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**CANCER VACCINES:
TECHNOLOGY, PRODUCTS, MARKETS AND
BUSINESS OPPORTUNITIES**

REPORT #401 250 PAGES JUNE 1996 \$1,550

A new round of prototype tumor vaccines is expected to advance in clinical trials in the next two to three years. Some vaccines represent a broad-based approach, attempting to trigger the whole immune system, while others are directed at specific targets. This report provides a comprehensive analysis of the cancer vaccine sector in terms of: **basic science** (tumorigenesis, oncogenes, tumor-suppressor genes, mitogenic growth factors and growth inhibitory factors, viral causes, apoptosis, immune response, tumor antigens, immune surveillance); **technology** (antiviral vaccines against cancer, nonspecific and specific active immunotherapy, whole tumor cell vaccines, gene transfer, protein antigens, adoptive immunotherapy, activated killer cells, tumor-infiltrating lymphocytes, passive immunotherapy, adjuvants); **indications and epidemiology** (worldwide incidence by disease severity and survival and mortality statistics for major cancers); **products under development** (a comprehensive database of cancer vaccines in development worldwide, including developer/affiliate, technology and clinical status); **market opportunities worldwide** (by indication based on candidate populations and suggested treatment costs); and **developer profiles** (over 50 companies).

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Table 1
Combination Approaches in Clinical Trials Against MDR Cancers

| MDR-reversing Agent | Chemotherapeutic Agent | Status/Location/Indication |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| SDZ PSC 833 (5 mg/kg PO qd) | Fluorouracil (60-80 mg/m ² IV) | Phase I/USA/colorectal tumors (ASCO, Abs. 102) |
| SDZ PSC 833 (12.5 mg/kg PO q 12 hours for 8 days) | Vincristine (1.5 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 103) |
| SDZ PSC 833 (4 mg/kg q 8 hours 8 times) (750 µg) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 104) |
| SDZ PSC 833 (5 mg/kg q 8 hours or 20 mg/kg/d) | Etoposide (1.0 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 105) |
| SF788 (escalating continuous IV infusion of 100, 240, 320, 400, 480 mg over 4 hours) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 106) |
| SF788 (MTD was 96-104 mg/m ² as a 30 minute IV infusion) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 107) |
| VX-710 | Fluorouracil | Phase I/USA/colorectal tumors (ASCO, Abs. 108) |
| VX-710 | Doxorubicin | Phase I/USA/colorectal tumors (ASCO, Abs. 109) |
| L.S. R. barbituric sulfonamide (BSO) (0.75 gm/kg x 24 to 1.5 gm/kg x 48, 5 continuous infusions) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 110) |
| Demigipitate (oral) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 111) |
| Mitomycin (escalating starting at 4 gm, 5 gm and 6 gm, PO, q week 3 hours prior to vincristine) | Vincristine (1.5 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 112) |
| IFN-α 2b (escalating dose from 0.5 million to 1 million on days 5-9) + hydroxyurea (500 mg q 8 hours, days 5-9) + tamoxifen (10 mg/m ² , days 1-10) + streptozocin (500 mg/m ² , days 6-9) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 113) |
| Interleukin-2 (10 million IU/m ² IV q 7 days) + N-deethyl-2-[4-(phosphorothioylthio)amino] ethanesulfonamide (DTPP) (240 mg/m ² over 80 to 100 minutes weekly) | Doxorubicin (1.2 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 114) |
| L-verapamil (125 mg/m ² PO q 4 hours beginning 24 hours before and continuing for 24 hours after paclitaxel infusion) | Paclitaxel (175 mg/m ² IV q 3 weeks) | Phase I/USA/colorectal tumors (ASCO, Abs. 115) |
| Deverapamil (240-1200 mg/m ² /day) | Etoposide (1.0 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 116) |
| Deverapamil (3000 mg/d) | Vincristine (1.5 mg/m ² IV q 7 days) | Phase I/USA/colorectal tumors (ASCO, Abs. 117) |

Table 2
Lung Cancer Incidence and Mortality by Gender in Selected Countries Worldwide in 1995

| Country | Death Rate | | | Incidence Rate | | |
|------------------|------------|--------|-------|----------------|--------|-------|
| | Male | Female | Total | Male | Female | Total |
| Group 1 | | | | | | |
| UK | 99.7 | 44.1 | 71.3 | 41,447 | 52.9 | 78.8 |
| Germany | 79.0 | 18.2 | 47.3 | 38,426 | 82.7 | 21.8 |
| Italy | 101.7 | 16.0 | 58.0 | 33,574 | 107.8 | 19.9 |
| France | 90.1 | 12.2 | 50.2 | 28,992 | 95.5 | 14.6 |
| Spain | 76.0 | 7.3 | 41.1 | 16,143 | 80.8 | 8.8 |
| Holland | 100.9 | 17.4 | 58.7 | 5,105 | 107.0 | 20.9 |
| Belgium | 128.2 | 15.6 | 70.8 | 7,099 | 135.9 | 18.7 |
| Greece | 88.1 | 14.7 | 50.8 | 5,212 | 93.4 | 17.6 |
| Denmark | 82.8 | 66.3 | 84.4 | 3,245 | 87.8 | 55.8 |
| Portugal | 47.2 | 9.9 | 27.9 | 3,759 | 50.0 | 11.9 |
| Ireland | 63.4 | 28.6 | 46.0 | 1,595 | 67.2 | 34.3 |
| Subtotal | 89.1 | 20.1 | 53.8 | 187,899 | 94.4 | 24.1 |
| Group 2 | | | | | | |
| Austria | 72.1 | 21.5 | 45.9 | 3,608 | 76.4 | 25.8 |
| Sweden | 45.9 | 21.3 | 33.5 | 2,937 | 48.7 | 25.6 |
| Switzerland | 71.8 | 13.8 | 42.2 | 2,933 | 75.9 | 16.6 |
| Finland | 64.3 | 14.9 | 39.0 | 1,970 | 68.4 | 17.9 |
| Norway | 53.2 | 20.2 | 36.5 | 1,591 | 56.4 | 24.2 |
| Subtotal | 60.1 | 18.3 | 38.8 | 13,039 | 63.7 | 22.0 |
| Group 3 | | | | | | |
| Poland | 90.3 | 16.8 | 52.6 | 20,387 | 95.7 | 20.5 |
| Yugoslavia (old) | 67.7 | 12.3 | 39.7 | 9,576 | 71.8 | 14.8 |
| Czech Republic | 100.1 | 15.8 | 58.9 | 9,032 | 106.1 | 19.0 |
| Hungary | 125.8 | 30.6 | 76.3 | 7,994 | 133.3 | 36.7 |
| Romania | 55.4 | 10.7 | 32.8 | 7,705 | 58.7 | 12.8 |
| Bulgaria | 64.6 | 12.5 | 38.1 | 3,382 | 68.5 | 15.0 |
| Subtotal | 81.4 | 15.5 | 47.8 | 58,077 | 86.2 | 18.6 |
| Group 4 | | | | | | |
| Old USSR | 65.4 | 7.2 | 34.7 | 99,147 | 69.3 | 8.6 |
| USA | 74.1 | 46.0 | 59.8 | 157,400 | 74.6 | 54.8 |
| Group 5 | | | | | | |
| Japan | 49.0 | 17.2 | 32.8 | 40,563 | 51.9 | 20.6 |
| Canada | 77.2 | 31.9 | 54.2 | 13,730 | 81.8 | 38.3 |
| Argentina | 46.9 | 8.3 | 27.2 | 8,871 | 49.7 | 10.0 |
| Australia | 60.3 | 18.5 | 39.8 | 6,212 | 63.9 | 24.4 |
| Cuba | 49.8 | 18.3 | 34.2 | 3,328 | 52.6 | 22.0 |
| Hong Kong | 62.1 | 31.6 | 47.1 | 2,603 | 65.8 | 37.9 |
| Chile | 17.6 | 6.5 | 12.0 | 1,362 | 18.7 | 7.8 |
| New Zealand | 57.6 | 25.1 | 41.2 | 1,262 | 61.1 | 30.1 |
| Uruguay | 83.8 | 7.3 | 44.6 | 1,317 | 88.8 | 8.8 |
| Singapore | 42.2 | 16.3 | 29.4 | 796 | 44.7 | 19.6 |
| Israel | 27.8 | 10.7 | 19.2 | 776 | 29.3 | 12.8 |
| Costa Rica | 11.1 | 5.5 | 8.3 | 201 | 11.8 | 6.6 |

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Table 3
Drugs in Development for the Treatment of Melanoma

| Primary Developer/Allylicity | Generic Name/Number/Brand Name | Drug Type/Target/Mechanism/Action | Status/Location/Indication | Comments |
|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------------|
| Ajinomoto/Nagasaki U. BioChem Pharma | Recombinant BCG (Bacillus Calmette Guerin) vaccine | Host-vector system applied to recombinant foreign antigens from living BCG using the oncoantigen as a carrier/tra and extra cellular antigens | Clinical/USA/Indication | Approved/USA, Canada/bladder cancer |
| Amplified (licensee)/Research Corporation Technologies (licensee)/U. Arizona, Arizona Cancer Center (original developer) | Amplified compound | Antineoplastic analog of anisole/dibenzofuran-inhibitor | Pre-clinical/USA/R16 melanoma | |

Table 4
Profile of Approved Platinum-based Drugs

| Indications | Side Effects | Treatment Regimen | AWP per Treatment/USA Sales / USA Sales Traded | Estimated WW Market |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|---------------------|
| Metastatic testicular (curative), ovarian (adjuvant), bladder, renal/bladder, and bladder cancer alone or in combination; also used of label in the treatment of small cell lung, head and neck, cervix and breast cancer | Less emetogenic than cisplatin; myelosuppression; peripheral neuropathy, mostly dose limiting; bladder, cervix and breast cancer | 20 mg/m ² IV daily for 5 days (alone or in combination) for testicular cancer; 75 mg/m ² with cyclophosphamide (Cytoxan, Bristol-Myers Squibb) or 100 mg/m ² (alone) IV once every 4 weeks 50-70 mg/m ² IV once every 3-4 weeks | \$531.1 per treatment/1993 \$145.0 | 1994 \$285.9 |
| Advanced ovarian cancer; also used off label in the treatment of small cell lung, head and neck, bladder, cervix and breast cancer | Less emetogenic than cisplatin; myelosuppression, mostly dose limiting; bladder, cervix and breast cancer | 360 mg/m ² IV once every 4 weeks or intravenous 5151 mg/m ² /22,000 mg/m ² in combination | \$1,206 per treatment/1993 \$285.0 | 1994 \$285.9 |

Platinum complexes based on the structure of carboplatin demonstrated no advantage. One series of compounds containing a 1,2-diaminocyclohexane (dact) carrier ligand (e.g., oxaliplatin, tetraplatin), that demonstrated circumvention of acquired cisplatin resistance in some preclinical tumor models (mainly murine leukemia), is currently in clinical trials. However, clinical results have been disappointing, because the drugs have shown little evidence of activity in cisplatin-resistant disease and appear to cause severe neurotoxicity. Exhibit 19 lists selected platinum-based drugs and related agents in development.

Oxaliplatin. Debiopharm's (Lansanne, Switzerland) oxaliplatin (L-OHP) is currently awaiting registration in Europe. L-OHP has been evaluated in patients with advanced gastric cancer (Engachi, M. et al, ICAC95, Abs. # P259). Drug was intravenously administered as bolus, continuous or chronomodulated infusion (circadian delivery); a dose of 130 mg/m² q 7 weeks did not produce untoward side effects (Kikorian, A. et al, ICAC95 Abs. P-562). In a phase II trial, chronomodulated delivery of 5-FU, FA and oxaliplatin produced objective response rate of 58% in 93 patients with metastatic colorectal cancer. In another trial, seven European centers enrolled 92 patients with previously untreated metastatic colorectal cancer. To compare chronomodulated with constant rate drug delivery to see how they affect therapeutic outcome. A regimen of daily administration of 5-FU (800 mg/m² per day), FA (300 mg/m² per day), and L-OHP (20 mg/m² per day) for 5 days was repeated every 21 days (10-day intermission) in ambulatory patients with the use of a programmable in-time pump. In one group (47 patients) drug delivery was kept constant over a 24-day period while it was chronomodulated (maximum delivery of 5-FU and FA infusions at 0400 hours and maximum delivery of L-OHP at 1600 hours) in the other group (45 patients). Twenty-four of 45 patients (53%) in the group receiving chronomodulated therapy exhibited an objective response compared with 15 of 47 patients (32%) in the constant infusion group. The median progression-free survival was 11 and 8 months, respectively, and the median survival was 19 months and 14.9 months. Chronomodulated delivery was both more effective and less toxic (Levi FA, et al, NCL 1994 Nov 2, 86(21):1608-17). Debiopharm has signed a license agreement with Eli Lilly (Paris, France) in Europe and is negotiating with a licensee in Japan.

Tetraplatin. Upjohn's tetraplatin was administered in 20 patients at a dose range of 4.4-90.8 mg/m² IV, given over 20 minutes on a day 1 and day 8 schedule, every 28 days. Nausea/vomiting occurred in 40% of patients but was well controlled with standard antiemetic therapy. However, renal toxicity, hepatotoxicity and severe neurotoxicity precluded further use of his regimen (Schäfer RJ, et al, Cancer Research, 1994 Feb 1, 54(3):709-17).

JH 2149 is one of a novel class of platinum-containing ammine-sulfonamide platinum(IV) dicarboxylates (mixed amines), synthesized at the Drug Development Section, Institute of Cancer Research (Belmont, Sutton, UK), in collaboration with the Johnson Matthey Technology Centre

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