INSTITUT PASTEUR — UNIVERSITE PIERRE & MARIE CURIE

**The 2nd PSU International Teaching Platform on Tumour Immunology and Immunotherapy**

Jointly organized by
Prince of Songkla University, Université Pierre et Marie Curie (Paris 6) and Institut Pasteur

December 15 – 20, 2003
At The Department of Biomedical Sciences
Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla, Thailand

Lecture 2:
Tumour biology and immune surveillance
Prof. Hervé Fridman

December 15, 2003



## LE CANCER EN FRANCE *

| | 1980 | 2000 |
|---|---|---|
| **INCIDENCE** | 170 000 | 278 000 (↗ 63%) |
| **MORTALITE** | 125 000 | 150 000 (↗ 20%) |

* Rapport de la Commission d'orientation sur le cancer (janvier 2003)



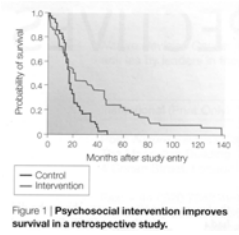



Figure 1 | **Psychosocial intervention improves survival in a retrospective study.**

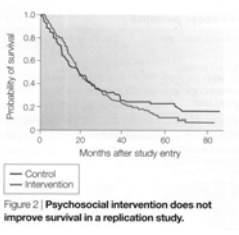



Figure 2 | **Psychosocial intervention does not improve survival in a replication study.**



## Different Kinds of Cancer

**Diseases in which cells grow and spread unrestrained throughout the body**

Organs and Tissues

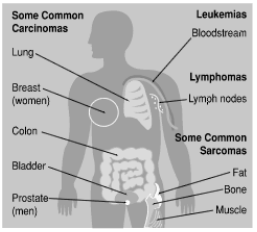
Carcinomas, the most common types of cancer, arise from the cells that cover external and internal body surfaces (lung, breast, colon…).

Sarcomas are cancers arising from cells found in the supporting tissues of the body (bone, cartilage, fat, connective tissue, and muscle).

Immune System

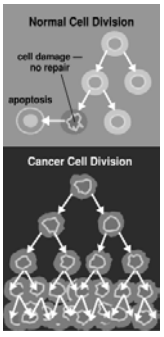
Lymphomas are cancers that arise in the lymph nodes and tissues of the body's immune system.

Leukemias are cancers of the immature blood cells that grow in the bone marrow and accumulate in the periphery.

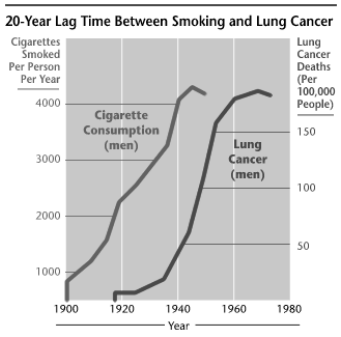





| Some Prefixes Used in Naming Cancers | |
|---|---|
| PREFIX | MEANING |
| adeno- | gland |
| chrondro- | cartilage |
| erythro- | red blood cell |
| hemangio- | blood vessels |
| hepato- | liver |
| lipo- | fat |
| lympho- | lymphocyte |
| melano- | pigment cell |
| myelo- | bone marrow |
| myo- | muscle |
| osteo- | bone |





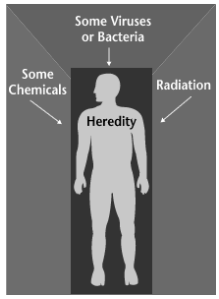



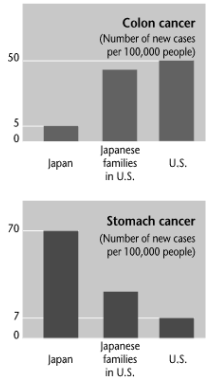
| Some Viruses Associated With Human Cancers | |
|---|---|
| **VIRUS** | **TYPE of CANCER** |
| Epstein-Barr virus | Burkitt's lymphoma |
| Human papillomavirus | Cervical cancer |
| Hepatitis B virus | Liver cancer |
| Human T-cell lymphotrophic virus | Adult T-cell leukemia |
| Kaposi's sarcoma-associated herpesvirus | Kaposi's sarcoma |

**Genes Implicated in Cancer**

- Oncogenes
- Tumor suppressor genes
- DNA repair genes

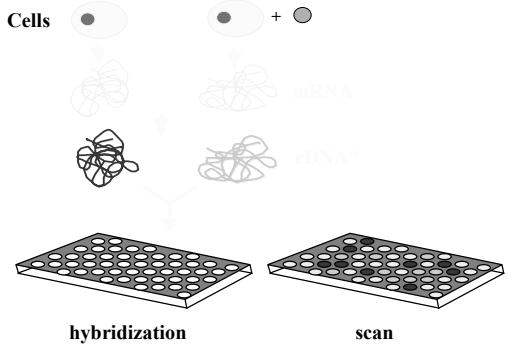




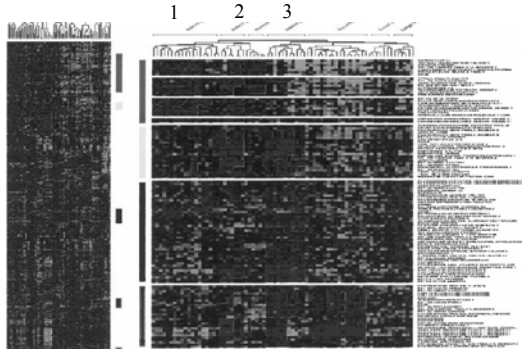



# DNA microarrays






# Lung Adenocarcinoma




**Garber ME *et al.* (2001) Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA, 98, 13784-13789.**



# Lung Adenocarcinoma

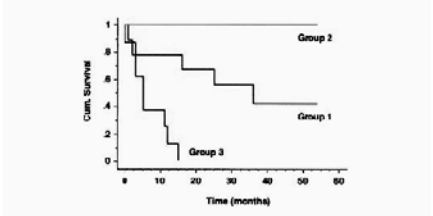
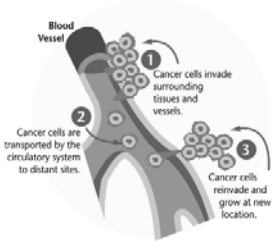



**Fig. 4.** Kaplan–Meier curves show differences in survival for AC subgroups. AC groups 1–3 were defined by hierarchical clustering (see Fig. 1). Cumulative survival, plotted on the *y* axis, represents percentage of patients living for the indicated times.

**Garber ME *et al.* (2001) Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA, 98, 13784-13789.**



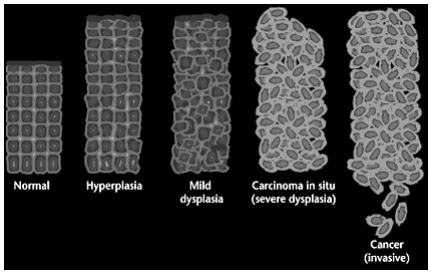
**Cancers are capable of spreading through the body by two mechanisms: Invasion and Metastasis**




**Invasion** refers to the direct migration and penetration by cancer cells into neighbouring tissues.

**Metastasis** refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade normal tissues elsewhere in the body.

## Cancer Progression




**How the immune system controls (or not) cancer progression?**



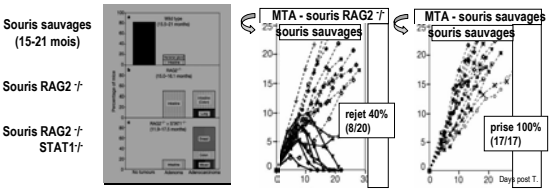
## Anti-tumour immunity

*un sujet de controverse*

- Augmentation de l'incidence des tumeurs surtout d'origine virale chez les immunodéprimés
- Succès modestes mais incontestables de protocoles d'immunothérapie (IL-2, IFNs, TILs…)
- Valeur pronostique de l'environnement immunologique des tumeurs
- Expériences d 'immunisation contre des tumeurs syngéniques => Ag tumoraux
- Souris invalidées pour l'IFN-$\gamma$ R, STAT-1 ou la perforine : plus sensibles au MCA



## Immune Surveillance




(Shankaran et al.Nature2001)

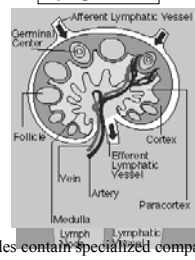


## The Immune System

The immune system is a bodywide network of cells and organs that has evolved to defend the body against pathogens.

Org… …tem


Lymph Node



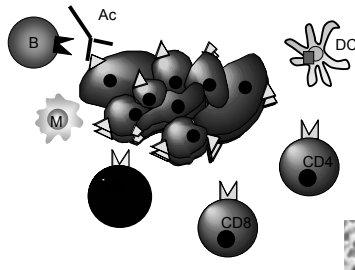

Lymph nodes contain specialized compartments where immune cells congregate, and encounter antigens.



## Immune System

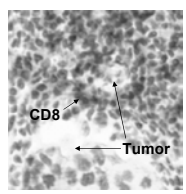
| Cells of the Immune System | Principle of the Immune System |
|---|---|
| T Cells, B Cells | **Adaptive Immunity**: - Distinct antigenic specificities<br>- Highly specific recognition of foreign antigens<br>- Potent mechanisms for elimination of pathogens bearing such antigens<br>- Capacity to display immunologic memory<br>- Tolerance to self-antigens |
| NK Cells, Eosinophils, Basophils, Mast Cells, Monocytes, Macrophages, Dendritic Cells, PMN | **Innate Immunity**: Consists of molecules and cells that recognize only specific conserved constituents of microorganisms, and whose efficacy is not significantly increased by previous exposure.<br>Inflammatory responses |



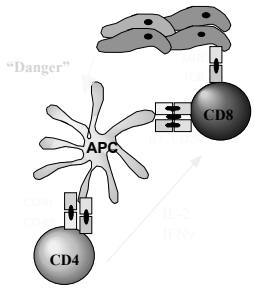



**Tumour Ag**
- differentiation
- mutated genes
- tumour testis
- viral proteins
…

**Tumoral micro-environnement**



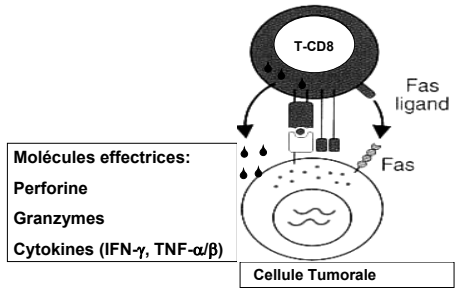
## Tumor killing






## CD8+ T lymphocytes and the anti-tumoral response

**Un des effecteurs majeurs dans la réponse anti-tumorale**
**Deux caractéristiques principales**






## Tumour Antigens

**A Peptides dérivés d'antigènes reconnus par des lymphocytes T-CD8**

**1 Antigènes de différenciation mélanocytaire**
- **Mart-1 (Melan A)**
- **Gp100 (pmel-17)**
- **Tyrosinase**
- **TRP1 (gp75)**
- **TRP2**
- **MSH- R**

**2 Cancer-Testis antigen**
- Mage 1, Mage 2, Mage 3, Mage 12
- Bage, Gage, Rage
- NY-ESO-1
- N-acetylglucosaminyltransferase V (peptide intronique).



## Tumour Antigens

**3 Antigènes mutés**
- **β catenine**
- **CDK-4**
- **Caspase-8**
- **KIA0205**
- **HLA-A2**

**4 Antigènes surexprimés dans les tumeurs**
- **G-250**
- **Her-2/neu**
- **p53**
- **Telomerase catalytic protein**
- **ACE**
- **α foeto-proteine (αFP)**



## Tumour Antigens

**B peptides dérivés d'antigènes reconnus par des lymphocytes T-CD4**

**1 Peptides dérivés d'antigènes non mutés**
- **gp100**
- **Mage 1**
- **Mage 3**
- **Tyrosinase**
- **NY-ESO-1**

**2 Peptides dérivés d'antigènes mutés**
- **Triosephosphate isomerase**
- **CDC-27**
- **LDLR-FUT**



## MUC-1

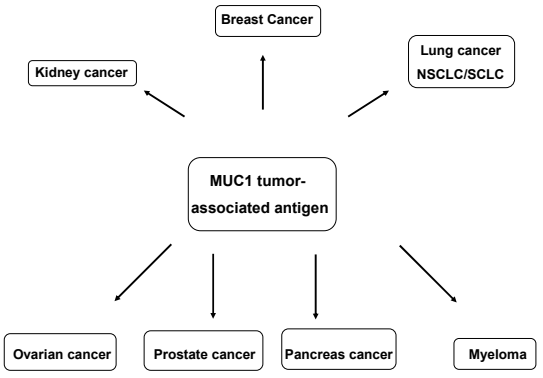
**- Large transmembrane glycoprotein which belongs to the mucin family**

**- 20 Amino-acid sequence which is repeated between 20 and 125 times per Muc-1 molecule**

**- Found on the apical surface of mucin secreting normal epithelial cells.**

**- In tumor - Muc 1 is overexpressed on the whole cell surface**

**- Muc 1 glycosylation pattern is altered exposing new cancer-specific epitopes to immune system.**






**IN VIVO IMMUNIZATION EXPERIMENTS USING RECOMBINANT MUC 1 VIRUS**

**1) IN MICE**

| Strain of mouse | Immunogen | Tumour challenge | Rejection of tumor challenge |
|---|---|---|---|
| DBA | Vaccine control | P815-Muc1 | 0/44 (0%) |
| DBA | Vaccine-Muc 1 | P815-Muc1 | 13/45 (29%) |

**Acres Transgene**

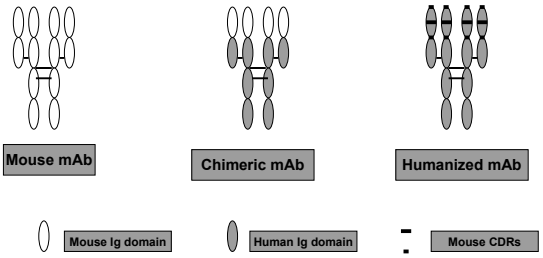
**2) IN RATS**

**Vaccination with recombinant vaccinia virus expressing Muc 1 prior to challenge with Muc1 + tumor prevented tumor development in 60-80% of animals**

**Hareuveni et al 1990**



# From Mouse to Humanized mAbs






## Antibody-based immunological therapies

Scott MA and Welt S, Current Opinion in Immunology, 9:717, 1997.

**Major tumor associated antigens targeted by monoclonal antibodies in clinical trials.**

| Categories | Examples of antigens | Tumor types | References |
|---|---|---|---|
| Lymphomas/leukemias | | | |
| Differentiation antigens | CD5 | T cell leukemia/lymphoma | [21] |
| | CD19, CD20, CD21, CD22, CD37 | B cell lymphoma | [4••,5–7,9] |
| | CD30 | Hodgkin's lymphoma | [44] |
| | CD33, CD45 | AML | [10–13] |
| | CAMPATH-1 (CDw52) | Lymphoid malignancies (T and B cell) | [14] |
| | HLA-DR | B cell lymphoma | [21] |
| | Anti-idiotype | B cell lymphoma | [8] |
| Solid tumors | | | |
| Cell surface antigens | | | |
| Glycoproteins | CEA, TAG-72, Ep-CAM, MUC1 | Epithelial tumors (breast, colon, lung) | [16,22•,32,33] |
| | Folate binding protein | Ovarian tumors | [43] |
| | A33 | Colorectal carcinoma | [23,24••,25,26] |
| | G250 | Renal carcinoma | [37,38] |
| Glycolipids | Gangliosides (e.g. GD2, GD3) | Neuroectodermal tumors | [40,41] |
| Carbohydrates | Lex | Epithelial tumors (breast, colon, lung) | [27•,36] |
| | CA-125 | Ovarian carcinoma | [21] |
| Intracellular antigens | Ferritin | Hodgkin's disease, hepatoma | [21] |
| Growth factor receptors | EGFR | Lung, breast, head and neck tumors | [47] |
| | $p185^{HER2}$ | Breast, ovarian tumors | [34••,35] |
| | IL-2 receptor | T and B cell neoplasms | [15] |
| Stromal/extracellular antigens | FAP-α | Epithelial tumors (colon, breast, lung) | [48] |
| | Tenascin | Glioblastoma multiforms | [21] |
| | Metalloproteinases | Epithelial tumors | [3•] |