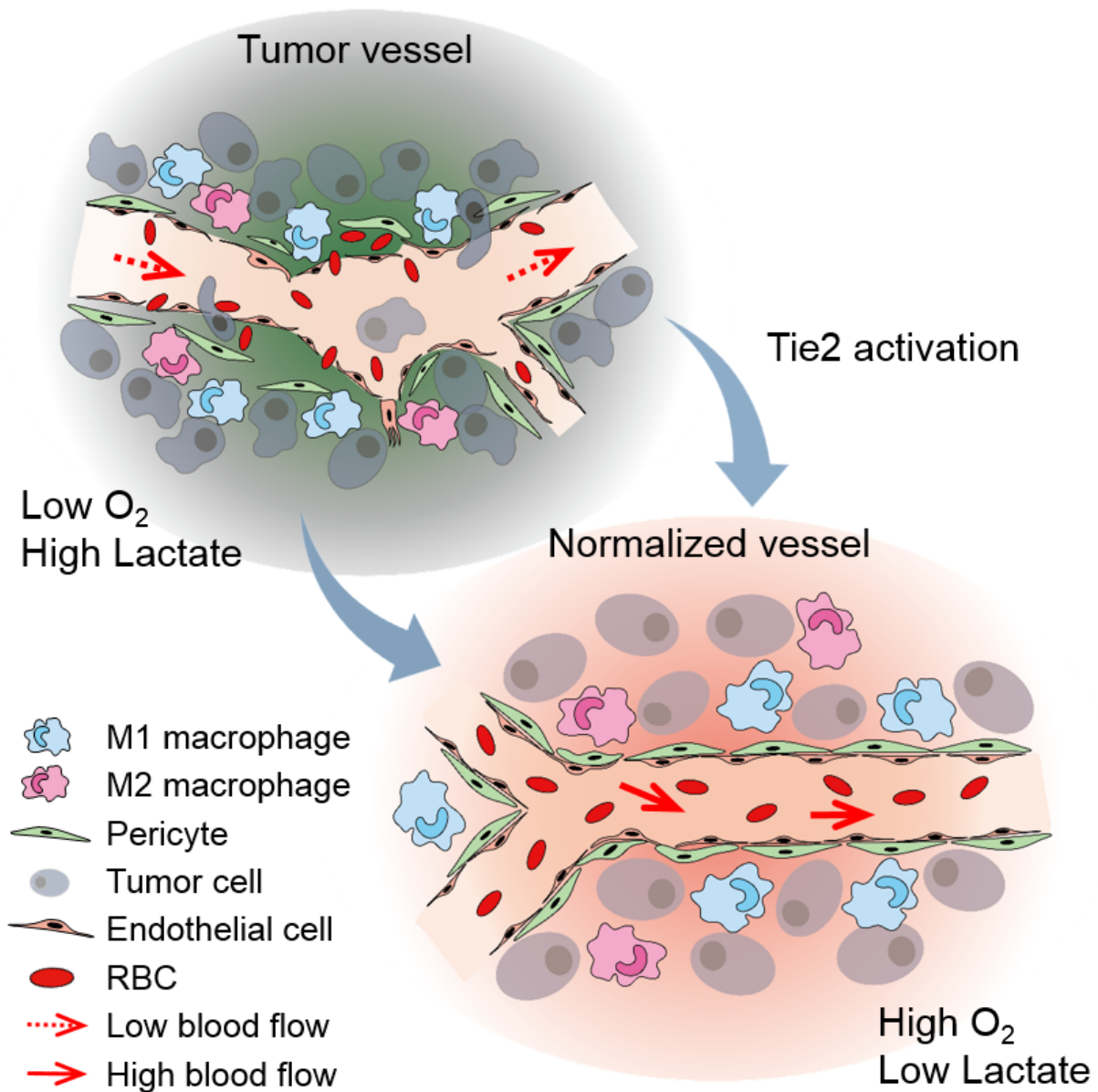


The antibody that normalizes tumor vessels

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Schematic drawing of a blood vessel around tumors before and after treatment

with ABTAA. The picture above shows a typical tumor vasculature characterized by damaged walls, red blood cells leakage and detached pericytes. Activating Tie2 on endothelial cells with the antibody ABTAA restores the normal vessel architecture: endothelial and pericytes on the vessel walls are stabilized, the delivery of blood is improved, and the anticancer drugs are more likely to reach the tumor core. Credit: Institute for Basic Science (IBS)

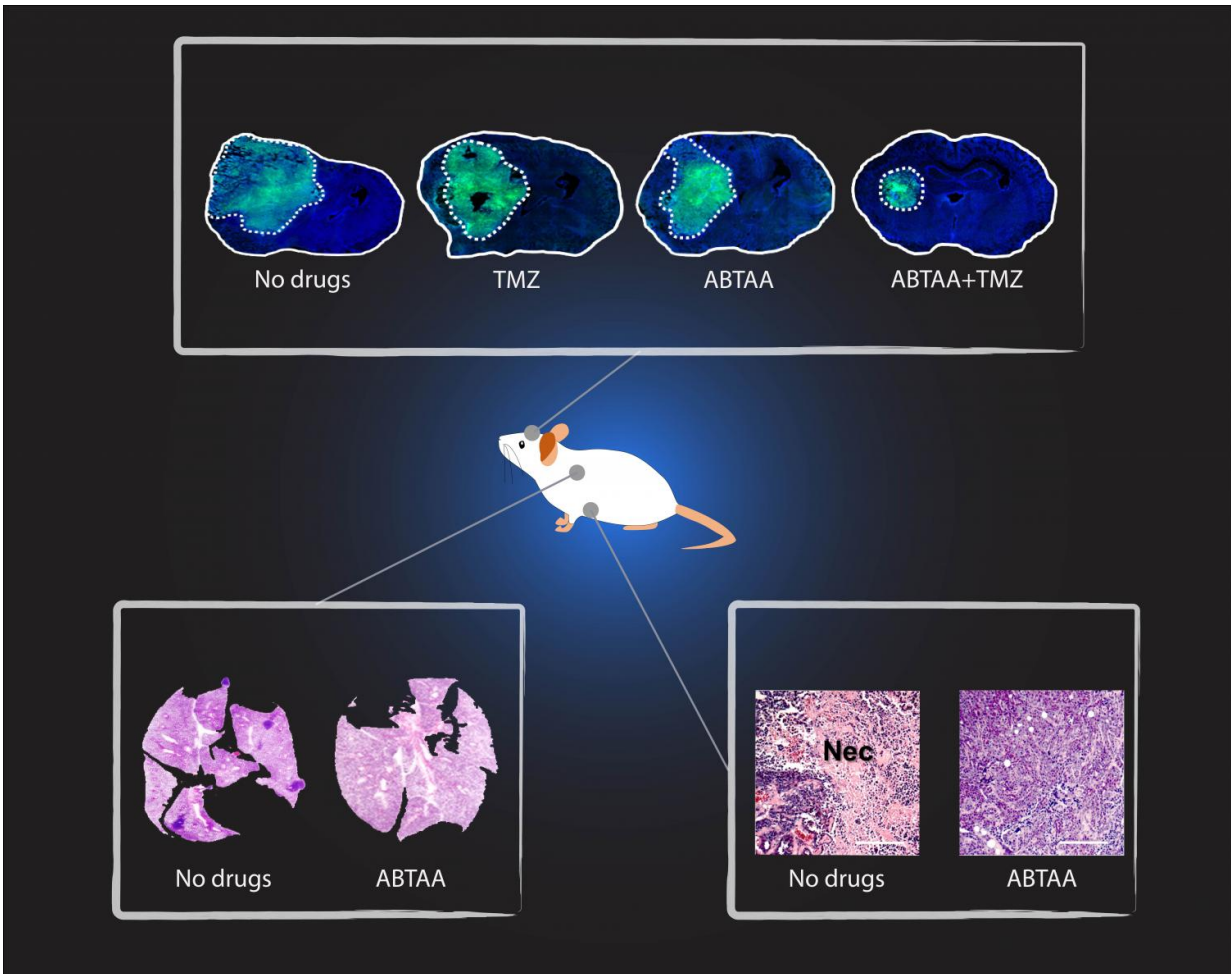
An important parcel must be delivered to the correct place. It is so important that it can be a question of life or death. However, uneven streets and missing railings risk to bring it off the road and leave it undelivered. This is not the trailer of a drama, but what happens to anti-cancer drugs traveling towards the tumor area, but unable to reach it because of dysfunctional blood vessels. The Center for Vascular Research, within the Institute for Basic Science (IBS) discovered that their antisepsis antibody ABTAA (Ang2-Binding and Tie2-Activating Antibody) also reduces tumor volume and improves the delivery of anti-cancer drugs. Published in *Cancer Cell*, this study demonstrates that ABTAA restores the structural and functional integrity of tumor blood vessels in three different tumor models: breast, lungs and brain.

Blood vessels inside and around an established tumor can be described as a chaotic and dysfunctional labyrinth. While the inner walls of healthy blood vessels are surrounded and supported by endothelial cells and other cells called pericytes; in the established tumor, the endothelial junctions are broken apart and pericytes are also detached. Blood flow into and from the tumor is severely retarded and tumor vessels lacking an intact vessel wall become leaky. This microenvironment causes limited drug delivery to the tumor and leads to inadequate oxygen supply (hypoxia) and even metastasis. IBS scientists found that the antibody ABTAA normalizes the tumor vessels and hence, change the whole [tumor microenvironment](#). "We call it normalization of tumor vessels,

because it resembles closely the wall architecture of healthy, normal vessels," explains PARK Jin-Sung, first author of the study. And continues: "Tumor can adapt to hypoxia and get more aggressive, so we tried to prevent this transition by normalizing tumor vessels. ABTAA changes the whole tumor environment, oxygenation status and level of lactate, so that the immune cells and drugs can reach the core regions of the tumor more easily. In this way, we create a favorable ground for tumor treatment."

In an attempt to generate antibodies targeting the protein Ang2, which is specifically expressed by endothelial cells in stressful conditions like in tumor, the team unexpectedly discovered that ABTAA has a peculiar way of working and a dual function. ABTAA indeed not only blocks Ang2, but it is also able to activate Tie2 at the same time. Tie2 is a receptor present on the cell membrane of endothelial cells. ABTAA causes Ang2 to cluster together and to strongly activate Tie2 receptors. "If we activate Tie2, we can efficiently normalize [tumor vessels](#), enhance drug delivery and change the whole microenvironment," explains KOH Gou Young, Director of the Center for Vascular Research.

Several pharmaceutical companies are developing Ang2-blocking antibodies to cure cancer. However, even if these antibodies significantly inhibit [tumor progression](#), they do not stop [tumor hypoxia](#). Moreover, most of the [anti-cancer drugs](#) target the tumor at its early stage, when tumors are still hard to diagnose. ABTAA, instead, works with tumors that are already rooted: "When the tumor is established, hypoxia is the main driver of tumor progression. So, if we eliminate hypoxia, we make the tumor more mild, by reducing its progression and metastasis," comments Koh.



The antibody ABTAA alone and in combination with other anti-cancer drugs has a beneficial effect in reducing tumor volume. ABTAA was tested in mice with brain tumor (glioma), lung or breast cancer. The image shows the improvements: reduction in glioma tumor size, reduction in metastatic colonies in lung tumor and decrease in necrotic regions in breast tumor. Credit: IBS

IBS researchers tested ABTAA in mice with three different types of tumors that show high levels of Ang2: glioma (a type a brain tumor), lung carcinoma and breast cancer. They also compared the effect of ABTAA with ABA, another antibody that blocks Ang2 but misses the Tie2 activating properties. In all three cases, ABTAA was superior to

ABA in inducing tumor vessel normalization, which led to a better delivery of the anti-cancer drugs into the tumor core region.

Glioma is one of the so-called intractable disease, because of its poor prognosis and treatment. IBS scientists found that the glioma volume was reduced 39% by ABTAA and 17% by ABA. ABTAA profoundly reduced vascular leakage and edema formation in glioma through promoting vascular tightening. Moreover, when ABTAA was administered together with the chemotherapeutic drug temozolomide (TMZ), the tumor volume reduces further (76% by ABTAA+TMZ, 51% by ABA+TMZ, and 36% by TMZ).

In the Lewis Lung Carcinoma (LLC) tumor model, the research team administered ABTAA together with a chemotherapeutic drug called cisplatin (Cpt) and observed a greater suppression of [tumor growth](#) (52%) compared with the controls and increased overall survival. Moreover, ABTAA+Cpt led to a marked increase in necrotic area within tumors.

Finally, in a spontaneous breast cancer model, ABTAA delayed tumor growth and enhanced the anti-[tumor](#) effect of Cpt.

In the future, the team would like to further understand the underlying relationship between faulty blood vessels and diseases. "We would like to apply this antibody to an organ that is rich in [blood vessels](#), that is the eye, and see if this antibody can be useful to treat eye diseases such as age-related macular degeneration and diabetic retinopathy," concludes Koh.

More information: *Cancer Cell*, [DOI: 10.1016/j.ccell.2016.10.018](https://doi.org/10.1016/j.ccell.2016.10.018)

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