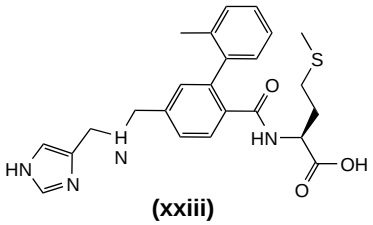
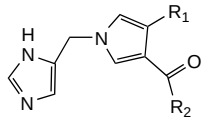


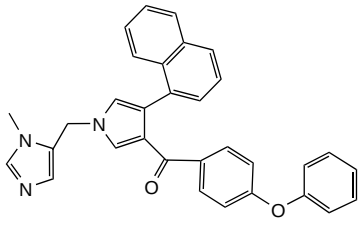
(xxiii)

permeability and poor oral bioavailability [10]. Recently, Lee and coworkers [11] have reported a new series of inhibitors, which lack the carboxylic and the thiol moieties, based on a non-peptidic template. The new compounds are 3-aryl-4-aryloyl-1-(1*H*-imidazol-5-yl)-methylpyrroles **(xxiv–xxxiv)**. SAR studies showed that: (1) the hydrophobic aromatic substituent at C-3 of the pyrrole is crucial to the inhibitory potency of this series; (2) reduction of the ketone led to a 10-times loss in activity, which suggests that the ketone has an important role as both a hydrogen bond acceptor and as a geometric restrictor; and (3) methylation at N-1 of the imidazole ring increased the potency, suggesting that the N-3 imidazole could be involved in binding with the Zn^{2+} of Ftase. The most potent compound was **(xxviii)** (IC_{50} = 4.6 nM).



(xxiv–xxxiv)

R_1 = phenyl, 1-napthyl, 2-napthyl
R_2 = phenyl, substituted-phenyl



(xxviii)

Although further studies are required to ascertain the real importance of these pyrrole derivatives, they represent a new class of FTIs that do not have the problematic thiol and carboxylate groups. Therefore, they could be valuable for the development of farnesyltransferase inhibitors as clinically useful anticancer agents.

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Drug delivery

A drug-loaded tumor cell system for lung targeting

The current prognosis for a patient with lung cancer is not promising; the eventual death rate is over 90%. Additionally, metastatic cancers often metastasize to the lung, producing further complications. Most anticancer drugs are cytotoxic to healthy tissues, so there is a limited dose that can be administered in a patient's lifetime; this dose is often insufficient to eradicate the cancer. Therefore, a cancer-targeting drug delivery system that is selective for tumor cells versus healthy tissue would be a significant advance. Several approaches have been tried, including liposomes, antibody-linked drug molecules and soluble macromolecule drug conjugates, but each of these methods has drawbacks. There is still a need for a practical tumor-targeting drug delivery system.

There is considerable evidence that metastasis is a nonrandom and organ-specific process. The ease of interaction of tumor cells with the endothelium is thought to be the underlying factor determining the organ preference of metastasis. Successful blood-borne metastasis depends on the ability of a tumor cell to form emboli with other tumor cells and adhere to endothelial cells of the target organ of metastasis. Several adhesion molecules, including integrins, immunoglobulins and selectins, mediate these tumor–host interactions. Clinical findings have also shown that the lung is a major target organ of metastasis, with nearly 40% of all malignancies developing lung metastases, as most blood-borne metastatic cells are filtered out in the pulmonary vesicular system after they are shed into the circulatory system from primary tumors.

Shao and coworkers have recently demonstrated the application of drug-loaded tumor cells (DLTCs) as a drug delivery system for metastatic tumor cell targeting, particularly in the lungs. Two recent papers report the preparation and pharmacokinetics of DLTCs and their application to the treatment of lung cancer in an animal model [1,2]. The group hypothesized that DLTCs in which the tumor cells are functionally dead will retain their membrane surface structure and can be used as an ideal drug carrier, not only for lung-tumor targeting but also for the prevention of metastasis by competing for endothelial metastatic binding sites with the live tumor cells.

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To test this hypothesis, Shao and colleagues prepared DLTCs from B16-F10 murine melanoma cells and doxorubicin. B16-F10 cells metastasize primarily to the lung and are easily killed by brief heat treatment. Doxorubicin is a broad-spectrum antineoplastic drug, but its application is limited by severe adverse effects, in particular its cardiotoxicity. The incorporation of doxorubicin into DLTCs should promote selective lung targeting, increase anti-lung cancer activity by concentrating the drug in the pulmonary system, and reduce systemic side effects caused by circulation of the drug throughout the body.

Doxorubicin-loaded DLTCs were prepared by incubating a B16-F10 tumor cell suspension in PBS buffer with various drug:cell ratios of doxorubicin. The suspension was heated to 70°C for 1 minute, which left no viable tumor cells. Without this heating process, ~4% of the tumor cells survived loading with drug and remained viable. The protocol used was able to provide a maximum loading of 120 μg drug per 10^6 cells. *In vitro* drug release studies showed that the total amount of doxorubicin released from DLTCs depends on the cell concentration. At high cell concentrations, the percentage release was lowered as a result of binding of the drug at the cell nuclei. The intracellular drug content was lowered during the first 10 days and remained steady without further drug loss, much of which could be attributed to drug binding to the culture tube walls. Stability studies showed that after six months of storage the DLTCs were still acceptable for use in studies.

To study *in vivo* drug distribution, C57BL mice were injected with a 30 μg dose of doxorubicin either in solution or DLTC dosage form. After the animals were euthanized, the examination of various tissues showed that different dosage forms of doxorubicin resulted in different organ distributions of the drug. The free solution gave the highest drug levels in the liver, kidney and spleen, whereas the DLTC form resulted in higher levels of drug in the lungs. The drug concentration in the lungs corresponding to the DLTC dosage form was approximately threefold higher than the free solution. The differences in drug distribution to the heart and serum were statistically insignificant between the solution and DLTC dosage forms.

The DLTC system was then tested for its effectiveness in treating lung metastasis in mice. Several experiments were performed in which C57BL mice were first inoculated with live B16-F10 tumor cells and then treated with various dosing regimens of doxorubicin. In all experiments, animals were sacrificed on day 14 following live tumor inoculation and lung metastases were examined. The degree of metastasis in doxorubicin-treated groups was compared to a control group treated with an injection of the vehicle, phosphate buffer. In the first experiment, animals were treated with daily doses of 25 μg doxorubicin, either in solution or in DLTC, given on days 1–3 following live tumor cell inoculation. The solution dosage form resulted in a 60% inhibition of lung metastasis, compared with the control. By contrast, over 99% of the metastasis was inhibited by DLTC. In the second experiment, animals were treated with daily doses of 25 μg doxorubicin in solution or in DLTC, given on days 6–10 following live tumor-cell inoculation. In this case, the solution dosage form resulted in a modest 30% inhibition of metastasis, whereas the DLTC dosage form resulted in an 85% inhibition, compared with the control. In the third experiment, single 25 μg doses of doxorubicin in DLTCs were administered on days 1, 2, 3 or 4 following live tumor cell inoculation. When DLTCs were given on days 1 or 2, they inhibited lung metastasis by 79% or 63%, respectively. In comparison, when DLTCs were administered on days 3 or 4, they inhibited lung metastasis by ~50%. The inhibitory action of DLTC decreases with respect to the delay of time in treatment. Compared with the results from the first experiment, the single dose regimen of DLTC given on days 1 or 2 is equally or more effective compared with the multiple dose regimen of the solution dosage form.

This study demonstrates the lung targeting ability of DLTCs. There are several other distinct advantages to this drug delivery approach. The effectiveness of early, single dose DLTC treatment indicates that the DLTC interacts with blood-borne tumor cells and prevents them from reaching the endothelium-binding site. In addition, DLTCs that aggregate with blood-borne metastatic cells are expected to kill tumor cells before they migrate into the endothelial tissue, eradicate cancer in the targeted organ and compete with the same binding sites, preventing live tumor cells from binding. Finally, immune reactions are expected to be minimal, and could be decreased further by preparing the DLTCs from the tumor cells of an individual patient. If this approach proves effective in clinical trials, it could be useful as a treatment for metastatic cancers, perhaps even in the prevention of metastasis.

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