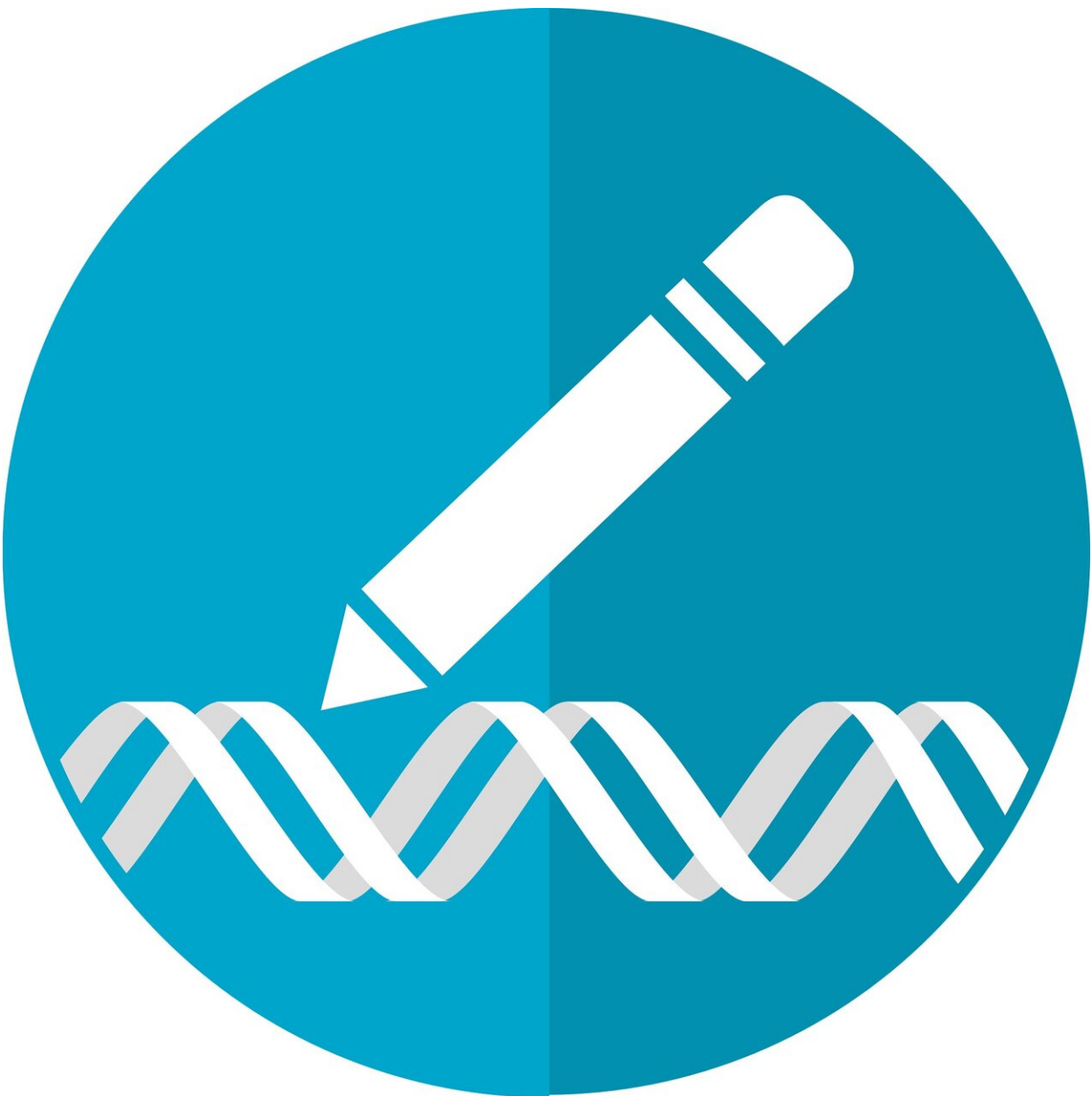


Stem cells, CRISPR and gene sequencing technology are basis of new brain cancer model

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Using genetically engineered human pluripotent stem cells, University of California San Diego School of Medicine researchers created a new type of cancer model to study *in vivo* how glioblastoma, the most common and aggressive form of brain cancer, develops and changes over time.

"We have developed stem cell models that are CRISPR-engineered to have tumor-associated driver mutations in glioblastoma, which harbor essentially all features of patient-derived tumors, including extrachromosomal DNA amplification," said co-senior author Frank B. Funari, Ph.D., professor in the Department of Pathology at UC San Diego School of Medicine and head of the Laboratory of Tumor Biology in the San Diego branch of the Ludwig Institute for Cancer Research.

"These models, or avatars as we call them, enable us to study human tumor development over long periods *in vivo*, which has not been feasible with patient-derived [tissue samples](#) which already harbor other genetic changes."

Reporting in the January 28, 2020 issue of *Nature Communications*, researchers used CRISPR editing to make precise mutations in an otherwise "normal" genome to create the genetic conditions that enable tumor development. The resulting avatars are unique in that they behave like a grade 4 glioma—a fast-growing type of tumor that starts in the glial cells of the brain—in their level of pathology, transcriptome signatures, engineered genetic alterations and evolution of genetic mutations, such as the emergence of extrachromosomal DNA and chromosomal rearrangements.

"The addition of single-cell RNA sequencing and computational tools enabled efficient analysis of big data to truly evaluate the surprising intra-tumor heterogeneity present in our avatars which replicates what is seen in patients samples," said co-senior author Gene W. Yeo, Ph.D., professor in the Department of Cellular and Molecular Medicine and the Institute for Genomic Medicine at UC San Diego and faculty member in the Sanford Consortium for Regenerative Medicine.

Existing mouse models work for testing drugs for specific mutations, but do not account for the diverse ways that tumors can develop. Human tissue samples do not allow for standardization in testing. This new avatar modeling system, said the authors, provides a platform for standardized studies on tumor biology and evolution.

"We can now test which mutations predicted by cancer genome projects are truly tumor-driving, and how they become invasive," said Yeo. "More importantly, these cancer avatars provide systematic, well-controlled opportunities for drug discovery."

Glioblastoma is highly malignant. Standard treatment is aggressive: surgery, followed by chemotherapy and radiation. Yet most tumors recur within six months. The two-year survival rate is 30 percent.

This avatar mimics the intra-tumor heterogeneity observed in people, making it a good option for detailed examination of [tumor](#) evolution and searching for therapeutic vulnerabilities based on driver genetics, said Furnari.

"Next steps include screening drugs, testing other mutations in adult and pediatric brain tumors as well as to evaluate if these approaches can model tumors in other tissues, such as the pancreas and lung," said Furnari.

More information: Koga, T et al. Longitudinal assessment of tumor development using cancer avatars derived from genetically engineered pluripotent stem cells. *Nat Commun* 11, 550 (2020).

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