

Cancer Genes & Personalized Therapy

Hsing-Jien Kung
UC Davis Cancer Center

Human genome and cancer genes

Cancer as a disease of gene
mutation

Cancer therapy: conventional and
targeted, combination and
personalized



3 billion letters

...ATGCGCCTATT.....

DNA → RNA → Protein

23对染色体 = DNA (去氧核酸) = 基因 (Genes)

30,000 基因 → 30,000 蛋白质

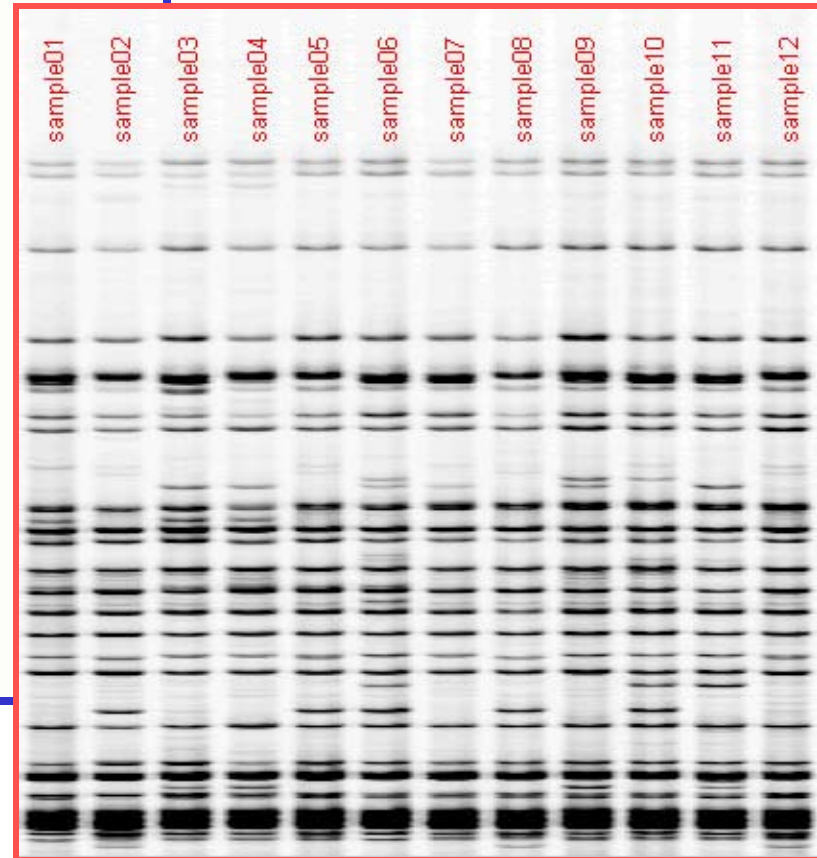
人与人 99.9% 相同

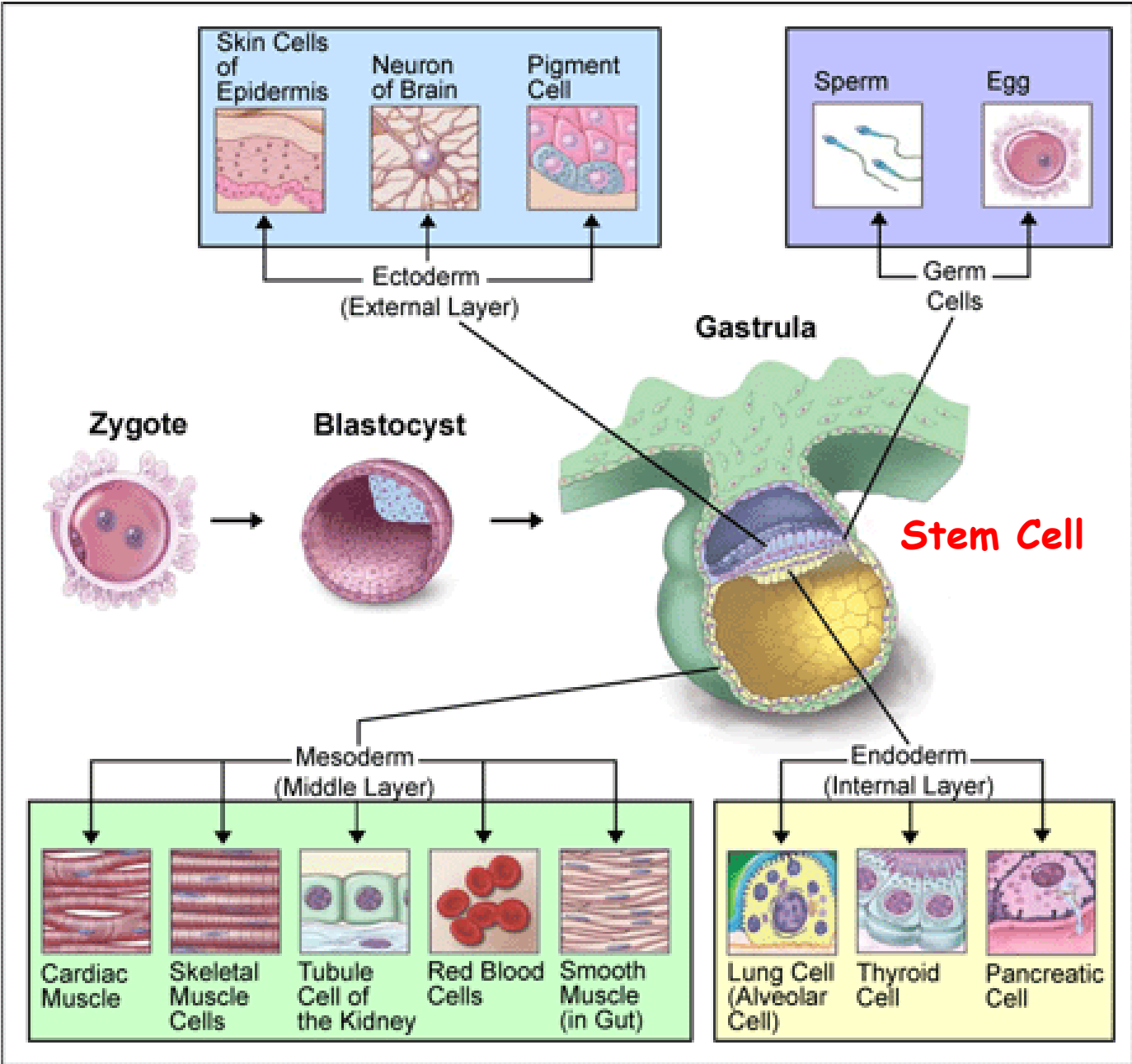
猴 99.0% "

鼠 90.0% "

鸡 70.0% "

構造相似, 組合功用不一, 設計不一
決定體形, 長像, 疾病傾向, 性向.





Cancer Notes

CANCER is a disease of uncontrolled growth caused by DNA damages and altered gene expression

CANCER is a genetic disease with heritable traits and mutated genes

~30,000 genes encoded by human genome

~15,000 genes expressed in a given cell, cancer or normal

cancer and normal cells differ by the expression of >1,000 genes

In a given cancer cell, the significant reprogramming of gene expression is caused by the alteration of a few genes (say 10), which are the programmers or triggers

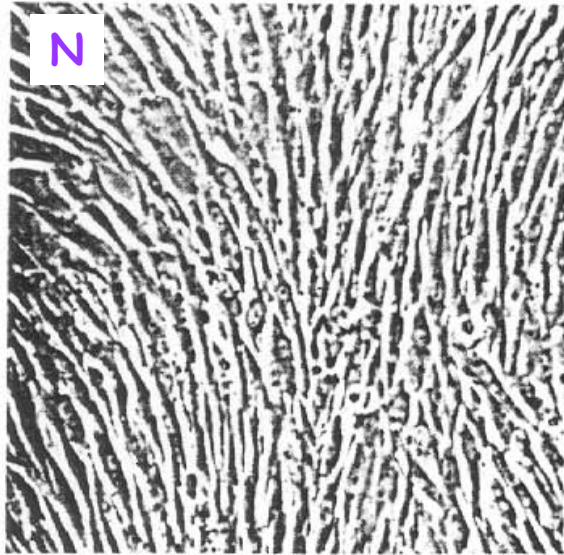
They are called **ONCOGENES** and **TUMOR SUPPRESSOR GENES**

In human genome, there are about 100 each, but individual cancers result from the alterations of different sets of 10 or fewer.

N: normal cells

T: tumor cells

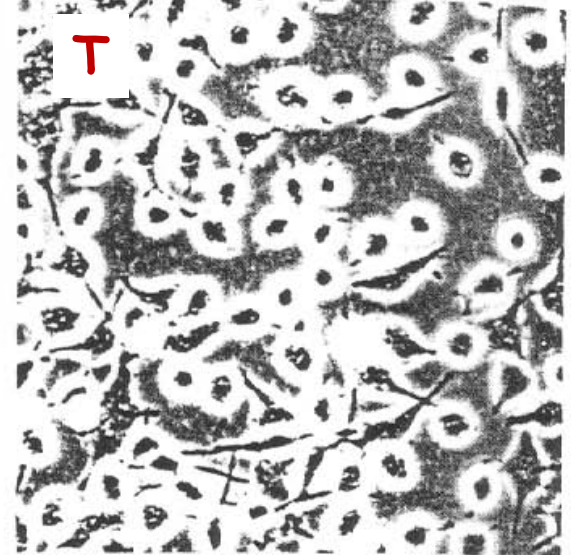
(a)



(b)



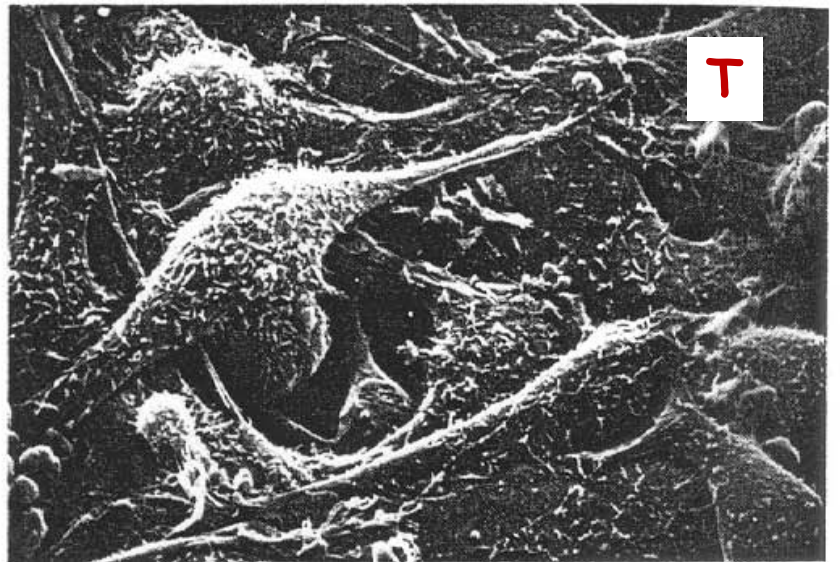
(c)



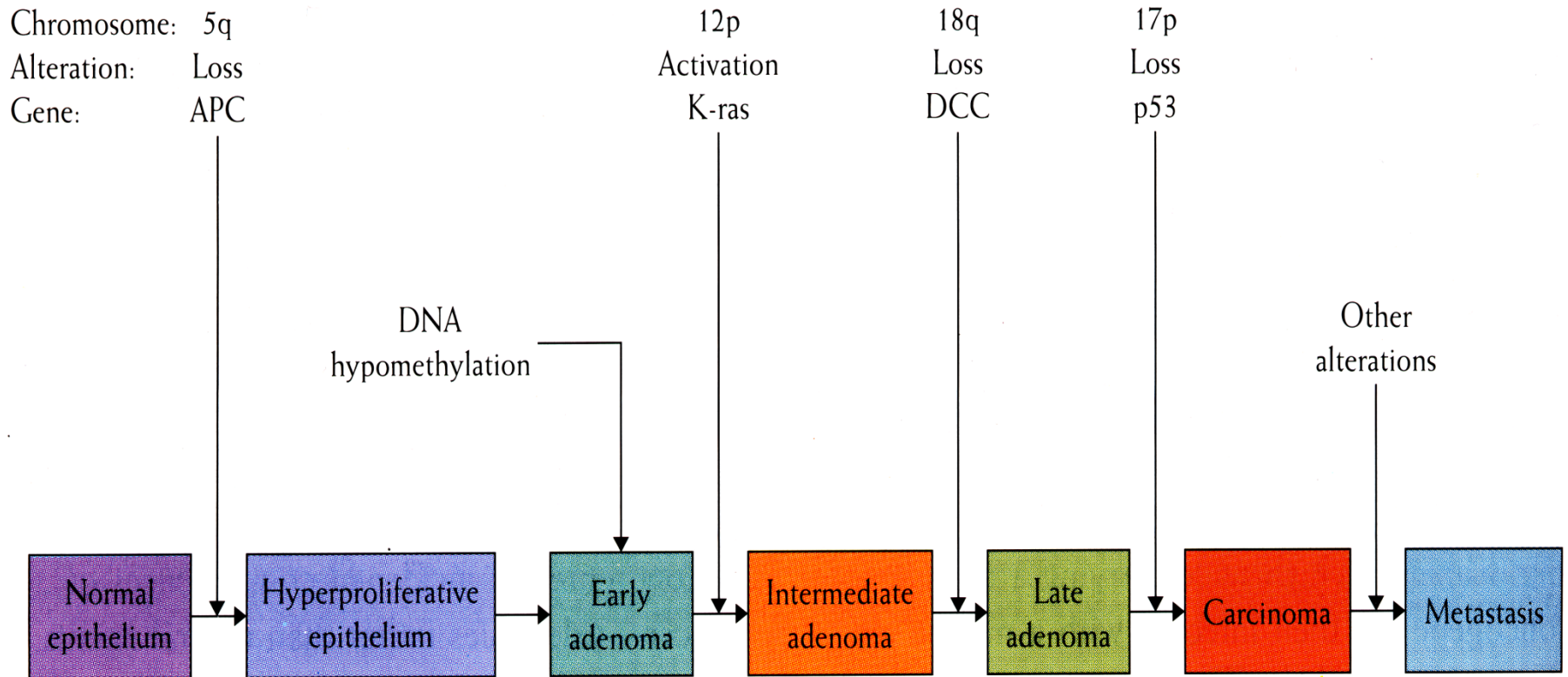
(d)



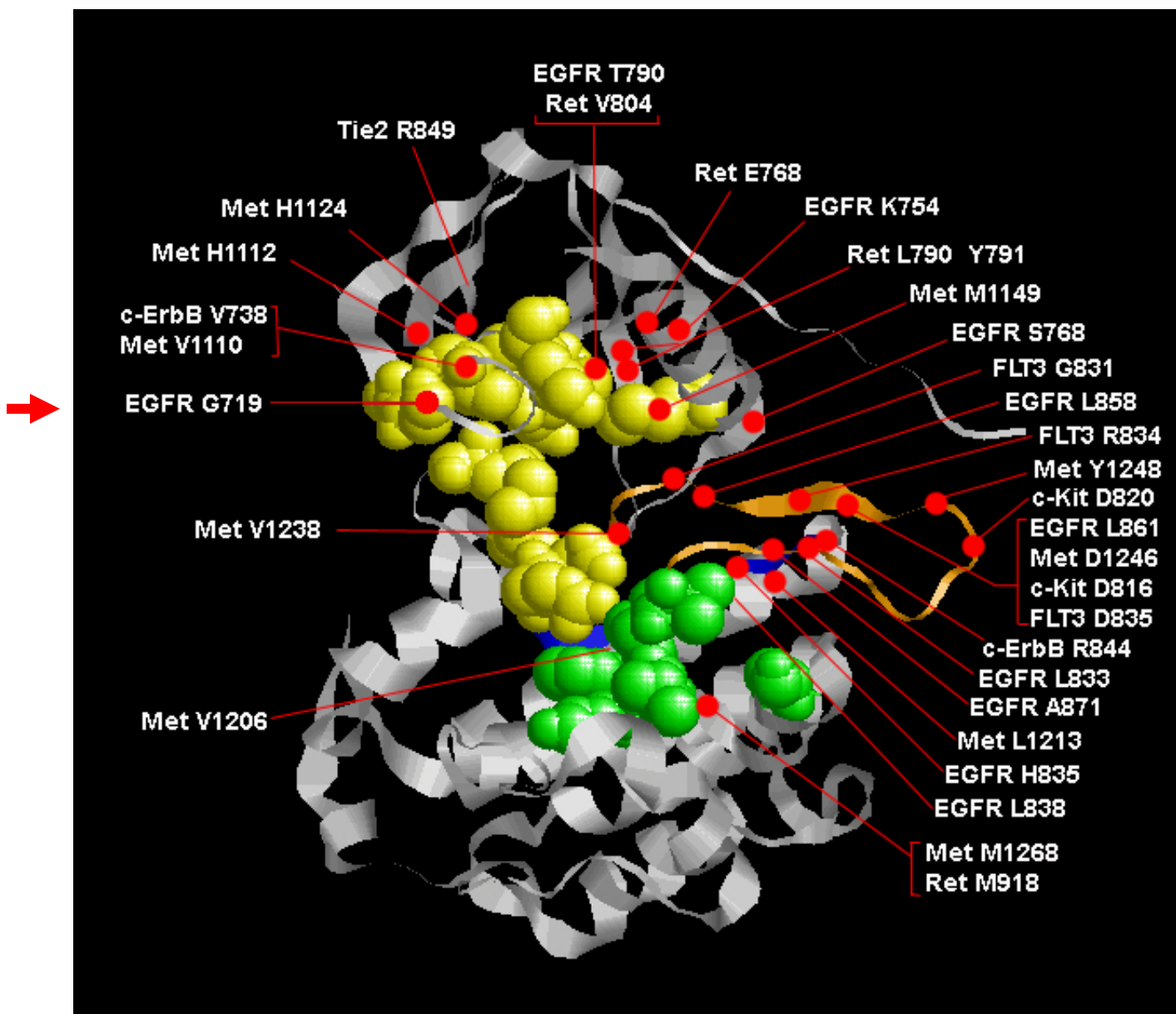
(e)



Multi-step oncogenesis



Oncogenic mutations of tyrosine kinases



Dr. LY Wang

Ghosh, P, Qiu, Y, Wang LY, Kung, HJ (2008) Tyrosine kinase: oncogenic mutations and therapeutic targeting in cancer (in press) in Molecular Oncology Causes and Treatments for Cancer. Ed, Sawyers, C, Gelman, E, and Rauscher F, III.

Tyrosine Kinase Inhibitors As Cancer Therapeutics

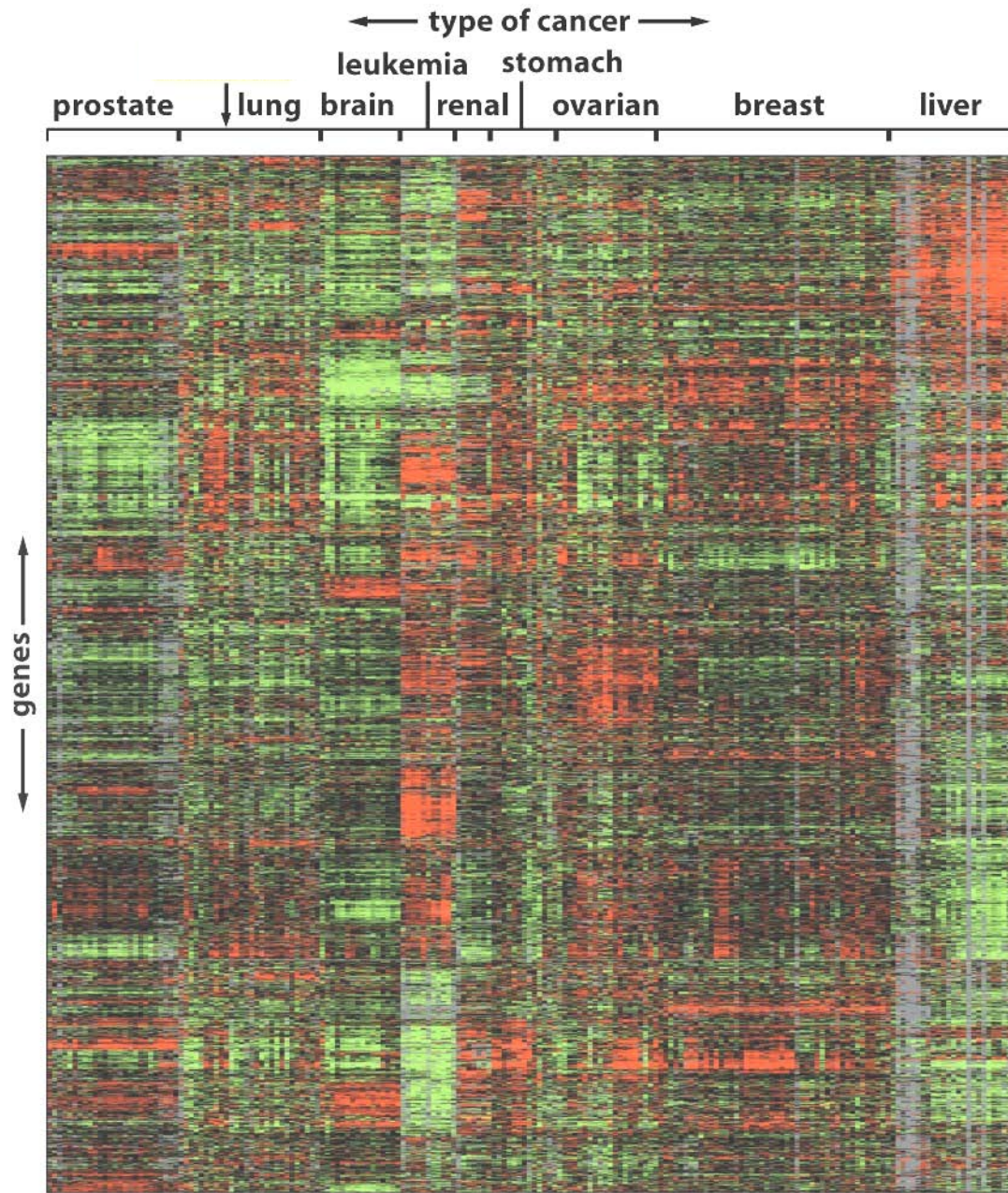
| Inhibitor | TK | type | Target Cancer | Status |
|---------------------|------------|---------------------|------------------|-----------------|
| Herceptin | Her2/ErbB2 | monoclonal antibody | Breast cancer | approved |
| Gleevec | Abl | small molecule | Myeloid leukemia | approved |
| IMC-C225 | EGFR | monoclonal antibody | Colon Cancer | Phase III trial |
| Iressa | EGFR | small molecule | Lung Cancer | Phase III trial |
| Tarcerva | EGFR | small molecule | Head and Neck | Phase III trial |
| SU5416 semaxanib | VEGFR | small molecule | Colon cancer | Phase III trial |
| IMC-1C11 | VEGFR | monoclonal antibody | Colon Cancer | Phase I trial |

Krause & Van Etten (NEJM, 2005 353:172)
TK as targets for cancer therapy

Gene Expression Profiles

Microarray analysis

Red: high expression
Green: low expression



Conventional Therapy

Genotoxic Stress

(Poison to death)

Etoposide, Doxorubicin,
cis-platin, Taxol

Damage DNA

Metabolic Stress

(starve to death)

Arginase, Asparaginase

Remove nutrition

Targeted Therapy

Tyrosine kinase inhibitors

Herceptin, Gleevec, Iressa

Growth inhibition

Combination Therapy

Personalized Therapy

Cancer Update from Johns Hopkins 2009

6. **Chemotherapy involves poisoning** the rapidly-growing cancer cells and also destroys rapidly-growing healthy cells in the bone marrow, gastrointestinal tract etc, and can cause organ damage, like liver, kidneys, heart, lungs etc.

7. Radiation while destroying cancer cells also burns, scars and damages healthy cells, tissues and organs.


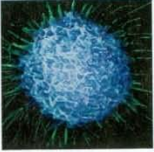

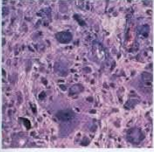

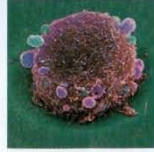
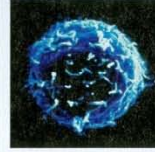
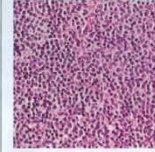

8. Initial treatment with chemotherapy and radiation will often reduce tumor size. However prolonged use of chemotherapy and radiation do not result in more tumor destruction.

10. Chemotherapy and radiation can cause cancer cells to mutate and become resistant and difficult to destroy. Surgery can also cause cancer cells to spread to other sites.

11. An effective way to battle cancer is to starve the cancer cells by not feeding it with the foods it needs to multiply..

*CANCER CELLS FEED ON:

a. Sugar is a cancer-feeder. By cutting off sugar it cuts off one important food supply to the cancer cells. Sugar substitutes like NutraSweet, Equal, Spoonful, etc are made with Aspartame and it is harmful. A better natural substitute would be Manuka honey or molasses, but only in very small amounts. Table salt has a chemical added to make it white in color. Better alternative is Bragg's aminos or sea salt.

| SKIN | PROSTATE | BREAST | BRAIN | PANCREATIC | LUNG | LEUKEMIA | LYMPHOMA NON-HODGKIN'S | HODGKIN'S |
|---|--|---|---|---|---|---|--|---|
|  |  |  |  |  |  |  |  |  |
| <p>Diagnosis</p> <p>The old-fashioned way is best for detecting melanoma, the most serious skin cancer—by looking for and keeping track of irregular moles.</p> <p>62,480 new melanoma cases in the U.S. expected in 2008; 27% (if spread) to 95% (if localized) five-year survival rate</p> <p>91%</p> <p>TREATMENT</p> <p>Surgery can often remove early tumors, but if the melanoma has penetrated more deeply and widely into the body, doctors may also choose to take out some lymph nodes and add radiation or chemotherapy. Efforts to create a vaccine to corral cancer cells are under way.</p> <p>Outlook</p> <p>About 80% of melanomas are detected early, before they have spread, and can be cured. Screening programs and self-exams are key</p> | <p>Diagnosis</p> <p>A blood test for the prostate-specific antigen (PSA) is the most common screen. A physical exam can also pick up changes in the gland's size or shape.</p> <p>186,320 new cases in the U.S. expected in 2008; 27% (if spread) to 95% (if localized) five-year survival rate</p> <p>99%</p> <p>TREATMENT</p> <p>Doctors can cut out contained growths, while radioactive seeds implanted in the tumor can destroy from within. Newer beam devices can focus radiation on the prostate from outside the body. Hormone therapies can also shrink growths and stall the cancer.</p> <p>Outlook</p> <p>It's one of the more curable cancers, as long as it is detected early. Cases still remain high among African-American men.</p> | <p>Diagnosis</p> <p>Physical exams and, past age 40, annual mammograms can detect up to 90% of cases in women.</p> <p>184,450 new cases in the U.S. expected in 2008; 27% (if spread) to 95% (if localized) five-year survival rate</p> <p>27%</p> <p>95%</p> <p>TREATMENT</p> <p>Search efforts have brought breast-cancer therapies closest to personalized medicine. The first targeted cancer drug, Herceptin, was designed to seek and destroy breast cancers containing the HER2neu protein. The latest test, Oncotype Dx, a 21-gene screen, can predict the likelihood that a woman's cancer will recur and even whether she will respond to chemotherapy.</p> <p>Outlook</p> <p>No other cancer comes with so many treatment options, which means more women than ever before can—and will continue to—survive</p> | <p>Diagnosis</p> <p>There is no screening test for brain cancer, and symptoms such as headache, blurred vision and seizure are often the first signs.</p> <p>21,810 new cases in the U.S. expected in 2008; 32% five-year survival rate</p> <p>32%</p> <p>TREATMENT</p> <p>Surgery, radiation and chemotherapy are the standard anticancer measures. But because growths in the brain are difficult to reach with these methods, researchers are testing a number of potentially more effective ones, including harnessing immune cells via vaccination, and cutting up the tumors and cutting off the cancer's blood supply using targeted drug therapies.</p> <p>Outlook</p> <p>New treatment options have only recently started to emerge, but a better understanding of the molecular mechanisms behind</p> | <p>Diagnosis</p> <p>No screening exists, so only 7% of cases are detected early. The rest are spotted when pain or other symptoms occur.</p> <p>37,680 new cases in the U.S. expected in 2008; 5% (if spread) to 20% (if localized) five-year survival rate</p> <p>5%</p> <p>20%</p> <p>TREATMENT</p> <p>Some of the cancer, but because it is often found late, chemotherapy and radiation are rarely enough. Doctors have a poor understanding of what drives pancreatic cancer, which means that even the latest targeted drugs are ineffective. Most research efforts are focused on finding better ways to detect the disease sooner so the tumor can be removed before it spreads.</p> <p>Outlook</p> <p>It may be one of the toughest cancers to treat today, but that might change as a deeper understanding of what causes pancreatic cancer is</p> | <p>Diagnosis</p> <p>Doctors are investigating whether X-rays or spiral CT scans are better at finding lung cancers early.</p> <p>215,020 new cases in the U.S. expected in 2008; 15% (if spread) to 49% (if localized) five-year survival rate</p> <p>15%</p> <p>45%</p> <p>TREATMENT</p> <p>Some of the cancer, but because it is often found late, chemotherapy and radiation are rarely enough. Doctors have a poor understanding of what drives pancreatic cancer, which means that even the latest targeted drugs are ineffective. Most research efforts are focused on finding better ways to detect the disease sooner so the tumor can be removed before it spreads.</p> <p>Outlook</p> <p>Survival rates remain stubbornly low, but smarter treatments combined with better screening tests may soon raise those percentages. The</p> | <p>Diagnosis</p> <p>Routine blood tests can reveal the hallmark of the disease—an abnormal number of white blood cells.</p> <p>44,270 new U.S. cases expected in 2008; 21%-75% five-year survival rate, the most powerful new anticancer treatment to come along in decades, was introduced. Its first target—chronic myeloid leukemia, a difficult-to-treat blood cancer. By disabling a signaling pathway inside the cancer cell, Gleevec does what chemo and radiation can't: attack the tumor from the inside out. That proved effective for other leukemias as well; some childhood versions now have an 81% five-year survival rate.</p> <p>21-75%</p> <p>TREATMENT</p> <p>Chemotherapy is an old reliable, but highly specialized antibodies that target proteins coating the cancer cell's surface are proving effective killers as well. While leukemias are destroyed from the inside out, lymphomas appear to be vulnerable to the traditional attack on the outer flanks—provided that the antibodies are designed to find the right lymphoma targets.</p> <p>Outlook</p> <p>New treatments provide hope that non-Hodgkin's cases can be controlled, but the incidence of the disease has climbed since the 1970s for</p> | <p>Diagnosis</p> <p>Swollen lymph nodes may be the first sign of this most common variety of lymphoma, which can occur in 30 different forms.</p> <p>66,120 new cases in the U.S. expected in 2008; 63% five-year survival rate</p> <p>63%</p> <p>TREATMENT</p> <p>Alternating rounds of radiation and chemotherapy are the most effective treatment option. During the disease's early stages, radiation focused on the affected lymph nodes may prevent the lymphoma from spreading.</p> <p>Outlook</p> <p>Once nearly always fatal, this lymphoma is now predominantly treatable, owing to early detection and judiciously applied therapies.</p> | <p>Diagnosis</p> <p>Swollen nodes in the neck or chest are a first sign. It may be revealed during X-rays for flulike symptoms.</p> <p>8,220 new cases diagnosed in the U.S. annually; 85% five-year survival rate</p> <p>85%</p> <p>TREATMENT</p> <p>Alternating rounds of radiation and chemotherapy are the most effective treatment option. During the disease's early stages, radiation focused on the affected lymph nodes may prevent the lymphoma from spreading.</p> <p>Outlook</p> <p>Once nearly always fatal, this lymphoma is now predominantly treatable, owing to early detection and judiciously applied therapies.</p> |