epithelial cells in severe asthma.
- ❖ MiR-19a down-regulates the expression of the *TGFβRII* gene leading to p15 (*CDKN2B*) repression and then to the epithelium thickness observed in severe asthmatic patients.
- ❖ Our study uncovers a new regulatory pathway involving miR-19a in severe asthma.
- ❖ Down-regulation of miR-19a expression may be explored as a potential new therapy to modulate epithelium repair in asthma.

Acknowledgments



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Dr. Michel Laviolette

Dr Qutayba Hamid

Dr. Mahmoud Rouabhia

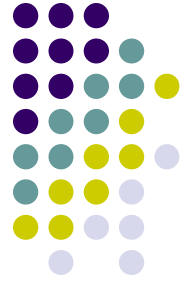


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