**Lay summary**

The first year of this project showed greater cell dispersal in breast tumor cells that express high levels of the Tau gene (Fig.1). Elevated Tau expression is usually associated with Alzheimer’s disease, but the PI’s group published earlier that Tau is also highly expressed in 53% of Stage 4 breast tumors. Tau protein stabilizes filaments inside tumor cells called microtubules. Since breast epithelial cells use these microtubules to sense their environment and move, overstabilization of microtubules can cause increased tumor cell invasion (Fig.2). In preclinical studies this year, our group demonstrated that reducing microtubule stabilization with a FDAapproved therapy, Vinorelbine, could strongly reduce metastasis of circulating tumor cells. A single 24-hour treatment with Vinorelbine improved the survival of mice challenged with lung metastatic breast tumors from 8 weeks to 30 weeks (Fig.3). However, the broad microtubule disruption with Vinorelbine can cause significant side effects, so in the next project year, we will test methods to reduce microtubule stabilization by inhibiting Tau as a more precise target than how existing cancer therapies disrupt all microtubules indiscriminately. Since there are existing Alzheimer’s drugs available for targeting Tau, we are looking forward to testing if these Tau drugs can be repurposed to reduce the tumor cell dispersal and invasion that can allow existing metastatic tumors to spread throughout distant organs in more dangerous ways. If successful, these studies could show that targeting Tau can help reduce the aggressive spread of metastatic breast tumors, but potentially without the severe side effects of broadly disrupting all microtubules.