Leptomeningeal metastasis represents a rare but fatal outcome of disseminated cancer. Although much has been learned through observational studies, retrospective analyses and case reports, understanding of the molecular mechanisms underlying this complication has been hampered by lack of a mouse model. Therefore, our objective was to create an interrogable mouse model that separates the molecular characteristics required for cancer cell access to the leptomeningeal space from those needed for cancer cell survival within the CSF. To accomplish this, human and mouse cancer cell lines were subjected to multiple rounds of in vivo selection. First, the cells were selected for survival within the leptomeninges: Parental cell lines were directly injected into the CSF via the cisterna magna and tumor cell growth was monitored with bioluminescent imaging. Cancer cells were collected from the basilar meninges and expanded in culture. After three rounds of this selection, the cells were designated “LeptoR3”. Second, the cells were selected for characteristics allowing for cancer cells to access the leptomeningeal space. The triple-selected “LeptoR3” cells were disseminated hematogenously via intracardiac injection. Mice were monitored for development of leptomeningeal metastases with bioluminescent imaging. After development of leptomeningeal metastasis, these cells were collected, designated “LeptoIC” and expanded in culture. Finally, the Lepto IC, Lepto R3 and parental cell lines were subjected to gene expression profiling by RNASeq. The transcriptomal profiles of these cell lines demonstrate that leptomeningeal metastases employ a distinct array of genes to gain access to the leptomeningeal space and to survive once there. These mouse models represent a powerful tool for the molecular dissection of leptomeningeal metastasis.