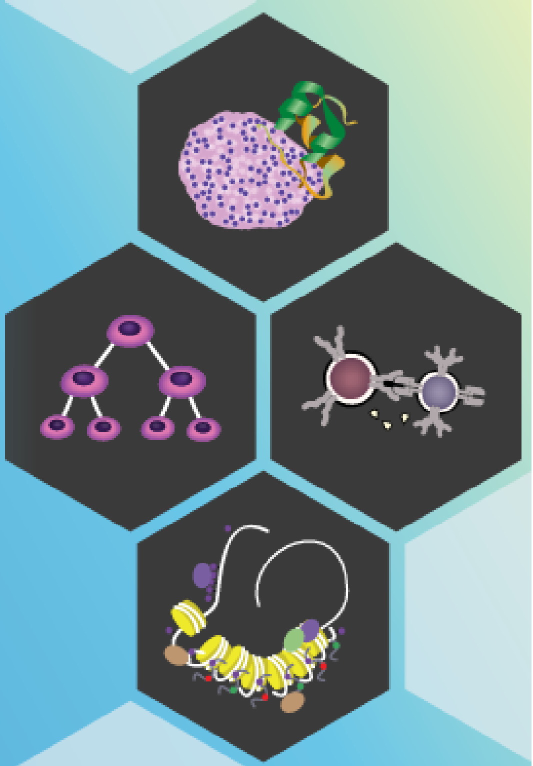
2024 RACHMIEL LEVINE-ARTHUR RIGGS

# Diabetes Research Symposium

# Approaches for Extrahepatic Site for Cell Transplant



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# Disclosures

- I do not have any relevant financial relationships.

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

**STATE LAW:**

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

***EXEMPTION:***

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

***This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.***

# Approaches for Extrahepatic Site for Cell Transplant

## Outline

1. Intraportal vs. extrahepatic sites – Graft density as a critical difference
2. Approaches for extrahepatic site transplant – Enhanced revascularization and oxygen support
3. Scientific gaps for successful extrahepatic site strategy – Unknown hypoxia resistance of islets

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# Clinical need for extrahepatic sites for islet grafts

- **Searching for minimally invasive procedures**

  (vs. intraportal injection)
- **Avoiding suboptimal environment of the liver**

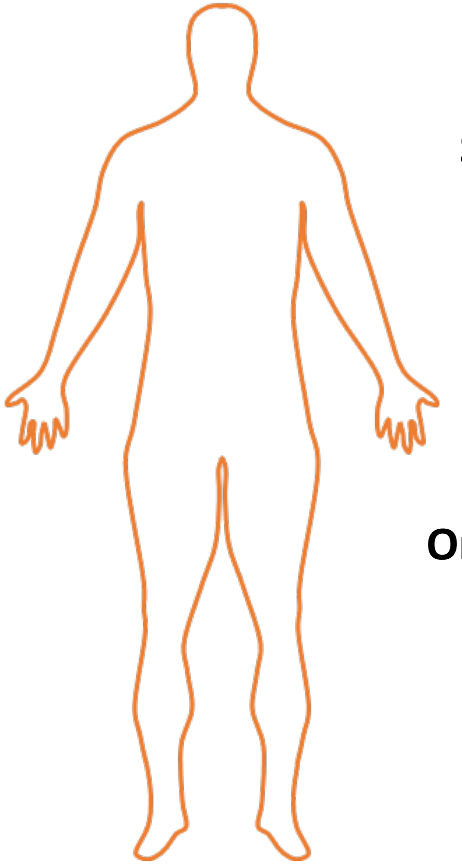
  (Direct exposure to blood: Instant Blood Mediated Inflammatory Reaction)
- **Seeking post-transplant retrievability**

  (Especially for stem cell-derived beta cells)

# Clinical Trials for extrahepatic islet transplantations

**Intramuscular**

Pancreatic Islets and Parathyroid Gland Co-transplantation for Treatment of Type 1 Diabetes (PARADIGM)
NCT03977662
2019–
University of California, San Francisco



**SubQ**

Device-Less Technique in Islet Transplantation
NCT05073302
2021–
University of Alberta

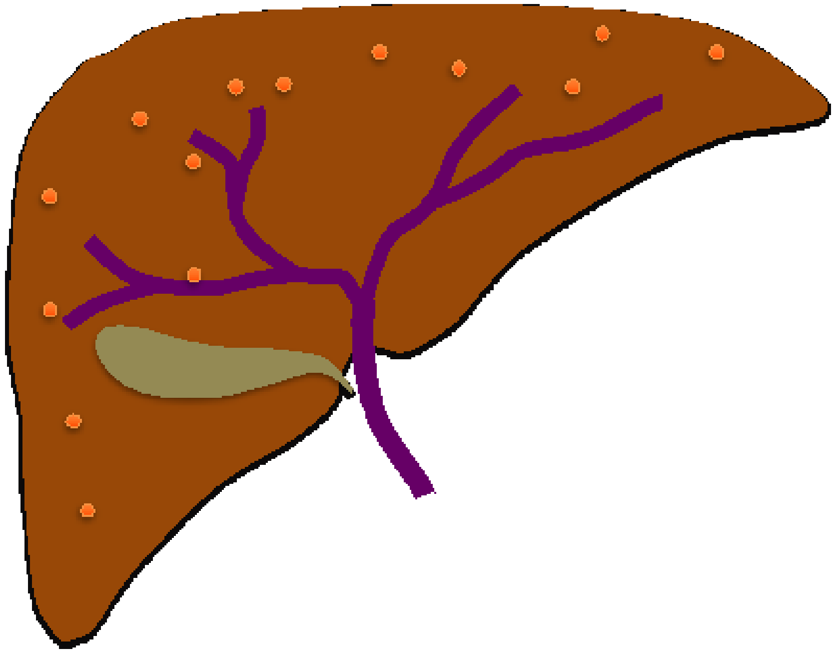
**Omentum**

Allogeneic Islet Cells Transplanted Onto the Omentum
NCT02213003
2014–
University of Miami

**However, in reality, we still transplant the islets into the liver.**

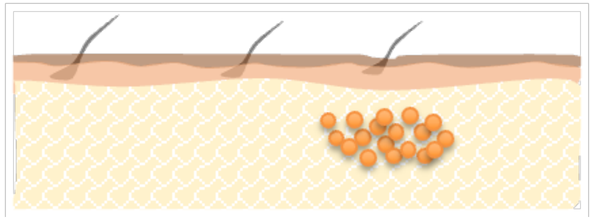
# Why are extrahepatic sites challenging for islets?

Liver site



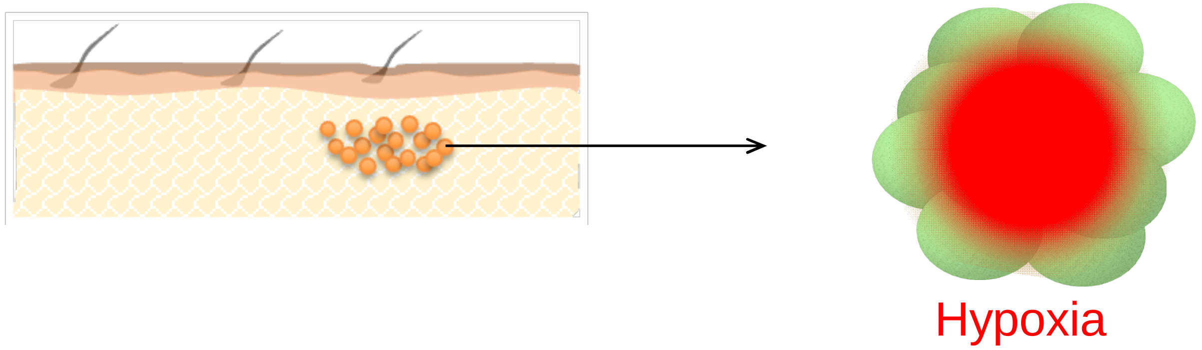
vs.

Extrahepatic sites



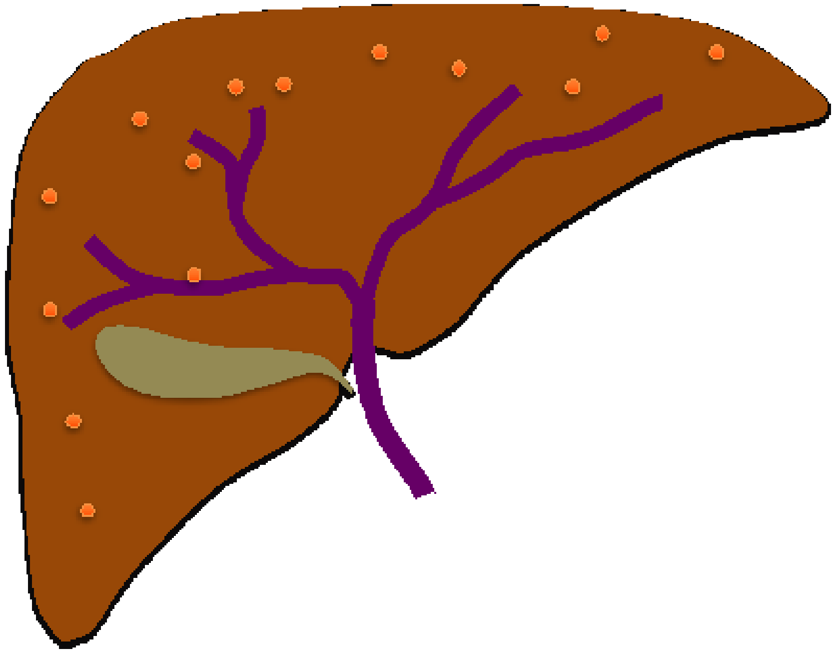
# Hypoxia in extrahepatic sites?

Subcutaneous sites



# Are extrahepatic sites more hypoxic than the liver?

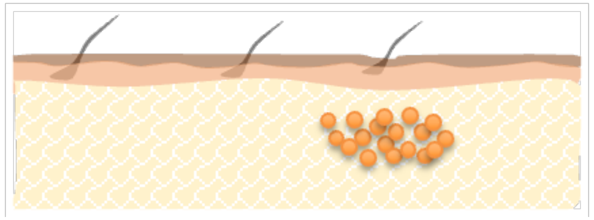
Liver site



40 – 50 mmHg

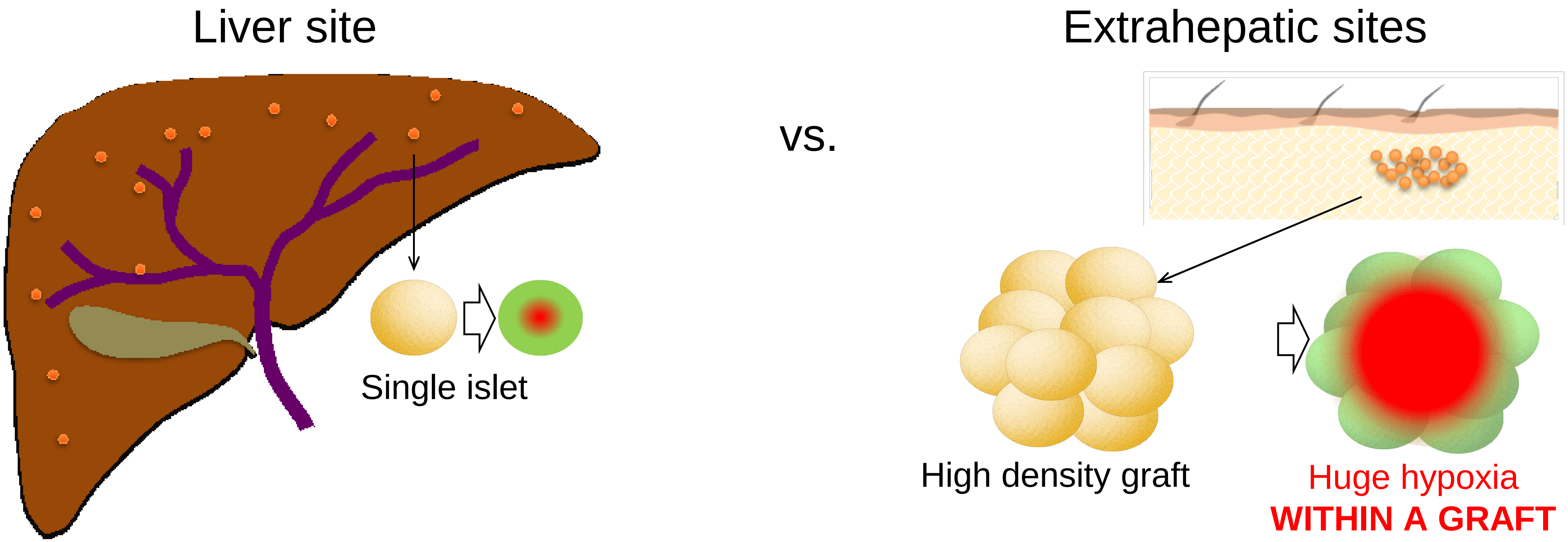
vs.

Extrahepatic sites



35 – 50 mmHg

# High density graft induces the hypoxia **within** the graft



# Short summary (1)

High graft density is an inherent bottleneck in extrahepatic site islet transplantations.

# Approaches for Extrahepatic Site for Cell Transplant

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# Enhanced revascularization and Oxygen support for islet grafts

| Enhanced revascularization | Oxygen support |
|---|---|
| Pre-vascularization (of the graft bed)<br>Post-transplant vascularization<br>• Proangiogenic factors<br>• Endothelial cell co-transplantations | • Chemical $O_2$ generation<br>• Electrical $O_2$ generation<br>• Photosynthesis-based $O_2$ generation<br>• Oxygen carriers<br>• Systemic oxygenation via inhalation |

Potential questions:

✓ Which is better?

✓ Should we do both?

# Can enhanced revascularization counteract the graft hypoxia?

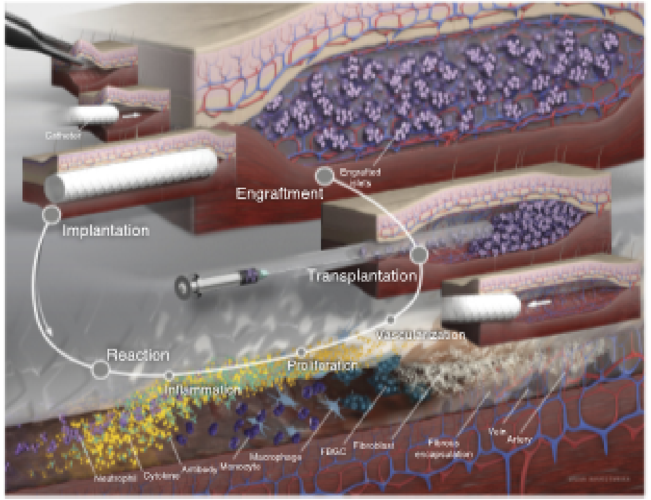
Numerous papers have demonstrated that enhanced revascularization (and "pre"vascularization) strategies improve islet engraftment.

ARTICLES

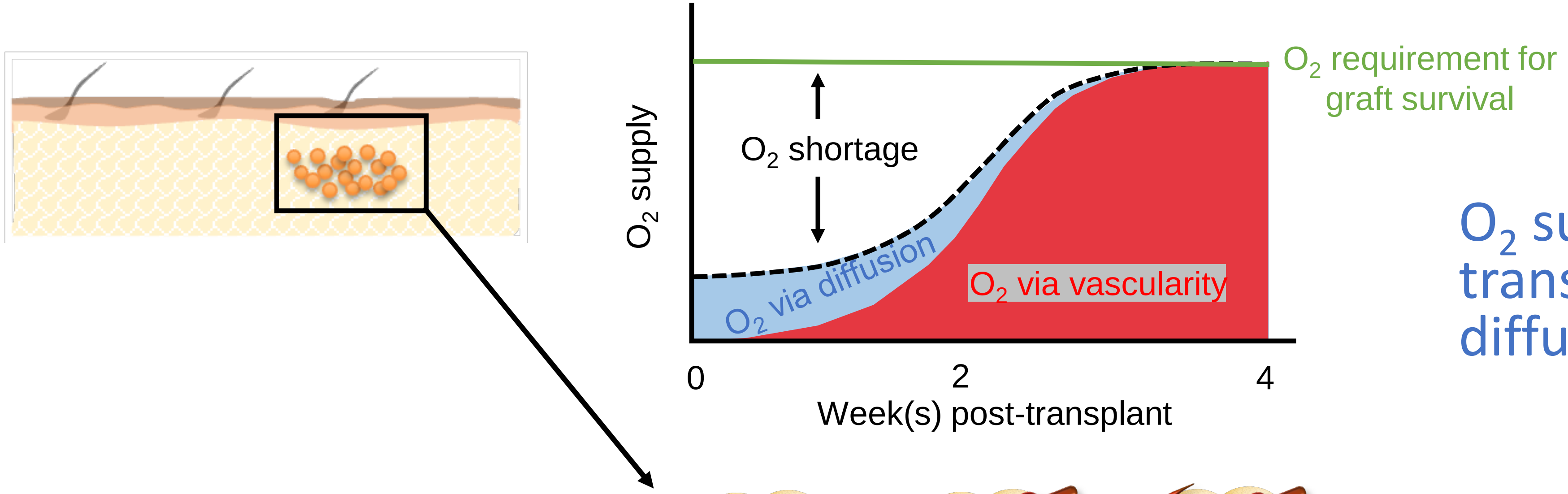
nature biotechnology

A prevascularized subcutaneous device-less site for islet and cellular transplantation

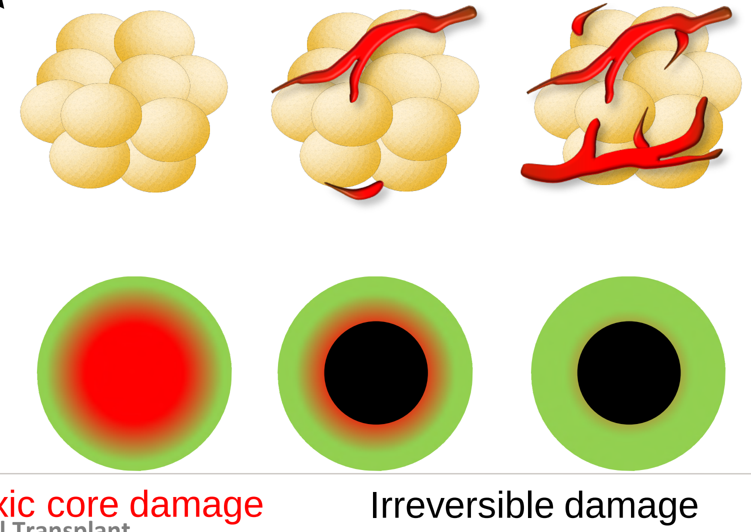
Andrew R Pepper[1], Boris Gala-Lopez[1], Rena Pawlick[1], Shaheed Merani[1], Tatsuya Kin[1,2] & A M James Shapiro[1,2]

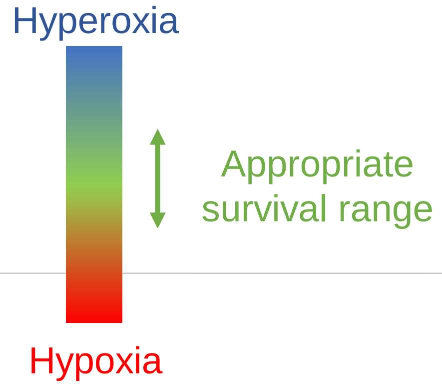


# Islet graft revascularization takes several weeks

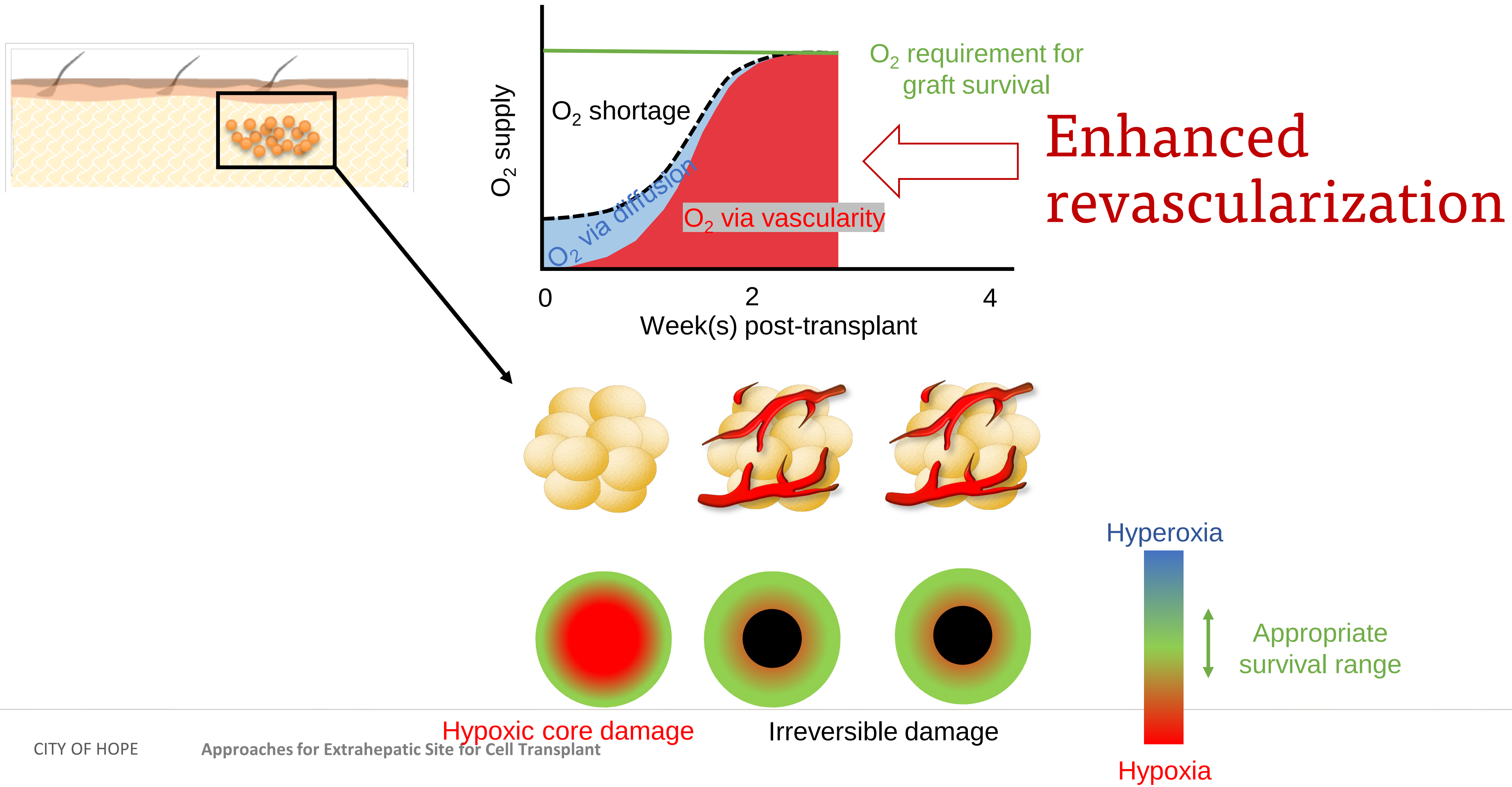



O$_2$ supply in the early post-transplant phase relies on the diffusion



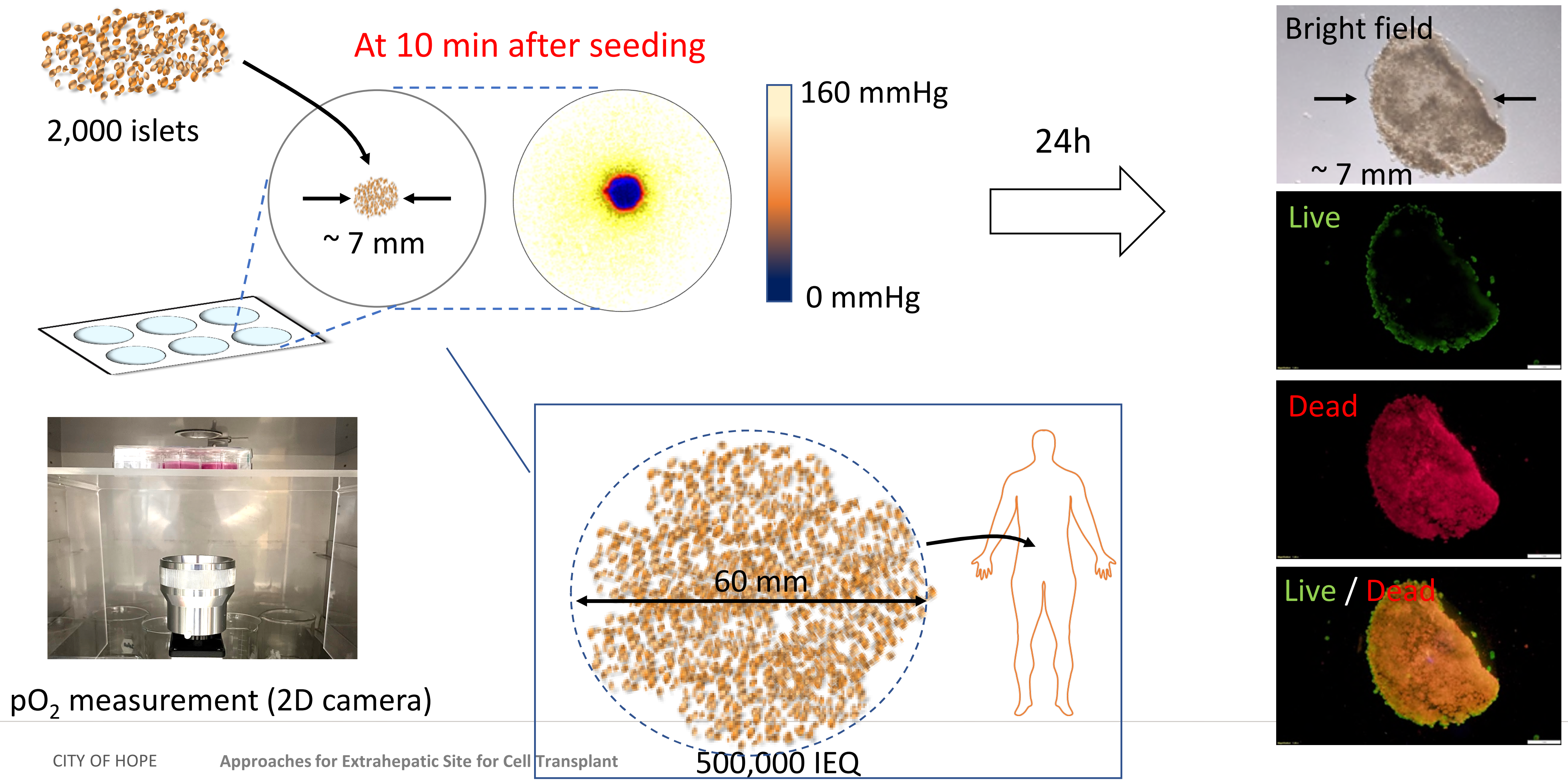



# Enhanced revascularization reduces the duration of hypoxia



# Can't islets survive in hypoxia until they are vascularized?

# Hypoxia-induced graft death occurs before revascularization can take effect



# Short summary (2)

Oxygen support is required for the islet graft in the early post-transplantation phase, even with enhanced revascularization.

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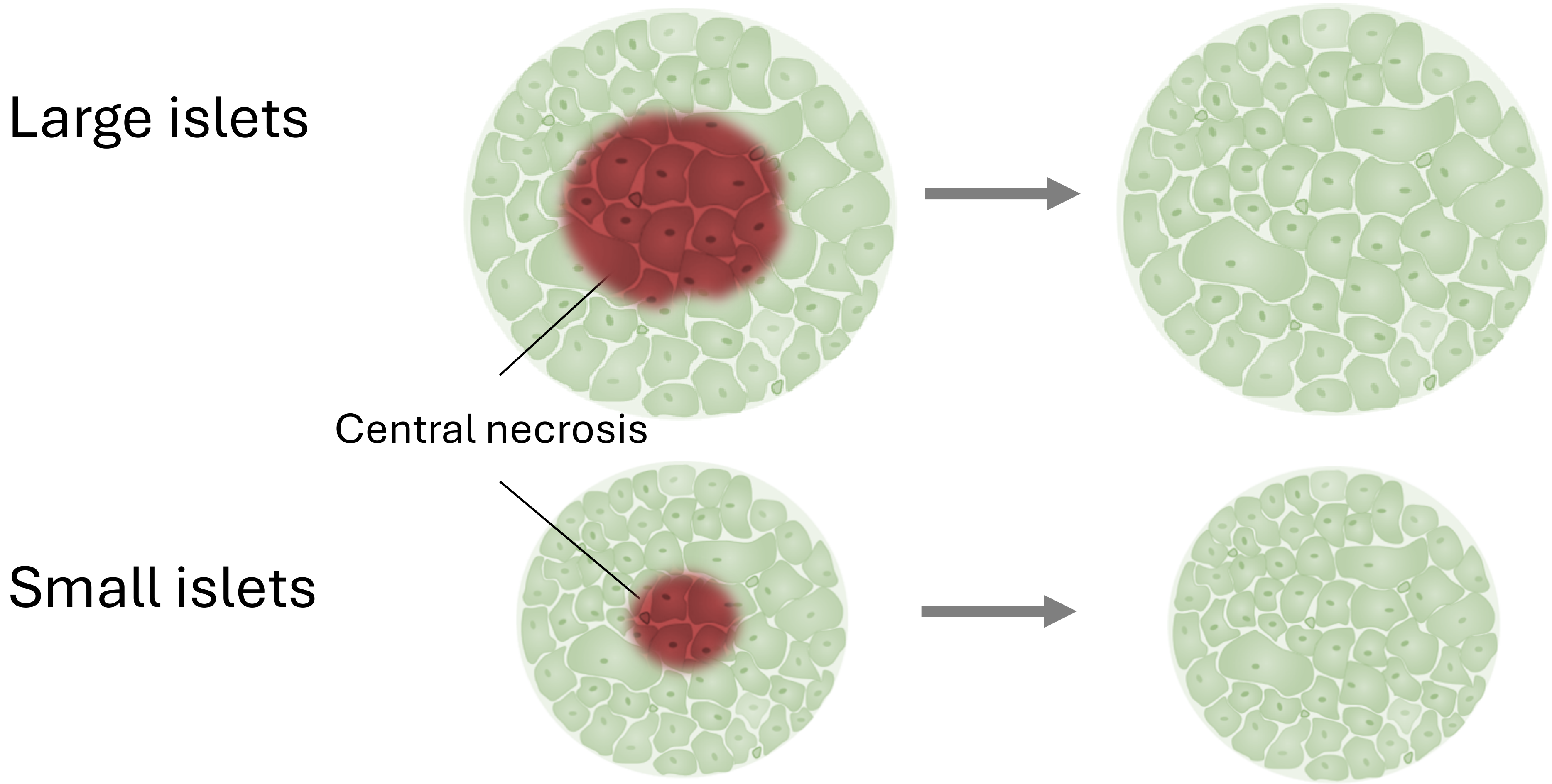
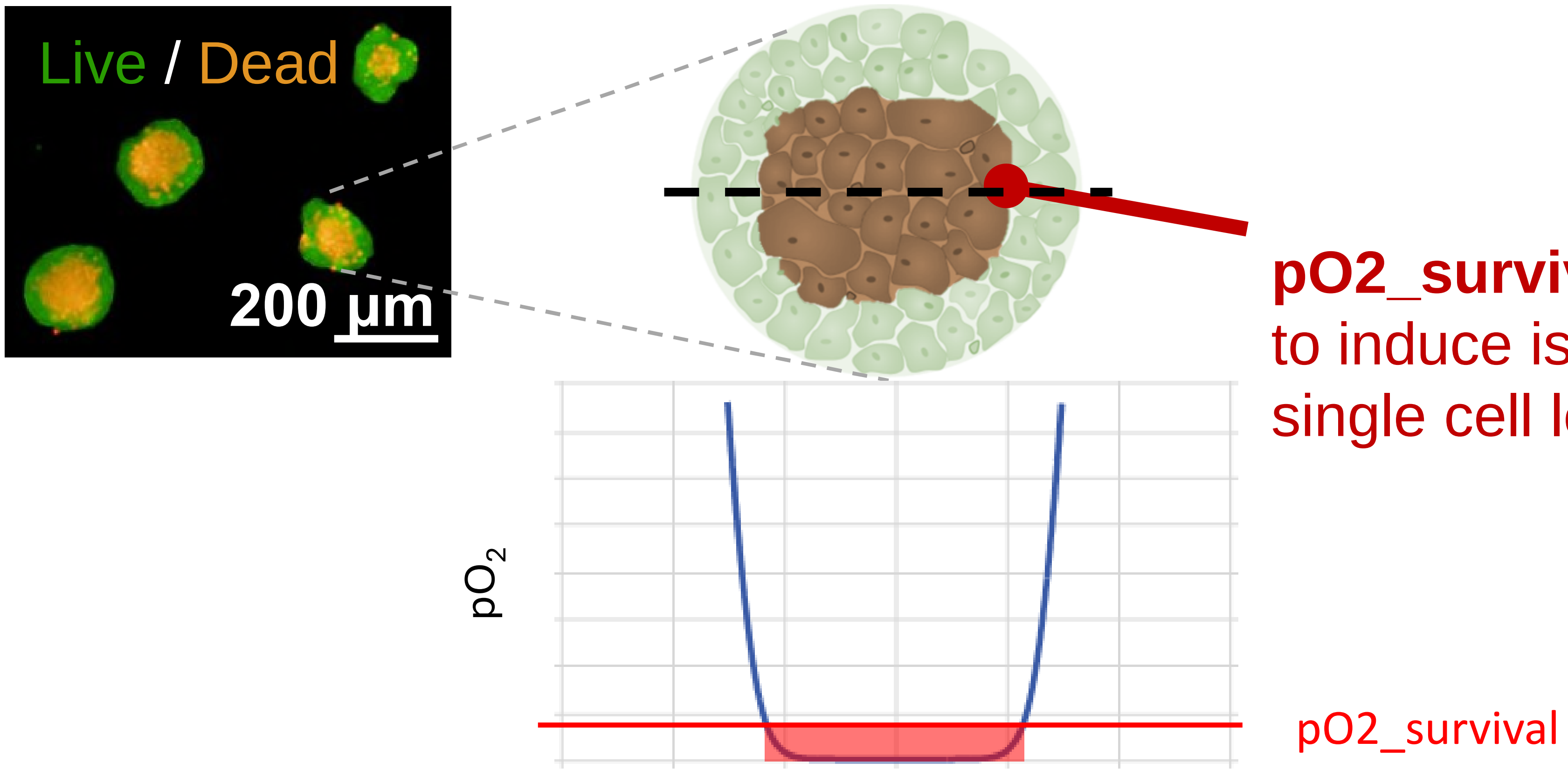
# Now we would like to supply $O_2$ to islets.

- How much $O_2$ should we supply to islets?
- What is the minimum $O_2$ level islets can tolerate?

# Our goal is to ensure all islets survive

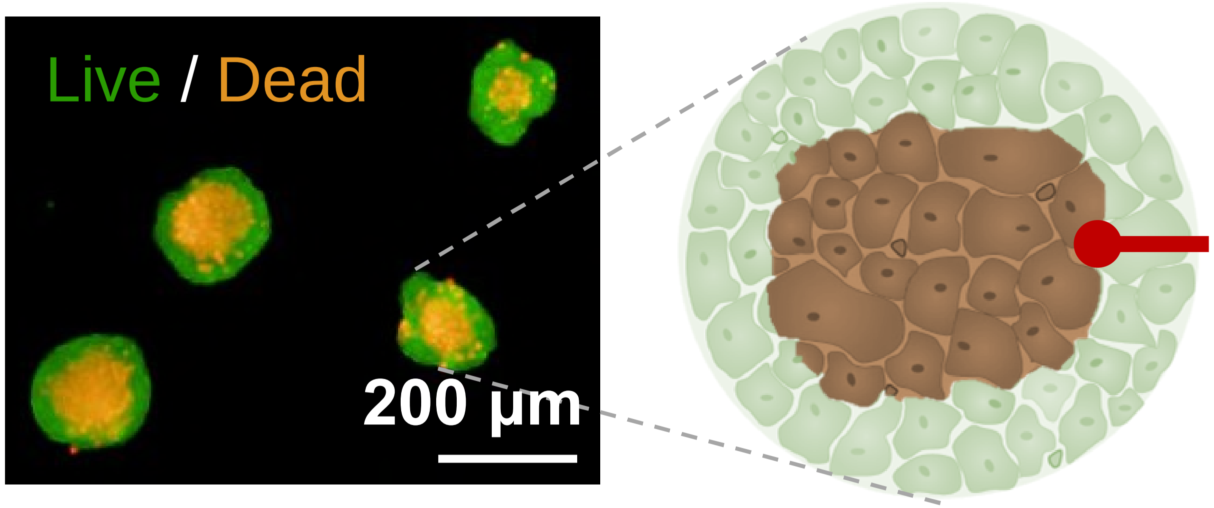


# We propose "pO2_survival" as a marker for hypoxia resistance




**pO2_survival:** $pO_2$ threshold to induce islet cell death in single cell level

# Do you know the pO2_survival of adult pancreatic islet cells?




**pO2_survival** = XX mmHg

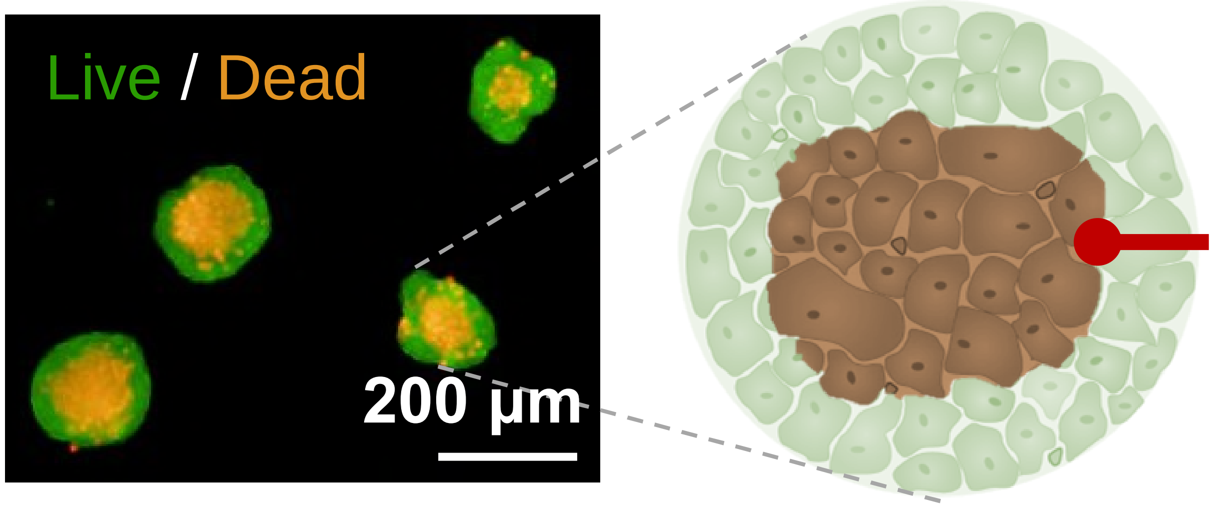
a. 100 mmHg

b. 10 mmHg

c. 2 mmHg

d. 0.1 mmHg

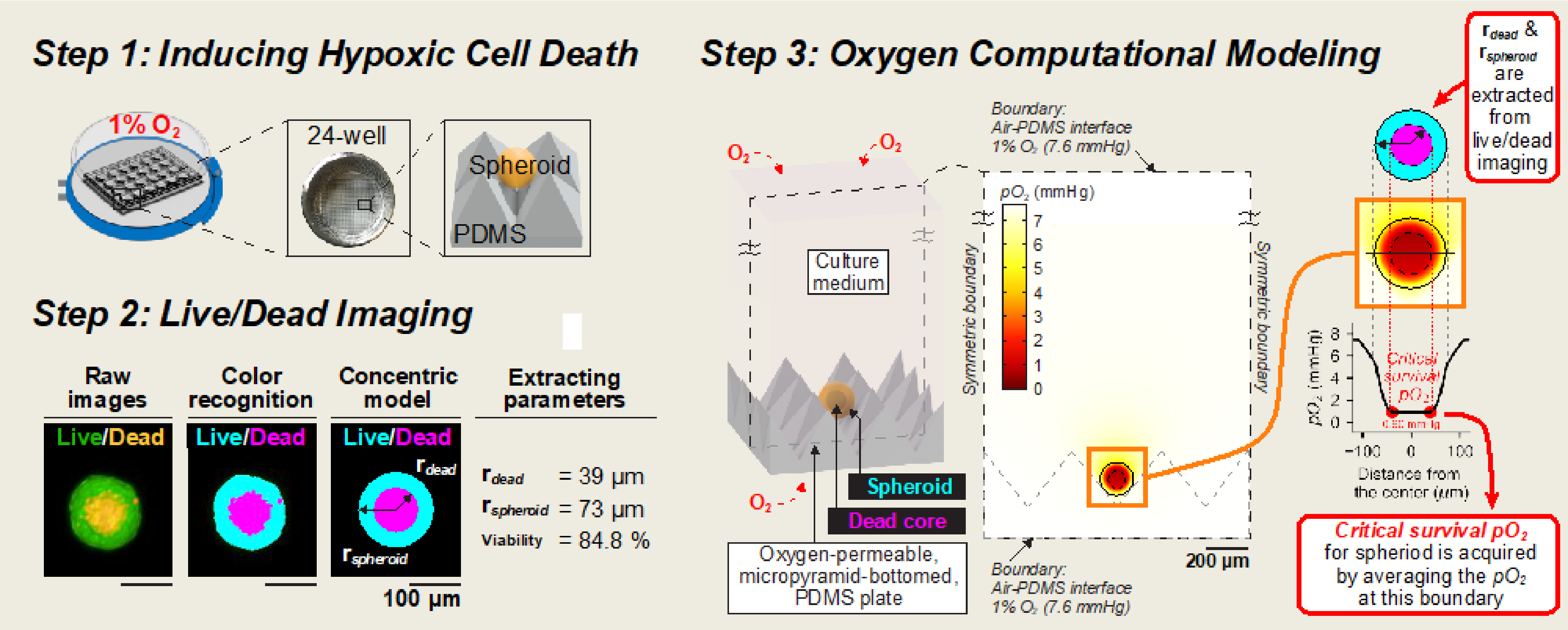
# Do you know the pO2_survival of adult pancreatic islet cells?




**pO2_survival** = XX mmHg

a. 100 mmHg
b. 10 mmHg
c. 2 mmHg
d. 0.1 mmHg

# A novel approach to determine critical survival $pO_2$ for islet spheroids

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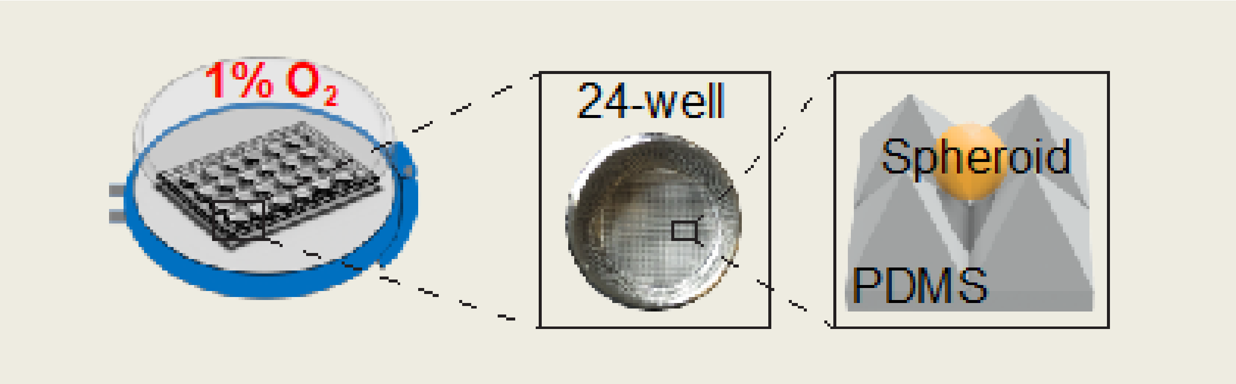
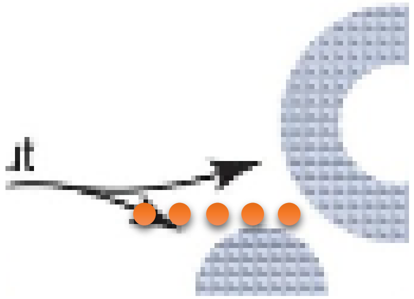
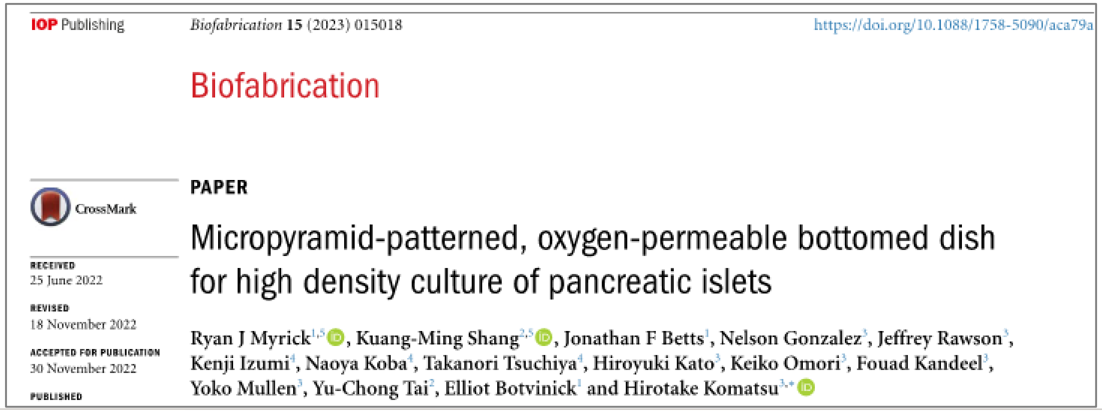
*First published March 18, 2024; doi:10.1152/ajpcell.00024.2024*

# Step 1: Inducing Hypoxic Cell Death in a Precisely Controlled 1% Hypoxia





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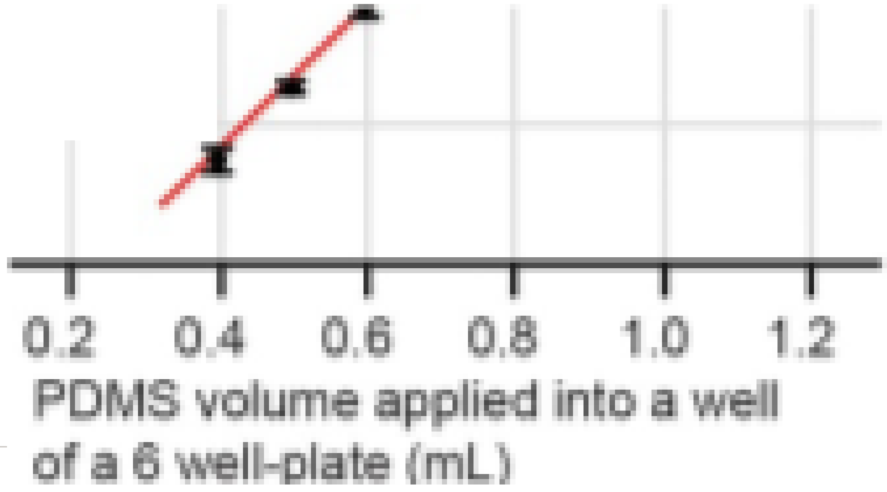
PAPER

## Micropyramid-patterned, oxygen-permeable bottomed dish for high density culture of pancreatic islets

Ryan J Myrick[1,5], Kuang-Ming Shang[2,5], Jonathan F Betts[1], Nelson Gonzalez[3], Jeffrey Rawson[3], Kenji Izumi[4], Naoya Koba[4], Takanori Tsuchiya[4], Hiroyuki Kato[3], Keiko Omori[3], Fouad Kandeel[3], Yoko Mullen[3], Yu-Chong Tai[2], Elliot Botvinick[1] and Hirotake Komatsu[3,*]



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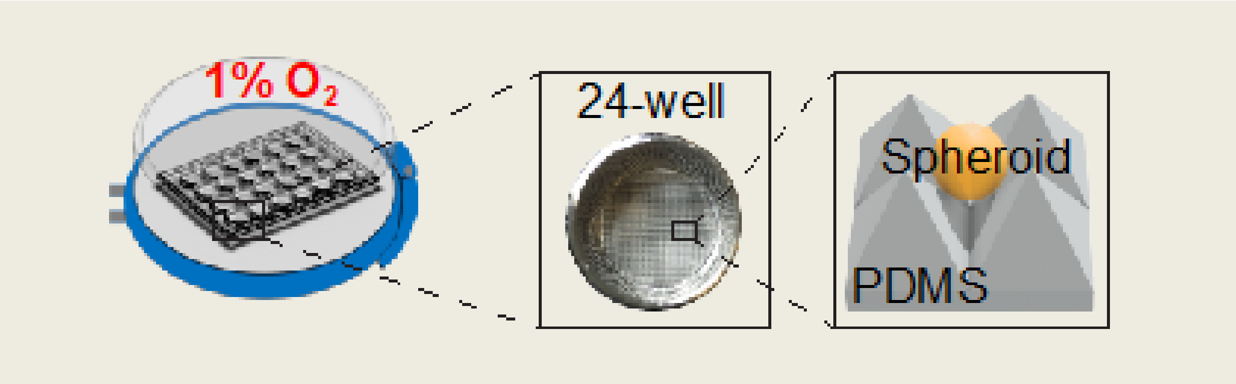
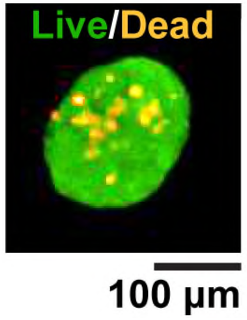
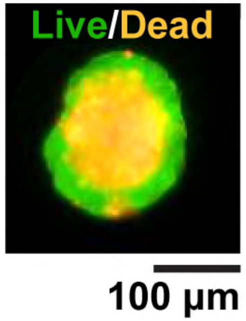


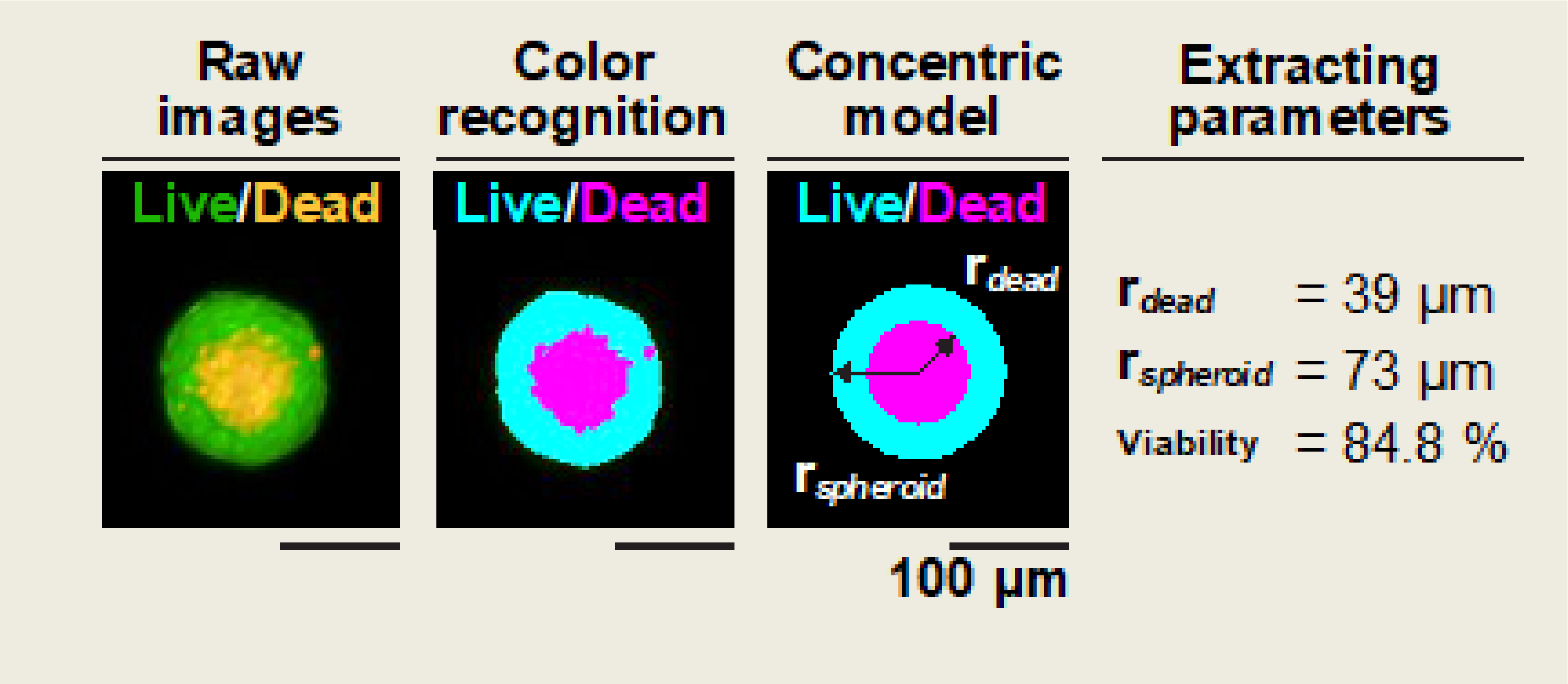

1% $O_2$ for 48h



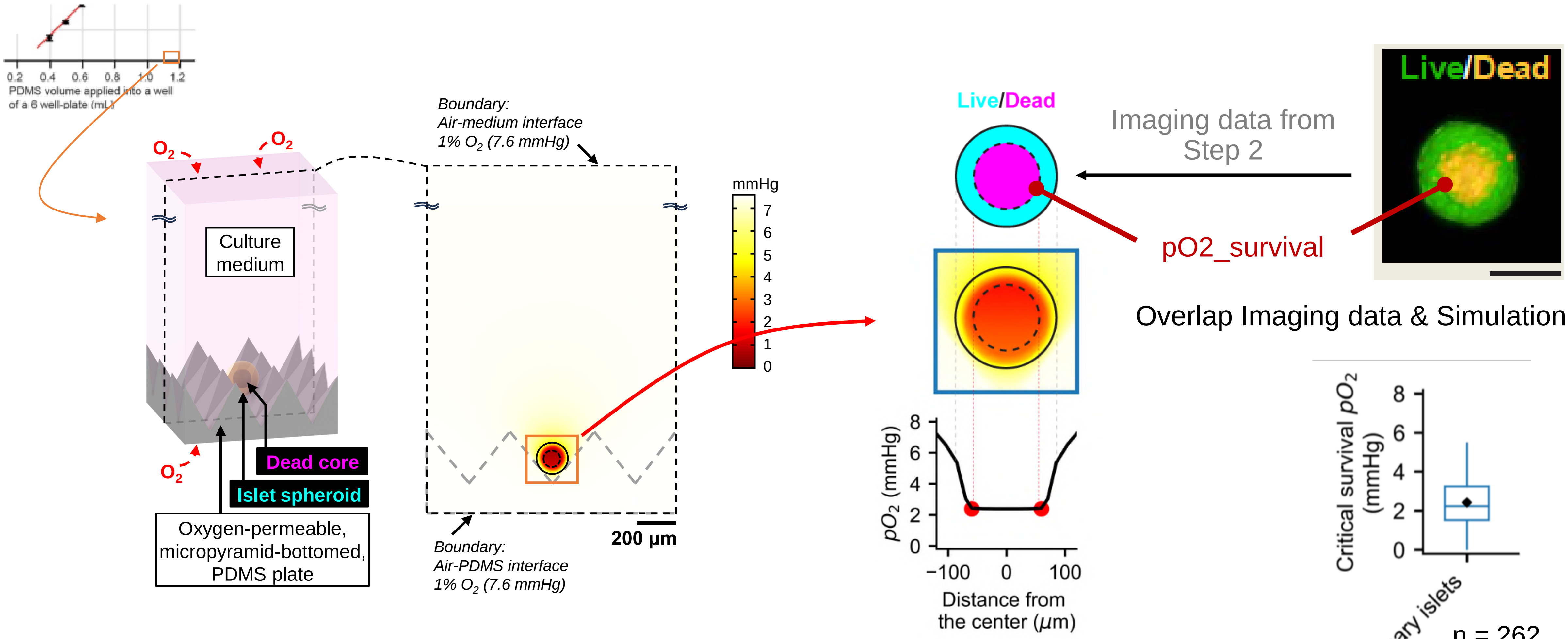

Pre-culture (no central necrosis)

Post-culture (with hypoxia-induced central necrosis)

# Step 2: Live / Dead Imaging



# Step 3: Oxygen Computational Modeling




Overlap Imaging data & Simulation

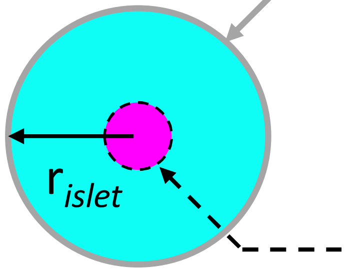



pO2_survival = 2.4 mmHg

# Why is it important?

# How can we use the pO2_survival?

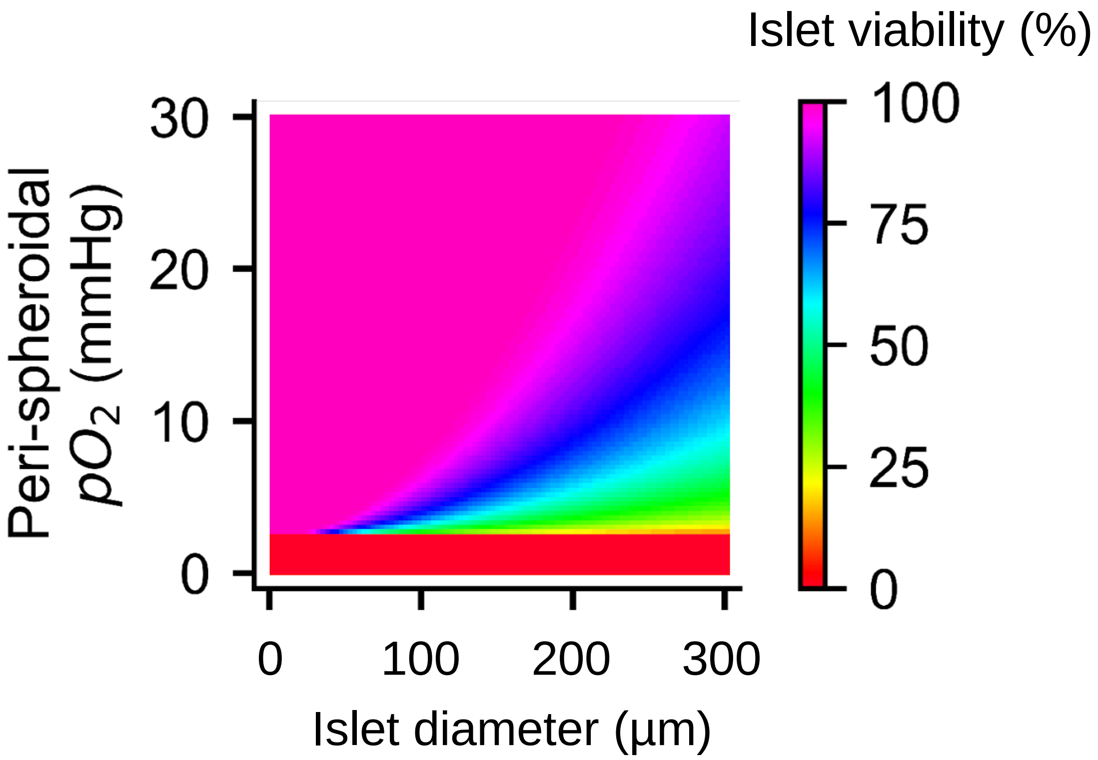
# Prediction of islet viability under various $O_2$ conditions



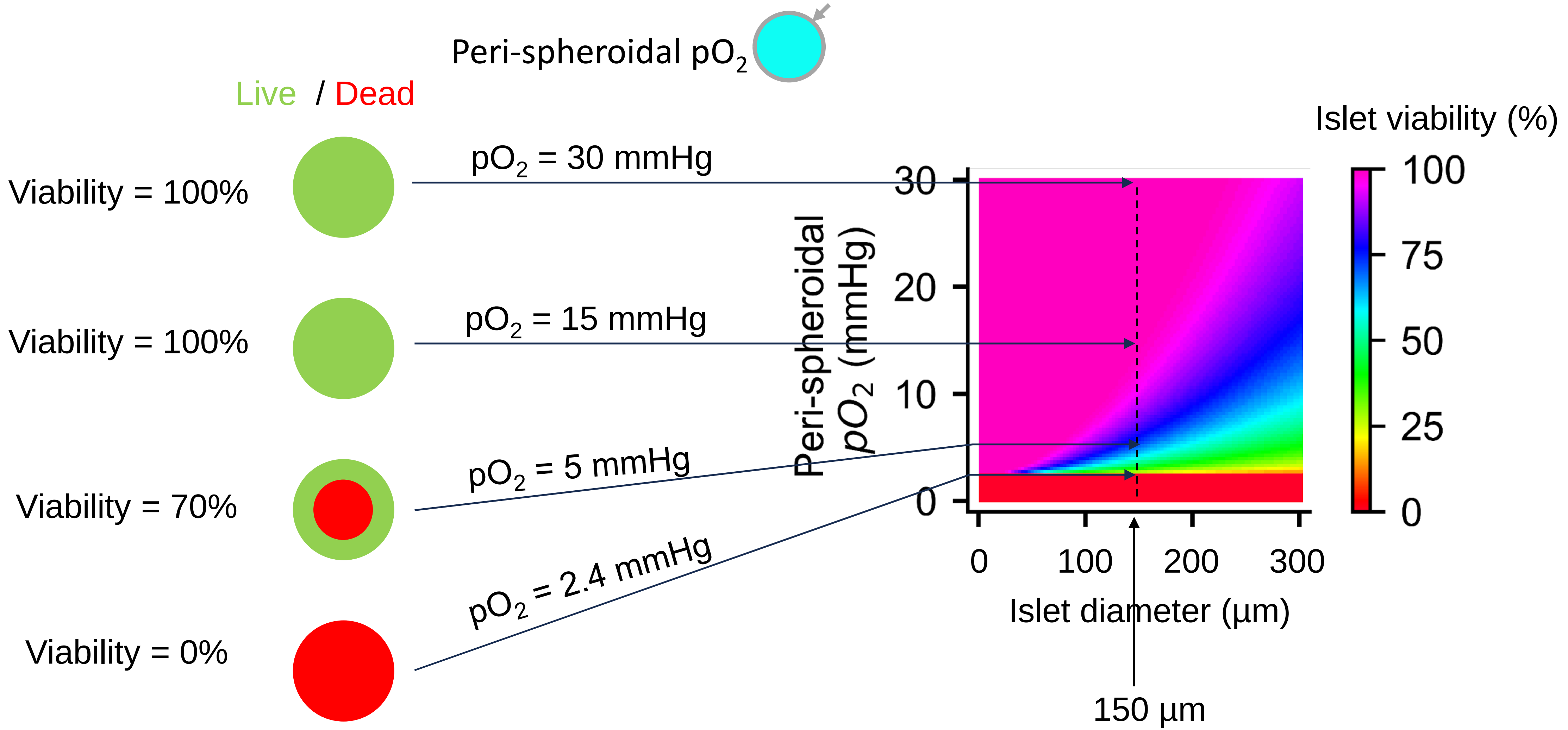

Peri-spheroidal $pO_2$
(Variable)

Critical survival $pO_2$
Fixed value (2.4 mmHg)

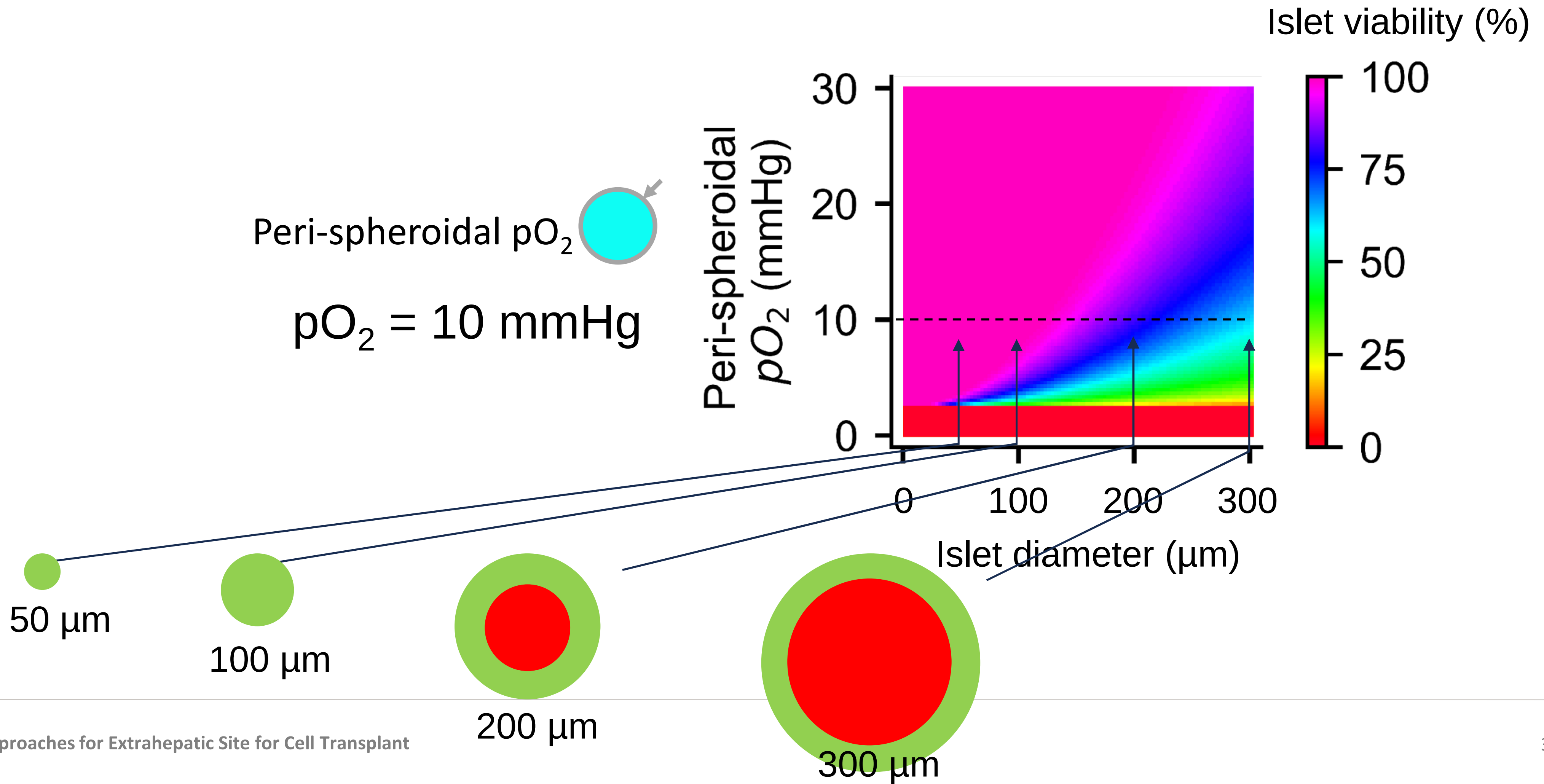
*Predict viability*



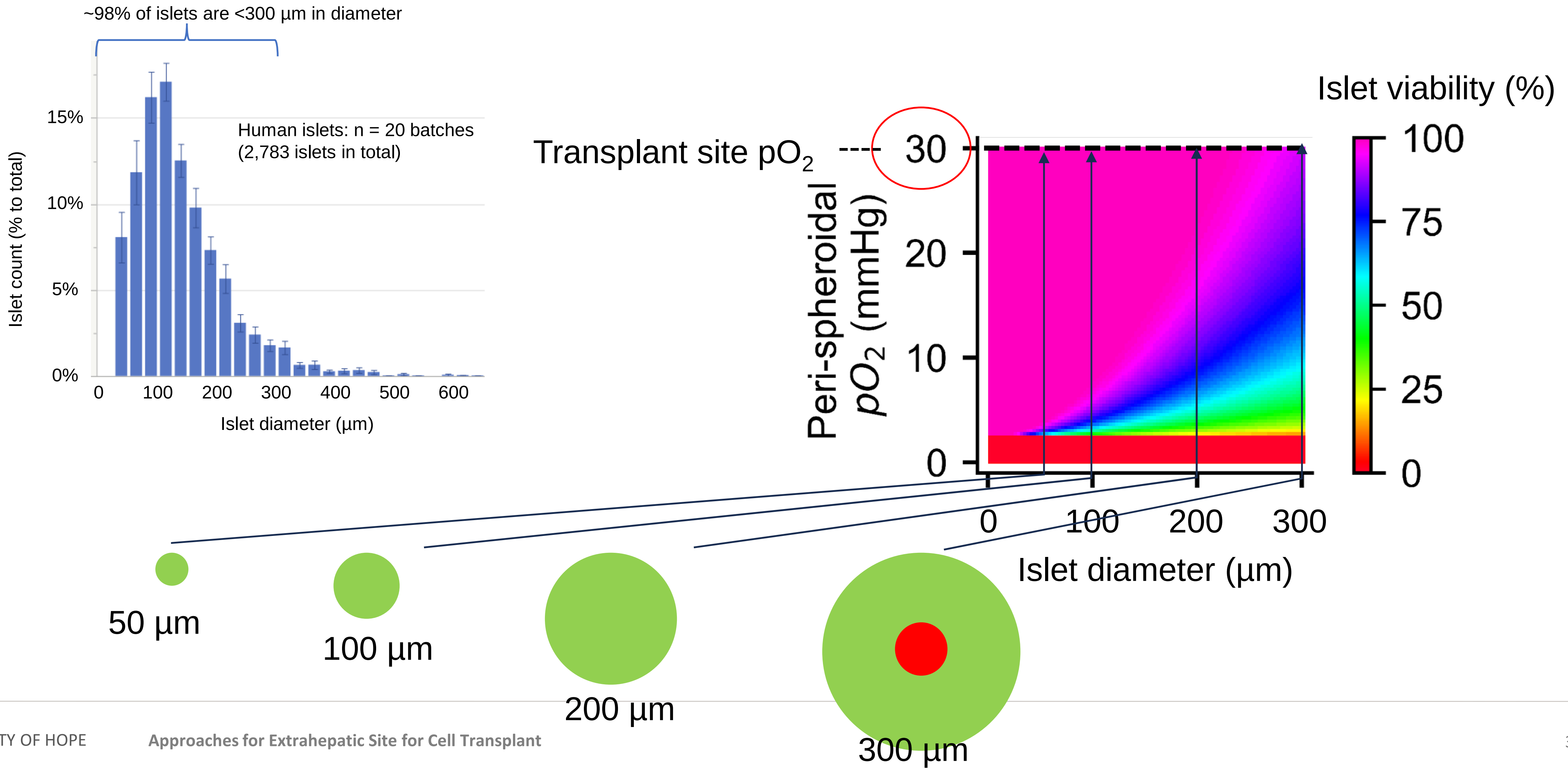
# Prediction of islet viability under various $O_2$ conditions



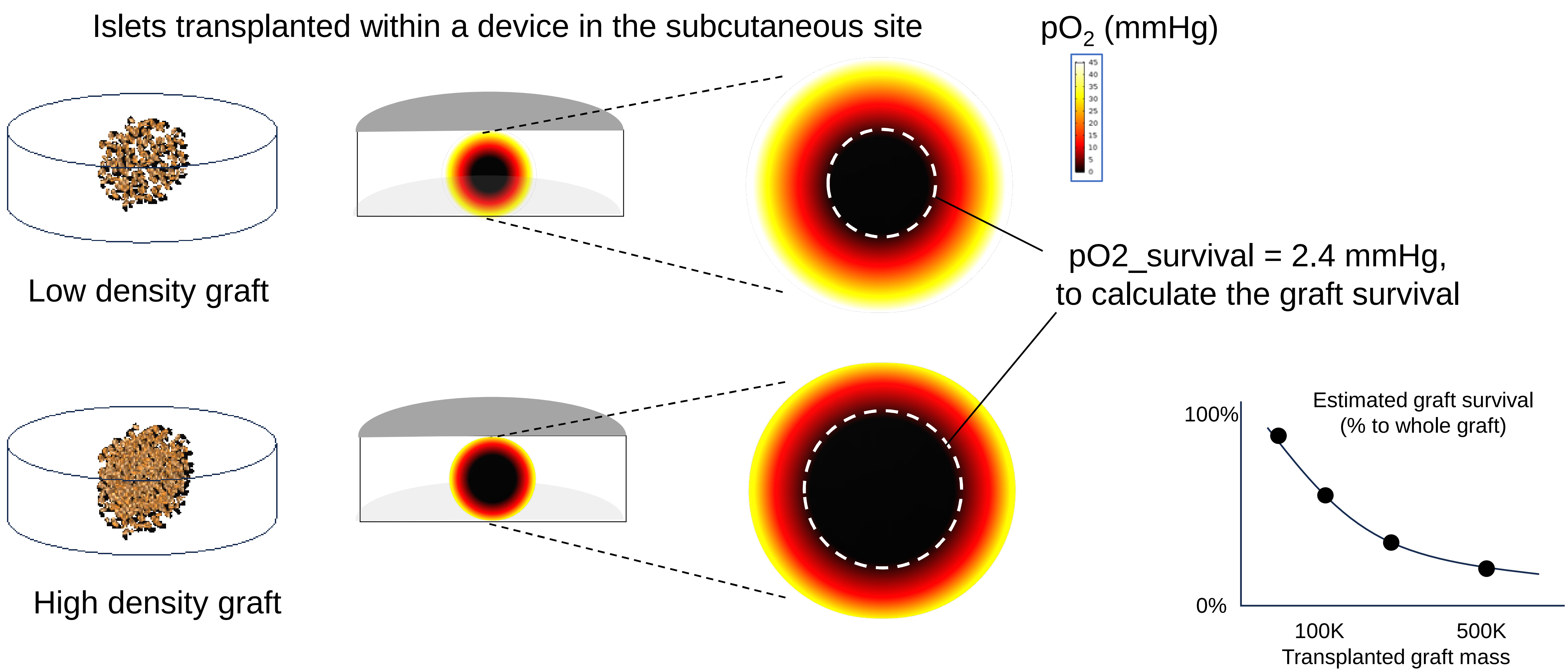
# Prediction of islet viability under various $O_2$ conditions



# Islet viability prediction in transplantation sites



# Graft survival rate / Organoid survival using $O_2$ simulations



# Short summary (3)

Understanding pO2 survival (the $O_2$ threshold for islet death) is useful for predicting islet graft survival under various conditions.

# Overall Summary

1. High graft density in extrahepatic sites is a critical obstacle, inducing hypoxia WITHIN the graft.
2. Enhanced revascularization does not fully counteract the graft hypoxia, especially in the acute post-transplant phase.
3. Understanding the hypoxia resistance ($pO2\_survival$) of islet cells is crucial for predicting islet survival and developing oxygenation strategies.

# Acknowledgements

## Investigators / collaborators

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UCSF
University of California
San Francisco

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- Hiroyuki Kato
- Islet isolation team
- Islet quality control team

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- Dr. Colin Cook
- Dr. Kuang-Ming Shang (Allen)

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- Greg Szot
- Hiroyuki Kato

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JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

NIH National Institute of Diabetes and Digestive and Kidney Diseases