TNP-470 is an antiangiogenic synthetic analog of fumagillin whose development was suspended in the 1990s, despite its efficacy for a wide range of cancers, mainly because of neurologic side effects and also because the relative insolubility of TNP-470 precluded its oral administration. To prevent TNP-470 from crossing the blood–brain barrier, it was reformulated as the conjugate caplostatin (see Section 4.2), but the drug still could not be effectively administered and required continuous intravenous infusions. These problems were solved with the development of the orally active, nontoxic micellar formulation lodamin, which can be chronically administered for cancer therapy or metastasis prevention.[109] It is prepared by conjugating TNP-470 to a copolymer formed by monomethoxy polyethylene glycol/polylactic acid. Because this copolymeric form is amphiphilic, in an aqueous medium it self-assembles into micelles where TNP-470 is protected within the core. Orally administered lodamin enters rapidly into circulation and maintains higher levels in serum relative to free TNP-470.

7.3 GOLD NANOPARTICLES

Due to their unique optical and electronic properties, gold nanoparticles have found biomedical applications in specific aspects of diagnosis and treatment of cancer,[110] acting by several mechanisms.

Gold nanoparticles accumulate at tumor sites due to the EPR effect, and the high density of atoms on their surfaces greatly enhances their receptor binding affinity. One of these nanomedicines that has entered clinical trials is CYT-6091, a PEGylated colloidal gold–rhTNF used as a platform for the delivery of tumor necrosis factor R (TNFR) to solid tumors.[111]

Gold nanoparticles are also being developed for the treatment of hormone-dependent malignancies such as breast and prostate cancers in which estrogen and androgen receptors can serve as targets for tissue-selective drug delivery. For instance, tamoxifen is selectively delivered from PEGylated gold nanoparticles to breast cancer cells at concentrations more than 10,000-fold higher than the drug alone (Figure 13.50).[112]

Active targeting significantly improved the cellular accumulation in the target cells of gold nanoparticles.[113] Those conjugated with cetuximab were quickly internalized by pancreatic adenocarcinoma and colorectal adenocarcinoma cancer cells overexpressing EGFR.[114] Cetuximab was conjugated via a covalent hydrazide–thiol heterobifunctional linker by oxidizing with $NaIO_4$ the

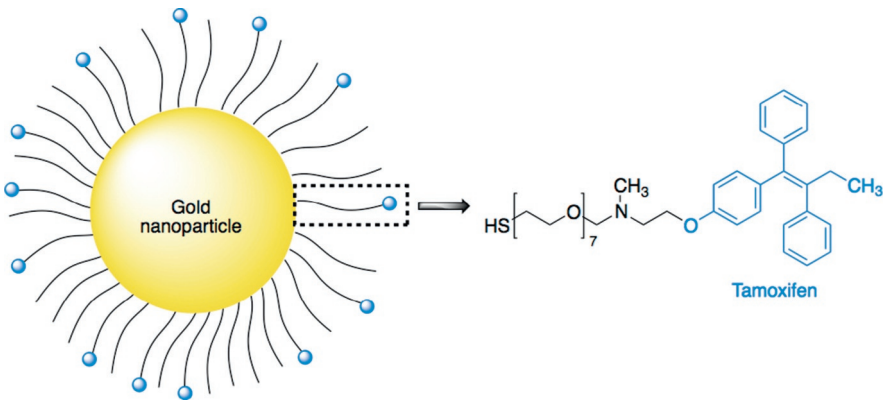

FIGURE 13.50

A gold nanoparticle for the delivery of tamoxifen.