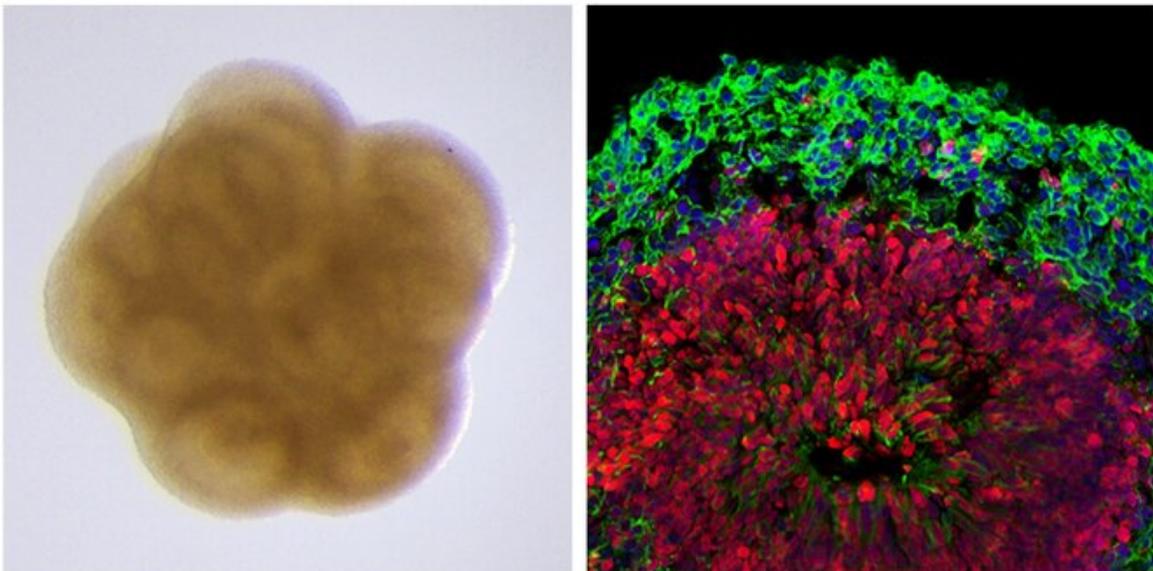


# Researchers develop miniature brain models to study Alzheimer's causes and test drug development

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The stereo image (left) and immunostaining image (right) of brain organoids (BO) at Day 50. Green: TUJ1, red: SOX2. Credit: City of Hope

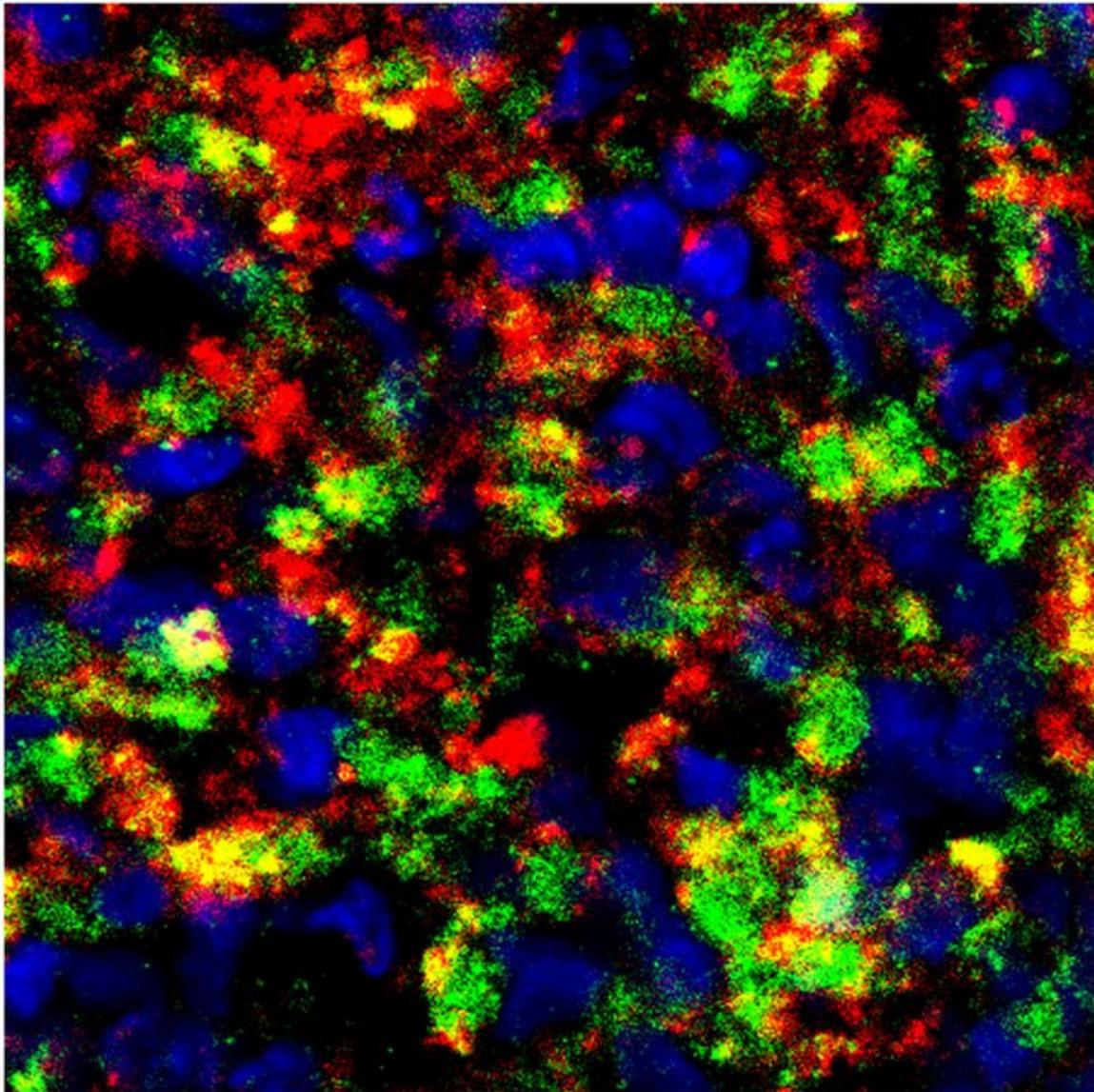
Researchers led by City of Hope, a world-renowned research and treatment center for cancer, diabetes and other life-threatening diseases, have developed a powerful miniature brain platform to study the mechanistic causes of Alzheimer's disease and to test dementia drugs in

development, reports a new study published today in *Advanced Science*.

"Drug development for Alzheimer's disease has run into challenges due to incomplete understanding of the disease's pathological mechanisms," said Yanhong Shi, Ph.D., the Herbert Horvitz Professor in Neuroscience and director of the Division of Stem Cell Biology Research within the Department of Developmental and Stem Cell Biology at Beckman Research Institute of City of Hope.

"Preclinical research in this arena predominantly uses animal models, but there is a huge difference between humans and animals such as rodents, especially when it comes to brain architecture. We, at City of Hope, have created a miniature brain model that uses human stem cell technology to study Alzheimer's disease, and hopefully, to help find treatments for this devastating illness."

City of Hope researchers were able to model sporadic Alzheimer's disease, the most common form of the condition, using "[brain organoids](#)" derived using human induced pluripotent stem cell (hiPSC) technology. Because Alzheimer's is a disease of age, the scientists exposed the models to serum to mimic age-associated blood-brain barrier breakdown. Then they ran the organoids through different experiments to test known Alzheimer's biomarkers, including elevated levels of amyloid plaques and tau tangles as well as synaptic breaks linked to cognitive decline, among other pathological phenotypes brought on by the condition.



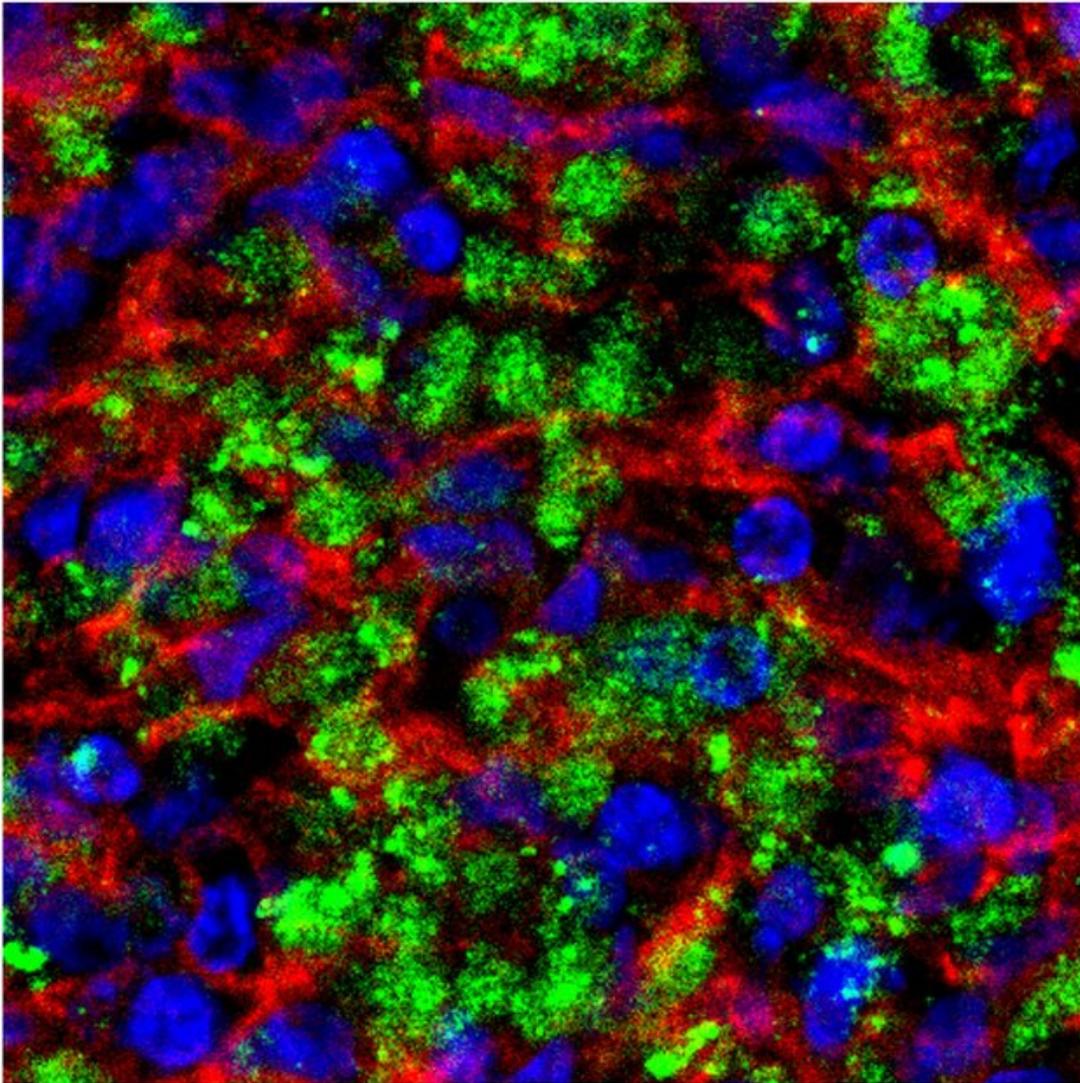
Serum exposure induces amyloid  $\beta$  ( $A\beta$ ) (green) and beta-secretase 1 (BACE) (red) in BO. Credit: City of Hope

More than 6 million people are living with Alzheimer's disease, which kills more people than breast and [prostate cancer](#) combined, reports the Alzheimer's Association. The heartbreaking degenerative disease affects

not only the individual diagnosed with the condition, but also their primary caregiver, family and friends. No cure currently exists, and available treatments merely address symptoms rather than the root cause.

"Other studies using brain organoids to examine Alzheimer's disease used miniature brain models that are phenotypically young, but to truly understand what happens when Alzheimer's strikes, we need to use age-associated models, and that's what we did in this research project when we exposed the miniature brains to serum," said Xianwei Chen, Ph.D., first author of the study and postdoctoral fellow at City of Hope. "We believe the age-associated brain organoids we generated will provide a powerful platform for us to find effective treatments for disorders affecting the human body's most complex organ."

Preclinical research using brain organoids found that exposure to serum from blood could induce multiple Alzheimer's symptoms, suggesting combination therapies targeting multiple pathological alterations likely would be more effective than single-target therapies currently in development. The researchers studied late-onset or sporadic Alzheimer's disease, which accounts for most cases (95% sporadic vs. 5% inherited). They found that attempting a single therapy—for example inhibiting only amyloid or tau proteins—did not reduce the levels of tau or amyloid, respectively, suggesting that these two key biomarkers likely cause disease progression independently. Moreover, exposure to serum from blood—which mimics a leaky blood-brain barrier—could cause breaks in synaptic connections that help brains remember things and function properly.



Serum exposure induces amyloid  $\beta$  ( $A\beta$ ) (green) in BO. Red: MAP2. Credit: City of Hope

Matt Huentelman, Ph.D., professor of neurogenomics at the Translational Genomics Research Institute (TGen), said the brain model developed by City of Hope provides a new avenue for examining

emerging treatments for this memory-robbing disease. Huentelman is a leading expert in the genetic study of Alzheimer's disease and was not part of this study.

"Using the model developed in this City of Hope-led study could help accelerate the evaluation of potential treatment options, giving a new sense of hope to Alzheimer's patients and their families," he said.

The study, "Modeling sporadic Alzheimer's [disease](#) in human [brain](#) organoids under serum exposure," was done in collaboration with University of California Irvine, Banner Sun Health Research Institute, Banner Alzheimer's Institute and Washington University in St. Louis.

**More information:** Modeling sporadic Alzheimer's disease in human brain organoids under serum exposure, *Advanced Science* (2021).

Provided by City of Hope National Medical Center

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