

THE DEVELOPMENT AND USE OF AN *EX VIVO* PRIMARY CELL MODEL OF THE HUMAN AIRWAY EPITHELIUM TO INVESTIGATE PULMONARY VIRAL INFECTIONS

HOST-PATHOGEN INTERACTIONS

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- How does virus evade our cellular innate immune responses?

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- How does our cells compensate for this viral repression of immunity?

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- What the key anti-viral mechanisms our cells use?

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How viruses interact with the host to modulate infections

- How does virus evade our cellular innate immune responses?
- How does our cells compensate for this viral repression of immunity?
- What the key anti-viral mechanisms our cells use?
- Hopefully one day find a broad spectrum anti-viral treatment comparable to penicillin treatment of bacterial infections

HOST-PATHOGEN INTERACTIONS

Viruses of interest:

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- Herpes Viruses (DNA viruses)

HOST-PATHOGEN INTERACTIONS

Viruses of interest:

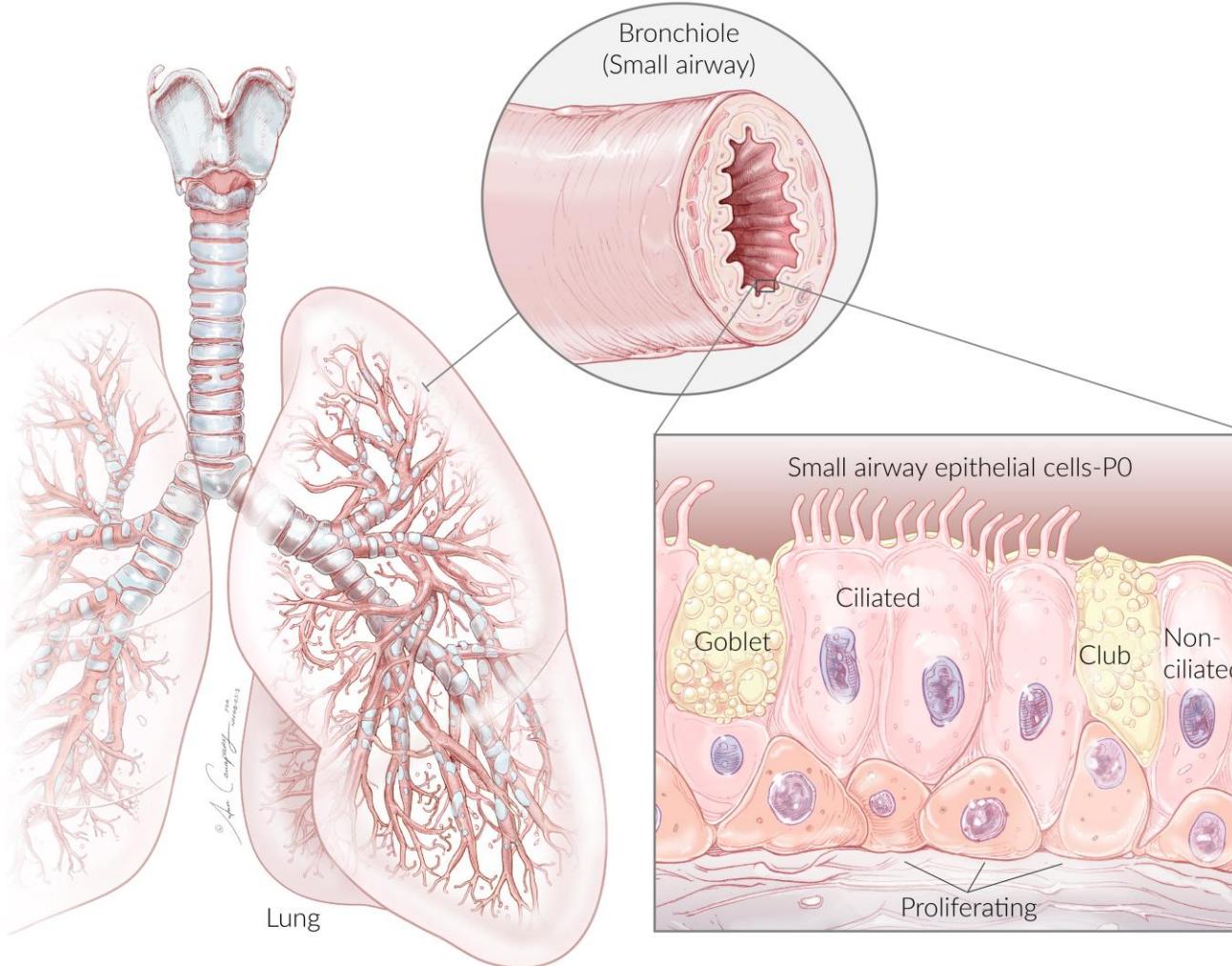
- Herpes Viruses (DNA viruses)
- Influenza A Virus (RNA virus)
- SARS-CoV-2 (RNA virus)

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THE HUMAN AIRWAY EPITHELIUM



ESTABLISHED MODELS OF AIRWAY INFECTIONS

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In Vitro:

ESTABLISHED MODELS OF AIRWAY INFECTIONS

In Vitro:

A549

Huh-7

MDCK

ESTABLISHED MODELS OF AIRWAY INFECTIONS

In Vitro:

A549 – lung cancer cell line - lack interferon signaling

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Relevance in investigating host-pathogen interactions?

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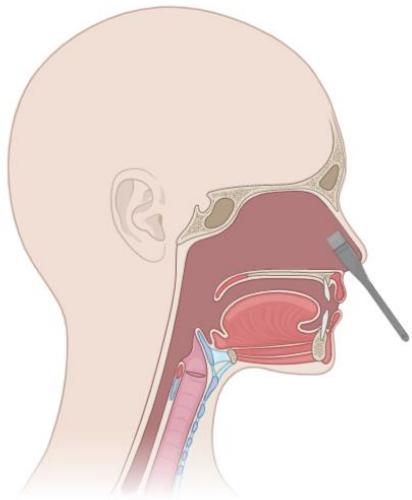
Various In vivo models

- Not applicable when investigating cellular immunity

The search for a relevant model was initiated!

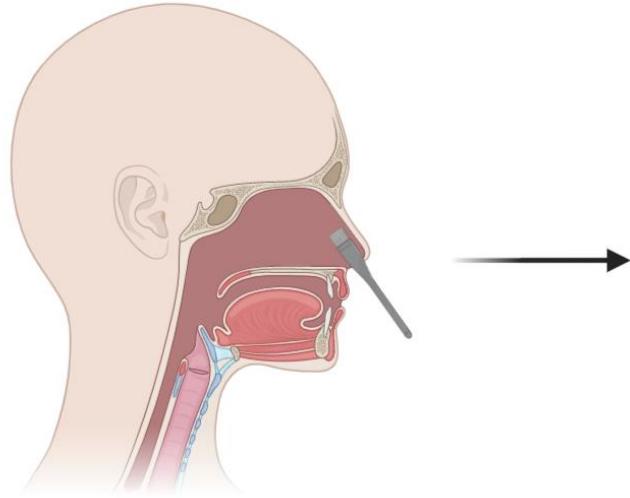
THE HPAE-ALI MODEL IN BRIEF

Step 1: Isolation of nasal
epithelial cells



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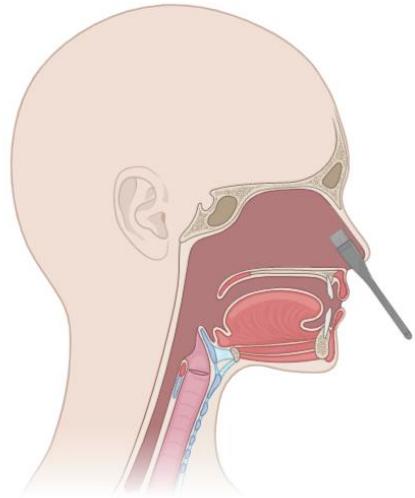


Step 2: Dedifferentiation and
expansion of basal cells



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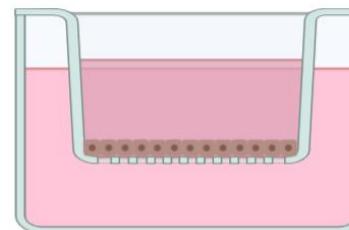
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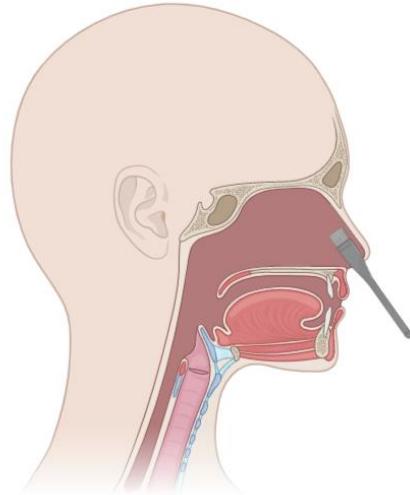


Step 3: Plating of basal cells in
Liquid-Liquid conditions



THE HPAE-ALI MODEL IN BRIEF

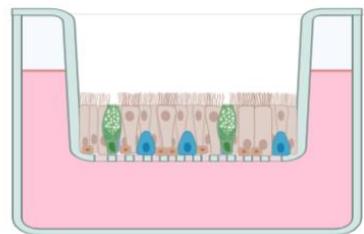
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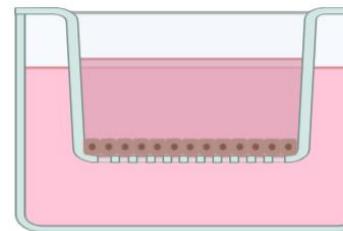
Step 2: Dedifferentiation and expansion of basal cells



Step 4: Differentiation of epithelium in air-liquid interphase



Step 3: Plating of basal cells in Liquid-Liquid conditions



Ciliated cells



Goblet cells



Non ciliated columnar cells

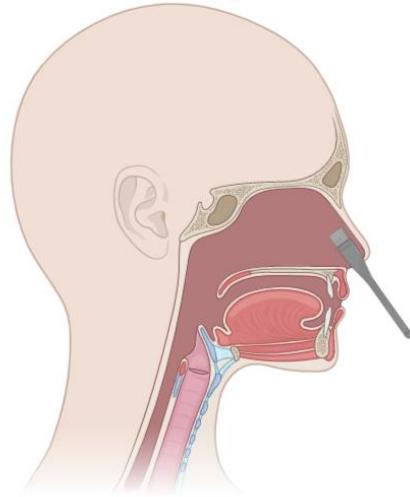


Basal cells



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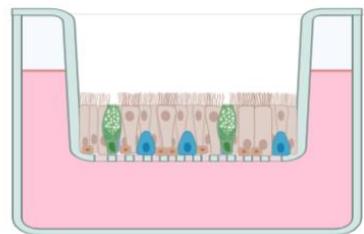
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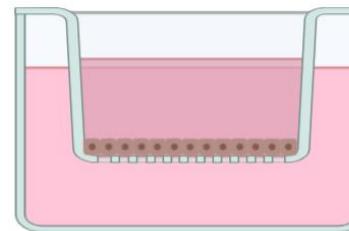
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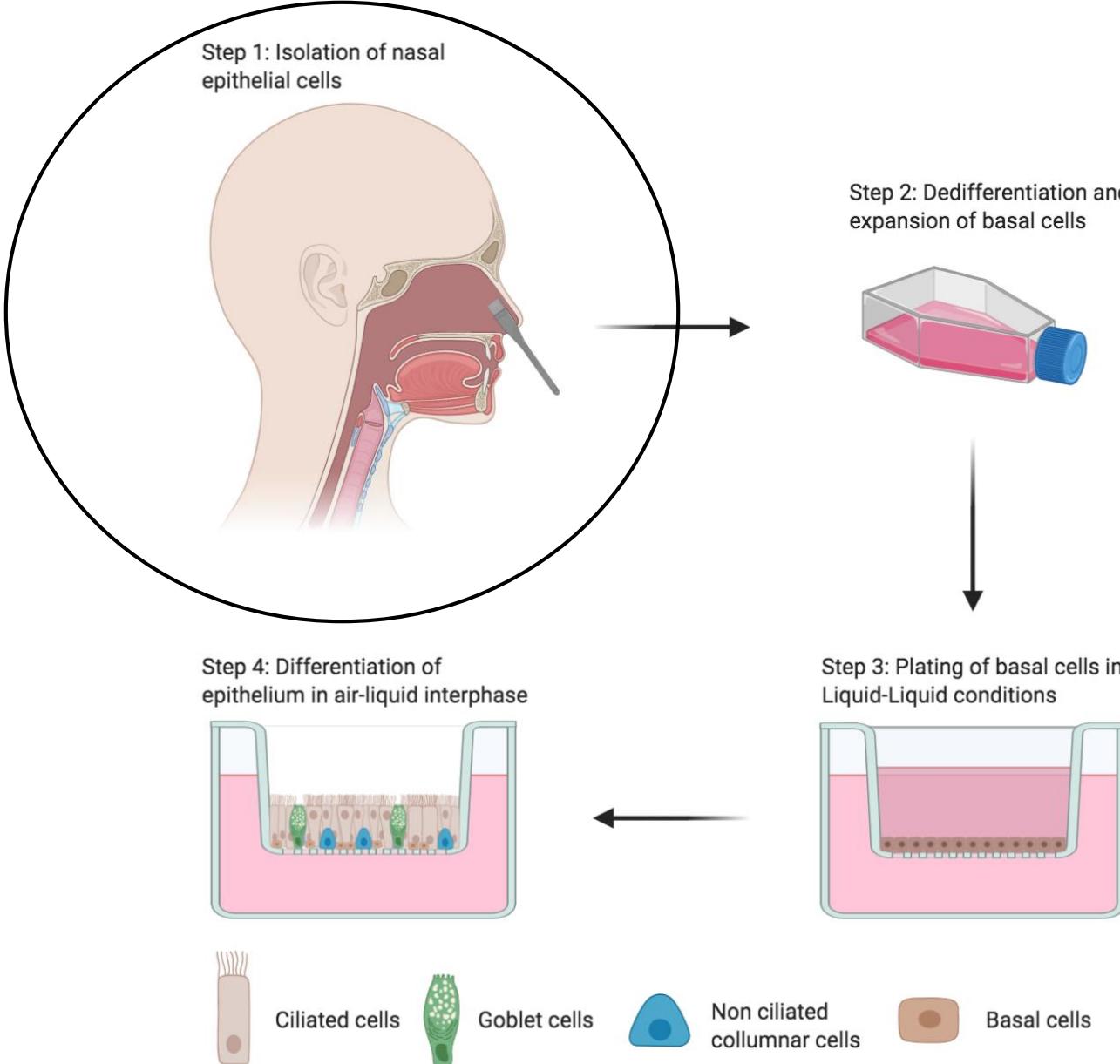
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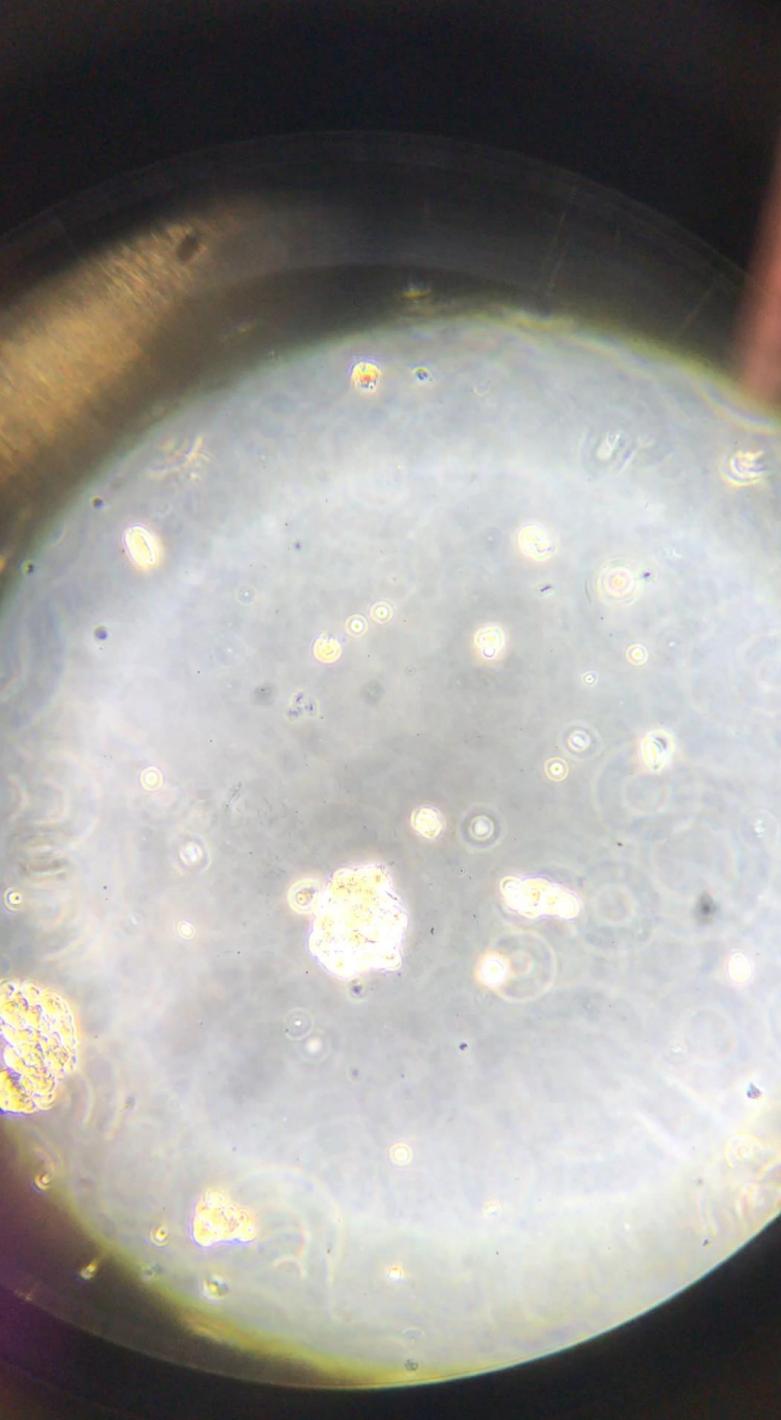
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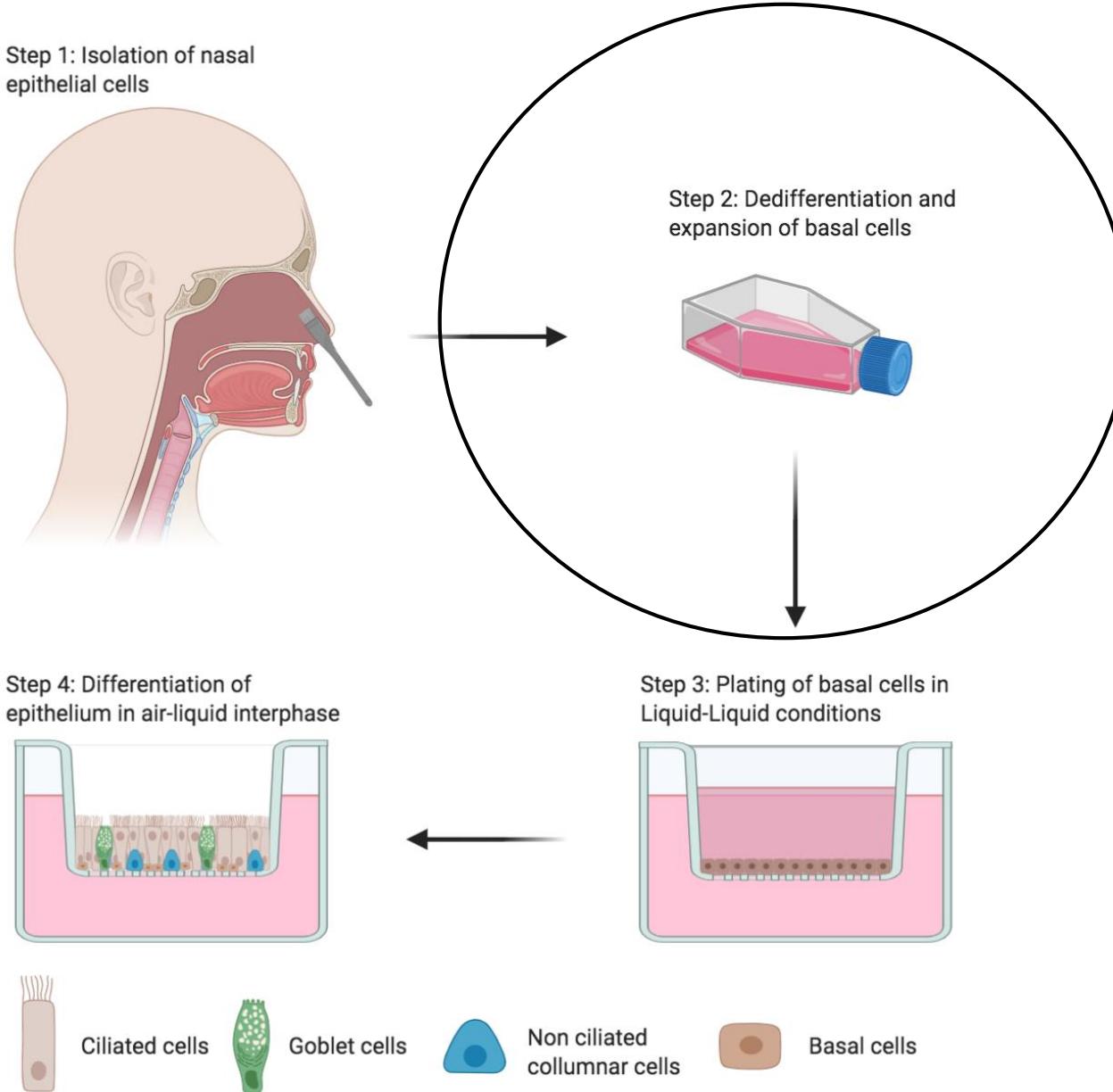
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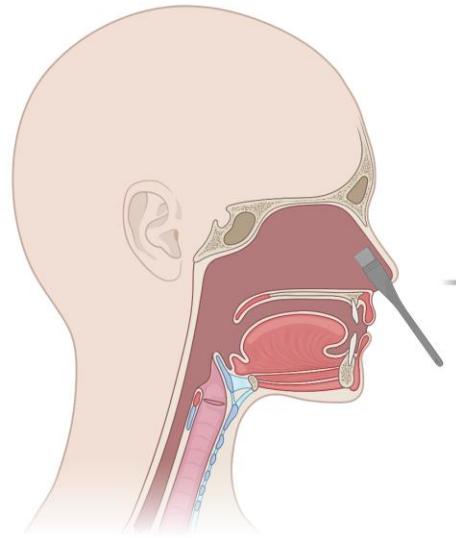
HARVESTING



THE HPAE-ALI MODEL IN BRIEF



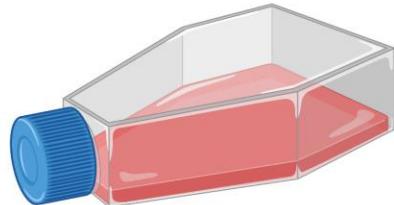
CULTURING



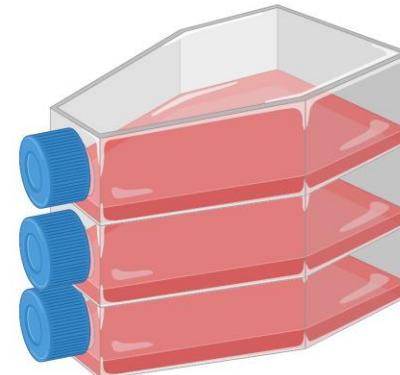
Dedifferentiation
In T10



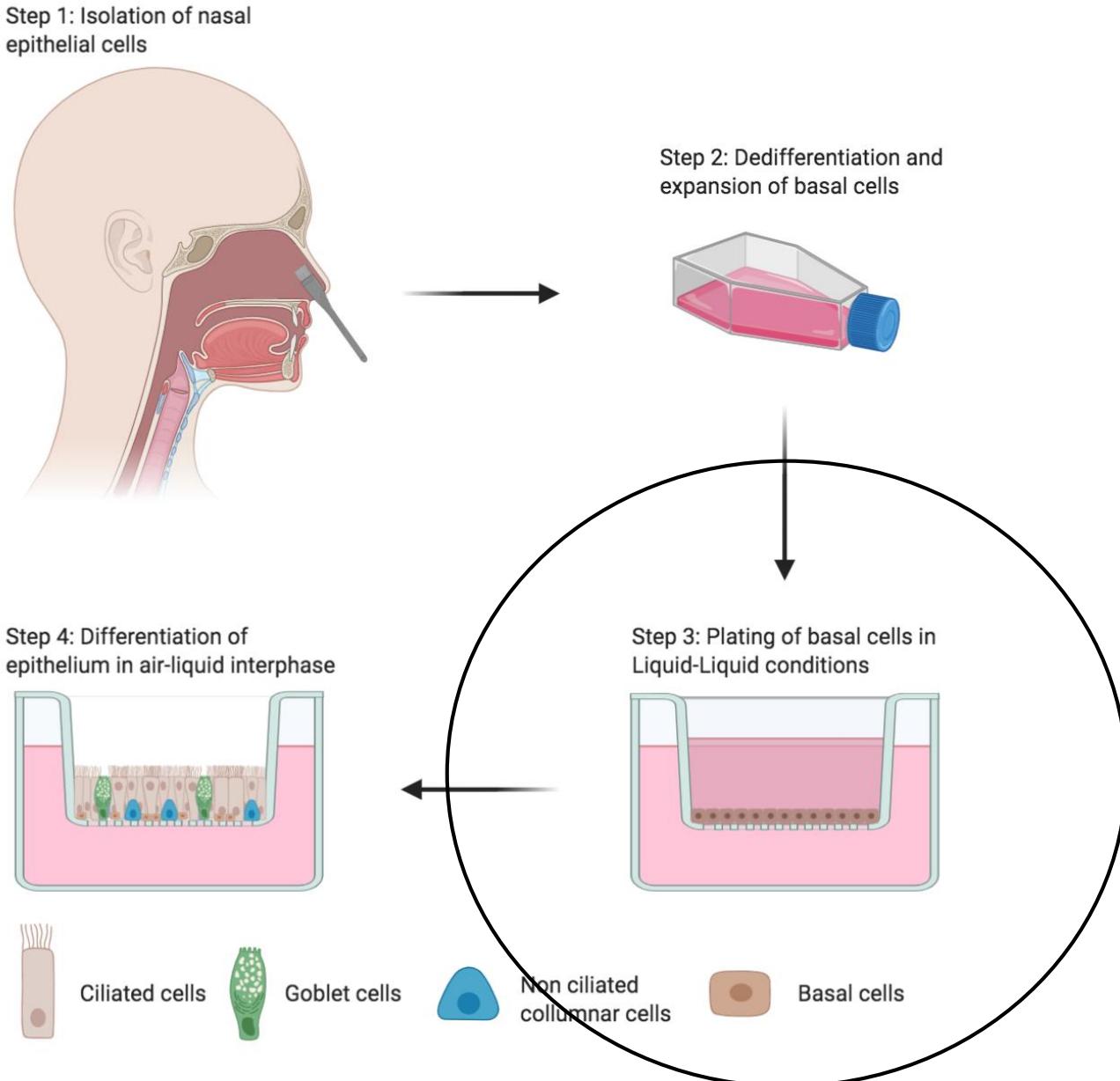
Expansion of basal cells
In 1xT75



Expansion of basal cells
In 3xT75



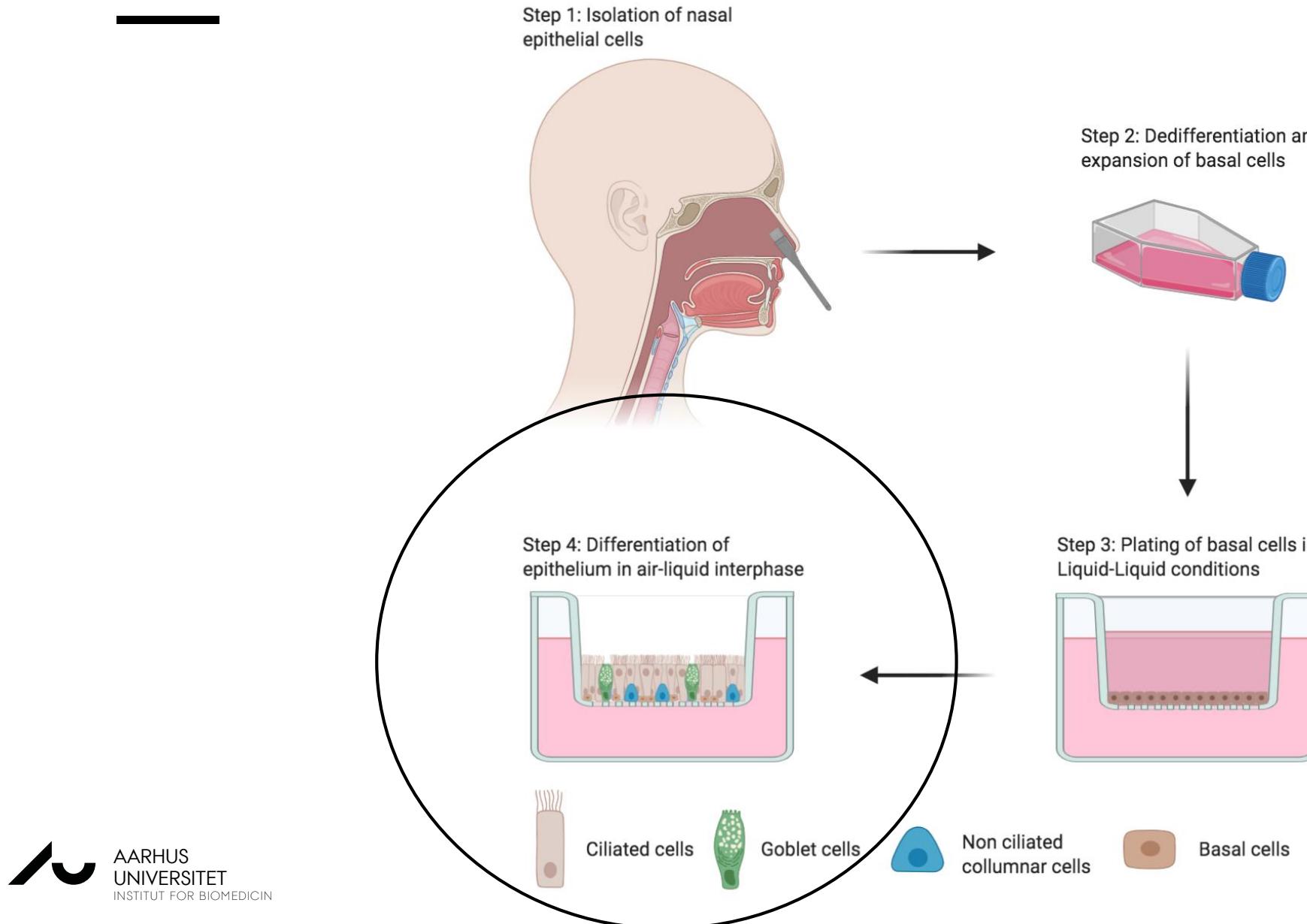
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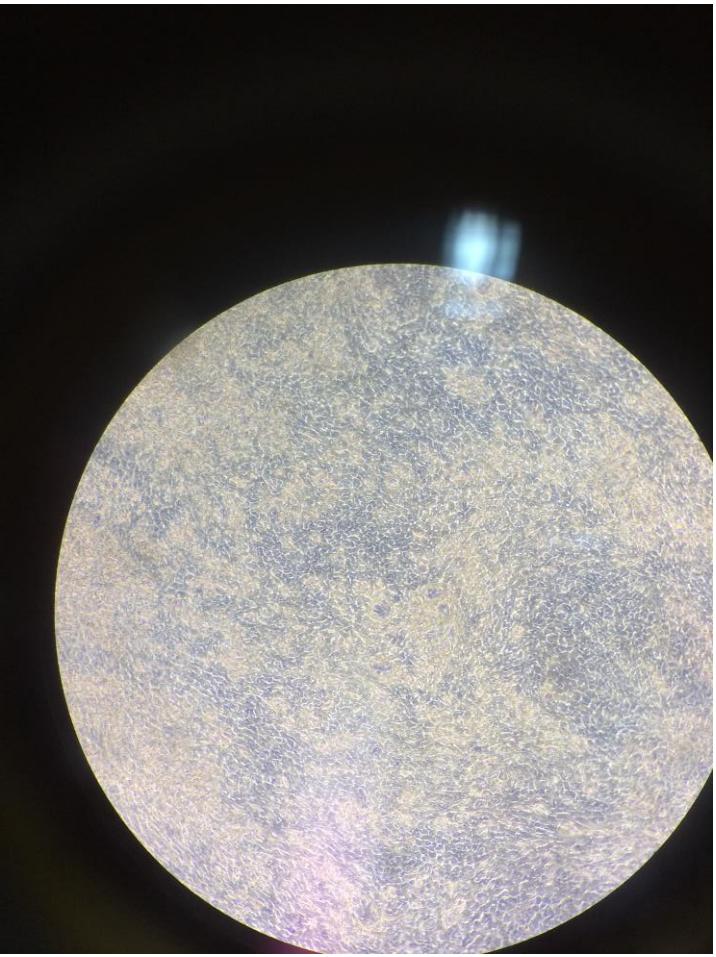
PLATING



THE HPAE-ALI MODEL IN BRIEF



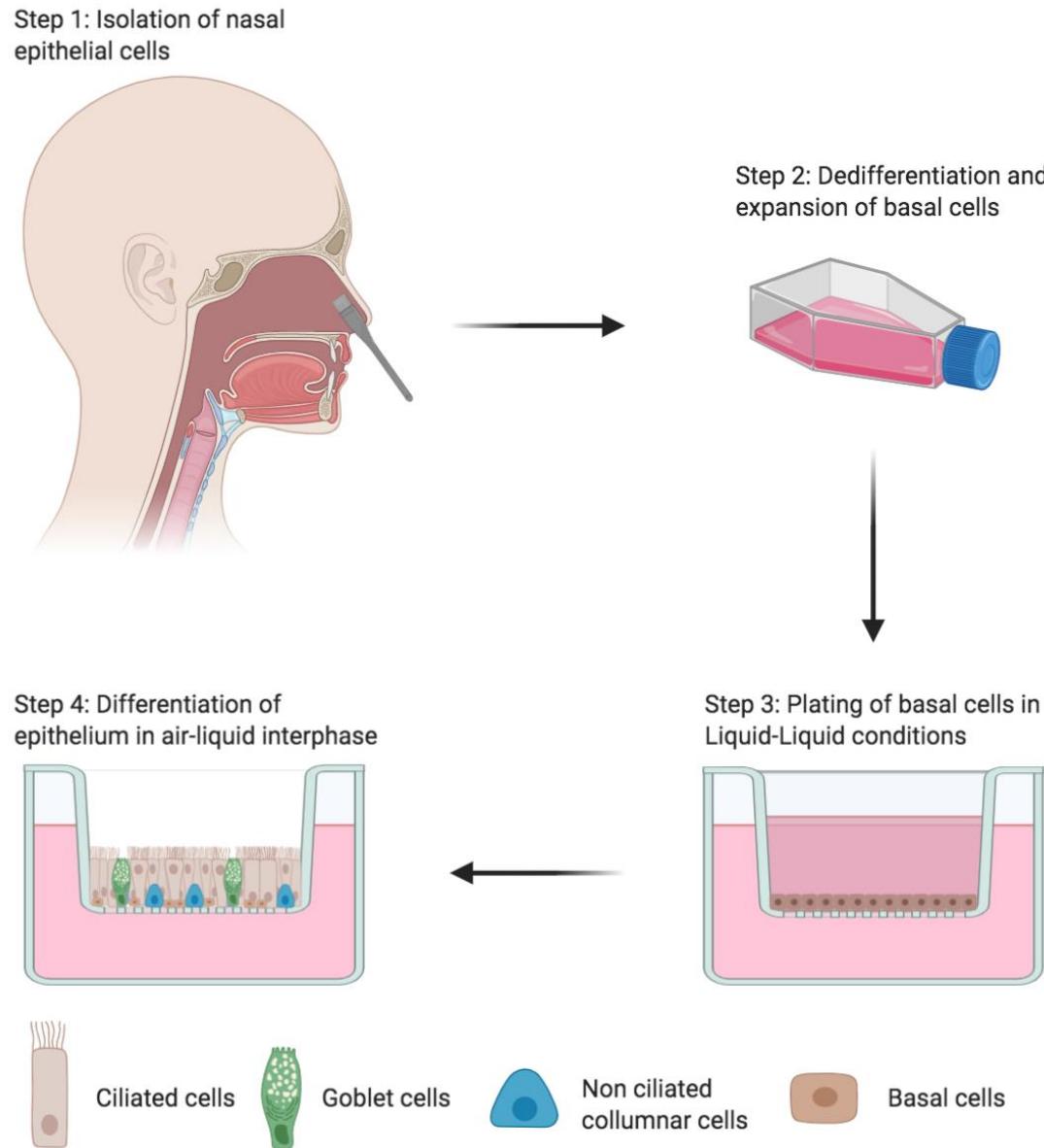
THE DIFFERENTIATED CULTURES



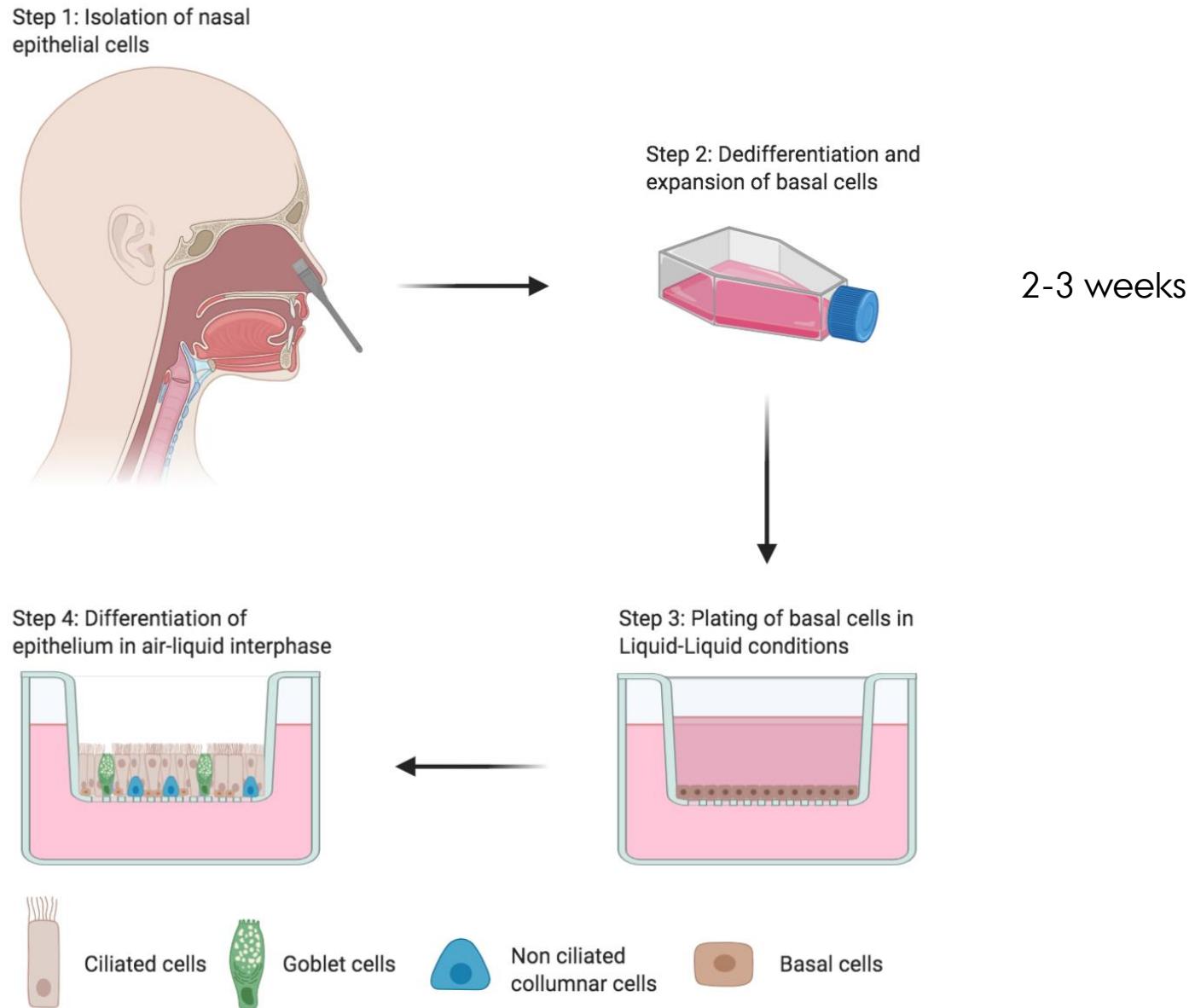
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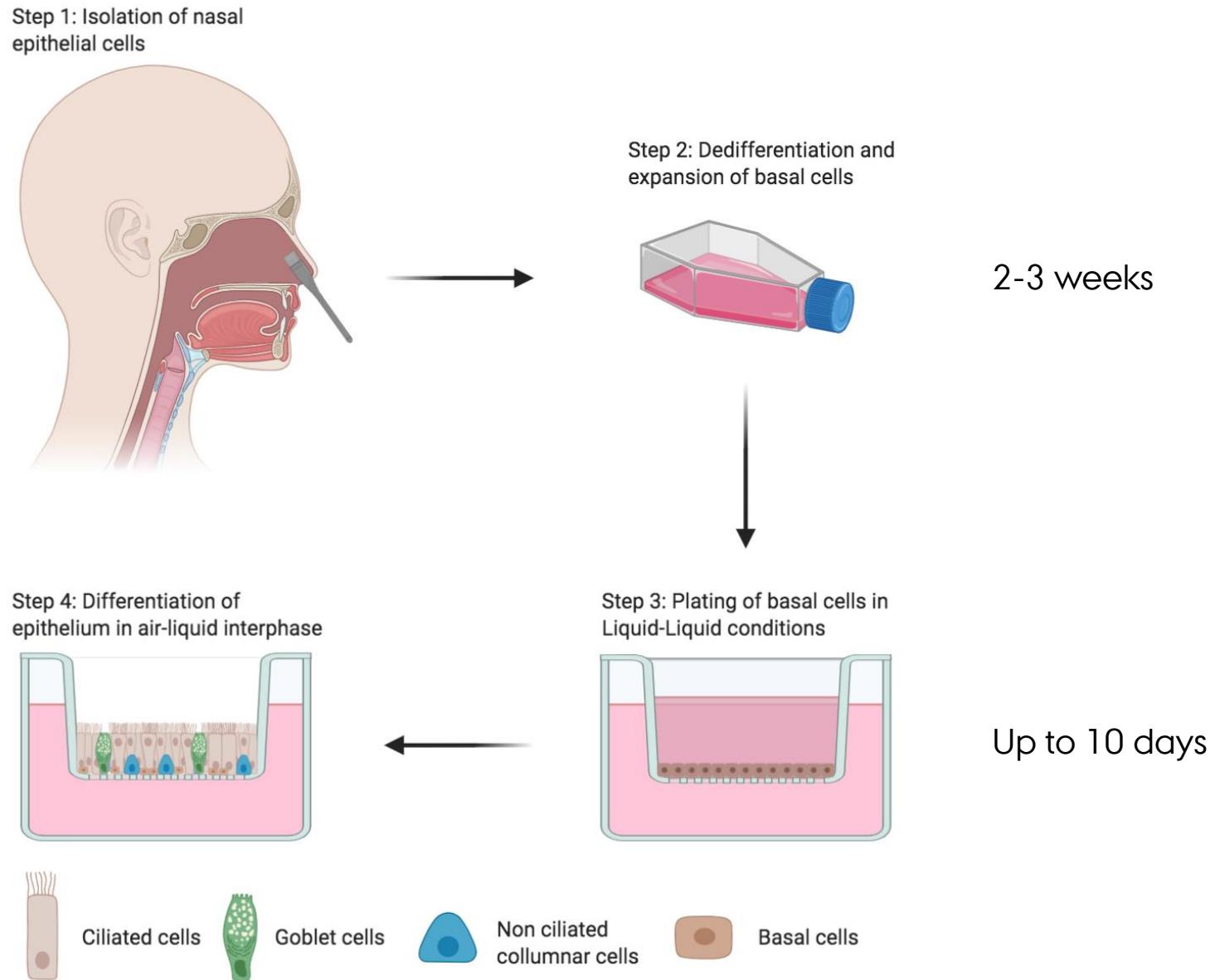
THE HPAE-ALI MODEL - A TIME CONSUMING AFFAIR



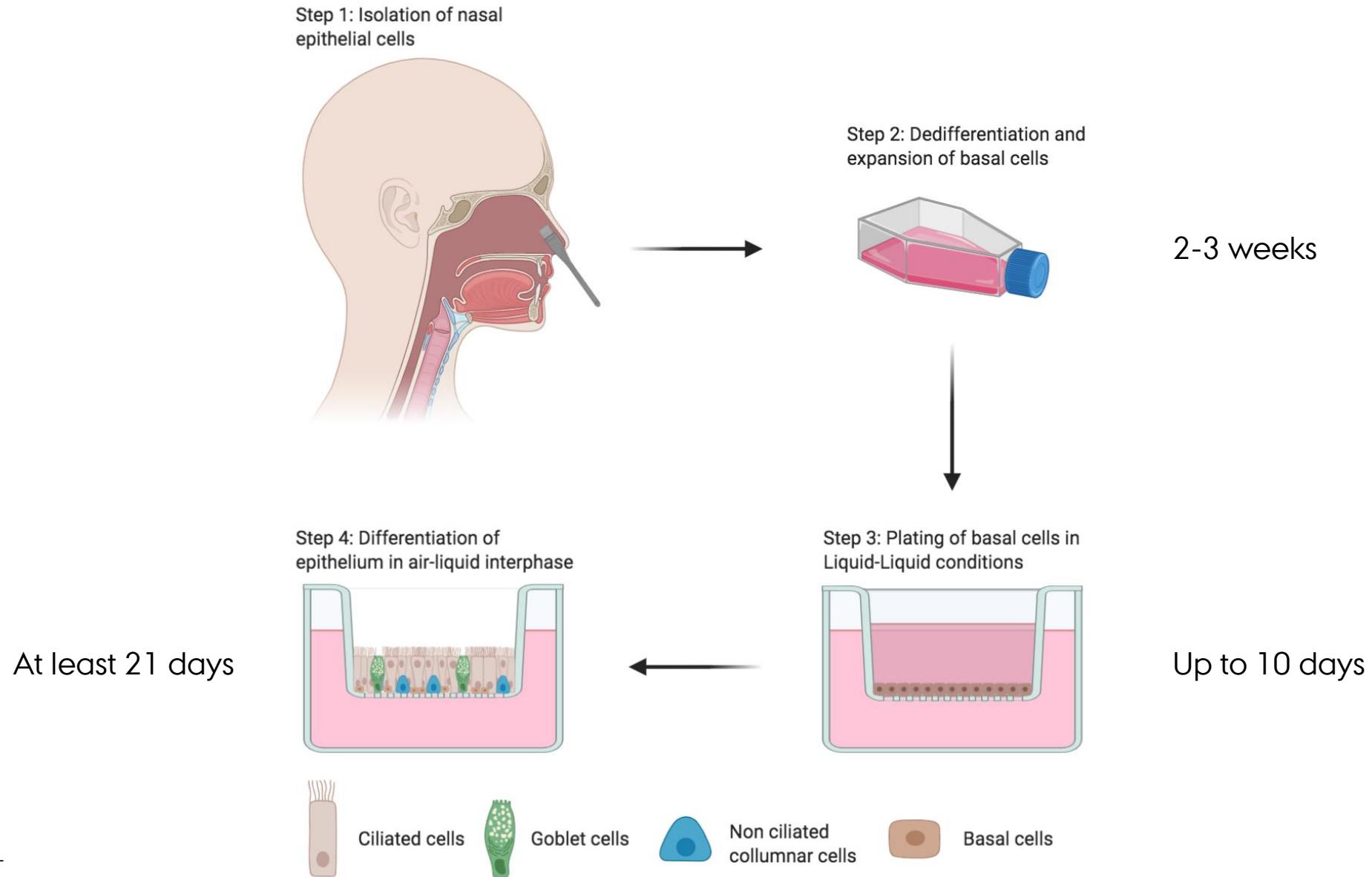
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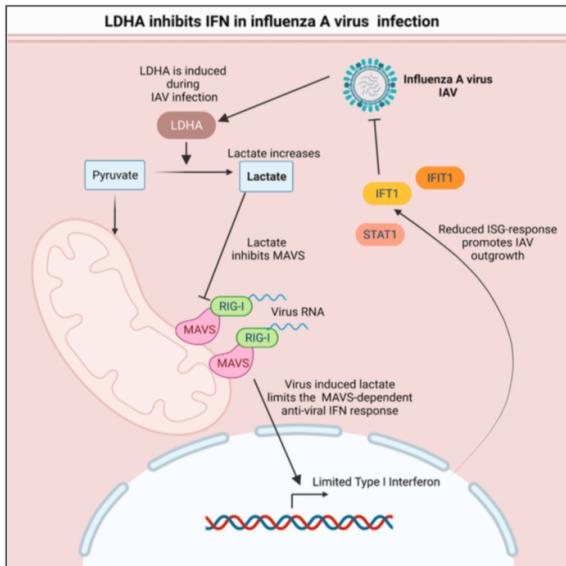
RECENTLY PUBLISHED PHD PROJECT

iScience

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Article

Influenza A induces lactate formation to inhibit type I IFN in primary human airway epithelium



Jacob Thyrsed,
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Hansen, Christian
Kanstrup Holm

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Highlights
IAV and SARS-CoV-2 infections yield virus-specific changes in glucose metabolism

IAV and SARS-CoV-2 induce LDHA and lactate production in human airway epithelium

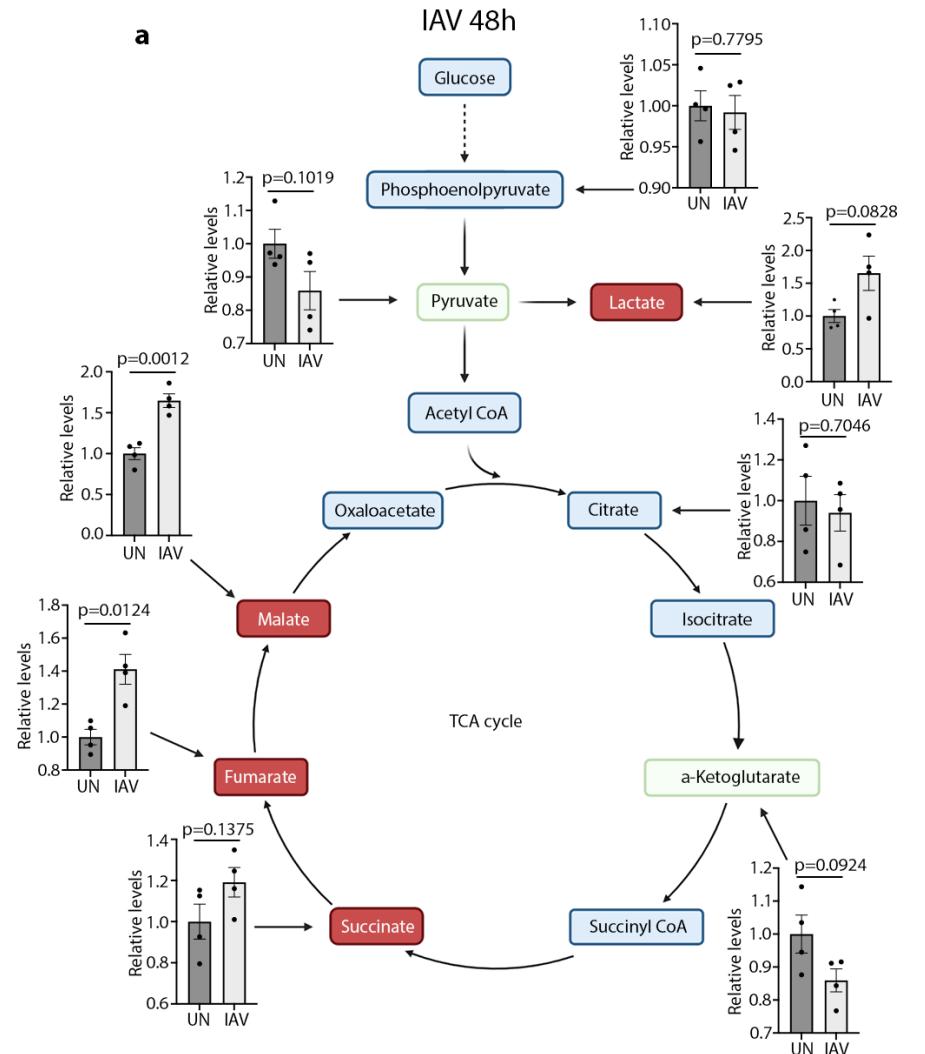
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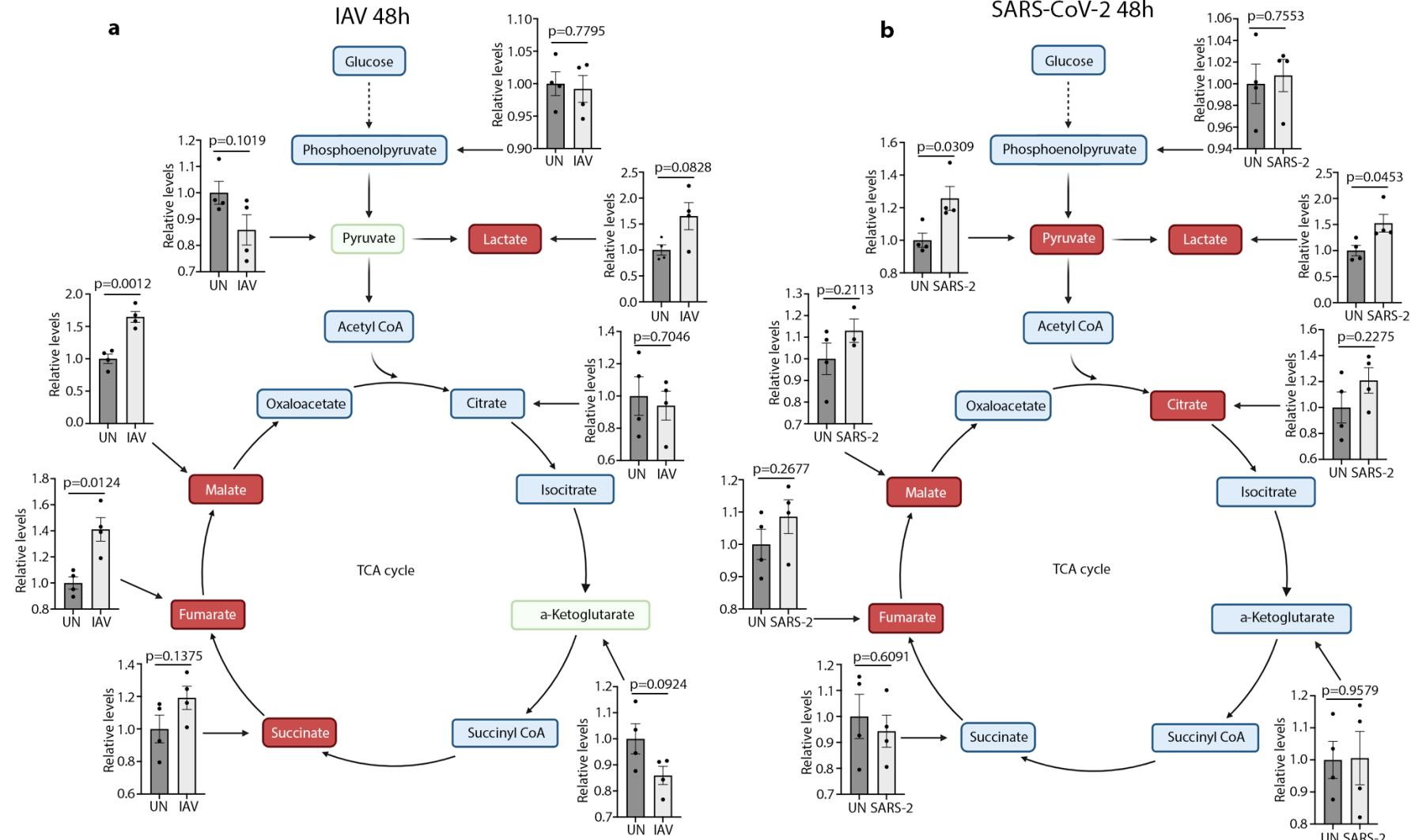
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FIRST THING WE DID – LARGE SCALE METABOLOMICS

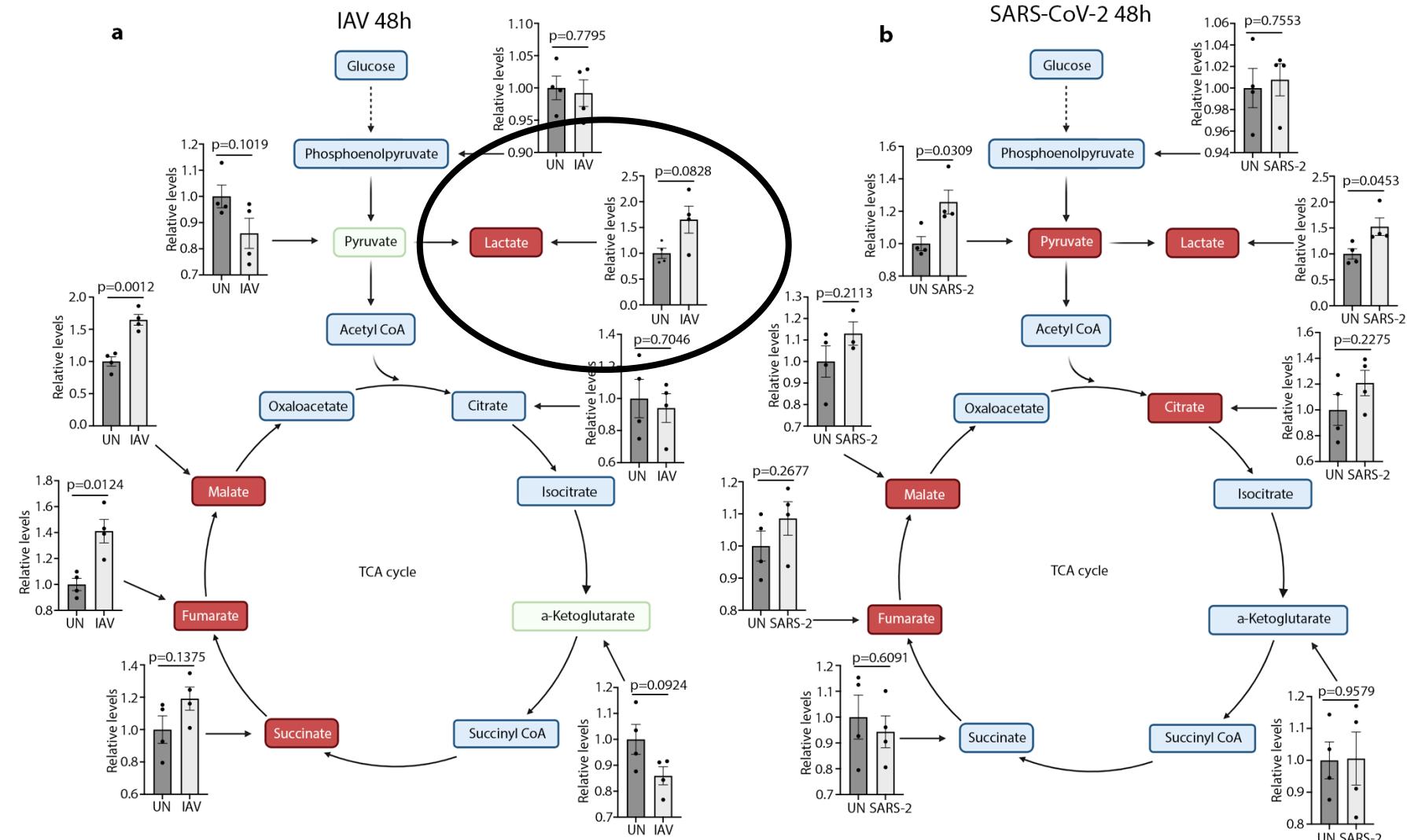
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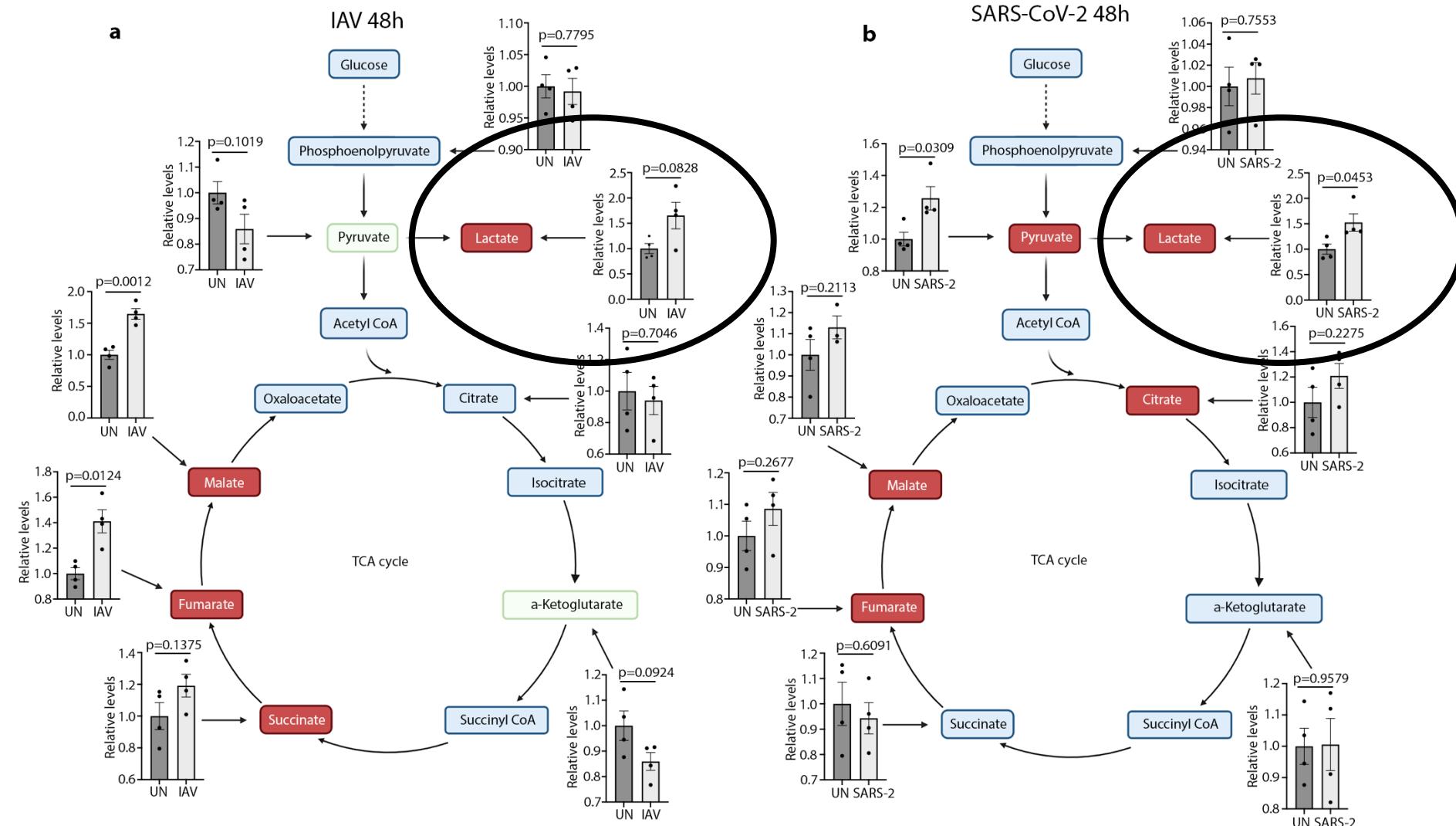
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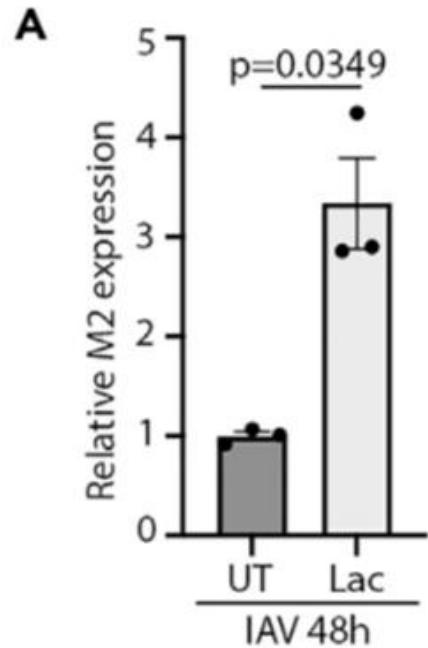
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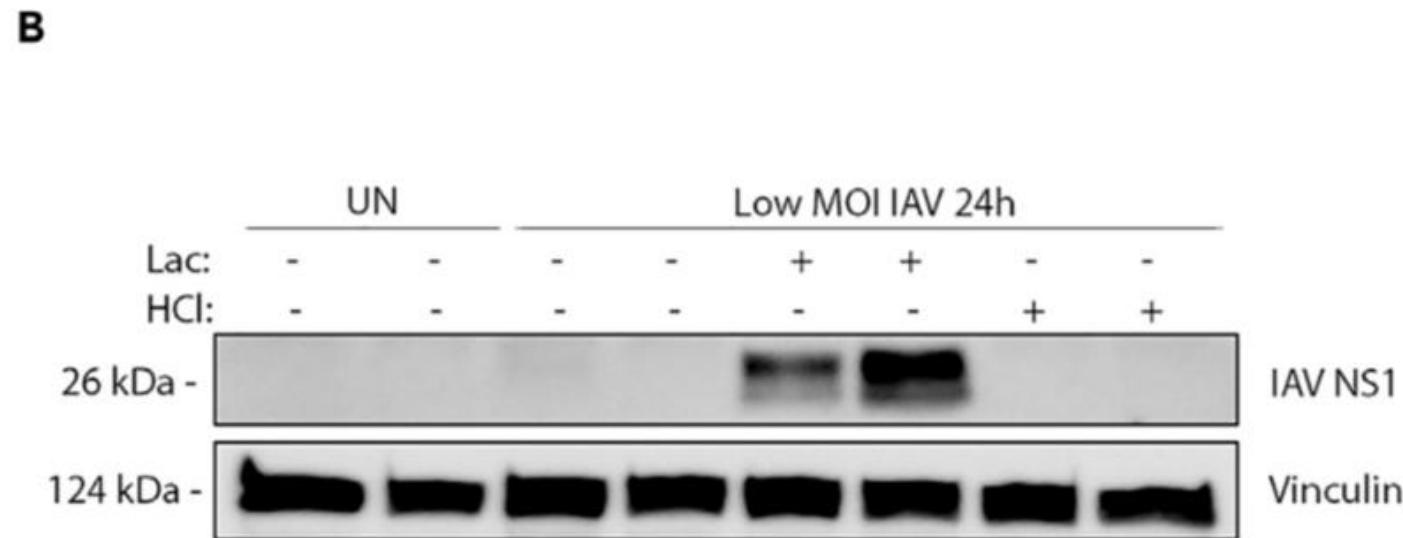
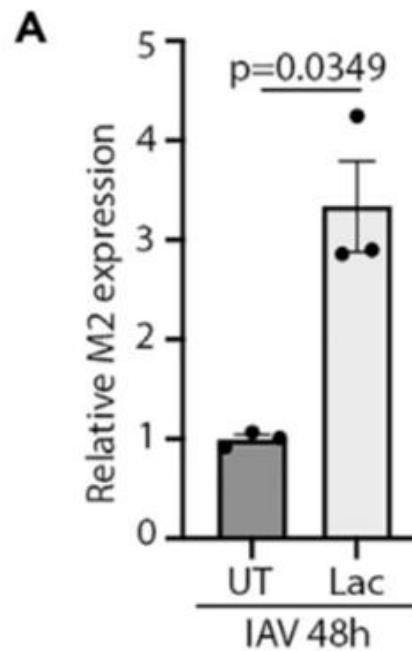
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LACTATE IS HIGHLY PRO-VIRAL



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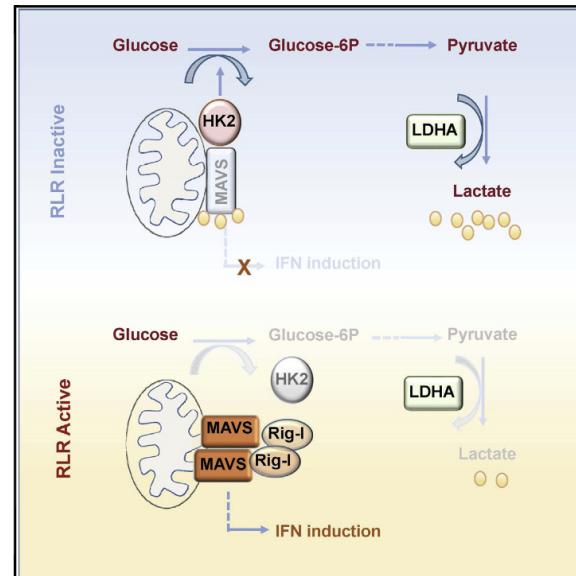


A POTENTIAL MECHANISM

Cell

Lactate Is a Natural Suppressor of RLR Signaling by Targeting MAVS

Graphical Abstract



Authors

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Zhi-Gang Xu, ..., Xuemin Zhang, Huiyan Li,
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hulin@wakehealth.edu

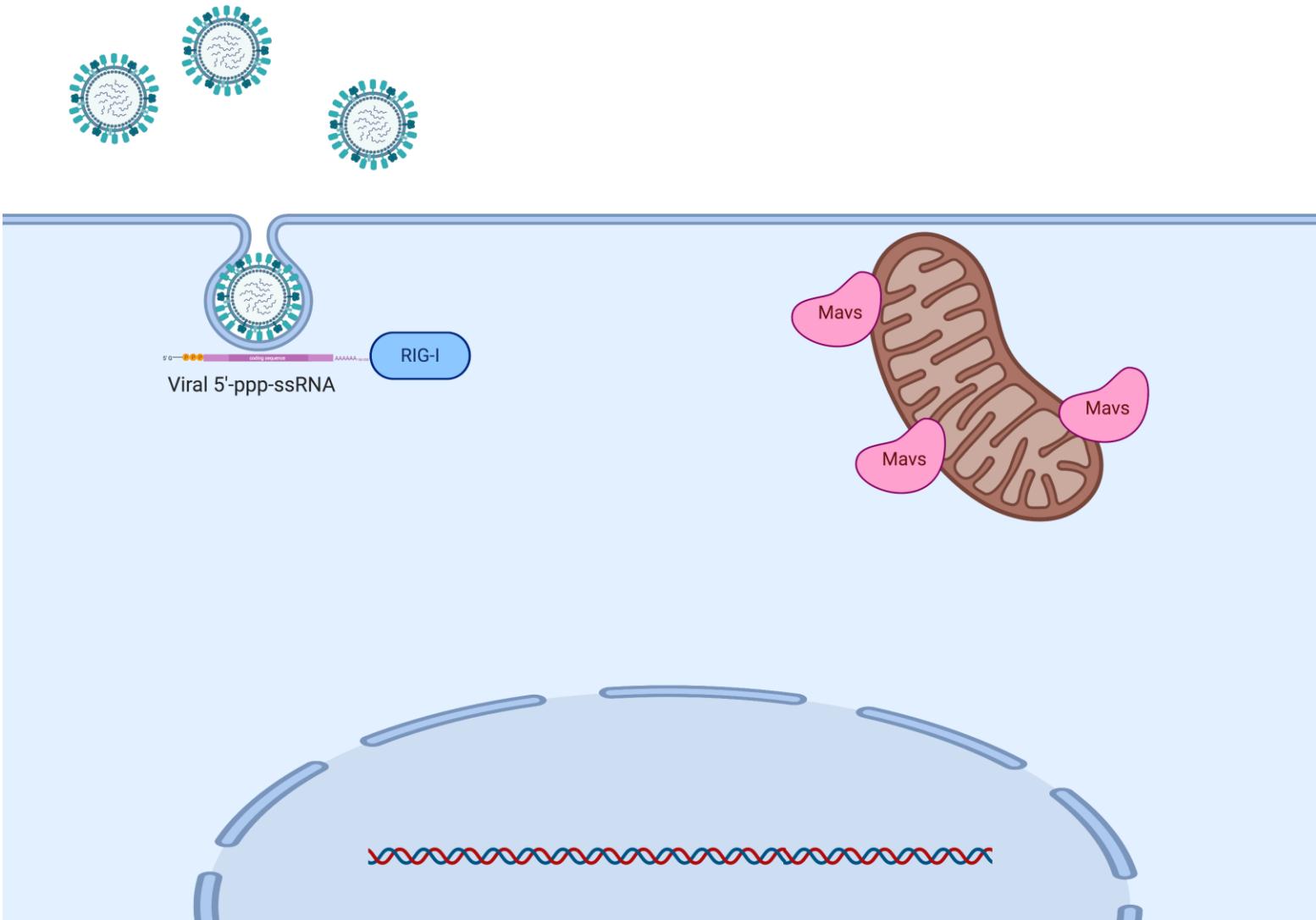
In Brief

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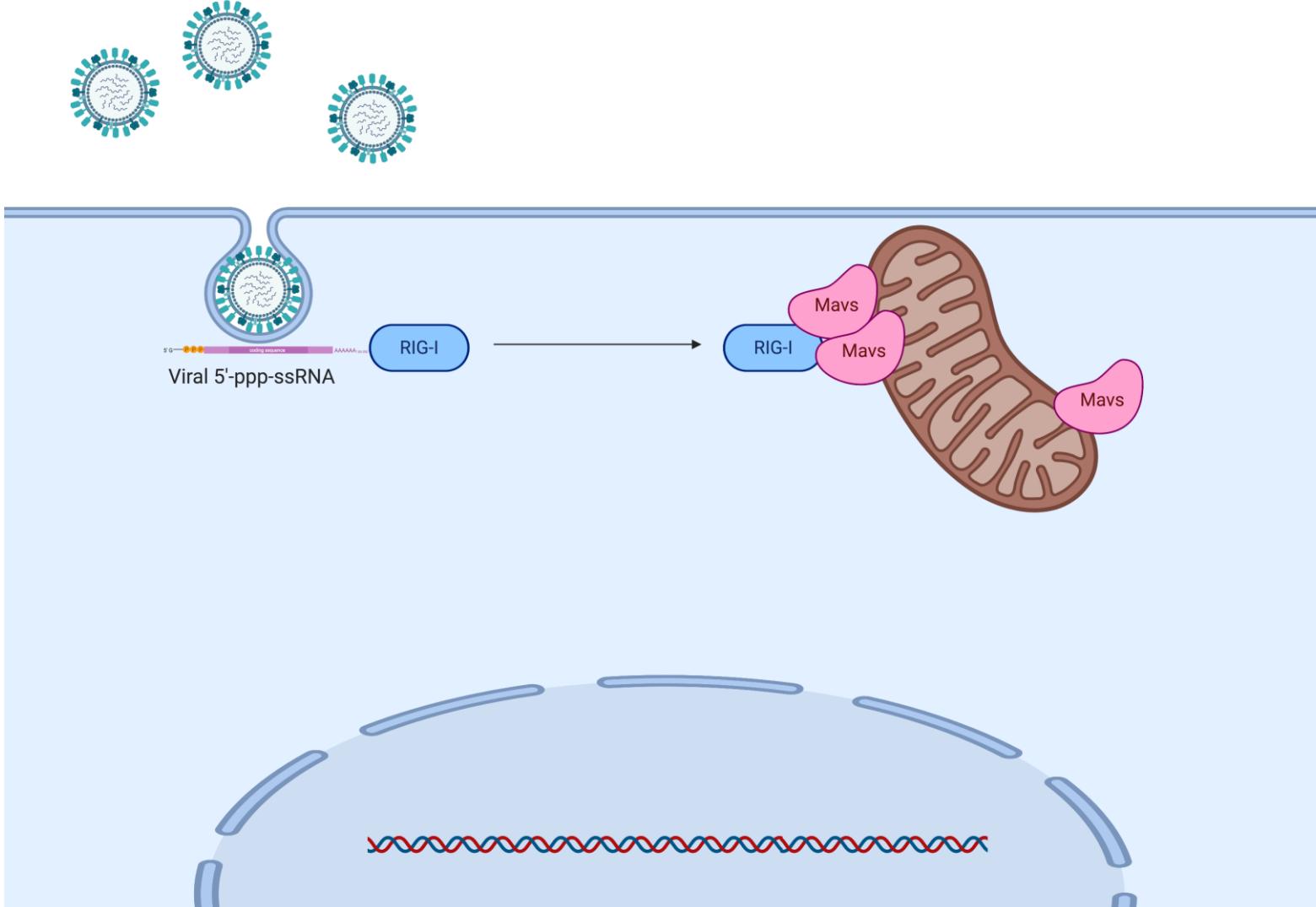
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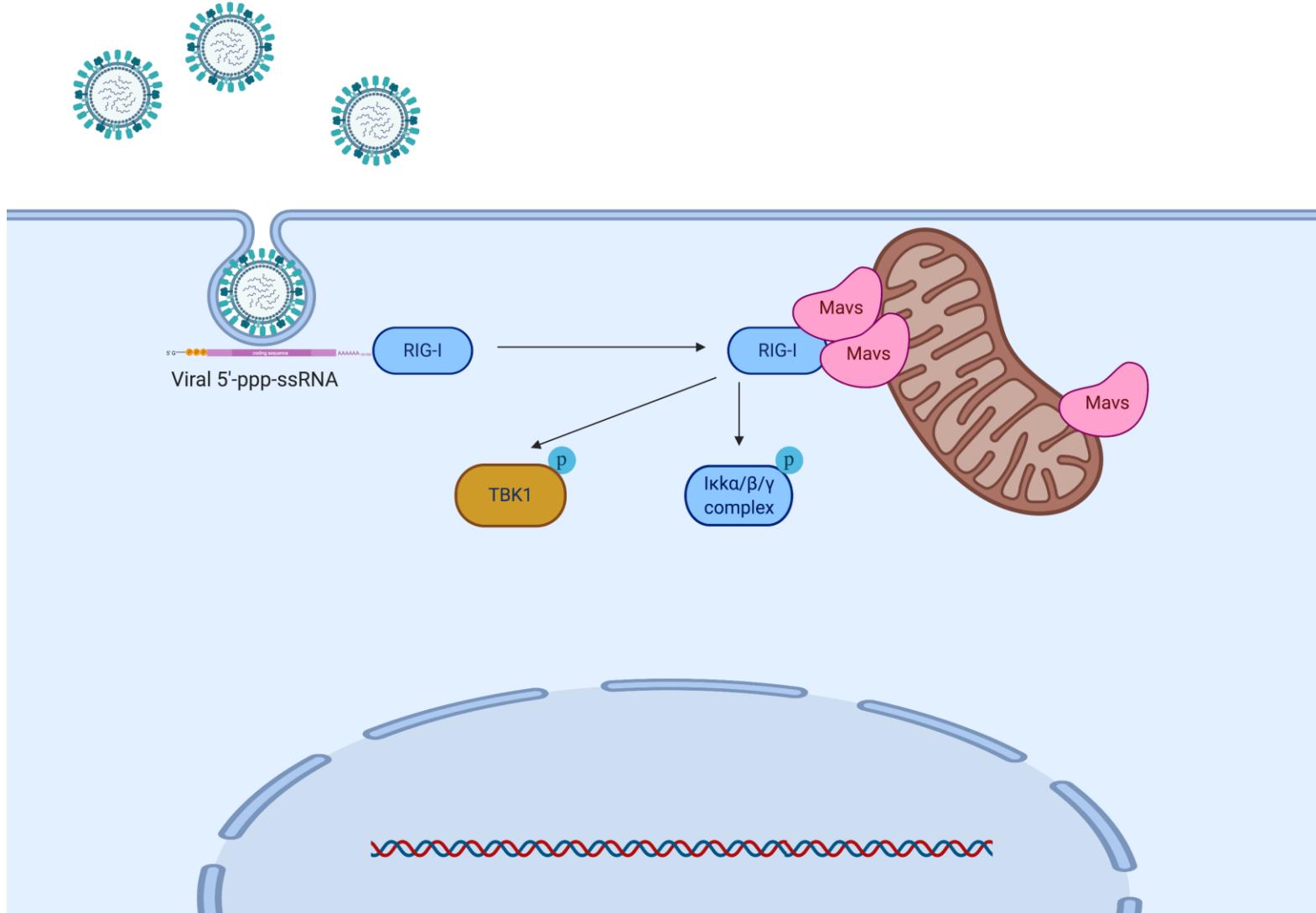
RIG-I SIGNALING



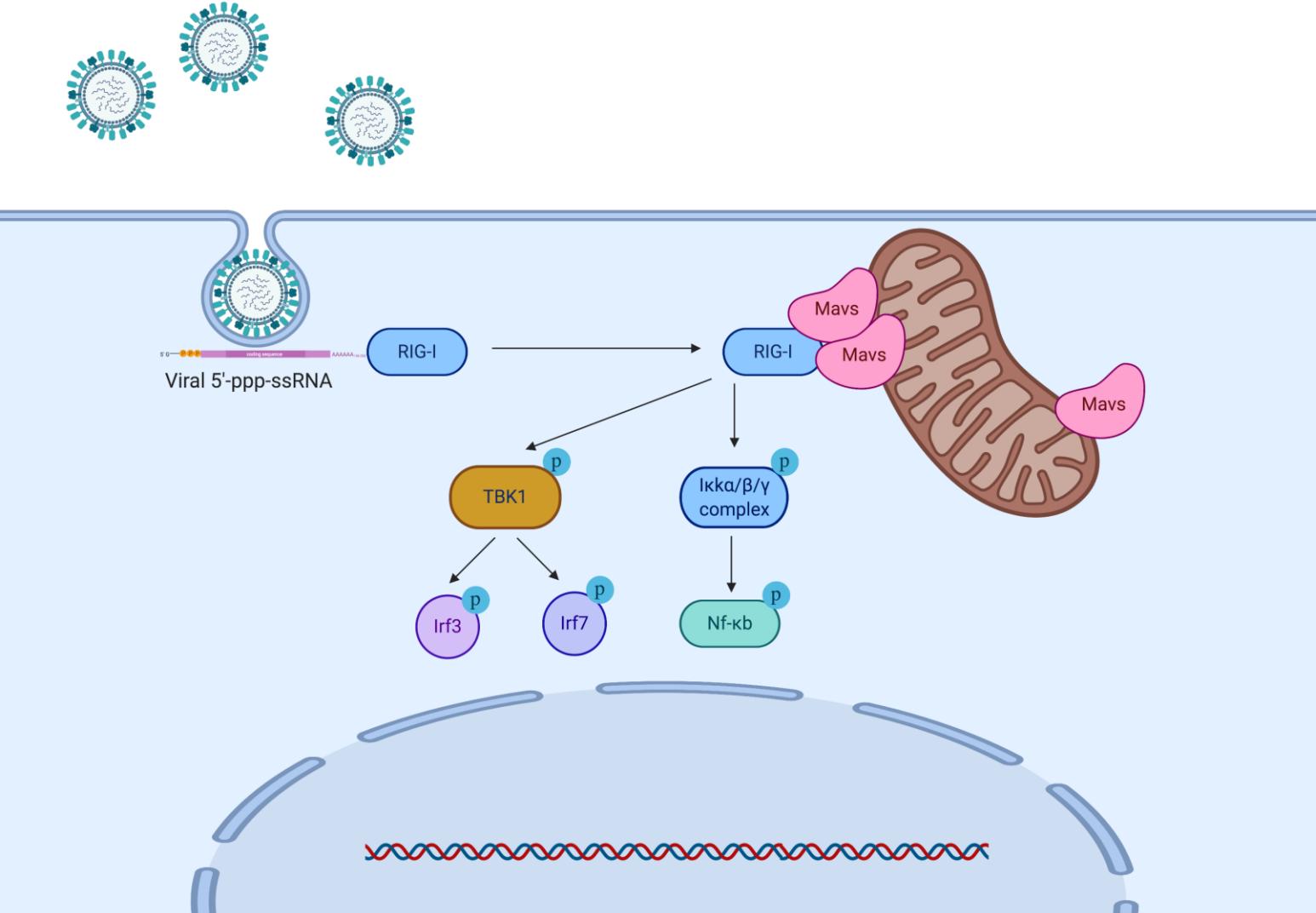
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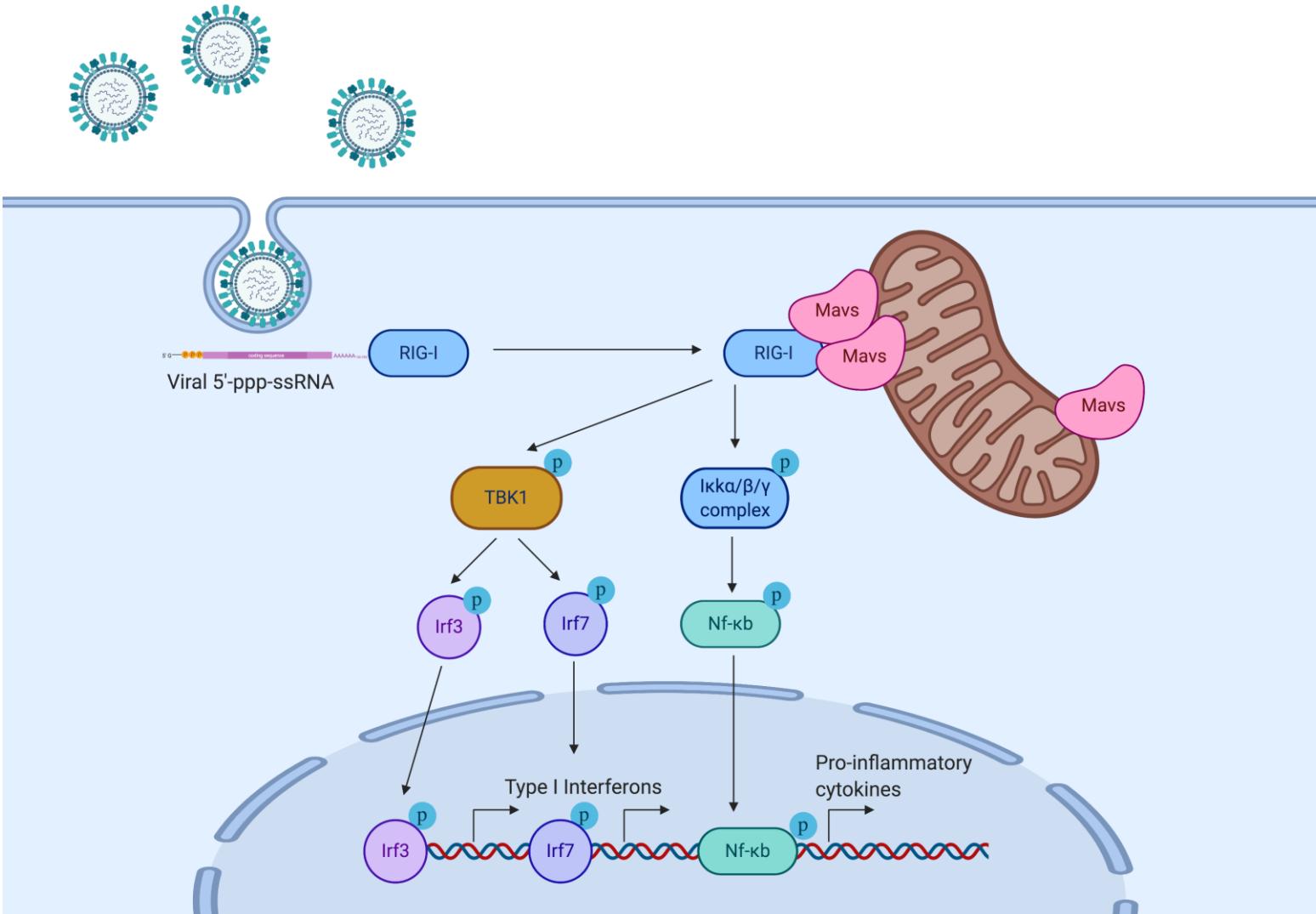
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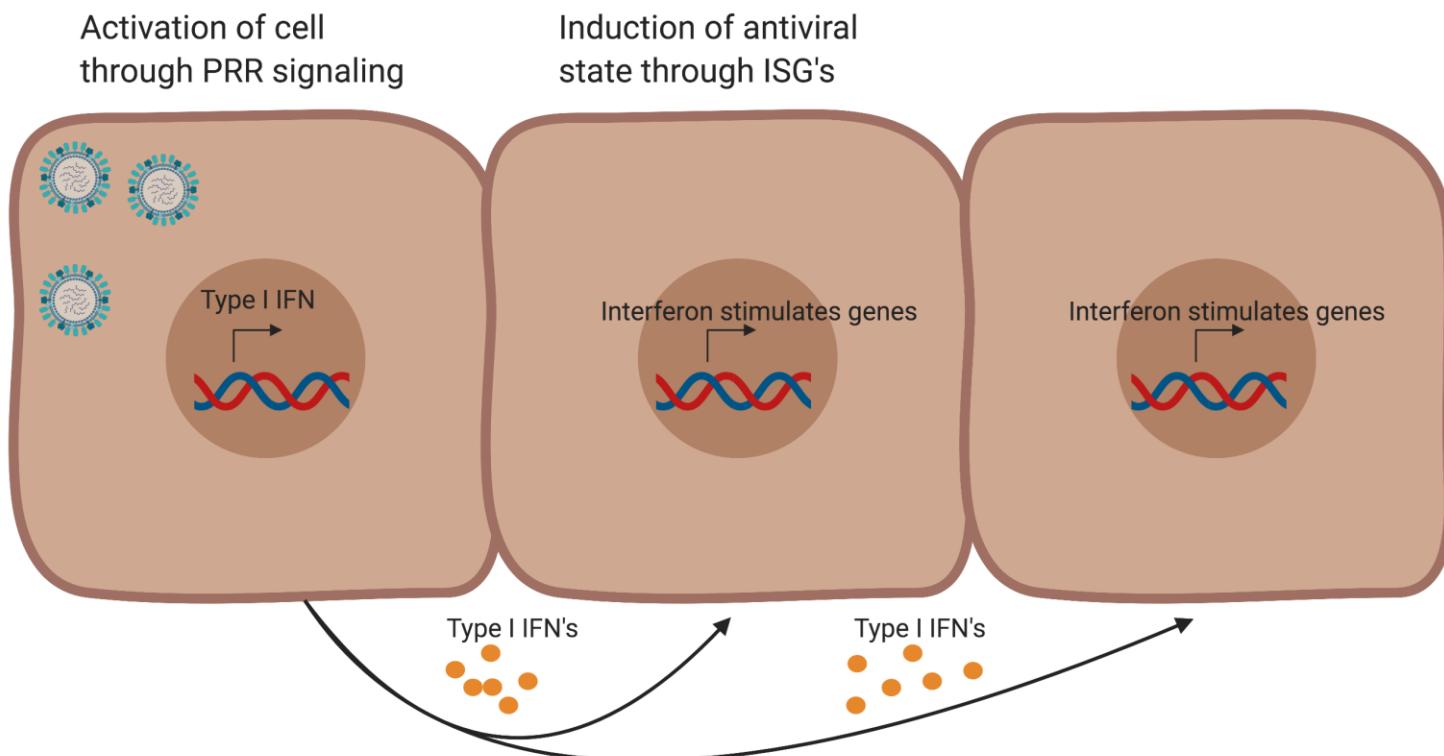
RIG-I SIGNALING



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TYPE I INTERFERON RESPONSES

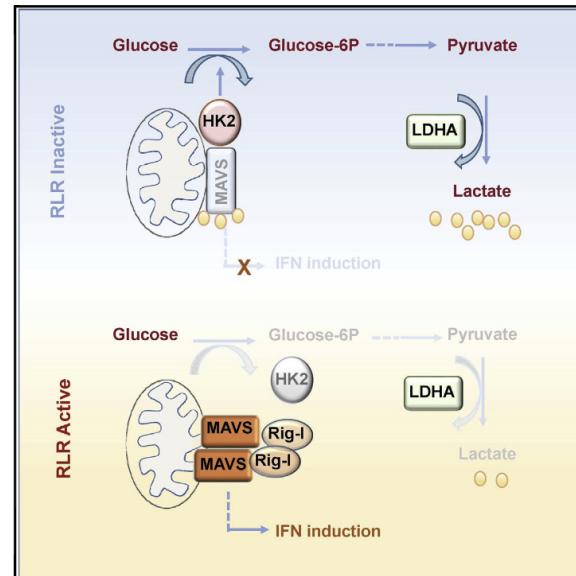


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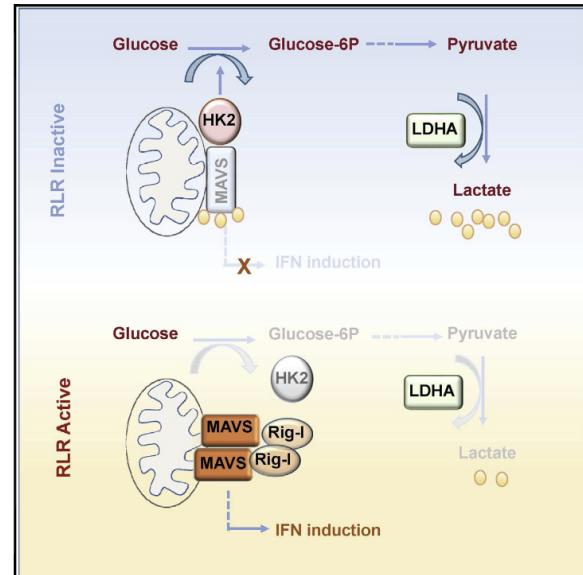
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Done in human cancer cell models using viruses that is not pathogenic to humans

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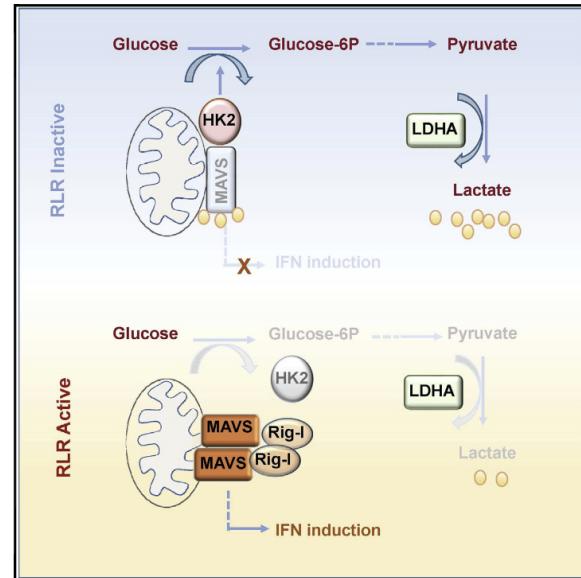
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Is this also relevant in a model of primary human airway epithelium using a highly pathogenic virus such as IAV?

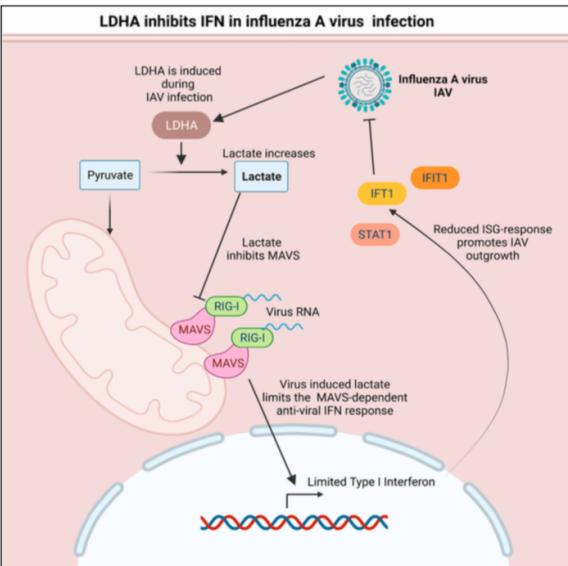
IT IS!

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Article

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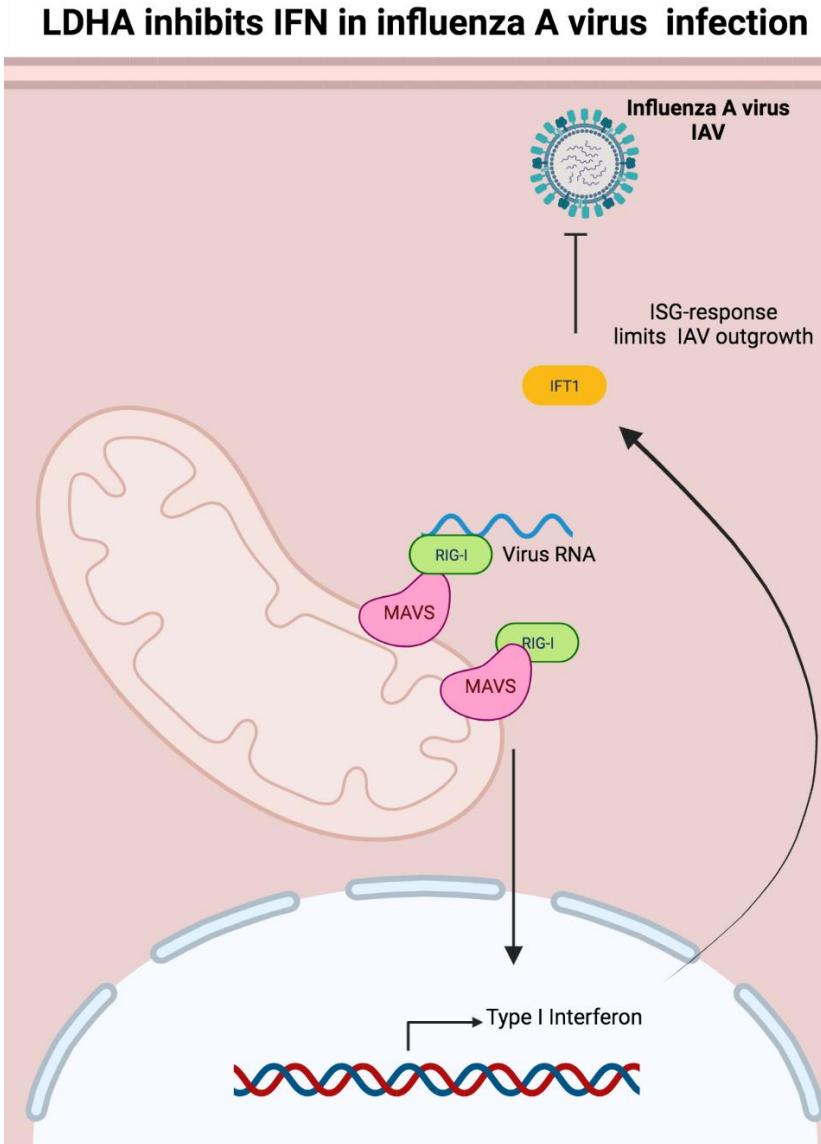
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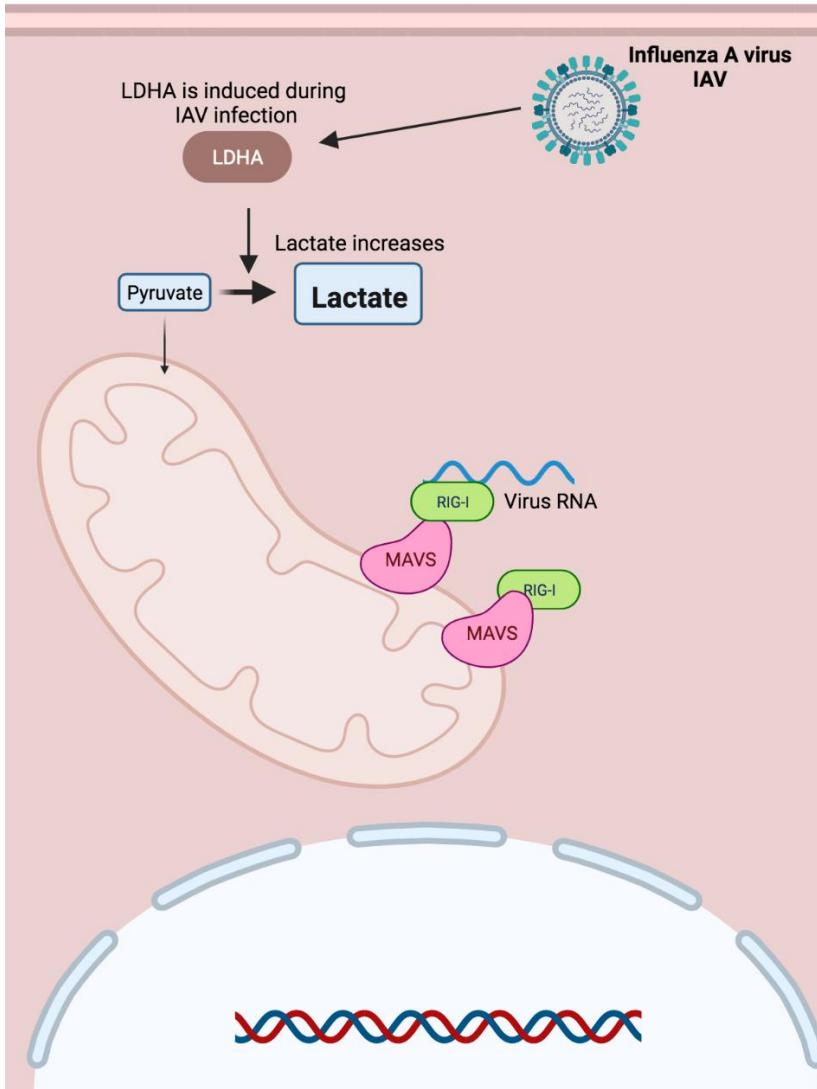
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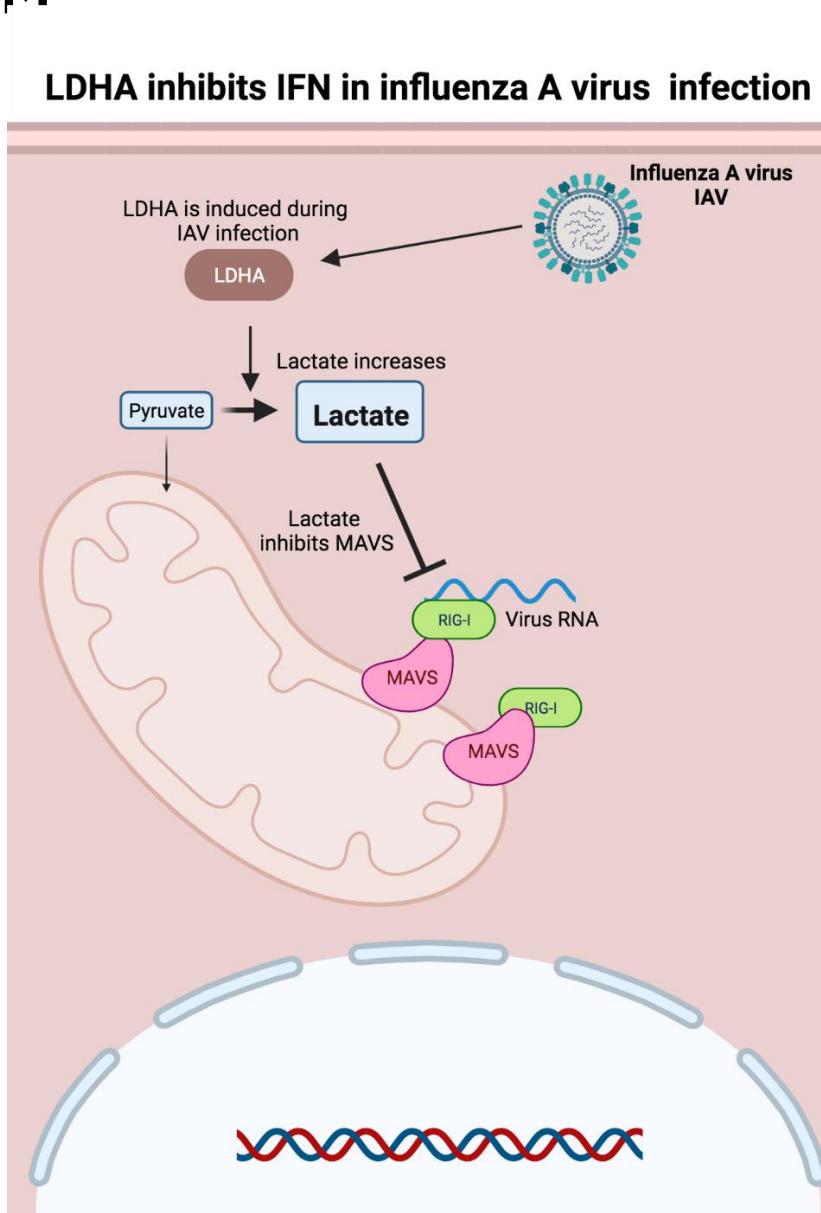


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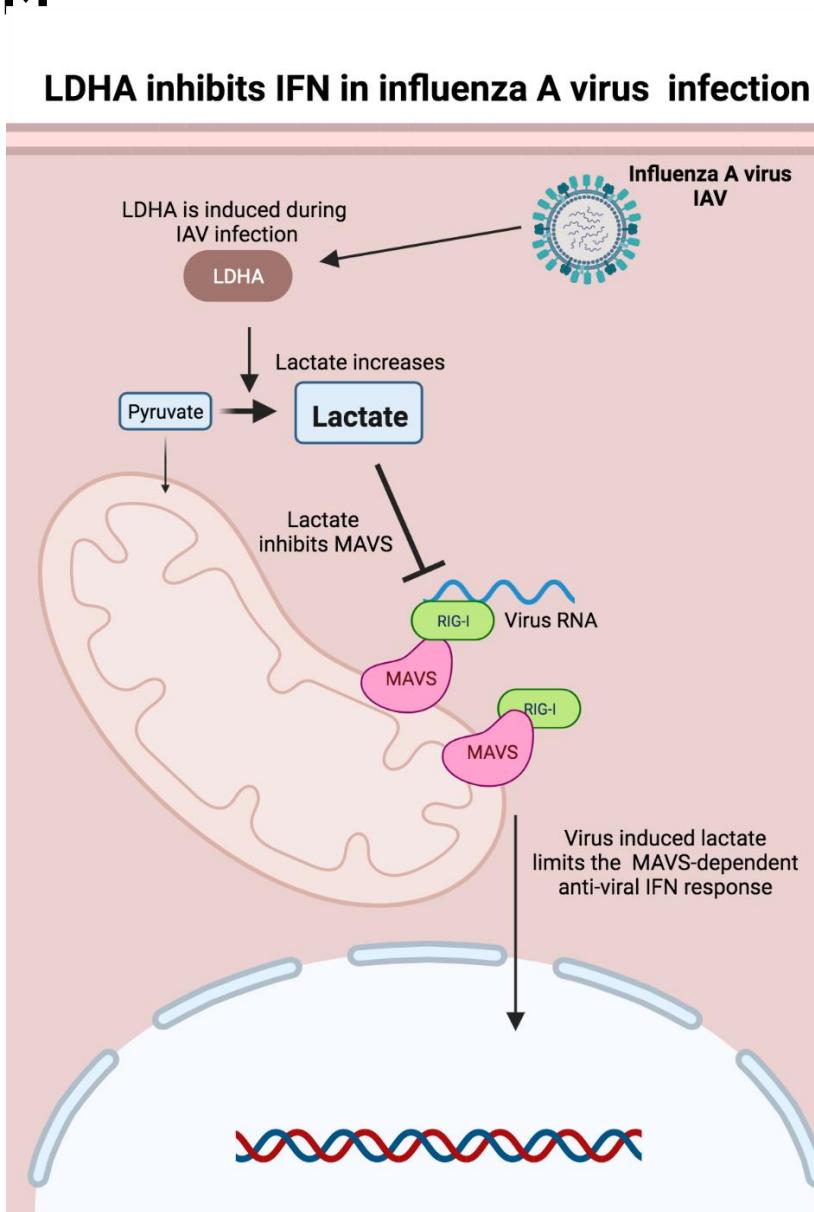
LDHA inhibits IFN in influenza A virus infection



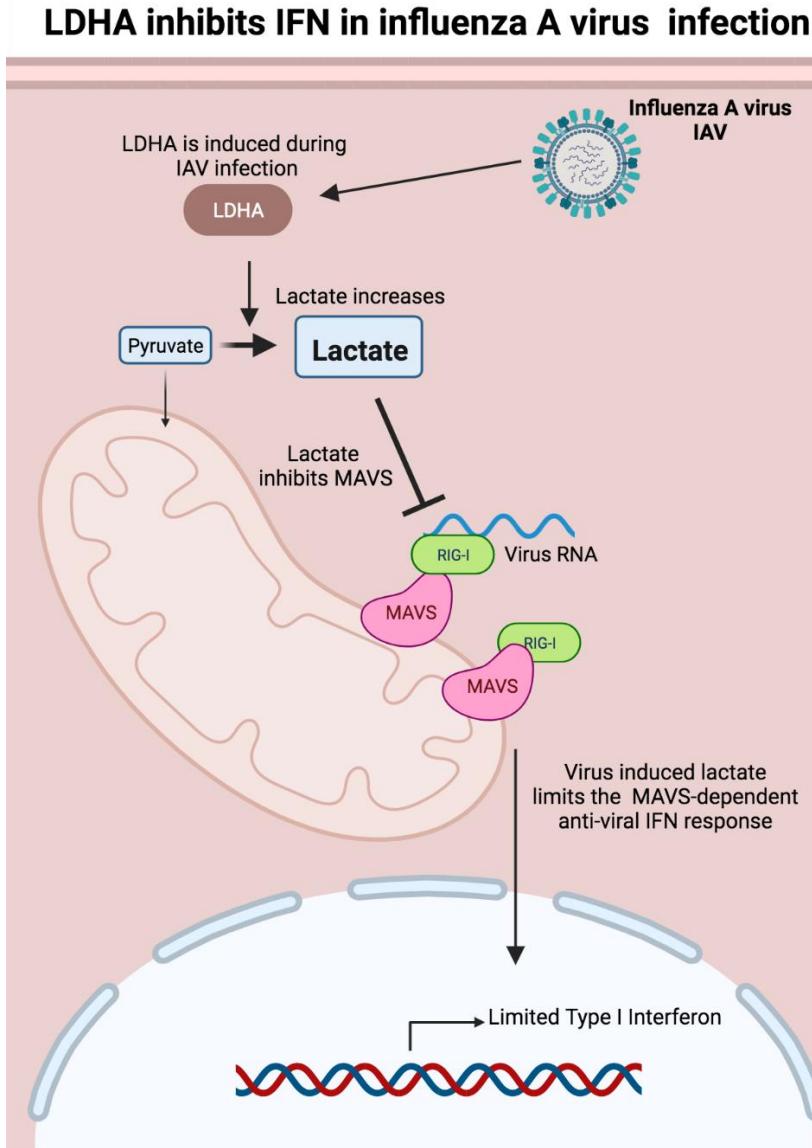
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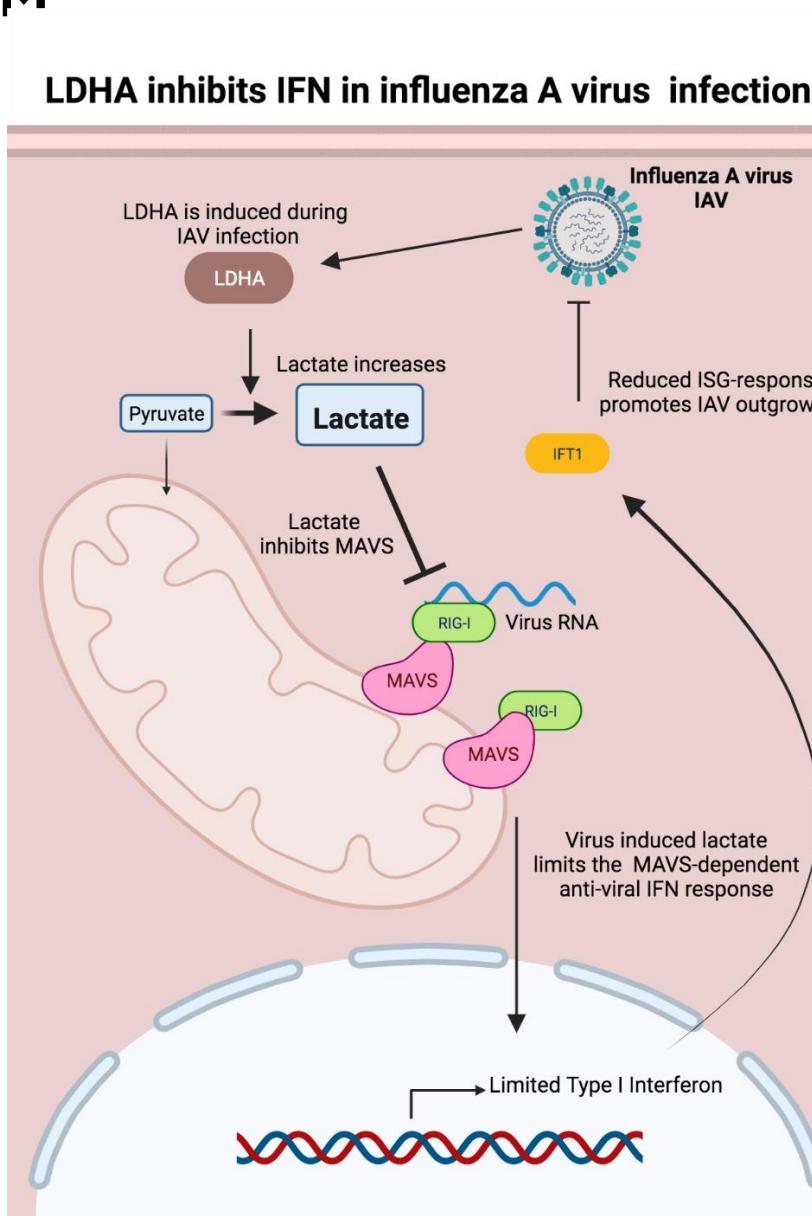
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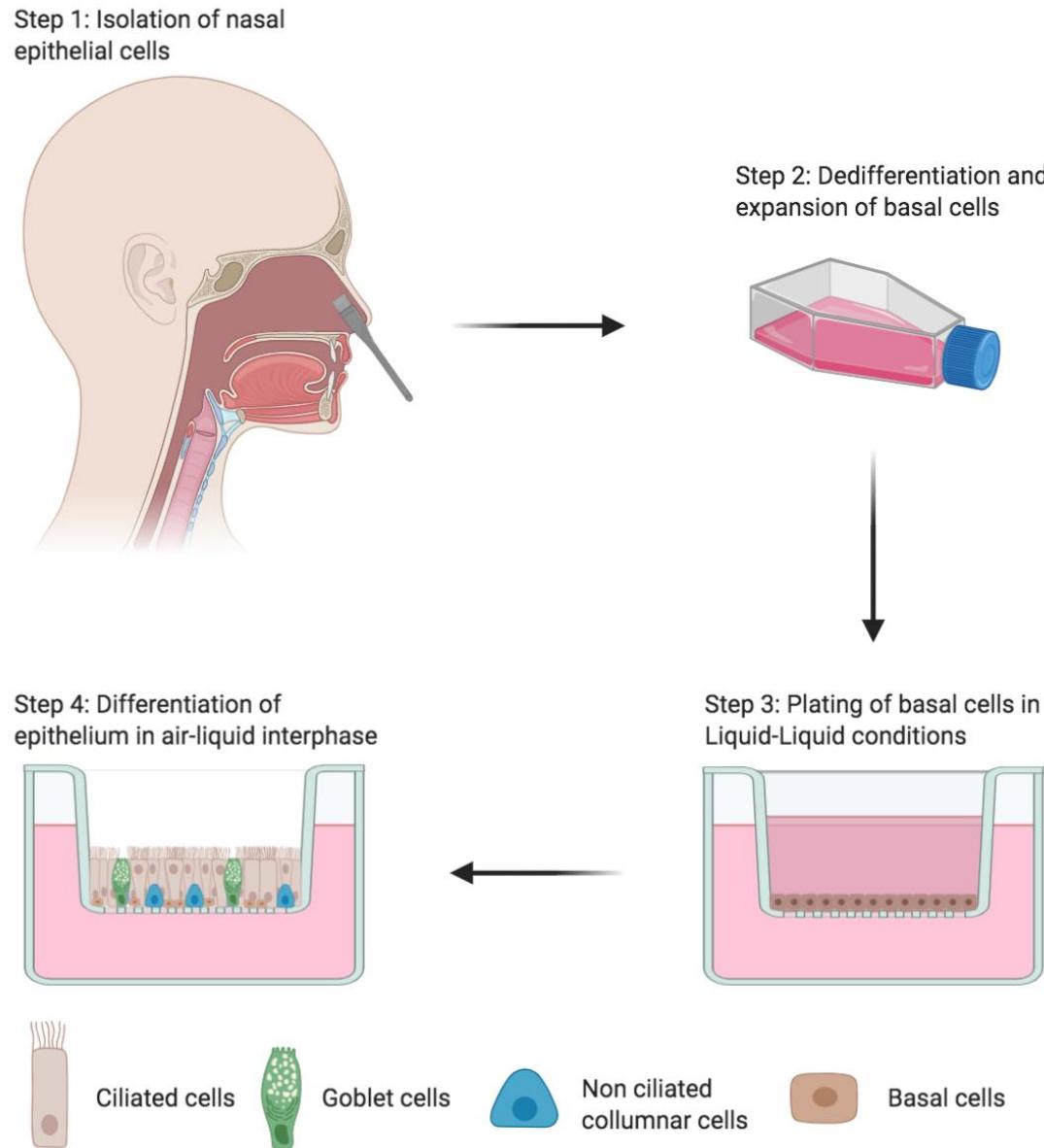
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INFLUENZA A INDUCES LACTATE FORMATION TO INHIBIT TYPE I IFN IN PRIMARY HUMAN AIRWAY EPITHELIUM



THE HPAE-ALI MODEL – AS CLOSE AS WE GET



THANK YOU FOR LISTENING

THANK YOU!

**All current and former
members of the Holm Lab:**

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Anne Thilke
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- Ester M. & Konrad Kristian Sigurdssons Dyreværnsfond
- Beckett-fonden
- Kong Christian IX og Dronning Louises Jubilæumslegat
- Direktør Emil C. Hertz og Hustru Inger Hertz' Fond
- Christian Larsen og Dommer Ellen Larsens Legat



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