Human Pluripotent Stem Cell Models for COVID-19 Disease Modeling and Drug Screening

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Big Picture

- Patient
  - Reprogramming
  - Directed Differentiation
  - Tissue Engineering
  - Patient-specific pluripotent stem cells
- Replacement Therapy
  - Drug Discovery
  - Patient-specific tissue or organ
Approaches

- Hypothesis-driven (Candidate approach)
- Discovery-driven (Screening approach)

Libraries:
- Chemical libraries
- Growth factor libraries
- Extracellular matrix libraries
- Hormone libraries
COVID-19 affect multiple organs.

Growing evidence suggests the coronavirus, mostly known to cause respiratory illness, can also affect many of the body’s primary organs.

https://projects.sfchronicle.com/2020/virus-organs-graphic/
hPSC-derived Cell/Organoid Models to Study SARS-CoV-2
Cells in the Lung, Colon, and Endocrine Cells Express ACE2 the SARS-CoV-2 Putative Entry Receptor

Lung

Pancreatic endocrine cells

Colon

Cells in the Lung, Colon, and Endocrine Cells Express ACE2 the SARS-CoV-2 Putative Entry Receptor

Cells in the Lung, Colon, and Endocrine Cells Express ACE2 the SARS-CoV-2 Putative Entry Receptor

Cells in the Lung, Colon, and Endocrine Cells Express ACE2 the SARS-CoV-2 Putative Entry Receptor
Human Colon, Beta cells, and Lung Support SARS-CoV-2 Viral Entry

In collaboration with David Ho
scRNA-seq of hPSC-derived Lung Organoids

In collaboration with Joyce Chen

https://www.biorxiv.org/content/10.1101/2020.05.05.079095v1
Lung Organoid Are Permissive to SARS-CoV-2 Infection

In collaboration with Joyce Chen
Human Lung Organoids Support SARS-CoV-2 Viral Replication

In collaboration with Ben TenOever

Weill Cornell Medicine

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hPSC-derived Lung Organoids Shows the Similar Immune Response as COVID-19 Patients

In collaboration with Ben TenOever

Weill Cornell Medicine

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COVID-19 and Diabetes

Zhu et.al., *Cell Metabolism*, 2020
ACE2 expression in Human Islets

Yang et.al., Cell Stem Cell, 2020
Human Islets can be infected by SARS-CoV-2
Human Pancreatic Endocrine Cells Support SARS-CoV-2 Viral Replication

In collaboration with Ben TenOever
Immuno-Response of SARS-CoV-2 Infected Endocrine Cells

In collaboration with Ben TenOever
Global Registry of COVID-19 Associated Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

New-Onset Diabetes in Covid-19

http://covidiab.e-dendrite.com/

Potential Anti-SARS-CoV-2 Treatment and Timeline

COVID-19: PROJECTED TIMELINE FOR TREATMENT AND PREVENTION

There are 66 programs working on 3 different approaches:

- **7** repurposed drugs
- **16** antibodies
- **43** vaccines

Development of two screening platforms to identify potent drugs that block SARS-CoV-2 Viral Entry-lung organoids
Drugs block SARS-CoV-2 infection
# Imatinib and COVID-19 Clinical Trial

<table>
<thead>
<tr>
<th>Row</th>
<th>Saved</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>Recruiting</td>
<td><strong>Trial of Imatinib for Hospitalized Adults With COVID-19</strong></td>
<td>COVID-19</td>
<td>• Drug: Imatinib&lt;br&gt;• Drug: Placebo oral tablet</td>
<td>University of Maryland Medical Center&lt;br&gt; Baltimore, Maryland, United States</td>
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<td>2</td>
<td></td>
<td>Not yet recruiting</td>
<td><strong>The Safety &amp; Efficacy of Imatinib for the Treatment of SARS-COV-2 Induced Pneumonia</strong></td>
<td>COVID-19</td>
<td>• Drug: Imatinib Mesylate&lt;br&gt;• Drug: Standard of Care</td>
<td>Hospital Universitario de Fuencarral&lt;br&gt; Fuencarral, Madrid, Spain</td>
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<td>3</td>
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<td>Recruiting</td>
<td><strong>Clinical Trial to Evaluate Efficacy of 3 Types of Treatment in Patients With Pneumonia by COVID-19</strong></td>
<td>COVID-19 Pneumonia</td>
<td>• Drug: Hydroxychloroquine&lt;br&gt;• Drug: Lopinavir/ritonavir&lt;br&gt;• Drug: Imatinib tablets&lt;br&gt;• Drug: Baricitinib Oral Tablet</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Not yet recruiting</td>
<td><strong>IMATINIB IN COVID-19 DISEASE IN AGED PATIENTS.</strong></td>
<td>SARS Virus</td>
<td>• Drug: Experimental drug</td>
<td>CHU Bordeaux&lt;br&gt; Bordeaux, France&lt;br&gt; CH de Versailles&lt;br&gt; Le Chesnay, France</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Recruiting</td>
<td><strong>Treatments to Decrease the Risk of Hospitalization or Death in Elderly Outpatients With Symptomatic SARS-CoV-2 Infection (COVID-19)</strong></td>
<td>Corona Virus Infection&lt;br&gt;Sars-CoV2</td>
<td>• Dietary Supplement: Vitamins&lt;br&gt;• Drug: Imatinib&lt;br&gt;• Drug: Favipiravir&lt;br&gt;• Drug: Telmisartan</td>
<td>Bordeaux university Hospital Bordeaux, France</td>
</tr>
</tbody>
</table>

Show study NCT04357613: IMATINIB IN COVID-19 DISEASE IN AGED PATIENTS.
Summary

- Colon organoids
- Lung organoids
- Pancreatic endocrine cells
- Liver organoids
- Endothelial cells
- Cardiomyocytes
- Macrophages
- Microglia
- Cortical neurons
- Dopaminergic neurons

- SARS-NCDX2DAPI
- SARS-NKRT20DAPI
- SARS-CoV2

- Mock
- SP-CSARS-SDAP
- INSSARS-SDAI

- EC50=4.86 μM
- IC50=37.3 μM

- CoV-2 (Fold Change)
- -Log10 P
- 0
- 20
- 40
- -10 0 +10 +20 -20

- MOCK v.s SARS-CoV-2
- IL1A
- CXCL8
- CXCL6
- CXCL11
- IL1B

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