Leonardo da Vinci (1452-1519) wrote that “The supreme misfortune is when theory outstrips performance.” The field of modern immunotherapy is an example of this phenomenon.

In the past two decades, detailed knowledge of the cellular and molecular basis of immunologic processes has increased at a rapid pace, while the molecular characterization of multiple cancer antigens over the past 10 years has catapulted studies of tumor immunology into the mainstream of immunologic research. The conjunction of these two areas of knowledge has provided a theoretical framework for the development of new approaches to cancer immunotherapy, as well as reagents with which to perform immune manipulations that heretofore were unattainable. “Performance” has lagged behind these theoretical advances, although strong reasons exist for optimism that effective immunotherapies can be developed in the near future.

The past decade has seen substantial progress in efforts to define the antigens recognized on cancer cells. The past decade has seen substantial progress in efforts to define the antigens recognized on cancer cells.

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The past decade has seen substantial progress in efforts to define the antigens recognized on cancer cells. By screening cDNA libraries obtained from tumors and assaying the transfectants using lymphocytes with anti-tumor activity, a variety of genes encoding tumor antigens have now been characterized (Table 2). The DNA and amino acid sequences of these antigens have been determined, as have the immunodominant peptides restricted by major histocompatibility complex antigens.

The antigens fall into four major categories (Table 2). Many of the antigens found in melanoma patients are melanocyte-differentiation antigens expressed not only on melanomas but also on normal melanocytes, the cell of origin of this cancer. By mechanisms still undetermined, the growth of the melanoma has broken tolerance to these normal antigens. Destruction of the tumor, therefore, can lead to destruction of normal melanocytes, which accounts for the vitiligo often seen in responding patients. A second class of antigens includes those uniquely expressed in the cancer as well as in germ cells of the testis. Both the melanocyte-differentiation and cancer-testis antigens are normal nonmutated proteins. A third class of antigens involves those tumor-specific mutations that are unique to the individual patient. In contrast to the melanocyte-differentiation and cancer-testis antigens, these antigens are not widely shared and thus would represent suitable targets only for the indivi-

| Table 1 |
| --- |
| Response of Patients Treated with High-Dose Bolus IL-2 |
| Diagnosis | Complete Response | Partial Response | Total |
| | No. (%) | No. (%) | No. (%) |
| --- | --- | --- | --- |
| Melanoma | 12(6.6) | 15(8.2) | 27(14.8) |
| Renal cancer | 21(9.3) | 22(9.7) | 43(19.0) |
| Total | 33(8.1) | 37(9.0) | 70(17.1) |

| Table 2 |
| --- |
| Duration of Response in Patients Treated Using High-Dose Bolus IL-2 |
| Diagnosis | Complete Response (Months)* | Partial Response (Months) |
| --- | --- | --- |
| Melanoma | 148+,96+,95+,93+,91+,84+,80+,71+,71+,70+,16,12 | 35,31,19,10,10,8,8,7,5,5,5,4,4,2 |
| Renal cancer | 134+,126+,123+,94+,94+,90+,87+,86+,86+,79+,70+,64+,63+,60+,49+,46+,39+,35,23,19,19 | 52,30,30,22,20,17,16,15,14,14,13,11,9,8,7,7,6,4,4,4 |

*"+" indicates ongoing response, as of March 1, 1998.
Of 33 patients with complete response, 27 remain in complete response at 39 to 148 months.
ual patients expressing these mutations or expressing unique viral genes. The discovery of these genes and gene products has opened the door to the development of immunotherapies that were not possible only a few years ago. Examples of approaches to cancer immunotherapies uniquely based on the identification of the genes encoding cancer regression antigens are shown in Table 3.

Active immunotherapies currently being investigated, including immunization with purified antigens, immunodominant peptides, DNA, and recombinant viruses, can be administered either alone or in combination with cytokine adjuvants. Unique passive immunotherapies have also become possible due to the ability to generate tumor reactive T cells in vitro by sensitization to the specific antigens present on tumors. Techniques for the generation of cloned populations of anti-tumor cells have been developed, as have techniques to isolate the T cell receptors that recognize tumor antigens. The transduction of lymphoid effector cells or hematopoietic stem cells with the genes encoding T cell receptors that recognize specific antigens can provide another source of cells for use in cell transfer therapies.

The first reports of the successful use of immunotherapies capable of mediating the regression of established tumor in patients with melanoma utilizing immunization with immunodominant peptides have been published. In a study that used a modified peptide from the gp100 tumor antigen administered in conjunction with IL-2, for example, 42% of melanoma patients showed objective

| Antigen Category | Gene | MHC Restriction |
|------------------|------|----------------|
| Melanocyte-differentiation | MART-1/MelanA | A2, B45 |
| | gp100 | A2, A3, A24 |
| | Tyrosinase | A1, A2, A24, DR4 |
| | TRP-1 | A31 |
| | TRP-2 | A2, A31, A68 |
| Cancer testis | MAGE-1 | A1, Cw16 |
| | MAGE-3 | A1, A2, B44 |
| | GAGE-1/2 | Cw16 |
| | BAGE | Cw16 |
| | RAGE | B7 |
| | NY-ESO-1 | A2, A31 |
| Tumor specific | CDK-4 | A2 |
| | β catenin | A24 |
| | MUM-1 | B44 |
| | Caspase-8 | B35 |
| | KIAA0205 | B44 |
| | HPVE7 | A2 |
| Widely expressed | SART-1 | A26 |
| | PRAME | A24 |
| | p15 | A24 |
cancer regression. Although most immunotherapy studies have dealt with melanoma patients, the discovery of antigens on other tumor types and the principles learned in patients with melanoma can lead to the extension of these studies to patients with more common tumors.

In the past decade, a new era of cancer immunotherapy has begun, based on the identification of genes encoding cancer regression antigens. Immunotherapies based on a molecular understanding of immune processes, as well as the antigens being targeted, represent encouraging steps toward the development of effective immunotherapies for the treatment of patients with cancer.

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