depleted lymphocytes expressed little IL-2-mediated augmentation of activity against these target cells and (b) most of this IL-2-mediated augmentation of activity was located in the large granular lymphocyte-enriched fraction of the lymphocyte population. Recombinant IL-2 also augmented the activity of lung NK cells against K562 and lung cancer cell targets, almost as effectively as with blood NK cells. We currently are evaluating the capacity of IL-2 to augment NK activity against freshly isolated autologous lung cancer cells.

**Discussion**

The data presented here suggest a potential therapeutic role for recombinant human IL-2 in the treatment of lung cancer. This therapy may involve systemically administered IL-2 with or without the adoptive transfer of IL-2-activated killer (LAK) cells to patients with advanced, nonresectable, drug-resistant tumors. It may involve the use of IL-2 as adjuvant therapy in individuals undergoing resection for primary lung cancer, based on the knowledge that many of these individuals have small metastatic deposits that are undetectable using current methods but which, by virtue of their small mass, may be susceptible to lysis by immune mechanisms such as IL-2-activated NK cells. It is possible that therapeutic methods such as these may be most effective when used in conjunction with other existing therapeutic modalities such as chemotherapy or radiotherapy. We are currently evaluating these concepts.

**Mechanisms of Drug Resistance**

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Cancers may be categorized according to drug response. These categories are:

1. Cancers in which responses occur, leading to a normal lifespan.
2. Cancers in which some response occurs, with an increase in survival.
3. Cancers in which there is a response to drug treatment, but increased survival has not been conclusively shown.
4. Cancers in which there is only a marginal response or no response to drug therapy.

Lung cancer is an example of the fourth and most difficult category of drug response. Why some cancers are curable with drug treatment and others are not is still not understood. The usual clinical scenario of even the most responsive tumors is the disappearance of the tumor (remission), with a future relapse and drug resistance. Cellular and molecular biology has not given us methods to investigate the phenomenon of tumor drug resistance. Tumor-mutant cells have been isolated to allow laboratory analysis of the biochemical basis of cell resistance.

Multidrug resistance denotes a complex cancer cell phenotype of cross-resistance to a wide variety of unrelated drugs. Multidrug resistance (MDR) is a term used to describe cells that have become resistant not only to one class of drugs, but also to other agents against which they have not been selected. This phenomenon is of great clinical importance. It means we cannot predict resistance patterns when selecting for resistance to a particular drug. It also means we cannot predict the resistance pattern that will result with the use of a single drug agent. Finally, MDR cells are more likely to survive and therefore kill the host.

The MDR phenotype is characterized by:

1. Cross-resistance to unrelated drugs.
2. Decreased accumulation of drugs within the cell.
3. Increased expression of P-glycoprotein. It is this protein that is believed to cause the MDR phenotype.

Monoclonal antibodies have been prepared against the membranes from human and hamster MDR and non-MDR cells. This has allowed recognition of a receptor that correlates with MDR. P-glycoprotein is a 170,000 molecular weight glycoprotein recognized by antibodies to resistant cells. The amount of drug resistance and P-glycoprotein can be correlated. It is believed that P-glycoprotein is present in drug-sensitive cells and increases in amount with resistant cells.

Leukemic cells have been transplanted into mice, and the mice then treated with chemotherapy. This results in most mice being cured, but in those who are not cured, the tumors are resistant to chemotherapy. In such animals, P-glycoprotein is increased. In patients with ovarian carcinoma, pleural and ascitic fluid tumor cells showed increasing P-glycoprotein with emergence of MDR. The same has been seen in other tumors, such as sarcomas and lung cancer. Overexpression of P-glycoprotein has not been seen in normal cells or in pretreatment tumors. The overexpression of P-glycoprotein appears to give a selective advantage to tumor cells.

Dr. Ling and his associates have cloned the cDNA for P-glycoprotein. Multidrug resistant cells have been found to have increased amounts of P-glycoprotein gene sequence. It is believed that the P-glycoprotein gene sequence represents a multigene family of 4-5 genes. This gene has been mapped to the chromosomal location 7q36.

DNA transfection experiments have been conducted in which the P-glycoprotein gene has been introduced into non-MDR cells. Recipient cells that then develop MDR have been found to have increased expression of MDR genes. It also appears that only a few members of the gene family are necessary for the MDR phenotype to be expressed.

The normal function of P-glycoprotein is unknown. It probably has a basic function within the cell and MDR is only

**References**

2. Robinson BW, Pinkston E, Crystal RG. Natural killer cells are present in the normal human lung but are functionally impotent. J Clin Invest 1984; 74:942-50

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a grotesque overexpression of this normal gene. Its function has been speculated to be that of a transport protein. The protein has a transmembrane domain and a highly conserved cytoplasmic domain.

While P-glycoprotein appears to be important in developing the MDR phenotype, it may not explain nondrug resistance of tumors prior to treatment with chemotherapy. However, because of its probable importance in the MDR phenotype, it is possible to speculate that clinical strategies can be developed to deal with MDR. These include use of drugs not involved in the MDR phenotype; exploitation of collateral drug sensitivity; use of chemosensitizers; targeting of monoclonal antibodies to P-glycoprotein; and targeting of drugs to the P-glycoprotein.