Contrast Agent Trials in Swine

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Mammography continues to be the method of choice for the early detection of breast cancer. However, because this technique is not as selective or specific as one would wish, and does not deliver reliable results for every level of tissue density, alternatives are being sought. Near-infrared fluorescence mammography, which works with rays of near-infrared (NIR) light instead of X-rays, is a highly promising technique—although effective contrast agents have thus far been lacking.

A team led by John V. Frangioni at the Beth Israel Deaconess Medical Center of the Harvard Medical School in Boston, Massachusetts, has developed a contrast agent that makes visible the microcalcifications related to malignant breast tumors. The researchers report in the journal *Angewandte Chemie* that in validation trials in swine their new contrast agent distinguishes specific calcium salts in soft tissues, as well as depicting bones.

As breast cancer develops, calcium salts are deposited in breast tissue. These microscopic calcium deposits consist mostly of hydroxyapatite, a salt containing calcium and phosphate that is also present in bones.

As the basis of their NIR contrast agent, the researchers chose to use the osteoporosis drug pamidronate, a biphosphonate. Biphosphonates, which are also used for the treatment of bone metastases in breast cancer patients, preferentially bind to bone. Frangioni and his team attached a dye that both absorbs light and fluoresces in the NIR region of the spectrum to a pamidronate derivative. Light in this region of the

spectrum penetrates especially well into living tissue without damaging it, and is also easy to detect.

Thanks to a simplified, reliable synthetic route to a new pamidronate derivative developed by Kumar R. Bhushan, the American team has now been able to synthesize large quantities of a contrast agent called Pam800—enough to run a trial with large animals. Pigs are particularly well suited to such trials because their organs are of approximately the same size as human organs.

As confirmed by surgical incisions, intravenously administered Pam800 reveals the bones of pigs with very high sensitivity. When hydroxyapatite is injected into the soft tissues, the contrast agent marks only the tiny hydroxyapatite crystals with high selectivity and sensitivity. This could allow it to selectively reveal malignant abnormal tissue. The swine trials demonstrated that the use of real-time NIR fluorescence images even make possible image-guided surgery of the soft tissues and bones.

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