

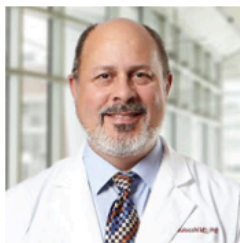
NEW DOUBLE TRANSGENIC MODEL OF MCL ACCELERATES SEARCH FOR CURATIVE TREATMENT

A multi-center research team co-led by scientists at the OSUCCC – James has developed a mouse model of mantle cell lymphoma (MCL) that allows for testing of new therapies in the context of a functional immune system.



Supported in part by funding from Pelotonia – the community and annual cycling event series that raises money for cancer research at Ohio State – the study was published in the journal [Clinical Cancer Research](#). **Lapo Alinari, MD, PhD**, and **Robert Baiocchi, MD, PhD**, both of the Leukemia and Hematologic Malignancies (LHM) Program at the OSUCCC – James, were co-corresponding authors along with Samir Parekh, MD, PhD, of the Icahn School of Medicine at Mount Sinai, New York.

MCL is rare subtype of B-cell non-Hodgkin lymphoma that accounts for just 5-7% of all lymphomas. While disease progression rates have improved thanks to new drug therapies like ibrutinib and venetoclax, there is no curative treatment for this subtype, which has seen a rising incidence over recent decades.



The authors state that, with their new mouse model, researchers for the first time can gain granular insight into the molecular pathogenesis/signaling pathways and immune system responses in MCL. They can also test new and repurposed drug candidates on mice with the same gene anomaly that humans with MCL have undergone.

Importantly, their model will also give researchers insight into ibrutinib resistance in MCL, an event that typically marks the end of remission.

In MCL, the *CCND1* gene produces the protein cyclin D1. It was long thought to be the primary oncogene (a gene that when activated can cause cancer) in MCL development, as its overexpression through a genetic translocation causes cell cycle dysregulation and uncontrolled proliferation. However, efforts to replicate this mechanism in mice have failed. They don't develop MCL; instead, they are characterized by normal B-cell development, suggesting that additional genetic insults are needed for lymphomagenesis.

Knowing that SRY-Box Transcription Factor 11 (SOX11) is also an oncogene in MCL, the researchers engineered a double transgenic mouse model by combining *CCND1* with *SOX11*, producing $\text{E}\mu\text{-SOX11CCND1}$. When engrafted with $\text{E}\mu\text{-SOX11CCND1}$ malignant cells, immunocompetent wild-type C57Bl/6 mice undergo a clonal expansion of B cells that molecularly resembles human MCL.

Drs. Baiocchi and Alinari are optimistic that this model will fast-track immunotherapy drug testing for patients with MCL, perhaps leading to a curative treatment. Dr. Alinari is using this model to test a chimeric antigen receptor (CAR) T-cell product targeting CD74, which is abundantly expressed in MCL. Their next steps would be to develop it for clinical use in patients.

In addition to Pelotonia funding, the team's research is made possible through a five-year NIH programmatic grant and a Specialized Center of Research (SCOR) grant through the Leukemia & Lymphoma Society. It also was supported by The Ohio State University Presidential Fellowship.

Co-first authors for this study were **Hedieh Jafari** and **Fiona Brown-Burke, PhD**, both currently or formerly at Ohio State. Other co-authors now or formerly at Ohio State include **JoBeth Helmig-Mason**; **Ian Hout**; **Sydney Leon**; **Mackenzie Long**; **Wing Keung Chan, PhD**; **Walter Hanel, MD, PhD**; **Kara Corps, DVM, PhD**; **Alessandro La Ferlita, PhD**; **Satishkumar Singh, PhD**; **Rosario Distefano, PhD**; **Rosa Lapalombella, PhD**; and **Lalit Sehgal, PhD**.